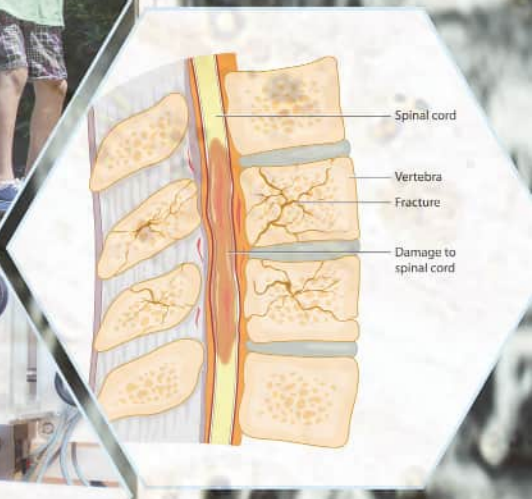
DIAGNOSIS AND TREATMENT OF SPINAL CORD INJURY

THE NEUROSCIENCE OF SPINAL CORD INJURY



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Diagnosis and Treatment of Spinal Cord Injury

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The Neuroscience of Spinal Cord Injury

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ACADEMIC PRESS
An imprint of Elsevier

Academic Press is an imprint of Elsevier
125 London Wall, London EC2Y 5AS, United Kingdom
525 B Street, Suite 1650, San Diego, CA 92101, United States
50 Hampshire Street, 5th Floor, Cambridge, MA 02139, United States
The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, United Kingdom

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ISBN 978-0-12-822498-4
SET ISBN 978-0-323-99198-8

Publisher: Nikki Levy
Acquisitions Editor: Natalie Farra
Editorial Project Manager: Timothy Bennett
Production Project Manager: Paul Prasad Chandramohan
Cover Designer: Mark Rogers

Typeset by STRAIVE, India

Dedication

I would like to dedicate this book to my wonderful daughter, Dr. Caragh Brien, of whom I am so incredibly proud.
Colin R. Martin

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Contents

29. Exploring the exogenous and endogenous effects of melatonin on spinal cord injury

Dewan Md. Sumsuzzman, Kanghui Park, and Yonggeun Hong

30. High-intensity interval training in individuals with spinal cord injury

Byron Lai, Jereme Wilroy, and Gordon Fisher

31. Stem cells and chronic spinal cord injury: Overview

Leonardino A. Digma, Pavan S. Upadhyayula, Joel R. Martin, and Joseph D. Ciacci

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Preface

Spinal injury affects about 10 million people annually worldwide. Many of these injuries are preventable and occur due to falls, violence, and road traffic accidents. However, spinal cord damage may also result from nontraumatic injury, for example, due to toxins, infection, cancer, intervertebral disc damage, and vascular disease.

Spinal injuries may cause significant, lifelong disabilities and thereby impact the family unit. Symptoms are varied and include paresthesia, spasticity, and loss of motor control. In extreme cases, affected individuals are chair- or bedbound for life. These debilitating injuries may also be accompanied by severe pain. Loss of bladder and bowel control increases dependency and further reduces quality of life.

Diagnosis is generally based on symptoms and various imaging techniques in the clinical context of a traumatic injury to the spinal cord. Various syndromes are associated with spinal cord injury (e.g., central, anterior, and posterior cord syndromes). However, a variety of pathological processes are involved in the initiation of primary and secondary damage to the spinal cord.

Physical trauma may be accompanied by multiorgan cellular and biochemical injury. These injuries include neurodegeneration, free radical damage, changes in gene expression, and physiological changes such as loss of the regulation of blood pressure. So the manifestation of symptoms and signs from any given injury may be highly variable.

The patient's functional outcome predominantly depends on the level of spinal column injury (i.e., cervical, thoracic, lumbar, or sacral), the location of the damage within the spinal cord (e.g., central, anterior, posterior), and the severity. This functional outcome may be modified to some extent by medical therapies and rehabilitation.

To fully comprehend and positively influence the trajectory of patients' outcomes, it is necessary to understand the fundamental principles of the conditions that arise as a result of spinal cord injury. Presently, the availability of much of this information is sporadic, in different scientific domains, and designed for different scientific specialties. Spinal cord injuries are diverse, so a multidisciplinary approach is needed. This is addressed in the two-volume set *The Neuroscience of Spinal Cord Injury* comprising the 2 books:

Diagnosis and Treatment of Spinal Cord Injury
Cellular, Molecular, Physiological, and Behavioral Aspects of Spinal Cord Injury

This book, *Diagnosis and Treatment of Spinal Cord Injury*, has the following six sections:

- *Setting the scene: introductory chapters*
- *Clinical features of spinal injury*
- *Diagnosis and evaluation*
- *Treatments: experimental and clinical*
- *Rehabilitation in spinal injury*
- *Resources*

Each chapter has the following sections:

- *An abstract (published online)*
- *Key facts*
- *Mini-dictionary of terms*
- *Applications to other areas of neuroscience*
- *Summary points*

The sections *Key facts, Mini-dictionary of terms,* and *Summary points* enable the reader to cross the transintellectual and transdisciplinary divides. The section *Applications to other areas of neuroscience* presents the translational aspects of the chapter and the applicability of the information.

The Neuroscience of Spinal Cord Injury is designed for research and teaching purposes. It is suitable for neurologists, surgeons, trauma specialists, psychologists, health scientists, public health workers, doctors, pharmacologists, and research scientists. It is valuable as a personal reference book and also for academic libraries that cover the domains of trauma and neurology. Contributions are leading national and international experts including those from world-renowned institutions. It is suitable for undergraduate and postgraduate students as well as lecturers and academic professors.

Rajkumar Rajendram, Victor R. Preedy, and Colin R. Martin
(Editors)

Section A

Setting the scene: Introductory chapters

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Chapter 1

Traumatic spinal cord injury and outcomes in low-resource settings

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Abbreviations

ASIA	American Spinal Injury Association
ATLS	advanced trauma life support
CT	computerized tomography
GSW	gunshot wound
HIC	high-income country
ICU	intensive care unit
LMIC	low- and middle-income country
MRI	magnetic resonance imaging
RTI	road traffic injury
TSCI	traumatic spinal cord injury
YLD	years lived with disability

Introduction

Traumatic spinal cord injuries (TSCIs) are devastating under any circumstance. However, patients in low-resource settings face unique challenges as they experience delays to care, a lack of prehospital care, and limited proper immobilization during transport, resulting in significantly higher in-hospital mortality than patients in high-income countries (HICs) (Bickenback, 2013; Eaton, Mukuzunga, Grudziak, & Charles, 2019; Lakhey, Jha, Shrestha, & Niraula, 2005). While long-term mortality of TSCI in HICs is now primarily due to chronic diseases, TSCI patients in low-income countries continue to die of preventable secondary causes (Bickenback, 2013). Those who survive struggle with access to proper assistive devices, rehabilitation services, follow up and health maintenance, and community reintegration (Bickenback, 2013). Moreover, while TSCI incidence is stable or decreasing in HICs, rates in low- and middle-income countries (LMICs) continue to rise (Jazayeri, Beygi, Shokraneh, Hagen, & Rahimi-Movaghar, 2015). Though most of the available evidence regarding the epidemiology and outcomes of TSCIs comes from HICs, the limited data from LMICs provide essential insights into improving TSCI prevention and management. This chapter will discuss the epidemiology, etiology, treatments, and outcomes of TSCIs in different LMICs globally.

Epidemiology

The worldwide incidence of traumatic spinal cord injury (TSCI) is between a quarter and 1 million people annually (Bickenback, 2013). The Global Burden of Disease Study reported a global age-standardized incidence rate of 13 per 100,000 and a prevalence of 368 per 100,000 in 2016. The regions with the highest reported incidence of TSCIs are central and eastern Europe and central Asia. Because of armed conflict, Syria, Yemen, Iraq, and Afghanistan have the highest incidence (James et al., 2019) (Fig. 1). The incidence of TSCI appears to be stable or decreasing in HICs, but increasing in LMICs (Jazayeri et al., 2015). In 2016, TSCIs were responsible for an estimated 9.5 million years lived with disability (YLDs) (James et al., 2019). Available evidence on the epidemiology of TSCIs comes from HICs, but the limited data from LMICs provide essential insight into improving TSCI prevention and management strategies.

Diagnosis and Treatment of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822498-4.00001-4

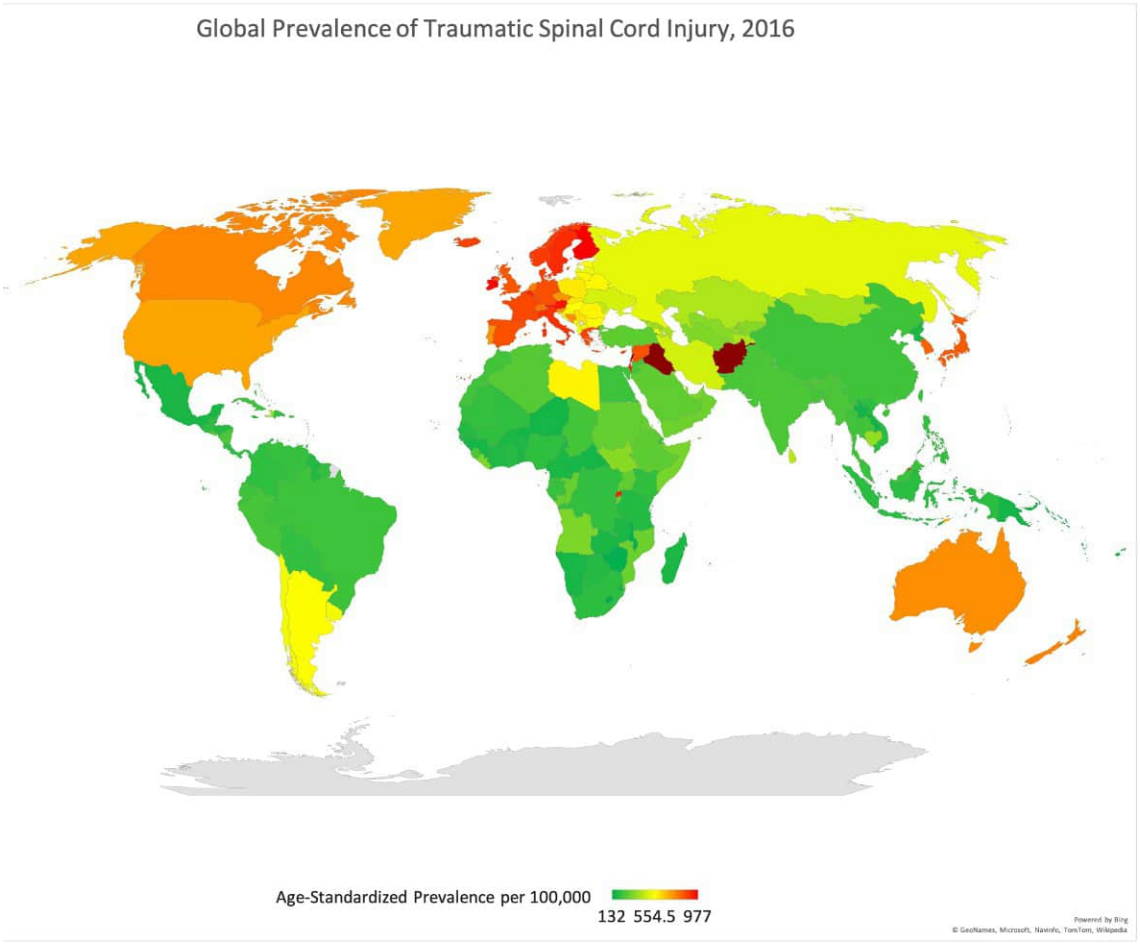

FIG. 1 Global prevalence of traumatic spinal cord injury. The figure illustrates the age-standardized prevalence of TSCI per 100,000 people by country in 2016 (James et al., 2019). The countries with prevalence over 1300 per 100,000, shown in *dark red*, are Lebanon, Iraq, and Afghanistan.

Sex and age

Males are disproportionately affected by TSCIs (Kang et al., 2017), with some countries reporting a male preponderance of over 90% (Deconinck, 2003; Gosselin & Coppotelli, 2005). Males are more likely to be in situations that place them at risk for TSCI or participate in high-risk activities (Kang et al., 2017) (Fig. 2).

In HICs, TSCIs follow a bimodal age distribution, with one peak in the second to third decade and another peak after age 65 (Kang et al., 2017). In LMICs, TSCIs predominantly affect younger patients. In the Eastern Mediterranean (specifically Iran, Pakistan, and Afghanistan), the mean age range is 26–38 years (Chabok et al., 2010; Deconinck, 2003). Similarly, in Southeast Asia, Sub-Saharan Africa, and Latin America, the mean age is 30–44 years (Barbetta et al., 2018; Bellet, Rashid, Jusabani, Dekker, & Temu, 2019). Studies in China and India report a mean age range of 45–51 years (Aleem et al., 2017; Zhou et al., 2016).

Etiology

The most common cause of TSCIs in most regions is falls, followed by road traffic injuries (RTIs) (James et al., 2019).

Falls

Falls are the most common cause of TSCIs in Southeast Asia, parts of the Eastern Mediterranean, Sub-Saharan Africa, and the Western Pacific. In Southeast Asia, falls are responsible for 53%–84% of TSCIs (Bellet et al., 2019; Dhakal, Paudel, Dhungana, Gurung, & Kawaguchi, 2018). Falls in these regions are primarily occupation-related (Agarwal, Sud, &

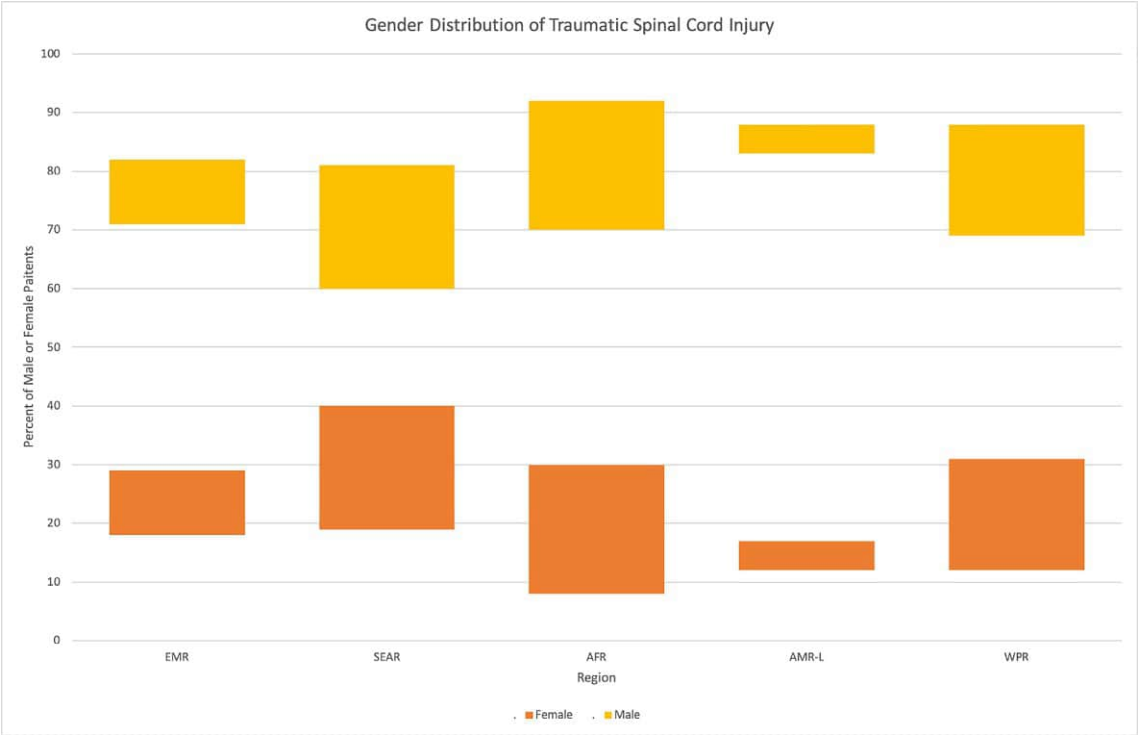

FIG. 2 Gender distribution of traumatic spinal cord injury by region. The range of proportions of spinal cord injured patients by sex is shown by region. *EMR*, Eastern Mediterranean; *SEAR*, Southeast Asia; *AFR*, Africa; *AMR-L*, Latin America; *WPR*, Western Pacific.

Shishehbor, 2016; Dhakal et al., 2018). In Iran and Pakistan, construction workers and well diggers are at high risk for falls due to unsafe work environments (Derakhshanrad, Yekaninejad, Vosoughi, Sadeghi Fazel, & Saberi, 2016; Rathore, Hanif, Farooq, Ahmad, & Mansoor, 2008). In Sub-Saharan Africa, falls are common from roofs, scaffolds, trees, or electric poles (Leidinger et al., 2019; Löfvenmark et al., 2015). In Cambodia, approximately 50% of TSCIs are secondary to falls from trees or houses (Choi et al., 2017; Makhni et al., 2019). Malaysia's high rates of falling TSCIs are attributed to migrant workers in high-risk conditions with limited safety regulations (Ibrahim et al., 2013). In China, falls are responsible for over 60% of TSCIs due to increased construction of buildings and subways (Liu et al., 2012; Liu, Liu, Gao, Li, & Li, 2020).

Falls from standing are also common. LMIC's growing aging population has resulted in more individuals vulnerable to TSCIs from ground-level falls (Yuan, Shi, Cao, Li, & Feng, 2018). Also, ground-level falls while carrying heavy objects atop one's head are common, particularly for females in Sub-Saharan Africa (Moshi, Sundelin, Sahlen, & Sörlin, 2017).

Road traffic injuries

RTIs are the most common cause of TSCIs in Sub-Saharan Africa, Latin America, and parts of the Western Pacific. Studies from Ghana, Nigeria, and Botswana report up to 80% of TSCIs are due to RTIs (Ametefe et al., 2016; Löfvenmark et al., 2015). While in Malawi, Tanzania, and Sierra Leone, RTIs and falls are evenly distributed (Eaton, Hanif, Grudziak, & Charles, 2017; Gosselin & Coppotelli, 2005). In Latin America, 39%–44% of TSCIs are due to RTIs (Bellucci et al., 2015). Within the Western Pacific, RTIs are the most common cause of TSCI in Malaysia, responsible for 66% of cases (Ibrahim et al., 2013). One-third of TSCIs in Cambodia are due to RTIs, most of which can be attributed to motorcycle collisions (Choi et al., 2017; Makhni et al., 2019).

RTIs have surpassed falls as the leading cause of TSCIs in locations with rapid increases in motorization. In Brazil, RTIs are the leading etiology of TSCI in 2003, as the number of motorcycles in Brazil has increased by 491% (Bellucci et al., 2015). In high population centers in China, such as Beijing, RTIs have surpassed falls as the most common cause of TSCIs, as the number of private vehicles has increased from 1.2 million in 2002 to 4.8 million in 2010 (Chen et al., 2017; Hua et al., 2013; Yuan et al., 2018). Factors contributing to high rates of RTIs in Sub-Saharan Africa and other LMICs include lack of road maintenance, unsafe driving, road unworthy vehicles, and poor enforcement of traffic laws (Ametefe et al., 2016; Chen et al., 2017; Obalum, Giwa, Adekoya-Cole, & Enweluzo, 2009).

Violence and other causes

Violence has generally become a less common cause of TSCIs worldwide. However, in areas with active conflict and terrorism, such as in North Africa and the Middle East (specifically Syria, Yemen, Iraq, and Afghanistan), it is the most common cause of TSCIs (James et al., 2019). A study in Afghanistan found 59% of TSCI cases were due to bullets or shrapnel (shelling, gunshots, and mine explosions) (Deconinck, 2003). In Brazil, gun violence is responsible for nearly 30% of TSCIs (Barbetta et al., 2018; Bellucci et al., 2015). In South Africa, violence is a significant contributor, as up to 60% of TSCIs are attributed to gun violence, stabbing, and blunt assault mechanisms (Eaton et al., 2019; Löfvenmark et al., 2015). Assault is a less commonly reported cause of TSCIs in the rest of Sub-Saharan Africa, accounting for 2%–10% (Eaton et al., 2019; Löfvenmark et al., 2015).

Finally, sports-related activities compose a small proportion of TSCIs globally, such as diving into shallow water (6%–12% of Brazil's TSCIs), winter sports ($\leq$5% of TSCIs in China) (Bellucci et al., 2015; Chen et al., 2017; Liu et al., 2020). In Sub-Saharan Africa, specifically Nigeria and Botswana, sports-related activity is responsible for an estimated 2% of TSCIs (Löfvenmark et al., 2015; Obalum et al., 2009). A study from Iran reported a relationship between education level and TSCI etiology. Sports become a more common cause of TSCI with increasing years of education (primarily diving, gymnastics, wrestling), while violence and being struck by falling objects became less common (Derakhshanrad et al., 2016).

Spinal cord level and severity

Overall complete cervical injuries are the most common, however significant TSCI level and severity variations exist globally (Kang et al., 2017). For example, the thoracic spine is the most commonly injured spinal level in Pakistan, Iran, and Afghanistan, with cervical injuries composing 30% of TSCIs (Deconinck, 2003; Derakhshanrad et al., 2016; Rathore et al., 2008). However, most Afghani patients have complete thoracic or lumbar injuries, and only 7% have cervical injuries, which is reflected in improved survival (Deconinck, 2003).

In Sub-Saharan Africa, the cervical spine is the most common injured site (30%–68% of cases), followed by the thoracic (10%–39%) and lumbar spine (4%–59%) (Ametefe et al., 2016; Bellet et al., 2019). Injury severity, however, varies significantly. In South Africa, Malawi, Tanzania, and Ghana, complete injuries range from 23% to 48% of patients, whereas up to 92% of TSCIs are complete in Nigeria and Sierra Leone (Ametefe et al., 2016; Bellet et al., 2019; Gosselin & Coppotelli, 2005; Obalum et al., 2009).

In Brazil, the most common location of TSCI is the thoracic spine (46%–61%), with approximately 60% being complete (Barbetta et al., 2018; Bellucci et al., 2015). Cervical injuries in Brazil were more common in automobile collisions, whereas thoracic injuries were more associated with motorcycle collisions and GSWs (Barbetta et al., 2018).

In China, 47%–76% of TSCIs are reported to be cervical, and 14%–55% of injuries are complete (Chen et al., 2017). Beijing has higher tetraplegia rates and complete injuries than other regions in China (Yuan et al., 2018). The cervical spine is generally the most common location of injury in Southeast Asia and the Western Pacific. In both regions, falls are associated with lumbar injuries and motorcycle and automobile collisions with cervical injuries (Agarwal, Upadhyay, & Raja, 2007; Choi et al., 2017). In Cambodia, lumbar injuries are more common than cervical injuries (Fig. 3) (Choi et al., 2017; Makhni et al., 2019).

Diagnosis

Diagnosis of TSCI relies on a combination of history and clinical findings with the use of radiographic adjuncts. Clinical findings include flaccid paralysis and lack of response to painful stimuli below the level of injury, as well as bradycardia, priapism, and paradoxical breathing (Kebaish & Harris, 2020).

A complete TSCI produces total loss of all motor and sensory function below the level of injury. Nearly 50% of all TSCIs are complete. Even with a complete TSCI, the spinal cord is rarely completely transected. More commonly, loss of function is caused by a contusion to the spinal cord or ischemia of the spinal cord. In an incomplete TSCI, some function remains below the primary level of the injury.

Clinicians commonly utilize the American Spinal Injury Association (ASIA) grading scale to describe the injury severity (Kirshblum et al., 2011).

- ASIA A: a complete spinal cord injury with no sensory or motor function preserved
- ASIA B: an incomplete sensory injury with complete motor function loss

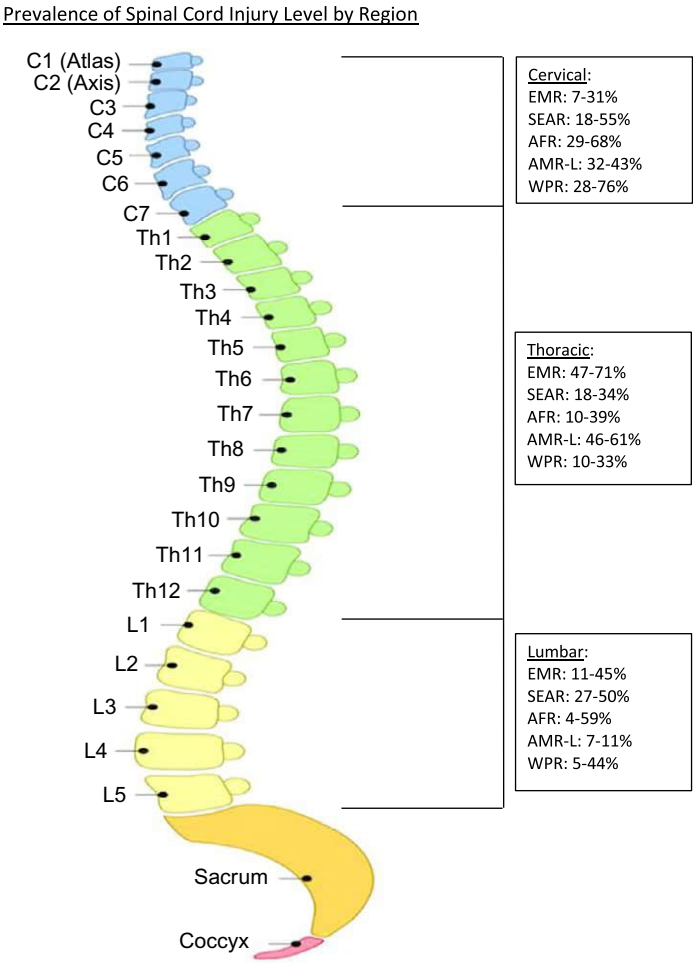

FIG. 3 Distribution of traumatic spinal cord injury level by region. The range of prevalence of injuries at different spinal levels across regions is reported from the available literature. *EMR*, Eastern Mediterranean; *SEAR*, Southeast Asia; *AFR*, Africa; *AMR-L*, Latin America; *WPR*, Western Pacific.

- ASIA C: an incomplete motor injury, where there is some movement, but less than half the muscle groups are anti-gravity (can lift against the force of gravity with a full range of motion)
- ASIA D: an incomplete motor injury with more than half of the muscle groups are anti-gravity
- ASIA E: normal

The more severe the injury, the less likely recovery will occur. Historically, the radiological diagnosis of TSCI started with plain spine radiography. However, with the technological advancements and availability, the entire spine may be imaged with computerized tomography (CT) as an initial screen to identify fractures and other bony abnormalities. For patients with known or suspected injuries, magnetic resonance imaging (MRI) helps delineate spinal cord anatomy and detect any blood clots, herniated disks, or masses that may be compressing the spinal cord. MRI is recommended if feasible and is especially useful if CT findings are discordant with symptoms and for surgical planning (Kebaish & Harris, 2020).

The majority of data regarding the imaging modalities used in diagnosing TSCI in LMICs come from Sub-Saharan Africa. Most patients received plain radiographs in those studies that reported diagnostic methods (71%–100%) (Bellet et al., 2019; Eaton et al., 2019). CT scans and MRIs are less commonly utilized. Reasons included lack of availability in the treatment facility or patient inability to pay for the diagnostic test. Between 7% and 59% of patients had a CT scan, and 41%–72% had an MRI (Ametefe et al., 2016; Leidinger et al., 2019). For reference, a 2019 survey of emergency medicine providers found that 99% and 97% of respondents in HICs reported access to in-hospital plain radiography and CT, respectively. Of respondents in LMICs, 91% reported access to in-hospital plain radiography, and 65% reported access to in-hospital CT (Alibhai, Hendrikse, & Bruijns, 2019).

Prehospital and acute management

Care provided during the first 24–48 h following a traumatic TSCI is critical and can significantly influence TSCI outcomes (Gélis et al., 2011). Prehospital management requires rapid evaluation, including measurement of vital signs and level of consciousness; initiation of injury management, spinal immobilization to preserve neurological function until long-term spinal stability is established, and control of bleeding, body temperature, and pain; and prompt and safe access to the healthcare system.

Prehospital care is underdeveloped in low-income countries. Emergency medical services are frequently inadequate or nonexistent. For example, in Tehran, Iran, only one-third of patients with spinal injuries are transported by emergency medical services (Sharif-Alhoseini & Rahimi-Movaghar, 2014). Similarly, in Botswana, only 20% of patients are transported by ambulance (Löfvenmark et al., 2015). Difficult terrain and transportation costs delay care, and patients may not arrive at a hospital for several days after their injury. Studies from Tanzania and Nepal reported approximately one-third of patients took greater than 2 days from injury to reach a hospital (Bellet et al., 2019; Dhakal et al., 2018; Lakhey et al., 2005). In Afghanistan, the average time to a hospital after sustaining TSCI was 3.4 days (Deconinck, 2003).

Due to cost and resource limitations in LMICs, spinal precautions are infrequently practiced in the prehospital setting. Among patients with cervical spine injuries in Nepal, only 36% arrived at the hospital with a cervical collar (Munakomi, Bhattarai, & Cherian, 2017). In India, up to 98% of TSCI patients are not adequately immobilized (Aleem et al., 2017; Dhamangaonkar, Joshi, Kumar, & Goregaonkar, 2013). A study from Malawi reported that 37% of patients with TSCI had cervical collars placed at some point during their hospitalization and that no other spinal braces were utilized (Eaton et al., 2019).

Treatment strategies

Management of spinal cord injuries is divided into phases. Acute phase management is based on Advanced Trauma Life Support (ATLS) principles, including prioritizing and treating life-threatening injuries to maximize survival, treating disabling injuries to minimize impairment, and limiting pain and suffering. Assessment should begin immediately upon arrival at the hospital and include: a medical history, signs and symptoms, neurological examination, radiological imaging, and laboratory testing (Bickenback, 2013). Signs and symptoms of spinal cord injury include weakness, sensory and motor deficits, bowel and bladder dysfunction, anatomical deformity, and localized tenderness.

Decisions about the best management strategy depend on the environment, available infrastructure, and surgical expertise. For TSCIs, there are risks and benefits to both nonoperative and surgical management. Many factors must be considered to determine the most appropriate management approach, including the level of injury, type of fracture, degree of instability, presence of neural compression, and impact of other concurrent injuries. Nonoperative management involves measures to immobilize the spine and to reduce dislocation with bed rest, traction of the spine, or the wearing of orthoses for 2–3 months. Indications for surgical management include spinal column stabilization and spinal cord decompression by reducing a dislocation or removing fracture fragments that cause neural compression.

Operative management of TSCI, within the first 48 h, has been associated with improved neurologic outcomes (Furlan, Noonan, Cadotte, & Fehlings, 2011). Nonoperative management of these injuries is associated with a fourfold increase in mortality than those with similar injuries managed operatively (Lessing, Lazaro, et al., 2020). Also, operative intervention is associated with early mobilization, better neurologic improvement, and higher return to wage-earning jobs (Lessing, Zuckerman, et al., 2020).

In LMICs, a high proportion of patients presenting with spinal cord injury do not undergo operative intervention. Studies have shown 0%, 30%, and 60% of TSCI patients undergo surgical intervention in Malawi, Nigeria, and Ghana, respectively (Eaton et al., 2019; Nwankwo & Uche, 2013). The primary reasons expressed in studies for nonoperative management or delays in surgical intervention are a paucity of neurosurgical workforce, lack of patient finances, delays in imaging access, and unavailability of operating room access (Nwankwo & Uche, 2013).

Globally, approximately 22.6 million new cases need neurosurgery consults annually, with 13.8 million persons requiring surgical intervention (Dewan Rattani, Baticulon, et al., 2019; Kanmounye et al., 2020). However, approximately 5.2 million neurosurgical cases go untreated, primarily due to lack of neurosurgical services and inadequate surgical workforce, with Africa bearing the lowest surgeon densities (Dewan, Rattani, Fieggen, et al., 2019). In 2018, the median workforce densities (neurosurgeons per 100,000 population) by WHO region were Americas (0.54), Africa (0.05), Eastern Mediterranean (0.34), Europe (0.99), South-East Asia (0.13), and Western Pacific (0.11) (Fig. 4) (Kanmounye et al., 2020). Approximately one neurosurgeon per 212,000 people is required to meet the healthcare demands from neurotrauma

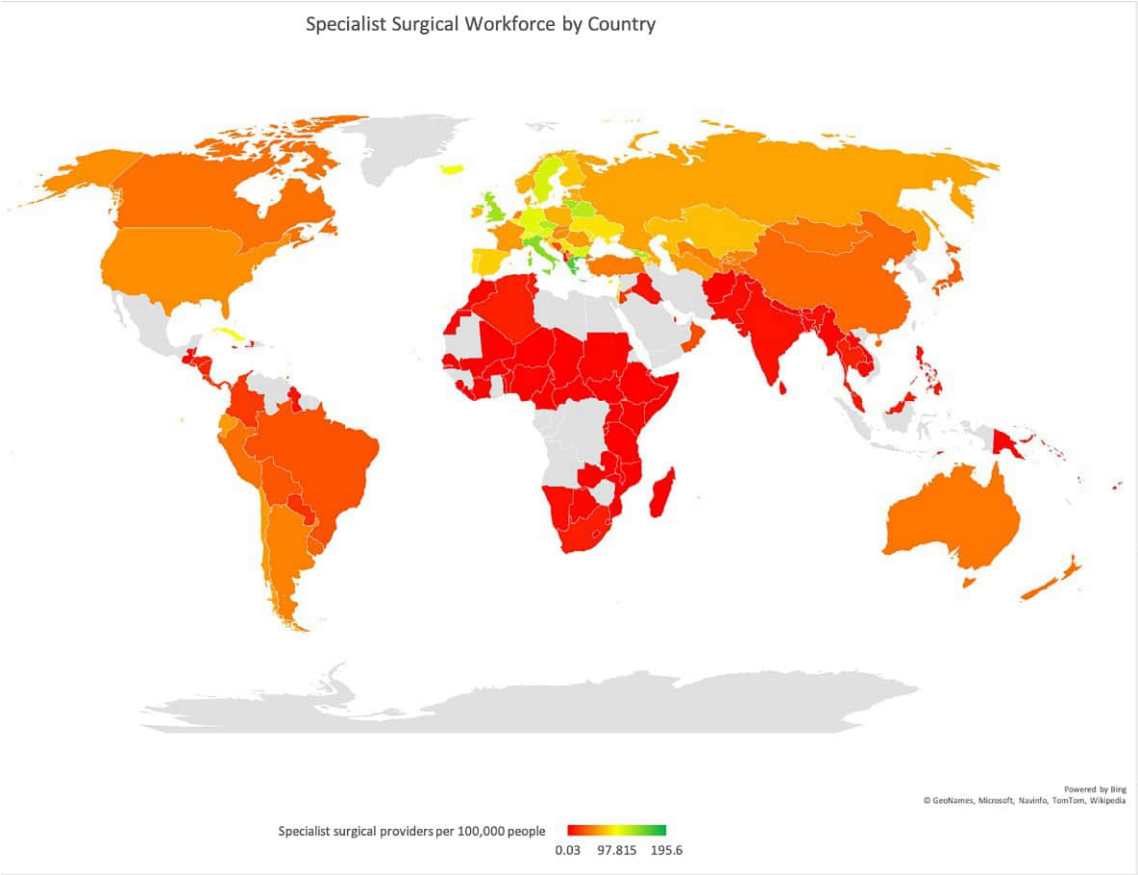

FIG. 4 Specialist surgical workforce by country. The figure displays the number of specialist surgical providers per 100,000 people (World Bank, 2018).

adequately, and an estimated 23,300 additional neurosurgeons globally are needed to address this significant deficit (Corley, Lepard, Barthélemy, Ashby, & Park, 2019).

Surgical care to patients and their families is often cost-prohibitive (James et al., 2019; Kumar et al., 2018). It is expected that patients and families must gather the funds to pay for the cost of surgical supplies, implants, or diagnostic radiology. High implant costs for spinal cord operative management can often lead to delay or deferment of operative treatment (James et al., 2019; Kumar et al., 2018). A Tanzanian study determined nonoperative management costs 212 USD per patient compared to 731 USD per patient for operative management (Lessing, Zuckerman, et al., 2020). However, operative management was determined to be cost-effective as the incremental cost per disability-adjusted life years averted was 112–158, 47–67, 50–71, 41–58 USD for quadriplegic, paraplegic, neurologic improvement, and neurologically intact patients, respectively (Lessing, Zuckerman, et al., 2020).

Ancillary support is also challenging in low-resource environments for patients needing treatment for spinal cord injuries. There is a lack of intensive care unit (ICU) beds and respiratory, physical, and occupational therapy. In the United States, the ICU bed density is approximately 20–32 beds per 100,000 population, compared to 5 beds per 100,000 in the United Kingdom, 2.8–4.6 beds per 100,000 in China, and 0.34–1.57 beds per 100,000 population in India (Gooch & Kahn, 2014; Murthy & Wunsch, 2012). There is a lack of critical care data in Sub-Saharan Africa. The estimated ICU bed density in Malawi is 0.1 beds per 100,000 population (Fig. 5).

Post-acute medical care and rehabilitation

Appropriate medical care and rehabilitation can prevent TSCI complications and help patients achieve a meaningful life. Rehabilitation, defined as a "set of measures that assist individuals in achieving and obtaining optimal functioning in the interaction with their environments" (World Health Organization, 2011), should commence in the acute phase for people

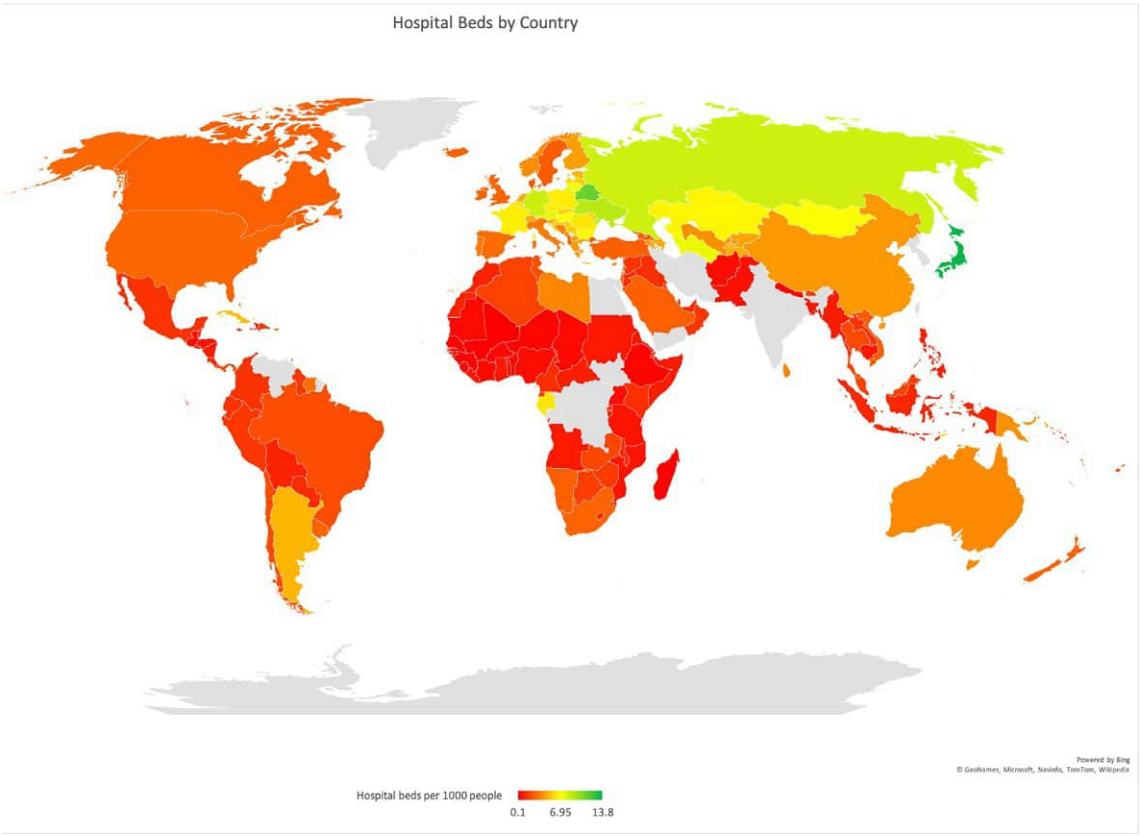

FIG. 5 Number of hospital beds by country. This figure shows the number of hospital beds per 1000 people by country (World Bank, 2015).

with TSCI, continue to be available to promote functioning, and be available in a range of different settings from the hospital through to the home and community environments.

Loss of normal bladder function is one of the most significant consequences for people who have sustained TSCIs. Inadequate management of bladder function leads to secondary complications such as UTIs, urinary retention, incontinence, stones in the kidneys and urinary tract, and reflux of urine (Consortium for Spinal Cord Medicine, 2006). These urinary complications can result in renal failure (Wolfe et al., 2010).

Neurogenic bowel is a common condition following TSCI. It is associated with many gastrointestinal problems, including poor colonic motility, prolonged bowel transit time, chronic constipation, abdominal distension, and fecal incontinence (Correa & Rotter, 2000). People with TSCI who experience a neurogenic bowel are often afraid of possible bowel incontinence, which can significantly impact an individual's ability to return to former social roles and activities (Krassioukov, Eng, Claxton, Sakakibara, & Shum, 2010; World Health Organization, 2011). Adequate management of bowel function can be challenging where resources are limited (Yasmeen, Rathore, Ashraf, & Butt, 2010).

Rehabilitation should aim to help people overcome these limitations by improving trunk and limb function, modifying the person's immediate environment, and providing assistive devices and other reasonable accommodations to enable individuals to continue family and work roles. The reality in most LMIC is that access to rehabilitation is somewhat limited, and most patients are ultimately cared for at home in the community. In a study in rural Uganda, impaired sexual (90%) and bowel/bladder function (80%), depression and chronic pain (85%), skin break-down, and urinary infections (57%) recognized complications of long-term TSCI (Stothers, Macnab, Mukisa, Mutabazi, & Bajunirwe, 2017). Major problems articulated were lack of care for patients living at home, lack of support for family caregivers, and limited aids to living, including wheel-chairs and crutches. Locally made walking aids are prevalent, but most patients rely on family members for their mobility.

In LMICs, infections and septicemia caused by urinary tract complications and pressure sores are still the leading cause of death for people with TSCI (Gosselin & Coppotelli, 2005; Hoque, Grangeon, & Reed, 1999). In Zimbabwe, 7% of individuals with TSCI died from septicemia due to pressure sores while being hospitalized (Correa & Rotter, 2000). With regular turning to relieve pressure points and proper nursing care, pressure sores could be prevented.

Life expectancy for individuals with TSCI in less-resourced settings is shorter than for the average population and persons with TSCI in HICs. Septicemia resulting from urinary tract infections and pressure sores was still the leading cause of death and had the most significant impact on life expectancy and daily life among individuals with TSCI. The findings confirm that individuals with TSCI and their families in low-income settings face substantial challenges in their everyday life because of limited financial, medical, social, and technical support. Poverty has an even more significant impact on people with TSCI in low-income countries, contributing to individual suffering and a high mortality rate due to limited access to rehabilitation services, including appropriate wheelchairs and medical treatment for complications, such as infections, pressure sores, and respiratory problems, common to people with TSCI.

Appropriate and timely medical care and rehabilitation can significantly reduce mortality, morbidity, and disability in TSCI patients. Access to specialized and health care can lead to better outcomes and a productive and enjoyable life for people with TSCI.

Applications to other areas of neuroscience

The two most common causes of TSCI falls, and road traffic injuries (RTIs) are also the two most common causes of traumatic brain injury (TBI) (James et al., 2019). Co-occurrence of TBI and TSCI is common, especially in cervical TSCI (Macciocchi, Seel, Thompson, Byams, & Bowman, 2008). Studies that have specifically evaluated this co-occurrence found that patients who sustain TSCI have a 16%–60% chance of sustaining a TBI (Macciocchi et al., 2008). Moreover, there is evidence that TBI in TSCI patients is significantly underdiagnosed in up to 60% of cases, which may be even higher in LMICs that have limited access to resources such as imaging and neuropsychological testing (Sharma, Bradbury, Mikulis, & Green, 2014). Not surprisingly, patients with dual diagnoses experience worse functional outcomes than patients with TSCI alone (Garlanger, Beck, & Cheville, 2018).

Recognition of this relationship has several important implications. First, efforts to reduce traumatic mechanisms can be expected to minimize TSCIs and TBIs by improving road safety and working conditions. Second, a high index of suspicion is essential for patients who are at risk for TBI, especially in low-resource settings with limited access to diagnostic adjuncts. Lastly, patients with dual diagnoses require special consideration when planning for discharge from a hospital or rehabilitation center. TSCI alone presents a massive challenge in low-resource settings. A concurrent TBI will severely impact functional independence and community reintegration.

Key facts of global traumatic spinal cord injury epidemiology and etiology

- The global incidence is between 250,000 and 1 million annually.
- Males are more commonly affected than females, and at least two-thirds of patients are males in most countries.
- In high-income countries (HICs), TSCIs occur in a bimodal age distribution. In low- and middle-income countries (LMICs), however, TSCIs predominantly affect younger patients.
- The two most common causes of TSCIs worldwide are falls and road traffic injuries (RTIs).
- In areas where active armed conflict is common, such as the Middle East, violence is the leading cause of TSCIs.

Summary points

- The global incidence of TSCI is between 250,000 and 1 million annually.
- Males are more commonly affected than females worldwide.
- The two most common causes of TSCI are falls and road traffic injuries (RTIs).
- There is significant global variation in the distribution of spinal cord injury level and severity.
- Patients in LMICs experience significant delays to care following TSCI.
- Due to the lack of resources in LMICs, a high proportion of patients with TSCI who would benefit from surgical treatment do not undergo operative management.
- Rehabilitation services in LMICs are limited, and patients in these settings have difficulty gaining independence and preventing long-term complications of TSCIs.
- In LMICs, infections and septicemia caused by urinary tract infections and pressure sores are the leading cause of death for people with TSCIs.
- Life expectancy for individuals with TSCIs in LMICs is lower than that of the average population and lower than that of individuals with TSCI in HICs.

References

Agarwal, S., Sud, K., & Shishehbor, M. H. (2016). Nationwide trends of hospital admission and outcomes among critical limb ischemia patients from 2003–2011. *Journal of the American College of Cardiology*, *67*(16), 1901–1913. https://doi.org/10.1016/j.jacc.2016.02.040.

Agarwal, P., Upadhyay, P., & Raja, K. (2007). A demographic profile of traumatic and non-traumatic spinal injury cases: A hospital-based study from India. *Spinal Cord*, *45*(9), 597–602. https://doi.org/10.1038/sj.sc.3102005.

Aleem, I. S., DeMarco, D., Drew, B., Sancheti, P., Shetty, V., Dhillon, M., … Bhandari, M. (2017). The burden of spine fractures in India: A prospective multicenter study. *Global Spine Journal*, *7*(4), 325–333. https://doi.org/10.1177/2192568217694362.

Alibhai, A., Hendrikse, C., & Bruijns, S. R. (2019). Poor access to acute care resources to treat major trauma in low- and middle-income settings: A self-reported survey of acute care providers. *African Journal of Emergency Medicine*, *9*(January), S38–S42. https://doi.org/10.1016/j.afjem.2019.01.004.

Ametefe, M. K., Bankah, P. E., Yankey, K. P., Akoto, H., Janney, D., & Dakurah, T. K. (2016). Spinal cord and spine trauma in a large teaching hospital in Ghana. *Spinal Cord*, *54*(12), 1164–1168. https://doi.org/10.1038/sc.2016.57.

Barbetta, D., Smanioto, T., Poletto, M., Ferreira, R., Lopes, A., Casaro, F., … Ogashawara, T. (2018). Spinal cord injury epidemiological profile in the Sarah Network of Rehabilitation Hospitals—A Brazilian population sample. *Spinal Cord Series and Cases*, *4*(1), 2–7. https://doi.org/10.1038/s41394-018-0049-8.

Bellet, F. D., Rashid, S. M., Jusabani, M. A., Dekker, M. C. J., & Temu, R. J. (2019). The characteristics of cervical spinal cord trauma at a North Tanzanian referral hospital: A retrospective hospital-based study. *Pan African Medical Journal*, *33*, 1–7. https://doi.org/10.11604/pamj.2019.33.82.18353.

Bellucci, C. H. S., De Castro Filho, J. E., Gomes, C. M., De Bessa, J., Battistella, L. R., Rubio De Souza, D., … Barros Filho, T. E. P. (2015). Contemporary trends in the epidemiology of traumatic spinal cord injury: Changes in age and etiology. *Neuroepidemiology*, *44*(2), 85–90. https://doi.org/10.1159/000371519.

Bickenback, J. (2013). *International perspectives on spinal cord injury*. Retrieved from http://apps.who.int/iris/bitstream/10665/94190/1/9789241564663_eng.pdf.

Chabok, S. Y., Safaee, M., Alizadeh, A., Dafchahi, M. A., Taghinnejadi, O., & Koochakinejad, L. (2010). Epidemiology of traumatic spinal injury: A descriptive study. *Acta Medica Iranica*, *48*(5), 308–311.

Chen, R., Liu, X., Han, S., Dong, D., Wang, Y., Zhang, H., … Yao, M. (2017). Current epidemiological profile and features of traumatic spinal cord injury in Heilongjiang province, Northeast China: Implications for monitoring and control. *Spinal Cord*, *55*(4), 399–404. https://doi.org/10.1038/sc.2016.92.

Choi, J. H., Park, P. J., Din, V., Sam, N., Iv, V., & Park, K. B. (2017). Epidemiology and clinical management of traumatic spine injuries at a major government hospital in Cambodia. *Asian Spine Journal*, *11*(6), 908–916. https://doi.org/10.4184/asj.2017.11.6.908.

Consortium for Spinal Cord Medicine. (2006). Bladder management for adults with spinal cord injury: A clinical practice guideline for healthcare providers. *Journal of Spinal Cord Medicine*, *29*(5), 527–573.

Corley, J., Lepard, J., Barthélemy, E., Ashby, J. L., & Park, K. B. (2019). Essential neurosurgical workforce needed to address neurotrauma in low- and middle-income countries. *World Neurosurgery*, *123*, 295–299. https://doi.org/10.1016/j.wneu.2018.12.042.

Correa, G. I., & Rotter, K. P. (2000). Clinical evaluation and management of neurogenic bowel after spinal cord injury. *Spinal Cord*, *38*(5), 301–308. https://doi.org/10.1038/sj.sc.3100851.

Deconinck, H. (2003). The health condition of spinal cord injuries in two Afghan towns. *Spinal Cord*, *41*(5), 303–309. https://doi.org/10.1038/sj.sc.3101443.

Derakhshanrad, N., Yekaninejad, M. S., Vosoughi, F., Sadeghi Fazel, F., & Saberi, H. (2016). Epidemiological study of traumatic spinal cord injuries: Experience from a specialized spine center in Iran. *Spinal Cord*, *54*(10), 901–907. https://doi.org/10.1038/sc.2016.10.

Dewan, M. C., Rattani, A., Baticulon, R. E., Faruque, S., Johnson, W. D., Dempsey, R. J., … Shrime, M. G. (2019). Operative and consultative proportions of neurosurgical disease worldwide: Estimation from the surgeon perspective. *Journal of Neurosurgery*, *130*(April), 1098–1106. https://doi.org/10.3171/2017.10.JNS17347.1098.

Dewan, M. C., Rattani, A., Fieggen, G., Arraez, M. A., Servadei, F., Boop, F. A., … Park, K. B. (2019). Global neurosurgery: The current capacity and deficit in the provision of essential neurosurgical care. Executive summary of the global neurosurgery initiative at the program in global surgery and social change. *Journal of Neurosurgery*, *130*(4), 1055–1064. https://doi.org/10.3171/2017.11.JNS171500.

Dhakal, G. R., Paudel, S., Dhungana, S., Gurung, G., & Kawaguchi, Y. (2018). Epidemiological characteristics of dorsal and lumbar spine trauma presenting to a trauma hospital in Kathmandu, Nepal: Formulation of a national spine policy. *Spine Surgery and Related Research*, *2*(4), 249–252. https://doi.org/10.22603/ssrr.2017-0087.

Dhamangaonkar, A. C., Joshi, D., Kumar, R., & Goregaonkar, A. B. (2013). Neurological deficits presenting to an urban tertiary care centre in Mumbai: An epidemiological study. *Malaysian Orthopaedic Journal*, *7*(1), 36–40. https://doi.org/10.5704/moj.1303.014.

Eaton, J., Hanif, A. B., Grudziak, J., & Charles, A. (2017). Epidemiology, management, and functional outcomes of traumatic brain injury in sub-Saharan Africa. *World Neurosurgery*, *108*, 650–655. https://doi.org/10.1016/j.wneu.2017.09.084.

Eaton, J., Mukuzunga, C., Grudziak, J., & Charles, A. (2019). Characteristics and outcomes of traumatic spinal cord injury in a low-resource setting. *Tropical Doctor*, *49*(1), 62–64. https://doi.org/10.1177/0049475518808969.

Furlan, J. C., Noonan, V., Cadotte, D. W., & Fehlings, M. G. (2011). Timing of decompressive surgery of spinal cord after traumatic spinal cord injury: An evidence-based examination of pre-clinical and clinical studies. *Journal of Neurotrauma*, *28*(8), 1371–1399. https://doi.org/10.1089/neu.2009.1147.

Garlanger, K. L., Beck, L. A., & Cheville, A. L. (2018). Functional outcomes in patients with co-occurring traumatic brain injury and spinal cord injury from an inpatient rehabilitation facility's perspective. *Journal of Spinal Cord Medicine*, *41*(6), 718–730. https://doi.org/10.1080/10790268.2018.1465744.

Gélis, A., Stéfan, A., Colin, D., Albert, T., Gault, D., Goossens, D., … Coudeyre, E. (2011). Therapeutic education in persons with spinal cord injury: A review of the literature. *Annals of Physical and Rehabilitation Medicine*, *54*(3), 189–210. https://doi.org/10.1016/j.rehab.2011.03.004.

Gooch, R. A., & Kahn, J. M. (2014). ICU bed supply, utilization, and health care spending: An example of demand elasticity. *Journal of the American Medical Association*, *311*(6), 567–568. https://doi.org/10.1016/S0965-8564(99)00047-6.

Gosselin, R. A., & Coppotelli, C. (2005). A follow-up study of patients with spinal cord injury in Sierra Leone. *International Orthopaedics*, *29*(5), 330–332. https://doi.org/10.1007/s00264-005-0665-3.

Hoque, F., Grangeon, C., & Reed, K. (1999). Spinal cord lesions in Bangladesh: An epidemiological study 1994–1995. *Spinal Cord*, *37*(12), 858–861. https://doi.org/10.1038/sj.sc.3100938.

Hua, R., Shi, J., Wang, X., Yang, J., Zheng, P., Cheng, H., … An, Y. (2013). Analysis of the causes and types of traumatic spinal cord injury based on 561 cases in China from 2001 to 2010. *Spinal Cord*, *51*(3), 218–221. https://doi.org/10.1038/sc.2012.133.

Ibrahim, A., Lee, K. Y., Kanoo, L. L., Tan, C. H., Hamid, M. A., Hamedon, N. M., & Haniff, J. (2013). Epidemiology of spinal cord injury in hospital Kuala Lumpur. *Spine*, *38*(5), 419–424. https://doi.org/10.1097/BRS.0b013e31826ef594.

James, S. L., Bannick, M. S., Montjoy-Venning, W. C., Lucchesi, L. R., Dandona, L., Dandona, R., … Zaman, S. B. (2019). Global, regional, and national burden of traumatic brain injury and spinal cord injury, 1990–2016: A systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Neurology*, *18*(1), 56–87. https://doi.org/10.1016/S1474-4422(18)30415-0.

Jazayeri, S. B., Beygi, S., Shokraneh, F., Hagen, E. M., & Rahimi-Movaghar, V. (2015). Incidence of traumatic spinal cord injury worldwide: A systematic review. *European Spine Journal*, *24*(5), 905–918. https://doi.org/10.1007/s00586-014-3424-6.

Kang, Y., Ding, H., Zhou, H., Wei, Z., Liu, L., Pan, D., & Feng, S. (2017). Epidemiology of worldwide spinal cord injury: A literature review. *Journal of Neurorestoratology*, *6*, 1–9. https://doi.org/10.2147/jn.s143236.

Kanmounye, U. S., Lartigue, J. W., Sadler, S., Yuki Ip, H. K., Corley, J., Arraez, M. A., & Park, K. (2020). Emerging trends in the neurosurgical workforce of low- and middle-income countries: A cross-sectional study. *World Neurosurgery*, *142*, e420–e433. https://doi.org/10.1016/j.wneu.2020.07.067.

Kebaish, K., & Harris, A. (2020). Spine and spinal cord injuries. In J. Cameron, & A. Cameron (Eds.), *Current surgical therapy* (13th ed., pp. 1221–1223). Philadelphia: Elsevier.

Kirshblum, S. C., Waring, W., Biering-Sorensen, F., Burns, S. P., Johansen, M., Schmidt-Read, M., … Krassioukov, A. (2011). Reference for the 2011 revision of the International Standards for Neurological Classification of Spinal Cord Injury. *Journal of Spinal Cord Medicine*, *34*(6), 547–554. https://doi.org/10.1179/107902611X13186000420242.

Krassioukov, A., Eng, J. J., Claxton, G., Sakakibara, B. M., & Shum, S. (2010). Neurogenic bowel management after spinal cord injury: A systematic review of the evidence. *Spinal Cord*, *48*(10), 718–733. https://doi.org/10.1038/sc.2010.14.

Kumar, R., Lim, J., Mekary, R. A., Rattani, A., Dewan, M. C., Sharif, S. Y., … Park, K. B. (2018). Traumatic spinal injury: Global epidemiology and worldwide volume. *World Neurosurgery*, *113*, e345–e363. https://doi.org/10.1016/j.wneu.2018.02.033.

Lakhey, S., Jha, N., Shrestha, B. P., & Niraula, S. (2005). Aetioepidemiological profile of spinal injury patients in Eastern Nepal. *Tropical Doctor*, *35*(4), 231–233. https://doi.org/10.1258/004947505774938756.

Leidinger, A., Kim, E. E., Navarro-Ramirez, R., Rutabasibwa, N., Msuya, S. R., Askin, G., … Härtl, R. (2019). Spinal trauma in Tanzania: Current management and outcomes. *Journal of Neurosurgery: Spine*, *31*(1), 103–111. https://doi.org/10.3171/2018.12.SPINE18635.

Lessing, N. L., Lazaro, A., Zuckerman, S. L., Leidinger, A., Rutabasibwa, N., Shabani, H. K., & Härtl, R. (2020). Nonoperative treatment of traumatic spinal injuries in Tanzania: Who is not undergoing surgery and why? *Spinal Cord*. https://doi.org/10.1038/s41393-020-0474-y.

Lessing, N. L., Zuckerman, S. L., Lazaro, A., Leech, A. A., Leidinger, A., Rutabasibwa, N., … Härtl, R. (2020). Cost-effectiveness of operating on traumatic spinal injuries in low-middle income countries: A preliminary report from a major East African referral center. *Global Spine Journal*. https://doi.org/10.1177/2192568220944888.

Liu, J., Liu, H.-W., Gao, F., Li, J., & Li, J.-J. (2020). Epidemiological features of traumatic spinal cord injury in Beijing, China. *Journal of Spinal Cord Medicine*, 1–7. https://doi.org/10.1080/10790268.2019.1654190.

Liu, P., Yao, Y., Liu, M. Y., Fan, W. L., Chao, R., Wang, Z. G., … Zhao, J. H. (2012). Spinal trauma in mainland China from 2001 to 2007: An epidemiological study based on a nationwide database. *Spine*, *37*(15), 1310–1315. https://doi.org/10.1097/BRS.0b013e3182474d8b.

Löfvenmark, I., Norrbrink, C., Nilsson-Wikmar, L., Hultling, C., Chakandinakira, S., & Hasselberg, M. (2015). Traumatic spinal cord injury in Botswana: Characteristics, aetiology, and mortality. *Spinal Cord*, *53*(2), 150–154. https://doi.org/10.1038/sc.2014.203.

Macciocchi, S., Seel, R. T., Thompson, N., Byams, R., & Bowman, B. (2008). Spinal cord injury and co-occurring traumatic brain injury: Assessment and incidence. *Archives of Physical Medicine and Rehabilitation*, *89*(7), 1350–1357. https://doi.org/10.1016/j.apmr.2007.11.055.

Makhni, M. C., Vatan, N. M., Park, P. J., Kabeer, Z. A., Cerpa, M., Choi, J.-H., … Park, K. B. (2019). Path to prevention of spinal trauma in a low- to middle-income country. *JAAOS: Global Research and Reviews*, *3*(10). https://doi.org/10.5435/jaaosglobal-d-19-00080, e1900080.

Moshi, H., Sundelin, G., Sahlen, K. G., & Sörlin, A. (2017). Traumatic spinal cord injury in the north-east Tanzania – Describing incidence, etiology, and clinical outcomes retrospectively. *Global Health Action*, *10*(1). https://doi.org/10.1080/16549716.2017.1355604.

Munakomi, S., Bhattarai, B., & Cherian, I. (2017). Prospective observational research on the clinical profile and outcome analysis among a cohort of patients sustaining traumatic cervical spine and cord injury in a peripheral tertiary spine care centre in Nepal. *F1000Research*, *6*, 1–16. https://doi.org/10.12688/f1000research.12911.1.

Murthy, S., & Wunsch, H. (2012). Clinical review: International comparisons in critical care—Lessons learned. *Critical Care*, *16*(2). https://doi.org/10.1186/cc11140.

Nwankwo, O. E., & Uche, E. O. (2013). Epidemiological and treatment profiles of spinal cord injury in southeast Nigeria. *Spinal Cord*, *51*(6), 448–452. https://doi.org/10.1038/sc.2013.10.

Obalum, D. C., Giwa, S. O., Adekoya-Cole, T. O., & Enweluzo, G. O. (2009). Profile of spinal injuries in Lagos, Nigeria. *Spinal Cord*, *47*(2), 134–137. https://doi.org/10.1038/sc.2008.93.

Rathore, M. F. A., Hanif, S., Farooq, F., Ahmad, N., & Mansoor, S. N. (2008). Traumatic spinal cord injuries at a tertiary care rehabilitation institute in Pakistan. *Journal of the Pakistan Medical Association*, *58*(2), 53–57.

Sharif-Alhoseini, M., & Rahimi-Movaghar, V. (2014). Hospital-based incidence of traumatic spinal cord injury in Tehran, Iran. *Iranian Journal of Public Health*, *43*(3), 331–341.

Sharma, B., Bradbury, C., Mikulis, D., & Green, R. E. (2014). Missed diagnosis of traumatic brain injury in patients with traumatic spinal cord injury. *Journal of Rehabilitation Medicine*, *46*(4), 370–373. https://doi.org/10.2340/16501977-1261.

Stothers, L., Macnab, A. J., Mukisa, R., Mutabazi, S., & Bajunirwe, F. (2017). Traumatic spinal cord injury in Uganda: A prevention strategy and mechanism to improve home care. *International Journal of Epidemiology*, *46*(4), 1086–1090. https://doi.org/10.1093/ije/dyx058.

Wolfe, D. L., Ethans, K., Hill, D., Hsieh, J. T. C., Mehta, S., Teasell, R. W., & Askes, H. (2010). Bladder health and function following spinal cord injury. In J. J. Eng, R. W. Teasell, W. C. Miller, D. L. Wolfe, A. F. Townson, J. T. C. Hsieh, … B. M. Sakakibara (Eds.), *Spinal Cord Injury Rehabilitation Evidence. Version 3.0* (pp. 1–19). Vancouver.

World Bank. (2015). *Hospital beds per 1000 people*. Retrieved November 20, 2020, from https://data.worldbank.org/indicator/SH.MED.BEDS.ZS.

World Bank. (2018). *Specialist surgical workforce*. World Bank.

World Health Organization. (2011). *Summary world report on disability* (pp. 1–24). World Health. Retrieved from www.who.int/about/licensing/copyright_form/en/index.html%0Ahttp://www.larchetoronto.org/wordpress/wp-content/uploads/2012/01/launch-of-World-Report-on-Disability-Jan-27-121.pdf.

Yasmeen, R., Rathore, F. A., Ashraf, K., & Butt, A. W. (2010). How do patients with chronic spinal injury in Pakistan manage their bowels? A cross-sectional survey of 50 patients. *Spinal Cord*, *48*(12), 872–875. https://doi.org/10.1038/sc.2010.46.

Yuan, S., Shi, Z., Cao, F., Li, J., & Feng, S. (2018). Epidemiological features of spinal cord injury in China: A systematic review. *Frontiers in Neurology*, *9*(AUG), 1–12. https://doi.org/10.3389/fneur.2018.00683.

Zhou, Y., Wang, X. B., Kan, S. L., Ning, G. Z., Li, Y. L., Yang, B., … Feng, S. Q. (2016). Traumatic spinal cord injury in Tianjin, China: A single-center report of 354 cases. *Spinal Cord*, *54*(9), 670–674. https://doi.org/10.1038/sc.2015.173.

Chapter 2

Biomechanics and patterns of spine injuries associated with spinal cord injury

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List of abbreviations

CCS Central cord syndrome
PLC Posterior ligamentous complex
TSCI Traumatic spinal cord injury

Introduction

Worldwide, approximately 30 million individuals live with a traumatic spinal cord injury (TSCI), and about 1 million new cases of TSCI occur annually, and these numbers are expected to increase in view of population growth. Annually, 150,000 spine fractures are treated in the United States. Among those, close to 20% are associated with spinal cord injury (SCI) (Buchowski, Kuhns, Bridwell, & Lenke, 2008). A spinal fracture and/or dislocation occurs in about 65% of all TSCI.

TSCI contributes to a considerable burden on patient's lives because of lifelong functional disabilities and major psychosocial challenges. Accordingly, the severity of the spine injuries is usually associated with the severity of the SCI, in line with increased burden of healthcare resource utilization. Although management of the underlying spine injuries further contributes to the economic burden of TSCI, it is strongly influencing the clinical outcomes of patients.

TSCIs are most often due to a traumatic event, mainly falls and motor vehicle accidents. While motor vehicle accidents remain the most common cause of TSCI, there is an increasing incidence of TSCI due to low-energy trauma such as falls (Chen, He, & DeVivo, 2016; Pickett, Campos-Benitez, Keller, & Duggal, 2006).

Because of physiological changes due to aging, elderly individuals are particularly at increased risk of sustaining a TSCI from low-energy trauma such as a fall from their height.

In keeping with the aging of the general population, a demographic shift is observed toward older TSCI patient's population (Ahn et al., 2017) with pre-existing spondylotic spinal stenosis and without significant traumatic spinal instability.

Understanding the biomechanics and patterns of the common types of spine injuries associated with SCI is central to the management of individuals with TSCI, and will be featured in this chapter.

Pathogenesis of TSCI: The critical role of spine biomechanics

Several studies (Al-Habib et al., 2011; Wagnac et al., 2019; Wilson, Cadotte, & Fehlings, 2012) demonstrated the importance of the mechanism and level of energy of the traumatic event as predictors of the severity of TSCI. When compared with low-velocity trauma (e.g., fall from standing height), high-velocity mechanisms of trauma (e.g., motor-vehicle accidents) more often result in increased spinal cord damage, particularly in the white matter (Mattucci et al., 2019). The mechanism and level of energy of the trauma are only moderately associated with the outcomes, because they only partially reflect the level of energy that was actually transferred to the spinal cord during the trauma. During the trauma, the primary injury to the spinal cord occurs due to the physical insult and local energy transferred to the spinal cord, thereby causing direct damage to neural tissues and its blood vessels. It is believed that the morphological pattern of the spine injury is a better reflection of the underlying dynamics and local energy sustained by the spinal cord during the trauma than the mechanism of trauma and global level of energy (Goulet, Richard-Denis, Petit, Diotalevi, & Mac-Thiong, 2020). During the trauma, energy is transferred to the spinal cord by direct or indirect mechanisms originating from the spine injury.

Diagnosis and Treatment of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822498-4.00002-6

Direct injury occurs from contusion of the spinal cord by vertebral bone and soft tissues (intervertebral disc and/or ligaments) in direct contact with the spinal cord.

Indirect injury to the spinal cord results from the motion (e.g., flexion, hyperextension, axial compression, distraction, dislocation, etc.) between spinal elements during the trauma, causing excessive tension, shear, torsion, compression, and/or bending loads on the spinal cord.

The type of loads sustained by the spinal cord will influence the extent of tissue damage (Chen et al., 2016), contributing to the heterogeneity of the clinical outcomes observed following a TSCI (Mattucci et al., 2019). Contusion causes a relatively localized damage, as opposed to dislocation (causing mainly shear stress) and distraction which result in more asymmetrical damage that can extend further rostrally and caudally (Chen et al., 2016).

The acute surgical management is critical in TSCI patients and serves two purposes: neurological decompression and spinal stabilization. Neurological decompression entails removal of bone, blood, and disco-ligamentous structures that impinges the spinal cord, whereas spinal stabilization is achieved by spinal instrumentation rigidly connecting the unstable segments of the spine. Acute surgery ultimately aims at limiting the secondary injury to the spinal cord. The pattern of spine injury contributes to the secondary injury of the spinal cord through direct and indirect mechanisms. The residual compression of the spinal cord for example from the typical vertebral bone fragment retropulsed in the spinal canal with thoracolumbar burst fractures directly exerts loads on the spinal cord. In parallel, residual misalignment or instability between spinal elements can also exert undue loads on the spinal cord through an indirect mechanism, further contributing to the secondary injury of the spinal cord if it has not been addressed properly. Careful and prompt assessment of the clinical stability is therefore key after a TSCI.

In line with the definition by White 3rd, Johnson, Panjabi, and Southwick (1975), we define traumatic spinal instability to be the loss of the ability of the spine to maintain normal alignment and motion between spinal segments in such a way that a secondary injury to the spinal cord will not occur.

Patterns of spine injuries associated with spinal cord injuries

TSCI can be associated with a stable or unstable spine, and we suggest that TSCI should be categorized accordingly to guide its management.

Traumatic spinal cord injury in a stable spine

Different terminologies have been used previously to describe TSCI not associated with overt spinal instability. The term SCIWORA (Spinal Cord Injury Without Radiographic Abnormality) was proposed by Pang and Wilberger Jr. (1982) in 1982 to describe TSCI occurring in children without evidence of spine injuries such as fracture or dislocation on plain radiographs or tomography. Given the inherent elasticity of the vertebral column in children, they suggest that the vertebral column can deform in flexion, hyperextension or distraction in such a way that the spinal cord can be injured without concomitant damage of the vertebral column. SCIWORA more frequently involves the cervical spinal cord because spinal mobility is greater in the cervical than the thoracic and lumbar spine. In the adult population, SCIWORA has also been used to describe TSCI associated with underlying spondylotic changes, spinal stenosis, ossification of posterior longitudinal ligament, ligamentous abnormalities, and/or traumatic disc herniation (Asan, 2018; Boese et al., 2016; Boese & Lechler, 2013; Gupta et al., 1999), in the absence of fracture or dislocation. Many authors (Como et al., 2012; Dreizin et al., 2015) warn about the misapplication of the term SCIWORA in adults considering that these patients will commonly have underlying canal stenosis and significant degenerative changes—which are radiographic abnormalities per se—and instead propose the use of the term SCIWOCTET (Spinal Cord Injury Without Computed Tomography Evidence of Trauma) or SCIWORET (Spinal Cord Injury Without Radiographic Evidence of Trauma) in these patients.

For the cervical spine, proper identification of TSCI with a stable spine is important because they are typically associated with improved recovery (Paquet et al., 2018). While the presence or absence of radiographic/tomographic findings can help to understand the pathomechanism of the injury and guide treatment, the central aspect to SCIWORA, SCIWORET, and SCIWOCTET is that they usually are not associated with overt spinal instability. For these conditions, the spinal cord is at higher risk of injury either due to the altered biomechanics of the spine or to the decreased space available for the spinal cord. The current authors believe that the overarching concept for these aforementioned terms is the absence of spinal instability, and that these terms should be used with caution because they underestimate the importance of spinal trauma and biomechanics in the context of TSCI. Radiological evidence of trauma can include a wide range

of findings, and should not be interpreted without consideration of the spinal stability. The authors instead propose to use the term TSCI with a stable spine in order to account for the biomechanical and surgical aspects involved in the management of TSCI. Indeed, TSCI with a stable spine does not preclude the presence of minor spinal injuries such as spinous process fractures that do not impair the clinical stability of the spine and do not require surgical stabilization.

In adults, underlying degenerative changes are usually observed, but the literature does not provide specific outcome predictors based on the evaluation of the underlying spondylosis.

Animal models repeatedly showed a strong correlation between the amount of spinal cord compression and severity of the neurological impairment. However, in adult trauma patients the correlation between cord compression observed on MRI and the neurological impairment remains unclear. Interestingly, normal aging of the spine commonly implies degenerative changes that cause reduction of the diameter of the spinal canal called spinal stenosis, especially at the cervical level. Literature does not provide specific outcome predictors based on the evaluation of the underlying spondylosis. In a population of adult low-velocity cervical trauma—CCS—Aarabi et al., 2011 found a somewhat counterintuitive association between maximal cord compression on MRI and neurological recovery.

The CCS is a common clinical syndrome observed after a cervical TSCI and is typically observed in the presence of a stable spine. It has been described initially by Schneider, Cherry, and Pantek (1954) and is characterized by a disproportionate greater motor impairment in the upper extremities and varying degree of bladder dysfunction and sensory loss. The central cord syndrome is mainly prevalent in the elderly population with pre-existing spondylotic cervical stenosis (McKinley, Santos, Meade, & Brooke, 2007; Molliqaj, Payer, Schaller, & Tessitore, 2014). The mechanism of trauma typically involves a fall from someone's height with cervical hyperextension. During hyperextension of the cervical spine, spinal cord damage associated with the central cord syndrome results from posterior compression from inward bulging of the ligamentum flavum and from anterior compression from marginal osteophytes and/or bulging discs (Schneider et al., 1954). The greater impairment in the upper extremities results from the injury to the spinal gray matter and lateral corticospinal tracts (Collignon, Martin, Lenelle, & Stevenaert, 2002). More specifically, it is believed that the predominant involvement of the upper extremities is due to the somatotopic arrangement of the lateral corticospinal tracts, such that the medial (more central) portion of the corticospinal tract controlling upper extremity motor function sustains a greater injury than the lateral portion controlling lower extremity motor function (Schneider, Thompson, & Bebin, 1958). However, this hypothesis has been challenged by different authors who observed a uniform damage to the lateral corticospinal tract, suggesting that motor fibers descending to the upper and lower extremities are interlaced (Nathan & Smith, 1955; Quencer et al., 1992).

In a finite-element analysis, Bailly et al. suggest that the presence of hypertrophic ligamentum flavum induced specific stress and strain distributions consistent with previous histologic findings related to central cord syndrome. The presence of a disc bulging alone was not associated with such a pattern, but when combined with hypertrophic ligamentum flavum, increased the overall level of stress and strain in the lateral corticospinal tract (Fig. 1)

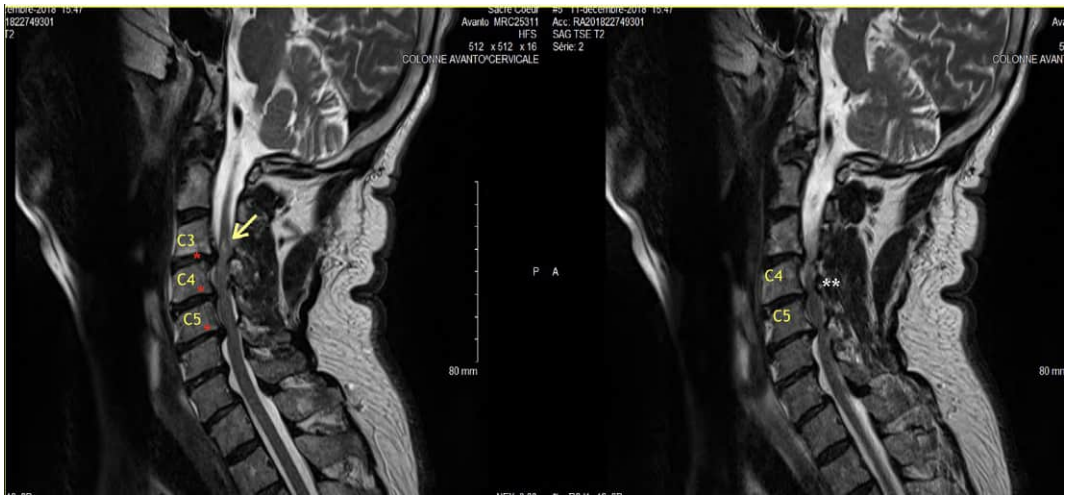

FIG. 1 Hyperextension cervical trauma in a stable spine with degenerative changes. CCS. (*) red asterisks, Bulging disc C3–C4, C4–C5, C5–C6. (**) White asterisks, thickened ligamentum flavum multilevel mainly C4–C5. Yellow arrow showing spinal cord edema and hypersignal in C3 level.

Traumatic spinal cord injury in an unstable spine

While TSCI in a stable spine occurs predominantly at the cervical level due to the increased range of motion and frequent preexisting canal stenosis, unstable injuries occur commonly at all spinal levels. The neurological level of injury strongly relates to the neurological recovery, and it is common to distinguish between high cervical (C1–C4), low cervical (C5–C8), thoracic (T1–T10), and thoracolumbar (T11–L2) TSCI (Dvorak et al., 2014). These categories account for the functional activity of the spinal cord, including breathing, upper versus lower extremity function, trunk control, and bowel/bladder function. However, other anatomical and morphological criteria should also be considered to further delineate the level of injury and characterize the trauma biomechanics when classifying and managing the unstable spine associated with TSCI.

There are three basic categories or types used in a similar manner to the AO thoracolumbar fracture classification system to describe primary injury morphology. The "Type A" injuries are fractures that result in compression of the vertebra with intact tension band. "Type B" injuries include failure of the posterior or anterior tension band through distraction with physical separation of the subaxial spinal elements while maintaining continuity of the alignment of the spinal axis without translation or dislocation. "Type C" includes those injuries with displacement or translation of one vertebral body relative to another in any direction; anterior, posterior, lateral translation, or vertical distraction. Injuries are first classified by their level and either C, B, or A in this order (Vaccaro et al., 2016).

Cervical spine injuries (C0–C7)

TSCI with an unstable spine are highly prevalent in the cervical spine for different reasons. The cervical spine is vulnerable to several types of trauma mechanisms, including motor vehicle accidents, diving, sports injuries, and falls. When compared to the thoracic and lumbar spine, the bony elements in the cervical spine are smaller and the disco-ligamentous structures are weaker so that they are more exposed to injuries.

In line with the demographic shift to an older population, the increasing prevalence of cervical degenerative changes and pre-existing spondylotic stenosis increases the likelihood to sustain a TSCI in association with a cervical trauma.

Upper cervical spine injuries (C0–C2)

TSCI following traumatic spine injuries occurring at the occipito-cervical or atlanto-axial level are highly distinct from subaxial injuries due to the increased risk of mortality and poor recovery. It is thought that between 8% and 19% of fatal cervical spine injuries result from occipito-cervical dislocation (Bucholz, Burkhead, Graham, & Petty, 1979). In addition, occipito-cervical and atlanto-axial levels have a highly distinct bony/soft tissue anatomy and biomechanical behavior, which require particular attention for evaluation and management. The spinal canal is also particularly large at these levels; it is widest between the C1 and C3 levels (AP diameter 16–30 mm) and progressively narrows caudally (14–23 mm).

Occipito-cervical dislocation is associated with high mortality rates because a high-energy trauma—and high level of energy transferred to the spinal cord—is required to damage the strong ligamentous structures at the occipito-cervical junction, which comprise the tectorial membrane and alar ligament (Alker et al., 1975).

TSCI is seen infrequently with isolated C1 fracture (Lee & Woodring, 1991). A TSCI occurs when the transverse ligament is torn and atlanto-axial instability occurs. The mechanism of SCI is similar to that occurring with isolated rupture of the transverse ligament or odontoid fracture: the spinal cord will be compressed between the posteriorly displaced odontoid and the posterior arch of C1.

Subaxial cervical spine injuries (C3–C7)

The Spinal Trauma Study Group (Vaccaro et al., 2007) provided new insight on the morphological features of subaxial cervical trauma that need to be considered in TSCI, through the proposal of a novel classification system. In line with previous studies (Chen et al., 2016), they consider that the severity and outcome of TSCI depend on the morphology of the lesion, which results in different loading conditions in the spinal cord. Based on their concept, we propose that TSCI with unstable subaxial cervical spine be classified following this increasing order of severity:

(1) Compression injury without involvement of the posterior vertebral wall.
(2) Burst injury with involvement of the posterior vertebral wall.
(3) Distraction injury such as a hyperextension injury involving rupture of anterior longitudinal ligament and intervertebral disc or a flexion-distraction injury involving disruption of posterior ligaments and facet capsules.
(4) Translation/rotation injury which is typical of bilateral facet dislocation.

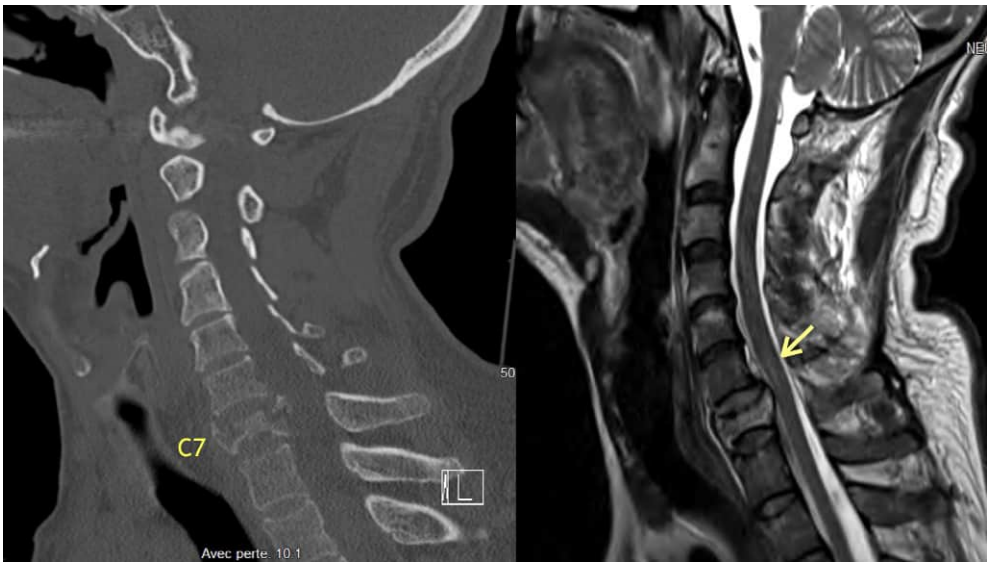

FIG. 2 Burst fracture of C7 and significant energy transferred to the spinal cord from retropulsion of the posterior wall into the spinal canal causing spinal cord edema (yellow arrow).

TSCI is unlikely with a compression injury sparing the posterior vertebral wall, unless significant kyphosis occurs (Yokota et al., 2019). A TSCI is more likely with burst fractures when significant energy is transferred to the spinal cord from retropulsion of the posterior wall into the spinal canal (Fig. 2)

Hyperextension injury causes distraction of the spinal cord that can lead to neural damage. In addition, spinal cord damage can result from inward bulging of the ligamentum flavum in the presence of a spondylotic spine, by a mechanism similar to that described above for cervical TSCI in a stable spine. A hyperextension injury—and less frequently a translation injury—is typically observed with a cervical TSCI in patients with a rigid spine (e.g., ankylosing spondylitis, diffuse idiopathic skeletal hyperostosis or ossification of the posterior longitudinal ligament). For these patients, the presence of an epidural hematoma causing the SCI should also be ruled out (Fig. 3)

Facet dislocations are most common in the subaxial cervical spine because a lesser magnitude of force is required to produce the dislocation, as compared to the thoracic and lumbar spine (Holdsworth, 1970). This is mainly due to the

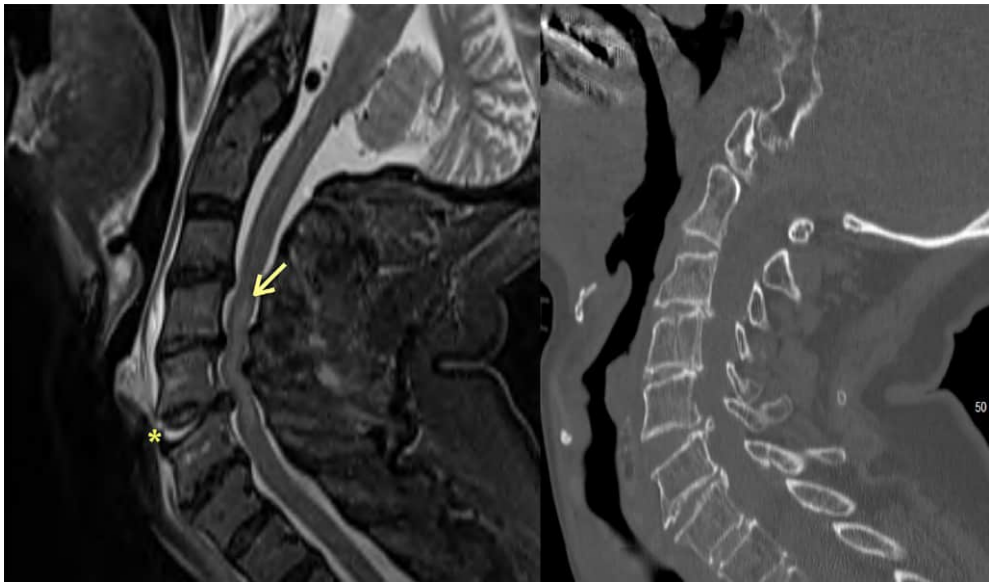

FIG. 3 Hyperextension injury in a mobile spine ct and irm, showing disc rupture (yellow asterisk) and spinal cord edema (arrow).

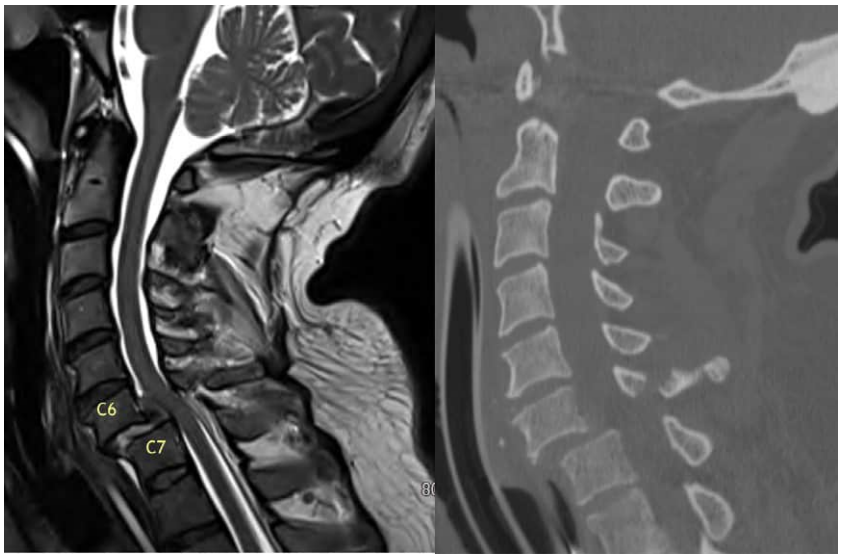

FIG. 4 Cervical dislocation C6–C7.

increased mobility, distinctive orientation of the superior articular facets (Ebraheim, Patil, Liu, Haman, & Yeasting, 2008), and smaller osseous and ligamentous structures of the cervical spine. Facet dislocation typically occurs as a result of a hyperflexion injury and is commonly associated with SCI (Sekhon & Fehlings, 2001; Tator, 1983).

During the trauma, the primary injury to the spinal cord results from the distraction of the spinal cord posteriorly as well as the resulting translation and/or rotation between dislocated vertebrae causing shear stresses on the spinal cord. After the trauma, a secondary injury to the spinal cord is accentuated by the shear and compression loading from residual translation and/or rotation between vertebrae, which needs to be managed by surgery.

Wilson et al. showed that cervical dislocation is more frequently associated with severe neurological deficit and high-energy trauma mechanisms, and results in a diminished potential for recovery (Wilson et al., 2013) (Fig. 4)

Thoracic spine injuries (T1–T10)

The pathomechanism and outcome of thoracic injuries significantly differ from cervical injuries because of the inherent stability provided by the thoracic cage (i.e., ribs and sternum). Each thoracic vertebra has a diarthrodial articulation with a rib on each side, thereby increasing the stability of the thoracic spine and potentially decreasing the incidence of degenerative changes since reduced mobility.

The thoracic facet joints are aligned with the coronal plane to allow for axial rotation. The ratio of the canal size to the spinal cord size is relatively small in the thoracic spine, which increases the risk of neurologic injury even with small amounts of canal intrusion.

The tenuous blood supply (critical watershed area) in the upper thoracic region also exposes the spinal cord between T4 and T10 at increased risk of SCI with a spine trauma.

In aging individuals with osteoporosis, a minor trauma can cause a compression fracture in the thoracic spine, usually below T4 and most often at the thoracolumbar region. However, a TSCI is rarely seen with osteoporotic compression fractures, even in the presence of a marked kyphotic deformity. When a TSCI occurs after minor trauma in an osteoporotic patient, it is usually secondary to a burst fracture with a retropulsed fragment into the spinal canal, and the onset of neurological deficit is typically gradual rather than acute. For patients with a rigid spine (e.g., ankylosing spondylitis and diffuse idiopathic skeletal hyperostosis), a hyperextension or translation spine injury should be suspected in the presence of a TSCI at the thoracic level, even if a minor trauma has occurred.

More often, thoracic TSCI results from high-energy trauma mechanisms. Thorough clinical and radiological evaluation of the thoracic cage should be performed to assess the stability of the spine injury because the great majority of thoracic TSCI will involve an associated disruption of the thoracic cage.

Associated fractures of the sternum and/or ribs should raise the suspicion for severe spinal instability. Because most thoracic TSCI result from high-energy trauma, the initial neurological deficit is usually severe, and the prognosis is often poor (Bourassa-Moreau et al., 2016; Zariffa et al., 2011) (Fig. 5).

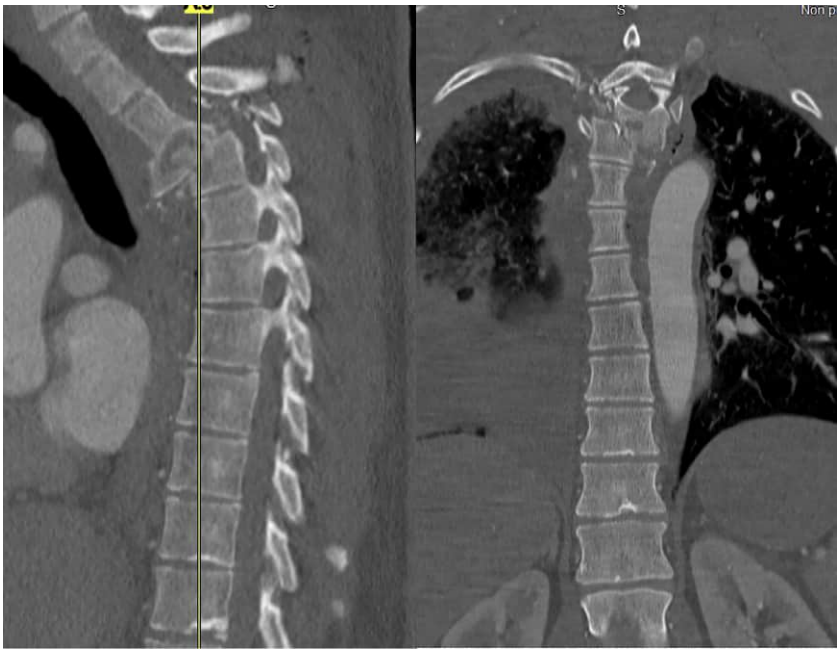

FIG. 5 Complete injury SCI, dislocation, and chest trauma. Complex comminuted fracture with lateral dislocation of the D3–D4 vertebrae and discontinuity of the spinal canal. Multiple bilateral rib fractures, Right hemothorax. Extensive right subpleural pulmonary contusion and minimal right apical pleural detachment.

Thoracolumbar spine injuries (T11–L2)

The thoracolumbar junction between T11 and L2 is the most frequent site for TSCI in an unstable spine for both osteoporotic and nonosteoporotic individuals.

There is an increased stress concentration in this region because it is a transition zone from the stiff thoracic spine/cage and the mobile lumbar spine. The straight alignment of the thoracolumbar region between the supra-adjacent thoracic kyphosis and subjacent lumbar lordosis also increases the transfer of axial compression loads through this region and resulting risk of compression and burst fractures.

While compression fractures are usually not associated with TSCI, thoracolumbar burst fractures can be associated with a TSCI due to a bony fragment retropulsed into the spinal canal and compressing the spinal cord.

In the presence of a TSCI, determining the morphological pattern of the thoracolumbar fracture seems particularly useful to characterize the severity of the injury and the prognosis for neurological recovery. Different authors (Keynan et al., 2006; Martineau, Goulet, Richard-Denis, & Mac-Thiong, 2019) propose that the energy directly transferred to the spinal cord during the trauma is strongly related to the local morphological pattern of thoracolumbar fractures, as opposed to the global level of energy or mechanism of the trauma.

The morphological pattern of thoracolumbar injury also provides insight into the dynamics of the SCI during the trauma, more so than the residual compression of the spinal cord after the trauma from the retropulsed fragment.

It is well recognized that the dynamic spinal canal encroachment during the trauma is significantly greater than the static canal encroachment seen on posttrauma imaging. Accordingly, the degree of canal occlusion observed after the trauma is not related to the neurological outcome (Boerger, Limb, & Dickson, 2000; Herndon & Galloway, 1988; Mohanty & Venkatram, 2002).

Goulet et al. have shown that posterior translation of the posteroinferior wall of the vertebral body, presence of comminution of the bony fragment retropulsed into the spinal canal and complete lamina fracture were strongly associated with neurological recovery.

These findings suggest that these morphological features—characterizing damaged bony structures directly in contact with the spinal cord—should be assessed routinely in TSCI patients to estimate the local level of energy transferred to the spinal cord and the prognosis for recovery. Conversely, vertebral body comminution, local/segmental kyphosis, and the degree of canal compromise were not associated with the neurological outcome. In their finite-element computational simulation of TSCI for thoracolumbar burst fractures, Diotalevi et al. tested 16 typical clinical scenarios with varying degree of comminution, velocity, and displacement of the bony fragment retropulsed into the spinal canal, as well as the presence or absence of a fracture of the posteroinferior vertebral body wall.

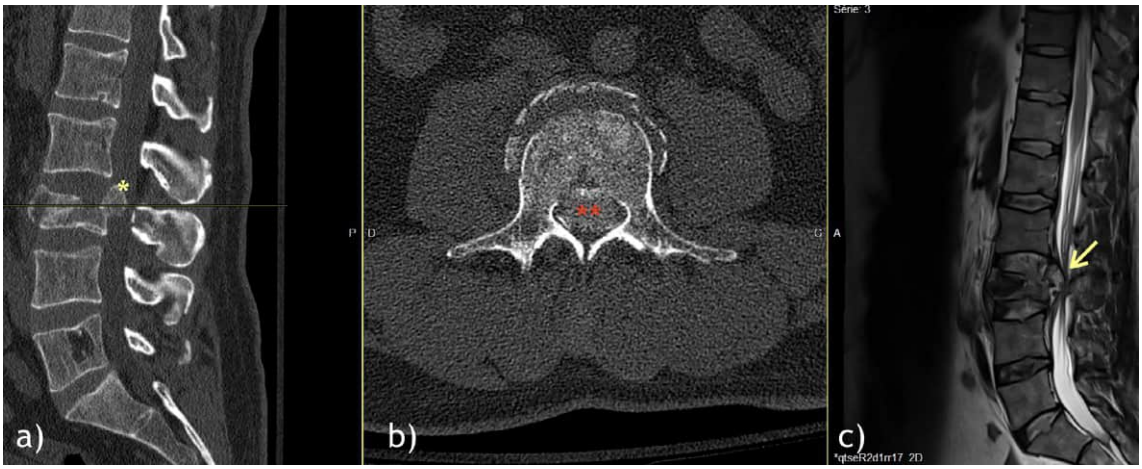

FIG. 6 Burst T3. (A) Translation posterior wall. [yellow asterisk (*)] (B) comminution of the fragment and lamina fracture [red asterisks (**)]. (C) MRI showing compression and cord edema (Yellow arrow).

They observed that the velocity of the retropulsed fragment was the most important factor influencing the stresses and strains on the spinal cord, followed by a fracture of the posteroinferior vertebral body wall and sagittal rotation of the retropulsed fragment (Diotalevi et al., 2020) (Fig. 6)

The Spinal trauma Study Group put a strong emphasis on the assessment of the posterior ligamentous complex (PLC) (supraspinous ligament, interspinous ligament, ligamentum flavum, and facet joint capsules) to further assess the stability of thoracolumbar spine injuries (Vaccaro et al., 2006). Rupture of the PLC entails a poor prognosis for healing because, unlike bone fracture, ligaments do not recover its pretrauma tensile strength after complete rupture.

Although the loss of integrity of PLC is a crucial element for surgeons to determine indication for surgery in thoracolumbar trauma, it remains to be defined whether injury to the PLC is associated with the occurrence a severity of TSCI.

Flexion-distraction spine injuries most often result from falls, car accident (seat belt injury), and unrestrained vehicle accidents (Wagnac et al., 2019). It is estimated that a small number (about 10%–15%) of flexion-distraction injuries in the thoracolumbar spine will lead to a SCI through a mechanism of distraction of the spinal cord. On the opposite, translation/rotation spinal injuries in the thoracolumbar spine typically result from a high-energy trauma mechanism and lead to severe TSCI due to the high shear stresses causing primary and secondary damage to the spinal cord. In the AO classification the type C injuries are translational injuries in any axis. No further subdivision is necessary since all Type C injuries are highly unstable due to separation, displacement, or translation of 1 vertebral body (or elements of it) relative to another in any direction.

Applications to other areas of neuroscience

Here we reviewed the basic biomechanical concepts of traumatic spinal cord injuries associated with spine injuries. We have also reviewed the local mechanisms by which the spinal cord is damaged during traumatic events, and we describe the interactions between spinal osteoligamentous elements and the spinal cord during and after the trauma.

The knowledge transferred in this chapter will help neuroscientists to better understand and study the primary and secondary spinal cord injuries occurring after a trauma. This work also underscores the importance of combining clinical and biomechanical knowledge for assessing and treating individuals following a traumatic SCI. For example, we have highlighted the relevance of using computational models for simulating and investigating traumatic spinal cord injuries. The concepts presented in this chapter could be applied for designing new preclinical models of traumatic SCI, or for planning on innovating research protocols. It is becoming clear that combining expertise in neurosciences and biomechanical engineering is key in the development of a more comprehensive understanding of traumatic spinal cord injuries in the future.

Mini-dictionary of terms

Traumatic spinal cord injury in a stable spine: SCI that causes neurological compromise and in the images there is no fracture or unstable injury, generally called CCS or SCIWORA.

Spinal cord distraction: Structural alteration in the white matter, sparing the most myelinated axons and causing extensive lesion cavity.

Hypertrophic ligamentum flavum: Thickening of the ligamentum flavum for the aging process causing central canal stenosis and associated to TSCI in a stable spine combined with trauma in hyperextension.

Finite-element analysis: Physical phenomenon simulation using a numerical technique called finite element method (FEM) to reproduce some situations and reduce the number of physical prototypes to optimize study designs.

Dynamic spinal canal encroachment: Invasion of the canal that occurs with movement or by gravity It is well recognized that the dynamic spinal canal encroachment during the trauma is significantly greater than the static canal encroachment seen on post-trauma imaging (Panjabi et al., 1995; Wilcox et al., 2003).

Key facts

Key facts of central cord syndrome (CCS) or spinal cord injury (SCI) in a stable spine.

- Not all the SCIs happen in an unstable spine. In a spine with limited capacity of the vertebral canal, extra physiologically motion can result in SCI.
- Due to aging of population there is a growing number of patients with cervical SCI without instability associated with degenerative changes of the cervical spine.
- Traumatic central cord syndrome (TCCS) is a clinical entity that implies predominant impairment of upper extremities compared to relatively spared lower extremities in the setting of an incomplete SCI.
- TCCS is often found in elderly patients with degenerative cervical spine and no over spinal instability, despite being the most common incomplete SCI it lacks well defined diagnostic criteria.

Key facts of morphology of the fractures and biomechanical factors of SCI.

- Between variables such as low- and high-energy trauma and fracture morphological patterns, are these last ones which explain in a better way the level of energy transferred to the spinal cord.
- Cadaveric and animal models are used to study biomechanics of fractures, finding burst fractures and dislocations as the most common injury patterns, also to understand the biology of spinal cord injury and the effects of other relevant factors as injury mechanism, injury velocity, and residual compression.
- The weight-drop animal injury model was developed in 1911 and has evolved significantly, and it can classify the SCI mechanism, such as contusion, compression, dislocation, distraction, and transection.

Summary points

- Indirect injury to the spinal cord results from the motion (e.g., flexion, hyperextension, axial compression, distraction, dislocation, etc.) between spinal elements during the trauma, causing excessive tension, shear, torsion, compression and/or bending loads on the spinal cord.
- In line with the definition by White and Panjabi, we define traumatic spinal instability to be the loss of the ability of the spine to maintain normal alignment and motion between spinal segments in such a way that a secondary injury to the spinal cord will not occur.
- Wilson et al. showed that cervical dislocation is more frequently associated with severe neurological deficit and high-energy trauma mechanisms, and results in a diminished potential for recovery.
- More often, thoracic TSCI results from high-energy trauma mechanisms. Thorough clinical and radiological evaluation of the thoracic cage should be performed to assess the stability of the spine injury because the great majority of thoracic TSCI will involve an associated disruption of the thoracic cage.
- The velocity of a retropulsed fragment was the most important factor influencing the stresses and strains on the spinal cord, followed by a fracture of the postero-inferior vertebral body wall and sagittal rotation of the retropulsed fragment.
- Although the loss of integrity of PLC is a crucial element for surgeons to determine indication for surgery in thoracolumbar trauma, it remains to be defined whether injury to the PLC is associated with the occurrence and severity of TSCI.

References

Aarabi, B., Alexander, M., Mirvis, S. E., Shanmuganathan, K., Chesler, D., Maulucci, C., et al. (2011). Predictors of outcome in acute traumatic central cord syndrome due to spinal stenosis. *Journal of Neurosurgery Spine*, *14*(1), 122–130. https://doi.org/10.3171/2010.9.SPINE09922.

Ahn, H., Lewis, R., Santos, A., Cheng, C. L., Noonan, V. K., Dvorak, M. F., et al. (2017). Forecasting financial resources for future traumatic spinal cord injury care using simulation modeling. *Journal of Neurotrauma*, *34*(20), 2917–2923. Epub 2017 Aug 24. PMID: 28594315; PMCID: PMC5653147 https://doi.org/10.1089/neu.2016.4936.

Al-Habib, A. F., Attabib, N., Ball, J., Bajammal, S., Casha, S., & Hurlbert, R. J. (2011). Clinical predictors of recovery after blunt spinal cord trauma: Systematic review. *Journal of Neurotrauma*, *28*(8), 1431–1443. https://doi.org/10.1089/neu.2009.1157.

Alker, G. J., Oh, Y. S., Leslie, E. V., Lehotay, J., Panaro, V. A., & Eschner, E. G. (1975). Postmortem radiology of head neck injuries in fatal traffic accidents. *Radiology*, *114*(3), 611–617. https://doi.org/10.1148/114.3.611.

Asan, Z. (2018). Spinal cord injury without radiological abnormality in adults: Clinical and radiological discordance. *World Neurosurgery*, *114*, e1147–e1151. https://doi.org/10.1016/j.wneu.2018.03.162.

Boerger, T. O., Limb, D., & Dickson, R. A. (2000). Does 'canal clearance' affect neurological outcome after thoracolumbar burst fractures? *Journal of Bone and Joint Surgery. British Volume (London)*, *82*(5), 629–635. https://doi.org/10.1302/0301-620x.82b5.11321.

Boese, C. K., & Lechler, P. (2013). Spinal cord injury without radiologic abnormalities in adults: a systematic review. *Journal of Trauma and Acute Care Surgery*, *75*(2), 320–330. https://doi.org/10.1097/TA.0b013e31829243c9. 23702634.

Boese, C. K., Muller, D., Broer, R., Eysel, P., Krischek, B., Lehmann, H. C., et al. (2016). Spinal cord injury without radiographic abnormality (SCIWORA) in adults: MRI type predicts early neurologic outcome. *Spinal Cord*, *54*(10), 878–883. https://doi.org/10.1038/sc.2016.13.

Bourassa-Moreau, E., Mac-Thiong, J. M., Li, A., Ehrmann Feldman, D., Gagnon, D. H., Thompson, C., et al. (2016). Do patients with complete spinal cord injury benefit from early surgical decompression? Analysis of neurological improvement in a prospective cohort study. *Journal of Neurotrauma*, *33*(3), 301–306. https://doi.org/10.1089/neu.2015.3957.

Bucholz, R. W., Burkhead, W. Z., Graham, W., & Petty, C. (1979). Occult cervical spine injuries in fatal traffic accidents. *The Journal of Trauma*, *19*(10), 768–771. https://doi.org/10.1097/00005373-197910000-00009.

Buchowski, J. M., Kuhns, C. A., Bridwell, K. H., & Lenke, L. G. (2008). Surgical management of posttraumatic thoracolumbar kyphosis. *The Spine Journal*, *8*(4), 666–677. https://doi.org/10.1016/j.spinee.2007.03.006.

Chen, Y., He, Y., & DeVivo, M. J. (2016). Changing demographics and injury profile of new traumatic spinal cord injuries in the United States, 1972–2014. *Archives of Physical Medicine and Rehabilitation*, *97*(10), 1610–1619. https://doi.org/10.1016/j.apmr.2016.03.017.

Collignon, F., Martin, D., Lenelle, J., & Stevenaert, A. (2002). Acute traumatic central cord syndrome: Magnetic resonance imaging and clinical observations. *Journal of Neurosurgery*, *96*(1 Suppl), 29–33. https://doi.org/10.3171/spi.2002.96.1.0029.

Como, J. J., Samia, H., Nemunaitis, G. A., Jain, V., Anderson, J. S., Malangoni, M. A., et al. (2012). The misapplication of the term spinal cord injury without radiographic abnormality (SCIWORA) in adults. *Journal of Trauma and Acute Care Surgery*, *73*(5), 1261–1266. https://doi.org/10.1097/TA.0b013e318265cd8c.

Diotalevi, L., Bailly, N., Wagnac, E., Mac-Thiong, J. M., Goulet, J., & Petit, Y. (2020). Dynamics of spinal cord compression with different patterns of thoracolumbar burst fractures: Numerical simulations using finite element modelling. *Clinical Biomechanics (Bristol, Avon)*, *72*, 186–194. https://doi.org/10.1016/j.clinbiomech.2019.12.023.

Dreizin, D., Kim, W., Kim, J. S., Boscak, A. R., Bodanapally, U. K., Munera, F., et al. (2015). Will the real SCIWORA please stand up? Exploring clinicoradiologic mismatch in closed spinal cord injuries. *AJR. American Journal of Roentgenology*, *205*(4), 853–860. https://doi.org/10.2214/AJR.14.13374.

Dvorak, M. F., Noonan, V. K., Fallah, N., Fisher, C. G., Rivers, C. S., Ahn, H., et al. (2014). Minimizing errors in acute traumatic spinal cord injury trials by acknowledging the heterogeneity of spinal cord anatomy and injury severity: An observational Canadian cohort analysis. *Journal of Neurotrauma*, *31*(18), 1540–1547. https://doi.org/10.1089/neu.2013.3278.

Ebraheim, N. A., Patil, V., Liu, J., Haman, S. P., & Yeasting, R. A. (2008). Morphometric analyses of the cervical superior facets and implications for facet dislocation. *International Orthopaedics*, *32*(1), 97–101. https://doi.org/10.1007/s00264-006-0286-5.

Goulet, J., Richard-Denis, A., Petit, Y., Diotalevi, L., & Mac-Thiong, J. M. (2020). Morphological features of thoracolumbar burst fractures associated with neurological outcome in thoracolumbar traumatic spinal cord injury. *European Spine Journal*, *29*(10), 2505–2512. https://doi.org/10.1007/s00586-020-06420-9. Epub 2020 May 19. PMID: 32424639.

Gupta, S. K., Rajeev, K., Khosla, V. K., Sharma, B. S., Paramjit, Mathuriya, S. N., et al. (1999). Spinal cord injury without radiographic abnormality in adults. *Spinal Cord*, *37*(10), 726–729. https://doi.org/10.1038/sj.sc.3100900.

Herndon, W. A., & Galloway, D. (1988). Neurologic return versus cross-sectional canal area in incomplete thoracolumbar spinal cord injuries. *The Journal of Trauma*, *28*(5), 680–683. https://doi.org/10.1097/00005373-198805000-00022.

Holdsworth, F. (1970). Fractures, dislocations, and fracture-dislocations of the spine. *The Journal of Bone and Joint Surgery American Volume*, *52*(8), 1534–1551. https://www.ncbi.nlm.nih.gov/pubmed/5483077.

Keynan, O., Fisher, C. G., Vaccaro, A., Fehlings, M. G., Oner, F. C., Dietz, J., et al. (2006). Radiographic measurement parameters in thoracolumbar fractures: A systematic review and consensus statement of the spine trauma study group. *Spine (Phila Pa 1976)*, *31*(5), E156–E165. https://doi.org/10.1097/01.brs.0000201261.94907.0d.

Lee, C., & Woodring, J. H. (1991). Unstable Jefferson variant atlas fractures: An unrecognized cervical injury. *AJNR—American Journal of Neuroradiology*, *12*(6), 1105–1110. https://www.ncbi.nlm.nih.gov/pubmed/1763734.

Martineau, J., Goulet, J., Richard-Denis, A., & Mac-Thiong, J.-M. (2019). The relevance of MRI for predicting neurological recovery following cervical traumatic spinal cord injury. *Spinal Cord*, *57*(10), 866–873. https://doi.org/10.1038/s41393-019-0295-z.

Mattucci, S., Speidel, J., Liu, J., Kwon, B. K., Tetzlaff, W., & Oxland, T. R. (2019). Basic biomechanics of spinal cord injury—How injuries happen in people and how animal models have informed our understanding. *Clinical Biomechanics (Bristol, Avon)*, *64*, 58–68. https://doi.org/10.1016/j.clinbiomech.2018.03.020.

McKinley, W., Santos, K., Meade, M., & Brooke, K. (2007). Incidence and outcomes of spinal cord injury clinical syndromes. *The Journal of Spinal Cord Medicine*, *30*(3), 215–224. https://doi.org/10.1080/10790268.2007.11753929.

Mohanty, S. P., & Venkatram, N. (2002). Does neurological recovery in thoracolumbar and lumbar burst fractures depend on the extent of canal compromise? *Spinal Cord*, *40*(6), 295–299. https://doi.org/10.1038/sj.sc.3101283.

Molliqaj, G., Payer, M., Schaller, K., & Tessitore, E. (2014). Acute traumatic central cord syndrome: A comprehensive review. *Neurochirurgie*, *60*(1–2), 5–11. https://doi.org/10.1016/j.neuchi.2013.12.002.

Nathan, P. W., & Smith, M. C. (1955). Long descending tracts in man. I. Review of present knowledge. *Brain*, *78*(2), 248–303. https://doi.org/10.1093/brain/78.2.248.

Pang, D., & Wilberger, J. E., Jr. (1982). Spinal cord injury without radiographic abnormalities in children. *Journal of Neurosurgery*, *57*(1), 114–129. https://doi.org/10.3171/jns.1982.57.1.0114. PMID: 7086488.

Panjabi, M. M., Kifune, M., Wen, L., Arand, M., Oxland, T. R., Lin, R. M., et al. (1995). Dynamic canal encroachment during thoracolumbar burst fractures. *Journal of Spinal Disorders*, *8*(1), 39–48. https://www.ncbi.nlm.nih.gov/pubmed/7711368.

Paquet, J., Rivers, C. S., Kurban, D., Finkelstein, J., Tee, J. W., Noonan, V. K., et al. (2018). The impact of spine stability on cervical spinal cord injury with respect to demographics, management, and outcome: A prospective cohort from a national spinal cord injury registry. *The Spine Journal*, *18*(1), 88–98. https://doi.org/10.1016/j.spinee.2017.06.032.

Pickett, G., Campos-Benitez, M., Keller, J., & Duggal, N. (2006). Epidemiology of traumatic spinal cord injury in Canada. *Spine*, *31*(7), 799–805.

Quencer, R. M., Bunge, R. P., Egnor, M., Green, B. A., Puckett, W., Naidich, T. P., et al. (1992). Acute traumatic central cord syndrome: MRI-pathological correlations. *Neuroradiology*, *34*(2), 85–94. https://doi.org/10.1007/BF00588148.

Schneider, R. C., Cherry, G., & Pantek, H. (1954). The syndrome of acute central cervical spinal cord injury; with special reference to the mechanisms involved in hyperextension injuries of cervical spine. *Journal of Neurosurgery*, *11*(6), 546–577. https://doi.org/10.3171/jns.1954.11.6.0546.

Schneider, R. C., Thompson, J. M., & Bebin, J. (1958). The syndrome of acute central cervical spinal cord injury. *Journal of Neurology, Neurosurgery, and Psychiatry*, *21*(3), 216–227. https://doi.org/10.1136/jnnp.21.3.216.

Sekhon, L. H., & Fehlings, M. G. (2001). Epidemiology, demographics, and pathophysiology of acute spinal cord injury. *Spine (Phila Pa 1976)*, *26*(24 Suppl), S2–12. https://doi.org/10.1097/00007632-200112151-00002.

Tator, C. H. (1983). Spine-spinal cord relationships in spinal cord trauma. *Clinical Neurosurgery*, *30*, 479–494. https://doi.org/10.1093/neurosurgery/30.cn_suppl_1.479.

Vaccaro, A. R., Hulbert, R. J., Patel, A. A., Fisher, C., Dvorak, M., Lehman, R. A., Jr., et al. (2007). The subaxial cervical spine injury classification system: A novel approach to recognize the importance of morphology, neurology, and integrity of the disco-ligamentous complex. *Spine (Phila Pa 1976)*, *32*(21), 2365–2374. https://doi.org/10.1097/BRS.0b013e3181557b92.

Vaccaro, A. R., Koerner, J. D., Radcliff, K. E., Oner, F. C., Reinhold, M., Schnake, K. J., et al. (2016). AOSpine subaxial cervical spine injury classification system. *European Spine Journal*, *25*(7), 2173–2184. https://doi.org/10.1007/s00586-015-3831-3.

Vaccaro, A. R., Lee, J. Y., Schweitzer, K. M., Jr., Lim, M. R., Baron, E. M., Oner, F. C., et al. (2006). Assessment of injury to the posterior ligamentous complex in thoracolumbar spine trauma. *Spine J.*, *6*(5), 524–528. https://doi.org/10.1016/j.spinee.2006.01.017. Epub 2006 Jul 11 16934721.

Wagnac, E., Mac-Thiong, J. M., Arnoux, P. J., Desrosiers, J. M., Menard, A. L., & Petit, Y. (2019). Traumatic spinal cord injuries with fractures in a Quebec level I trauma center. *The Canadian Journal of Neurological Sciences*, *46*(6), 727–734. https://doi.org/10.1017/cjn.2019.252.

White, A. A., 3rd, Johnson, R. M., Panjabi, M. M., & Southwick, W. O. (1975). Biomechanical analysis of clinical stability in the cervical spine. *Clinical Orthopaedics and Related Research*, *109*, 85–96. https://doi.org/10.1097/00003086-197506000-00011. PMID: 1132209.

Wilcox, R. K., Boerger, T. O., Allen, D. J., Barton, D. C., Limb, D., Dickson, R. A., et al. (2003 Nov). A dynamic study of thoracolumbar burst fractures. *The Journal of Bone and Joint Surgery. American Volume*, *85*(11), 2184–2189. https://doi.org/10.2106/00004623-200311000-00020. 14630851.

Wilson, J. R., Cadotte, D. W., & Fehlings, M. G. (2012). Clinical predictors of neurological outcome, functional status, and survival after traumatic spinal cord injury: A systematic review. *Journal of Neurosurgery. Spine*, *17*(1 Suppl), 11–26. https://doi.org/10.3171/2012.4.AOSPINE1245.

Wilson, J. R., Vaccaro, A., Harrop, J. S., Aarabi, B., Shaffrey, C., Dvorak, M., et al. (2013). The impact of facet dislocation on clinical outcomes after cervical spinal cord injury: Results of a multicenter North American prospective cohort study. *Spine (Phila Pa 1976)*, *38*(2), 97–103. https://doi.org/10.1097/BRS.0b013e31826e2b91.

Yokota, K., Maeda, T., Kawano, O., Mori, E., Takao, T., Sakai, H., et al. (2019). Progression of local kyphosis after conservative treatment for compressive cervical spine fracture with spinal cord injury. *Journal of Orthopaedic Surgery and Research*, *14*(1), 98. https://doi.org/10.1186/s13018-019-1115-z.

Zariffa, J., Kramer, J. L., Fawcett, J. W., Lammertse, D. P., Blight, A. R., Guest, J., et al. (2011). Characterization of neurological recovery following traumatic sensorimotor complete thoracic spinal cord injury. *Spinal Cord*, *49*(3), 463–471. https://doi.org/10.1038/sc.2010.140.

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Chapter 3

Body, action, and space representations in people affected by spinal cord injuries

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List of abbreviations

BR body representation
PPS peripersonal space
RT response times
SCI spinal cord injury

Introduction

Anecdotical reports concerning modifications of the perception of the body, space, and action following a spinal cord injury (SCI) are well known to professionals that have experienced with these patients as they can report body misperceptions (e.g., phantom limb or body loss), misrepresentations of space (e.g., body or limbs position, distance lengthening), changes in action representation (e.g., illusionary and phantom limb movement leading to muscular fatigue) (Cole, 2004; Conomy, 1973; Curt, Yengue, Hilti, & Brugger, 2011; Scandola et al., 2017). These sensations, linked to pain, the level of the lesion and the time passed since the lesion onset (Scandola, Aglioti, Avesani, et al., 2017), are symptoms of neuroplastic changes in areas related to the body, space, and action representation.

A spinal cord interruption, especially when this is not developmental but acquired, abruptly changes the brain–body communication. This modification alters the balance between the body sensorial inputs, the signals sent toward it, and the brain activity, leading to abnormalities in cortical and subcortical activity. Consequently, the brain neuroplastically changes itself (Nardone et al., 2013) into brain networks that are involved in body, space, and action representations. Therefore, modifications in these cognitive functions are likely to occur.

This chapter is organized as: a first section reviewing the main literature concerning neuroplastic modifications in SCI individuals, underlying those related to the body, space, or action representations, the following three sections will show the experimental outcomes from studies concerning these representations in SCI individuals, and a fourth section will highlight the experimental results showing the effects of rehabilitative trainings on these representations.

Finally, a concluding section will present the main findings, interpretations, and connections.

The neuroplasticity following SCI and the networks involved in the body, space, and action representations

Neuroplasticity mechanisms have been recently investigated in SCI. Different levels of activation in the sensory and motor cortices have shown, particularly a reduction of activity in areas corresponding to paralyzed limbs (Jurkiewicz, Mikulis, Fehlings, & Verrier, 2010) along with increased activation in areas corresponding to spared body parts (Aguilar et al., 2010; Curt, Bruehlmeier, Leenders, Roelcke, & Dietz, 2002).

Other studies (Henderson, Gustin, Macey, Wrigley, & Siddall, 2011) showed the expansion of the cortical hand area toward the leg area during upper limbs movements. An enlargement of the face representation in the surrounding areas in monkeys after SCI was observed in the primary and nonprimary somatosensory cortices (Tandon, Kambi, Lazar, Mohammed, & Jain, 2009).

Other works found a general reorganization of somatotopic areas (Ghosh et al., 2012; Lundell et al., 2011) and their degeneration over time (Freund et al., 2013).

Diagnosis and Treatment of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822498-4.00003-8

All these neuroplastic changes relate to the body, space, and action representations; indeed, all the somatotopic areas are involved in BR (Berlucchi & Aglioti, 2010). Moreover, in BR, the posterior parietal cortex, integrating multisensory inputs and outputs has a fundamental role (Bonda, Petrides, Frey, & Evans, 1995) as this brain area is directly involved in the neuroplasticity following SCI, because of the sensorial modifications.

The understanding of others' actions and space representations rely also on somatosensory cortices. In fact, the fronto-parietal "mirror" network (Rizzolatti, Cattaneo, Fabbri-Destro, & Rozzi, 2014) includes the ventral premotor cortex and the inferior frontal gyrus. Space perception involves the intraparietal sulcus, the lateral occipital complex, and the premotor cortex (Makin, Holmes, & Zohary, 2007; Sereno & Huang, 2006) in the peripersonal space representation, while the extra-personal space perception is linked to an occipito-parietal circuit, a parieto-prefrontal pathway, and a parieto-premotor one (Kravitz, Saleem, Baker, & Mishkin, 2011).

The unbalance between the somatosensory and other sensory feedbacks, causing fundamental changes in the neurological system after SCI, might cause of maladaptive neuroplasticity in these cognitive representations, causing modifications that may be subtle, or evident like phantom sensations (Moore, Stern, Dunbar, Kostyk, & Gehi, & Corkin, 2000) and neuropathic pain (Wrigley et al., 2009).

The body representations

Body ownership is an important aspect of our body representations (BR) and can be defined as the sensation that a bodily part is part of our body. Relevant disturbances can lead to Asomatognosia (Jenkinson, Moro, & Fotopoulou, 2018), namely abnormalities in various facets of body ownership such as the experienced existence, visual self-recognition, and sense of belonging to contralesional body parts.

This facet of BR, investigated by the rubber-hand paradigm, appears to be modified according to neuroplastic cortical modifications. In the commonest version of the rubber-hand illusion (see Fig. 1, Botvinick & Cohen, 1998), participants

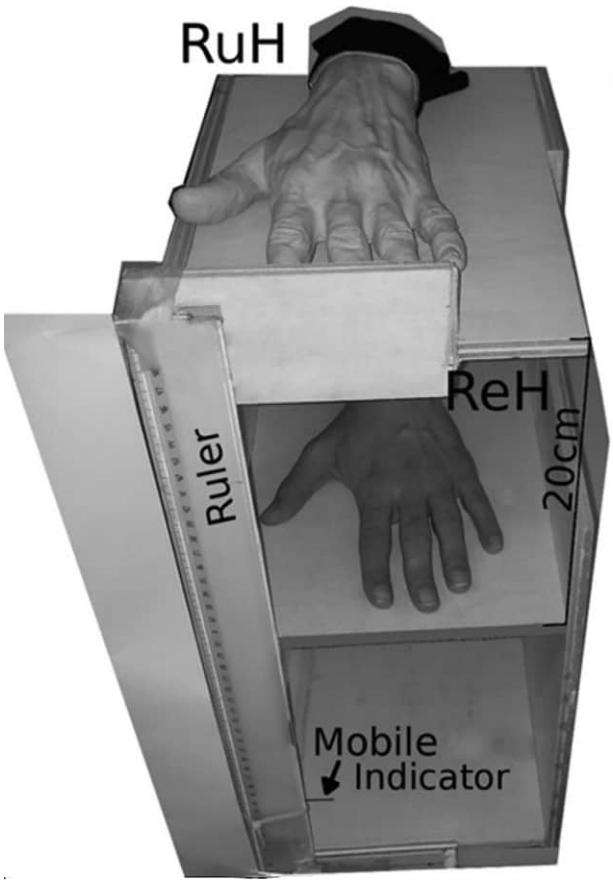

FIG. 1 Rubber hand experimental set-up used in Scandola et al. (2014): Experimental wooden box (RuH, Rubber Hand; ReH, Real Hand), the mobile indicator was always visible to the participant laterally to the box.

observe a rubber-hand, i*n a congruent position with* their own body, synchronously touched with their hand, hidden from sight (Botvinick & Cohen, 1998). An asynchronous rubber-hand/real-hand touch should not elicit a body ownership sensation and, therefore, is used as control condition (Botvinick & Cohen, 1998).

In hand representation-deprived tetraplegics, the ownership sensation toward a rubber hand can be elicited by the synchronous tactile stimulation of the left cheek and the rubber hand (see Fig. 2; Scandola et al., 2014). This is probably caused by the overlapping of the cheek somatic and motor representations over the representation of the hand that are normally contiguously represented (Ramachandran, Stewart, & Rogers-Ramachandran, 1992). A similar result with synchronous visuo-tactile stimulation of the upper back and rubber legs in SCI individuals with complete paraplegia was found (Pozeg et al., 2017). Moreover, the subjective verbal report of the sensation of body ownership toward a body part seems to be captured by the mere vision of the body part, especially when there is a total lack of tactile sensations (lower limbs in people affected by complete paraplegia: Scandola et al., 2020; rubber hand in a patient affected by tetraplegia: Tidoni, Grisoni, Liuzza, & Aglioti, 2014).

A further, implicit paradigm to study body ownership relies on the body-view enhancement effect. This task exploits the effect of visual stimuli appearing on our body that evoke faster reactions than visual stimuli appearing on the same space location, but on a neutral surface (Kao & Goodale, 2009). By a modified version of this paradigm, it was observed that individuals affected by complete paraplegia feel body ownership for the parts of the body that have spared sensory and motor functions, but also the same level of body ownership for their wheelchair, while the lower limbs show no body ownership (Scandola et al., 2019). Interestingly, the same task executed with the SCI participant seated in a different, never used before, wheelchair shows that this redefines their whole BR: there is *no* body ownership toward the new wheelchair, the lower limbs, nor for the part of the body that has spared motor and sensory functions (Scandola, Togni, et al., 2019).

The notion of body schema dates back to the seminal work of Head and Holmes (1911) and can be nowadays defined as the dynamic representation of body parts and their movements, which derives from multiple sensory and motor inputs (e.g., proprioceptive, vestibular, tactile, visual, efference copy). Patients with an impaired body schema are not able to distinguish the position of their arm when their eyes are closed.

A popular experimental paradigm investigating this aspect is the Mental Body Rotation paradigm (Parsons, 1987). According to this, individuals are asked to identify the laterality of a hand or a foot presented on screen at different rotations. The underlying mechanisms of decision imply that participants rotate the bodily stimuli congruent with their body and, therefore, response times (RTs), required to align series of gradually more rotated images to the vertical congruent with the body position, are slower. This leads to a typical RTs pattern, characteristic of a normal body schema representation, called bio-mechanical effect (Parsons, 1987).

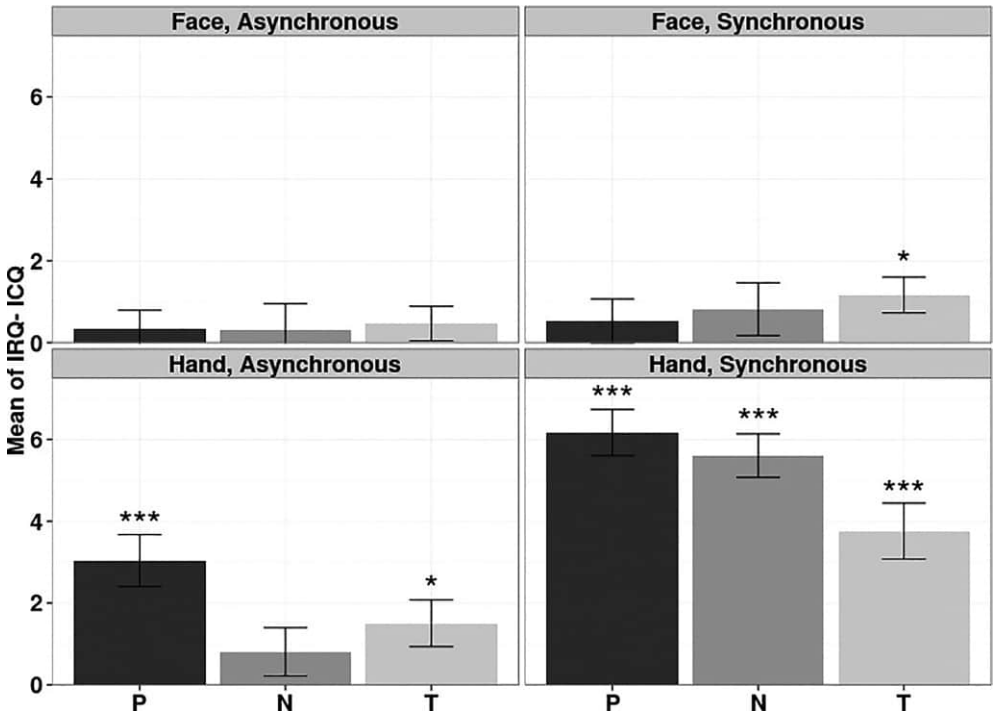

FIG. 2 Results from Scandola et al. (2014): Presence of body ownership in the paraplegics (P), tetraplegics (T), and control healthy (N) groups.

Mental Body Rotation paradigm confirms that complete SCI disrupts the influence of postural changes on the representation of the deafferented body parts (feet, but not hands) and, regardless the posture, whole-BR progressively deteriorates proportionally to SCI completeness (Ionta et al., 2016), as a direct effect of the somato-sensation lack in the affected body-parts in SCI individuals.

Indeed, in SCI participants, the misproprioception of the paralyzed body parts is not uncommon (77% of cases) and it is present in all people affected by complete tetraplegia (Scandola, Aglioti, Avesani, et al., 2017).

Also Disownership-like and Somatoparaphrenia-like sensations (sensations of not owning their own limbs, even attributing them to someone else, as in the latter case) are often reported (48% and 46%, respectively), altogether to illusory motion of paralyzed body parts (51%).

In all these cases, these bodily illusions are connected to the time since the lesion onset, the level of injury, and the presence of pain (Scandola, Aglioti, Avesani, et al., 2017).

Interestingly, these bodily illusions are less evident in presence of neuropathic and visceral pain. This apparently counterintuitive result addresses toward the fact that, in a deafferented/deefferented body, a pain sensation coming from the impaired body part is used by our cognitive system as a surrogate BR.

The action representation

The representation of actions is fundamental in our everyday life. It allows us to plan our gestures, interact with the environment and other people. The representation of actions is based on the fronto-parietal "mirror" network (Aglioti, Cesari, Romani, & Urgesi, 2008; Avenanti, Candidi, & Urgesi, 2013; Calvo-Merino, Glaser, Grèzes, Passingham, & Haggard, 2004; Panasiti, Pavone, & Aglioti, 2016).

In matching-to-sample experiments, participants are presented with a single stimulus called the sample and then with two choice stimuli called the comparisons. The participants have to select the comparison that matches the sample. A version of this paradigm that used images of bodies that could be different for body action or body form, for the whole body, in its upper part, or in the lower part, was applied to a sample of complete paraplegics and healthy controls (Pernigo et al., 2012). Results showed that complete paraplegics participants had slower reaction times and greater errors incidence, in body images that were different for the lower part of the body, than the control group of healthy participants.

These results were confirmed and widened by using a Temporal Occlusion Paradigm (Scandola, Aglioti, et al., 2019) where participants observed two sets of videos depicting an actor who attempted to climb onto a platform using a wheelchair or rollerblades. Each video could end in three different ways: (a) successfully (the actor went up the step), (b) failing (the actor stopped before the step without going up), or (c) falling (the actor fell without going up). Each video was cut in five different durations at 600, 1200, 1800, 2400, and 3000 ms. In the shortest (600 ms) clip, only preparatory body movements were shown, while in the longest (3000 ms), the complete action (see Fig. 3).

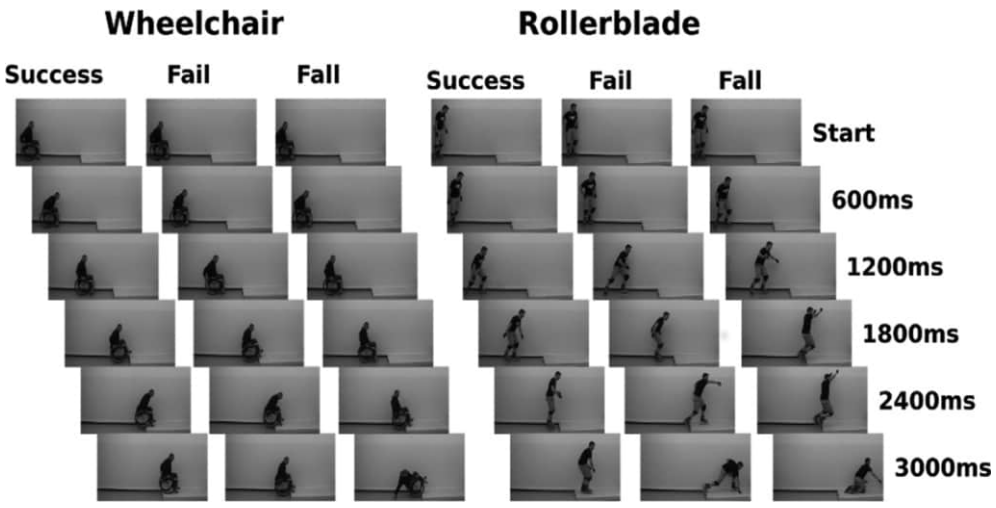

FIG. 3 Stimuli used in Scandola, Aglioti, et al. (2019): Wheelchair and rollerblade videos at different durations (Start, 600, 1200, 1800, 2400, 3000 ms) for the three endings.

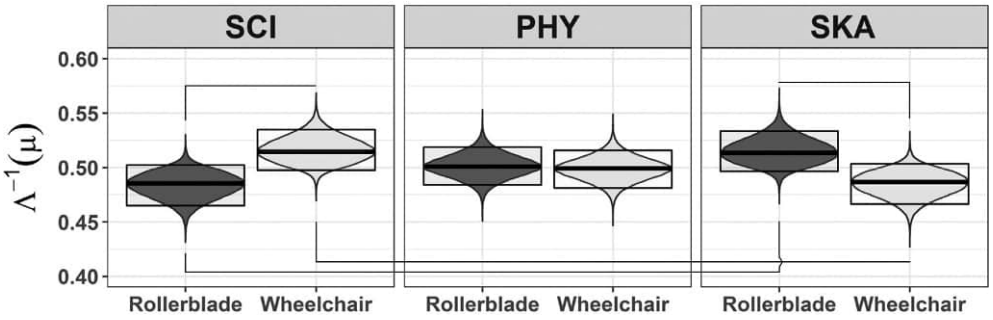

FIG. 4 Results from (Scandola, Aglioti, et al., 2019): a Temporal Occlusion Paradigm in anticipating the ending of wheelchair or rollerblade videos in *SCI* = spinal cord injured people; *PHY* = physiotherapists; *SKA* = skaters. Higher values mean better performance.

Participants had to report the outcome of the video choosing among success, fail, or fall. Participants were divided in three groups: the complete paraplegics group, the expert skaters group, and a group composed by physiotherapists that had at least 1 year of experience in a spinal-unit, but no experience in rollerblades or other skating tools.

Results from this study showed that complete paraplegics participants had a worse performance in rollerblades videos compared to the Skaters group, but also compared to the Physiotherapists group, inexperienced in skating (see Fig. 4), suggesting that abnormalities in the mirror system for the lower limbs affect the recognition of lower limbs' actions in a subtle, but still worsening way compared to a group that had no direct experience in the action.

A further indication regarding modifications in the action representation system derives from the tendon-vibration illusion, able to induce illusory perception of movement (Tidoni et al., 2015). The application of this illusion to individuals affected by SCI induced movement illusions that were qualitatively different from the healthy control sample (e.g., as if the arm wanted to extend itself, or a sensation of pushing against something) that may reflect different reorganization processes following SCI (Fusco, Tidoni, Barone, Pilati, & Aglioti, 2016).

The modifications in the action representations could also affect the learning of new motor sequences. In fact, according to Bloch and colleagues (Bloch, Tamir, Vakil, & Zeilig, 2016), it exists a specific deficit in implicit learning of motor sequences in SCI people, and it may be extended even in the motor learning abilities consequently a SCI lesion.

However, complete SCI participants demonstrated a better performance in forecasting the outcome of wheelchair action in a Temporal Occlusion Paradigm than Physiotherapists working in a Spinal Cord Unit and a group of expert skaters (Scandola, Aglioti, et al., 2019). Interestingly, experimental results confirmed that agonistic wheelchair-basket players showed a better performance with images changing only in the upper-part of the body than control healthy agonistic basketball players (Pernigo et al., 2012); moreover, a greater EEG observational contingent negative variation waveform, considered a marker of action effect prediction, during the evaluation of free throws videos, than control participants (Özkan, Pezzetta, Moreau, Abreu, & Aglioti, 2019). Finally, Bloch, Shaham, Vakil, Ashkenazi, and Zeilig (2020) with a different experimental paradigm could not replicate the impairment of implicit motor learning previously reported. Therefore, the motor learning impairment in SCI is probably not present, or it is very specific for some motor nonecological tasks.

Another aspect of action representation is the motor imagery. This can be defined as the act to internally represent an action, without its execution (Jackson, Lafleur, Malouin, Richards, & Doyon, 2001). Nonetheless, motor imagery involves the activation of brain structures involved in action performance, such as premotor areas and the left intraparietal sulcus, even *if* at a minor level than actual action performance (Bonda et al., 1995; Decety, 1996; Nikulin, Hohlefeld, Jacobs, & Curio, 2008).

While in some studies, motor imagery seems to be spared after SCI (Decety & Boisson, 1990; Hotz-Boendermaker et al., 2008), altered cortical activations were found (Alkadhi et al., 2005; Cramer, Orr, Cohen, & Lacourse, 2007).

In particular, during motor imagery tasks, the primary and nonprimary motor cortices, and subcortical structures are more activated in individuals affected by SCI than control subjects (Alkadhi et al., 2005), even if the imagery does not involve paralyzed limbs (Alkadhi et al., 2005). Similarly, the minor activation of the primary motor cortex shown by healthy individuals during imagined movements compared to real movements, it is not present after SCI (Di Rienzo et al., 2014), suggesting that after SCI, the motor cortices are activated in the same way during motor imagery or real movements.

Experimental reports suggest that these effects lead to a different motor imagery strategy after SCI for subjective responses (Fiori et al., 2014). In fact, from behavioral investigations, motor imagery after SCI appears to be somatotopographically organized, with higher ability for the spared body parts, and it is impaired in presence of neuropathic pain (Scandola, Aglioti, Pozeg, et al., 2017).

The space representation

The study of the space representation, since the seminal works by Rizzolatti and colleagues (Rizzolatti, Scandolara, Matelli, & Gentilucci, 1981) was divided in extrapersonal and peripersonal space, two spaces that can be broadly defined respectively as the space outside and within the reach of our limbs.

PPS representation is somatotopically organized: different extensions were found for the hands, trunk, head, and lower limbs (Schicke, Bauer, & Röder, 2009; Serino et al., 2015; Stone, Kandula, Keizer, & Dijkerman, 2017). It is modulated by several aspects of our everyday life, such as action (Brozzoli, Cardinali, Pavani, & Farnè, 2010), danger and fear (Sambo, Liang, Cruccu, & Iannetti, 2011), and stimuli valence (Spaccasassi, Romano, & Maravita, 2019).

PPS is somatotopically modulated by the presence of SCI, but this representation can be recovered with an action-based training. While the upper limbs PPS representation in paraplegics is preserved (Scandola, Aglioti, Bonente, Avesani, & Moro, 2016; Scandola et al., 2020; Sedda et al., 2018), the PPS around the lower limbs is shrunk (Scandola et al., 2016, 2020). However, applying passive mobilization on lower limbs can recover their PPS representation (Scandola et al., 2016).

The representation of the extrapersonal space is also modulated by action and metabolic energy. According to the Economy of Action principle (Proffitt, 2006), the perceptual representation of the space around us is modulated by our metabolic energy, in order to spare energetic resources, mostly when they are lacking. Therefore, when we are in a low physiological condition, or in a physically demanding situation, distances to be (implicitly) walked are perceived longer, and slopes are perceived stepper (Proffitt, 2006).

Indeed, experimental results showed that in estimating the slope of a hill or distance, people tend to overestimate when wearing a heavy backpack (Bhalla & Proffitt, 1999). These effects may be elicited by poor physical health, fatigue (Bhalla & Proffitt, 1999), while the opposite effect is appreciable after the assumption of energy beverages (Schnall, Zadra, & Proffitt, 2010). Thus, the characteristics of the perceptual representation of the extrapersonal space that are potentially linked to a bodily demanding action will be overestimated to prevent the action execution. Therefore, perceptual errors are natural, and they increase as the required effort increases.

In a virtual-reality task, participants affected by complete paraplegia saw a flag depicted on an ascending wheelchair ramp that could have different degrees of slant. Participants had to estimate the distance from the flag on their own wheelchair, or on a wheelchair never used before.

Distance estimation errors were modulated by the degrees of slant of the ramp only when they were seated on their own wheelchair, while on the other wheelchair, the estimation errors were constant (Scandola, Togni, et al., 2019), suggesting that only when they are on their wheelchair they are able to implicitly represent the action of reaching the flag, allowing a representation of space that follows the Economy of Action principle (Proffitt, 2006).

The effects of rehabilitation on the body, action, and space representations

Physiotherapy interventions can significantly affect, not only from a rehabilitative point of view, but they can likewise be beneficial for the body, action, and space representations.

In particular, the effects of physiotherapy training on body schema representation were studied on a sample of 21 individuals affected by SCI. Before starting the training, and at the end of it, participants underwent a Mental Body Rotation paradigm (Parsons, 1987), with stimuli depicting a left or right hand, foot, or a body (Scandola, Dodoni, et al., 2019). Before the training, SCI participants and a group of healthy participants showed the same pattern for hands and bodies stimuli, while with feet stimuli, only the healthy group showed the bio-mechanical effect. Interestingly, the level of completeness of the lesion covaried with RTs with feet stimuli: slower RTs were associated with more complete lesions, suggesting a greater difficulty in processing stimuli concerning paralyzed body parts.

After the physiotherapy intervention, the bio-mechanical effect appeared also with feet stimuli in the SCI group, showing that a rehabilitative intervention has also effects on the body schema representation (Scandola, Dodoni, et al., 2019).

Another fascinating study, added to the normal physiotherapy rehabilitation a motor imagery training to tetraplegic patients and a control group. Results from magneto-encephalography showed that before the training in the SCI group, there was a compensatory recruitment, with a higher activation of more areas during motor imagery tasks than the control group. Immediately after the training, and after 2 additional months, the SCI group showed a recruitment similar to the control group (Di Rienzo, Guillot, Daligault, et al., 2014).

The impact of rehabilitative training, in particular when they involve the mobilization of paralyzed limbs, is evident also in the PPS representation. In 2016, a study from our group noticed that PPS in complete paraplegics individuals is shrunk around the feet, though a passive mobilization lasting 15 min can recover it (Scandola et al., 2016).

FIG. 5 Pictures from the videos used in Scandola et al. (2020). (A) Video in first-person perspective of passive mobilization. (B) Video in first-person perspective of no mobilization.

Importantly, this recovery is not present when the passive-mobilization is only visual (e.g., the lower limbs are not actually moved, but participants observe a virtual-reality video showing their legs being moved, see Fig. 5).

Results clearly showed that in complete paraplegic participants, the real motor component of the passive mobilization is needed for PPS representation recovery (Scandola et al., 2020). Connected with this latter finding, complete paraplegic individuals could detect when their legs were moved, even if they could not see them, notwithstanding their lack of proprioception (see Fig. 6), better than random guesses (Scandola et al., 2020). Moreover, PPS recovery was modulated by interoception sensitivity in participants affected by incomplete paraplegia: greater interoceptive sensitivity leads to a greater lower-limbs PPS recovery (Scandola et al., 2020).

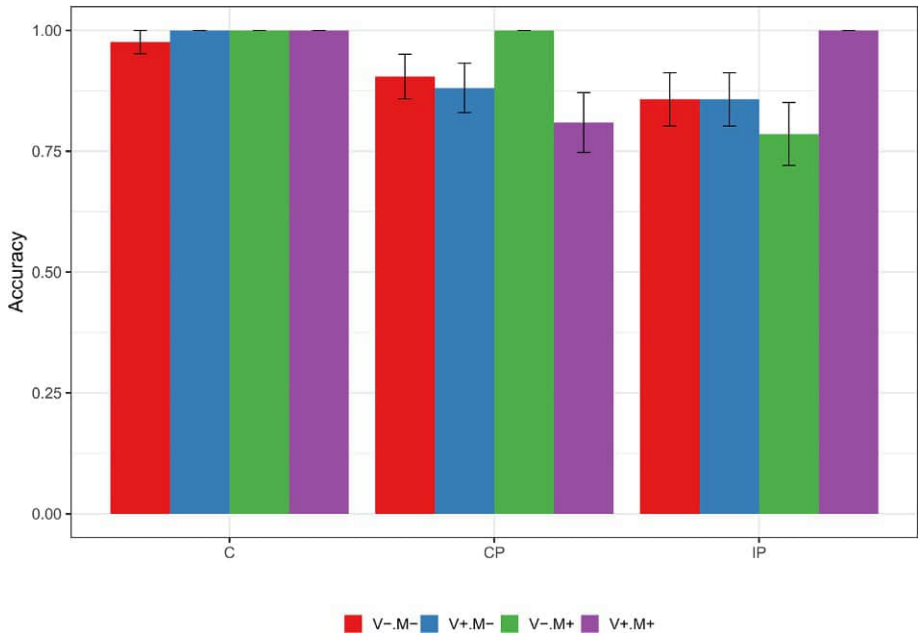

FIG. 6 Accuracies of the detection of motion of the lower legs during the 4 stimulations: V+ = video showing passive visual mobilization, *V-* = video showing no visual mobilization; *M+* = real mobilization; *M−* = no real mobilization. *C* = control group; *CP* = complete paraplegics group; *IP* = incomplete paraplegics group. *Adapted from Scandola, M., Aglioti, S. M., Lazzeri, G., Avesani, R., Ionta, S., & Moro, V. (2020). Visuo-motor and interoceptive influences on peripersonal space representation following spinal cord injury.* Scientific Reports, 10*(1), 1–16. https://doi.org/10.1038/s41598-020-62080-1*.

Conclusions

The neuroplastic changes following SCI involve modifications of the body, space, and action representations (see Table 1 for a summary). Modifications in such representations are often considered as a cause of maladaptive plasticity that is related to phantom limb and neuropathic pain (Moore et al., 2000; Wrigley et al., 2009).

Modifications in the body, action, and space representations seem to follow the somato-topography rule: but only representations involving paralyzed limbs (Scandola, Aglioti, et al., 2019; Scandola et al., 2016, 2020, 2014).

Importantly, the possibility of new motor learnings and the action-dependent recovery of the representation of the space suggest top-down and bottom-up influences on above representations (Bloch et al., 2020; Pernigo et al., 2012; Scandola et al., 2016, 2020).

Also, BRs are impacted by bottom-up and top-down influences. For example, neuropathic and visceral pain sensations coming from the part of the body that is deafferented/deefferented seem to protect from body illusions, working as surrogate of normal BR (Scandola, Aglioti, Avesani, et al., 2017). Moreover, the wheelchair does not seem only the most iconic symbol representing the condition of individuals affected by SCI, but also a tool that is able to shape and define their BRs (Scandola, Togni, et al., 2019), and the extrapersonal space representation (Scandola, Togni, et al., 2019).

These results indicate that the body, space, and action representations rehabilitation is possible, and it might have beneficial neuroplastic effects on maladaptive plastic mechanisms (Di Rienzo, Guillot, Mateo, et al., 2014; Scandola et al., 2016, 2020). A further step might be a training focused on these representations, that side by side to a conventional physiotherapy training could improve rehabilitative outcomes.

Applications to other areas of neuroscience

In this chapter, we have reviewed the neuroplastic modifications in the body, space, and action representations following complete or incomplete spinal cord injuries.

TABLE 1 Summary of the main findings concerning body, action, and space representations in spinal cord injuries.

Domain	Subdomain	Finding	References
Body representation	*Explicit body ownership*	Visuo-tactile stimulations induce body ownership over a rubber body part, also when the tactile stimulus is administered to a body part that is different from the rubber one. This may be caused by the neuroplasticity involving the motor and somato-sensory cortexes, or by the mere vision of the rubber body part	Scandola et al. (2014), Pozeg et al. (2017), Tidoni et al. (2014)
	Implicit body ownership	Body Ownership is somatotopically modulated over the body, reduced over the paralyzed and anesthetized body parts, and it is extended to the wheelchair. The use of a new wheelchair can impair Body Ownership over the whole body	Scandola, Togni, et al. (2019)
	Body schema	Complete SCI impairs body schema on the representation of the deafferented body parts (feet, but not hands) and, regardless the posture, whole-BR progressively deteriorates proportionally to SCI completeness, as a direct effect of the somato-sensation lack in the affected body-parts in SCI individuals Body Schema can be recovered after physiotherapeutic interventions	Ionta et al. (2016), Scandola, Dodoni, et al. (2019)
	Body illusions	Various body representation illusions are reported for SCI individuals: • Misproprioception of the paralyzed body: 77% • Disownership-like sensation: 48% • Somatoparaphrenia-like sensations: 46% • Illusory motion of paralyzed body parts: 51% These are reduced by the presence of visceral or neuropathic pain: pain sensations coming from the impaired body part are used by our cognitive system as a surrogate body representations in absence of other somatic sensations	Scandola, Aglioti, Avesani, et al. (2017)

TABLE 1 Summary of the main findings concerning body, action, and space representations in spinal cord injuries—cont'd

Domain	Subdomain	Finding	References
Action representation	*Action discrimination*	Complete paraplegics participants have slower reaction times and greater errors incidence, in body images that were different for the lower part of the body, than the control group of healthy participants Agonistic wheelchair-basket players have a better performance with images changing only in the upper-part of the body than control healthy agonistic basketball players A greater EEG observational contingent negative variation waveform (marker of action effect prediction) is observed during the evaluation of free throws videos, than control participants	Pernigo et al. (2012), Özkan et al. (2019)
	Action anticipation	Complete paraplegics participants have worse performances in guessing the final outcome of rollerblades videos compared to the Skaters group, but also compared to the Physiotherapists group, inexperienced in skating, suggesting that abnormalities in the mirror system for the lower limbs affects the recognition of lower limbs' actions in a subtle, but still worsening way compared to a group that had no direct experience in the action	Scandola, Aglioti, et al. (2019)
	Tendon vibration illusion	Movement illusions are qualitatively different from the healthy control sample (e.g., as if the arm wanted to extend itself, or a sensation of pushing against something), reflecting different reorganization processes following SCI	Fusco et al. (2016)
	Implicit learning	In a study (Bloch et al., 2016) SCI participants showed a specific deficit in implicit learning of motor sequences However, this result was not confirmed by the result of another study of the same group (Bloch et al., 2020)	Bloch et al. (2016), Bloch et al. (2020)
	Motor imagery	During motor imagery tasks, the primary and non-primary motor cortices, and subcortical structures are more activated in individuals affected by SCI than control subjects. SCI participants use a different strategy for motor imagery based on memory instead of on body representations, and it is impaired by neuropathic pain sensations. Adding motor imagery tasks to the normal physiotherapy rehabilitation for 2 months leads to a normalization in the cortical activation of SCI participants	Alkadhi et al. (2005), Di Rienzo, Guillot, Daligault, et al. (2014), Fiori et al. (2014), Scandola, Aglioti, Pozeg, et al. (2017)
Space representation	*Peripersonal space*	PPS in SCI is somatotopically impaired: the representation of upper-lesion body parts is spared, while the representation of lower-lesion body parts is shrunk. The application of passive mobilization on lower limbs can induce a short-term recovery. This passive mobilization must involve actual mobilization: the simple observation of movement is not enough	Scandola et al. (2016), Scandola et al. (2020), Sedda et al. (2018)
	Extrapersonal space	Distance estimation errors are modulated by the embodiment of the wheelchair in use. If the tool used to move in the surrounding space is embodied (i.e., they are using their own wheelchair), the distance estimation errors are modified by the difficulty in reaching that distance, as in healthy subjects that are able to internally represent the action. If the wheelchair is not embodied (i.e., they are using a never-used-before wheelchair), the action representation becomes impossible and purely visual strategies are then used in order to estimate space	Scandola, Togni, et al. (2019)

The neuroscientists, or the neurologists interested in the modifications of these representations, and their interconnections with rehabilitative and theoretical or neurophysiological aspects, will be interested in these studies.

The study of the body, space, and action representations has often used studies on neurological patients (Buxbaum, Giovannetti, & Libon, 2000; Candia, Wienbruch, Elbert, Rockstroh, & Ray, 2003; Canzoneri, Marzolla, Amoresano, Verni, & Serino, 2013; Sirigu, Grafman, Bressler, & Sunderland, 1991; Soman, Steeves, & Lang, 2009; Tinazzi, Fiorio, Bertolasi, & Aglioti, 2004). However, SCI participants may represent an ideal model to explore to what extend sensorimotor deficits alter cognitive functions. In fact, in this population, all the postlesional changes in cognitive functions do not depend on brain damage or modifications in their body form but are exclusively related to the loss of sensory–motor afferences from as well as efferences to the disconnected body parts.

Furthermore, for the neuroscientists interested in rehabilitation of cognitive and motor skills, the above-reviewed studies here reviewed show trainings that are designed to counter maladaptive plasticity and neuropathic pain, and improve adaptive neuroplasticity (Mateo et al., 2015; Scandola et al., 2020; Scandola, Dodoni, et al., 2019).

Mini-dictionary of terms

Neuroplasticity: the natural modifications of the brain areas, through growth and reorganization.
Body ownership: our sensation of owning a part of our body.
Rubber hand illusion: an experimental paradigm used to investigate body ownership, where a sensation of body ownership is elicited toward a rubber hand by means of synchronous visuo-tactile stimulation of the rubber hand and the participant's real hand.
Body-view enhancement effect: visual stimuli appearing on our body evoke faster reactions than visual stimuli appearing on the same space location, but on a neutral surface.
Body schema: the representation of the body parts position, in relation to the rest of the body.
Mental Body Rotation Paradigm: In this experimental paradigm, individuals are asked to identify the laterality of a hand or a foot presented on screen at different rotations. The underlying mechanisms of decision imply that participants rotate the body stimuli in a canonical position congruent with their body and therefore, response times (RTs) required to align series of gradually more rotated images to the vertical, congruent with the body position, are slower. This leads to a typical RTs pattern, characteristic of a normal body schema representation, called bio-mechanical effect.
Motor imagery: the act to internally represent an action, without its execution. It has to do with the activation of the same brain areas involved in the execution of the action, even though at a minor level.
Peripersonal space: the space within the reach of our limbs.
Extrapersonal space: the space outside the reach of our limbs.
Temporal Occlusion Paradigm: in this experimental paradigm, participants are asked to predict the outcome of an action seen in a video that has been occluded at a specific time-point, before the end of the action.

Key facts of neuroplasticity following spinal cord injury

1. Brain modifications after spinal cord lesion starts within minutes from the lesion, as seen in animal models
2. The neuroplasticity leads to reduction of activity in the areas corresponding to paralyzed limbs
3. In the brain areas connected to the upper-lesion body parts the activity is increased
4. This neuroplasticity can cause phantom limb sensations
5. Maladaptive neuroplasticity can cause neuropathic pain
6. It is also the cause of modifications in body, action, and space representations

Summary points

1. The neuroplastic modifications following a spinal cord injury change the body, action, and space representations with maladaptive consequences
2. The modifications in the body representations do not only involve the parts of the body below the lesion, but also the whole body
3. In individuals with chronic spinal cord injuries, that use the wheelchair for a long time, the wheelchair is part of their body representation and can define it
4. The action representation is impaired for the parts of the body below the lesion
5. The peripersonal space representation is somato-topographically modified: it only involves the parts of the body that are below the lesion
6. The body, action, and space representations can be rehabilitated using motor imagery and physiotherapeutic training.

References

Aglioti, S. M., Cesari, P., Romani, M., & Urgesi, C. (2008). Action anticipation and motor resonance in elite basketball players. *Nature Neuroscience*, *11*(9), 1109–1116. https://doi.org/10.1038/nn.2182.

Aguilar, J., Humanes-Valera, D., Alonso-Calvino, E., Yague, J. G., Moxon, K. A., Oliviero, A., et al. (2010). Spinal cord injury immediately changes the state of the brain. *Journal of Neuroscience*, *30*(22), 7528–7537. https://doi.org/10.1523/JNEUROSCI.0379-10.2010.

Alkadhi, H., Brugger, P., Boendermaker, S. H., Crelier, G. R., Curt, A., Hepp-Reymond, M.-C., et al. (2005). What disconnection tells about motor imagery: Evidence from paraplegic patients. *Cerebral Cortex*, *15*(2), 131–140. https://doi.org/10.1093/cercor.

Avenanti, A., Candidi, M., & Urgesi, C. (2013). Vicarious motor activation during action perception: Beyond correlational evidence. *Frontiers in Human Neuroscience*, *7*(May), 185. https://doi.org/10.3389/fnhum.2013.00185.

Berlucchi, G., & Aglioti, S. M. (2010). The body in the brain revisited. *Experimental Brain Research. Experimentelle Hirnforschung. Expérimentation Cérébrale*, *200*(1), 25–35. https://doi.org/10.1007/s00221-009-1970-7.

Bhalla, M., & Proffitt, D. R. (1999). Visual–motor recalibration in geographical slant perception. *Journal of Experimental Psychology: Human Perception and Performance*, *25*(4), 1076–1096. Retrieved from http://psycnet.apa.org/journals/xhp/25/4/1076/.

Bloch, A., Shaham, M., Vakil, E., Ashkenazi, S. S., & Zeilig, G. (2020). Examining implicit procedural learning in tetraplegia using an oculomotor serial reaction time task. *PLoS One*, *15*(4), 1–13. https://doi.org/10.1371/journal.pone.0232124.

Bloch, A., Tamir, D., Vakil, E., & Zeilig, G. (2016). Specific deficit in implicit motor sequence learning following spinal cord injury. *PLoS One*, *11*(6), 1–13. https://doi.org/10.1371/journal.pone.0158396.

Bonda, E., Petrides, M., Frey, S., & Evans, A. (1995). Neural correlates of mental transformations of the body-in-space. *Proceedings of the National Academy of Sciences of the United States of America*, *92*(24), 11180–11184. https://doi.org/10.1073/pnas.92.24.11180.

Botvinick, M., & Cohen, J. (1998). Rubber hands "feel" touch that eyes see. *Nature*, *391*(6669), 756. https://doi.org/10.1038/35784.

Brozzoli, C., Cardinali, L., Pavani, F., & Farnè, A. (2010). Action-specific remapping of peripersonal space. *Neuropsychologia*, *48*(3), 796–802. https://doi.org/10.1016/j.neuropsychologia.2009.10.009.

Buxbaum, L. J., Giovannetti, T., & Libon, D. (2000). The role of the dynamic body schema in praxis: Evidence from primary progressive apraxia. *Brain and Cognition*, *44*(2), 166–191. https://doi.org/10.1006/brcg.2000.1227.

Calvo-Merino, B., Glaser, D. E., Grèzes, J., Passingham, R. E., & Haggard, P. (2004). Action observation and acquired motor skills: An fMRI study with expert dancers. *Cerebral Cortex*, *15*(8), 1243–1249. https://doi.org/10.1093/cercor/bhi007.

Candia, V., Wienbruch, C., Elbert, T., Rockstroh, B., & Ray, W. (2003). Effective behavioral treatment of focal hand dystonia in musicians alters somatosensory cortical organization. *Proceedings of the National Academy of Sciences of the United States of America*, *100*(13), 7942–7946. https://doi.org/10.1073/pnas.1231193100.

Canzoneri, E., Marzolla, M., Amoresano, A., Verni, G., & Serino, A. (2013). Amputation and prosthesis implantation shape body and peripersonal space representations. *Scientific Reports*, *3*, 2844. https://doi.org/10.1038/srep02844.

Cole, J. (2004). *Still lives: Narratives of spinal cord injury*. MIT Press.

Conomy, J. P. (1973). Disorders of body image after spinal cord injury. *Neurology*, *23*(8), 842. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/4737080.

Cramer, S. C., Orr, E. L. R., Cohen, M. J., & Lacourse, M. G. (2007). Effects of motor imagery training after chronic, complete spinal cord injury. *Experimental Brain Research*, *177*(2), 233–242. https://doi.org/10.1007/s00221-006-0662-9.

Curt, A., Bruehlmeier, M., Leenders, K. L., Roelcke, U., & Dietz, V. (2002). Differential effect of spinal cord injury and functional impairment on human brain activation. *Journal of Neurotrauma*, *19*(1), 43–51. https://doi.org/10.1089/089771502753460222.

Curt, A., Yengue, C. N., Hilti, L. M., & Brugger, P. (2011). Supernumerary phantom limbs in spinal cord injury. *Spinal Cord*, *49*(5), 588–595. https://doi.org/10.1038/sc.2010.143.

Decety, J. (1996). Neural representations for action. *Reviews in the Neurosciences*, *7*(4), 285–297. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9044503.

Decety, J., & Boisson, D. (1990). Effect of brain and spinal cord injuries on motor imagery. *European Archives of Psychiatry and Clinical Neuroscience*, *240*(1), 39–43. https://doi.org/10.1007/BF02190091.

Di Rienzo, F., Guillot, A., Daligault, S., Delpuech, C., Rode, G., & Collet, C. (2014). Motor inhibition during motor imagery: A MEG study with a quadriplegic patient. *Neurocase*, *20*(5), 524–539. https://doi.org/10.1080/13554794.2013.826685.

Di Rienzo, F., Guillot, A., Mateo, S., Daligault, S., Delpuech, C., Rode, G., et al. (2014). Neuroplasticity of prehensile neural networks after quadriplegia. *Neuroscience*, *274*, 82–92. https://doi.org/10.1016/j.neuroscience.2014.05.021.

Fiori, F., Sedda, A., Ferrè, E. R., Toraldo, A., Querzola, M., Pasotti, F., et al. (2014). Motor imagery in spinal cord injury patients: Moving makes the difference. *Journal of Neuropsychology*, *8*(2), 199–215. https://doi.org/10.1111/jnp.12020.

Freund, P., Weiskopf, N., Ashburner, J., Wolf, K., Sutter, R., Altmann, D. R., et al. (2013). MRI investigation of the sensorimotor cortex and the corticospinal tract after acute spinal cord injury: A prospective longitudinal study. *Lancet Neurology*, *12*(9), 873–881. https://doi.org/10.1016/S1474-4422(13)70146-7.

Fusco, G., Tidoni, E., Barone, N., Pilati, C., & Aglioti, S. M. (2016). Illusion of arm movement evoked by tendon vibration in patients with spinal cord injury. *Restorative Neurology and Neuroscience*, *34*(5), 815–826. https://doi.org/10.3233/RNN-160660.

Ghosh, A., Peduzzi, S., Snyder, M., Schneider, R., Starkey, M., & Schwab, M. E. (2012). Heterogeneous spine loss in layer 5 cortical neurons after spinal cord injury. *Cerebral Cortex (New York, N.Y. : 1991)*, *22*(6), 1309–1317. https://doi.org/10.1093/cercor/bhr191.

Head, H., & Holmes, G. (1911). Sensory disturbances from cerebral lesions. *Brain*, *34*(2–3), 102–254. https://doi.org/10.1093/brain/34.2-3.102.

Henderson, L. A., Gustin, S. M., Macey, P. M., Wrigley, P. J., & Siddall, P. J. (2011). Functional reorganization of the brain in humans following spinal cord injury: Evidence for underlying changes in cortical anatomy. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *31*(7), 2630–2637. https://doi.org/10.1523/JNEUROSCI.2717-10.2011.

Hotz-Boendermaker, S., Funk, M., Summers, P., Brugger, P., Hepp-Reymond, M.-C., Curt, A., et al. (2008). Preservation of motor programs in paraplegics as demonstrated by attempted and imagined foot movements. *Neuro Image*, *39*(1), 383–394. https://doi.org/10.1016/j.neuroimage.2007.07.065.

Ionta, S., Villiger, M., Jutzeler, C. R., Freund, P., Curt, A., & Gassert, R. (2016). Spinal cord injury affects the interplay between visual and sensorimotor representations of the body. *Scientific Reports*, *6*(1), 20144. https://doi.org/10.1038/srep20144.

Jackson, P. L., Lafleur, M. F., Malouin, F., Richards, C., & Doyon, J. (2001). Potential role of mental practice using motor imagery in neurologic rehabilitation. *Archives of Physical Medicine and Rehabilitation*, *82*(8), 1133–1141. https://doi.org/10.1053/apmr.2001.24286.

Jenkinson, P. M., Moro, V., & Fotopoulou, A. (2018). Definition: Asomatognosia. *Cortex*, *101*, 300–301. https://doi.org/10.1016/j.cortex.2018.02.001.

Jurkiewicz, M. T., Mikulis, D. J., Fehlings, M. G., & Verrier, M. C. (2010). Sensorimotor cortical activation in patients with cervical spinal cord injury with persisting paralysis. *Neurorehabilitation and Neural Repair*, *24*(2), 136–140. https://doi.org/10.1177/1545968309347680.

Kao, K.-L. C., & Goodale, M. A. (2009). Enhanced detection of visual targets on the hand and familiar tools. *Neuropsychologia*, *47*(12), 2454–2463. https://doi.org/10.1016/j.neuropsychologia.2009.04.016.

Kravitz, D. J., Saleem, K. S., Baker, C. I., & Mishkin, M. (2011). A new neural framework for visuospatial processing. *Nature Reviews Neuroscience*, *12*(4), 217–230. https://doi.org/10.1038/nrn3008.

Lundell, H., Christensen, M. S., Barthélemy, D., Willerslev-Olsen, M., Biering-Sørensen, F., & Nielsen, J. B. (2011). Cerebral activation is correlated to regional atrophy of the spinal cord and functional motor disability in spinal cord injured individuals. *NeuroImage*, *54*(2), 1254–1261. https://doi.org/10.1016/j.neuroimage.2010.09.009.

Makin, T. R., Holmes, N. P., & Zohary, E. (2007). Is that near my hand? Multisensory representation of peripersonal space in human intraparietal sulcus. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *27*(4), 731–740. https://doi.org/10.1523/JNEUROSCI.3653-06.2007.

Mateo, S., Di Rienzo, F., Bergeron, V., Guillot, A., Collet, C., & Rode, G. (2015). Motor imagery reinforces brain compensation of reach-to-grasp movement after cervical spinal cord injury. *Frontiers in Behavioral Neuroscience*, *9*(September), 1–12. https://doi.org/10.3389/fnbeh.2015.00234.

Moore, C. I., Stern, C. E., Dunbar, C., Kostyk, S. K., Gehi, A., & Corkin, S. (2000). Referred phantom sensations and cortical reorganization after spinal cord injury in humans. *Proceedings of the National Academy of Sciences of the United States of America*, *97*(26), 14703–14708. https://doi.org/10.1073/pnas.250348997.

Nardone, R., Höller, Y., Brigo, F., Seidl, M., Christova, M., Bergmann, J., et al. (2013). Functional brain reorganization after spinal cord injury: Systematic review of animal and human studies. *Brain Research*, *1504*, 58–73. https://doi.org/10.1016/j.brainres.2012.12.034.

Nikulin, V. V., Hohlefeld, F. U., Jacobs, A. M., & Curio, G. (2008). Quasi-movements: A novel motor-cognitive phenomenon. *Neuropsychologia*, *46*(2), 727–742. https://doi.org/10.1016/j.neuropsychologia.2007.10.008.

Özkan, D. G., Pezzetta, R., Moreau, Q., Abreu, A. M., & Aglioti, S. M. (2019). Predicting the fate of basketball throws: An EEG study on expert action prediction in wheelchair basketball players. *Experimental Brain Research*, *237*(0123456789), 3363–3373. https://doi.org/10.1007/s00221-019-05677-x.

Panasiti, M. S., Pavone, E. F., & Aglioti, S. M. (2016). Electrocortical signatures of detecting errors in the actions of others: An EEG study in pianists, non-pianist musicians and musically naïve people. *Neuroscience*, *318*, 104–113. https://doi.org/10.1016/j.neuroscience.2016.01.023.

Parsons, L. M. (1987). Imagined spatial transformations of one's hands and feet. *Cognitive Psychology*, *19*(2), 178–241. https://doi.org/10.1016/0010-0285(87)90011-9.

Pernigo, S., Moro, V., Avesani, R., Miatello, C., Urgesi, C., & Aglioti, S. M. (2012). Massive somatic deafferentation and motor deefferentation of the lower part of the body impair its visual recognition: A psychophysical study of patients with spinal cord injury. *The European Journal of Neuroscience*, *36*(11), 3509–3518. https://doi.org/10.1111/j.1460-9568.2012.08266.x.

Pozeg, P., Palluel, E., Ronchi, R., Solca, M., Al-Khodairy, A. W., Jordan, X., et al. (2017). Virtual reality improves embodiment and neuropathic pain caused by spinal cord injury. *Neurology*, *89*(18), 1894–1903. https://doi.org/10.1212/WNL.0000000000004585.

Proffitt, D. R. (2006). Embodied perception and the economy of action. *Perspectives on Psychological Science*, *1*(2), 110–122. https://doi.org/10.1111/j.1745-6916.2006.00008.x.

Ramachandran, V. S., Stewart, M., & Rogers-Ramachandran, D. C. (1992). Perceptual correlates of massive cortical reorganization. *Neuroreport*, *3*(7), 583–586. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1421112.

Rizzolatti, G., Cattaneo, L., Fabbri-Destro, M., & Rozzi, S. (2014). Cortical mechanisms underlying the organization of goal-directed actions and mirror neuron-based action understanding. *Physiological Reviews*, *94*(2), 655–706. https://doi.org/10.1152/physrev.00009.2013.

Rizzolatti, G., Scandolara, C., Matelli, M., & Gentilucci, M. (1981). Afferent properties of periarcuate neurons in macaque monkeys. II. Visual responses. *Behavioural Brain Research*, *2*(2), 147–163. https://doi.org/10.1016/0166-4328(81)90053-X.

Sambo, C. F., Liang, M., Cruccu, G., & Iannetti, G. D. (2011). Defensive peripersonal space: The blink reflex evoked by hand stimulation is increased when the hand is near the face. *Journal of Neurophysiology*, *44*. https://doi.org/10.1152/jn.00731.2011.

Scandola, M., Aglioti, S. M., Avesani, R., Bertagnoni, G., Marangoni, A., & Moro, V. (2017). Corporeal illusions in chronic spinal cord injuries. *Consciousness and Cognition*, *49*, 278–290. https://doi.org/10.1016/j.concog.2017.01.010.

Scandola, M., Aglioti, S. M., Avesani, R., Bertagnoni, G., Marangoni, A., & Moro, V. (2019). Anticipation of wheelchair and rollerblade actions in spinal cord injured people, rollerbladers, and physiotherapists. *PLoS One*, *14*(3). https://doi.org/10.1371/journal.pone.0213838, e0213838.

Scandola, M., Aglioti, S. M., Bonente, C., Avesani, R., & Moro, V. (2016). Spinal cord lesions shrink peripersonal space around the feet, passive mobilization of paraplegic limbs restores it. *Scientific Reports*, *6*(April), 24126. https://doi.org/10.1038/srep24126.

Scandola, M., Aglioti, S. M., Lazzeri, G., Avesani, R., Ionta, S., & Moro, V. (2020). Visuo-motor and interoceptive influences on peripersonal space representation following spinal cord injury. *Scientific Reports*, *10*(1), 1–16. https://doi.org/10.1038/s41598-020-62080-1.

Scandola, M., Aglioti, S. M., Pozeg, P., Avesani, R., & Moro, V. (2017). Motor imagery in spinal cord injured people is modulated by somatotopic coding, perspective taking, and post-lesional chronic pain. *Journal of Neuropsychology*, *11*(3), 305–326. https://doi.org/10.1111/jnp.12098.

Scandola, M., Dodoni, L., Lazzeri, G., Arcangeli, C. A., Avesani, R., Moro, V., et al. (2019). Neurocognitive benefits of physiotherapy for spinal cord injury. *Journal of Neurotrauma*. https://doi.org/10.1089/neu.2018.6123. neu.2018.6123.

Scandola, M., Tidoni, E., Avesani, R., Brunelli, G., Aglioti, S. M., & Moro, V. (2014). Rubber hand illusion induced by touching the face ipsilaterally to a deprived hand: Evidence for plastic "somatotopic" remapping in tetraplegics. *Frontiers in Human Neuroscience*, *8*, 404. https://doi.org/10.3389/fnhum.2014.00404.

Scandola, M., Togni, R., Tieri, G., Avesani, R., Brambilla, M., Aglioti, S. M., et al. (2019). Embodying their own wheelchair modifies extrapersonal space perception in people with spinal cord injury. *Experimental Brain Research*, *237*(10), 2621–2632. https://doi.org/10.1007/s00221-019-05618-8.

Schicke, T., Bauer, F., & Röder, B. (2009). Interactions of different body parts in peripersonal space: How vision of the foot influences tactile perception at the hand. *Experimental Brain Research*, *192*(4), 703–715. https://doi.org/10.1007/s00221-008-1587-2.

Schnall, S., Zadra, J. R., & Proffitt, D. R. (2010). Direct evidence for the economy of action: Glucose and the perception of geographical slant. *Perception*, *39*(4), 464–482. https://doi.org/10.1068/p6445.

Sedda, A., Ambrosini, E., Dirupo, G., Tonin, D., Valsecchi, L., Redaelli, T., et al. (2018). Affordances after spinal cord injury. *Journal of Neuropsychology*, 1–16. https://doi.org/10.1111/jnp.12151.

Sereno, M. I., & Huang, R.-S. (2006). A human parietal face area contains aligned head-centered visual and tactile maps. *Nature Neuroscience*, *9*(10), 1337–1343.

Serino, A., Noel, J.-P., Galli, G., Canzoneri, E., Marmaroli, P., Lissek, H., et al. (2015). Body part-centered and full body-centered peripersonal space representations. *Scientific Reports*, *5*(November), 18603. https://doi.org/10.1038/srep18603.

Sirigu, A., Grafman, J., Bressler, K., & Sunderland, T. (1991). Multiple representations contribute to body knowledge processing. Evidence from a case of autotopagnosia. *Brain: A Journal of Neurology*, *114*(Pt 1), 629–642. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/2004260.

Soman, T., Steeves, T. D. L., & Lang, A. E. (2009). Alien hand syndrome and dystonia in a pediatric patient. *Movement Disorders: Official Journal of the Movement Disorder Society*, *24*(10), 1557–1559. https://doi.org/10.1002/mds.22620.

Spaccasassi, C., Romano, D., & Maravita, A. (2019). Everything is worth when it is close to my body: How spatial proximity and stimulus valence affect visuo-tactile integration. *Acta Psychologica*, *192*(October 2018), 42–51. https://doi.org/10.1016/j.actpsy.2018.10.013.

Stone, K. D., Kandula, M., Keizer, A., & Dijkerman, H. C. (2017). Peripersonal space boundaries around the lower limbs. *Experimental Brain Research*. https://doi.org/10.1007/s00221-017-5115-0 (0123456789).

Tandon, S., Kambi, N., Lazar, L., Mohammed, H., & Jain, N. (2009). Large-scale expansion of the face representation in somatosensory areas of the lateral sulcus after spinal cord injuries in monkeys. *The Journal of Neuroscience*, *29*(38), 12009–12019. https://doi.org/10.1523/JNEUROSCI.2118-09.2009.

Tidoni, E., Fusco, G., Leonardis, D., Frisoli, A., Bergamasco, M., & Aglioti, S. M. (2015). Illusory movements induced by tendon vibration in right- and left-handed people. *Experimental Brain Research*, *233*(2), 375–383. https://doi.org/10.1007/s00221-014-4121-8.

Tidoni, E., Grisoni, L., Liuzza, M. T., & Aglioti, S. M. (2014). Rubber hand illusion highlights massive visual capture and sensorimotor face-hand remapping in a tetraplegic man. *Restorative Neurology and Neuroscience*, *32*(5), 611–622. https://doi.org/10.3233/RNN-130385.

Tinazzi, M., Fiorio, M., Bertolasi, L., & Aglioti, S. M. (2004). Timing of tactile and visuo-tactile events is impaired in patients with cervical dystonia. *Journal of Neurology*, *251*(1), 85–90. https://doi.org/10.1007/s00415-004-0282-x.

Wrigley, P. J., Press, S. R., Gustin, S. M., Macefield, V. G., Gandevia, S. C., Cousins, M. J., et al. (2009). Neuropathic pain and primary somatosensory cortex reorganization following spinal cord injury. *Pain*, *141*(1–2), 52–59. https://doi.org/10.1016/j.pain.2008.10.007.

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Chapter 4

Methods for treating pain and painful syndromes in spinal cord injury: Medications, therapies, interventions, and neuromodulation

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List of abbreviations

AB	able-bodied
CNS	central nervous system
DRGS	dorsal root ganglion stimulation
IL	interleukin
PAG	periaqueductal gray
PNS	peripheral nerve stimulation
PT	physical therapy
RVM	rostral ventromedial medulla
SNRI	serotonin-norepinephrine reuptake inhibitor
SCI	spinal cord injury
SCS	spinal cord stimulation
tDCS	transcranial direct current stimulation
TENS	transcutaneous electrical nerve stimulation

Introduction

Pain frequently limits activities, decreases quality of life, and leads to significant psychological impairment independent of other functional deficits after SCI (Craig et al., 2015; Elliott & Frank, 1996; Finnerup et al., 2016). In general, SCI pain is not well understood from the cellular, molecular, and even spinal cord pathway levels (Siddall, Taylor, & Cousins, 1997).

Sixty-five percent to eighty percent of individuals with SCI live with chronic pain, and nearly one third rate this pain as severe (Cardenas, Bryce, Shem, Richards, & Elhefni, 2004; Finnerup et al., 2016; Siddall, Mcclelland, Rutkowski, & Cousins, 2003). About half of all individuals with SCI suffer from pain so severe that it interferes with function and rehabilitation independent of deficits related to their SCI (Siddall & Loeser, 2001). It is generally believed that level of injury does not have an influence on the degree of post-SCI chronic pain. Penetrating injuries may be more likely to result in chronic pain (Richards, Stover, & Jaworski, 1990), and there is some evidence that incomplete lesions lead to more chronic pain than complete lesions (Beric, Dimitrijevic, & Lindblom, 1988; Davidoff, Roth, Guarracini, Sliwa, & Yarkony, 1987).

Pain after SCI can generally be divided into nociceptive, visceral, at-level neuropathic, and below-level neuropathic (Siddall et al., 1997). It is theorized that SCI pain may be fairly unique and related to relative serotonin, norepinephrine, and dopamine deficits due to loss of supraspinal inhibition (Boadas-Vaello et al., 2016; Bourne, Machado, & Nagel, 2014; Heinricher, Tavares, Leith, & Lumb, 2009). Additionally, there is a well-described inflammatory milieu that occurs after SCI and may contribute to an additional inflammatory basis of pain (Chambel, Tavares, & Cruz, 2020). Furthermore, post-SCI changes are noted in synaptic dendrites in individuals who experience significant pain, suggesting a dynamic neuroplastic component to pain (Benson, Reimer, & Tan, 2020). It is likely the unique combination central nervous system (CNS)

Diagnosis and Treatment of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822498-4.00004-X

TABLE 1 Classification of spinal cord injury-related pain.

Classification	Definition
Nociceptive somatic pain	Pain from skin, subcutaneous tissues, bones, joints, connective tissue, muscle, and tendons. Often occurs from overuse, age-related breakdown, or acute injury
Nociceptive visceral pain	Pain from organs and supporting structures. Often occurs with internal injury or infection
At-level neuropathic pain	Pain within 2 levels of the segment of the spinal cord that is injured. Often central or peripheral (radicular) pain that has typical neuropathic qualities
Below-level neuropathic pain	Pain below the level of the injured spinal cord segment related to disruption of the typical neural connections

Original table: These are the four generally agreed-upon classifications of pain as it related to the spinal cord-injured population.

TABLE 2 Characteristics of different pain types.

	Nociceptive pain		
	Somatic pain	**Visceral pain**	**Neuropathic pain**
Pain origin	Skin, subcutaneous tissues, mucous membrane, joints, connective tissue, muscle, and bone	Organs, organ capsule or covering, connecting and supporting structures	Central or peripheral nerves
Location	Localized	Generalized or diffuse	Radiating or specific
Quality	Pinprick, stabbing, sharp, sore, aching	Cramping, throbbing, squeezing, pressure, or sharp	Burning, "pins and needles," tingling, electrical, or lancinating
Mechanism of pain	A-delta fiber activity Located in the periphery	C Fiber activity Involving deeper innervation	Nondermatomal (central), or dermatomal (periphery)
Clinical examples	• Sickle cell crisis • Superficial burns and lacerations • Stomatitis • Intramuscular injections • Spasticity-mediated pain • Bone metastases	• Colic spasm • Appendicitis • Kidney stone • Chronic pancreatitis • IBS • Angina • Menstrual cramps	• Trigeminal neuralgia • Avulsion neuralgia • Posttraumatic neuralgia • Radiculopathy • Peripheral neuropathy • Phantom limb • Herpetic neuralgia

Original table: Differentiating pain generators is important in determining a treatment algorithm. These are the general characteristics of different types of pain.

changes after SCI creates a "pro-pain" state, and not surprisingly, SCI pain is often refractory to medical treatments (Siddall & Loeser, 2001; Widerström-Noga, 2017b).

The treatment of SCI-related pain often comes down to using a multimodal approach with medications, physical interventions, treatment of underlying conditions like spasticity, treatment of acquired overuse syndromes, and potentially the use of neuromodulation interventions. The typical categories of SCI-related pain can be reviewed in Tables 1 and 2.

Application to other areas of neuroscience

There is a growing emphasis on the connection between physical experiences and psychologic interpretation that goes beyond pain management. One particular area of interest has been the neural pathway between the amygdala, periaqueductal gray matter, and rostral ventromedial medulla (RVM). The amygdala stores emotional experiences. It is connected to the periaqueductal gray matter, which contains a high concentration of opioid, cannabinoid, and endorphin receptors (Basbaum & Fields, 1978). The RVM is not involved in generating an initial pain response but does help regulate the maintenance of neuropathic pain (Vera-Portocarrero et al., 2006). The ventral posteromedial nucleus plays a major role in central

sensitization, a condition of the nervous system that is associated with development and maintenance of chronic pain that is caused by increased excitability of cell membranes, synaptic efficiency, and reduced inhibition of nociceptive pathways (Latremoliere & Woolf, 2009). The plasticity of neurons that undergo central sensitization has been the target of newer therapies, though significant mechanistic gaps in our understanding remain (Latremoliere & Woolf, 2009).

These pathways significantly influence pain processing, decision-making, avoidant behavior, and personality expression (Yin et al., 2020) and are thought to modulate opioid-induced analgesia (Samineni et al., 2017). Additionally, recent studies showed modulating this pathway impacts the extent of depression-associated pain in mice under chronic stress (Yin et al., 2020). Physical activity, such as Tai Chi and cycling, has been shown to modulate this opioid pathway, thereby reducing overall pain levels and reducing levels of circulating inflammatory markers (Liu et al., 2019). This concept is fundamental to the use of physical activity to combat pain in patients with depression.

Main narrative text

Physical therapy and exercise

In the AB population, the clinical treatment of pain generally progresses from noninterventional PT-based treatment to more aggressive interventional treatments such as injections and ultimately surgery if there continues to be minimal to no improvement and depending on the pain generator (Patrick, Emanski, & Knaub, 2014; Will, Bury, & Miller, 2018). There are important similarities and differences in treating pain after SCI compared to the AB population. The most common subset of pain in the SCI population is neuropathic pain, either at or below the level of injury (E. Widerström-Noga, 2017a) and generally is not as responsive to PT (Akyuz & Kenis, 2014). However, many individuals have concomitant nociceptive pain (Widerström-Noga, 2017a) that may be more receptive to traditional PT interventions.

Eighty percent of those with SCI pain found PT and exercise helpful to a large extent, second only to cannabis and alcohol in terms of treatment effect (Heutink, Post, Wollaars, & Van Asbeck, 2011). Other studies in the United States (Widerström-Noga & Turk, 2003) noted half of respondents who participated in PT reported "considerable" pain reduction and a study from Sweden (Norrbrink Budh & Lundeberg, 2004) noted very high satisfaction rates despite overall low levels of PT utilization. Telehealth PT using high-dose scapular stabilizing and rotator cuff strengthening program in SCI individuals with signs of impingement syndrome was effective in reducing shoulder pain by more than 50% after 24 weeks (Van Straaten, Cloud, Morrow, Ludewig, & Zhao, 2014).

Exercise has been used as an augmentative strategy for many chronic conditions including osteoarthritis, peripheral vascular disease, low back pain, and fibromyalgia (Buckelew et al., 1998; Ettinger, 1997; Hayden et al., 2019; Lane, Ellis, Watson, & Leng, 2014) and there is a linear relationship between frequency, duration, and intensity of exercise and chronic pain (Landmark, Romundstad, Borchgrevink, Kaasa, & Dale, 2011). There are few high-quality studies assessing exercise and pain in the SCI population. Norrbrink, Lindberg, Wahman, and Bjerkefors (2012) noted significant improvement in pain scales and number of days per week with pain in nociceptive and neuropathic pain levels after training on a double-poling ergometer three times per week for 10 weeks at 70%–100% peak heart rate during intervals.

Recently, due to increased consensus on the benefits of exercise after SCI, an SCI exercise guideline was released (Ginis et al., 2018). The PAG, which has high concentrations of opioid and cannabinoid receptors sends projections to the RVM and both areas are activated by aerobic exercise (Chen et al., 2018; Sluka, O'Donnell, Danielson, & Rasmussen, 2013; Stagg et al., 2011). Additionally, there is an antiinflammatory cascade involving downregulation of pro-inflammatory Interleukin (IL)-1B and Tumor necrosis factor-alpha and upregulation of antiinflammatory IL-6 and IL-10 (Chen, Li, Chen, Li, & Hung, 2012; Jankord & Jemiolo, 2004). Some of the potential improvement in pain as it relates to exercise may be a partial function of improved psychological well-being (Latimer, Martin Ginis, Hicks, & McCartney, 2004).

Medications

Medications targeting neuropathic pain after SCI are the best studied. Pregabalin (Lyrica) and gabapentin (Neurontin) are antiepileptics and considered first-line medications in the treatment of neuropathic pain in patients with SCI injury (Loh et al., 2016). In 2012, pregabalin (Lyrica) became the first and remains the only Federal Drug Administration approved medication for neuropathic pain in patients with SCI in the United States. Its approval was based on two double blind placebo controlled randomized trials (Cardenas et al., 2013; Siddall et al., 2006). In the study by Siddall et al. (2006), 70 patients showed improvement in pain and sleep when compared to the control arm of 67 patients. Cardenas et al. (2013) studied 220 patients and exhibited improvement in pain 1 week into treatment. Mehta, McIntyre, Janzen, Loh,

and Teasell (2016) published an updated systematic review from their 2010 publication (Teasell et al., 2010) and cited 13, level-1 randomized controlled trials supporting both the anticonvulsants pregabalin and gabapentin.

Antidepressants are also utilized in treating neuropathic pain in SCI. Like pregabalin (Lyrica) and gabapentin (Neurontin), the tricyclic antidepressants amitriptyline (Elavil), nortriptyline (Pamelor), imipramine (Tofranil), and desipramine (Norpramin) are first-line medications. These medications have only demonstrated efficacy in patients with concomitant depression (Mehta et al., 2016). More recently venlafaxine revealed similar effects to amitriptyline in subjects with pain and depression (Richards et al., 2015). Other antidepressants, such as duloxetine, have not proven to be effective in patients with pain related to SCI (Vranken et al., 2011). Taken together, the serotonin-norepinephrine reuptake inhibitors (SNRIs) duloxetine (Cymbalta) and venlafaxine (Effexor) are considered second-line medications.

Despite common use in practice, opioids have inferior efficacy than previously mentioned medications. Tramadol, a synthetic opioid with SNRI properties, has some efficacy and is a third-line medication (Loh et al., 2016; Norrbrink & Lundeberg, 2009). As a sole agent, tramadol should be employed before other opioids such as oxycodone. Oxycodone is considered a fourth-line medication and has only level 4 evidence supporting its use (Loh et al., 2016; Mehta et al., 2016).

The effects of cannabinoids are mediated via the CB_1 and CB_2 G-protein receptors, where CB_1 is widely expressed in the CNS (Zajicek & Apostu, 2011). Interestingly, CB_1 is upregulated following SCI (Knerlich-Lukoschus et al., 2011). The analgesic properties of cannabinoids are mediated through the PAG (Heinricher et al., 2009; Raichlen, Foster, Gerdeman, Seillier, & Giuffrida, 2012). Indirect effects on opiate, serotonin, NMDA, and GABA receptors link endocannabinoids to other pain-related pathways (Hill, 2015; Raichlen et al., 2012; Woolridge et al., 2005). A metaanalysis of five randomized control trials suggests that inhaled cannabis may provide short-term relief for about 20% of patients with neuropathic pain (Andreae et al., 2015). Future studies are needed to assess long-term effects of cannabinoids on neuropathic pain, specifically as it relates to SCI, as well as the optimal route of administration (Inglet et al., 2020). The mechanism of action for medications typically used for the treatment of SCI-related pain can be reviewed in Table 3.

TABLE 3 Medication management of pain in spinal cord injury.

Class of medication	Targeted category of pain	Mechanism of action	Monitoring
Anticonvulsant • Gabapentin • Pregabalin	Neuropathic	GABA analog	- Peripheral edema - Weight gain - Dose adjustment for renal impairment
Antidepressant, tricyclic • Amitriptyline • Nortriptyline	Neuropathic	Inhibit reuptake of serotonin and/or norepinephrine at the presynaptic neuronal membrane pump	- Behavior changes, suicidality - Anticholinergic effects (e.g., constipation, urinary retention)
Antidepressant, serotonin/ norepinephrine reuptake inhibitor • Duloxetine • Venlafaxine	Neuropathic	Inhibits neuronal serotonin and norepinephrine reuptake; weakly inhibits dopamine reuptake	- Behavior changes, suicidality - Avoid use in those with hepatic impairment - Dose adjustment for renal impairment
Nonsteroidal antiinflammatory drug • Ibuprofen • Naproxen • Celecoxib* • Diclofenac • Indomethacin • Ketorolac • Meloxicam • Nabumetone	Nociceptive	Inhibits cyclooxygenase-1 and 2 (COX-1 and 2) enzymes, resulting in decreased formation of prostaglandin precursors; decrease proinflammatory cytokine levels	- Cardiovascular thrombotic events - Gastrointestinal bleeding, ulceration, and perforation - Avoid use in those with renal disease

TABLE 3 Medication management of pain in spinal cord injury—cont'd

Class of medication	Targeted category of pain	Mechanism of action	Monitoring
Nonopioid analgesic • Acetaminophen • Paracetamol	Nociceptive	Not fully known, analgesic effects likely due to activation of CNS descending serotonergic inhibitory pathways	- Hepatotoxicity
Opioid • Buprenorphine • Codeine • Fentanyl • Hydrocodone • Hydromorphone • Methadone • Nalbuphine • Oxycodone • Tramadol	Nociceptive	Binds to opiate receptors in the CNS, inhibiting ascending pain pathways	- CNS depression - Respiratory depression - Hypotension - Constipation
Cannabis	Nociceptive	Activation of the endogenous endocannabinoid system through CB1 and CB2 receptors	- Psychoactive properties - Dizziness - - Nausea, vomiting - Fatigue, drowsiness
Baclofen	Spasticity	GABA agonist at the GABA B receptor	- Lowers seizure threshold - Consider dose adjustment for renal impairment - CNS depression - Urinary retention
Dantrolene	Spasticity	Inhibits the release of calcium from sarcoplasmic reticulum	- Peripherally acting on skeletal muscle - Hepatotoxicity; monitor liver function closely
Alpha 2 adrenergic agonist • Clonidine • Tizanidine	Spasticity	Increasing presynaptic inhibition; reduces facilitation of spinal motor neurons	- Orthostatic hypotension - Drowsiness, dizziness - Bradycardia - Monitor liver function
Benzodiazepine • Diazepam	Spasticity	Facilitates GABA effects on the GABA A receptor	- Caution with concomitant use of opioids - CNS depression - Use with caution in those with renal and hepatic impairment and respiratory disease

Original table: Outline of the mechanism of action of various types of pain medications commonly used for SCI pain.

"Typical" nociceptive pain interventions

SCI individuals, especially those who use a wheelchair to traverse the community are predisposed to upper-body overuse injuries (Requejo et al., 2008) and almost three fourth of individuals with paraplegia have early osteoarthritis of the shoulders (Lal, 1998). Interestingly, shoulder pain and decreased passive range of motion is also present in the acute phase of SCI (Finley et al., 2020). Peripheral nerve stimulation (PNS) is a well-established treatment for poststroke shoulder pain (Wilson et al., 2018) but has not frequently been used for treating SCI-related pain. There is one case report showing improvement in shoulder pain after SCI with PNS use (Mehech, Mejia, Nemunaitis, Chae, & Wilson, 2018).

While literature is lacking with regard to specific interventions for non-SCI-related nociceptive pain, it should be treated just as it would be in the able-bodied population. For instance, tendinopathy is a common condition in the able-bodied population and also has a high prevalence in the SCI population due to overuse, as noted above. Traditionally tendinopathy has been treated with physical therapy, nonsteroidal antiinflammatory medications, and corticosteroid injections which can address the inflammatory component but not the degenerative component of the disorder. Orthobiologics such as platelet-rich plasma (PRP), autologous conditioned serum and stem cells have shown for various degrees of promise (Paoloni, DeVos, Hamilton, Murrell, & Orchard, 2011; Roberts & Rosenbaum, 2012; Wehling et al., 2007) should be considered in the SCI population as they would be in the AB population, if appropriate.

At least 65% of patients with chronic SCI have symptoms of spasticity (Adams & Hicks, 2005) and pain frequently coincides with spasticity (Finnerup, 2017; Holtz, Lipson, Noonan, Kwon, & Mills, 2017). In general, the pain associated with spasticity is felt to be nociceptive muscle pain, similar to that of tetanic contractions. The incidence of spasticity is correlated to incomplete injuries and higher level of injury (Holtz et al., 2017; Skold, Levi, & Seiger, 1999).

Oral antispasticity medications act systemically and can be divided into 3 categories based upon mechanism of action: (1) GABA receptor agonists (e.g., baclofen and diazepam), (2) alpha-2 receptor agonists (e.g., tizanidine), and (3) peripheral acting decouplers of excitation-contraction at the neuromuscular level (e.g., dantrolene) (Burchiel & K Hsu, 2001; Gracies, Nance, Elovic, McGuire, & Simpson, 1997; Kita & Goodkin, 2000; Rode, Maupas, Luaute, Courtois-Jacquin, & Boisson, 2003).

Injection of local chemodenervation agents results in impairment of the nerve (Lui, Sarai, & Mills, 2015). This technique minimizes systemic side effects associated with oral antispasticity medications and is the preferred for treating focal spasticity (Kirshblum, 1999; Lui et al., 2015). The chemodenervation agents most commonly used are phenol, ethanol, local anesthetics, and botulinum toxin (Lui et al., 2015). Botulinum toxin is the most widely used chemodenervation agent and similarly has a temporary effect. Phenol and ethanol exert a semi-permanent effect (Adams & Hicks, 2005; Kirshblum, 1999; Lui et al., 2015).

If oral drug treatment is ineffective in controlling spasticity or is otherwise not tolerated, consideration should be given to intrathecal delivery of baclofen (Burchiel & K Hsu, 2001; Gracies et al., 1997; Kita & Goodkin, 2000; Korenkov, Niendorf, Darwish, Glaeser, & Gaab, 2002). Bypassing the blood-spinal cord barrier allows as much as four times the concentration and lower dose of baclofen to be delivered to the spinal cord relative to an oral dose (Burchiel & K Hsu, 2001; Kita & Goodkin, 2000; Korenkov et al., 2002). Catheter and pump maintenance, appropriate dosage of baclofen, timely refill of the pump, and avoidance of abrupt interruption of baclofen administration are paramount to intrathecal pump management (Burchiel & K Hsu, 2001; Kita & Goodkin, 2000).

Surgery, typically in the form of rhizotomy or tendon lengthening, may be performed to improving function or correcting a deformity related to spasticity in refractory cases (Adams & Hicks, 2005; Ghai, Garg, Hooda, & Gupta, 2013).

Neuromodulation

The presence of pain induces top-down modulation where the various cerebral regions act in unison to upregulate or downregulate pain signals (Martins & Tavares, 2017), mainly through the PAG and RVM (Heinricher et al., 2009). Serotonin, norepinephrine, and dopamine are released at the supraspinal and spinal levels to modulate pain levels and there is a relative deficiency in these peptides after SCI (Bourne et al., 2014).

There is also evidence for dendritic spine remodeling at the level of the spinal cord. After induction of neuropathic pain there is an adaptive and time-dependent response at the level of dorsal horns where neurons develop increased dendritic spine density, redistribute spines closer to the cell body, and increase the spine head surface area, which in turn alters excitatory potential propagation (Benson, Reimer, & Tan, 2020). Animal studies looking at dendritic spines pre- and postneuropathic injury note significant structural anomalies in the steady state fluctuations of spines (Benson et al., 2020). Taken in total, there is accumulating evidence that "pain memory" is at least in part a function carried out by the spinal cord itself and could partly explain the treatment resistant nature of neuropathic pain after SCI (Benson, Fenrich, et al., 2020; Benson, Reimer, et al., 2020; Ji, Kohno, Moore, & Woolf, 2003; Tan & Waxman, 2012; Tan, 2015). Disruption of these intrinsic neuromodulation pathways is postulated to be a unique factor in pain as a side effect of SCI and a differentiator of other peripheral sources of neuropathic pain (Benson, Reimer, et al., 2020; Bourne et al., 2014; Chambel et al., 2020; Heinricher et al., 2009).

Many have hypothesized on medications and interventions that may be of clinical utility given the aforementioned intrinsic neuromodulatory deficits present after SCI. The International Neuromodulation Society defines therapeutic neuromodulation as "the alteration of nerve activity through targeted delivery of a stimulus, such as electrical stimulation or chemical agents, to specific neurological sites in the body." Examples of neuromodulation that have been applied or could potentially be applied in the setting of SCI include SCS, dorsal root ganglion stimulation (DRGS), PNS, and transcranial direct current stimulation (tDCS).

Spinal cord stimulation in SCI

Spinal cord stimulation (SCS) is the most common neuromodulatory intervention in the treatment of pain in patients with SCI. It was first trialed in patients with SCI almost 50 years ago. Previous studies have hypothesized multiple mechanism of action such as gait control theory, dorsal column retrograde stimulation, modulation of centralized pain processing, and even action at the spinal cord level with the alteration of neurotransmitter release (Arle, Carlson, Mei, Iftimia, & Shils, 2014). To date there have been no randomized trials examining efficacy of SCS in patients with SCI. A review of 27 studies cited an average of 30%–40% of pain relief (Lagauche, Facione, Albert, & Fattal, 2009) using various forms of SCS. Traditional SCS utilizes tonic 40–60 Hz stimulation placed on the epidural surface of the dorsal column, often resulting in paresthesia in the distribution that overlaps with the distribution of pain (Chakravarthy, Richter, Christo, Williams, & Guan, 2018). More recently, high-frequency SCS has been applied at low amplitudes resulting in paresthesia free subthreshold sensory activation (Chakravarthy et al., 2018) and has shown promising results for the treatment of refractory neuropathic pain in non-SCI individuals (Kapural et al., 2016). Interestingly, multiple studies looking at SCS have noted concomitant decreased spasticity (Aduddell, Romman, Burlison, & Doulatram, 2015; Dombovy-Johnson, Hunt, Morrow, Lamer, & Pittelkow, 2020; Harandi & Kapural, 2018; Li, Quidgley-Nevares, & Walker, 2011) and pain medication use (Aduddell et al., 2015; Delille, Ahmad, Baeza-Dager, & Mena, 2012; Dombovy-Johnson et al., 2020; Harandi & Kapural, 2018; Li et al., 2011). The potential for multimodal treatment is particularly interesting in this population. Both reviews suggest individuals with incomplete tetraplegia or paraplegia may benefit more than complete injuries (Dombovy-Johnson et al., 2020; Lagauche et al., 2009).

Other forms of neuromodulation

Other forms of neuromodulation for pain are less common in SCI. tDCS over the motor cortex has shown modest decreases in pain (Ngernyam et al., 2015; Soler et al., 2010). However, both studies had small sample sizes and a study by Wrigley et al. (2013) found no improvement in longstanding neuropathic pain after SCI with the use of tDCS suggesting the effect is either less robust or potentially more beneficial in the acute to subacute phase. PNS, as noted previously, has been described as a treatment for post-SCI shoulder pain from chronic overuse injuries.

DRGS is a similar in nature to SCS except the leads are placed on the dorsal root ganglion instead of the epidural space. Stimulation of the DRG is thought to still work in a downstream effect on the spinal cord but has been particularly helpful with the treatment of regional neuropathic pain, such as complex regional pain syndrome (Harrison, Epton, Bojanic, Green, & FitzGerald, 2018). However, there is a case report of bilateral L2 DRGS improving spasticity and low back pain after SCI (Soloukey et al., 2020).

Mini-dictionary of terms

Nociceptive pain: Pain from a noxious or potentially harmful stimulus. Nociceptive pain is well localized and corresponds to damage to skin, joints, muscle, bone, or connective tissue. It is typically described as sharp, achy, throbbing, etc.

Visceral pain: Pain from internal organs. Visceral pain is generally poorly localized and described as deep, squeezing, pressure, or aching.

At-level neuropathic pain: Pain in a dermatomal distribution that reflects damage to the spinal cord at the level of the individual's spinal cord injury (SCI). Occasionally, this can feel "band-like" or "squeezing," but often feels like "numbness," "pins-and-needles," or "tingling."

Below-level neuropathic pain: Pain that corresponds to damaged nerves in the spinal cord that typically provide sensation to an area below the level of the individual's SCI. Below-level neuropathic pain is typically described as "numbness," "pins-and-needles," or "tingling."

Neuromodulation: the alteration of nerve activity through targeted delivery of a stimulus, such as electrical stimulation or chemical agents, to specific neurological sites in the body.

Spinal cord stimulation (SCS): Implantable device where leads are placed in the epidural space overlying the dorsal columns. SCS devices send mild pulses of electricity at various frequencies depending on the device and settings that help dampen neuropathic pain.

Dorsal root ganglion stimulator (DRGS): Similar to an SCS but is instead implanted with the leads on the dorsal root ganglion. In general, DRGS is favored for regional pain.

Peripheral nerve stimulator (PNS): A permanent or temporary implantable lead that is placed in close proximity to a peripheral nerve. PNS devices stimulate mixed motor and sensory nerves at submaximal intensity with the goal of decreasing pain that is related to irritation, damage, or improper function of a single nerve.

Transcranial direct current stimulation (tDCS): constant, low direct current electrical stimulus that is applied to specific cortical areas through surface scalp electrodes.

Supraspinal pathways: Ascending and descending pathways that relay information to, from, and through the spinal cord. Disruption of different supraspinal pathways plays a critical role in many aspects of SCI, including pain.

Key facts of pain after SCI

- Sixty-five percent to eighty percent of individuals with SCI live with chronic pain.
- One third of individuals with chronic pain after SCI rate this pain as severe and more than half note that pain interferes with their daily function independent of their other SCI deficits such as paralysis.
- Level of injury does not seem to influence the degree of associated pain, although there is some evidence that incomplete spinal cord injuries are more painful.
- Up to 80% of those with pain and SCI find PT to be helpful.
- Pregabalin is the only FDA-approved treatment for neuropathic SCI pain, although antiepileptic and antidepressant medications are commonly used and supported by literature.
- Neuromodulation is currently lacking evidence, but small studies are promising and a future direction of additional research.

Summary points

- The PAG is a central pain relay center that modulates pain signals to the RVM and spinal cord effectively upregulating and downregulating pain signals.
- SCI disrupts this relay and leads to a relative deficiency in supraspinal inhibition and deficiency in spinal levels of serotonin, norepinephrine, and dopamine.
- Neuropathic pain after SCI is commonly treated with membrane-stabilizing agents.
- Nociceptive pain after SCI should be treated like nociceptive pain in the AB population.
- Neuromodulation is an interesting treatment possibility, although further research is needed.

References

Adams, M. M., & Hicks, A. L. (2005). Spasticity after spinal cord injury. *Spinal Cord*, *43*(10), 577–586. https://doi.org/10.1038/sj.sc.3101757.

Aduddell, B., Romman, A., Burlison, S., & Doulatram, G. (2015). Use of spinal cord stimulator (SCS) in a case of refractory neuropathic pain due to syringomelia. In *Regional anesthesia and pain medicine conference: 14th annual pain medicine meeting of the American Society of Regional Anesth Pain Medicine, ASRA, 41(2).*

Akyuz, G., & Kenis, O. (2014, March). Physical therapy modalities and rehabilitation techniques in the management of neuropathic pain. *American Journal of Physical Medicine and Rehabilitation*. https://doi.org/10.1097/PHM.0000000000000037.

Andreae, M. H., Carter, G. M., Shaparin, N., Suslov, K., Ellis, R. J., Ware, M. A., … Sacks, H. S. (2015). Inhaled Cannabis for chronic neuropathic pain: A Meta-analysis of individual patient data. *The Journal of Pain*, *16*(12), 1221–1232. https://doi.org/10.1016/j.jpain.2015.07.009.

Arle, J. E., Carlson, K. W., Mei, L., Iftimia, N., & Shils, J. L. (2014). Mechanism of dorsal column stimulation to treat neuropathic but not nociceptive pain: Analysis with a computational model. *Neuromodulation: Technology at the Neural Interface*, *17*(7), 642–655. https://doi.org/10.1111/ner.12178.

Basbaum, A. I., & Fields, H. L. (1978). Endogenous pain control mechanisms: Review and hypothesis. *Annals of Neurology*, *4*(5). https://doi.org/10.1002/ana.410040511.

Benson, C. A., Fenrich, K. K., Olson, K. L., Patwa, S., Bangalore, L., Waxman, S. G., & Tan, A. M. (2020). Dendritic spine dynamics after peripheral nerve injury: An intravital structural study. *Journal of Neuroscience*, *40*(22). https://doi.org/10.1523/JNEUROSCI.2858-19.2020.

Benson, C. A., Reimer, M. L., & Tan, A. M. (2020). Dendritic spines in the spinal cord: Live action pain. *Neuroscience Insights*. https://doi.org/10.1177/2633105520951164. SAGE Publications Ltd.

Beric, A., Dimitrijevic, M. R., & Lindblom, U. (1988). Clinical section central dysesthesia syndrome in spinal cord injury patients. *Pain*, *34*, 109–116.

Boadas-Vaello, P., Castany, S., Homs, J., Álvarez-Pérez, B., Deulofeu, M., & Verdú, E. (2016, May 1). Neuroplasticity of ascending and descending pathways after somatosensory system injury: Reviewing knowledge to identify neuropathic pain therapeutic targets. *Spinal Cord*. https://doi.org/10.1038/sc.2015.225. Nature Publishing Group.

Bourne, S., Machado, A. G., & Nagel, S. J. (2014, October 1). Basic anatomy and physiology of pain pathways. *Neurosurgery Clinics of North America*. https://doi.org/10.1016/j.nec.2014.06.001. W.B. Saunders.

Buckelew, S. P., Conway, R., Parker, J., Deuser, W. E., Read, J., Witty, T. E., … Kay, D. R. (1998). Biofeedback/relaxation training and exercise interventions for fibromyalgia: A prospective trial. *Arthritis and Rheumatism*, *11*(3), 196–209. https://doi.org/10.1002/art.1790110307.

Burchiel, K. J., & K Hsu, F. P. (2001, December). Pain and spasticity after spinal cord injury: Mechanisms and treatment. *Spine*. https://doi.org/10.1097/00007632-200112151-00024.

Cardenas, D. D., Bryce, T. N., Shem, K., Richards, J. S., & Elhefni, H. (2004). Gender and minority differences in the pain experience of people with spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *85*(11), 1774–1781. https://doi.org/10.1016/j.apmr.2004.04.027.

Cardenas, D. D., Nieshoff, E. C., Suda, K., Goto, S. I., Sanin, L., Kaneko, T., … Knapp, L. E. (2013). A randomized trial of pregabalin in patients with neuropathic pain due to spinal cord injury. *Neurology*, *80*(6), 533–539. https://doi.org/10.1212/WNL.0b013e318281546b.

Chakravarthy, K., Richter, H., Christo, P. J., Williams, K., & Guan, Y. (2018). Spinal cord stimulation for treating chronic pain: Reviewing preclinical and clinical data on paresthesia-free high-frequency therapy. *Neuromodulation*, *21*(1), 10–18. https://doi.org/10.1111/ner.12721.

Chambel, S. S., Tavares, I., & Cruz, C. D. (2020, July). Chronic pain after spinal cord injury: Is there a role for neuron-immune dysregulation? *Frontiers in Physiology*. https://doi.org/10.3389/fphys.2020.00748. Frontiers Media S.A.

Chen, Y. H., Lee, H. J., Lee, M. T., Wu, Y. T., Lee, Y. H., Hwang, L. L., … Chiou, L. C. (2018). Median nerve stimulation induces analgesia via orexininitiated endocannabinoid disinhibition in the periaqueductal gray. *Proceedings of the National Academy of Sciences of the United States of America*, *115*(45), E10720–E10729. https://doi.org/10.1073/pnas.1807991115.

Chen, Y. W., Li, Y. T., Chen, Y. C., Li, Z. Y., & Hung, C. H. (2012). Exercise training attenuates neuropathic pain and cytokine expression after chronic constriction injury of rat sciatic nerve. *Anesthesia and Analgesia*, *114*(6), 1330–1337. https://doi.org/10.1213/ANE.0b013e31824c4ed4.

Craig, A., Nicholson Perry, K., Guest, R., Tran, Y., Dezarnaulds, A., Hales, A., … Middleton, J. (2015). Prospective study of the occurrence of psychological disorders and comorbidities after spinal cord injury archives of physical medicine and rehabilitation. *Archives of Physical Medicine and Rehabilitation*, *96*, 1426–1460. https://doi.org/10.1016/j.apmr.2015.02.027.

Davidoff, G., Roth, E., Guarracini, M., Sliwa, J., & Yarkony, G. (1987). Function-limiting dysesthetic pain syndrome among traumatic spinal cord injury patients: A cross-sectional study. *Pain*, *29*, 39–48.

Delille, M., Ahmad, U. F., Baeza-Dager, J. M., & Mena, J. (2012). Neuropathic pain improvement in Incomplete Spinal cord injury after spinal cord stimulator trial: A case series. *PM & R: The Journal of Injury, Function, and Rehabilitation*, *1*, S325–S326.

Dombovy-Johnson, M. L., Hunt, C. L., Morrow, M. M., Lamer, T. J., & Pittelkow, T. P. (2020). Current evidence lacking to guide clinical practice for spinal cord stimulation in the treatment of neuropathic pain in spinal cord injury: A review of the literature and a proposal for future study. *Pain Practice*, *20*(3), 325–335. https://doi.org/10.1111/papr.12855.

Elliott, T. R., & Frank, R. G. (1996). Depression following spinal cord injury. *Archives of Physical Medicine and Rehabilitation*. https://doi.org/10.1016/S0003-9993(96)90263-4. W.B. Saunders.

Ettinger, W. H. (1997). A randomized trial comparing aerobic exercise and resistance exercise with a health education program in older adults with knee osteoarthritis. *JAMA*, *277*(1), 25. https://doi.org/10.1001/jama.1997.03540250033028.

Finley, M., Euiler, E., Trojian, T., Gracely, E., Schmidt-Read, M., Frye, S. K., … Geigle, P. R. (2020). Shoulder impairment and pain of individuals with newly acquired spinal cord injury compared to uninjured peers. *Spinal Cord Series and Cases*, *6*(1). https://doi.org/10.1038/s41394-020-0318-1.

Finnerup, N. B. (2017, December 1). Neuropathic pain and spasticity: Intricate consequences of spinal cord injury. *Spinal Cord*. https://doi.org/10.1038/sc.2017.70. Nature Publishing Group.

Finnerup, N. B., Jensen, M. P., Norrbrink, C., Trok, K., Johannesen, I. L., Jensen, T. S., & Werhagen, L. (2016). A prospective study of pain and psychological functioning following traumatic spinal cord injury. *Spinal Cord*, *54*(10), 816–821. https://doi.org/10.1038/sc.2015.236.

Ghai, A., Garg, N., Hooda, S., & Gupta, T. (2013). Spasticity—Pathogenesis, prevention and treatment strategies. *Saudi Journal of Anaesthesia*. https://doi.org/10.4103/1658-354X.121087.

Ginis, K. A. M., Van Der Scheer, J. W., Latimer-Cheung, A. E., Barrow, A., Bourne, C., Carruthers, P., … Goosey-Tolfrey, V. L. (2018). Evidence-based scientific exercise guidelines for adults with spinal cord injury: An update and a new guideline. *Spinal Cord*, *56*, 308–321. https://doi.org/10.1038/s41393-017-0017-3.

Gracies, J. M., Nance, P., Elovic, E., McGuire, J., & Simpson, D. M. (1997). Traditional pharmacological treatments for spasticity. Part II: General and regional treatments. *Muscle & Nerve Supplement*, *6*, S92–120.

Harandi, S., & Kapural, L. (2018). Four-extremity neurostimulation using two cervical octapolar leads and high frequency of 10 kHz. *Pain Practice*, *18*(2), 269–272. https://doi.org/10.1111/papr.12593.

Harrison, C., Epton, S., Bojanic, S., Green, A. L., & FitzGerald, J. J. (2018, April 1). The efficacy and safety of dorsal root ganglion stimulation as a treatment for neuropathic Pain: A literature review. *Neuromodulation*. https://doi.org/10.1111/ner.12685. Blackwell Publishing Inc.

Hayden, J. A., Wilson, M. N., Stewart, S., Cartwright, J. L., Smith, A. O., Riley, R. D., … Yeung, E. W. (2019). Exercise treatment effect modifiers in persistent low back pain: An individual participant data meta-analysis of 3514 participants from 27 randomised controlled trials. *British Journal of Sports Medicine*. https://doi.org/10.1136/bjsports-2019-101205. BMJ Publishing Group.

Heinricher, M. M., Tavares, I., Leith, J. L., & Lumb, B. M. (2009, April). Descending control of nociception: Specificity, recruitment and plasticity. *Brain Research Reviews*. https://doi.org/10.1016/j.brainresrev.2008.12.009. NIH Public Access.

Heutink, M., Post, M. W. M., Wollaars, M. M., & Van Asbeck, F. W. A. (2011). Chronic spinal cord injury pain: Pharmacological and non-pharmacological treatments and treatment effectiveness. *Disability and Rehabilitation*, *33*(5), 433–440. https://doi.org/10.3109/09638288.2010.498557.

Hill, K. P. (2015). Medical marijuana for treatment of chronic pain and other medical and psychiatric problems: A clinical review. *JAMA: The Journal of the American Medical Association*. https://doi.org/10.1001/jama.2015.6199. Article, United States: American Medical Association.

Holtz, K. A., Lipson, R., Noonan, V. K., Kwon, B. K., & Mills, P. B. (2017). Prevalence and effect of problematic spasticity after traumatic spinal cord injury. In *Vol. 98. Archives of physical medicine and rehabilitation* (pp. 1132–1138). United States: Elsevier BV. Article https://doi.org/10.1016/j.apmr.2016.09.124.

Inglet, S., Winter, B., Yost, S. E., Entringer, S., Lian, A., Biksacky, M., … Mortensen, W. (2020, November 2). Clinical data for the use of Cannabis-based treatments: A comprehensive review of the literature. *Annals of Pharmacotherapy*. https://doi.org/10.1177/1060028020930189.

Jankord, R., & Jemiolo, B. (2004). Influence of physical activity on serum IL-6 and IL-10 levels in healthy older men. *Medicine and Science in Sports and Exercise*, *36*(6), 960–964. https://doi.org/10.1249/01.MSS.0000128186.09416.18.

Ji, R. R., Kohno, T., Moore, K. A., & Woolf, C. J. (2003). Central sensitization and LTP: Do pain and memory share similar mechanisms? *Trends in Neurosciences*. https://doi.org/10.1016/j.tins.2003.09.017. Elsevier Ltd.

Kapural, L., Yu, C., Doust, M. W., Gliner, B. E., Vallejo, R., Sitzman, B. T., … Burgher, A. H. (2016). Comparison of 10-kHz high-frequency and traditional low-frequency spinal cord stimulation for the treatment of chronic Back and leg pain: 24-month results from a multicenter, randomized, controlled pivotal trial. *Neurosurgery*, *79*(5), 667–676. https://doi.org/10.1227/NEU.0000000000001418.

Kirshblum, S. (1999). Treatment alternatives for spinal cord injury related spasticity. *Journal of Spinal Cord Medicine*, *22*(3), 199–217. https://doi.org/10.1080/10790268.1999.11719570.

Kita, M., & Goodkin, D. E. (2000, March). Drugs used to treat spasticity. *Drugs*. https://doi.org/10.2165/00003495-200059030-00006.

Knerlich-Lukoschus, F., Noack, M., von der Ropp-Brenner, B., Lucius, R., Mehdorn, H. M., & Held-Feindt, J. (2011). Spinal cord injuries induce changes in CB_1 cannabinoid receptor and C-C chemokine expression in brain areas underlying circuitry of chronic pain conditions. *Journal of Neurotrauma*, *28*(4), 619–634. https://doi.org/10.1089/neu.2010.1652.

Korenkov, A. I., Niendorf, W. R., Darwish, N., Glaeser, E., & Gaab, M. R. (2002). Continuous intrathecal infusion of baclofen in patients with spasticity caused by spinal cord injuries. *Neurosurgical Review*, *25*(4), 228–230. https://doi.org/10.1007/s10143-002-0221-1.

Lagauche, D., Facione, J., Albert, T., & Fattal, C. (2009, March). The chronic neuropathic pain of spinal cord injury: Which efficiency of neuropathics stimulations? *Annals of Physical and Rehabilitation Medicine*. https://doi.org/10.1016/j.rehab.2008.12.010.

Lal, S. (1998). Premature degenerative shoulder changes in spinal cord injury patients. *Spinal Cord*, *36*(3), 186–189. https://doi.org/10.1038/sj.sc.3100608.

Landmark, T., Romundstad, P., Borchgrevink, P. C., Kaasa, S., & Dale, O. (2011). Associations between recreational exercise and chronic pain in the general population: Evidence from the HUNT 3 study. *Pain*, *152*(10), 2241–2247. https://doi.org/10.1016/j.pain.2011.04.029.

Lane, R., Ellis, B., Watson, L., & Leng, G. C. (2014, July). Exercise for intermittent claudication. *Cochrane Database of Systematic Reviews*. https://doi.org/10.1002/14651858.CD000990.pub3. John Wiley and Sons Ltd.

Latimer, A. E., Martin Ginis, K. A., Hicks, A. L., & McCartney, N. (2004). An examination of the mechanisms of exercise-induced change in psychological well-being among people with spinal cord injury. *Journal of Rehabilitation Research and Development*, *41*(5), 643–651. https://doi.org/10.1682/JRRD.2003.04.0043.

Latremoliere, A., & Woolf, C. J. (2009). Central sensitization: A generator of pain hypersensitivity by central neural plasticity. *The Journal of Pain*, *10*(9). https://doi.org/10.1016/j.jpain.2009.06.012.

Li, Q., Quidgley-Nevares, A., & Walker, R. (2011). Utility of spinal cord stimulator to modulate lower Limb spasticity and pain in a patient with spinal cord injury: A case report. *PM & R: The Journal of Injury, Function, and Rehabilitation*, *1*, S288–S289.

Liu, J., Chen, L., Chen, X., Hu, K., Tu, Y., Lin, M., … Kong, J. (2019). Modulatory effects of different exercise modalities on the functional connectivity of the periaqueductal grey and ventral tegmental area in patients with knee osteoarthritis: A randomised multimodal magnetic resonance imaging study. *British Journal of Anaesthesia*, *123*(4). https://doi.org/10.1016/j.bja.2019.06.017.

Loh, E., Guy, S. D., Mehta, S., Moulin, D. E., Bryce, T. N., Middleton, J. W., … Wolfe, D. (2016). The Can Pain SCI clinical practice guidelines for rehabilitation management of neuropathic Pain after spinal cord: Introduction, methodology and recommendation overview. *Spinal Cord*, *54*(S1), S1–S6. https://doi.org/10.1038/sc.2016.88.

Lui, J., Sarai, M., & Mills, P. B. (2015). Chemodenervation for treatment of limb spasticity following spinal cord injury: A systematic review. *Spinal Cord*, *53*(4), 252–264. https://doi.org/10.1038/sc.2014.241.

Martins, I., & Tavares, I. (2017). Reticular formation and pain: The past and the future. *Frontiers in Neuroanatomy*, *11*, 1–14. https://doi.org/10.3389/fnana.2017.00051.

Mehech, D., Mejia, M., Nemunaitis, G. A., Chae, J., & Wilson, R. D. (2018). Percutaneous peripheral nerve stimulation for treatment of shoulder pain after spinal cord injury: A case report. *Journal of Spinal Cord Medicine*, *41*(1), 119–124. https://doi.org/10.1080/10790268.2017.1293329.

Mehta, S., McIntyre, A., Janzen, S., Loh, E., & Teasell, R. (2016). Systematic review of pharmacologic treatments of pain after spinal cord injury: An update. *Archives of Physical Medicine and Rehabilitation*, *97*(8), 1381–1391. e1 https://doi.org/10.1016/j.apmr.2015.12.023.

Ngernyam, N., Jensen, M. P., Arayawichanon, P., Auvichayapat, N., Tiamkao, S., Janjarasjitt, S., … Auvichayapat, P. (2015). The effects of transcranial direct current stimulation in patients with neuropathic pain from spinal cord injury. *Clinical Neurophysiology*, *126*(2), 382–390. https://doi.org/10.1016/j.clinph.2014.05.034.

Norrbrink Budh, C., & Lundeberg, T. (2004). Non-pharmacological pain-relieving therapies in individuals with spinal cord injury: A patient perspective. *Complementary Therapies in Medicine*, *12*(4), 189–197. https://doi.org/10.1016/j.ctim.2004.10.003.

Norrbrink, C., Lindberg, T., Wahman, K., & Bjerkefors, A. (2012). Effects of an exercise programme on musculoskeletal and neuropathic pain after spinal cord injury—Results from a seated double-poling ergometer study. *Spinal Cord*, *50*(6), 457–461. https://doi.org/10.1038/sc.2011.160.

Norrbrink, C., & Lundeberg, T. (2009). Tramadol in neuropathic pain after spinal cord injury a randomized, double-blind, placebo-controlled trial. *Clinical Journal of Pain*, *25*(3), 177–184. https://doi.org/10.1097/AJP.0b013e31818a744d.

Paoloni, J., DeVos, R. J., Hamilton, B., Murrell, G. A. C., & Orchard, J. (2011). Platelet-rich plasma treatment for ligament and tendon injuries. *Clinical Journal of Sport Medicine*, *211*. 37–35.

Patrick, N., Emanski, E., & Knaub, M. A. (2014). Acute and chronic low back pain. *Medical Clinics of North America*. https://doi.org/10.1016/j.mcna.2014.03.005. W.B. Saunders.

Raichlen, D. A., Foster, A. D., Gerdeman, G. L., Seillier, A., & Giuffrida, A. (2012). Wired to run: Exercise-induced endocannabinoid signaling in humans and cursorial mammals with implications for the "runner's high". *Journal of Experimental Biology*, *215*(8), 1331–1336. https://doi.org/10.1242/jeb.063677.

Requejo, P. S., Mulroy, S. J., Haubert, L. L., Newsam, C. J., Gronley, J. A. K., & Perry, J. (2008, April). Evidence-based strategies to preserve shoulder function in manual wheelchair users with spinal cord injury. *Topics in Spinal Cord Injury Rehabilitation*. https://doi.org/10.1310/sci1304-86.

Richards, J. S., Bombardier, C. H., Wilson, C. S., Chiodo, A. E., Brooks, L., Tate, D. G., … Fann, J. R. (2015). Efficacy of venlafaxine XR for the treatment of pain in patients with spinal cord injury and major depression: A randomized, controlled trial. *Archives of Physical Medicine and Rehabilitation*, *96* (4), 680–689. https://doi.org/10.1016/j.apmr.2014.11.024.

Richards, J. S., Stover, S. L., & Jaworski, T. (1990). Effect of bullet removal on subsequent pain in persons with spinal cord injury secondary to gunshot wound. *Journal of Neurosurgery*, *73*(3), 401–404. https://doi.org/10.3171/jns.1990.73.3.0401.

Roberts, T. T., & Rosenbaum, A. J. (2012). Bone grafts, bone substitutes and orthobiologics: The bridge between basic science and clinical advancements in fracture healing. *Oranogenesis*, *8*(4), 114–124.

Rode, G., Maupas, E., Luaute, J., Courtois-Jacquin, S., & Boisson, D. (2003). Medical treatment of spasticity. *Neuro-Chirurgie*, *49*(2–3 Pt 2), 247–255.

Samineni, V. K., Grajales-Reyes, J. G., Copits, B. A., O'Brien, D. E., Trigg, S. L., Gomez, A. M., … Gereau, R. W. (2017). Divergent modulation of nociception by glutamatergic and GABAergic neuronal subpopulations in the periaqueductal gray. *eNeuro*, *4*(2). https://doi.org/10.1523/ENEURO.0129-16.2017.

Siddall, P. J., Cousins, M. J., Otte, A., Griesing, T., Chambers, R., & Murphy, T. K. (2006). Pregabalin in central neuropathic pain associated with spinal cord injury: A placebo-controlled trial. *Neurology*, *67*(10), 1792–1800. https://doi.org/10.1212/01.wnl.0000244422.45278.ff.

Siddall, P. J., & Loeser, J. D. (2001). Pain following spinal cord injury. *Spinal Cord*, *39*(2), 63–73. https://doi.org/10.1038/sj.sc.3101116.

Siddall, P. J., Taylor, D. A., & Cousins, M. J. (1997). Classification of pain following spinal cord injury. *Spinal Cord*, *35*(2), 69–75. https://doi.org/10.1038/sj.sc.3100365.

Siddall, P. J., Mcclelland, J. M., Rutkowski, S. B., & Cousins, M. J. (2003). A longitudinal study of the prevalence and characteristics of pain in the first 5 years following spinal cord injury. *Pain*, *103*, 249–257. https://doi.org/10.1016/S0.

Skold, C., Levi, R., & Seiger, A. (1999). Spasticity after traumatic spinal cord injury: nature, severity, and location. *Archives of Physical Medicine and Rehabilitation*, *80*(12), 1548–1557.

Sluka, K. A., O'Donnell, J. M., Danielson, J., & Rasmussen, L. A. (2013). Regular physical activity prevents development of chronic pain and activation of central neurons. *Journal of Applied Physiology*, *114*(6), 725–733. https://doi.org/10.1152/japplphysiol.01317.2012.

Soler, M. D., Kumru, H., Pelayo, R., Vidal, J., Tormos, J. M., Fregni, F., … Pascual-Leone, A. (2010). Effectiveness of transcranial direct current stimulation and visual illusion on neuropathic pain in spinal cord injury. *Brain*, *133*(9), 2565–2577. https://doi.org/10.1093/brain/awq184.

Soloukey, S., Drenthen, J., Osterthun, R., de Rooij, J. D., De Zeeuw, C. I., Huygen, F. J. P. M., & Harhangi, B. S. (2020). Bilateral L2 dorsal root ganglion-stimulation suppresses lower limb spasticity following chronic motor complete spinal cord injury: A case report. *Brain Stimulation*, *13*(3), 637–639. https://doi.org/10.1016/j.brs.2020.02.005.

Stagg, N. J., Mata, H. P., Ibrahim, M. M., Henriksen, E. J., Porreca, F., Vanderah, T. W., & Malan, T. P. (2011). Regular exercise reverses sensory hypersensitivity in a rat neuropathic pain model: Role of endogenous opioids. *Anesthesiology*, *114*(4), 940–948. https://doi.org/10.1097/ALN.0b013e318210f880.

Tan, A. M., & Waxman, S. G. (2012). Spinal cord injury, dendritic spine remodeling, and spinal memory mechanisms. *Experimental Neurology*, *235*(1), 142–151. https://doi.org/10.1016/j.expneurol.2011.08.026.

Tan, A. M. (2015). Dendritic spine dysgenesis in neuropathic pain. In *Vol. 131. Progress in molecular biology and translational science* (pp. 385–408). Elsevier B.V. https://doi.org/10.1016/bs.pmbts.2014.12.001.

Teasell, R. W., Mehta, S., Aubut, J. A. L., Foulon, B., Wolfe, D. L., Hsieh, J. T. C., … Short, C. (2010). A systematic review of pharmacologic treatments of pain after spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *91*(5), 816–831. https://doi.org/10.1016/j.apmr.2010.01.022.

Van Straaten, M. G., Cloud, B. A., Morrow, M. M., Ludewig, P. M., & Zhao, K. D. (2014). Effectiveness of home exercise on pain, function, and strength of manual wheelchair users with spinal cord injury: A high-dose shoulder program with telerehabilitation. *Archives of Physical Medicine and Rehabilitation*, *95*(10), 1810–1817.e2. https://doi.org/10.1016/j.apmr.2014.05.004.

Vera-Portocarrero, L. P., Zhang, E. T., Ossipov, M. H., Xie, J. Y., King, T., Lai, J., & Porreca, F. (2006). Descending facilitation from the rostral ventromedial medulla maintains nerve injury-induced central sensitization. *Neuroscience*, *140*(4), 1311–1320. https://doi.org/10.1016/j.neuroscience.2006.03.016.

Vranken, J. H., Hollmann, M. W., Van Der Vegt, M. H., Kruis, M. R., Heesen, M., Vos, K., … Dijkgraaf, M. G. W. (2011). Duloxetine in patients with central neuropathic pain caused by spinal cord injury or stroke: A randomized, double-blind, placebo-controlled trial. *Pain*, *152*(2), 267–273. https://doi.org/10.1016/j.pain.2010.09.005.

Widerström-Noga, E. (2017a). Neuropathic pain and spinal cord injury: Phenotypes and pharmacological management. *Drugs*, *77*(9), 967–984. https://doi.org/10.1007/s40265-017-0747-8.

Wehling, P., Moser, C., Frisbie, D., McIlwraith, C. W., Kawcak, C. E., Krauspe, R., & Reinecke, J. A. (2007). Autologous conditioned serum in the treatment of orthopedic diseases: The orthokine therapy. *BioDrugs*, *21*(5), 323–332.

Widerström-Noga, E. (2017, June 1). Neuropathic pain and spinal cord injury: Phenotypes and pharmacological management. *Drugs*. https://doi.org/10.1007/s40265-017-0747-8. Springer International Publishing.

Widerström-Noga, E. G., & Turk, D. C. (2003, November). Types and effectiveness of treatments used by people with chronic pain associated with spinal cord injuries: Influence of pain and psychosocial characteristics. *Spinal Cord*. https://doi.org/10.1038/sj.sc.3101511.

Will, J. S., Bury, D. C., & Miller, J. A. (2018). Mechanical low back pain. *American Family Physician*, *98*(7), 421–428. Retrieved from https://pubmed-ncbi-nlm-nih-gov.proxy1.lib.tju.edu/30252425/.

Wilson, R. D., Bennett, M. E., Nguyen, V. Q. C., Bock, W. C., O'Dell, M. W., Watanabe, T. K., … Chae, J. (2018). Fully implantable peripheral nerve stimulation for hemiplegic shoulder pain: A multi-site case series with two-year follow-up. *Neuromodulation*, *21*(3), 290–295. https://doi.org/10.1111/ner.12726.

Woolridge, E., Barton, S., Samuel, J., Osorio, J., Dougherty, A., & Holdcroft, A. (2005). Cannabis use in HIV for pain and other medical symptoms. *Journal of Pain and Symptom Management*, *29*(4), 358–367. https://doi.org/10.1016/j.jpainsymman.2004.07.011.

Wrigley, P. J., Gustin, S. M., McIndoe, L. N., Chakiath, R. J., Henderson, L. A., & Siddall, P. J. (2013). Longstanding neuropathic pain after spinal cord injury is refractory to transcranial direct current stimulation: A randomized controlled trial. *Pain*, *154*(10), 2178–2184. https://doi.org/10.1016/j.pain.2013.06.045.

Yin, W., Mei, L., Sun, T., Wang, Y., Li, J., Chen, C., … Zhang, Z. (2020). A central amygdala–ventrolateral periaqueductal gray matter pathway for pain in a mouse model of depression-like behavior. *Anesthesiology*, *132*(5). https://doi.org/10.1097/ALN.0000000000003133.

Zajicek, J. P., & Apostu, V. I. (2011). Role of cannabinoids in multiple sclerosis. *CNS Drugs*, *25*(3), 187–201. https://doi.org/10.2165/11539000-000000000-00000.

Section B

Clinical features of spinal injury

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Chapter 5

Factors contributing to pressure injuries in traumatic spinal cord injury

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Abbreviations

ISNCSCI	International Standards for Neurological Classification of Spinal Cord Injury
NPIAP	National Pressure Injury Advisory Panel
PI	pressure injury
SCI	spinal cord injury
TSCI	traumatic spinal cord injury

Introduction

A pressure injury (PI), also known as pressure ulcer, pressure sore, bedsore, or decubitus ulcer, is defined as a circumscribed injury to the skin and/or underlying tissue due to pressure, or shear combined with pressure, causing ischemia, cell death, and tissue necrosis (European Pressure Ulcer Advisory Panel, National Pressure Injury Advisory Panel and Pan Pacific Pressure Injury Alliance, 2019; Ham, Schoonhoven, Schuurmans, & Leenen, 2017). It may present as an open wound or intact skin. The most commonly used pressure injury classification system, based on the extent of tissue involvement, is the one developed by the National Pressure Injury Advisory Panel (NPIAP) (Table 1) (Fig. 1) (European Pressure Ulcer Advisory Panel, National Pressure Injury Advisory Panel and Pan Pacific Pressure Injury Alliance, 2019). In order to accurately describe PI, staging can only be done after proper cleansing of the wound and exposure debridement of slough or eschar, thus sometimes postponing final staging of certain PI where necrotic tissue is present in the wound bed (European Pressure Ulcer Advisory Panel, National Pressure Injury Advisory Panel and Pan Pacific Pressure Injury Alliance, 2019). PI assessment should also include dimensions, tissue quality, quantity and quality of exudate, wounds edges, presence of tunneling or undermining, peri-wound condition, odor and signs of infections, or other complications (European Pressure Ulcer Advisory Panel, National Pressure Injury Advisory Panel and Pan Pacific Pressure Injury Alliance, 2019).

TABLE 1 Pressure injury stages according to the National Pressure Injury Advisory Panel (NPIAP).

Stage 1	Intact skin with a circumscribed zone of non-blanchable erythema
Stage 2	Partial-thickness skin damage where the dermis is exposed
Stage 3	Full-thickness skin damage where the fat is exposed, granulation tissue is present and wounds edges are rolled
Stage 4	Full-thickness skin damage where fascia, muscle, tendon, ligament, cartilage, or bone is exposed
Unstageable	Full-thickness skin damage where a Stage 3 or Stage 4 is suspected but cannot be determined due to presence of necrotic tissues
Deep tissue pressure injury	Intact or damaged skin with a circumscribed non-blanchable purple or dark red zone, or presence of epidermal separation exposing a dark wound bed or blood-filled blister

Pressure injury classification system, based on the extent of tissue involvement, developed by the National Pressure Injury Advisory Panel (NPIAP) (European Pressure Ulcer Advisory Panel, National Pressure Injury Advisory Panel and Pan Pacific Pressure Injury Alliance, 2019).

Diagnosis and Treatment of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822498-4.00005-1

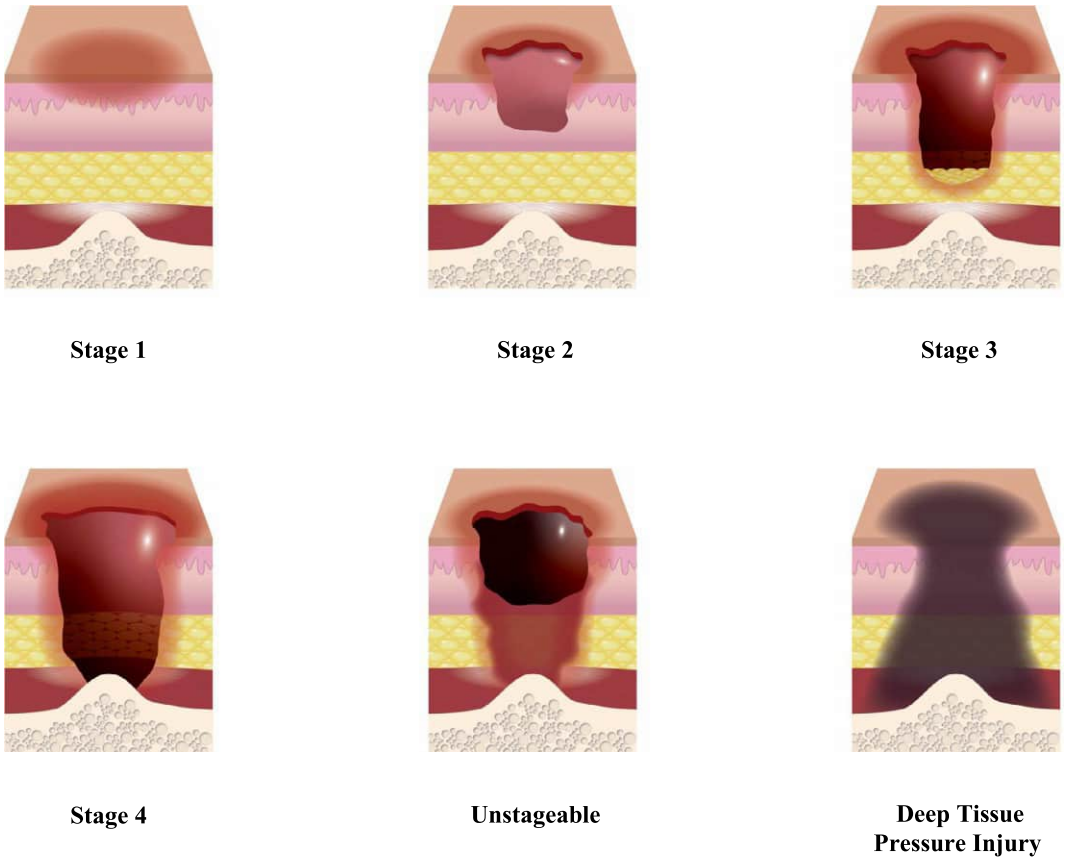

FIG. 1 Pressure injury stages. Schematic drawings of the different pressure injury stages (illustrated by Bréval Le Mestique).

Due to risk factors inherent to their condition, such as decreased sensation and mobility limitations, spinal cord injury (SCI) patients are at higher risk of developing a PI when compared to the general population (European Pressure Ulcer Advisory Panel, National Pressure Injury Advisory Panel and Pan Pacific Pressure Injury Alliance, 2019; Houghton & Campbell, 2013). Their occurrence can have significant physical, psychological, and functional consequences and may hinder independence, self-esteem, social well-being, and overall quality of life (Kisala, Tulsky, Choi, & Kirshblum, 2015; Street, Noonan, Cheung, Fisher, & Dvorak, 2015). Their prevention is therefore essential and should be an integral part of the medical and rehabilitation goals.

Pathophysiology of pressure injuries

Pressure and shear

Pressure and shear forces, especially over bony prominences or due to medical devices or other objects, are the principal factors associated with the development of PI. As a result of these forces, the loaded soft tissues will deform, causing strains and stresses which, if sustained, may lead to tissue damage (European Pressure Ulcer Advisory Panel, National Pressure Injury Advisory Panel and Pan Pacific Pressure Injury Alliance, 2019). Sustained soft tissue deformation leads to hypoxia, reduced lymphatic flow as well as reduced nutrient supply and removal of metabolic waste products which in turn causes cell death and tissue damage (Gawlitta, Li, et al., 2007; Gawlitta, Oomens, Bader, Baaijens, & Bouten, 2007; Gray, Worsley, Voegeli, & Bader, 2016). Pressure intensity and duration as well as tissue tolerance and vascular perfusion also play a significant role (European Pressure Ulcer Advisory Panel, National Pressure Injury Advisory Panel and Pan Pacific Pressure Injury Alliance, 2019).

Both low mechanical load for a long period and high load for a short period of time may result in tissue damage (Breuls, Bouten, Oomens, Bader, & Baaijens, 2003; Gawlitta, Li, et al., 2007; Gawlitta, Oomens, et al., 2007). To date, no universal safe tissue interface pressure threshold has been established, thus highlighting the importance of evaluating and addressing

all possible PI risk factors as tissue interface pressure measurement alone is insufficient (Coleman et al., 2014; Groah, Schladen, Pineda, & Hsieh, 2015; Oomens, Loerakker, & Bader, 2010).

Tissue tolerance

Different tissue types have varying degrees of tolerance to deformation with muscle tissues being more susceptible to damage than fat and skin (Salcido et al., 1994). The orientation of shear forces is also important as skin is more resistant to forces occurring in alignment with collagen fiber bundles than when they are applied perpendicular to fiber bundles (Destrade, Gilchrist, Prikazchikov, & Saccomandi, 2008).

In addition, soft tissue tolerance may be affected by many factors such as perfusion, micro-climate as well as patients and tissue characteristics (European Pressure Ulcer Advisory Panel, National Pressure Injury Advisory Panel and Pan Pacific Pressure Injury Alliance, 2019). For example, trauma victims have an increased risk of developing PI, with 45.8% of them developing within 48 h of admission (Ham et al., 2017). Because of the risk factors inherent to their condition, such as immobility, decreased autonomic control, hyper catabolic responses, and lack of protective response due to sensorimotor deficits (Houghton & Campbell, 2013; Michel et al., 2012), patients with traumatic spinal cord injury (TSCI) are almost 14 times more likely to develop a PI than other trauma patients (Grigorian et al., 2017).

Prevalence, impact, and cost of pressure injuries in patients with SCI

Pressure injuries (PI) are one of the most common complications following SCI with up to 80% of patients developing a PI at some point during their lifetime (Garber, Rintala, Hart, & Fuhrer, 2000; Kirshblum & Lin, 2018). Compared to other rehabilitation phases, the acute hospitalization represents the period with the highest PI risk (Brienza, Krishnan, Karg, Sowa, & Allegretti, 2018) with a prevalence ranging from 2.7% to 57% when compared to 15% to 54% in the chronic SCI stage (Brienza et al., 2018; Gelis et al., 2009b; van der Wielen, Post, Lay, Glasche, & Scheel-Sailer, 2016). Factors such as severe neurological deficits, altered level of consciousness, and multiple concomitant traumatic injuries lead to prolonged periods of immobility and decreased general health status, putting patients at higher risk of PI during acute care (Ham et al., 2017).

Most common locations and severity

During acute care and rehabilitation, when patients spend more time in a supine position, the most commonly affected areas include the ischium (28%), the sacrum (17%–27%), trochanters (12%–19%), and heels (9%–18%) (Kruger, Pires, Ngann, Sterling, & Rubayi, 2013). During the chronic stage, when patients spend more time in a sitting position, the ischium or perineum (48.3%), sacrum (37.2%), and trochanters (14.5%) are more susceptible to PI (Guihan et al., 2016).

Molano et al. have shown that in their cohort, the majority of PIs occurring during acute care were stage 2 and 3 (Molano Alvarez et al., 2004). For their part, Powers et al. have shown a predominance of stages 1 and 2 (Powers, Daniels, McGuire, & Hilbish, 2006). In a recent study, Ham et al. suggested that the number of stage 1 PI may be underestimated due to the absence of skin loss, making their identification sometimes more difficult and by the fact that they rapidly progress to more severe stages if not addressed (Ham et al., 2017).

Impact

Patients with TSCI who develop a PI during acute hospitalization have higher complication rates, significantly longer length of stay, and higher risk of recurrence (Klotz, Joseph, Ravaud, Wiart, & Barat, 2002; Street et al., 2015; Verschueren et al., 2011). Complications of PI such as wound infection, cellulitis, septic arthritis, osteomyelitis, sepsis, and malignant transformation (Marjolin's ulcers) may also occur (Houghton & Campbell, 2013). In some cases, PI can lead to surgical procedures, amputation, and sometimes even death due to an infection (Houghton & Campbell, 2013). Indeed, 7%–8% of patients with TSCI who develop a PI die from associated complications (Richards, Waites, Chen, Kogos, & Schmitt, 2004). PI also limit long-term functional outcome by interfering with rehabilitation (Hastings, Ntsiea, & Olorunju, 2015; Post, Dallmeijer, Angenot, van Asbeck, & van der Woude, 2005). Following the acute hospitalization, patients are at higher risks of developing a PI during the first year post-SCI or more than 25 years post-injury (National Spinal Cord Injury Statistical Center, 2019). After urinary tract infections, PI represent the second most common cause of re-hospitalization during the first year post-TSCI as well as in the following years, accounting for 11.3% of

re-hospitalizations at 1 year, 14.6% at 5 years, 17.5% at 10 years, and 21.3% at 20 years post injury (National Spinal Cord Injury Statistical Center, 2019).

Cost

It has been estimated that one-quarter of the cost of care for patients with SCI is associated with PI and thus represent a significant preventable financial burden. In 2013, in Canada, the occurrence of PI resulted in an additional $18,758 to the cost of acute hospitalization following TSCI (White et al., 2017). In the United Kingdom, PI treatment ranges from $2000 to $18,000 (Bennett, Dealey, & Posnett, 2004) while in the United States, annual health care costs per patient was estimated to be $73,021 higher for patients with PI when compared to patients without PI (Stroupe et al., 2011). Finally, a recent systematic review showed that interventions to prevent PI occurrence were considerably less expensive than the interventions for their treatment (Demarré et al., 2015).

Structural and physiological changes following SCI

Following SCI, multiple structural and physiological changes occur, decreasing the body's ability to maintain skin integrity, increasing the risk of tissue breakdown, and thus putting patients at higher risk of developing PI (Table 2).

Skin

Thinning of skin at load-bearing sites, decrease in skin distensibility in the remaining skin tissues, decrease in fibroblast activity, and increase in collagen catabolism are seen in patients with SCI with greater changes in skin distensibility,

TABLE 2 Structural and physiological changes following SCI.

Skin changes	– Skin thinning at load-bearing sites – Decrease in skin distensibility in the remaining skin tissues – Decreased fibroblast activity – Greater collagen catabolism – Decrease in type I to type III collagen ratio in skin below injury level
Disuse-induced muscle atrophy	– Fibers thinning – Decrease in numbers of slow-twitch fibers and increase in fast-twitch fibers below the level of injury – Increase in intra-muscular fat causing greater intra-muscular shear stresses at interfaces between muscle and intra-muscular fat tissues
Bone changes	– Flattening of ischial tuberosities due to chronic exposure to sitting mechanical loading coupled with cortical bone mass loss, shifting load transfer from weight-bearing ischial tuberosities to overlying soft tissues
Changes in macro- and micro-vasculature	– Vasodilation and impairment in tissue perfusion below injury level – Decrease in the density of both alpha- and beta-adrenergic receptors in the skin below injury level resulting in abnormal vascular response – Decrease in number and size of capillaries feeding skeletal muscle fibers – Decrease in lower limbs cutaneous blood when sitting
Chronic inflammation and immune function	– Decrease healing response by depression of immune system function – Chronic tissue inflammation decreases tissue tolerance and repair capacity further increasing tissue breakdown risk
Temperature dysregulation	– Increase in resting skin temperature and decrease in skin temperature reactivity in lower limbs
Sensory impairments	– Sensory deficits resulting in lack of protective response allowing the progression from ischemia to tissue breakdown and necrosis

Summary of the multiple structural and physiological changes occurring following SCI predisposing to pressure injuries (Carda, Cisari, & Invernizzi, 2013; Cotie, Geurts, Adams, & MacDonald, 2011; Cruse et al., 2000; Deitrick, Charalel, Bauman, & Tuckman, 2007; European Pressure Ulcer Advisory Panel, National Pressure Injury Advisory Panel and Pan Pacific Pressure Injury Alliance, 2019; Gefen, 2018; Gorgey & Dudley, 2007; Kirshblum & Lin, 2018; Kruger et al., 2013; Lachenbruch, Tzen, Brienza, Karg, & Lachenbruch, 2013; Linder-Ganz et al., 2008; Michel et al., 2012; Park, Seo, Han, & Lee, 2011; Patterson, Cranmer, Fisher, & Engel, 1993; Rappl, 2008; Rodriguez, Claus-Walker, Kent, & Stal, 1986; Rodriguez & Markowski, 1995; Ruschkewitz & Gefen, 2011; Scelsi, 2001; Schwab, Zhang, Kopp, Brommer, & Popovich, 2014; Sopher, Nixon, Gorecki, & Gefen, 2011; Thorfinn, Sjöberg, & Lidman, 2002; Wilczweski et al., 2012; Wu & Bogie, 2013; Yalcin, Akyuz, Onder, Unalan, & Degirmenci, 2013; Zeevi, Levy, Brauner, & Gefen, 2018).

elasticity, and viscoelasticity observed in patients with longer time elapsed since SCI (Park et al., 2011; Yalcin et al., 2013). A decrease in type I to type III collagen ratio is also seen in the skin below the level of injury which may further contribute to skin fragility following SCI by decreasing tensile strength (Rodriguez & Markowski, 1995).

Muscle and bone

In addition to normally occurring age-related muscle atrophy (Roubenoff, 1999), patients with SCI undergo significant disuse-induced muscle atrophy below the level of injury (Gorgey & Dudley, 2007) with greater atrophy seen at the level of ischial tuberosities (Wu & Bogie, 2013). Muscle atrophy decreases natural protective cushioning over bony prominences, increasing PI risk (Linder-Ganz & Gefen, 2009). Thinning of the fibers, decrease in the numbers of slow-twitch fibers, and increase in fast-twitch fibers may be seen as early as 4–6 weeks following TSCI (Carda et al., 2013). An increase in intra-muscular fat is also observed (Gorgey & Dudley, 2007), causing greater intra-muscular shear stresses at interfaces between muscle and intra-muscular fat tissues (Sopher et al., 2011; Wu & Bogie, 2013), thus further increasing PI risk. In addition, due to chronic exposure to sitting mechanical loading coupled with cortical bone mass loss, ischial tuberosities tend to flatten, shifting load transfer from weight-bearing ischial tuberosities to overlying soft tissues (Linder-Ganz et al., 2008).

Macro- and micro-vasculature

Changes in macro- and micro-vasculature also occur partly due to alteration in autonomic control. First, a loss of vascular tone is seen below the lesion resulting in vasodilation and thus decreasing vascular resistance and impairing tissue perfusion (Rappl, 2008). Also, a decrease in the density of both alpha- and beta-adrenergic receptors is observed in the skin below the level of injury in patients with longer-standing injuries resulting in abnormal vascular response (Rodriguez et al., 1986). When compared to patients without SCI, lower limbs cutaneous blood flow has been shown to decrease by at least 50% in patients with SCI when sitting (Deitrick et al., 2007). A decrease in number and size of capillaries feeding skeletal muscle fibers is also seen, making these muscles more susceptible to ischemia, especially during episodes of low blood pressure (Ruschkewitz & Gefen, 2011; Scelsi, 2001). Moreover, when compared to healthy controls, patients with SCI tend to have significantly higher sitting pressure and significantly lower transcutaneous oxygen tension levels, followed by slower reactive hyperemia when unloaded, translating into a lower rate of reperfusion (Patterson et al., 1993; Thorfinn et al., 2002). This therefore suggests a longer recovery time is required for patients with SCI following loading periods to allow appropriate tissue re-oxygenation before reloading the area.

Inflammation and immune function

A chronic systemic inflammatory response occurs following trauma and may predispose patients with SCI to PI and decrease healing response by depressing immune system function (Cruse et al., 2000; Schwab et al., 2014). Compromise in tissue perfusion paired with chronic tissue inflammation decrease tissue tolerance and repair capacity further increasing tissue breakdown risk (Gefen, 2018).

Temperature

Due to loss of autonomic control, temperature dysregulation is also common in patients with SCI. Cotie et al. have shown that an increase in resting skin temperature and a reduced skin temperature reactivity are seen in the lower limbs of patients with SCI (Cotie et al., 2011). In addition, urinary and/or fecal incontinence is common in patients with SCI further increasing the risk of moisture and maceration (Kirshblum & Lin, 2018; Wilczweski et al., 2012). An increase in body temperature, especially when coupled with excessive humidity and maceration, has a profound effect on tissue tolerance to damage and thus must not be overlooked especially when addressing support surfaces and medical devices (Lachenbruch et al., 2013; Wilczweski et al., 2012; Zeevi et al., 2018).

Sensory impairments

Finally, sensory deficits associated with SCI results in a lack of protective response due to decreased awareness of tissue injury thus allowing the progression from ischemia to tissue breakdown and necrosis (European Pressure Ulcer Advisory

Panel, National Pressure Injury Advisory Panel and Pan Pacific Pressure Injury Alliance, 2019; Kruger et al., 2013; Michel et al., 2012).

Risk assessment tools

The purpose of a risk assessment tool is to identify and stratify individuals who are more susceptible to PI occurrence in order to better evaluate and address risk factors and the adequacy of preventive measures. Although the SCIPUS and SCIPUS-A scales, which were specifically developed to assess patients with SCI during acute hospitalization and rehabilitation, show promise, they haven't demonstrated acceptable accuracy and, thus at this point, cannot be recommended (Mortenson & Miller, 2008). The two most common scales used to assess PI risk are the Braden Scale and the Norton Scale. The Braden Scale measures six domains: sensory perception, moisture, activity, mobility, nutrition, and friction/shear. Each domain is scored on a scale of 1–4 except for friction/shear which is score from 1 to 3. The total score thus ranges from 6 to 23, with lower score meaning greater risk for skin breakdown. Preventative measures should be put in place in patients with a score of 18 or less. The Norton Scale measures five domains: physical condition, mental condition, activity, mobility, and continence. Each domain is scored on a scale of 1–4 which are then summed to give a total score ranging from 5 (worst prognosis) to 20 (best prognosis). Similarly, preventive measures should be put in place in patients with a score of 16 or less (Mortenson & Miller, 2008).

Risk factors associated with pressure injuries in patients with traumatic spinal cord injury

As discussed, susceptibility, severity, and extent of PI depend on type, magnitude, and duration of mechanical load, but also on the mechanical properties of the tissue, tissue and bone morphology, tissue repair capacity as well as transport and thermal properties of tissues (Coleman et al., 2014). In addition to the structural and physiological changes occurring following an SCI described in the previous section, many other risk factors have been shown to influence key components of PI development thus making patients with TSCI even more vulnerable to PI. These may be classified as non-modifiable factors if they cannot be addressed and optimized, and modifiable factors if they can be reduced or changed (Table 3).

Non-modifiable factors

Patient characteristics

Whether older age (Brienza et al., 2018; Di Prinzio et al., 2019; Gelis et al., 2009a, 2009b; Ham et al., 2017; Marin et al., 2013; Wilczweski et al., 2012) and sex (Ash, 2002; Di Prinzio et al., 2019; Gelis et al., 2009a, 2009b; Sheerin et al., 2005; Wilczweski et al., 2012) are significant risk factors to PI development is still debated in the literature. However, it has been shown that 10–20 years post injury, SCI accelerates the physical and functional decline associated with aging which may further increase PI risk (Menter & Hudson, 1995). Although some studies have shown that race may be associated with PI occurrence (Chen et al., 2005; Guihan et al., 2008; Saunders et al., 2010), a recent study found that when controlled for socioeconomic status and healthcare access, race becomes a non-significant risk factor (Saunders et al., 2012). Indeed, patients with SCI with lower household income (Jorge et al., 2018; Saunders et al., 2010; Saunders et al., 2012), who are unemployed (Klotz et al., 2002; Krause et al., 2001; Krause & Broderick, 2004), who have lower educational levels (Chen et al., 2005; Klotz et al., 2002; Krause et al., 2001), and who are single (Chen et al., 2005; Gelis et al., 2009b; Krause et al., 2001) tend to be at higher risk of developing a PI.

Injury characteristics and associated conditions

The completeness of the TSCI (according to the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) (Kirshblum et al., 2011)) is significantly associated with greater PI risk (Brienza et al., 2018; Di Prinzio et al., 2019; Gelis et al., 2009a, 2009b; Gour-Provencal et al., 2020; Grigorian et al., 2017; Joseph & Nilsson Wikmar, 2016; Li et al., 2017; Marin et al., 2013; Marion et al., 2017; Verschueren et al., 2011). Higher levels of neurological injury may also be a higher risk of PI however this is still debated in the literature (Ash, 2002; Chen et al., 2005; Di Prinzio et al., 2019; Gelis et al., 2009b; Gour-Provencal et al., 2020; Grigorian et al., 2017; Krause & Broderick, 2004; Marin et al., 2013; Marion et al., 2017; Sheerin et al., 2005; Verschueren et al., 2011). Higher levels and complete injuries are associated with greater sensorimotor deficits, decreased autonomic control impairing micro-vascular response, greater risk of developing nutritional deficiencies, and more severe mobility limitations, all of which predispose to PI development

TABLE 3 Risk factors associated with pressure injuries in patients' traumatic spinal cord injury.

Non-modifiable risk factors	Modifiable risk factors
Older age (still debated)	Obesity or being underweight
Lower household income Unemployment Lower educational levels Single	Smoking and alcohol abuse (still debated) Substance abuse
Greater severity of injury (motor complete vs incomplete)	Dysthymic symptoms Schizophrenia Personality disorders Neurocognitive changes Delirium
Higher neurological level of injury (tetraplegia vs paraplegia) (still debated)	Medication use for pain, insomnia, spasticity, or stress
Poorer functional status	Longer admission delay between trauma site and the emergency department Longer time spent with immobilization device (>6 h) Longer surgical duration (>6 h)
Greater trauma severity and presence of concomitant traumatic injuries	Longer acute care length of stay
Hypotension, hypovolemic, or hemorrhagic shock, with prolonged periods of mean arterial pressure of <70 mmHg	Care management in a non-SCI-specialized center Surgical delay of >24 h
Mechanical ventilation	Medical complications
Patients with longer-standing TSCI, >25 years post SCI	Hypoalbuminemia Malnutrition Anemia (still debated)
Previous history of PI (stage 3 or 4 or requiring surgery)	Immobility in the frail Poor bed and wheelchair positioning
Presence of comorbidities (diabetes, metabolic syndrome, cardiovascular disease, peripheral vascular disease, pulmonary diseases, and renal disease)	No access to appropriate support surfaces Inappropriate turning in bed schedule Poor compliance Little or non-knowledge of PI prevention strategies

Summary of the non-modifiable and modifiable risk factors associated with pressure injuries in patients traumatic spinal cord injury (Ash, 2002; Bourassa-Moreau, Mac-Thiong, Feldman, Thompson, & Parent, 2013; Brienza et al., 2018; Chen, Devivo, & Jackson, 2005; DeJong et al., 2014; Di Prinzio et al., 2019; European Pressure Ulcer Advisory Panel, National Pressure Injury Advisory Panel and Pan Pacific Pressure Injury Alliance, 2019; Garber et al., 2000; Gater, 2007; Gelis et al., 2009a, 2009b; Gour-Provencal, Mac-Thiong, Feldman, Bégin, & Richard-Denis, 2020; Grigorian et al., 2017; Groah et al., 2015; Guihan et al., 2008, 2016; Ham et al., 2017; Ham, Schoonhoven, Schuurmans, & Leenen, 2014; Hatchett, Mulroy, Eberly, Haubert, & Requejo, 2016; Houghton & Campbell, 2013; Jorge, White, & Agarwal, 2018; Joseph & Nilsson Wikmar, 2016; Klotz et al., 2002; Krause & Broderick, 2004; Krause, Vines, Farley, Sniezek, & Coker, 2001; Krishnan et al., 2017; Le Fort, Espagnacq, Perrouin-Verbe, & Ravaud, 2017; Li, DiPiro, Cao, Szlachcic, & Krause, 2016; Li, DiPiro, & Krause, 2017; Marin, Nixon, & Gorecki, 2013; Marion et al., 2017; Mathew, Samuelkamaleshkumar, Radhika, & Elango, 2013; Michel et al., 2012; Morita, Yamada, Watanabe, & Nagahori, 2015; Parent, Barchi, LeBreton, Casha, & Fehlings, 2011; Ploumis et al., 2011; Rabadi & Vincent, 2011; Richard-Denis, Thompson, Bourassa-Moreau, Parent, & Mac-Thiong, 2016; Saunders & Krause, 2010; Saunders, Krause, & Acuna, 2012; Saunders, Krause, Peters, & Reed, 2010; Scelsi, 2001; Sheerin, Gillick, & Doyle, 2005; Smith, Guihan, LaVela, & Garber, 2008; Tate, Forchheimer, Krause, Meade, & Bombardier, 2004; van der Wielen et al., 2016; Verschueren et al., 2011; Wilczweski et al., 2012).

(Brienza et al., 2018; Ham et al., 2017; Kruger et al., 2013; Mathew et al., 2013; Michel et al., 2012). Similarly, patients with SCI with poorer functional status tend to be more susceptible to PI (Garber et al., 2000; Mathew et al., 2013; Saunders et al., 2010; Verschueren et al., 2011). According to the National Spinal Cord Injury Statistical Center patients with complete tetraplegia have the highest risk of developing a PI during acute care and rehabilitation, followed by patients with complete paraplegia, incomplete tetraplegia and incomplete paraplegia (National Spinal Cord Injury Statistical Center, 2006).

Greater trauma severity (Ham et al., 2014, 2017) as well as the presence of concomitant traumatic injuries such as fractures, organ trauma, and traumatic brain injury increase the risk of developing a PI, as they are generally associated with lower tissue perfusion pressure, longer surgical times, and a more precarious health status (Ash, 2002; European Pressure Ulcer Advisory Panel, National Pressure Injury Advisory Panel and Pan Pacific Pressure Injury Alliance, 2019; Ham et al., 2014, 2017). Hypotension, hypovolemic or hemorrhagic shock, with prolonged periods of mean arterial pressure of less than 70 mmHg during hospitalization is also associated with PI onset (Gelis et al., 2009a; Wilczweski et al., 2012). PI incidence significantly increases in patients requiring mechanical ventilation (Brienza et al., 2018; Ham et al., 2014).

Patients with longer-standing TSCI, especially those more than 25 years post injury, have a higher risk of PI occurrence (Gelis et al., 2009b; van der Wielen et al., 2016) and a greater susceptibility to PI management requiring recurrent hospital admissions (Goodman, Schindler, Washington, Bogie, & Ho, 2014). Similarly, patients with SCI with a previous history of PI, especially those with stage 3 or 4 or those requiring surgery, are at higher risk of PI recurrence (DeJong et al., 2014; Le Fort et al., 2017; Verschueren et al., 2011).

Comorbidities

The presence of comorbidities such as diabetes, metabolic syndrome, cardiovascular disease, peripheral vascular disease, pulmonary diseases, and renal disease has also been associated with PI onset (Ash, 2002; Di Prinzio et al., 2019; Gelis et al., 2009b; Guihan et al., 2008, 2016; Houghton & Campbell, 2013; Li et al., 2016; Marin et al., 2013; Michel et al., 2012).

Modifiable factors

Lifestyle habits, medication, and psychological factors

Some patients with SCI are at higher risk of obesity (Gater, 2007; Hatchett et al., 2016; Scelsi, 2001), resulting in greater compressive forces on weight-bearing sites, increasing PI susceptibility (Elsner & Gefen, 2008; Sopher, Nixon, Gorecki, & Gefen, 2010). Patients who are underweight are also at higher risk of PI (Krause et al., 2001).

Although smoking has been shown to have adverse effects on PI healing (Lane, Selleck, Chen, & Tang, 2016) by decreasing arterial oxygen tension, it is still debated in the literature whether it is a significant risk factor for PI occurrence (Di Prinzio et al., 2019; Gelis et al., 2009a, 2009b; Krause et al., 2001; Li et al., 2016, 2017; Marin et al., 2013) similar to alcohol abuse (Krause et al., 2001; Li et al., 2016, 2017; Tate et al., 2004). Substance abuse may increase the risk of self-negligent behaviors and thus has been observed to be a significant PI risk factor (Tate et al., 2004).

Patients with SCI and dysthymic symptoms, schizophrenia, personality disorders, neurocognitive changes, or delirium are all at higher risk of PI development (Di Prinzio et al., 2019; Gelis et al., 2009b; Krause & Broderick, 2004; Smith et al., 2008). The use of prescription medication for pain, insomnia, spasticity or stress may also increase PI susceptibility (Di Prinzio et al., 2019; Krause & Broderick, 2004; Li et al., 2017; Saunders & Krause, 2010).

Patient management and care

Admission delay between trauma site and the emergency department, longer time spent with an immobilization device (backboard, cervical collar) as well as longer duration of surgery have all been shown to drastically increase PI occurrence, especially after 6 h (European Pressure Ulcer Advisory Panel, National Pressure Injury Advisory Panel and Pan Pacific Pressure Injury Alliance, 2019; Ham et al., 2014; Parent et al., 2011). These factors lead to longer periods of immobility, decreasing tissue oxygenation over bony prominences and increasing temperature and humidity under the devices, thereby increasing PI susceptibility (Ham et al., 2014). It has also been suggested that patients who wear immobilization devices for longer periods of time tend to be patients with more severe injuries further increasing PI risk (Ham et al., 2014).

Receiving care in a SCI-specialized center and a surgical delay of less than 24 h are shown to be protective factors (Bourassa-Moreau et al., 2013; Parent et al., 2011; Ploumis et al., 2011; Richard-Denis et al., 2016). This can be explained by the fact that the SCI-specialized centers comprise qualified nurses and therapists, who better understand the specifics of the overall management of patients with SCI (Parent et al., 2011). Shorter acute care length of stay has also been associated with fewer PI (Ploumis et al., 2011; van der Wielen et al., 2016).

The occurrence of medical complications such as urinary tract infections and pneumonia also increases PI risk (Brienza et al., 2018; Gour-Provencal et al., 2020; Joseph & Nilsson Wikmar, 2016; Krishnan, Vodovotz, et al., 2017) as they cause decreased tissue oxygenation, decreased mobility, and an impaired inflammatory response, thereby compromising the patient's immunity and further predisposing them to PI (Brienza et al., 2018; Krishnan, Karg, Boninger, & Brienza, 2017; Krishnan, Vodovotz, et al., 2017). Hypoalbuminemia and malnutrition have also been associated with higher PI risk while low hemoglobin is still debated (Di Prinzio et al., 2019; Marin et al., 2013; Rabadi & Vincent, 2011).

Prevention strategies and patient compliance

Immobility in the frail, poor bed and wheelchair positioning and repositioning have been shown to increase PI risk (Groah et al., 2015). Access to appropriate support surface (Morita et al., 2015), turning in bed schedule, knowledge, and compliance to PI prevention strategies may be protective factors (Garber et al., 2000; Mathew et al., 2013; Morita et al., 2015).

Conclusion

Despite medical advances and improvement in knowledge through the years, pressure injuries remain a serious challenge throughout the acute hospitalization, rehabilitation, and community reintegration stages for both patients with TSCI and medical professionals. The repercussions are significant on the physical, psychological, functional, and financial states, and thus their prevention is crucial. Better identifying and addressing factors contributing to their occurrence is the first step toward improving patient outcome and quality of life. Although various factors have been identified as potential PI risk factors, no single component can explain PI occurrence on its own but rather a complex interaction of different factors, therefore highlighting the importance of a comprehensive management and care plan.

Applications to other areas of neuroscience

As reviewed in this chapter, due to risk factors inherent to their condition, patients with traumatic spinal cord injury (TSCI) are at higher risk of developing a pressure injury (PI). A recent retrospective analysis using data from the National Trauma Data Bank showed that, when adjusted for covariates, spinal cord injury was the strongest predictor of PI occurrence in adult trauma patients (OR 13.77, 95% CI 13.25–14.31, $P < 0.001$) (Grigorian et al., 2017). On univariable analysis, the odds (OR (95% CI)) of developing a PI in patients admitted between 2007 and 2015 was 1.77 (1.73–1.81) in patients with traumatic brain injury, 2.48 (2.34–2.62) in patients with cerebrovascular accident and 13.73 (13.22–14.25) in patients with SCI (Grigorian et al., 2017). Thus, similar to patients with SCI, individuals with traumatic brain injury, stroke, neurodegenerative diseases (such as dementia, Alzheimer's disease, and Parkinson's disease) or any other neurological conditions resulting in altered level of sensation, mobility, or mental status also are at increased risk of developing a PI (Jaul, Barron, Rosenzweig, & Menczel, 2018). Furthermore, the combination of neurological impairments with associated complicating conditions such as polypharmacy, malnutrition, and anemia further increases PI susceptibility (Jaul et al., 2018). Fife et al. showed that patients who are admitted to the neurologic intensive care unit are at higher risk of developing a PI especially if they have Braden scores of $\leq$16 and are underweight (Fife et al., 2001). These results may suggest that the factors contributing to PI in patients with TSCI may also be applicable to other neurological conditions and thus shouldn't be overlooked.

Mini-dictionary of terms

Atrophy: wasting or loss of muscle tissue.
Catabolism: metabolic pathways resulting in the breakdown of complex molecules into smaller particles.
Debridement: removal of dead or unhealthy tissues in a wound.
Ischemia: decrease blood flow to tissues causing reduction in oxygen and nutrient supplies.
Maceration: prolonged exposure to moisture resulting in softening and breaking down of skin.
Necrosis: premature death of cells and tissues.
Pressure: force vector that is perpendicular to the skin.
Shear: force vector that is tangential to the tissue contact surface.
Tunneling: channels extending from the initial injury site to subcutaneous tissues.
Undermining: extension of the injury in subcutaneous tissues under the wound borders.

Key facts of pressure injuries

- A pressure injury (PI) is defined as a circumscribed injury to the skin and/or underlying tissue due to pressure, or shear combined with pressure.
- Loaded soft tissues deform, causing strains and stresses which, if sustained, may lead to tissue damage.

- Muscles are more susceptible to damage than fat and skin as they have lower tolerance to deformation.
- Patients with sensory deficits are more prone to PI due to their lack of protective responses caused by decreased awareness of tissue injury.
- Complications of PI include wound infection, cellulitis, septic arthritis, osteomyelitis, sepsis, malignant transformation (Marjolin's ulcers), surgical procedures, amputation, and death from infection.

Summary points

- Susceptibility and extent of pressure injuries (PI) depend on type, magnitude, and duration of mechanical load, the mechanical properties of the tissue, tissue and bone morphology, tissue repair capacity as well as circulation and thermal properties of tissues.
- To date, no universal safe tissue interface pressure threshold has been established.
- Following spinal cord injury (SCI), multiple structural and physiological changes occur, decreasing the body's ability to maintain skin integrity, increasing the risk of tissue breakdown and thus increasing the risk of developing PI.
- Patients are at higher risks of developing a PI during the first year post-SCI or more than 25 years post injury.
- Patients with traumatic spinal cord injury (TSCI) who develop a PI during acute hospitalization have higher complication rates, significantly longer length of stay, higher risk of recurrence, and poorer long-term functional outcome.
- Non-modifiable risk factors include more severe TSCI, poorer functional outcome, greater trauma severity and the presence of concomitant traumatic injuries, hypotension, mechanical ventilation, longer time elapsed since TSCI, previous history of PI, lower household income, unemployment, being single, lower educational levels, and presence of comorbidities.
- Modifiable risk factors include obesity, substance abuse, dysthymic symptoms, schizophrenia, personality disorders, neurocognitive changes, delirium, medication use for pain, insomnia, spasticity or stress, longer admission delay from trauma site to emergency department, longer time spent with immobilization device, longer surgical duration, longer acute care length of stay, care management in a non-SCI-specialized center, surgical delay of >24 h, medical complications, hypoalbuminemia, malnutrition, immobility in the frail, poor bed and wheelchair positioning, no access to appropriate support surfaces, poor compliance, and little or non-knowledge of PI prevention strategies.
- Although various factors have been identified as potential PI risk factors, no single component can explain PI occurrence on its own but rather a complex interaction of different factors, therefore highlighting the importance of a comprehensive management and care plan.

References

Ash, D. (2002). An exploration of the occurrence of pressure ulcers in a British spinal injuries unit. *Journal of Clinical Nursing*, *11*(4), 470–478.

Bennett, G., Dealey, C., & Posnett, J. (2004). The cost of pressure ulcers in the UK. *Age and Ageing*, *33*(3), 230–235. https://doi.org/10.1093/ageing/afh086.

Bourassa-Moreau, E., Mac-Thiong, J. M., Feldman, D. E., Thompson, C., & Parent, S. (2013). Non-neurological outcomes after complete traumatic spinal cord injury: The impact of surgical timing. *Journal of Neurotrauma*, *30*(18), 1596–1601. https://doi.org/10.1089/neu.2013.2957.

Breuls, R. G., Bouten, C. V., Oomens, C. W., Bader, D. L., & Baaijens, F. P. (2003). Compression induced cell damage in engineered muscle tissue: An in vitro model to study pressure ulcer aetiology. *Annals of Biomedical Engineering*, *31*(11), 1357–1364. https://doi.org/10.1114/1.1624602.

Brienza, D., Krishnan, S., Karg, P., Sowa, G., & Allegretti, A. L. (2018). Predictors of pressure ulcer incidence following traumatic spinal cord injury: A secondary analysis of a prospective longitudinal study. *Spinal Cord*, *56*(1), 28–34. https://doi.org/10.1038/sc.2017.96.

Carda, S., Cisari, C., & Invernizzi, M. (2013). Sarcopenia or muscle modifications in neurologic diseases: A lexical or patophysiological difference? *European Journal of Physical and Rehabilitation Medicine*, *49*(1), 119–130.

Chen, Y., Devivo, M. J., & Jackson, A. B. (2005). Pressure ulcer prevalence in people with spinal cord injury: Age-period-duration effects. *Archives of Physical Medicine and Rehabilitation*, *86*(6), 1208–1213. https://doi.org/10.1016/j.apmr.2004.12.023.

Coleman, S., Nixon, J., Keen, J., Wilson, L., McGinnis, E., Dealey, C., … Nelson, E. A. (2014). A new pressure ulcer conceptual framework. *Journal of Advanced Nursing*, *70*(10), 2222–2234. https://doi.org/10.1111/jan.12405.

Cotie, L. M., Geurts, C. L., Adams, M. M., & MacDonald, M. J. (2011). Leg skin temperature with body-weight-supported treadmill and tilt-table standing training after spinal cord injury. *Spinal Cord*, *49*(1), 149–153. https://doi.org/10.1038/sc.2010.52.

Cruse, J. M., Lewis, R. E., Dilioglou, S., Roe, D. L., Wallace, W. F., & Chen, R. S. (2000). Review of immune function, healing of pressure ulcers, and nutritional status in patients with spinal cord injury. *Journal of Spinal Cord Medicine*, *23*(2), 129–135.

Deitrick, G., Charalel, J., Bauman, W., & Tuckman, J. (2007). Reduced arterial circulation to the legs in spinal cord injury as a cause of skin breakdown lesions. *Angiology*, *58*(2), 175–184. https://doi.org/10.1177/0003319707300353.

DeJong, G., Hsieh, C. H., Brown, P., Smout, R. J., Horn, S. D., Ballard, P., & Bouchard, T. (2014). Factors associated with pressure ulcer risk in spinal cord injury rehabilitation. *American Journal of Physical Medicine & Rehabilitation*, *93*(11), 971–986. https://doi.org/10.1097/phm.0000000000000117.

Demarré, L., Van Lancker, A., Van Hecke, A., Verhaeghe, S., Grypdonck, M., Lemey, J., … Beeckman, D. (2015). The cost of prevention and treatment of pressure ulcers: A systematic review. *International Journal of Nursing Studies*, *52*(11), 1754–1774. https://doi.org/10.1016/j.ijnurstu.2015.06.006.

Destrade, M., Gilchrist, M. D., Prikazchikov, D. A., & Saccomandi, G. (2008). Surface instability of sheared soft tissues. *Journal of Biomechanical Engineering*, *130*(6). https://doi.org/10.1115/1.2979869, 061007.

Di Prinzio, M. F., Argento, F. J., Barbalaco, L., Cazurro, M. E., Pereyra, A., Sanchez Correa, C., … Annaratone, A. (2019). Risk factors for the development and recurrence of pressure ulcers in patients with spinal cord injury: A systematic review. *Revista de la Facultad de Ciencias Médicas de la Universidad Nac. de Córdoba*, *76*(4), 242–256. https://doi.org/10.31053/1853.0605.v76.n4.24906.

Elsner, J. J., & Gefen, A. (2008). Is obesity a risk factor for deep tissue injury in patients with spinal cord injury? *Journal of Biomechanics*, *41*(16), 3322–3331. https://doi.org/10.1016/j.jbiomech.2008.09.036.

European Pressure Ulcer Advisory Panel, National Pressure Injury Advisory Panel and Pan Pacific Pressure Injury Alliance. (2019). Prevention and treatment of pressure ulcers/injuries: Clinical practice guideline. In E. Haesler (Ed.), *The international guideline* EPUAP/NPIAP/PPPIA.

Fife, C., Otto, G., Capsuto, E. G., Brandt, K., Lyssy, K., Murphy, K., & Short, C. (2001). Incidence of pressure ulcers in a neurologic intensive care unit. *Critical Care Medicine*, *29*(2), 283–290.

Garber, S. L., Rintala, D. H., Hart, K. A., & Fuhrer, M. J. (2000). Pressure ulcer risk in spinal cord injury: Predictors of ulcer status over 3 years. *Archives of Physical Medicine and Rehabilitation*, *81*(4), 465–471. https://doi.org/10.1053/mr.2000.3889.

Gater, D. R., Jr. (2007). Obesity after spinal cord injury. *Physical Medicine and Rehabilitation Clinics of North America*, *18*(2), 333–351. vii https://doi.org/10.1016/j.pmr.2007.03.004.

Gawlitta, D., Li, W., Oomens, C. W., Baaijens, F. P., Bader, D. L., & Bouten, C. V. (2007). The relative contributions of compression and hypoxia to development of muscle tissue damage: An in vitro study. *Annals of Biomedical Engineering*, *35*(2), 273–284. https://doi.org/10.1007/s10439-006-9222-5.

Gawlitta, D., Oomens, C. W., Bader, D. L., Baaijens, F. P., & Bouten, C. V. (2007). Temporal differences in the influence of ischemic factors and deformation on the metabolism of engineered skeletal muscle. *Journal of Applied Physiology (Bethesda, MD: 1985)*, *103*(2), 464–473. https://doi.org/10.1152/japplphysiol.01374.2006.

Gefen, A. (2018). The future of pressure ulcer prevention is here: Detecting and targeting inflammation early. *EWMA Journal*, *19*(2), 7–13.

Gelis, A., Dupeyron, A., Legros, P., Benaim, C., Pelissier, J., & Fattal, C. (2009a). Pressure ulcer risk factors in persons with SCI: Part I: Acute and rehabilitation stages. *Spinal Cord*, *47*(2), 99–107. https://doi.org/10.1038/sc.2008.107.

Gelis, A., Dupeyron, A., Legros, P., Benaim, C., Pelissier, J., & Fattal, C. (2009b). Pressure ulcer risk factors in persons with spinal cord injury part 2: The chronic stage. *Spinal Cord*, *47*(9), 651–661. https://doi.org/10.1038/sc.2009.32.

Goodman, B. L., Schindler, A., Washington, M., Bogie, K. M., & Ho, C. H. (2014). Factors in rehospitalisation for severe pressure ulcer care in spinal cord injury/disorders. *Journal of Wound Care*, *23*(4), 165–166. 168, 170–162 passim 10.12968/jowc.2014.23.4.165.

Gorgey, A. S., & Dudley, G. A. (2007). Skeletal muscle atrophy and increased intramuscular fat after incomplete spinal cord injury. *Spinal Cord*, *45*(4), 304–309. https://doi.org/10.1038/sj.sc.3101968.

Gour-Provencal, G., Mac-Thiong, J. M., Feldman, D. E., Bégin, J., & Richard-Denis, A. (2020). Decreasing pressure injuries and acute care length of stay in patients with acute traumatic spinal cord injury. *Journal of Spinal Cord Medicine*, 1–9. https://doi.org/10.1080/10790268.2020.1718265.

Gray, R. J., Worsley, P. R., Voegeli, D., & Bader, D. L. (2016). Monitoring contractile dermal lymphatic activity following uniaxial mechanical loading. *Medical Engineering & Physics*, *38*(9), 895–903. https://doi.org/10.1016/j.medengphy.2016.04.020.

Grigorian, A., Sugimoto, M., Joe, V., Schubl, S., Lekawa, M., Dolich, M., … Nahmias, J. (2017). Pressure ulcer in trauma patients: a higher spinal cord injury level leads to higher risk. *Journal of the American College of Clinical Wound Specialists*, *9*(1–3), 24–31. e21 https://doi.org/10.1016/j.jccw.2018.06.001.

Groah, S. L., Schladen, M., Pineda, C. G., & Hsieh, C. H. (2015). Prevention of pressure ulcers among people with spinal cord injury: A systematic review. *PM & R: Journal of Injury, Function, and Rehabilitation*, *7*(6), 613–636. https://doi.org/10.1016/j.pmrj.2014.11.014.

Guihan, M., Garber, S. L., Bombardier, C. H., Goldstein, B., Holmes, S. A., & Cao, L. (2008). Predictors of pressure ulcer recurrence in veterans with spinal cord injury. *Journal of Spinal Cord Medicine*, *31*(5), 551–559. https://doi.org/10.1080/10790268.2008.11754570.

Guihan, M., Sohn, M. W., Bauman, W. A., Spungen, A. M., Powell-Cope, G. M., Thomason, S. S., … Bates-Jensen, B. M. (2016). Difficulty in identifying factors responsible for pressure ulcer healing in veterans with spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *97*(12), 2085–2094. e2081 https://doi.org/10.1016/j.apmr.2016.05.025.

Ham, W., Schoonhoven, L., Schuurmans, M. J., & Leenen, L. P. (2014). Pressure ulcers from spinal immobilization in trauma patients: A systematic review. *Journal of Trauma and Acute Care Surgery*, *76*(4), 1131–1141. https://doi.org/10.1097/ta.0000000000000153.

Ham, H. W., Schoonhoven, L. L., Schuurmans, M. M., & Leenen, L. L. (2017). Pressure ulcer development in trauma patients with suspected spinal injury; the influence of risk factors present in the Emergency Department. *International Emergency Nursing*, *30*, 13–19. https://doi.org/10.1016/j.ienj.2016.05.005.

Hastings, B. M., Ntsiea, M. V., & Olorunju, S. (2015). Factors that influence functional ability in individuals with spinal cord injury: A cross-sectional, observational study. *South African Journal of Physiotherapy*, *71*(1), 235. https://doi.org/10.4102/sajp.v71i1.235.

Hatchett, P. E., Mulroy, S. J., Eberly, V. J., Haubert, L. L., & Requejo, P. S. (2016). Body mass index changes over 3 years and effect of obesity on community mobility for persons with chronic spinal cord injury. *Journal of Spinal Cord Medicine*, *39*(4), 421–432. https://doi.org/10.1080/10790268.2015.1133482.

Houghton, P. E., & Campbell, K. (2013). *Canadian best practice guidelines for the prevention and management of pressure ulcers in people with spinal cord injury: A resource handbook for clinicians*. Ontario Neurotrauma Foundation.

Jaul, E., Barron, J., Rosenzweig, J. P., & Menczel, J. (2018). An overview of co-morbidities and the development of pressure ulcers among older adults. *BMC Geriatrics*, *18*(1), 305. https://doi.org/10.1186/s12877-018-0997-7.

Jorge, A., White, M. D., & Agarwal, N. (2018). Outcomes in socioeconomically disadvantaged patients with spinal cord injury: A systematic review. *Journal of Neurosurgery. Spine*, *29*(6), 680–686. https://doi.org/10.3171/2018.5.Spine171242.

Joseph, C., & Nilsson Wikmar, L. (2016). Prevalence of secondary medical complications and risk factors for pressure ulcers after traumatic spinal cord injury during acute care in South Africa. *Spinal Cord*, *54*(7), 535–539. https://doi.org/10.1038/sc.2015.189.

Kirshblum, S. C., Burns, S. P., Biering-Sorensen, F., Donovan, W., Graves, D. E., Jha, A., … Waring, W. (2011). International standards for neurological classification of spinal cord injury (revised 2011). *Journal of Spinal Cord Medicine*, *34*(6), 535–546. https://doi.org/10.1179/204577211x13207446293695.

Kirshblum, S., & Lin, V. W. (2018). *Spinal cord medicine*. Springer Publishing Company.

Kisala, P. A., Tulsky, D. S., Choi, S. W., & Kirshblum, S. C. (2015). Development and psychometric characteristics of the SCI-QOL Pressure Ulcers scale and short form. *Journal of Spinal Cord Medicine*, *38*(3), 303–314. https://doi.org/10.1179/2045772315y.0000000017.

Klotz, R., Joseph, P. A., Ravaud, J. F., Wiart, L., & Barat, M. (2002). The Tetrafigap Survey on the long-term outcome of tetraplegic spinal cord injured persons: Part III. Medical complications and associated factors. *Spinal Cord*, *40*(9), 457–467. https://doi.org/10.1038/sj.sc.3101317.

Krause, J. S., & Broderick, L. (2004). Patterns of recurrent pressure ulcers after spinal cord injury: Identification of risk and protective factors 5 or more years after onset. *Archives of Physical Medicine and Rehabilitation*, *85*(8), 1257–1264. https://doi.org/10.1016/j.apmr.2003.08.108.

Krause, J. S., Vines, C. L., Farley, T. L., Sniezek, J., & Coker, J. (2001). An exploratory study of pressure ulcers after spinal cord injury: Relationship to protective behaviors and risk factors. *Archives of Physical Medicine and Rehabilitation*, *82*(1), 107–113. https://doi.org/10.1053/apmr.2001.18050.

Krishnan, S., Karg, P. E., Boninger, M. L., & Brienza, D. M. (2017). Association between presence of pneumonia and pressure ulcer formation following traumatic spinal cord injury. *Journal of Spinal Cord Medicine*, *40*(4), 415–422. https://doi.org/10.1080/10790268.2016.1180099.

Krishnan, S., Vodovotz, Y., Karg, P. E., Constantine, G., Sowa, G. A., Constantine, F. J., & Brienza, D. M. (2017). Inflammatory mediators associated with pressure ulcer development in individuals with pneumonia after traumatic spinal cord injury: A pilot study. *Archives of Physical Medicine and Rehabilitation*, *98*(9), 1792–1799. https://doi.org/10.1016/j.apmr.2016.12.018.

Kruger, E. A., Pires, M., Ngann, Y., Sterling, M., & Rubayi, S. (2013). Comprehensive management of pressure ulcers in spinal cord injury: Current concepts and future trends. *Journal of Spinal Cord Medicine*, *36*(6), 572–585. https://doi.org/10.1179/2045772313y.0000000093.

Lachenbruch, C., Tzen, Y. T., Brienza, D. M., Karg, P. E., & Lachenbruch, P. A. (2013). The relative contributions of interface pressure, shear stress, and temperature on tissue ischemia: A cross-sectional pilot study. *Ostomy/Wound Management*, *59*(3), 25–34.

Lane, C. A., Selleck, C., Chen, Y., & Tang, Y. (2016). The impact of smoking and smoking cessation on wound healing in spinal cord-injured patients with pressure injuries: A retrospective comparison cohort study. *Journal of Wound, Ostomy, and Continence Nursing*, *43*(5), 483–487. https://doi.org/10.1097/won.0000000000000260.

Le Fort, M., Espagnacq, M., Perrouin-Verbe, B., & Ravaud, J. F. (2017). Risk analyses of pressure ulcer in tetraplegic spinal cord-injured persons: A French long-term survey. *Archives of Physical Medicine and Rehabilitation*, *98*(9), 1782–1791. https://doi.org/10.1016/j.apmr.2016.12.017.

Li, C., DiPiro, N. D., Cao, Y., Szlachcic, Y., & Krause, J. (2016). The association between metabolic syndrome and pressure ulcers among individuals living with spinal cord injury. *Spinal Cord*, *54*(11), 967–972. https://doi.org/10.1038/sc.2016.53.

Li, C., DiPiro, N. D., & Krause, J. (2017). A latent structural equation model of risk behaviors and pressure ulcer outcomes among people with spinal cord injury. *Spinal Cord*, *55*(6), 553–558. https://doi.org/10.1038/sc.2017.9.

Linder-Ganz, E., & Gefen, A. (2009). Stress analyses coupled with damage laws to determine biomechanical risk factors for deep tissue injury during sitting. *Journal of Biomechanical Engineering*, *131*(1). https://doi.org/10.1115/1.3005195, 011003.

Linder-Ganz, E., Shabshin, N., Itzchak, Y., Yizhar, Z., Siev-Ner, I., & Gefen, A. (2008). Strains and stresses in sub-dermal tissues of the buttocks are greater in paraplegics than in healthy during sitting. *Journal of Biomechanics*, *41*(3), 567–580. https://doi.org/10.1016/j.jbiomech.2007.10.011.

Marin, J., Nixon, J., & Gorecki, C. (2013). A systematic review of risk factors for the development and recurrence of pressure ulcers in people with spinal cord injuries. *Spinal Cord*, *51*(7), 522–527. https://doi.org/10.1038/sc.2013.29.

Marion, T. E., Rivers, C. S., Kurban, D., Cheng, C. L., Fallah, N., Batke, J., … Street, J. T. (2017). Previously identified common post-injury adverse events in traumatic spinal cord injury-validation of existing literature and relation to selected potentially modifiable comorbidities: A prospective Canadian cohort study. *Journal of Neurotrauma*, *34*(20), 2883–2891. https://doi.org/10.1089/neu.2016.4933.

Mathew, A., Samuelkamaleshkumar, S., Radhika, S., & Elango, A. (2013). Engagement in occupational activities and pressure ulcer development in rehabilitated South Indian persons with spinal cord injury. *Spinal Cord*, *51*(2), 150–155. https://doi.org/10.1038/sc.2012.112.

Menter, R. R., & Hudson, L. M. (1995). Spinal cord injury clinical outcomes. In S. L. Stover, J. A. De Lisa, & G. G. Whiteneck (Eds.), *Spinal cord injury: Clinical outcomes from the model systems* Aspen Publishers.

Michel, J. M., Willebois, S., Ribinik, P., Barrois, B., Colin, D., & Passadori, Y. (2012). As of 2012, what are the key predictive risk factors for pressure ulcers? Developing French guidelines for clinical practice. *Annals of Physical and Rehabilitation Medicine*, *55*(7), 454–465. https://doi.org/10.1016/j.rehab.2012.08.003.

Molano Alvarez, E., Murillo Perez Mdel, A., Salobral Villegas, M. T., Dominguez Caballero, M., Cuenca Solanas, M., & Garcia Fuentes, C. (2004). Pressure sores secondary to immobilization with cervical collar: A complication of acute cervical injury. *Enfermería Intensiva*, *15*(3), 112–122.

Morita, T., Yamada, T., Watanabe, T., & Nagahori, E. (2015). Lifestyle risk factors for pressure ulcers in community-based patients with spinal cord injuries in Japan. *Spinal Cord*, *53*(6), 476–481. https://doi.org/10.1038/sc.2015.18.

Mortenson, W. B., & Miller, W. C. (2008). A review of scales for assessing the risk of developing a pressure ulcer in individuals with SCI. *Spinal Cord*, *46* (3), 168–175. https://doi.org/10.1038/sj.sc.3102129.

National Spinal Cord Injury Statistical Center. (2006). *2006 annual statistical report*. University of Alabama at Birmingham.

National Spinal Cord Injury Statistical Center. (2019). *The 2019 annual statistical report for the spinal cord injury model systems*. Birmingham, Alabama: National Spinal Cord Injury Statistical Center.

Oomens, C. W., Loerakker, S., & Bader, D. L. (2010). The importance of internal strain as opposed to interface pressure in the prevention of pressure related deep tissue injury. *Journal of Tissue Viability*, *19*(2), 35–42. https://doi.org/10.1016/j.jtv.2009.11.002.

Parent, S., Barchi, S., LeBreton, M., Casha, S., & Fehlings, M. G. (2011). The impact of specialized centers of care for spinal cord injury on length of stay, complications, and mortality: A systematic review of the literature. *Journal of Neurotrauma*, *28*(8), 1363–1370. https://doi.org/10.1089/neu.2009.1151.

Park, J. W., Seo, C. H., Han, S. H., & Lee, Y. G. (2011). Sympathetic influence on biomechanical skin properties after spinal cord injury. *Spinal Cord*, *49* (2), 236–243. https://doi.org/10.1038/sc.2010.95.

Patterson, R. P., Cranmer, H. H., Fisher, S. V., & Engel, R. R. (1993). The impaired response of spinal cord injured individuals to repeated surface pressure loads. *Archives of Physical Medicine and Rehabilitation*, *74*(9), 947–953.

Ploumis, A., Kolli, S., Patrick, M., Owens, M., Beris, A., & Marino, R. J. (2011). Length of stay and medical stability for spinal cord-injured patients on admission to an inpatient rehabilitation hospital: A comparison between a model SCI trauma center and non-SCI trauma center. *Spinal Cord*, *49*(3), 411–415. https://doi.org/10.1038/sc.2010.132.

Post, M. W., Dallmeijer, A. J., Angenot, E. L., van Asbeck, F. W., & van der Woude, L. H. (2005). Duration and functional outcome of spinal cord injury rehabilitation in the Netherlands. *Journal of Rehabilitation Research and Development*, *42*(3 Suppl. 1), 75–85.

Powers, J., Daniels, D., McGuire, C., & Hilbish, C. (2006). The incidence of skin breakdown associated with use of cervical collars. *Journal of Trauma Nursing*, *13*(4), 198–200.

Rabadi, M. H., & Vincent, A. S. (2011). Do vascular risk factors contribute to the prevalence of pressure ulcer in veterans with spinal cord injury? *Journal of Spinal Cord Medicine*, *34*(1), 46–51. https://doi.org/10.1179/107902610x12923394765652.

Rappl, L. M. (2008). Physiological changes in tissues denervated by spinal cord injury tissues and possible effects on wound healing. *International Wound Journal*, *5*(3), 435–444. https://doi.org/10.1111/j.1742-481X.2007.00360.x.

Richard-Denis, A., Thompson, C., Bourassa-Moreau, E., Parent, S., & Mac-Thiong, J. M. (2016). Does the acute care spinal cord injury setting predict the occurrence of pressure ulcers at arrival to intensive rehabilitation centers? *American Journal of Physical Medicine & Rehabilitation*, *95*(4), 300–308. https://doi.org/10.1097/phm.0000000000000381.

Richards, S., Waites, K., Chen, Y., Kogos, S., & Schmitt, M. M. (2004). The epidemiology of secondary conditions following spinal cord injury. *Topics in Spinal Cord Injury Rehabilitation*, *10*(1), 15–29. https://doi.org/10.1310/yxm3-85yw-8vug-nnur.

Rodriguez, G. P., Claus-Walker, J., Kent, M. C., & Stal, S. (1986). Adrenergic receptors in insensitive skin of spinal cord injured patients. *Archives of Physical Medicine and Rehabilitation*, *67*(3), 177–180. https://doi.org/10.1016/0003-9993(86)90073-0.

Rodriguez, G., & Markowski, J. (1995). Changes in skin morphology and its relationship to pressure ulcer incidence in spinal cord injury [ACRM abstract]. *Archives of Physical Medicine and Rehabilitation*, *76*(6), 593.

Roubenoff, R. (1999). The pathophysiology of wasting in the elderly. *Journal of Nutrition*, *129*(1S Suppl), 256s–259s. https://doi.org/10.1093/jn/129.1.256S.

Ruschkewitz, Y., & Gefen, A. (2011). Cellular-scale transport in deformed skeletal muscle following spinal cord injury. *Computer Methods in Biomechanics and Biomedical Engineering*, *14*(5), 411–424. https://doi.org/10.1080/10255842.2010.529804.

Salcido, R., Donofrio, J. C., Fisher, S. B., LeGrand, E. K., Dickey, K., Carney, J. M., … Liang, R. (1994). Histopathology of pressure ulcers as a result of sequential computer-controlled pressure sessions in a fuzzy rat model. *Advances in Wound Care*, *7*(5), 23–24. 26, 28 passim.

Saunders, L. L., & Krause, J. S. (2010). Personality and behavioral predictors of pressure ulcer history. *Topics in Spinal Cord Injury Rehabilitation*, *16*(2), 61–71. https://doi.org/10.1310/sci1602-61.

Saunders, L. L., Krause, J. S., & Acuna, J. (2012). Association of race, socioeconomic status, and health care access with pressure ulcers after spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *93*(6), 972–977. https://doi.org/10.1016/j.apmr.2012.02.004.

Saunders, L. L., Krause, J. S., Peters, B. A., & Reed, K. S. (2010). The relationship of pressure ulcers, race, and socioeconomic conditions after spinal cord injury. *Journal of Spinal Cord Medicine*, *33*(4), 387–395.

Scelsi, R. (2001). Skeletal muscle pathology after spinal cord injury: Our 20 year experience and results on skeletal muscle changes in paraplegics, related to functional rehabilitation. *BAM-PADOVA*, *11*(2), 75–86.

Schwab, J. M., Zhang, Y., Kopp, M. A., Brommer, B., & Popovich, P. G. (2014). The paradox of chronic neuroinflammation, systemic immune suppression, autoimmunity after traumatic chronic spinal cord injury. *Experimental Neurology*, *258*, 121–129. https://doi.org/10.1016/j.expneurol.2014.04.023.

Sheerin, F., Gillick, A., & Doyle, B. (2005). Pressure ulcers and spinal-cord injury: Incidence among admissions to the Irish national specialist unit. *Journal of Wound Care*, *14*(3), 112–115. https://doi.org/10.12968/jowc.2005.14.3.26750.

Smith, B. M., Guihan, M., LaVela, S. L., & Garber, S. L. (2008). Factors predicting pressure ulcers in veterans with spinal cord injuries. *American Journal of Physical Medicine & Rehabilitation*, *87*(9), 750–757. https://doi.org/10.1097/PHM.0b013e3181837a50.

Sopher, R., Nixon, J., Gorecki, C., & Gefen, A. (2010). Exposure to internal muscle tissue loads under the ischial tuberosities during sitting is elevated at abnormally high or low body mass indices. *Journal of Biomechanics*, *43*(2), 280–286. https://doi.org/10.1016/j.jbiomech.2009.08.021.

Sopher, R., Nixon, J., Gorecki, C., & Gefen, A. (2011). Effects of intramuscular fat infiltration, scarring, and spasticity on the risk for sitting-acquired deep tissue injury in spinal cord injury patients. *Journal of Biomechanical Engineering*, *133*(2). https://doi.org/10.1115/1.4003325, 021011.

Street, J. T., Noonan, V. K., Cheung, A., Fisher, C. G., & Dvorak, M. F. (2015). Incidence of acute care adverse events and long-term health-related quality of life in patients with TSCI. *Spine Journal*, *15*(5), 923–932. https://doi.org/10.1016/j.spinee.2013.06.051.

Stroupe, K., Manheim, L., Evans, C., Guihan, M., Ho, C., Li, K., … Smith, B. (2011). Cost of treating pressure ulcers for veterans with spinal cord injury. *Topics in Spinal Cord Injury Rehabilitation*, *16*(4), 62–73. https://doi.org/10.1310/sci1604-62.

Tate, D. G., Forchheimer, M. B., Krause, J. S., Meade, M. A., & Bombardier, C. H. (2004). Patterns of alcohol and substance use and abuse in persons with spinal cord injury: Risk factors and correlates. *Archives of Physical Medicine and Rehabilitation*, *85*(11), 1837–1847.

Thorfinn, J., Sjöberg, F., & Lidman, D. (2002). Sitting pressure and perfusion of buttock skin in paraplegic and tetraplegic patients, and in healthy subjects: A comparative study. *Scandinavian Journal of Plastic and Reconstructive Surgery and Hand Surgery*, *36*(5), 279–283. https://doi.org/10.1080/028443102320791824.

van der Wielen, H., Post, M. W., Lay, V., Glasche, K., & Scheel-Sailer, A. (2016). Hospital-acquired pressure ulcers in spinal cord injured patients: Time to occur, time until closure and risk factors. *Spinal Cord*, *54*(9), 726–731. https://doi.org/10.1038/sc.2015.239.

Verschueren, J. H., Post, M. W., de Groot, S., van der Woude, L. H., van Asbeck, F. W., & Rol, M. (2011). Occurrence and predictors of pressure ulcers during primary in-patient spinal cord injury rehabilitation. *Spinal Cord*, *49*(1), 106–112. https://doi.org/10.1038/sc.2010.66.

White, B. A. B., Dea, N., Street, J. T., Cheng, C. L., Rivers, C. S., Attabib, N., … Dvorak, M. F. (2017). The economic burden of urinary tract infection and pressure ulceration in acute traumatic spinal cord injury admissions: Evidence for comparative economics and decision analytics from a matched case-control study. *Journal of Neurotrauma*, *34*(20), 2892–2900. https://doi.org/10.1089/neu.2016.4934.

Wilczweski, P., Grimm, D., Gianakis, A., Gill, B., Sarver, W., & McNett, M. (2012). Risk factors associated with pressure ulcer development in critically ill traumatic spinal cord injury patients. *Journal of Trauma Nursing*, *19*(1), 5–10. https://doi.org/10.1097/JTN.0b013e31823a4528.

Wu, G. A., & Bogie, K. M. (2013). Not just quantity: Gluteus maximus muscle characteristics in able-bodied and SCI individuals—Implications for tissue viability. *Journal of Tissue Viability*, *22*(3), 74–82. https://doi.org/10.1016/j.jtv.2013.03.003.

Yalcin, E., Akyuz, M., Onder, B., Unalan, H., & Degirmenci, I. (2013). Skin thickness on bony prominences measured by ultrasonography in patients with spinal cord injury. *Journal of Spinal Cord Medicine*, *36*(3), 225–230. https://doi.org/10.1179/2045772312y.0000000088.

Zeevi, T., Levy, A., Brauner, N., & Gefen, A. (2018). Effects of ambient conditions on the risk of pressure injuries in bedridden patients-multi-physics modelling of microclimate. *International Wound Journal*, *15*(3), 402–416. https://doi.org/10.1111/iwj.12877.

Chapter 6

Venous thromboembolism in spinal cord injury—Prophylaxis, diagnosis and treatment

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Abbreviations

aPTT	activated partial thromboplastin time
CSCM	Consortium for Spinal Cord Medicine
CT	computed tomography
CTPA	CT pulmonary angiography
CUS	compression ultrasonography
DVT	deep venous thrombosis
GCS	graduated compression stockings
IPCD	intermittent pneumatic compression device
IVCF	inferior vena cava filter
LMWH	low-molecular-weight heparin
MRI	magnetic resonance imaging
PE	pulmonary embolism
PESI	pulmonary embolism severity index
SCI	spinal cord injury
UH	unfractionated heparin
VKA	vitamin K antagonists
VTE	venous thromboembolism

Introduction

The classical Virchow's postulate links the occurrence of venous thromboembolism (VTE) to the presence of a disruption of the circulatory flux, a damage of the endothelial tissue, or a hypercoagulability state. Immobility and palsy are prominent risk factors for VTE and are frequently seen in clinical rules used for its diagnosis (Duffett, Castellucci, & Forgie, 2020). Individuals with a spinal cord injury (SCI) present frequently not only with impaired mobility due to the associated neurological motor deficit, but endothelial injuries and a hypercoagulability condition may also arise as a consequence of the lesion mechanism, such as trauma or neoplasms, as well as secondary complications like infections or pressure ulcers (Agarwal & Mathur, 2009; Chung et al., 2014) (Fig. 1). Thus, SCI is associated with an increased risk of venous thromboembolism in its acute phase that may extend to its chronic phase (Casas, Sánchez, Arias, & Masip, 1977; Godat, Kobayashi, Chang, & Coimbra, 2015; Todd et al., 1976).

Many advances have been made regarding risk stratification for prophylaxis and diagnostic algorithms for VTE in the general population. The proposed strategies and clinical rules however have not been validated for individuals with SCI, posing a challenge for physicians involved in the care of such patients.

Epidemiology

The reported prevalence of VTE in spinal cord injury is variable. A study by Todd et al. (1976) based on screening in asymptomatic patients with serial scintigraphy with labeled fibrinogen identified clots in 100% of the 20 studied patients.

Diagnosis and Treatment of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822498-4.00006-3

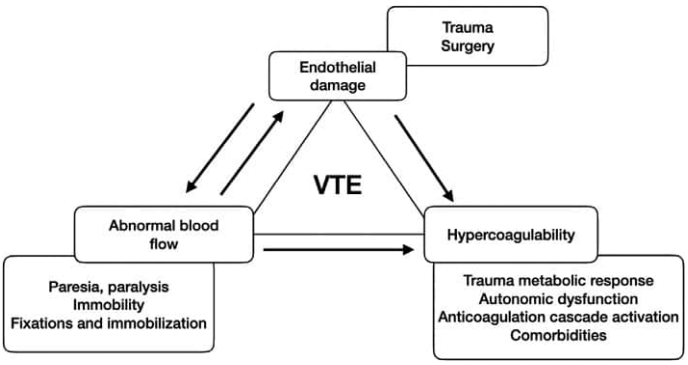

FIG. 1 Virchow's triad in spinal cord injury. This schematic representation illustrates how conditions frequently present in SCI exert a direct influence on VTE risk. *VTE*, venous thromboembolism; *SCI*, spinal cord injury. *(Based on Piran, S., & Schulman, S. (2019). Thromboprophylaxis in patients with acute spinal cord injury: A narrative review.* Semin Thromb Hemost, 45*(2), 150–156. © Georg Thieme Verlag KG.)*

Other studies that are based on clinical symptoms or less sensitive screening methods report a prevalence of 10% to 15% for deep venous thrombosis (DVT) and 5% to 10% for pulmonary embolism (PE).

The risk appears to be the highest in the first 12 weeks after the injury (Agarwal & Mathur, 2009; Casas et al., 1977), with a retrospective cohort study by Chung et al. (2014) reporting a 17 times risk increase for DVT and 3.5 times for EP within 3 months after an SCI in comparison to age- and sex-matched individuals from the general population. A study by Green (1992), however, didn't find an increased risk in the first 3 days after the lesion. It is postulated that factors like the flaccid paralysis occurring during the spinal shock phase and the need for immobilization secondary to multiple trauma may be of significance in the augmented risk during the acute stage of SCI (Fig. 2). Moreover, the dysregulation of the autonomic nervous system may lead to an imbalance of the hemostatic and fibrinolytic systems, and there is evidence of increased platelet reactivity to collagen and an imbalance in factor VIII to factor VIII-C ration (Kelly, Yoder, Tang, & Wakefield, 2010).

Published data on the incidence of VTE during the sub-acute and chronic phases of SCI are conflicting. There appears to be a reduction in this risk, approaching that of the general population, although somewhat higher. A study by Giorgi Pierfranceschi et al. (2013) reported an incidence of 34.4 VTE events per 100,000 patient-year during the first 90 days which was reduced to 0.3 events per 100,000 patient-year thereafter. Data from a systematic review indicate a PE incidence ranging from 0.5% to 6.0% and a DVT incidence between 2.0% and 8.0% in the sub-acute phase in patients under different prophylaxis strategies (Alabed, Belci, Van Middendorp, Al Halabi, & Meagher, 2016). The above-mentioned study by Chung et al. (2014) reported a cumulative risk of 1.19 times after the first year of the SCI, and studies evaluating individuals in the chronic stage demonstrated DVT incidences as low as 0.55 per 10,000 patients-day (de Almeida, Rodrigues, et al., 2019) and as high as 8% (Mackiewicz-Milewska et al., 2016) in patients admitted for rehabilitation treatment.

Without adequate treatment, the estimated mortality rates may reach 8% for DVT and 25% for PE. In studies performed with individuals with SCI, VTE may be responsible for up to 3% of all the deaths in those admitted for rehabilitation

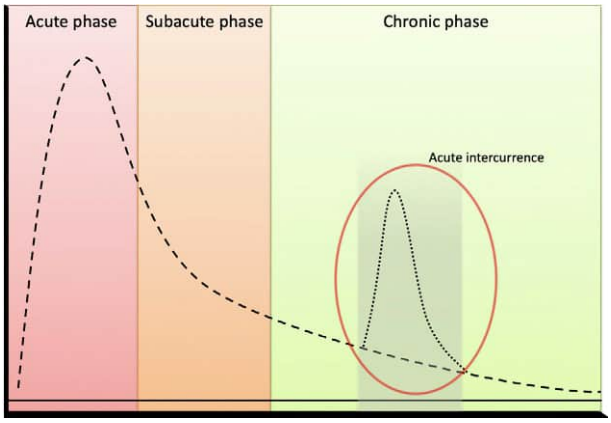

FIG. 2 Venous thromboembolism risk in spinal cord injury. VTE risk in SCI *(dashed lined)*: The risk is higher during the acute phase and decreases thereafter. Intercurrent clinical or surgical conditions may transiently elevate the risk during the chronic phase *(dotted line)*. The *solid line* represents the average VTE risk in the general population. *VTE*, venous thromboembolism; *SCI*, spinal cord injury.

(Green et al., 1994). In addition, individuals affected by VTE may present further clinical complications such as post-thrombotic syndrome, pulmonary hypertension, and recurrent VTE events (Kearon, 2003).

Screening

The rationale for screening for asymptomatic VTE is based on its high incidence in SCI, therefore being a probable and preventable cause of death during the acute phase. The identification of an asymptomatic thrombus could then lead to immediate treatment, which could hinder further complications. Proposed approaches involve performing serial lower limb duplex ultrasound (Kadyan, Clinchot, & Colachis, 2004), D-Dimer testing, or both used in combination (Kumagai et al., 2020; Masuda, Ueta, Shiba, & Iwamoto, 2015).

Even though the majority of thrombi have an origin in the lower limb circulation, up to half resolve spontaneously within 72 h, and only around a sixth of them lead to disturbance in the deep vein circulation (Kearon, 2003). Screening studies have been successful in demonstrating high sensitivity and in identifying a high number of asymptomatic VTE. As the majority of these were designed as diagnostic and not therapeutic studies, there is uncertainty about the clinical benefits of this strategy which may well lead to overdiagnosis and consequently overtreatment. Considering the bleeding risk associated with therapeutic anti-coagulation, patients might be exposed to unnecessary use of a dangerous medication.

Prophylaxis

Acute phase

Since the 1970s, uncontrolled studies proposed the use of pharmacological prophylaxis in acute SCI (Casas et al., 1977). Different approaches involving the use of unfractionated heparin (UH), vitamin K antagonists (VKA), low-molecular-weight heparin (LMWH), intermittent pneumatic compression (IPC) and electrostimulation alone or in different combinations have been tested. In comparison to mechanical prophylaxis alone, the use of pharmacological prophylaxis may lead to an absolute risk reduction of up to 15% in the incidence of VTE during the acute phase of SCI (Halim, Chhabra, Arora, & Kumar, 2014).

The major advantage of LMWH in comparison to UH is related to an average of 4% absolute reduction in the risk of bleeding (Investigators, 2003; Thumbikat, Poonnoose, Balasubrahmaniam, Ravichandran, & McClelland, 2002). Enoxaparin was the most frequently used LMWH in clinical trials involving individuals with SCI, but dosing strategies and duration of treatment were greatly varied, from 20 to 40 mg once a day, to 30 mg twice a day, from as little as 14 days up to 8 weeks or longer times based on patient mobility (Frisbie & Sasahara, 1981; Green et al., 1990; Merli et al., 1988; Merli, Crabbe, Doyle, Ditunno, & Herbision, 1992; Spivack & Aisen, 1997; Thumbikat et al., 2002), preventing these studies from being combined in a meta-analysis. Until now, we could not find any study comparing the same dosing strategy with different durations, allowing a more precise evaluation of the risk-benefit profiles of longer or shorter prophylaxis strategies.

Current guidelines agree that the pharmacological prophylaxis should be initiated as soon as possible during the acute phase, preferably within the first 72 h of the injury, taking into consideration the clinical status and, most importantly, the assessment of the risk of bleeding of the individual patient (CSCM, 2016; Fehlings et al., 2017). Recommendations regarding the duration of prophylaxis continue to be at least 8 and up to 12 weeks, which may be prolonged based on the assessment of the individual risk of VTE.

Sub-acute and chronic phase

Studies comparing prophylaxis strategies during the chronic phase of SCI are scarce. It is important to emphasize that in poor resource areas with limited access to specialized care, many individuals with SCI may only be admitted to inpatient rehabilitation already in the chronic phase. The delayed access to rehabilitation services may lead to early complications, such as structured articular mobility restrictions, pressure ulcers, recurrent infections, and obesity, which may further influence the risk of developing a VTE episode (Jorge, White, & Agarwal, 2018).

As discussed above, the risk of VTE decreases after the acute phase. The use of pharmacological prophylaxis is usually safe but encompasses nevertheless an elevation of the patient's basal risk of bleeding. Minor bleedings (hematomas at the injection site) may occur in up to 64% of patients during rehabilitation (Eichinger et al., 2018), and major bleeding events have been reported in individuals with SCI receiving prophylactic doses of LMWH (de Almeida, Gonzaga, Beraldo, & Amado, 2019). We suggest taking into consideration the individual patient risk factors, such as comorbidity, mobility, independence, concomitant use of other medications, presence of infections and near surgical procedures to decide whether or

not to initiate the pharmacological prophylaxis. Moreover, as suggested by the Consortium for Spinal Cord Medicine (CSCM) Clinical Practice Guidelines (2016), services involved in the care of individuals with SCI should have established policies regarding thromboprophylaxis which should be periodically revised and audited.

Non-pharmacological methods

Maintenance of adequate hydration, early mobilization, physical rehabilitation and promoting independence are classically described as general methods that should be applied to every patient. Intermittent pneumatic compression devices (IPCD) may be used as an alternative prophylaxis method if the risk of complications with the use of pharmacological methods is deemed to be prohibitive (CSCM, 2016). Only a small case series evaluated IPCD without a pharmacological method in individuals with SCI, reporting a 43% incidence of DVT mostly detected by screening, and only 18% of these being a proximal DVT (Chung, Lee, Kim, & Eoh, 2011). These devices are used continuously and, therefore, may interfere with the acute rehabilitation program.

A meta-analysis demonstrated that graduated compression stocking (GCS) may be effective in preventing DVT in hospitalized patients, especially those submitted to surgical and orthopedic interventions. This benefit was also seen in those receiving background thromboprophylaxis. Only two studies have used LMWH as background prophylaxis and no difference was found with the addition of GCS. Furthermore, none of the included studies compared GCS alone versus a pharmacological method (Sachdeva, Dalton, & Lees, 2018). Moreover, these devices may cause skin lesions and should not be used in conditions such as peripheral arterial disease and decompensated heart failure.

Current evidence doesn't support the prophylactic use of inferior vena cava filters (IVCF), and there may be an increased risk of VTE in individuals with SCI who underwent an IVCF implantation, even when receiving pharmacological prophylaxis (Gorman, Qadri, & Rao-Patel, 2009).

Diagnosis

The usual approach in the individual with suspected DVT or PE involves a clinical evaluation to estimate his pre-test probability based on signs, symptoms and risk factors, followed by a diagnostic strategy to rule in or rule out the diagnosis. The utility of diagnostic algorithms associated with clinical rules such as the Wells' criteria for DVT or PE, the Geneva score for PE or the PERC have been demonstrated in diverse clinical scenarios (Tritschler, Kraaijpoel, Le Gal, & Wells, 2018), but as of yet, are not validated for individuals with SCI.

Some of the clinical factors evaluated by these rules may have different significance and presentation in SCI (Table 1). Paresis or paralysis may be a major risk factor during the acute phase of an SCI, but this may not extend to the chronic phase. Benign postural lower limb edema is a frequent clinical sign in these individuals and may impair the clinical evaluation of a suspected DVT. Furthermore, the autonomic dysfunction in lesions above T6 may impair tachycardic responses (Krassioukov et al., 2012), as evaluated in some scores and pain complaints may be absent due to neurological impairment. In this scenario, it is reasonable to maintain a high level of clinical suspicion.

The test of choice for confirming or excluding the diagnosis will be based on the previously estimated pre-test probability. Moreover, the clinician should also consider how invasive the test is, the availability of the method, and trained staff for performing and interpreting the results and how high the clinical suspicion of DVT or PE is.

D-dimer

The D-dimer is a fibrin degradation product that is positive not only in VTE. Its high sensitivity—especially in quantitative and semi-quantitative tests—in general patients makes it a helpful test for ruling out the diagnosis of both DVT and PE in those with a low pre-test probability (Tritschler et al., 2018). This high sensitivity has been demonstrated in low-quality evidence studies in patients with SCI (Roussi et al., 1999) and other neurological conditions under rehabilitation treatment (Akman, Cetin, Bayramoglu, Isiklar, & Kilinc, 2004), but not as part of a diagnostic algorithm in these populations. The low specificity associated with the test is not enough to confirm the diagnosis; therefore, a positive result will lead to further testing. Despite its high sensitivity in patients presenting a high pre-test probability, a negative result won't be enough to safely rule out the diagnosis.

TABLE 1 Variables in clinical rules that may be influenced by spinal cord injury.

Wells' criteria for DVT
Asymmetric leg swelling
Whole limb edema
Tenderness along the deep venous system
Wells' criteria for PE
Heart rate above 100 bpm
Geneva score
Heart rate above 100 bpm (original score)
Heart rate above 94 bpm (revised and simplified scores)
Limb pain (revised and simplified scores)
PERC rule
Heart rate above 100 bpm
Unilateral edema

The table displays some of the risk factors present on commonly used clinical rules that may be difficult to evaluate due to neurological and autonomic dysfunction in SCI.

Lower limb ultrasonography

Compression ultrasound examination (CUS) is a highly sensitive and specific non-invasive test that may be performed as a point-of-care diagnostic strategy by trained physicians (Tritschler et al., 2018). Based on its widespread availability, non-invasiveness and ease of performance, CUS is the method of choice for the evaluation of patients with moderate or high pre-test DVT probability. This can be performed in strategies that evaluate the proximal venous circulation up to the level of the popliteal vein, requiring a follow-up examination after 1 week if negative, or a complete scan from the common femoral vein down to the deep calf veins, without a need for retesting (Wells, Ihaddadene, Reilly, & Forgie, 2018). Even though there is no specific study on the accuracy of this method in patients in SCI patients, ultrasonography seems like a reasonable method due to its availability and good performance of point-of-care examinations in comparison with expert radiologist evaluation, which may avoid delays in the diagnostic process (Fischer et al., 2019). For this same reason, lower limb sonography may be an acceptable strategy as a first examination to rule in PE in patients with a higher likelihood of this diagnosis and with clinical signs of DVT (Wells et al., 2018), but an isolated negative test is not enough to exclude it.

Lower limb venography

Venography, computerized tomography (CT), and magnetic resonance (MRI) venography are invasive methods requiring the use of contrast. Venography is considered the "gold standard" for the evaluation of the limb venous circulation. Even though a normal venography allows safe withholding of anti-coagulation, it is a limited method due to its restricted availability, costs, discomfort, and difficulties in obtaining standardized and good-quality images and proper evaluation (Bates et al., 2012). CT and MRI venography are promising methods that have demonstrated sensitivity and specificity around 95% in meta-analysis, but with high heterogeneity between studies (Abdalla et al., 2015; Thomas, Goodacre, Sampson, & van Beek, 2008). Therefore, they are not considered first-line diagnostic methods but are useful in situations where ultrasonography can't safely exclude the diagnosis, such as thrombosis in proximal or pelvic veins that are not compressible or in obese patients (Tritschler et al., 2018; Wells et al., 2018).

CT pulmonary angiography

CT pulmonary angiography (CTPA) has replaced ventilation/perfusion scintigraphy as the method of choice for the diagnosis of PE (Tritschler et al., 2018). With a high sensitivity and specificity, CTPA allows a fast and comprehensive evaluation of the pulmonary circulation and is largely available (Konstantinides et al., 2019). It also allows the evaluation of

pulmonary images which are useful for differential diagnosis. The constantly evolving technology and quality of images have led to a continual increase in sensitivity and, consequently, in the reported incidence of PE in the general population. This elevation occurred despite the current higher awareness of VTE and adherence to prophylaxis strategies and, according to studies performed in the United States, no concurrent elevation in age-adjusted mortality was observed, which suggests the occurrence of overdiagnosis (Dobler, 2019).

Small thrombus formation is not an infrequent event. One of the physiological functions of the normal lung may be to serve as a clot filter avoiding venous thrombi from reaching the systemic arterial circulation (Swan, Hitchen, Klok, & Thachil, 2019). The physician should, therefore, be aware of the potential risk involved in over-testing patients for PE, for instance, screening patients with a diagnosis of DVT for an asymptomatic PE.

Treatment

Anti-coagulation is the cornerstone of the treatment of VTE (Di Nisio, van Es, & Büller, 2016). The primary goal of the treatment is to avoid acute complications such as further embolization of deep vein originated thrombi, further impairment of pulmonary function or pulmonary circulation with consequent cardiovascular instability (Burgazli et al., 2013). Adequate quality therapeutic anti-coagulation may also improve late outcomes, such as post-thrombotic syndrome (Ten Cate-Hoek, 2018). Affected individuals should receive treatment to achieve rapid anti-coagulation with posterior long-term maintenance with adequate time in therapeutic range (TTR). A summary of commonly used medications is presented in Table 2.

Initial management

Initial treatment aims to quickly achieve effective anti-coagulation, which can be done both with parenteral and oral agents. Before initiating any anti-coagulant, the risk of bleeding as well as hemodynamic conditions of the individual should be assessed.

TABLE 2 Commonly used anti-coagulant agents.

	Class	Dosing	Effect reversal
Parenteral agents			
Heparin	UH	Bolus: 80 μg/kg IV Maintenance: 18 μg/kg h IV Adjust dose according to aPTT	Protamine
Enoxaparin	LMWH	1 mg/kg 12/12 h SC	May benefit from protamine use
Fondaparinux	Pentasaccharide	<50 kg: 5 mg SC daily 50–100 kg: 7.5 mg SC daily >100 kg: 10 mg SC daily	May benefit from andexanet alfa (off label) or activated prothrombin complex concentrate
Oral agents			
Apixaban	Factor Xa inhibitor	10 mg twice daily for 7 days followed by 5 mg twice daily	– Andexanet alfa (off label for edoxaban reversal)
Rivaroxaban		15 mg twice daily for 21 days followed by 20 mg daily	
Edoxaban		60 mg once daily	
Dabigatran	Direct thrombin inhibitor	150 mg twice daily	– Idarucizumab
Warfarin	Vitamin K antagonist	2–10 mg once daily for 2 days. Adjust according to INR	– Vitamin K (intravenous preparations) – Four-factor prothrombin complex concentrate – Fresh-frozen plasma

Characteristics of some of the anti-coagulants commonly used in clinical practice. Detailed information about anti-coagulation reversal is beyond the scope of this chapter. We recommend referring to the manufacturer's information for detailed dosing and administration orientation. aPTT, activated partial thromboplastin time; *INR*, international normatized ratio; *IV*, intravenous; *LMWH*, low-molecular-weight heparin; *SC*, subcutaneous; *UH*, unfractionated heparin.

There's no validated score for bleeding risk estimation in individuals with SCI receiving anti-coagulant treatment; therefore, a thorough assessment of comorbidities, previous traumas, and surgeries is mandatory (Table 3). For hemodynamically unstable individuals and those who may need urgent or emergent surgery or that may benefit from thrombolytic therapy, the use of short-acting and easily reversible anti-coagulants should be preferred.

Unfractionated heparin (UH) is a polysaccharide solution with an average molecular weight of 15,000 Da, most of them with a low binding affinity with the anti-thrombin molecule (Onishi, St Ange, Dordick, & Linhardt, 2016). It is administered intravenously initially as a bolus followed by a continuous infusion with monitoring of the activated partial thromboplastin time (aPTT) and infusion adjustments every 4 to 6 h (Hull et al., 1992; Raschke, Reilly, Guidry, Fontana, & Srinivas, 1993). It is the therapy of choice for individuals with chronic renal disease as well as for those in whom the need for rapid interruption and reversal of the anti-coagulant effect is a concern, which can be achieved with the use of the antidote protamine (Di Nisio et al., 2016).

Low-molecular-weight heparin (LMWH) is obtained through the enzymatic breakdown of heparin polysaccharides, potentiating its affinity to the anti-thrombin molecule and, consequently, its ability to inhibit factor Xa (Onishi et al., 2016). In comparison to UH, LMWH treatment is associated with a lower occurrence of thrombotic complications and major hemorrhages (Robertson & Jones, 2017). Other advantages are facilitated fixed weight-based dosing, a longer half-life facilitating dose scheduling, and a lower risk of heparin-induced thrombocytopenia (Weitz, 1997).

Pentasaccharides, such as Fondaparinux, are ultralow-molecular-weight heparins with a high binding affinity to anti-thrombin that strongly and indirectly inhibits factor Xa. Its major advantage is the facilitated dosing scheme based on a weight range. According to a meta-analysis, pentasaccharides may be as effective and safe when compared to standard treatments (Brandao, Junqueira, Rollo, & Sobreira, 2017). Studies appraised in this meta-analysis used different types of comparison treatments including UH or LMWH followed by oral vitamin K antagonists (VKA) which may have influenced the final results.

Novel oral anti-coagulants (NOACs) were developed aiming to eliminate the difficulties encountered when managing individuals using VKAs. They have a rapid onset, predictable therapeutic effect, a fixed-dose schedule, do not require laboratory monitoring nor dose adjustments, and appear to be safer regarding bleeding risk compared to VKAs (Oliphant, Jacobs, Kabra, & Das, 2013). Their action can be directed to thrombin (Dabigatran) or factor Xa inhibition (Apixaban, Edoxaban, and Rivaroxaban).

Only Rivaroxaban and Apixaban were evaluated as initial and long-term therapy without previous administration of LMWH. Rivaroxaban was evaluated both in a DVT (Bauersachs et al., 2010) and on a PE trial (Büller et al., 2012), each one with more than 3000 individuals, whereas only a third of the 5400 studied individuals on the Apixaban trial had PE (Agnelli et al., 2013). Overall, they were shown to be non-inferior to standard treatment, with a trend to less bleeding events (Gómez-Outes, Terleira-Fernández, Lecumberri, Suárez-Gea, & Vargas-Castrillón, 2014), however, to this moment, they are still more expensive in comparison to VKAs.

Anti-coagulation after initial management

After initial management, anti-coagulant treatment is maintained for 3 months or longer depending on the clinical presentation (whether DVT or PE), the individual ability to comply with the treatment, risk of recurrence, bleeding risk, costs, and clinical intercurrences. Oral agents are the preferred strategy, but LMWH and pentasaccharides are reasonable alternatives.

Vitamin K antagonists are the most frequently used oral anti-coagulant agents in the outpatient setting. Despite the necessity of constant laboratory monitoring and their narrow therapeutic range (Oliphant et al., 2013), they present lowest monthly cost considering the medication alone, are widely available and clinicians have been managing individuals using these agents for more than 60 years (Thean & Alberghini, 2016). The quality of the anti-coagulation is measured by the time in therapeutic range (TTR). A TTR below 65% is associated with a higher risk of both thromboembolic and bleeding events. Strategies to improve the TTR include management in anti-coagulation clinics, use of decision support systems, and point-of-care or self-testing (Schein et al., 2016). Adequate support through anti-coagulation clinics was shown to be effective even in poor resource and low level of formal education settings (Costa, Ferreira, Valacio, & Vieira Moreira, 2011).

NOACs are also used in long-term coagulation. Besides the above mentioned Apixaban and Rivaroxaban, the factor Xa inhibitor Edoxaban and the direct thrombin inhibitor Dabigatran have also been tested for the chronic anti-coagulation in individuals with VTE with results lying within the non-inferiority margin for VTE recurrence. There's no study with a direct comparison between these agents. A network meta-analysis pooling studies of the four agents failed to identify any specific benefit regarding VTE recurrence or VTE-related death, but there was a trend toward a reduction of clinically relevant bleeding with apixaban and dabigatran (Cohen et al., 2015). Patients using NOACs probably have a better TTR; nevertheless, the clinician should be aware that these medications are not indicated for patients with reduced renal function

TABLE 3 Risk factors for bleeding with anti-coagulant therapy.

Risk factors[a]			
Age > 65 years			
Age > 75 years			
Previous bleeding			
Cancer			
Metastatic cancer			
Renal failure			
Liver failure			
Thrombocytopenia			
Previous stroke			
Diabetes			
Anemia			
Antiplatelet therapy			
Poor anti-coagulant control			
Comorbidity and reduced functional capacity			
Recent surgery[b]			
Frequent falls			
Alcohol abuse			
	Estimated absolute risk of major bleeding (%)		
Categorization of risk of bleeding[c]	**Low risk (0 risk factors)[d]**	**Moderate risk (1 risk factor)[d]**	**High risk (≥2 risk factors)[d]**
Anti-coagulation 0 to 3 months			
Baseline risk (%)	0.6	1.2	4.8
Increased risk (%)	1	2	8
Total risk (%)	1.6[e]	3.2	12.8[f]
Anti-coagulation after first 3 months[g]			
Baseline risk (%/year)	0.3[h]	0.6	≥ 2.5
Increased risk (%/year)	0.5	1	≥ 4
Total risk (%/year)	0.8[i]	1.6[i]	≥ 6.5

[a] *The increase in bleeding associated with a risk factor will vary with (1) severity of the risk factor, (2) temporal relationships, and (3) how effectively a previous cause of bleeding was corrected.*
[b] *Important for parenteral anti-coagulation (e.g., first 10 days), but less important for long-term or extended anti-coagulation.*
[c] *Although there is evidence that risk of bleeding increases with the prevalence of risk factors, this categorization scheme has not been validated. Furthermore, a single risk factor, when severe, will result in a high risk of bleeding (e.g., major surgery within the past 2 days, severe thrombocytopenia).*
[d] *Compared with low-risk patients, moderate-risk patients are assumed to have a twofold risk and high-risk patients an eightfold risk of major bleeding.*
[e] *The 1.6% corresponds to the average of major bleeding with initial UFH or LMWH therapy followed by VKA therapy. We estimated baseline risk by assuming a 2.6 relative risk of major bleeding with anti-coagulation (refer to footnote g).*
[f] *Consistent with frequency of major bleeding observed in previous studies.*
[g] *It's estimated that anti-coagulation is associated with a 2.6-fold increase in major bleeding based on comparison of extended anti-coagulation with no extended anti-coagulation. The relative risk of major bleeding during the first 3 months of therapy may be greater than during extended VKA therapy because (1) the intensity of anti-coagulation with initial parenteral therapy may be greater than with VKA therapy; (2) anti-coagulant control will be less stable during the first 3 months; and (3) predispositions to anti-coagulant-induced bleeding may be uncovered during the first 3 months of therapy. However, studies of patients with acute coronary syndromes do not suggest a ≥ 2.6 relative risk of major bleeding with parenteral anti-coagulation (e.g., UFH or LMWH) compared with control.*
[h] *Estimated baseline risk of major bleeding for low-risk patients (and adjusted up for moderate- and high-risk groups as per footnote d).*
[i] *Consistent with frequency of major bleeding during prospective studies of extended anti-coagulation for VTE.*

and are more expensive than VKAs, and specific antidotes for anti-coagulation reversal are not widely available and are high-cost agents.

Special situations

Due to its ease of administration, LMWH may also be used for long term anti-coagulation in special situations, being for a long time the agent of choice in individuals with concomitant active neoplastic disease, as this strategy has demonstrated a lower VTE recurrence rate in clinical trials (Kahale et al., 2018). Recent studies have compared the agents Apixaban, Edoxaban and Rivaroxaban to LMWH for long term management of cancer associated VTE in a non-inferiority design. These agents were non-inferior to LMWH for the prevention of recurrent VTE, but there are concerns about a possible increased risk of bleeding especially in upper gastrointestinal cancer, acute leukemia, and primary or metastatic central nervous system tumors. Furthermore, NOACs may interact with different chemotherapeutic agents, therefore demanding a thorough evaluation of patients' bleeding risk, therapeutic plan as well as patients' preferences and prognosis (Duffett et al., 2020).

LMWH is also the preferred agent for pregnant women or women exposed to the possibility of pregnancy, due to a possible risk of fetal complications with other agents (Kearon et al., 2016).

ICVF may be an alternative for patients with VTE, whose clinical situation doesn't permit anti-coagulation, but there is no current evidence of benefit in the association of IVCF with anti-coagulation (Mismetti et al., 2015).

Outpatient management

The management of VTE was facilitated after the advent of the NOACs due to their ease of administration and lack of necessity for laboratory monitoring. Moreover, Apixaban and Rivaroxaban are also approved for the acute management of DVT and PE, which could permit the prescription of oral medication in the emergency department followed by discharge and outpatient management. This strategy may be associated with reduced costs, less exposure to nosocomial resistant microorganisms, and reduced use of available beds. On the other hand, there is the risk of delayed treatment of complications associated with progression of the thrombotic event or bleeding.

Outpatient treatment is an acceptable strategy both for DVT and PE in those patients whose embolic and bleeding risks are deemed to be low and have access to a medical center for surveillance or treatment of complications. The pulmonary embolism severity index (PESI) and the Hestia criteria (Table 4) have been used to assess disease severity in PE (Wolf et al., 2018), but these were not validated in individuals with SCI. Moreover, both the SCI associated autonomic dysfunction, risk of autonomic dysreflexia, reduced respiratory reserve in patients with higher lesions, and sensory impairment may influence the patient's risk and should be taken into consideration. A shared decision-making strategy where individuals are informed in detail about possible risks and benefits should be used.

Duration of anti-coagulation

To this moment no clinical trial was conducted specifically with individuals with SCI to determine the optimal duration of anti-coagulation. Guidelines directed at the general population agree on a treatment duration of at least 3 months for DVT, distal isolated DVT, and PE (Kearon et al., 2016; Konstantinides et al., 2019; Mazzolai et al., 2018). The decision of extending this period should be made on an individual basis, considering the risk of recurrence, especially the presence or resolution of provoking factors, and the risk of bleeding.

VTE occurring during the acute phase of SCI (i.e., during the period of higher thromboembolic risk) may be considered a provoked episode. During the chronic phase of SCI, individuals may be exposed in different periods to risk factors for VTE, such as bed rest due to fractures, pressure ulcers, or surgery. However, defining the most adequate treatment in otherwise healthy and active individuals with chronic SCI remains challenging.

Proposed strategies for this decision involving D-Dimer testing, evaluation of residual thrombosis (Carrier et al., 2011), clinical rules such as the HERDOO2, the DASH score, and the Vienna prediction model have demonstrated diverging results, lack external validation (Di Nisio et al., 2016; Tritschler et al., 2018) and individuals with SCI are underrepresented in the derivation and internal validations cohorts. Testing for inherited or acquired thrombophilia is not recommended after the first episode of provoked or unprovoked VTE and even a known thrombophilia may not necessarily grant an indication of long-term anti-coagulation after a VTE related to a strong provoking factor (Duffett et al., 2020).

TABLE 4 Pulmonary embolism severity index and Hestia rule.

Criteria	Points assigned
Pulmonary embolism severity index (PESI)	
Age in years (per year)	1
Male sex	10
History of cancer	30
History of heart failure	10
History of chronic lung disease	10
Systolic blood pressure < 100 mmHg	30
Pulse rate ≥ 110 per minute	20
Arterial oxygen saturation < 90%	20
Respiratory rate ≥ 30 per minute	20
Temperature < 36°C	20
Altered mental status	60
Score interpretation	
Class I, very low risk	<65
Class II, low risk	66–85
Class III, intermediate risk	86–105
Class IV, high risk	106–125
Class V, very high risk	>125
Hestia rule	
Is the patient hemodynamically unstable?[a]	
Is thrombolysis or embolectomy necessary?	
Active bleeding or high risk of bleeding?[b]	
>24 h of oxygen supply to maintain oxygen saturation > 90%?	
Is pulmonary embolism diagnosed during anti-coagulant treatment?	
Severe pain needing intravenous pain medication for >24 h?	
Medical or social reason for treatment in the hospital for >24 h (infection, malignancy, no support system)?	
Does the patient have a creatinine clearance of <30 mL/min?[c]	
Does the patient have severe liver impairment?[d]	
Is the patient pregnant?	
Does the patient have a documented history of heparin induced thrombocytopenia?	

HESTIA interpretation: If the answer to one of the questions is yes, in-hospital treatment is recommended. If the answer to all the questions is no, home treatment is recommended.
[a]*Including but not restricted to the following criteria: systolic blood pressure < 100 mmHg with heart rate > 100 beats/min; condition requiring admission to an intensive care unit.*
[b]*Gastrointestinal bleeding in the preceding 14 days, recent stroke (<4 weeks ago), recent operation (<2 weeks ago), bleeding disorder or thrombocytopenia (platelet count < 75.109/L), uncontrolled hypertension (systolic blood pressure > 180 mmHg or diastolic blood pressure > 110 mmHg).*
[c]*According to the Cockroft-Gault formula.*
[d]*Left to the discretion of the physician.*
Based on Roy, P. M., Moumneh, T., Penaloza, A., & Sanchez, O. (2017). Outpatient management of pulmonary embolism. *Thrombosis Research, 155,* 92–100.

Conclusion

VTE is a frequent complication of SCI and adequate prevention and management is a challenge for the multi-disciplinary team involved in the care of these individuals. There is a current lack of SCI-directed evidence, which is an exciting starting point for future research. There are remaining questions that need to be addressed regarding the optimal duration of pharmacological prophylaxis and anti-coagulation treatment, especially in individuals with chronic SCI.

Applications to other areas of neuroscience

In this chapter, we review the clinical management of venous thromboembolism including its epidemiology, prophylaxis, diagnosis, and management. Venous thromboembolism is a possible complication in individuals presenting with paresis or plegia, especially those with an acute presentation, such as acute stroke, brachial or lumbar plexus lesion.

The occurrences of deep venous thrombosis or pulmonary embolism are factors that may delay and interfere with the rehabilitation process and expose patients to a treatment that is not risk-free (Akman et al., 2004). Institution of adequate prophylaxis, defining precisely the ideal moment to initiate or interrupt pharmacological prophylaxis, is important in order to prevent not only venous thromboembolism but also iatrogenic bleeding. These are challenges that are also present when dealing with individuals with Guillain-Barré syndrome, acute ischemic or hemorrhagic stroke, and traumatic brain injury.

As medical knowledge is constantly evolving with the addition of new evidence from clinical research, the concepts presented here aim to help the healthcare provider in the process of clinical reasoning and decision making.

Mini-dictionary of terms

Acute phase: Comprises the first 12 weeks after a spinal cord injury.
Chronic phase: Spinal cord injury of 6 months or more.
Novel oral anti-coagulants: Also known as non-vitamin K antagonist oral anti-coagulants or NOACs are oral anti-coagulants that directly inhibit factor Xa or thrombin. They do not require laboratory monitoring.
Clinical rules or clinical prediction rules: Scores derived from risk factors, clinical characteristics and laboratory values that focus on probability estimation, in this chapter the probability of a venous thromboembolism diagnosis or recurrence.
Pre-test probability: Refers to the estimated probability of having a diagnosis before a test result is available.
Post-thrombotic syndrome: A consequence of valvular dysfunction on the venous circulation after a thrombotic event. Symptoms include limb edema, pain, skin pigmentation, and in severe grades venous ulcers.

Key facts of venous thromboembolism in spinal cord injury

- VTE is a frequent complication of SCI, especially during the acute phase.
- It was one of the major causes of death during acute treatment.
- VTE Prophylaxis has been researched since the 1970s, and most VTE studies in individuals with SCI are directed at prophylaxis strategies.
- Neurological deficits and autonomic dysfunction may interfere with the diagnostic process.
- Both VTE-associated and anti-coagulant-associated bleeding may cause delays in rehabilitation.

Summary points

- Pharmacological prophylaxis with LMWH should be used at least in the first 3 months after the SCI.
- The decision about pharmacological prophylaxis in patients with chronic SCI should be made on an individual basis.
- A high level of suspicion for the diagnosis should be maintained, but screening methods for VTE are not recommended.
- Classical clinical rules for the diagnosis of DVT and PE are not validated for individuals with SCI.
- Anticoagulation with parenteral or oral agents is the cornerstone of the treatment and should be used for at least 3 months.
- Prolongation of treatment should be made on an individual basis.
- Bleeding may occur even on prophylactic doses of anti-coagulants and sensorial deficit may delay the diagnosis.

References

Abdalla, G., Fawzi Matuk, R., Venugopal, V., Verde, F., Magnuson, T. H., Schweitzer, M. A., & Steele, K. E. (2015). The diagnostic accuracy of magnetic resonance venography in the detection of deep venous thrombosis: A systematic review and meta-analysis. *Clinical Radiology*, *70*(8), 858–871.

Agarwal, N. K., & Mathur, N. (2009). Deep vein thrombosis in acute spinal cord injury. *Spinal Cord*, *47*(10), 769–772.

Agnelli, G., Buller, H. R., Cohen, A., Curto, M., Gallus, A. S., Johnson, M., … AMPLIFY Investigators. (2013). Oral apixaban for the treatment of acute venous thromboembolism. *The New England Journal of Medicine*, *369*(9), 799–808.

Akman, M. N., Cetin, N., Bayramoglu, M., Isiklar, I., & Kilinc, S. (2004). Value of the D-dimer test in diagnosing deep vein thrombosis in rehabilitation inpatients. *Archives of Physical Medicine and Rehabilitation*, *85*(7), 1091–1094.

Alabed, S., Belci, M., Van Middendorp, J. J., Al Halabi, A., & Meagher, T. M. (2016). Thromboembolism in the sub-acute phase of spinal cord injury: A systematic review of the literature. *Asian Spine Journal*, *10*(5), 972–981.

Bates, S. M., Jaeschke, R., Stevens, S. M., Goodacre, S., Wells, P. S., Stevenson, M. D., … Guyatt, G. H. (2012). Diagnosis of DVT: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*, *141* (2 Suppl), e351S–e418S.

Bauersachs, R., Berkowitz, S. D., Brenner, B., Buller, H. R., Decousus, H., Gallus, A. S., … EINSTEIN Investigators. (2010). Oral rivaroxaban for symptomatic venous thromboembolism. *The New England Journal of Medicine*, *363*(26), 2499–2510.

Brandao, G. M., Junqueira, D. R., Rollo, H. A., & Sobreira, M. L. (2017). Pentasaccharides for the treatment of deep vein thrombosis. *Cochrane Database of Systematic Reviews*, *12*, CD011782.

Büller, H. R., Prins, M. H., Lensin, A. W., Decousus, H., Jacobson, B. F., Minar, E., … EINSTEIN–PE Investigators. (2012). Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *The New England Journal of Medicine*, *366*(14), 1287–1297.

Burgazli, K. M., Atmaca, N., Mericliler, M., Parahuleva, M., Erdogan, A., & Daebritz, S. H. (2013). Deep vein thrombosis and novel oral anticoagulants: A clinical review. *European Review for Medical and Pharmacological Sciences*, *17*(23), 3123–3131.

Carrier, M., Rodger, M. A., Wells, P. S., Righini, M., Gal, L. E., & G. (2011). Residual vein obstruction to predict the risk of recurrent venous thromboembolism in patients with deep vein thrombosis: A systematic review and meta-analysis. *Journal of Thrombosis and Haemostasis*, *9*(6), 1119–1125.

Casas, E. R., Sánchez, M. P., Arias, C. R., & Masip, J. P. (1977). Prophylaxis of venous thrombosis and pulmonary embolism in patients with acute traumatic spinal cord lesions. *Paraplegia*, *15*(3), 209–214.

Chung, S. B., Lee, S. H., Kim, E. S., & Eoh, W. (2011). Incidence of deep vein thrombosis after spinal cord injury: A prospective study in 37 consecutive patients with traumatic or nontraumatic spinal cord injury treated by mechanical prophylaxis. *The Journal of Trauma*, *71*(4), 867–870 (discussion 870–861).

Chung, W. S., Lin, C. L., Chang, S. N., Chung, H. A., Sung, F. C., & Kao, C. H. (2014). Increased risk of deep vein thrombosis and pulmonary thromboembolism in patients with spinal cord injury: A nationwide cohort prospective study. *Thrombosis Research*, *133*(4), 579–584.

Cohen, A. T., Hamilton, M., Mitchell, S. A., Phatak, H., Liu, X., Bird, A., … Batson, S. (2015). Comparison of the novel oral anticoagulants apixaban, dabigatran, edoxaban, and rivaroxaban in the initial and long-term treatment and prevention of venous thromboembolism: Systematic review and network Meta-analysis. *PLoS One*, *10*(12), e0144856.

Consortium for Spinal Cord Medicine. (2016). Prevention of venous thromboembolism in individuals with spinal cord injury: Clinical practice guidelines for health care providers, 3rd ed. *Topics in Spinal Cord Injury Rehabilitation*, *22*(3), 209–240.

Costa, G. L., Ferreira, D. C., Valacio, R. A., & Vieira Moreira, M. A. C. (2011). Quality of management of oral anticoagulation as assessed by time in therapeutic INR range in elderly and younger patients with low mean years of formal education: A prospective cohort study. *Age and Ageing*, *40*(3), 375–381.

de Almeida, R. L., Gonzaga, B. P. M., Beraldo, P. S. S., & Amado, V. M. (2019). Case report—Gluteal hematoma in two spinal cord patients on enoxaparin for venous thromboembolism prophylaxis: Evidence needed for a wiser choice. *Spinal Cord Series and Cases*, *5*, 36.

de Almeida, R. L., Rodrigues, C. C., Melo, E., Silva, C. A., Beraldo, P. S. S., & Amado, V. M. (2019). Comparison of two pharmacological prophylaxis strategies for venous thromboembolism in spinal cord injury patients: A retrospective study. *Spinal Cord*, *57*, 890–896. https://doi.org/10.1038/s41393-019-0293-1.

Di Nisio, M., van Es, N., & Büller, H. R. (2016). Deep vein thrombosis and pulmonary embolism. *Lancet*, *388*(10063), 3060–3073.

Dobler, C. C. (2019). Overdiagnosis of pulmonary embolism: Definition, causes and implications. *Breathe (Sheffield, England)*, *15*(1), 46–53.

Duffett, L., Castellucci, L. A., & Forgie, M. A. (2020). Pulmonary embolism: Update on management and controversies. *BMJ*, *370*, m2177.

Eichinger, S., Eischer, L., Sinkovec, H., Wittgruber, G., Traby, L., Kammer, M., … Wildburger, R. (2018). Risk of venous thromboembolism during rehabilitation of patients with spinal cord injury. *PLoS One*, *13*(3), e0193735.

Fehlings, M. G., Tetreault, L. A., Aarabi, B., Anderson, P., Arnold, P. M., Brodke, D. S., … Harrop, J. S. (2017). A clinical practice guideline for the management of patients with acute spinal cord injury: Recommendations on the type and timing of anticoagulant thromboprophylaxis. *Global Spine Journal*, *7*(3 Suppl), 212S–220S.

Fischer, E. A., Kinnear, B., Sall, D., Kelleher, M., Sanchez, O., Mathews, B., … Olson, A. P. J. (2019). Hospitalist-operated compression ultrasonography: A point-of-care ultrasound study (HOCUS-POCUS). *Journal of General Internal Medicine*, *34*(10), 2062–2067.

Frisbie, J. H., & Sasahara, A. A. (1981). Low dose heparin prophylaxis for deep venous thrombosis in acute spinal cord injury patients: A controlled study. *Paraplegia*, *19*(6), 343–346.

Giorgi Pierfranceschi, M., Donadini, M. P., Dentali, F., Ageno, W., Marazzi, M., Bocchi, R., & Imberti, D. (2013). The short- and long-term risk of venous thromboembolism in patients with acute spinal cord injury: A prospective cohort study. *Thrombosis and Haemostasis*, *109*(1), 34–38.

Godat, L. N., Kobayashi, L., Chang, D. C., & Coimbra, R. (2015). Can we ever stop worrying about venous thromboembolism after trauma? *Journal of Trauma and Acute Care Surgery*, *78*(3), 475–480 (discussion 480-471).

Gómez-Outes, A., Terleira-Fernández, A. I., Lecumberri, R., Suárez-Gea, M. L., & Vargas-Castrillón, E. (2014). Direct oral anticoagulants in the treatment of acute venous thromboembolism: A systematic review and meta-analysis. *Thrombosis Research*, *134*(4), 774–782.

Gorman, P. H., Qadri, S. F., & Rao-Patel, A. (2009). Prophylactic inferior vena cava (IVC) filter placement may increase the relative risk of deep venous thrombosis after acute spinal cord injury. *The Journal of Trauma*, *66*(3), 707–712.

Green, D. (1992). Prophylaxis of thromboembolism in spinal cord-injured patients. *Chest*, *102*(6 Suppl), 649S–651S.

Green, D., Chen, D., Chmiel, J. S., Olsen, N. K., Berkowitz, M., Novick, A., … Tolotta, M. (1994). Prevention of thromboembolism in spinal cord injury: Role of low molecular weight heparin. *Archives of Physical Medicine and Rehabilitation*, *75*(3), 290–292.

Green, D., Lee, M. Y., Lim, A. C., Chmiel, J. S., Vetter, M., Pang, T., … Meyer, P. R. (1990). Prevention of thromboembolism after spinal cord injury using low-molecular-weight heparin. *Annals of Internal Medicine*, *113*(8), 571–574.

Halim, T. A., Chhabra, H. S., Arora, M., & Kumar, S. (2014). Pharmacological prophylaxis for deep vein thrombosis in acute spinal cord injury: An Indian perspective. *Spinal Cord*, *52*(7), 547–550.

Hull, R. D., Raskob, G. E., Rosenbloom, D., Lemaire, J., Pineo, G. F., Baylis, B., … Brant, R. (1992). Optimal therapeutic level of heparin therapy in patients with venous thrombosis. *Archives of Internal Medicine*, *152*(8), 1589–1595.

Investigators, Spinal Cord Injury Thromboprophylaxis Investigators. (2003). Prevention of venous thromboembolism in the acute treatment phase after spinal cord injury: A randomized, multicenter trial comparing low-dose heparin plus intermittent pneumatic compression with enoxaparin. *The Journal of Trauma*, *54*(6), 1116–1124 (discussion 1125-1116).

Jorge, A., White, M. D., & Agarwal, N. (2018). Outcomes in socioeconomically disadvantaged patients with spinal cord injury: A systematic review. *Journal of Neurosurgery. Spine*, *29*(6), 680–686.

Kadyan, V., Clinchot, D. M., & Colachis, S. C. (2004). Cost-effectiveness of duplex ultrasound surveillance in spinal cord injury. *American Journal of Physical Medicine & Rehabilitation*, *83*(3), 191–197.

Kahale, L. A., Hakoum, M. B., Tsolakian, I. G., Matar, C. F., Terrenato, I., Sperati, F., … Akl, E. A. (2018). Anticoagulation for the long-term treatment of venous thromboembolism in people with cancer. *Cochrane Database of Systematic Reviews*, *6*, CD006650.

Kearon, C. (2003). Natural history of venous thromboembolism. *Circulation*, *107*(23 Suppl. 1), I22–I30.

Kearon, C., Akl, E. A., Ornelas, J., Blaivas, A., Jimenez, D., Bounameaux, H., … Moores, L. (2016). Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest*, *149*(2), 315–352.

Kelly, B. M., Yoder, B. M., Tang, C. T., & Wakefield, T. W. (2010). Venous thromboembolic events in the rehabilitation setting. *PM & R : The Journal of Injury, Function, and Rehabilitation*, *2*(7), 647–663.

Konstantinides, S. V., Meyer, G., Becattini, C., Bueno, H., Geersing, G. J., Harjola, V. P., … Zamorano, J. L. (2019). ESC guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The task force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). *The European Respiratory Journal*, *54*(3), 1–68. https://doi.org/10.1183/13993003.01647-2019. PMID: 31473594.

Krassioukov, A., Biering-Sørensen, F., Donovan, W., Kennelly, M., Kirshblum, S., Krogh, K., … Autonomic Standards Committee of the American Spinal Injury Association/International Spinal Cord Society. (2012). International standards to document remaining autonomic function after spinal cord injury. *The Journal of Spinal Cord Medicine*, *35*(4), 201–210.

Kumagai, G., Wada, K., Kudo, H., Asari, T., Ichikawa, N., & Ishibashi, Y. (2020). D-dimer monitoring combined with ultrasonography improves screening for asymptomatic venous thromboembolism in acute spinal cord injury. *The Journal of Spinal Cord Medicine*, *43*(3), 353–357.

Mackiewicz-Milewska, M., Jung, S., Kroszczyński, A. C., Mackiewicz-Nartowicz, H., Serafin, Z., Cisowska-Adamiak, M., … Rość, D. (2016). Deep venous thrombosis in patients with chronic spinal cord injury. *The Journal of Spinal Cord Medicine*, *39*(4), 400–404.

Masuda, M., Ueta, T., Shiba, K., & Iwamoto, Y. (2015). D-dimer screening for deep venous thrombosis in traumatic cervical spinal injuries. *The Spine Journal*, *15*(11), 2338–2344.

Mazzolai, L., Aboyans, V., Ageno, W., Agnelli, G., Alatri, A., Bauersachs, R., … Brodmann, M. (2018). Diagnosis and management of acute deep vein thrombosis: A joint consensus document from the European Society of Cardiology working groups of aorta and peripheral vascular diseases and pulmonary circulation and right ventricular function. *European Heart Journal*, *39*(47), 4208–4218.

Merli, G. J., Crabbe, S., Doyle, L., Ditunno, J. F., & Herbision, G. J. (1992). Mechanical plus pharmacological prophylaxis for deep vein thrombosis in acute spinal cord injury. *Paraplegia*, *30*(8), 558–562.

Merli, G. J., Herbison, G. J., Ditunno, J. F., Weitz, H. H., Henzes, J. H., Park, C. H., & Jaweed, M. M. (1988). Deep vein thrombosis: Prophylaxis in acute spinal cord injured patients. *Archives of Physical Medicine and Rehabilitation*, *69*(9), 661–664.

Mismetti, P., Laporte, S., Pellerin, O., Ennezat, P. V., Couturaud, F., Elias, A., … PREPIC2 Study Group. (2015). Effect of a retrievable inferior vena cava filter plus anticoagulation vs anticoagulation alone on risk of recurrent pulmonary embolism: A randomized clinical trial. *JAMA*, *313*(16), 1627–1635.

Oliphant, C. S., Jacobs, A., Kabra, R., & Das, P. (2013). Novel oral anticoagulants for the prevention and treatment of thromboembolism. *Future Cardiology*, *9*(6), 849–861.

Onishi, A., St Ange, K., Dordick, J. S., & Linhardt, R. J. (2016). Heparin and anticoagulation. *Frontiers in Bioscience*, *21*, 1372–1392.

Raschke, R. A., Reilly, B. M., Guidry, J. R., Fontana, J. R., & Srinivas, S. (1993). The weight-based heparin dosing nomogram compared with a "standard care" nomogram. A randomized controlled trial. *Annals of Internal Medicine*, *119*(9), 874–881.

Robertson, L., & Jones, L. E. (2017). Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for the initial treatment of venous thromboembolism. *Cochrane Database of Systematic Reviews*, *2*, CD001100.

Roussi, J., Bentolila, S., Boudaoud, L., Casadevall, N., Vallée, C., Carlier, R., … Bussel, B. (1999). Contribution of D-dimer determination in the exclusion of deep venous thrombosis in spinal cord injury patients. *Spinal Cord*, *37*(8), 548–552.

Sachdeva, A., Dalton, M., & Lees, T. (2018). Graduated compression stockings for prevention of deep vein thrombosis. *Cochrane Database of Systematic Reviews*, *11*, CD001484.

Schein, J. R., White, C. M., Nelson, W. W., Kluger, J., Mearns, E. S., & Coleman, C. I. (2016). Vitamin K antagonist use: Evidence of the difficulty of achieving and maintaining target INR range and subsequent consequences. *Thrombosis Journal*, *14*, 14.

Spivack, S. B., & Aisen, M. L. (1997). A comparison of low molecular weight heparin and low dose unfractionated heparin prophylaxis in subacute myelopathy. *The Journal of Spinal Cord Medicine*, *20*(4), 402–405.

Swan, D., Hitchen, S., Klok, F. A., & Thachil, J. (2019). The problem of under-diagnosis and over-diagnosis of pulmonary embolism. *Thrombosis Research*, *177*, 122–129.

Ten Cate-Hoek, A. J. (2018). Prevention and treatment of the post-thrombotic syndrome. *Research and Practice in Thrombosis and Haemostasis*, *2*(2), 209–219.

Thean, D., & Alberghini, M. (2016). Anticoagulant therapy and its impact on dental patients: A review. *Australian Dental Journal*, *61*(2), 149–156.

Thomas, S. M., Goodacre, S. W., Sampson, F. C., & van Beek, E. J. (2008). Diagnostic value of CT for deep vein thrombosis: Results of a systematic review and meta-analysis. *Clinical Radiology*, *63*(3), 299–304.

Thumbikat, P., Poonnoose, P. M., Balasubrahmaniam, P., Ravichandran, G., & McClelland, M. R. (2002). A comparison of heparin/warfarin and enoxaparin thromboprophylaxis in spinal cord injury: The Sheffield experience. *Spinal Cord*, *40*(8), 416–420.

Todd, J. W., Frisbie, J. H., Rossier, A. B., Adams, D. F., Als, A. V., Armenia, R. J., … Tow, D. E. (1976). Deep venous thrombosis in acute spinal cord injury: A comparison of 125I fibrinogen leg scanning, impedance plethysmography and venography. *Paraplegia*, *14*(1), 50–57.

Tritschler, T., Kraaijpoel, N., Le Gal, G., & Wells, P. S. (2018). Venous thromboembolism: Advances in diagnosis and treatment. *JAMA*, *320*(15), 1583–1594.

Weitz, J. I. (1997). Low-molecular-weight heparins. *The New England Journal of Medicine*, *337*(10), 688–698.

Wells, P. S., Ihaddadene, R., Reilly, A., & Forgie, M. A. (2018). Diagnosis of venous thromboembolism: 20 years of Progress. *Annals of Internal Medicine*, *168*(2), 131–140.

Wolf, S. J., Hahn, S. A., Nentwich, L. M., Raja, A. S., Silvers, S. M., Brown, M. D., & American College of Emergency Physicians Clinical Policies Subcommittee (Writing Committee) on Thromboembolic Disease. (2018). Clinical policy: Critical issues in the evaluation and management of adult patients presenting to the emergency department with suspected acute venous thromboembolic disease. *Annals of Emergency Medicine*, *71*(5), e59–e109.

Chapter 7

Osteoporosis-related fractures: What they are and how they occur following spinal cord injury

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Abbreviations

25(OH)D	25 hydroxyvitamin D
aBMD	areal bone mineral density
AIS	ASIA Impairment Scale
BMD	bone mineral density
BMI	Bone Mass Index
BWSTT	body-weight exercises supported treadmill training
CTX-I	type I collagen C-telopeptide
DEXA	dual-energy X-ray absorptiometry
EMS	electromyostimulation
ES	electrical stimulation
FAO	bone-specific alkaline phosphatase
FES	functional electrical stimulation
FRAX	fracture risk assessment tool
pQCT	quantitative computed tomography
PTH	parathyroid hormone
SCI	spinal cord injury
WHO	World Health Organization

Introduction

In 2017, approximately 22 million people around the world were living with a spinal cord injury (SCI), a rate increase of 14.21% in the last 10 years (GBD 2016 Traumatic Brain Injury and Spinal Cord Injury Collaborators, 2019). The better access to medical care resources such as emergency medical services and rehabilitation departments led to longer survival for this population (Frontera & Mollett, 2017). Henceforth, many consequences were related to SCI such as neurogenic bladder, neurogenic bowel, neuropathic pain, spasticity, and osteoporosis (Craven, Robertson, Delparte, Ashe, & Janice, 2008; Frontera and Mollett, 2017).

Osteoporosis affects the health of individuals with SCI because it increases the risk of fragility fractures with consequences related to fractures such as ulcers, immobility, depression and even death (Carbone et al., 2013; Jiang, Dai, & Jiang, 2006; Morse et al., 2009). Osteoporosis after SCI is defined as an excessive bone resorption after SCI and bone fragility fractures are defined as fractures caused by a trauma that would be insufficient for a normal bone to fracture (Craven et al., 2008; Zleik et al., 2019) or by minimally loaded situations (McPherson et al., 2014; Shields et al., 2005).

The impact of fractures on the lives of individuals with SCI suggests that most patients will be hospitalized after the fracture and undergone to surgery, and complications as worse performance in activities of daily living and ambulation after the fracture are mostly described. These issues mean increased disability and costs for the health system (Carbone et al., 2013).

Diagnosis and Treatment of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822498-4.00007-5

Special attention should be paid to the prevention of fractures, and appropriate treatments should be instigated to prevent excessive bone loss and futher investigations should be performed. Most of the physicians are not educated to measure risk factors for bone fragility fractures. Dual-energy X-ray absorptiometry (DEXA) should be performed in patients with SCI, likely before the occurrence of fractures. Bone remodeling markers could give us a clue of the resorption rate and treatments to prevent further loss should be consider.

Physiopathology

Bone demineralization after SCI occurs in a rate loss of approximately 4% per month in the first year (Battaglino, Lazzari, Garshick, & Morse, 2012; Bauman, Spungen, Morrison, Zhang, & Schwartz, 2005; Bauman, Wecht, et al., 2005), primarily in the knees. Demineralization begins in the early days, peaks around the 10th to 16th weeks and stabilizes around the 16th to 24th months (Battaglino et al., 2012; Bauman, Spungen, et al., 2005; Bauman, Wecht, et al., 2005). Recent studies suggest that the bone loss extends 3 to 8 years after SCI (Haider, Lobos, Simonian, Schnitzer, & Edwards, 2018). Previous studies demonstrated bone demineralization greater than 20% in the hip, 37% to 52% in the distal femur and 36% to 70% in proximal tibia after 1 to 3 years after SCI (Garland, Adkins, & Stewart, 2005; Haider et al., 2018; Troy & Morse, 2015).

Bone loss associated with SCI is related to immobility and metabolic changes (Bauman & Spungen, 2000; McPherson et al., 2014; Uebelhart, Demiaux-Domenech, Roth, & Chantraine, 1995). Individuals with SCI exhibit primarily hypercalcemia, hypercalciuria, hyperparathyroidism, decreased levels of osteocalcin, and higher levels of sclerotin. The loss of bone mineral density is 2 to 4 times greater than the loss that occurs in an immobilized individual without SCI (Uebelhart et al., 1995).

Other related factors may contribute to this bone loss, such as vitamin D deficiency and the use of methylprednisolone, anti-convulsant drugs, and psychotropic substances. Previous studies discovered that 14% to 32% of individuals with SCI were deficient in vitamin D (Bauman, Zhong, & Schwartz, 1995; Koutrakis et al., 2019). Even in tropical countries, vitamin D deficiency is a common health problem (Champs, Maia, Oliveira, de Melo, & Soares, 2020).

Fractures

The consequence of osteoporosis in individuals with SCI is fracture due to bone fragility. It usually occurs in transfers and activities with minimal or no trauma, such as low-speed falls, torsional stress (Akhigbe et al., 2015; Bethel et al., 2016). Studies (Akhigbe et al., 2015; Bethel et al., 2016; Champs et al., 2020) detected a specific time between SCI and fracture was 9 to 10 years, average age of first fracture for women 50+ and for men 40 + years-old (Champs et al., 2020). Fractures may occur in 25% to 46% of these individuals over their lifetimes (Bethel et al., 2016; Craven, Robertson, McGillivray, & Adachi, 2009; Morse et al., 2009). Fractures are primarily related to torsional forces during transfer, passive mobilization, compressive forces, and falls (Akhigbe et al., 2015; Bethel et al., 2016; Champs et al., 2020). It seems the most frequent fracture cause is due to falls from a wheelchair or even their own height while walking or standing (Champs et al., 2020). This result is not surprising because falls are a common health problem in individuals with SCI, and the prevention of falls should be a priority. Another study found transfer as the main cause of fracture (Akhigbe et al., 2015).

The risk of fracture after SCI is different from the risk of osteoporosis (Abderhalden et al., 2017; Cirnigliaro et al., 2017), individuals with tetraplegia have more osteoporosis than those with paraplegia, however, individuals with paraplegia have a higher frequency of fractures due to exposure to falls (Champs et al., 2020; Craven et al., 2009; Morse et al., 2009). Most places of fractures are in the tibia and/or distal fibula, distal femur, or hip/proximal femur and proximal tibia (Akhigbe et al., 2015; Bethel et al., 2016; Morse et al., 2009). It seems hip/proximal femur and distal tibia/fibula are as common as the distal femur (Champs et al., 2020). However, individuals who are ambulatory and wheelchair dependent may have different areas of fractures. Ambulatory individuals fracture more often the distal tibia/fibula, and wheelchair-bound patients fractured the distal and proximal femur (Champs et al., 2020). A second (15%) and third (2%) fracture are experienced by patients (Champs et al., 2020).

The impact of fractures on the lives of people with SCI suggests that most of the patients are hospitalized after the fracture, and some had complications. Almost one-third of the participants reported worse performance in activities of daily living and ambulation after the fracture had healed. Individuals with osteoporosis-related fractures after SCI had several complications. Most individuals were hospitalized, and half of them underwent surgery (Champs et al., 2020). These issues mean increased disability and costs for the health system.

Risk factors

Previous studies showed risk factors (Bethel et al., 2016; Garland et al., 2005; Morse et al., 2009) and the following ones were described associated with increased fracture criteria: AIS (ASIA Impairment Scale) A or B; age 40+ years old; SCI longer than 3 years; age at SCI of 16 years or less; three servings of coffee per day; smoking; women; family history of osteoporotic fractures; low bone mineral density; low weight Bone Mass Index (BMI) <19 kg/cm^2; alcohol intake greater than 30 g/day; paraplegia, and the use of corticosteroids (Craven et al., 2008, 2009). Studies by Craven developed protocols conducive to treatment based on these risk factors. Other aspects related to fractures are 25 hydroxyvitamin D [25(OH)D] levels less than 20 ng/mL (Koutrakis et al., 2019).

Diagnosis

Laboratory

Bone formation markers are useful in the management of SCI patients. Procollagen type I N-propeptide reflects osteoblastic activity, bone-specific alkaline phosphatase, which is a bone formation marker, is elevated on the first year after injury. Osteocalcin, another bone remodeling marker is reduced in the first year others (Bauman and Spungen, 2000; Uebelhart et al., 1995).

Bone resorption markers such as deoxypyridinoline, pyridinoline, sclerostin, and type I collagen C-telopeptide (CTX-I) can be used. CTX-I is increased in the second week after SCI and peaks between 2 and 4 months, and its levels can remain increased for up to 5 years (Bauman and Spungen, 2000; Uebelhart et al., 1995).

The immobilization resulting from acute SCI stimulates osteoclastic bone resorption and calcium homeostasis markers as parathyroid hormone (PTH) is reduced in the first year after injury, urinary calcium is elevated, serum calcium is increased, while ionized calcium is generally normal. These alterations peak from the 3rd to the 10rd month after SCI (Bauman and Spungen, 2000; Uebelhart et al., 1995).

Dual-energy X-ray absorptiometry

Dual-energy X-ray absorptiometry (DEXA) for patients with SCI is a confirmatory test to predict the future risk of fracture and also serves for ongoing monitoring of bone health and to access bone loss (McPherson et al., 2014) by the bone mineral density (BMD) measurements. It is precise and safe (Shields et al., 2005) since there were strong associations among different observers and it emits a very low level of radiation (0.1 mSV), that is, 1/10–1/30 less radiation than a chest X-ray. DEXA calculates the measurement of bone mineral density in g/cm^2 and protocols for calculating bone mineral density for patients with SCI already exist. Some studies suggested that low BMD in the hip predicted fracture in individuals with SCI (Abderhalden et al., 2017) and other authors suggested that DEXA measurement of the distal femur and proximal tibia, with specific protocols for the evaluation of these sites (Cirnigliaro et al., 2017; Garland et al., 2005; Morse et al., 2009) and for knee fracture thresholds of 0.78 g/cm^2 which a fracture may start to occur and fracture breakpoint of 0.49 g/cm^2 (Garland et al., 2005; Fig. 1).

The measurement of BMD of the knees is extremely important for monitoring bone loss, as the hip and spine do not show the highest losses of BMD after SCI and because osteoporosis is most severe below the level of the injury (Morse, Biering-Soerensen, et al., 2019; Morse, Troy, et al., 2019). It can be even more useful in those patients where assessing the spine and hip is not possible, such as cases with spine surgeries or hip heterotopic ossifications. The limitations for measuring BMD in the knees are fractures and orthopedic surgeries. In cases of flexion deformities, the assessment of bone mineral density can be performed in the lateral scans (Fig. 2).

Quantitative computed tomography

Quantitative computed tomography (pQCT) is also a safe method and evaluates density, volume and geometry, differentiates cortical bone and trabecular bone, but it is difficult to establish prediction, and have plus radiation, and aBMD <114 mg/cm^3 in the femur and aBMD <72 mg/cm^3 in the tibia are described as fracture thresholds (Garland et al., 2005; Liu et al., 2000).

Treatment

It is still under debate the best way to prevent fragility fractures after SCI (Morse, Biering-Soerensen, et al., 2019; Morse, Troy, et al., 2019). A diet rich in fruits and vegetables, daily doses of calcium of 1000 to 1200 mg vitamin D,

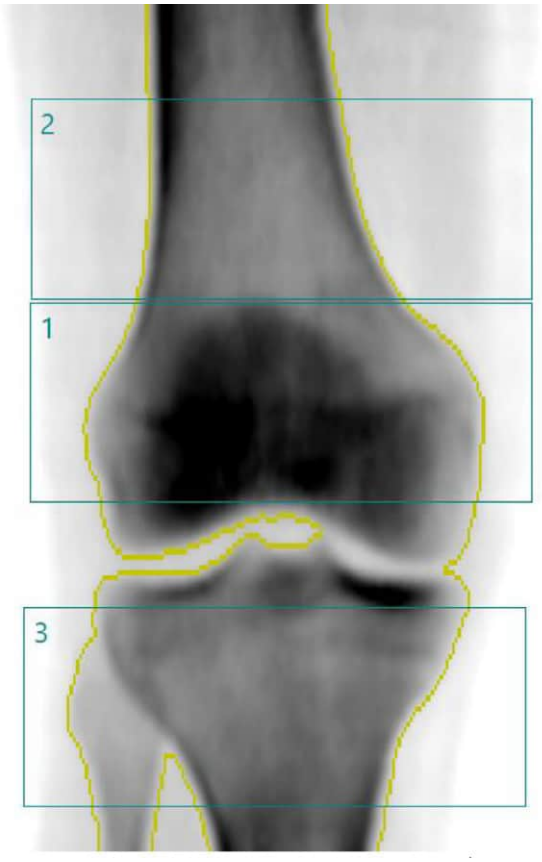

FIG. 1 Dual-energy X-ray absorptiometry (DEXA) scan image of the knee. The boxes delineate the regions of the affected area scanned at the distal femur (*blue box* 1: distal femoral epiphysis and *blue box* 2: distal femoral metaphysis) and the proximal tibial (*blue box* 3: proximal tibial epiphysis).

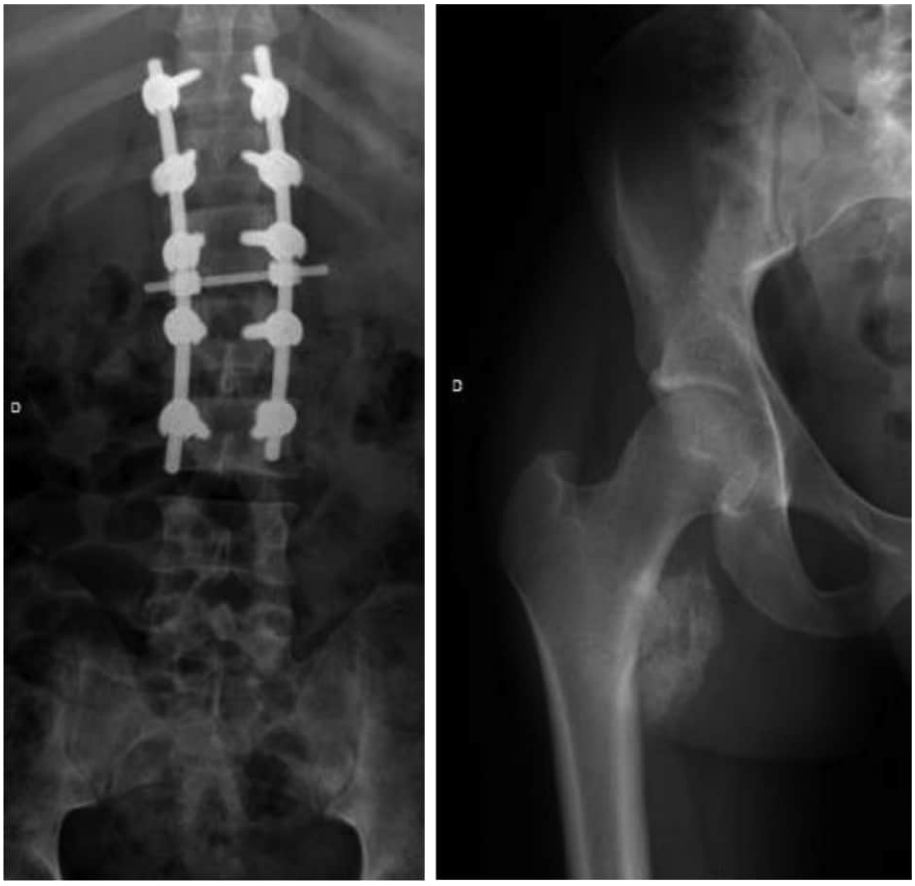

FIG. 2 Digital X rays scans of the spine and the hip. Spine surgeries and heterotopic ossifications in the hip artificially increase bone mineral density.

200 to 1000 iU/day aiming a serum level of 30 ng/dL, physical exercises, stop smoking and drinking alcoholic beverages and avoid over doses of coffee are contributive recommendations (Bauman et al., 2015; Koutrakis et al., 2019; Morse, Biering-Soerensen, et al., 2019; Morse, Troy, et al., 2019).

Pharmacologic therapy

Studies showed the efficacy of bisphosphonates in daily doses of alendronate 10 mg (orally) and calcium 500 mg to decrease bone turnover in people with SCI (Zehnder et al., 2004). Bisphosphonates were more effective if 25-OH > 33 ng/mL and vitamin D deficiency should be investigated because of osteomalacia risk (Morse, Biering-Soerensen, et al., 2019; Morse, Troy, et al., 2019). However, it is a medication with around 50% adherence despite being generally well-tolerated (Morse, Biering-Soerensen, et al., 2019; Morse, Troy, et al., 2019). The association of calcium 500 mg, alendronate, 70 mg weekly and vitamin D 400 U starting 10 days after SCI and use for twelve months to 24 months prevented the decrease of BMD in the distal tibial epiphysis in patients with SCI (Gilchrist et al., 2007; Zehnder et al., 2004). In contrast, the isolated use of 500 mg of calcium daily for the same period didn't prevent it (Gilchrist et al., 2007).

Pamidronate 60 mg usage, intravenously 4 times a year associated with dietary calcium (700 mg/day) and vitamin D, didn't prevent bone loss in the long term, in patients with spinal cord injury with complete motor injury (Bauman, Spungen, et al., 2005; Bauman, Wecht, et al., 2005). Zoledronic acid administered once a year, intravenously, showed a significant reduction in bone loss of lumbar spine, hip and trochanter with some side effects as myalgia, fever and nasal congestion (Shapiro et al., 2007). Another study described zoledronic acid administration failed to prevent bone loss at the knee in persons with acute spinal cord injury (Bauman et al., 2015).

Many complications are associated with bisphosphonates as hypocalcemia, gastrointestinal effects, osteomalacia, osteonecrosis of the jaw (1/10,000 patients) after more than 4 years of use, atrial fibrillation, hepatotoxicity, teratogenicity for women of childbearing age and it cannot be used in chronic renal failure.

Vitamin D is also effective (Bauman, Spungen, et al., 2005; Bauman, Wecht, et al., 2005). Vitamin D treatment determined significant reduction of urinary bone resorption markers despite neutral effects on bone formation markers (Bauman, Spungen, et al., 2005; Bauman, Wecht, et al., 2005).

Teriparatide reduced the risk of vertebral fractures at a dose of 20 μg daily, subcutaneously, when associated with robotic treatment. Teriparatide alone, did not improve BMD either on the spine or on the hip for patients with SCI (Chain, Koury, & Bezerra, 2012).

Denosumab inhibits osteoclast formation, prevents bone resorption, and reduces risk of spine fractures. A study by Gifre et al. (2016) treated 14 patients with SCI with denosumab, calcium, and vitamin D with improvement of bone mineral density in 12 months. Despite that, there are still poor evidence for people with SCI.

There is no consensus on the follow-up after staring pharmacologic therapy. It is recommended to repeat DEXA after 1 to 2 years after start of treatment (Morse, 2019).

Treatment with bisphosphonate has been done for 4 to 5 years and should be consider drug holiday after 3 to 5 years of use, because of its prolonged effect (Morse, Biering-Soerensen, et al., 2019; Morse, Troy, et al., 2019).

Rehabilitation/non-pharmacological therapy

One of the possible causes of osteoporosis after SCI is the inability to perform weight bearing activities and loss of the strengthening effects of bone stress related to muscular contraction and gravity. In this way, rehabilitation is an option for osteoporosis prevention and treatment after SCI focus on stimulation muscle contraction and weight bearing in order to stimulate the mechanical stress, to which bone is exposed to daily activities among healthy people (Craven et al., 2008; Dolbow et al., 2011).

The mechanostat theory, based on Wolff's law, states that mechanical loading influences bone structure by changing its mass (amount of bone) and architecture (its arrangement) to provide a structure that resists to habitual loads. There are strains within bone that are kept within certain limits by adding and removing bone tissue that could promote bone strengthening, depending on the applied forces. The paralysis secondary SCI causes a decrease in the mechanical load and results in bone tissue loss (Cirnigliaro et al., 2017; Dolbow et al., 2011).

Standing and walking

Supported standing with standing frames, tilt tables, long leg braces, wheelchair standing have long been used as a treatment for reducing and or delaying osteoporosis after SCI. It is traditionally incorporated in rehabilitation programs, even without proof of its effectiveness (Goktepe, Tugcu, Yilmaz, Alaca, & Gunduz, 2008).

There are three good quality studies that evaluate the influence of weight bearing activities in the acute phase of SCI, with controversial results (Alekna, Tamulaitiene, Sinevicius, & Juocevicius, 2008). It was observed that an early mobilized subject showed no or insignificant loss of trabecular bone when compared with non-interventional groups (De Bruin et al., 1999). In the same other way, two studies has found that patients who performed daily standing or walking exercises for more than 1 h, 5 times per week had significantly higher BMD in the lower extremities after 2 years, in comparison to those who did not perform standing movements (Alekna et al., 2008).

For the chronic phase, the results seemed more uniform, with very little evidence of any gain in BMD when the first year after injury had passed (Biering-Sørensen, Hansen, & Lee, 2009). Goktepe et al. found no significant effect on BMD in chronic patients after daily standing for less or more than 1 h for a period of 4 years (Goktepe et al., 2008). In the same way, a study by Kunkel et al. (1993) did not detect changes in fracture risk at femoral neck after standing in a frame program for 45 min twice a day for 5 months. Dudley-Javoroski et al. compared the effect of bone compressive loads using 0% body weight (no standing), 40% body weight (passive standing—"low dose"), and 150% body weight (quadriceps stimulation in supported stance—"high dose"). After a 3 year training protocol, 3 times a week, the high dos group had an attenuated BMD decline when compared to passive standing or no standing individuals. There were no differences between low-dose and no standing group, suggesting that BMD for participants doing passive stance is the same as those who performed no standing (Dudley-Javoroski & Shields, 2013).

Gait training with walking frame, orthosis, body-weight exercises supported treadmill training (BWSTT), and exoskeleton is among the activities of a rehabilitation program with the main purpose to facilitate ambulation SCI persons. Besides that, there are some studies investigating its benefits on bone loss after SCI, but up to now, there is no good quality evidence in favor of this kind of intervention. Carvalho et al. (2006) showed that a BWSTT (30%–50% weight relief) with neuromuscular electrical stimulation, twice a week, for 20 min, for 6 months, in tetraplegic individuals led to elevate bone formation and reduce bone resorption markers, although the BMD did not enough. Another study with 12 months of BWSTT training did not increase bone density in individuals with chronic incomplete SCI, but BMD did not decrease at fracture-prone sites (Giangregorio et al., 2006). Other studies involving ambulatory orthosis also observed that walking did not improve BMD (Ogilvie, Bowker, & Rowley, 1993; Thoumie et al., 1995).

Karelis et al., in a case report, noticed little benefits on locomotor training using a robotic exoskeleton 3 times/week, for 6 weeks. A previous case report study did not find BMD benefits after robotic-assisted BWSTT (Lokomat) for 1 h activity, 3 times a week, in a period of 3 months, in an acute SCI. It is important to be careful about fractures occurring during this activity as cited by Zleik et al. Some studies suggested that low BMD may be a relative contraindication for the use of these devices (Zleik et al., 2019).

The bone loss prevention/treatment needs intensive body loading and for a long period in order to maintain body mass. Although there is no BMD cut-off value to preclude patients from participating in rehab interventions, an assessment of fracture risk is indicated before activities such as standing and walking to ensure its safety (Cirnigliaro et al., 2017; Craven et al., 2008). It is recommended to avoid exercises that result in torsion of the distal lower extremity or that have a risk of falling (Craven et al., 2008).

Although practices for increased mobility and weight-bearing are clearly important to skeletal health in SCI, there is not sufficient evidence in their capability to maintain BMD of the lower extremity (Zleik et al., 2019). In summary, there is low evidence that more than 5 h per week standing exercises could preserve tibial BMD in acute (less than 1 year) SCI cases (Soleyman-Jahi et al., 2018).

Electrical stimulation

Electrical stimulation (ES) and Functional Electrical Stimulation (FES) involve the use of surface or implanted electrodes to stimulate muscular activity. Whereas both methods typically employ cyclical patterns of electrical stimulation that simulate natural muscular activity, FES is directed toward the attainment of purposeful movement such as cycling or walking.

FES is the most extensively investigated approach since it combines the benefits from electrical stimulation and mechanical loading of the lower extremity long bones. Although FES intervention has been demonstrated to improve muscle atrophy, solid evidence from a large-scale study is still lacking regarding its influence on sub-lesional BMD attenuation.

FES studies enrolled participants with both acute and chronic injuries and are therefore difficult to classify as pure prevention or treatment interventions. In one review study, Bauman and Cardozo (2015) described that FES training administered at the time of acute injury appears to markedly reduced bone loss at the site applied or, if administered to those with chronic SCI, was also efficacious, albeit with a reduced magnitude of effect, at the place to which the load was applied. Soleyman-Jahi et al. (2018) investigated in a literature review the prevention- and evidence-based treatments for

osteoporosis related to SCI. They discovered low-quality evidence indicating that ES provided no significant effects. Very low-quality evidence did not show any benefit for low-intensity (3 days per week) cycling with FES in chronic SCI.

Chang et al. (2013) carried out a meta-analysis study to investigate whether bisphosphonate administration or functional electrical stimulation (FES) training could effectively decrease bone mineral. They noticed that FES cycling did not significantly decrease BMD loss in acute SCI individuals. Whereas, for people with a chronic SCI, BMD demonstrated a significant increase near the site of maximal mechanical loading. Furthermore, the studies employing FES $\geq$5 days per week were likely to have better effectiveness than studies using FES $\leq$3 days per week (Chang et al., 2013).

In the acute phase, there is a non-randomized trial reporting that FES cycling provided 1 to 3 months after SCI can partially reduce BMD loss in distal femur (Lai et al., 2010). In addition, the effect on the attenuation of bone loss in the distal femur diminished once FES cycling was discontinued (Lai et al., 2010). Eser et al. (2003) measured the effect of an FES cycling intervention on bone mineral density (BMD) of the tibia in recently injured SCI people in a non-randomized clinical trial. The intervention consisted of 30-min FES cycling three times a week for 6 months. They concluded that FES cycling was not effective for improving bone mass at the tibial mid shaft during the first year after injury.

For the chronic phase, the studies are conflicting, but the investigations that show improvement seem to be those with a longer period of training, which is 12 months or more, 5 times/week (Belanger, Stein, Wheeler, Gordon, & Leduc, 2000; Chen et al., 2005). It is also evident that all these studies measured their improvement corresponding to the trabecular bone, in particular in the distal femur or the proximal tibia.

FES cycling studies that reported a positive effect on bone parameters used protocols of at least 3 sessions per week for 6 months in duration. The increase in bone parameters was in areas directly affected by the stimulated muscles. Although a study showed that the FES cycling intervention needed to be maintained or bone gains were lost (Chen et al., 2005). Frotzler et al. (2009) found that BMD was preserved in the distal locations of some participants in 12 months. They concluded that the high-volume FES-induced cycle training had clinical relevance as it could partially reverse bone loss and thus may reduce fracture risk at this fracture-prone site.

The use of ES to clinical care has been fraught with difficulties due to the labor intensive nature of the present approaches and the appreciation that any effect on bone is rapidly lost, when the ES training is either reduced in frequency or terminated (Belanger et al., 2000; Eser et al., 2003; Lai et al., 2010). Considerations for FES efficacy in osteoporosis in SCI should consider attention to the duration, frequency, and power of the output (Chang et al., 2013; Dudley-Javoroski & Shields, 2013). Guidelines include intensities with loads of 1–1.5 times body weight, sessions of 3 or more per week for several months to 1 or more years, and safety considerations to prevent fractures (Dolbow et al., 2011). Craven et al. (2008) considered that ES and FES should be used with caution in patients with combined hip and knee flexion contractures of $>$30, a prior lower extremity fracture, severe lower extremity spasticity, and/or significant ankle plantar flexion contractures.

Finally, although the use of FES cycling looks promising, the limited availability of cycle ergometry for home or longitudinal use may limit its generalization, if therapy cannot be maintained outside a clinical trial environment. The quality of evidence available in this field is poor. Some results suggest physical activity could attenuate bone loss (Chain et al., 2012; Goktepe et al., 2004). Studies reported benefits on arm bone mass maintenance but did not prevent demineralization in the lower body (Goktepe et al., 2004). The type of activity and training intensity were not well-described, and many studies used a self-reported physical activity as a reference.

Physical activity

The quality of evidence available in this field is poor. Some results suggest physical activity could attenuate bone loss (Chain et al., 2012; Goktepe et al., 2004). Two of them reported benefits on arm bone mass maintenance but did not prevent demineralization in the lower body (Goktepe et al., 2004). The type of activity and training intensity were not well-described, and many studies used a self-reported physical activity as a reference. Miyahara et al. found that the earlier the athlete started sports after injury, the higher the BMD of the legs. Further, a longer period of athletic career after restarting was significantly related to higher leg BMD.

Vibration

The mechanical vibration used to prevent and/or treat the loss of BMD mixed results (Alizadeh-Meghrazi, Masani, Popovic, & Craven, 2012; Asselin, Spungen, Muir, Rubin, & Bauman, 2011). Similar to FES, the specifications of the chosen full-body vibration platform, including intensity and frequency of vibration, signal transmission, and joint position and angle, could play a role in effectiveness (Alizadeh-Meghrazi et al., 2012; Asselin et al., 2011).

Ultrasound

Ultrasound does not seem to play a role in preventing or treating osteoporosis. The only randomized study by Warden et al. (2001) did not indicate any benefit of low-intensity pulsed ultrasound to prevent decreased BMD. Therapeutic pulsed ultrasound was applied to the heel of individuals with spinal cord injury for 20 min a day, 5 times a week for a period of 6 consecutive weeks. The contralateral heel was simultaneously treated with inactive United States. No improvement was observed in any of the parameters evaluated ($P > .05$). According to the authors, this finding may be related mainly to the inability of the US to effectively penetrate the external cortex of the bone due to its acoustic properties.

Combined treatments

There are few evaluated studies that combined interventions for the treatment of bone loss in chronic SCI. These studies assess the concomitant administration of pharmacological therapy with non-pharmacological rehabilitation interventions (Gordon, Wald, & Schnitzer, 2013; Morse, Biering-Soerensen, et al., 2019; Morse, Troy, et al., 2019). Morse, Biering-Soerensen, et al. (2019) and Morse, Troy, et al. (2019) investigated the combination of zoledronate (ZA) with FES-rowing. The results demonstrated that the osteogenic response to FES-rowing was dose-dependent and combination therapy with ZA and FES-row training had therapeutic potential to improve bone quality, and perhaps reduced fracture risk at the most common fracture site following SCI. Gordon et al. (2013) evaluated the response of bone to recombinant parathyroid hormone in combination with weight bearing. The results did not show a statistically significant increase in BMD of the lumbar spine (Gordon et al., 2013).

Conclusion

Special attention should be paid to prevent fractures, and appropriate treatment for preventing excessive bone loss and investigations should be performed in rehabilitation hospitals for patients with SCI. Most of the physicians are not educated to measure these risk factors. DEXA should be performed, mainly after an osteoporotic fracture and in fact DEXA should be performed before the occurrence of fracture to prevent such event. Bone remodeling markers (like CTX-I) could give us a clue of the resorption rate and treatment could prevent further loss. Consider identifying risk factors and establishing prevention programs and appropriate treatment. Campaigns to prevent falls and stimulate the appropriate identification and treatment of osteoporosis in individuals with SCI must be promoted.

The analysis of literature for treatments still show mixed results, although there is no guideline, treatment with pharmacological therapy should be considered for patients with SCI, risk factors for fractures and DEXA criteria for osteoporosis. Use of oral bisphosphonates as alendronate or intravenous zoledronic acid, have showen efficacy but further studies should be performed.

The studies suggest standardization of the osteometabolic evaluation of patients with SCI, it is recommended undergo to laboratory evaluation before treatment, 6 months after beginning pharmacological therapy and repeated on annual basis. DEXA should be performed before treatment, 1 year after and every 2 years. Discussions with patients about side effects of these medications are recommended. It is important to emphasize that the protection of typical fractures is greater than the side effects when used for the appropriate length of time.

The effects of non-pharmacological measures are insufficient as a sole modality for osteoporosis prevention and treatment. Several literature reviews were conducted along the time and realized that studies on the use of physical therapies to prevent bone demineralization were inconclusive. The detection of an effective clinical intervention in this study area will require rigorous minimization of bias through a randomized controlled clinical trial design and likely require the involvement of multiple centers. It will also be dependent on appropriate measurement, with adequate intensity and duration of the intervention to detect a treatment effect. However, given the difficulty in conducting large-scale randomized controlled trials to address these issues, many of these gaps can best be addressed by using a multi-faceted approach including a combination of literature synthesis, large longitudinal observational studies and an expert opinion. Any prospective intervention is likely to benefit from early timing after acute SCI.

Before a treatment prescription, it is important to take into consideration timing since SCI, type, frequency, intensity and duration of intervention and the patient's possibilities to follow-up with a long-term treatment. Exercise and pharmacological prescriptions have to be safe. The patient has to be informed about the treatment evidence, risks, benefits and burdens of each alternative (including no intervention) and, together, make a shared decision, depending on their goals, preferences and concerns.

Applications to other areas of neuroscience

In this chapter, we have reviewed the effects of osteoporosis after spinal cord injury and related fractures.

Osteoporosis after SCI is defined as an excessive bone resorption after SCI and bone fragility fractures caused by a trauma that would be insufficient for a normal bone to fracture (Craven et al., 2008; Zleik et al., 2019) or by minimally loaded situations (McPherson et al., 2014; Shields et al., 2005).

Osteoporosis is the most common silent disease in humans whose complication is fragility fractures. Osteoporosis is a treatable disease before fracture occurrence, and even if the first fracture occurred, there is benefit to prevent a new event.

Osteoporosis investigations should be performed for spinal cord injury, traumatic brain injury, neuromuscular disorders, and others because osteoporosis-related fractures in patients with chronic disabilities are a complication with consequences in activities of daily living and rehabilitation (Champs et al., 2020).

Dual-energy X-ray absorptiometry is an important method for diagnosis and should be performed in all patients with chronic disabilities (Garland et al., 2005).

The effects of non-pharmacological treatments are under debate, and studies showed the efficacy of bisphosphonates and Vitamin D to prevent fragility fractures (Bauman, Spungen, et al., 2005; Bauman, Wecht, et al., 2005; Gilchrist et al., 2007; Zehnder et al., 2004).

Campaigns to prevent falls are needed because falls are the first event related to fragility fractures (Champs et al., 2020).

Mini-dictionary of terms

Osteoporosis: According to the WHO, osteoporosis is defined as a low bone mass and micro-architectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture.

Fragility fractures: These are fractures caused by a force that usually doesn't cause a fracture as torsional forces during transfer, compressive forces, unknown, fall from wheelchair, self-passive mobilization, exercises, findings on X-ray, orthostatism or walking training, and others. Fractures because of fall from greater than standing height, sports injuries, and motor vehicle/motor cycle accidents are excluded.

Spinal cord injury: Damage of the spinal cord can be traumatic because of motor vehicle/motor cycle accidents, falls, and others or can be non-traumatic because of virus, tumors or demyelinating disorders, and others.

Dual-energy X-ray absorptiometry (DEXA): It calculates the measurement of bone mineral density in g/cm^2, is a confirmatory test to predict the future risk of fracture, and also serves for ongoing monitoring of bone health and to access bone loss by the bone mineral density (BMD) measurements.

Bisphosphonates: These are drugs capable to inhibit bone resorption.

Key facts of osteoporosis after spinal cord injury

- Bone demineralization after SCI occurs in a rate loss of approximately 4% per month in the first year, and bone loss can be extended 3 to 8 years after SCI.
- Bone loss associated with SCI is related to immobility and metabolic changes.
- Other related factors may contribute to this bone loss, such as vitamin D deficiency and the use of methylprednisolone, anti-convulsant drugs, and psychotropic substances.
- Studies demonstrated bone demineralization greater than 20% to 70% in lower limbs after SCI.

Key facts of fragility fractures after spinal cord injury

- The consequence of osteoporosis in individuals with SCI is fracture due to bone fragility.
- It usually occurs in transfers, falls and activities with minimal or no trauma.
- Fractures may occur in 25% to 46% of these people with SCI over their lifetimes.
- Most places of fractures are in the tibia and/or distal fibula, distal femur, or hip/proximal femur and proximal tibia.

Key facts of diagnosis of osteoporosis after spinal cord injury

- Osteometabolic evaluation of patients with SCI is recommended for evaluation before treatment, 6 months after beginning pharmacological therapy and repeated on annual basis.

- DEXA should be performed before treatment, 1 year after and every 2 years.
- DEXA measurement of the distal femur and proximal tibia, with specific protocols for the evaluation of these sites, is recommended.

Key facts of treatment for osteoporosis-related fractures after spinal cord injury

- Treatment with pharmacological therapy should be considered for patients with SCI and risk factors plus DEXA criteria for osteoporosis.
- The effects of non-pharmacological measures are insufficient as a sole modality for osteoporosis prevention and treatment.
- Discussions with patients about side effects of these medications are recommended.
- The patient has to be informed by a healthcare professional about the treatment evidence, risks, benefits, and burdens of each alternative (including no intervention), and together make a shared decision, depending on their goals, preferences, and concerns.

Summary points

- Osteoporosis affects the health of individuals with SCI because it increases the risk of fragility fractures with consequences.
- Most sites of fractures are in the tibia and/or distal fibula, distal femur, or hip/proximal femur and proximal tibia.
- Fractures are primarily related to torsional forces during transfer, passive mobilization, compressive forces, and falls.
- Special attention should be paid to the prevention of fractures, appropriate treatments should be instigated to prevent excessive bone loss, and investigations should be performed.
- Campaigns to prevent falls and stimulate the appropriate identification and treatment of osteoporosis in individuals with SCI must be promoted.
- Dual-energy X-ray absorptiometry (DEXA) is an important method for diagnosis.
- Treatment with pharmacological therapy for people with SCI with risk factors for SCI population should be considered.
- The patient has to be informed about the diagnosis and treatment options and make a shared decision for treatment, depending on their goals, preferences, and concerns.

References

Abderhalden, L., Weaver, F. M., Bethel, M., Demirtas, H., Burns, S., Svircev, J., et al. (2017). Dual-energy X-ray absorptiometry and fracture prediction in patients with spinal cord injuries and disorders. *Osteoporosis International*, *28*(3), 925–934.

Akhigbe, T., Chin, A. S., Svircev, J. N., Hoenig, H., Burns, S. P., Weaver, F. M., et al. (2015). A retrospective review of lower extremity fracture care in patients with spinal cord injury. *The Journal of Spinal Cord Medicine*, *38*(1), 2–9.

Alekna, V., Tamulaitiene, M., Sinevicius, T., & Juocevicius, A. (2008). Effect of weight-bearing activities on bone mineral density in spinal cord injured patients during the period of the first two years. *Spinal Cord*, *46*(11), 727–732.

Alizadeh-Meghrazi, M., Masani, K., Popovic, M. R., & Craven, B. C. (2012). Whole-body vibration during passive standing in individuals with spinal cord injury: Effects of plate choice, frequency, amplitude, and subject's posture on vibration propagation. *PM & R : The Journal of Injury, Function, and Rehabilitation*, *4*(12), 963–975.

Asselin, P., Spungen, A. M., Muir, J. W., Rubin, C. T., & Bauman, W. A. (2011). Transmission of low-intensity vibration through the axial skeleton of persons with spinal cord injury as a potential intervention for preservation of bone quantity and quality. *The Journal of Spinal Cord Medicine*, *34*(1), 52–59.

Battaglino, R. A., Lazzari, A. A., Garshick, E., & Morse, L. R. (2012). Spinal cord injury-induced osteoporosis: Pathogenesis and emerging therapies. *Current Osteoporosis Reports*, *10*(4), 278–285.

Bauman, W. A., & Cardozo, C. P. (2015). Osteoporosis in individuals with spinal cord injury. *PM & R : The Journal of Injury, Function, and Rehabilitation*, *7*(2), 188–201.

Bauman, W. A., Cirnigliaro, C. M., La Fountaine, M. F., Martinez, L., Kirshblum, S. C., & Spungen, A. M. (2015). Zoledronic acid administration failed to prevent bone loss at the knee in persons with acute spinal cord injury: An observational cohort study. *Journal of Bone and Mineral Metabolism*, *33*(4), 410–421.

Bauman, W. A., & Spungen, A. M. (2000). Metabolic changes in persons after spinal cord injury. *Physical Medicine and Rehabilitation Clinics of North America*, *11*(1), 109–140.

Bauman, W. A., Spungen, A. M., Morrison, N., Zhang, R. L., & Schwartz, E. (2005). Effect of vitamin D analog on leg bone mineral density in patients with chronic spinal cord injury. *Journal of Rehabilitation Research and Development*, *42*(5), 625–634.

Bauman, W. A., Wecht, J. M., Kirshblum, S., Spungen, A. M., Morrison, N., Cirnigliaro, C., et al. (2005). Effect of pamidronate administration on bone in patients with acute spinal cord injury. *Journal of Rehabilitation Research and Development*, *42*(3), 305–313.

Bauman, W. A., Zhong, Y. G., & Schwartz, E. (1995). Vitamin D deficiency in veterans with chronic spinal cord injury. *Metabolism, Clinical and Experimental*, *44*(12), 1612–1616.

Belanger, M., Stein, R. B., Wheeler, G. D., Gordon, T., & Leduc, B. (2000). Electrical stimulation: Can it increase muscle strength and reverse osteopenia in spinal cord injured individuals? *Archives of Physical Medicine and Rehabilitation*, *81*(8), 1090–1098.

Bethel, M., Bailey, L., Weaver, F., Harmon, R. L., Priebe, M. M., Le, B., et al. (2016). A historical study of appendicular fractures in veterans with traumatic chronic spinal cord injury: 2002-2007. *The Journal of Spinal Cord Medicine*, *39*(6), 686–692.

Biering-Sørensen, F., Hansen, B., & Lee, B. S. (2009). Non-pharmacological treatment and prevention of bone loss after spinal cord injury: A systematic review. *Spinal Cord*, *47*(7), 508–518.

Carbone, L. D., Chin, A. S., Burns, S. P., Svircev, J. N., Hoenig, H., Heggeness, M., et al. (2013). Morbidity following lower extremity fractures in men with spinal cord injury. *Osteoporosis International*, *24*(8), 2261–2267.

Carvalho, D. C., Garlipp, C. R., Bottini, P. V., Afaz, S. H., Moda, M. A., & Cliquet, A., Jr. (2006). Effect of treadmill gait on bone markers and bone mineral density of quadriplegic subjects. *Brazilian Journal of Medical and Biological Research*, *39*(10), 1357–1363.

Chain, A., Koury, J. C., & Bezerra, F. F. (2012). Physical activity benefits bone density and bone-related hormones in adult men with cervical spinal cord injury. *European Journal of Applied Physiology*, *112*(9), 3179–3186.

Champs, A. P. S., Maia, G. A. G., Oliveira, F. G., de Melo, G. C. N., & Soares, M. M. S. (2020). Osteoporosis-related fractures after spinal cord injury: A retrospective study from Brazil. *Spinal Cord*, *58*(4), 484–489.

Chang, K. V., Hung, C. Y., Chen, W. S., Lai, M. S., Chien, K. L., & Han, D. S. (2013). Effectiveness of bisphosphonate analogues and functional electrical stimulation on attenuating post-injury osteoporosis in spinal cord injury patients—A systematic review and meta-analysis. *PLoS One*, *8*(11), e81124.

Chen, S. C., Lai, C. H., Chan, W. P., Huang, M. H., Tsai, H. W., & Chen, J. J. (2005). Increases in bone mineral density after functional electrical stimulation cycling exercises in spinal cord injured patients. *Disability and Rehabilitation*, *27*(22), 1337–1341.

Cirnigliaro, C. M., Myslinski, M. J., La Fountaine, M. F., Kirshblum, S. C., Forrest, G. F., & Bauman, W. A. (2017). Bone loss at the distal femur and proximal tibia in persons with spinal cord injury: Imaging approaches, risk of fracture, and potential treatment options. *Osteoporosis International*, *28*(3), 747–765.

Craven, C., Robertson, L., Delparte, J., Ashe, M., & Janice, J. E. (2008). Sublesional osteoporosis prevention, detection, and treatment: A decision guide for rehabilitation clinicians treating patients with spinal cord injury. *Critical Reviews in Physical and Rehabilitation Medicine*, *20*(4), 277–321.

Craven, B. C., Robertson, L. A., McGillivray, C. F., & Adachi, J. D. (2009). Detection and treatment of sublesional osteoporosis among patients with chronic spinal cord injury. *Topics in Spinal Cord Injury Rehabilitation*, *14*(4), 1–22.

De Bruin, E. D., Frey-Rindova, P., Herzog, R. E., Dietz, V., Dambacher, M. A., & Stüssi, E. (1999). Changes of tibia bone properties after spinal cord injury: Effects of early intervention. *Archives of Physical Medicine and Rehabilitation*, *80*(2), 214–220.

Dolbow, D. R., Gorgey, A. S., Daniels, J. A., Adler, R. A., Moore, J. R., & Gater, D. R., Jr. (2011). The effects of spinal cord injury and exercise on bone mass: A literature review. *NeuroRehabilitation*, *29*(3), 261–269.

Dudley-Javoroski, S., & Shields, R. K. (2013). Active-resisted stance modulates regional bone mineral density in humans with spinal cord injury. *The Journal of Spinal Cord Medicine*, *36*(3), 191–199. https://doi.org/10.1179/2045772313Y.0000000092.

Eser, P., de Bruin, E. D., Telley, I., Lechner, H. E., Knecht, H., & Stussi, E. (2003). Effect of electrical stimulation-induced cycling on bone mineral density in spinal cord-injured patients. *European Journal of Clinical Investigation*, *33*(5), 412–419.

Frontera, J. E., & Mollett, P. (2017). Aging with spinal cord injury: An update. *Physical Medicine and Rehabilitation Clinics of North America*, *28*(4), 821–828.

Frotzler, A., Coupaud, S., Perret, C., Kakebeeke, T. H., Hunt, K. J., & Eser, P. (2009). Effect of detraining on bone and muscle tissue in subjects with chronic spinal cord injury after a period of electrically-stimulated cycling: A small cohort study. *Journal of Rehabilitation Medicine*, *41*(4), 282–285.

Garland, D., Adkins, R., & Stewart, C. (2005). Fracture threshold and risk for osteoporosis and pathologic fractures in individuals with spinal cord injury. *Topics in Spinal Cord Injury Rehabilitation*, *11*(1), 61–69.

GBD 2016 Traumatic Brain Injury & Spinal Cord Injury Collaborators. (2019). Global, regional, and national burden of traumatic brain injury and spinal cord injury, 1990-2016: A systematic analysis for the global burden of disease study 2016. *The Lancet Neurology*, *18*(1), 56–87.

Giangregorio, L. M., Webber, C. E., Phillips, S. M., Hicks, A. L., Craven, B. C., Bugaresti, J. M., et al. (2006). Can body weight supported treadmill training increase bone mass and reverse muscle atrophy in individuals with chronic incomplete spinal cord injury? *Applied Physiology, Nutrition, and Metabolism*, *31*(3), 283–291.

Gifre, L., Vidal, J., Carrasco, J. L., Muxi, A., Portell, E., Monegal, A., et al. (2016). Denosumab increases sublesional bone mass in osteoporotic individuals with recent spinal cord injury. *Osteoporosis International*, *27*(1), 405–410.

Gilchrist, N. L., Frampton, C. M., Acland, R. H., Nicholls, M. G., March, R. L., Maguire, P., et al. (2007). Alendronate prevents bone loss in patients with acute spinal cord injury: A randomized, double-blind, placebo-controlled study. *The Journal of Clinical Endocrinology and Metabolism*, *92*(4), 1385–1390.

Goktepe, A. S., Tugcu, I., Yilmaz, B., Alaca, R., & Gunduz, S. (2008). Does standing protect bone density in patients with chronic spinal cord injury? *The Journal of Spinal Cord Medicine*, *31*(2), 197–201.

Goktepe, A. S., Yilmaz, B., Alaca, R., Yazicioglu, K., Mohur, H., & Gunduz, S. (2004). Bone density loss after spinal cord injury: Elite paraplegic basketball players vs. paraplegic sedentary persons. *American Journal of Physical Medicine & Rehabilitation*, *83*(4), 279–283.

Gordon, K. E., Wald, M. J., & Schnitzer, T. J. (2013). Effect of parathyroid hormone combined with gait training on bone density and bone architecture in people with chronic spinal cord injury. *PM & R : The Journal of Injury, Function, and Rehabilitation*, *5*(8), 663–671.

Haider, I. T., Lobos, S. M., Simonian, N., Schnitzer, T. J., & Edwards, W. B. (2018). Bone fragility after spinal cord injury: Reductions in stiffness and bone mineral at the distal femur and proximal tibia as a function of time. *Osteoporosis International*, *29*(12), 2703–2715.

Jiang, S. D., Dai, L. Y., & Jiang, L. S. (2006). Osteoporosis after spinal cord injury. *Osteoporosis International*, *17*(2), 180–192.

Koutrakis, N. E., Goldstein, R. L., Walia, P., Polak, M. M., Lazzari, A. A., Tun, C. G., et al. (2019). Vitamin D, diet, and lifestyle in a chronic SCI population. *Spinal Cord*, *57*(2), 117–127.

Kunkel, C. F., Scremin, A. M., Eisenberg, B., Garcia, J. F., Roberts, S., & Martinez, S. (1993). Effect of "standing" on spasticity, contracture, and osteoporosis in paralyzed males. *Archives of Physical Medicine and Rehabilitation*, *74*(1), 73–78.

Lai, C. H., Chang, W. H., Chan, W. P., Peng, C. W., Shen, L. K., Chen, J. J., et al. (2010). Effects of functional electrical stimulation cycling exercise on bone mineral density loss in the early stages of spinal cord injury. *Journal of Rehabilitation Medicine*, *42*(2), 150–154.

Liu, C. C., Theodorou, D. J., Theodorou, S. J., Andre, M. P., Sartoris, D. J., Szollar, S. M., et al. (2000). Quantitative computed tomography in the evaluation of spinal osteoporosis following spinal cord injury. *Osteoporosis International*, *11*(10), 889–896.

McPherson, J. G., Edwards, W. B., Prasad, A., Troy, K. L., Griffith, J. W., & Schnitzer, T. J. (2014). Dual energy X-ray absorptiometry of the knee in spinal cord injury: Methodology and correlation with quantitative computed tomography. *Spinal Cord*, *52*(11), 821–8255.

Morse, L. (2019). Osteoporosis prophylaxis in acute SCI. *Spinal Cord Series and Cases*, *5*(1), 27.

Morse, L. R., Battaglino, R. A., Stolzmann, K. L., Hallett, L. D., Waddimba, A., Gagnon, D., et al. (2009). Osteoporotic fractures and hospitalization risk in chronic spinal cord injury. *Osteoporosis International*, *20*(3), 385–392.

Morse, L. R., Biering-Soerensen, F., Carbone, L. D., Cervinka, T., Cirnigliaro, C. M., Johnston, T. E., et al. (2019). Bone mineral density testing in spinal cord injury. ISCD official position. *Journal of Clinical Densitometry*, *22*(4), 554–566.

Morse, L. R., Troy, K. L., Fang, Y., Nguyen, N., Battaglino, R., Goldstein, R. F., et al. (2019). Combination therapy with zoledronic acid and FES-row training mitigates bone loss in paralyzed legs: Results of a randomized comparative clinical trial. *JBMR Plus*, *3*(5), e10167.

Ogilvie, C., Bowker, P., & Rowley, D. I. (1993). The physiological benefits of paraplegic orthotically aided walking. *Paraplegia*, *31*(2), 111–115.

Shapiro, J., Smith, B., Beck, T., Ballard, P., Dapthary, M., BrintzenhofeSzoc, K., et al. (2007). Treatment with zoledronic acid ameliorates negative geometric changes in the proximal femur following acute spinal cord injury. *Calcified Tissue International*, *80*(5), 316–322.

Shields, R. K., Schlechte, J., Dudley-Javoroski, S., Zwart, B. D., Clark, S. D., Grant, S. A., et al. (2005). Bone mineral density after spinal cord injury: A reliable method for knee measurement. *Archives of Physical Medicine and Rehabilitation*, *86*(10), 1969–1973.

Soleyman-Jahi, S., Yousefian, A., Maheronnaghsh, R., Shokraneh, F., Zadegan, S. A., Soltani, A., et al. (2018). Evidence-based prevention and treatment of osteoporosis after spinal cord injury: A systematic review. *European Spine Journal*, *27*(8), 1798–1814.

Thoumie, P., Le Claire, G., Beillot, J., Dassonville, J., Chevalier, T., Perrouin-Verbe, B., et al. (1995). Restoration of functional gait in paraplegic patients with the RGO-II hybrid orthosis. A multicenter controlled study. II: Physiological evaluation. *Paraplegia*, *33*(11), 654–659.

Troy, K. L., & Morse, L. R. (2015). Measurement of bone: Diagnosis of SCI-induced osteoporosis and fracture risk prediction. *Topics in Spinal Cord Injury Rehabilitation*, *21*(4), 267–274.

Uebelhart, D., Demiaux-Domenech, B., Roth, M., & Chantraine, A. (1995). Bone metabolism in spinal cord injured individuals and in others who have prolonged immobilisation. A review. *Paraplegia*, *33*(11), 669–673.

Warden, S. J., Bennell, K. L., Matthews, B., Brown, D. J., McMeeken, J. M., & Wark, J. D. (2001). Efficacy of low-intensity pulsed ultrasound in the prevention of osteoporosis following spinal cord injury. *Bone*, *29*(5), 431–436.

Zehnder, Y., Risi, S., Michel, D., Knecht, H., Perrelet, R., Kraenzlin, M., et al. (2004). Prevention of bone loss in paraplegics over 2 years with alendronate. *Journal of Bone and Mineral Research*, *19*(7), 1067–1074.

Zleik, N., Weaver, F., Harmon, R. L., Le, B., Radhakrishnan, R., Jirau-Rosaly, W. D., et al. (2019). Prevention and management of osteoporosis and osteoporotic fractures in persons with a spinal cord injury or disorder: A systematic scoping review. *The Journal of Spinal Cord Medicine*, *42*(6), 735–759.

Chapter 8

Understanding the effects of prolonged cervical spinal cord compression on the brain. Current knowledge and future challenges

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Abbreviations

BOLD	blood oxygen level-dependent
CS	cervical spondylosis
CST	corticospinal tract
CSM	cervical spondylosis myelopathy
DTI	diffusion tensor imaging
FA	fractional anisotropy
FC	functional connectivity
GM	gray matter
fMRI	functional magnetic resonance imaging
MD	mean diffusivity
MR	magnetic resonance
MRI	magnetic resonance imaging
M1	primary motor cortex
RSNs	resting-state networks
RS-fMRI	resting-state functional MR imaging
SCI	spinal cord injury
SMC	sensorimotor cortex
SMA	supplementary motor area
S1	primary sensory cortex
SMG	supramarginal gyri
WM	white matter

Introduction

Compression of the cervical spinal cord can be caused by a wide range of causes, but the most common is cervical spondylosis (CS), a chronic degenerative process that affects the vertebral bodies and inter-vertebral discs of the cervical spine (Table 1). CS is frequently found in asymptomatic adults after the fifth decade of life, but may progress to disk herniation, bone spur formation, compression of the spinal cord, and cervical spondylotic myelopathy (CSM) (Kelly, Groarke, Butler, Poynton, & Byrne, 2012).

The compression of the spinal cord by CS is a slow and progressive process caused by the reduction of the spinal canal diameter by dynamic and static factors (de Oliveira Vilaça et al., 2016). In CS, any flexion or extension of the cervical spine causes the intermittent compression of the spinal cord. This progressive compression leads to several changes such as apoptosis of the anterior horn neurons, ischemia, gradual spongy necrosis, demyelination of the white matter (WM), and Wallerian degeneration (Fig. 1; Grabher, Mohammadi, David, & Freund, 2017). Despite it may affect one single segment of the

Diagnosis and Treatment of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822498-4.00008-7

TABLE 1 Summary of the main causes of spinal cord compression.

Traumatic causes	Atraumatic causes
Vehicular accidents	Degenerative spondylosis
Falls	Intervertebral disk herniation
Violence	Metastatic disease
Sports	Primary spinal cord tumor
Recreation activities	Spinal epidural abscess
	Spinal epidural hematoma
	Scoliosis
	Rheumatoid arthritis
	Bone diseases

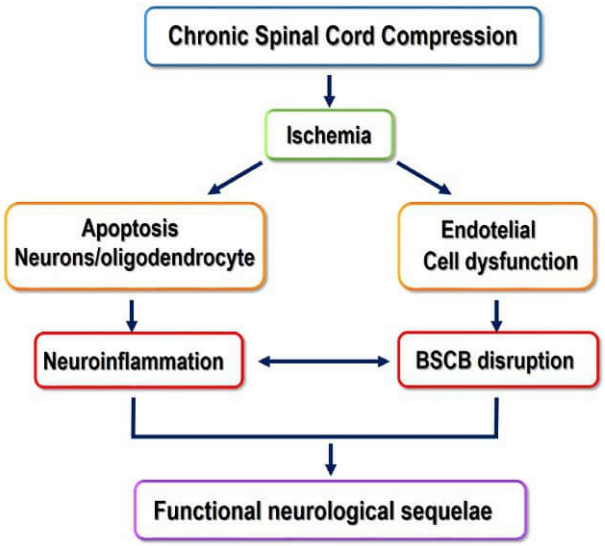

FIG. 1 Representative scheme of the pathophysiology of cervical spondylotic myelopathy. Chronic compression of the spinal cord causes chronic ischemia that damages oligodendrocytes and neurons eliciting an inflammatory response, endothelial cell loss, and disruption of the blood-spinal cord barrier (BSCB). Neuronal loss and axonal damage lead to neurological impairment. *Unpublished figure*.

spine, multi-level involvement is very frequent, generally at the lower segments. Contrary to the lumbar spine, which encloses only a small part of the spinal cord, stenosis of the cervical spinal canal can induce a direct compromise of the whole spinal cord and severe neurological deficits.

Characteristically, in CS, the severity of compression and deficits varies greatly across individuals. Some patients experience a benign form of the disease with stable periods lasting from months to years, while others develop CSM with neurological deficits and a considerable deterioration over time (Baron & Young, 2007; Edwards, Riew, Anderson, Hilibrand, & Vaccaro, 2003). If CSM fully develops, the symptoms are progressive and in a stepwise manner (de Oliveira Vilaça et al., 2016), with a wide range of clinical manifestations including weakening or sensory loss in one or more limbs, gait unsteadiness, fine motor deficits, and non-specific neck and shoulder pain with or without radiculopathy.

Diagnosis of CSM is based on physical examination and clinical imaging, usually with Magnetic Resonance Imaging (MRI). MRI allows to evaluate the vertebral discs, ligaments, subarachnoid space, spinal cord, and quantify the spinal stenosis. Still, it lacks sensitivity to provide information about the integrity of the spinal cord, presents a poor correlation with neurological and functional impairment, and does not provide reliable prognostic information to predict surgical outcomes (Martin et al., 2016). Recent advances in MR techniques have started to overcome these limitations by providing invaluable information about CSM pathology, with several studies reporting that prolonged cervical spine compression affects not

only local structures but also distally from the site of injury. For instance, numerous brain changes, such as cortical and subcortical atrophy, functional reorganization of the sensorimotor cortex (SMC), and connectivity impairment, have been reported (Bernabéu-Sanz, Mollá-Torró, López-Celada, Moreno-López, & Fernández-Jover, 2020; Chen et al., 2017). These observations have had a great impact on the understanding of CSM, framing the disease as multi-factorial and complex, with its pathophysiology still being poorly understood. In this sense, a clear limitation to advancing in the field of CSM pathology has been the lack of reliable animal models.

Understanding the sequence of structural and functional changes of CSM at the brain level, and defining their effects on the clinical outcome is of crucial importance to better understand the disease, to prevent its fatal consequences, and to develop the best evidence-based rehabilitation therapies. In the next sections, we will summarize the current knowledge on the effects of prolonged spinal cord compression on the brain (Figs. 2–5).

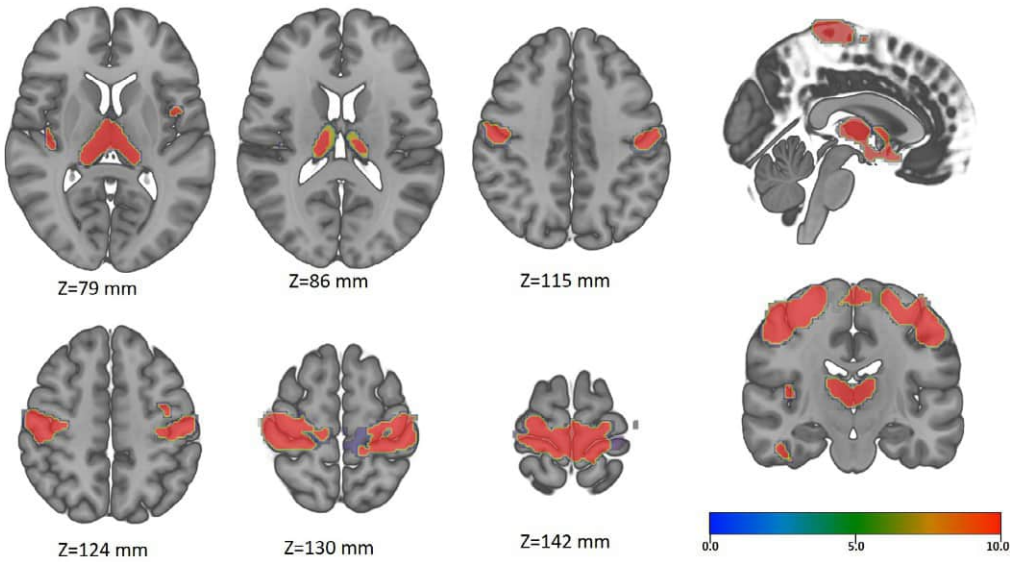

FIG. 2 Representation of the regional areas with significant cortical volume reduction in a group of patients with prolonged cervical spine compression. The results were obtained from a voxel-based morphometry analysis in a group of 64 subjects (32 cervical spondylosis patients vs. 32 healthy controls, $P < .05$ corrected), suggesting that prolonged cervical spine compression led to thalami, sensorimotor cortex, and supplementary motor area atrophy. *Unpublished figure*.

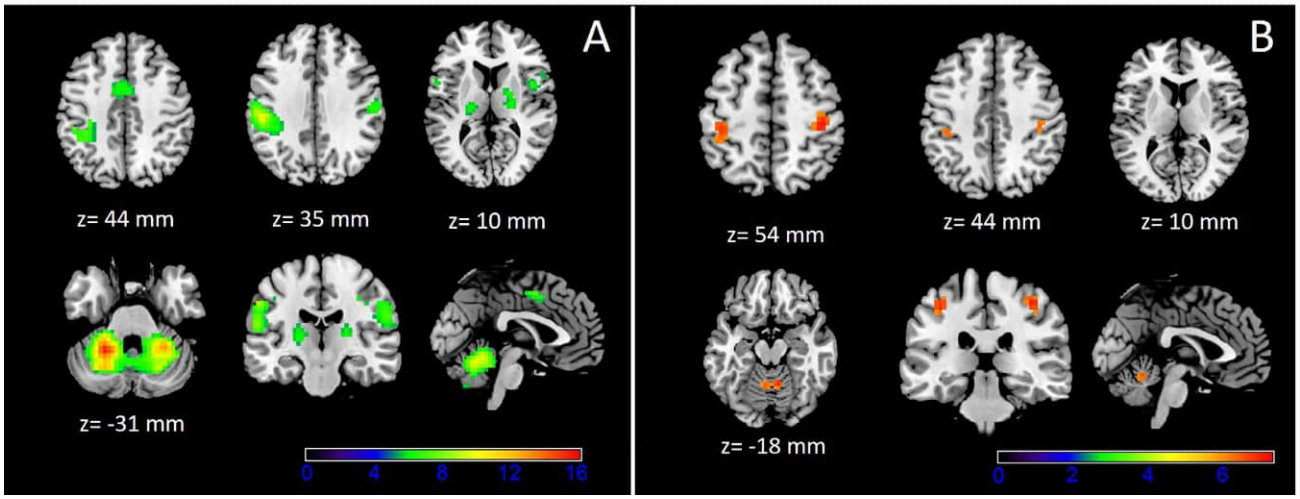

FIG. 3 Functional MRI results showing the differences in the brain activation pattern in a group of cervical spondylosis patients ($n = 32$) (A) and age-matched healthy controls ($n = 32$) (B) during a bilateral finger-tapping task. The activation maps correspond to a second-level analysis in axial, coronal, and sagittal planes in the MNI space ($P < .05$ corrected, $k = 10$). The patients presented a higher number of activated cortical and subcortical areas than healthy controls. *Unpublished figure*.

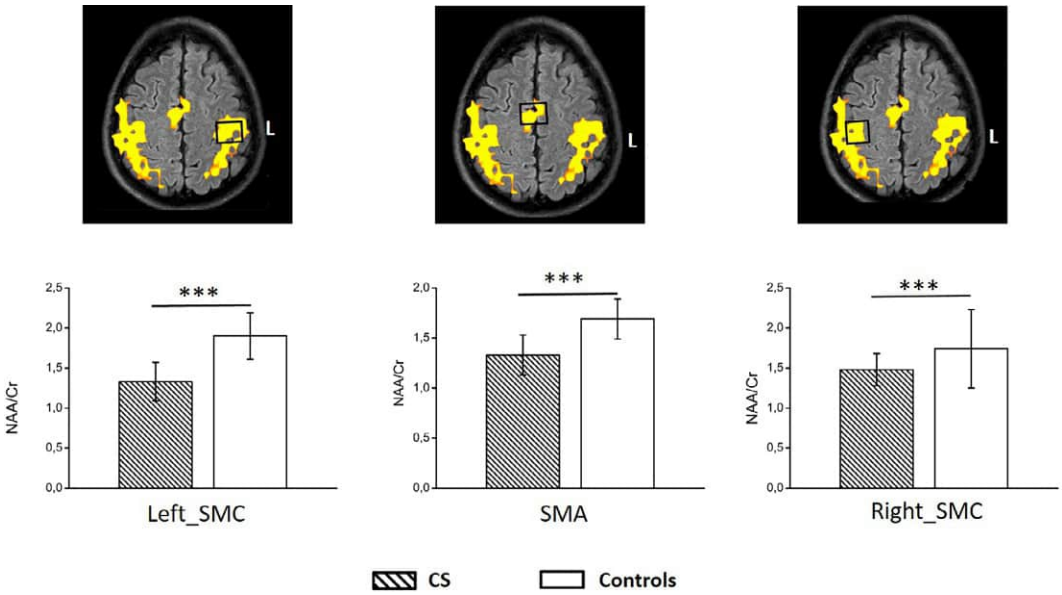

FIG. 4 MR-spectroscopy results of the motor cortex of cervical spondylosis patients (CS, n=32) and healthy controls (HC, n=32). The volume of interest was located on the activated area in both the primary sensorimotor cortex (SMC) and supplementary motor area (SMA) after a bilateral finger-tapping fMRI task paradigm (see *upper image* as example of voxel location for measurements). Graphs represent the NAA/ Cr (mean ± SD) values obtained after quantification in each group. A significant reduction was observed in all areas compared to controls suggesting significant neuronal/axonal damage. *** represents $P < .001$ after unpaired t-test. *NAA*, N-acetylaspartate; *Cr*, creatine. *Unpublished figure*.

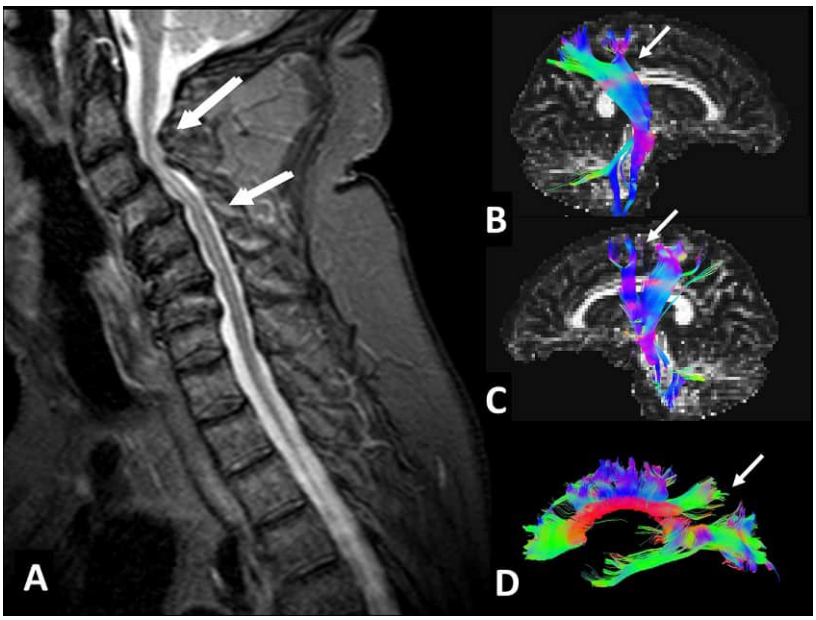

FIG. 5 Tractography results obtained in a patient with cervical spondylosis myelopathy. (A) Sagittal STIR of a 69-year-old male with cervical spondylosis and myelopathy at C2-C5 levels, significant cervical lordosis loss, and several diffuse herniated discs from C2 to C7. Clinically the patient only presented bilateral manual clumsiness. No cervicalgia or cervicobrachialgia was present. (B, C, D) Tractography results suggested significant bilateral and symmetrical axonal damage affecting both corticospinal tracts at the distal-anterior regions (B, C) and the *corpus callosum* (A) at the superior and posterior parietal projection fibers of both hemispheres *(see arrows)*. Commissural fibers were preserved. *Unpublished figure*.

Cervical spine compression causes brain atrophy

There is increasing evidence supporting that spinal cord injury (SCI) may cause destructive cortical changes ranging from atrophy of projecting neurons to cell death (Freund et al., 2013; Hains, Black, & Waxman, 2003). In animal models, after SCI, the disruption of the motor efferents and sensory afferents results in atrophic changes of the neural sensorimotor systems (Hains et al., 2003). Indeed, several studies have demonstrated that SCI can induce cortical atrophy on the supraspinal network, whose degree correlates with the spinal cord atrophy (Freund et al., 2011, 2013) and the functional status (Freund et al., 2011).

There are still a few works exploring the effect of prolonged spinal cord compression by CS in the brain. However, the results are consistent reporting cortical atrophy in the primary SMC, with additional volume changes at the thalami, specifically at the pulvinar nuclei (Bernabéu-Sanz et al., 2020; Woodworth, Holly, Mayer, Salamon, & Ellingson, 2019). Furthermore, supplementary brain areas related to the execution of complex movements (such as gait, grasp, and fine hand-motor coordination) are also atrophied (Bernabéu-Sanz et al., 2020; Woodworth et al., 2019). Metabolic studies using MR-spectroscopy on CSM patients have also reported neuronal damage and impaired metabolism on the SMC that is not recovered or may worsen after surgery in spite of clinical improvement (Aleksanderek et al., 2017; Goncalves, Stevens, Doyle-Pettypiece, Bartha, & Duggal, 2016).

In a recent study regarding chronic CS, a consistent pattern of brain changes associated with neurological function and neck pain was observed (Woodworth et al., 2019). Specifically, cortical thinning in the superior frontal regions, anterior cingulate, insula, and precuneus were present. Furthermore, atrophy in the putamen, BA3a, and primary motor regions when worsening neurological symptoms was reported. Taking into account the role of BA3a as an afferent receiver of proprioception (Panchuelo et al., 2020), the observed atrophy in this study may explain the deficits in proprioception (gait and hand function) reported in CSM patients (Theodore, 2020).

CS patients may also present brain changes to chronic pain in the same fashion as other chronic pain conditions. Specifically, a cortical thinning within the insula and anterior cingulate cortex has been reported (Freund et al., 2011). Finally, a faster rate of cortical thinning and atrophy compared to age-matched healthy subjects in CS patients has been observed (Woodworth et al., 2019).

The significance of these findings is that despite CS has been traditionally considered as a benign disease typically present in the old-age population, it may, if not properly monitored, harm the brain inducing progressive atrophy. In this sense, the CS-related brain atrophy may become a potential obstacle to clinical recovery after surgery, even if significant repair is achieved at the site of compression.

Cervical spine compression causes neural plasticity to preserve function

One of the most fascinating characteristics of the central nervous system is its ability to self-repair, reorganize after injury, and compensate for functional loss. This mechanism, known as neural plasticity (or functional reorganization), is present in numerous brain conditions (Cohen, Quarta, Bravi, Granato, & Minciacchi, 2017) and has also been observed in SCI. The exact mechanism is not fully understood but may occur through synaptic modifications of pre-existing connections and/or by the development of new circuitries (Holly, Dong, Albistegui-DuBois, Marehbian, & Dobkin, 2007).

Several studies have shown that SCI, although it does not directly involve cortical neurons, may alter the functional activation pattern of the SMC. These observations have been achieved with different physiological and imaging techniques such as functional MRI (fMRI). fMRI is a non-invasive imaging modality that allows to detect changes in brain activation over a period of time while a specific task is being performed. It can be used to localize areas of brain activation secondary to several cognitive and motor tasks, allowing to map the cortical representation of neural activation (Buchbinder, 2016).

In CSM patients, fMRI studies have shown the existence of significant changes in the cortical activation pattern during sensorimotor tasks. These changes consist of the expansion of the cortical representation for the affected limb by the inclusion of adjacent motor territories (Dong et al., 2008). Recruitment of supplementary areas outside the SMC including *globus pallidus*, left thalamus, caudate nucleus, and both cerebellum hemispheres have been reported. Additionally, decreased activation in SMA and both SMC, as well as increased activation of both cerebellum hemispheres, has been observed (Bernabéu-Sanz et al., 2020). Interestingly, the displacement and activation of the sensorimotor areas in CSM appeared in the vicinity of the areas with gray matter (GM) atrophy, suggesting that the displacement and recruitment of new cortical areas may be mediated by adaptive changes to GM atrophy (Henderson, Gustin, Macey, Wrigley, & Siddall, 2011). This functional reorganization is closely associated with the severity of the SCI (Zhou et al., 2015), helping to maintain a residual motor function, and contributing to its restoration if the disease progression is halted (Dong et al.,

2008). Indeed, these adaptive changes may also explain why some CSM patients with significant SCI are able to perform motor activities with apparently minor neurological deficits.

Comparison of pre-operative and post-operative studies has shown that surgical decompression of the cervical spine leads to cortical reorganization, probably by the recovery of conduction in the preserved axons at the spinal cord (Green et al., 2015). After surgical decompression, the altered SMC recruitment pattern gradually disappears (Holly et al., 2007), and everything progresses toward an activation pattern similar to the observed in healthy controls (Dong et al., 2008). There is an increased activation in the contralateral primary motor cortex (M1) concomitant with the improvement of the motor function and the extent of spinal cord expansion (Bhagavatula et al., 2016; Tam, Barry, Bartha, & Duggal, 2010). Also, a gradual disappearance of the ipsilateral primary SMC activation in addition to a progressive increase in the contralateral SMC and SMA is observed (Dong et al., 2008). This normalization continues over time and can be enhanced by activity-dependent mechanisms related to task practice and learning.

In summary, according to recent studies, CSM patients present compensatory mechanisms that consist of an increase and expansion of the cortical representation of the motor areas, especially those devoted to the hands. After the surgery, there is a tendency to normalization of the sensorimotor representation. However, the reported results are not completely consistent. This is probably because CSM patients form a heterogeneous group with different levels of impairment, different degrees of SCI, and different natural histories. In addition, there is no uniformity in the timing of imaging after the surgery. Still, the reported observations provide direct evidence of neuronal plasticity in the SMC of CSM patients that may play a main role in the post-operative motor functional recovery.

Cervical spine compression changes the functional connectivity of the brain

Few studies have analyzed the alterations of the whole-brain network in CSM. These studies have been performed with resting-state functional MR imaging (RS-fMRI), a new technique that allows evaluating the functional relationship between brain areas, and enables the visualization of brain functional connectivity (FC) between spatially separated brain regions. RS-fMRI is a robust method that uses the endogenous brain activity detectable with blood oxygen level-dependent (BOLD) to identify areas that are interacting at rest. With RS-fMRI spontaneous low-frequency BOLD-fluctuations in neural activity (known as amplitude of low-frequency fluctuation) are detected, allowing to establish the different anatomically correlated functional networks (Smitha et al., 2017). As a result, the resting-state networks (RSNs) maps are obtained which represent topographies of functionally connected regions across the brain, helping to detect functionally relevant changes after injury to the central nervous system, if present.

In CSM, RS-fMRI studies have reported that compression of the cervical spinal cord alters the connectivity pattern of the sensorimotor and visual cortices of the brain. Specifically, an overall increase in the FC in the sensorimotor cortex and supplementary areas (precuneus, superior frontal gyrus, and anterior cingulate), and between the cerebellum and the pre- and post-central gyri has been reported. This increased FC correlates with the worsening of the neurological symptoms, suggesting that the altered FC between the SMC and supplementary areas might represent compensatory mechanisms for accomplishing motor tasks (Woodworth, Holly, Salamon, & Ellingson, 2018).

In a recent study, increased brain activity in the primary SMC and decreased brain activity in visual cortices and both supramarginal gyri (SMG) were observed. Characteristically after surgical decompression, the brain activity of the sensorimotor and visual cortices normalized (Takenaka et al., 2019). In another study by Chen et al., the authors only reported decreased neural activity in the primary visual cortex of CSM patients and an increased FC between the visual cortex and the posterior cingulate lobe (Chen et al., 2018). These observations suggested that the visual cortices were impaired, which accounted for the blurred vision observed in the patients of the study. Interestingly, the visual impairment also improved after surgical decompression. Considering that the cingulate gyri are related to the dorsal attention network, that in turn is involved in the control of visual attention (Fox, Corbetta, Snyder, Vincent, & Raichle, 2006), the authors concluded that the enhanced FC in the visual attention network was an adaptive mechanism to compensate for the diminished activity observed on the primary visual cortex.

In another study, increased FC between the left thalamus, the visual system (bilateral lingual gyrus, cuneus), and the right cerebellum posterior lobe, that correlated with the sensory scores (Peng, Tan, He, & Ou, 2020), were found. Moreover, decreased FC between the sensory and motor cortices was observed. The authors concluded that the increased FC in the visual-related network acted as a compensatory mechanism to the decreased somatosensory transmission information detected in the patients. Likewise, increased FC between the brainstem and visual cortex in both posterior parietal cortices and its association with neurological impairment and neck disability has been described in CSM (Wang, Laiwalla, Salamon, Ellingson, & Holly, 2020).

While the altered FC in the SMC is in line with previous fMRI literature during sensory and motor tasks, the observation of increased FC in the visual cortex is surprising as CS is not a primary visual disorder. In this sense, Wang et al. propose that the observed increased FC in the visual cortex may be secondary to the need for more visual input to optimize body movements, mechanics, and balance (Wang et al., 2020). This observation is in line with the work of Chen et al., where the authors suggest a compensatory compensation for the insufficient input from the proprioceptive system (Chen et al., 2018).

In summary, brain plasticity is present in CSM patients to overcome functional deficits. The main changes are long-term FC reorganizations in the sensorimotor regions and areas assisting in the regulation of movement and sensory perception. This altered connectivity between various sub-networks may have prognostic potential and/or therapeutic implications in CS patients.

Cervical spine compression also damages the brain WM

Progressive chronic compression of the spinal cord also results in many pathological changes in the WM that are detectable using diffusion tensor imaging (DTI). DTI is an MRI technique that allows the evaluation of micro-structural changes in the WM by measuring the motility and orientation (anisotropy) of water molecules in tissues. DTI evaluates several parameters, the most important are: (1) mean diffusivity (MD), and (2) fractional anisotropy (FA). FA is a scalar value between 0 and 1 that evaluates the preferred direction of which diffusion occurs in the central nervous system and is the most sensitive parameter to detect SCI (Guan et al., 2017). FA is largely attributed to the transverse axonal barriers in WM (i.e., myelin sheath, axon membrane) restricting the water diffusion to a preferred longitudinal orientation. Reduced FA values indicate a disturbance in the directional orientation of nerve fibers and are associated with reduced myelin integrity (Chen et al., 2017).

In CSM, most of the DTI studies have been centered on the local changes at the spinal cord, reporting differences in diffusion characteristics of the water molecules at the site of compression, that are associated with increased neurological dysfunction (Ellingson, Salamon, Grinstead, & Holly, 2014; Guan et al., 2017; Martin et al., 2016). Specifically, decreased FA values have been found in stenotic segments (Guan et al., 2017) in the lateral and posterior column of WM suggesting significant myelin damage (Cui et al., 2014). Likewise, decreased FA values and increased MD values have been found in CS patients in the early stages of the disease even in cases without visible myelopathy in the MRI examination (Banaszek, Bladowska, Szewczyk, Podgórski, & Sąsiadek, 2014); suggesting that DTI presents higher sensitivity in myelopathy detection compared to conventional MRI.

In the brain, current studies in SCI have mostly analyzed the effect of traumatic etiology. In these reports the results show WM damage in supraspinal areas along the corticospinal tracts in the medulla, pons, midbrain, posterior limbs of the internal capsule (Freund et al., 2011, 2013; Guleria et al., 2008), and both centrum semiovale (Koskinen et al., 2014). Furthermore, the CST damage correlates with the brain functional reorganization, the lower cross-sectional spinal cord area, and the upper limb ability (Freund et al., 2012). Characteristically, this WM damage starts early after the traumatic SCI, with a pronounced and progressive decrease of the spinal cord area concomitant with a reduction in the cranial CST and GM volume at the SMC (Freund et al., 2013). These changes are assumed to be induced by retrograde degeneration along the CST axons that over time results in shrinkage of the soma of corticospinal projecting neurons. Overall, the studies in traumatic SCI suggest widespread changes in WM micro-structure in the CST and in areas adjacent to the SMC that in turn associate with the clinical state of the patients.

Although there are few reports on CS, similar results have been found suggesting that CS causes anterograde and retrograde degeneration of the spinal WM tracts, resulting in axonal loss and demyelination that may extend cranially to cerebral regions. For instance, micro-structural changes in the ventral horns above the level of injury that correlated with diffusivity changes in the CST have been observed (Grabher et al., 2017). Similarly, Wen et al. observed WM damage at the region of the CST that correlated with the myelopathy severity in CSM patients (Wen, Cui, Mak, Luk, & Hu, 2014). Thus, both studies suggest a direct association between neurodegeneration affecting the motor system at the spinal cord, the CST integrity, and clinical impairment.

Characteristically, in CS patients, significant WM damage at both CST independently of the affected limb and *corpus callosum* has been reported. At the corpus callosum, significant damage to the superior and posterior parietal projection fibers, areas related to motor and touch-stimulation (Fabri, Pierpaoli, Barbaresi, & Polonara, 2014) were observed. Tractography results on CS patients also suggested a common pattern of WM damage, being affected the anterior-distal segments, regions directly linked to the motor cortex. The preserved regions at both CST were those arising from S1, which are more posterior and medial than those of M1 and thus less vulnerable to compression. Besides, a direct association between the damage at the CST, the clinical scores, and the evolution after surgery was observed (Bernabéu-Sanz et al., 2020). These

observations suggest that CST metrics with DTI may be used as a potential biomarker in the clinical setting to determine the impact of the disease and predict outcomes (Bernabéu-Sanz et al., 2020).

The CST is the largest descending pathway that connects the motor cortex to the brain stem and spinal cord and is mainly responsible for the movement of the distal extremities, particularly fine motor activities of the hand (Jang, Medicine, & Medicine, 2014). It is particularly vulnerable to the negative effects of cervical spinal compression suffering early demyelination. Recent reports on SCI both of traumatic and compressive origin suggest that the predominant pathological mechanism on both conditions is the demyelination of the ascending and descending CST fibers, leading to a progressive loss of axonal conductivity (Dong et al., 2008), with additional connectivity impairment between the SMC and the brainstem (Wang et al., 2020). The impact of the CST damage in the brain cortex has been previously described in other pathologies such as stroke. In these patients, whereas the degree of CST injury strongly predicts the resulting motor impairment (Lotze et al., 2012; Stinear et al., 2007), the neurological function tends to be preserved by the reorganization and recruitment of new pathways as well as other motor network nodes to optimize the residual neurological function (Pantano, Petsas, Tona, & Sbardella, 2015; Ward, 2011). In this sense, it is believed that most of the axotomized CST neurons are able to maintain the sensory-motor circuits through axonal sprouting (Zdunczyk et al., 2018). However, if CST neurons are damaged, whittling down the population by spinal compression over time may lead to some critical threshold to impairment. This could be the reason why some CSM patients do not present a significant clinical improvement of their symptoms after surgery.

In summary, spinal cord compression leads to significant WM damage mainly at the corticospinal tracts leading to a progressive loss of axonal conductivity that extends cranially to the brain. This reduced connectivity associates with the neurological impairment and may constitute a potential barrier for motor recovery after surgery.

Conclusion and future perspectives

As the population ages, the incidence of CSM will increase, but the knowledge of the effects of CSM in the brain is still sparse. On the other hand, there are no high-evidence studies providing well-founded recommendations for the best treatment modality. Considering that CSM has a potentially devastating outcome more studies are needed to better clarify the evolution of the disease and its consequences. Furthermore, to improve clinical outcomes the strategies should be equally targeted on the recruited adjacent cortex and the primary SMC. In this framework, we propose that increased collaborations among clinicians, experts in neuroimaging techniques, and basic researchers will enhance our ability for a better management of the disease.

Applications to other areas of neuroscience

Cervical spondylosis myelopathy (CSM) is the major cause of disability in the elderly and, despite significant ongoing research, current therapeutic approaches have limited effectiveness and are far from satisfactory (Shiban & Meyer, 2014). One potential barrier is that current treatments generally assume intact neural motor systems for driving limb movements, but we should consider that this condition can lead to neuronal damage distal to the spinal lesion and cerebral reorganization. Therefore, the brain atrophy and the damage of cortical pathways in CSM could become a potential obstacle for achieving full and effective function recovery, even after successful surgical repair at the site of compression.

Advanced neuroimaging techniques can be applied to detect specific secondary brain damage in CSM. However, brain reorganization is not a static process, but rather very dynamic. Cortical reorganization starts early after spinal cord injury, and its impact over time will depend on a complex balance between spinal recovery and supraspinal reorganization (Freund et al., 2013). Thus, it is crucial to better understand how the brain reorganizes after the injury, as well as develop cost-effective therapies to maximize functional recovery. In this framework, therapies designed to enhance brain plasticity could provide functional benefits for these patients both before and following surgery (Sharma, Classen, & Cohen, 2013).

The findings of a progressive degenerative pattern in spinal cord compression suggest the need to properly monitor the disease. Advanced Magnetic Resonance techniques may present a main role in non-invasive assessment to better predict the patient's outcome as well as to identify the patients that will most likely benefit from different therapies and prioritize which patients will precise surgery more urgently.

Mini-dictionary of terms

Cervical spondylosis: Term to define the progressive degenerative changes that affect all the components of the cervical spine (i.e., inter-vertebral discs, facet joints, joints of Luschka, ligamenta flava, and laminae).

Cervical spondylosis myelopathy: Term to define injury to the spinal cord due to severe compression caused by cervical spondylosis.
Corticospinal tract: White matter motor pathway that connects the cerebral cortex with the lower motor neurons and interneurons in the spinal cord.
Diffusion tensor imaging: MR technique based on the diffusion of water molecules of the tissues that allows to obtain information about the white matter architecture and integrity.
MR-spectroscopy: MR technique that allows to obtain the chemical composition of tissues, it is used to explore in vivo tissue metabolism and to detect and monitor several pathologies.
Functional magnetic resonance imaging: A technique that allows to obtain the brain activation pattern of a subject while performing a specific task. It is commonly used in the clinical setting to map cortical-activated areas before surgery to preserve their function. It is also widely used in research to study differences in brain activation patterns.
Functional reorganization: Also known as neural plasticity, neuroplasticity, or brain plasticity. The ability of the central nervous system to adapt in response to lesions or changes in the environment. This process could be accomplished through the recruitment of new/different neural networks, changes in the connectivity pattern, and the formation of new synapses.
Resting-state functional magnetic resonance imaging: A technique that allows to obtain the connectivity pattern of functional brain areas at rest that are spatially separated.
Sensorimotor cortex: Brain area located at the pre-central and post-central gyri which contain the primary motor and somatosensory areas of the brain.
Supplementary motor area: Brain area located in the midline cortex, anterior to the primary motor cortex that is responsible for movement control and coordination.

Key facts of spinal cord compression

- The most common cause is cervical spondylosis which is frequently found in asymptomatic adults after the fifth decade of life.
- Cervical spondylosis may progress to cervical spondylosis myelopathy, a progressive condition that causes incomplete spinal cord injury and associated neurological impairment in a stepwise manner.
- At present most of the studies have been focused on the local changes at the cervical spine, showing apoptosis of the anterior horn neurons, gradual spongy necrosis, demyelination of the white matter, and Wallerian degeneration.
- Cervical spondylosis may present some similarities with traumatic spinal cord injury.
- Cervical spondylosis leads to adaptive changes in the brain to compensate for the functional loss, causing a wide range of clinical manifestations.

Key facts of advanced MRI techniques

- Present high sensitivity to detect neural damage secondary to cervical spondylosis.
- Allow a better understanding of the consequences of cervical spine compression in the brain.
- May be useful for identifying those patients at risk of severe impairment.
- May help the non-invasive assessment of cervical spondylosis, to better predict outcomes and to identify the patients that most likely will benefit from different therapies.

Summary points of cervical spine compression

- Leads to brain atrophy of the sensorimotor cortex, thalami, supplementary motor areas, and a faster rate of cortical thinning and atrophy related to age.
- Causes functional reorganization of the sensorimotor cortex that is more significant for the hand.
- Alters the FC of the brain at the sensorimotor cortex and visual cortex to compensate for the functional loss.
- Leads to white matter demyelination of corticospinal tracts, which extend cranially to the brain cortex mainly at the primary motor area.
- Causes myelin damage at the corpus callosum, mainly at the superior and posterior parietal projection fibers that are related to motor and touch-stimulation.

References

Aleksanderek, I., McGregor, S., Stevens, T., Goncalves, S., Bartha, R., & Duggal, N. (2017). Cervical spondylotic myelopathy: Metabolite changes in the primary motor cortex after surgery. *Radiology*, *282*(3), 817–825. https://doi.org/10.1148/radiol.2016152083.

Banaszek, A., Bladowska, J., Szewczyk, P., Podgórski, P., & Sąsiadek, M. (2014). Usefulness of diffusion tensor MR imaging in the assessment of intramedullary changes of the cervical spinal cord in different stages of degenerative spine disease. *European Spine Journal*, *23*(7), 1523–1530. https://doi.org/10.1007/s00586-014-3323-x.

Baron, E. M., & Young, W. (2007). Cervical spondylotic myelopathy: A brief review of its pathophysiology, clinical course, and diagnosis. *Neurosurgery*, *60*(1 Suppl), 35–41.

Bernabéu-Sanz, A., Mollá-Torró, J. V., López-Celada, S., Moreno-López, P., & Fernández-Jover, E. (2020). MRI evidence of brain atrophy, white matter damage, and functional adaptive changes in patients with cervical spondylosis and prolonged spinal cord compression. *European Radiology*, *30*(1), 357–369. https://doi.org/10.1007/s00330-019-06352-z.

Bhagavatula, I. D., Shukla, D., Sadashiva, N., Saligoudar, P., Prasad, C., & Bhat, D. I. (2016). Functional cortical reorganization in cases of cervical spondylotic myelopathy and changes associated with surgery. *Neurosurgical Focus*, *40*(6), 1–7. https://doi.org/10.3171/2016.3.FOCUS1635.

Buchbinder, B. R. (2016). Functional magnetic resonance imaging. In *Vol. 135. Handbook of clinical neurology* (pp. 61–92). Elsevier B.V. https://doi.org/10.1016/B978-0-444-53485-9.00004-0.

Chen, Z., Wang, Q., Liang, M., Zhao, R., Zhu, J., Xiong, W., et al. (2018). Visual cortex neural activity alteration in cervical spondylotic myelopathy patients: A resting-state fMRI study. *Neuroradiology*, *60*(9), 921–932. https://doi.org/10.1007/s00234-018-2061-x.

Chen, Y. Y., Zhang, X., Lin, X. F., Zhang, F., Duan, X. H., Zheng, C. S., et al. (2017). DTI metrics can be used as biomarkers to determine the therapeutic effect of stem cells in acute peripheral nerve injury. *Journal of Magnetic Resonance Imaging*, *45*(3), 855–862. https://doi.org/10.1002/jmri.25395.

Cohen, E. J., Quarta, E., Bravi, R., Granato, A., & Minciacchi, D. (2017). Neural plasticity and network remodeling: From concepts to pathology. In *Vol. 344. Neuroscience* (pp. 326–345). Elsevier. https://doi.org/10.1016/j.neuroscience.2016.12.048.

Cui, J. L., Li, X., Chan, T. Y., Mak, K. C., Luk, K. D. K., & Hu, Y. (2014). Quantitative assessment of column-specific degeneration in cervical spondylotic myelopathy based on diffusion tensor tractography. *European Spine Journal*, *24*(1), 41–47. https://doi.org/10.1007/s00586-014-3522-5.

de Oliveira Vilaça, C., Orsini, M., Leite, M. A. A., de Freitas, M. R. G., Davidovich, E., Fiorelli, R., et al. (2016). Cervical spondylotic myelopathy: What the neurologist should know. *Neurology International*, *8*(4), 69–73. Press Publications https://doi.org/10.4081/ni.2016.6330.

Dong, Y., Holly, L. T., Albistegui-Dubois, R., Yan, X., Marehbian, J., Newton, J. M., et al. (2008). Compensatory cerebral adaptations before and evolving changes after surgical decompression in cervical spondylotic myelopathy: Laboratory investigation. *Journal of Neurosurgery. Spine*, *9*(6), 538–551. https://doi.org/10.3171/SPI.2008.10.0831.Compensatory.

Edwards, C. C., Riew, K. D., Anderson, P. A., Hilibrand, A. S., & Vaccaro, A. F. (2003). Cervical myelopathy: Current diagnostic and treatment strategies. *The Spine Journal*, *3*(1), 68–81. https://doi.org/10.1016/S1529-9430(02)00566-1.

Ellingson, B. M., Salamon, N., Grinstead, J. W., & Holly, L. T. (2014). Diffusion tensor imaging predicts functional impairment in mild-to-moderate cervical spondylotic myelopathy. *The Spine Journal : Official Journal of the North American Spine Society*, *14*(11), 2589–2597. https://doi.org/10.1016/j.spinee.2014.02.027.

Fabri, M., Pierpaoli, C., Barbaresi, P., & Polonara, G. (2014). Functional topography of the corpus callosum investigated by DTI and fMRI. *World Journal of Radiology*, *6*(12), 895–906. https://doi.org/10.4329/wjr.v6.i12.895.

Fox, M., Corbetta, M., Snyder, A., Vincent, J., & Raichle, M. (2006). Spontaneous neuronal activity distinguishes human dorsal and ventral attention system. *Proceedings of the National Academy of Sciences of the United States of America*, *103*(26), 10046–10051.

Freund, P., Weiskopf, N., Ashburner, J., Wolf, K., Sutter, R., Altmann, D. R., et al. (2013). MRI investigation of the sensorimotor cortex and the corticospinal tract after acute spinal cord injury: A prospective longitudinal study. *The Lancet Neurology*, *12*(9), 873–881. https://doi.org/10.1016/S1474-4422(13)70146-7.

Freund, P., Weiskopf, N., Ward, N. S., Hutton, C., Gall, A., Ciccarelli, O., et al. (2011). Disability, atrophy and cortical reorganization following spinal cord injury. *Brain*, *134*(6), 1610–1622. https://doi.org/10.1093/brain/awr093.

Freund, P., Wheeler-Kingshott, C. A., Nagy, Z., Gorgoraptis, N., Weiskopf, N., Friston, K., et al. (2012). Axonal integrity predicts cortical reorganisation following cervical injury. *Journal of Neurology, Neurosurgery and Psychiatry*, *83*(6), 629–637. https://doi.org/10.1136/jnnp-2011-301875.

Goncalves, S., Stevens, T. K., Doyle-Pettypiece, P., Bartha, R., & Duggal, N. (2016). N-acetylaspartate in the motor and sensory cortices following functional recovery after surgery for cervical spondylotic myelopathy. *Journal of Neurosurgery: Spine*, *25*(4), 436–443. https://doi.org/10.3171/2016.2.SPINE15944.

Grabher, P., Mohammadi, S., David, G., & Freund, P. (2017). Neurodegeneration in the spinal ventral horn prior to motor impairment in cervical spondylotic myelopathy. *Journal of Neurotrauma*, *34*(15), 2329–2334. https://doi.org/10.1089/neu.2017.4980.

Green, A., Cheong, P. W. T., Fook-Chong, S., Tiruchelvarayan, R., Guo, C. M., Yue, W. M., et al. (2015). Cortical reorganization is associated with surgical decompression of cervical spondylotic myelopathy. *Neural Plasticity*, *2015*. https://doi.org/10.1155/2015/389531.

Guan, L., Chen, X., Hai, Y., Ma, X., He, L., Wang, G., et al. (2017). High-resolution diffusion tensor imaging in cervical spondylotic myelopathy: A preliminary follow-up study. *NMR in Biomedicine*, *30*(10), 1–11. https://doi.org/10.1002/nbm.3769.

Guleria, S., Gupta, R. K., Saksena, S., Chandra, A., Srivastava, R. N., Husain, M., et al. (2008). Retrograde Wallerian degeneration of cranial corticospinal tracts in cervical spinal cord injury patients using diffusion tensor imaging. *Journal of Neuroscience Research*, *86*(10), 2271–2280. https://doi.org/10.1002/jnr.21664.

Hains, B. C., Black, J. A., & Waxman, S. G. (2003). Primary cortical motor neurons undergo apoptosis after axotomizing spinal cord injury. *Journal of Comparative Neurology*, *462*(3), 328–341. https://doi.org/10.1002/cne.10733.

Henderson, L. A., Gustin, S. M., Macey, P. M., Wrigley, P. J., & Siddall, P. J. (2011). Functional reorganization of the brain in humans following spinal cord injury: Evidence for underlying changes in cortical anatomy. *Journal of Neuroscience*, *31*(7), 2630–2637. https://doi.org/10.1523/JNEUROSCI.2717-10.2011.

Holly, L., Dong, Y., Albistegui-DuBois, R., Marehbian, J., & Dobkin, B. (2007). Cortical reorganization in patients with cervical spondylotic myelopathy. *Journal of Neurosurgery. Spine*, *6*(6), 544–551. https://doi.org/10.3171/spi.2007.6.6.5.Cortical.

Jang, S. H., Medicine, P., & Medicine, C. (2014). The corticospinal tract from the viewpoint of BRain rehabilitation. *Journal of Rehabilitation Medicine*, *46*(31), 193–199. https://doi.org/10.2340/16501977-1782.

Kelly, J. C., Groarke, P. J., Butler, J. S., Poynton, A. R., & Byrne, J. M. O. (2012). The natural history and clinical syndromes of degenerative cervical spondylosis. *Advances in Orthopedics*, 2012. https://doi.org/10.1155/2012/393642.

Koskinen, E. A., Hakulinen, U., Brander, A. E., Luoto, T. M., Ylinen, A., & Öhman, J. E. (2014). Clinical correlates of cerebral diffusion tensor imaging findings in chronic traumatic spinal cord injury. *Spinal Cord*, *52*(3), 202–208. https://doi.org/10.1038/sc.2013.163.

Lotze, M., Beutling, W., Loibl, M., Domin, M., Platz, T., Schminke, U., et al. (2012). Contralesional motor cortex activation depends on ipsilesional corticospinal tract integrity in well-recovered subcortical stroke patients. *Neurorehabilitation and Neural Repair*, *26*(6), 594–603. https://doi.org/10.1177/1545968311427706.

Martin, A. R., Aleksanderek, I., Cohen-Adad, J., Tarmohamed, Z., Tetreault, L., Smith, N., et al. (2016). NeuroImage: Clinical translating state-of-the-art spinal cord MRI techniques to clinical use: A systematic review of clinical studies utilizing DTI, MT, MWF, MRS, and fMRI. *NeuroImage. Clinical*, *10*, 192–238. https://doi.org/10.1016/j.nicl.2015.11.019. YNICL.

Panchuelo, R. M. S., Eldeghaidy, S., Marshall, A., McGlone, F., Francis, S. T., & Favorov, O. (2020). A nociresponsive specific area of human somatosensory cortex within BA3a: BA3c? *NeuroImage*, *221*. https://doi.org/10.1016/j.neuroimage.2020.117187.

Pantano, P., Petsas, N., Tona, F., & Sbardella, E. (2015). The role of fMRI to assess plasticity of the motor system in MS. *Frontiers in Neurology*, *6*, 55. https://doi.org/10.3389/fneur.2015.00055.

Peng, X., Tan, Y., He, L., & Ou, Y. (2020). Alterations of functional connectivity between thalamus and cortex before and after decompression in cervical spondylotic myelopathy patients: A resting-state functional MRI study. *Neuroreport*, 365–371. https://doi.org/10.1097/WNR.0000000000001346.

Sharma, N., Classen, J., & Cohen, L. G. (2013). Neural plasticity and its contribution to functional recovery. In *Vol. 110. Handbook of clinical neurology* (pp. 3–12). Elsevier B.V. https://doi.org/10.1016/B978-0-444-52901-5.00001-0.

Shiban, E., & Meyer, B. (2014). Treatment considerations of cervical spondylotic myelopathy. *Neurology: Clinical Practice*, *4*(4), 296–303. https://doi.org/10.1212/CPJ.0000000000000050.

Smitha, K., Raja, K., Arun, K., Rajesh, P., Thomas, B., Kapilamoorthy, T., et al. (2017). Resting state fMRI: A review on methods in resting state connectivity analysis and resting state networks. *The Neuroradiology Journal*, *30*(4), 305–317.

Stinear, C. M., Barber, P. A., Smale, P. R., Coxon, J. P., Fleming, M. K., & Byblow, W. D. (2007). Functional potential in chronic stroke patients depends on corticospinal tract integrity. *Brain*, *130*(1), 170–180. https://doi.org/10.1093/brain/awl333.

Takenaka, S., Kan, S., Seymour, B., Makino, T., Sakai, Y., Kushioka, J., et al. (2019). Towards prognostic functional brain biomarkers for cervical myelopathy: A resting-state fMRI study. *Scientific Reports*, *9*(1), 1–8. https://doi.org/10.1038/s41598-019-46859-5.

Tam, S., Barry, R. L., Bartha, R., & Duggal, N. (2010). Changes in functional magnetic resonance imaging cortical activation after decompression of cervical spondylosis: Case report. *Neurosurgery*, *67*(3), 2–7. https://doi.org/10.1227/01.NEU.0000374848.86299.17.

Theodore, N. (2020). Degenerative cervical spondylosis. *New England Journal of Medicine*, *383*(2), 159–168. Massachussetts Medical Society https://doi.org/10.1056/NEJMra2003558.

Wang, C., Laiwalla, A., Salamon, N., Ellingson, B. M., & Holly, L. T. (2020). Compensatory brainstem functional and structural connectivity in patients with degenerative cervical myelopathy by probabilistic tractography and functional MRI. *Brain Research*, *1749*(May), 147129. https://doi.org/10.1016/j.brainres.2020.147129.

Ward, N. (2011). Assessment of cortical reorganisation for hand function after stroke. *The Journal of Physiology*, *589*(Pt 23), 5625–5632. https://doi.org/10.1113/jphysiol.2011.220939.

Wen, C. Y., Cui, J. L., Mak, K. C., Luk, K. D. K., & Hu, Y. (2014). Diffusion tensor imaging of somatosensory tract in cervical spondylotic myelopathy and its link with electrophysiological evaluation. *The Spine Journal*, *14*(8), 1493–1500. https://doi.org/10.1016/j.spinee.2013.08.052.

Woodworth, D. C., Holly, L. T., Mayer, E. A., Salamon, N., & Ellingson, B. M. (2019). Alterations in cortical thickness and subcortical volume are associated with neurological symptoms and neck pain in patients with cervical spondylosis. *Clinical Neurosurgery*, *84*(3), 588–597. https://doi.org/10.1093/neuros/nyy066.

Woodworth, D. C., Holly, L. T., Salamon, N., & Ellingson, B. M. (2018). Resting-state functional magnetic resonance imaging connectivity of the brain is associated with altered sensorimotor function in patients with cervical spondylosis. *World Neurosurgery*, *119*, 1–10. https://doi.org/10.1016/j.wneu.2018.07.257.

Zdunczyk, A., Schwarzer, V., Mikhailov, M., Bagley, B., Rosenstock, T., Picht, T., et al. (2018). The corticospinal reserve capacity: Reorganization of motor area and excitability as a novel pathophysiological concept in cervical myelopathy. *Clinical Neurosurgery*, *83*(4), 810–818. https://doi.org/10.1093/neuros/nyx437.

Zhou, F., Wu, L., Liu, X., Gong, H., Luk, K. D. K., & Hu, Y. (2015). Characterizing thalamocortical disturbances in cervical spondylotic myelopathy: Revealed by functional connectivity under two slow frequency bands. *PLoS One*, *10*(6), 1–13. https://doi.org/10.1371/journal.pone.0125913.

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Chapter 9

Spasticity in spinal cord injury

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List of abbreviations

ADL	activities of daily living
AIS	ASIA impairment scale
FES	functional electrical stimulation
SC	spinal cord
SCI	spinal cord injury

Introduction

Spasticity is a common complication after spinal cord injury (SCI) that occurs in the context of an upper motor neuron injury syndrome, and may develop even years after the acute injury leading to further loss of function (Harrington & Bockenek, 2011; Rekand, Hagen, & Grønning, 2012).

Spasticity was defined by Lance (1980) as "a motor disorder characterized by a velocity dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyper excitability of the stretch reflex, as one component of the upper motoneuron syndrome." Dynamic phenomena were not included, so the Ability Network (an international panel of clinical experts to develop management algorithms to guide and standardize assessment, treatment and outcomes in SCI people with disabling spasticity) recommends Pandyan definition (Burns et al., 2016): "Disordered sensorimotor control, resulting from an upper motor neuron injury, presenting as intermittent or sustained involuntary activation of muscles."

Considering every SCI people regardless of the time of evolution, neurological level or extent, the prevalence of spasticity is approximately 65% according to the studies of Harrington and Bockenek (2011). Some studies have been conducted on SCI complications; Joseph, Ismail, Naicker, Ying, and Mohammad (2009) demonstrated an incidence of 25%–37% in acute traumatic SCI, New, Rawicki, and Bailey (2002) showed an incidence of 15%–36% in acute nontraumatic SCI, and in papers by Adams and Hicks (2005) or Rekand et al. (2012), incidence of chronic SCI is estimated about 65%–93%. There is no significant correlation among neurological level, ASIA Impairment Scale (AIS) grade, and spasticity, but Adams and Hicks (2005) related severe spasticity with cervical levels and grade A, and a highest prevalence of spasticity among people with grade C.

Pathophysiology of spasticity

The stretch reflex is a monosynaptic reflex that originates in the muscle spindles with any stimulus (not just stretch) and travels through an afferent pathway to the spinal cord (SC) where it synapses with the corresponding alpha motor neuron and contracts the muscle fibers where it is has produced the stimulus. If the stimulus is prolonged, the Golgi tendon organs are activated, and via interneurons Ib, the previous contraction can be relaxed. Studies by Whitlock (1990) show that spasticity is generally due to a lowered threshold of phasic or tonic stretch reflexes; when inhibitory signals are lost due to spinal cord damage, the segmental reflexes are released and become hyperactive. In addition, other spinal mechanisms are postulated, such as fusimotor hyperexcitability, axonal sprouting, reduction of presynaptic inhibition, and reduction of reciprocal inhibition.

Roy and Edgerton (2012) described that clinical features of spasticity depend on the greater or lesser loss of the ability to voluntarily modulate the level of activity of a given motor pool and the capacity of the interneurons that project to these motor pools to recruit the appropriate combination of them.

Diagnosis and Treatment of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822498-4.00009-9

Besides, there are plastic alterations in affected muscles. Basically, spasticity causes fibrosis, atrophy of muscle fibers, decrease in the elastic properties, decrease in the number of sarcomeres, accumulation of connective tissue, and alteration of contractile properties toward tonic muscle characteristics.

Manifestations of spasticity in spinal injuries

According to Decq (2003), two classification criteria can be used: the place where the stimulus for spasticity is located, which differentiates between intrinsic if the stimulus emerges within the central nervous system, and extrinsic if the afferences come from other structures such as the skin, muscles, and joints; also if there is no resultant movement, a tonic or static component is described, and if there is any movement, a phasic or dynamic component is described. So, we can distinguish three main types of spasticity:

(a) Intrinsic tonic spasticity: hypertonia.
(b) Intrinsic phasic spasticity: clonus and osteotendinous hyperreflexia.
(c) Extrinsic spasticity: spasms.

The presence of triggers was described by Phadke, Balasubramanian, Ismail, and Boulias (2013); these exacerbating factors can cause a patient with a SCI and a normal or decreased tone to present intense or frequent spasms. The most important triggers are neurogenic bowel (constipation) and bladder problems (hyperreflexia). The supine position is associated with more intense hypertonia and increased likelihood to provoke spasms, and according with Sadeghi, Mclvor, Finlayson, and Sawatzky (2016), the most frequent clinical sign is usually spasms when making any transfer. Other factors such as pregnancy, cold, circadian rhythm, pressure ulcers, menstrual cycle, stress, and even tight clothing also increase spasticity, while acute and severe infections (sepsis) and syringomyelia can cause both an increase of spasticity as a sudden absence of spasticity.

The ability to achieve functional goals may be impaired due to spasticity and can even make the length of hospital stay last longer, according to Richard-Denis, Nguyen, and Mac-Thiong (2020).

Assessment of spasticity and its consequences

Tone measurement

The most widely used method is the Modified Ashworth Scale (Table 1) because, although it is a Likert-type scale and therefore has been criticized for its possible lack of reliability, multiple studies have been carried out and showed that can be considered the most appropriate due to its reliability and test-retest agreement (Baunsgaard, Nissen, Christensen, & Biering-Sørensen, 2016; Meseguer-Henarejos, Sánchez-Meca, López-Pina, & Hernández, 2018). The Tardieu scale is based on the pendulum test and consists of performing the stretching of a muscle between two points and two speeds, but in SCI, it is still considered only as complementary.

Assessment of dynamic phenomena

The frequency and intensity of spasms can be measured using the Penn spasm intensity or frequency scales, but there is a more specific scale for SCI developed by Benz, Hornby, Bode, Scheidt, and Schmit (2005), called the Spinal Cord Assessment Tool Spastic reflexes (SCATS, Table 2).

TABLE 1 Modified Ashworth Scale (Bohannon & Smith, 1987).

0. No increase in tone
1. Slight increase in tone with a catch, or minimal resistance at the end of the range of movement (ROM)
1+. Slight increase in tone with a catch, followed with minimal resistance throughout the remainder (less than half) of the ROM
2. Marked increase in tone through most of the ROM, but limb is easily moved
3. Considerable increase in tone; passive movement difficult
4. Limb rigid or contracted

TABLE 2 Spinal Cord Assessment Tool for Spastic reflexes (SCATS).
Clonus of ankle plantar flexors with rapid passive dorsiflexion of foot
0. No reaction
1. Mild: clonus <3 s
2. Moderate: clonus lasts between 3 and 10 s
3. Severe: clonus >10 s
Flexor spasms in response to pinprick on foot plantar surface with leg and hip in full extension
0. No reaction
1. Mild: extension of great toe or <10 degrees of hip/knee flexion
2. Moderate: 10–30 degrees of hip/knee flexion
3. Severe: >30 degrees of hip/knee flexion
Extensor spasms of quadriceps muscle after extension of leg from a position of hip/knee flexion
0. No reaction
1. Mild: spasms last <3 s
2. Moderate: spasms last between 3 and 10 s
3. Severe: spasms last >10 s

Functional assessment

From the Ability Network (Nene et al., 2018), it is recommended to measure as functional results:

- Joint alterations can be rated by goniometry.
- Interferences of spasticity with activities of daily living are assessed using the Measure of Independence in SCI version III (SCIM III).
- The ability to walk is estimated through Walking Index in SCI scale (WISCI II).
- The impact on the quality of life can also be analyzed, especially with specific scales such as Spinal Cord Injury Spasticity Evaluation Tool (SCI-SET, Table 3) or Patient-Reported Impact of Spasticity Measure (PRISM, Table 4). Generic scales are often not very suitable for SCI, since walking well or performing standing activities are considered signs of a

TABLE 3 Spinal Cord Injury Spasticity Evaluation Tool (Adams, Ginis, & Hicks, 2007).
−3. Extremely problematic
−2. Moderately problematic
−1. Somewhat problematic
0. No effect
1. Somewhat helpful
2. Moderately helpful
3. Extremely helpful
Evaluation of spasticity effects on components of daily life over a 7 days-period: showering, dressing/undressing, transfers, sitting positioning, preparation of meals, eating, drinking, small hand movements (writing, use of computer), household chores, recreational activities, enjoyment of social outings, standing/weight-bear, walking, stability/balance, muscle fatigue, flexibility of joints, therapy/exercise routine, manual or power wheelchair use, lying positioning, change positions in bed, getting to sleep, quality of sleep, sex life, annoyment feeling, embarrassing feeling, social comfort, physical comfort, pain, concern with feeling, concern with getting injured, concern with accidentally injuring someone else, concentration, control over one's own body, need for help.

TABLE 4 Patient-Reported Impact of Spasticity Measure (Cook et al., 2007).
Evaluation of spasticity effects on life experiences over a 7-day period
0. Never true for me
1. Rarely true for me
2. Sometimes true for me
3. Often true for me
4. Very often true for me

good quality of life; however, scales such as the SF-36 or the Euro-QOL are still recommended by the Ability Network (Ertzgaard, Nene, Kiekens, & Burns, 2019).

Subjective evaluation

Generally, patients can evaluate their own spasticity with a numerical rating scale, but they can describe their spasticity through specific signs.

Other types of assessment

Ultrasound appearance of spastic muscles can be used, and there are studies (e.g., Hara et al., 2018) that compare the liability of improvement of poststroke spastic muscles treated with botulinum toxin according to its echo intensity (Heckmatt scale), confirming that increased intensity has worse prognostic, since it corresponds to a more chronic and severe spasticity. There is also no useful correlation with neurophysiological parameters.

Treatment of spasticity

Treatment indications

Spasticity may be useful to improve sitting or standing balance, facilitate activities of daily living (ADL) and transfers, maintain muscle mass and venous return. According with Stevenson (2010), treatment is necessary when we find functional disadvantages, and is aimed at preventing joint limitations, reducing pain, facilitating positioning, treating pressure ulcers, hygiene, and facilitating ADLs and transfers.

Modalities of treatment in spinal injury

Since the intensity of spasticity can vary in intensity throughout the same day and eradication treatment is not possible, the management of spasticity should focus on EDUCATION; the patient must learn what spasticity is, its signs and symptoms and its consequences, and how they can be prevented, starting with avoiding exacerbating factors.

(a) **Control of triggers**. The first point in treatment is to eliminate the triggering factors, since although they do not cause spasticity, they are usually present when it appears or worsens.
(b) **Positioning**. The most appropriate posture is sitting; in the wheelchair, the patient must have hips, ankles, and knees flexed at 90 degrees and a slight inclination of the seat, in bed it is recommended lateral decubitus with more forced flexion of the hip and knee of the lower limb located just above the bed. You may improve spasticity using standing devices.
(c) **Physical modalities**. Studies by Gebler (1990) have shown that most of them have a short-lasting effect to be significant, and is based on the maintenance of the myotatic reflex by prolonging a stimulus (stretching, cold) and therefore the stimulation of the Golgi reflex.
   – Stretching. It should be held for at least 1 min to achieve muscle relaxation and increase ranges of motion. It can be done through self-stretching, casting, splinting, or within a physical therapy protocol.
   – Cold or heat application.

- Orthotics and splints. They are used to allow long-term stretching, but they should only be used in moderate spasticity or to maintain outcomes from another previous treatment.
- Muscle-strengthening. In this way, we mitigate the functional repercussions that traction of the antagonist spastic muscle can have on any muscle.
- Electrical stimulation. The repeated application of tetanic contractions by high frequencies >2500 Hz can fatigue the spastic muscle, but this effect is short-lasting, and even long-term may lead to increase spasticity, especially in incomplete injuries. Functional electrical stimulation (FES) is used to strengthen antagonist muscles.
- Robotic systems can work both by causing prolonged stretching and by strengthening antagonists, showed by Alcobendas-Maestro et al. (2012).
- Passive cycling is postulated as a treatment for strengthening weak muscles. In a study by Krause, Szecsi, and Straube (2008), it is shown that there may be improvement in spasticity but the significance is demonstrated with FES compared to passive cycling. The rest of the studies collected in the metaanalysis by Phadke et al. (2019) show that passive cycling can only achieve subjective improvement but objectively there are no effects or there is even a worsening in spasticity.
- Other modalities. Huang et al. (2019) performed a randomized controlled trial on kinesiotaping for spasticity in stroke patients resulting in short-lasting improvement, but there are no trials within SCI people. Shockwaves have been used in poststroke spasticity, and a systematic review by Dymarek et al. (2020) confirms moderate improvement, but it has not been studied in SCI either.

(d) **Oral drugs**. Its characteristics have been studied by Kita and Goodkin (2000), and its specific use for SCI patients has been described by Taricco, Pagliacci, Telaro, and Adone (2006).

- Baclofen. It is considered the gold standard drug because it acts by binding to receptors just in the spinal cord, since it is a structural analog of gamma-amino-butyric acid (GABA, an inhibitory neurotransmitter) and an agonist of GABA-B receptors. In adults, you can start with 15 mg daily in 3 doses and increase every 4–7 days 15 mg daily. Start dosage can be 15 mg/day divided in 3 doses and titration may be 15 mg each 4–7 days; in older patients or with comorbidities, the titration should be slower, and in children, dosage starts with 2.5 mg/day to a maximum dose of 30 mg/day in children 2–7 years and 60 mg/day in children older than 7. Side effects are dose-dependent; the most frequent are fatigue and drowsiness, it can also cause muscle weakness, confusion, dizziness, hypotension, or constipation.
- Diazepam. It binds to GABA-A receptors and causes presynaptic inhibition in the spinal cord. Side effects include sedation and cognitive impairment. Its main indication would be night spasms, prescribing 5 mg daily.
- Clonazepam. It is another benzodiazepine that is typically used when spasms predominate, the starting dose is 0.5 mg daily and requires a slower titration because of its side effects (withdrawal syndrome may be more dangerous).
- Tizanidine. It is an α2 agonist that acts by inhibiting the release of excitatory amino acids in SC interneurons. The most frequent side effects are drowsiness, dizziness, hypotension, or xerostomia, the starting dose is 4 mg daily. The effectiveness of tizanidine, usually considered as a second-line drug, is backed by the largest study.
- Clonidine. It is also an α2 agonist, but it causes hypotension more frequently, so it is not recommended in tetraplegic patients.

(e) **Intrathecal medication**. Studies by McIntyre et al. (2014) and Khurana and Garg (2014) show that baclofen pumps may be considered when high dosages of baclofen are required or there is no response with any other treatment. A programmable pump is implanted into the abdomen, from where a catheter conveys the baclofen into the intrathecal space, usually at the lumbar level since there is greater concentration of GABA receptors in the lumbar spinal cord. Prior to implantation of the pump, all candidates undergo a trial via lumbar puncture, with a dose of 50 μg of baclofen; tone and spasms are measured each 2 h, and if there is positive outcome (spasticity improves), we proceed to gradually withdraw oral drugs and then increase the dose of baclofen in the pump up to the optimum dose (average is 400–500 μg/day), which is kept refilling the reservoir pump at regular intervals (3–6 months). Most adverse effects occur during the titration phase and include drowsiness, headache, nausea, weakness, and hypotension; other complications may be due to mechanical problems (dislodgment, disconnection, kinking, blockage), pump failure, or infection. Any interruption of intrathecal baclofen delivery may result in a severe baclofen withdrawal syndrome that is usually characterized by a sudden increase of spasticity, pruritus, hyperthermia, autonomic dysregulation, seizures, coma, rhabdomyolysis, disseminated intravascular coagulation, and multisystem organ failure.

(f) **Local injections**. They are indicated in focal spasticity. Local phenol injections are discussed in the corresponding chapter. Studies by Palazón-García, Alcobendas-Maestro, Esclarin-Ruz, and Benavente-Valdepeñas (2019) have

shown that focal spasticity is described in some cases of AIS C or D injuries. Botulinum toxin serotype A is produced by the *Clostridium botulinum* bacterium, and is a metalloprotease which, in nerve endings, proteolitically cleaves synaptosomal associated protein (SNAP-25) to inhibit the fusion of the synaptic vesicle with the presynaptic membrane of the axon terminal, and thus ultimately relax the muscle Botulinum toxin can also be used if there are muscles that cause worse functional repercussions (e.g., hip adductors to allow bladder indwelling).

(g) **Surgery**. In SCI, it is not used as an etiological treatment, but it can be applied as a correction of complications (tenotomies and tendon transfers).

(h) **Other treatments**. Studies by Krause and Straube (2003) have reported that repetitive magnetic stimulation at the lumbar nerve roots can decrease lower limbs spasticity in SCI patients, and Korzhova et al. (2018) found that repetitive transcranial magnetic stimulation may be effective against spasticity in SCI patients, even more than against cerebral spasticity.

Outcome measures after treatment

It is performed by means of comparison with previous measurements, the global tolerance to the treatment, and a subjective assessment by the patient. It is also possible to assess the achievement of the objectives set before the treatment, or Patient Global Impression of Change scale, as stated in protocol by Alcobendas-Maestro, Palazón-García, Vargas-Baquero, and Esclarin-Ruz (2015).

Management protocol for spasticity in spinal cord injury

There are studies on the application of one or other treatments such as that of Holtz, Szefer, Noonan, and Mills (2018) but there are no specific protocols or algorithms of management nowadays for spasticity in SCI. Most of the systematic reviews and metaanalysis have been performed on spasticity due to stroke or several mixed pathologies, so no evidence can be shown for any technique for SCI as stated by Taricco et al. (2006) and Khan, Amatya, Bensmail, and Yelnik (2019). A protocol for this treatment is then proposed:

(a) **Positioning and exercise**: The first step is to promote an adequate positioning and educate the patient in the need to exercise daily; during acute in-patient phase, this exercise will be performed in the context of physical therapy, and then in chronic phase perform only mobilizations or stretching as maintenance.

(b) **Control of triggering factors**: It can be considered as the first part of the treatment because it is the first factor to be taken into account when spasticity appears or is decompensated.

(c) **Baclofen**: If spasticity must be treated, the first-line drug is baclofen. We start with a dosage of 15 mg/day divided into 3 doses (lower dosage for children, elderly people or concomitant drugs), and in 3–4 days, it can be increased to 30 mg/day; we must wait 2 weeks to significantly evaluate the effect.
- If the response to treatment is partial, we increase to 45 mg/day and if now the response is complete, the same dosage is maintained.
- If there is no response for 4 weeks, we can go directly to next point by withdrawing baclofen.
- If there is a partial response after 3 weeks with baclofen at 45–60 mg/day and spasticity remains with much functional interference, a second-line drug is added, and this depends on the spasticity features.

(d) **Second-line drugs**:
- Only phasic spasticity. If the only symptom not controlled by baclofen is night spasms diazepam is added in a single nightly dose. If there are spasms or other dynamic phenomena all day long then clonazepam is added.
- Predominance of hypertonia. In general, the drugs preferred as adjuvants to baclofen are tizanidine or clonidine, considering that if the patient has a cervical SCI, we only choose tizanidine.
- Focal spasticity. If there are less than four muscle groups involved in spasticity, botulinum toxin is used. If spasticity is initially generalized but after administration of baclofen or others only focal spasticity persists, botulinum toxin is also indicated.

(e) **Third-line treatment**. If we are using two of the drugs mentioned earlier with a dose close to the maximum allowed or effective, we can add one of the others as third drug (e.g., if we use baclofen and tizanidine, we can associate diazepam). If one of the drugs mentioned earlier cannot be added as a third drug (elderly patients, prevention of adverse events), we can test other drugs with less recognized efficacy or focus on physical modalities (e.g., hydrotherapy).

(f) **Failure of all the treatments**. If we are using three or four oral drugs, we have every exacerbating factor controlled, the patient performs physical activity, and despite everything spasticity is still intense or disabling, we will consider the

intrathecal baclofen pump. We must perform a previous baclofen test dose (positive if instillation of a 50 μg bolus produces improvement of spasticity), there must be permeable intrathecal flow, the patient must be motivated and psychologically stable, and there must have been a minimum time of evolution of the lesion (usually 9–12 months).

Applications to other areas of neuroscience

Differences between spasticity of cerebral and spinal origin (Alcobendas-Maestro et al., 2015; Harrington & Bockenek, 2011).

- The most frequent presentation of spasticity when the origin is spinal is generalized and diffuse, while focal spasticity is more frequent when the origin is cerebral.
- Regarding hypertonia, patients with SCI develop a more intense spasticity, and the clasp knife phenomenon is more frequent.
- The most affected muscles in SCI are extensors (antigravity muscles), especially in the lower extremities, while people with stroke or cerebral palsy show specific synergies (hemiparesis, diparesis) with greater involvement of flexor muscles.
- Regarding intrinsic phasic spasticity, clonus of the plantar flexors is more frequent when the origin is spinal, and patellar clonus is rare if the origin of the spasticity is not cerebral.
- Extrinsic spasticity is more common in SCI; lower limb extensor spasms are the most prevalent spastic sign in SCI. The most important stimulus in SCI is the extension of the hip (especially the last 20 degrees). The highest concentration of mechanoreceptors in people with cerebrovascular diseases is in the knees.
- Spinal spasticity is further exacerbated by visceral diseases.
- SCI patients show shortening of muscles due to prolonged postures, and the most frequent affected muscles are hamstrings that are shortened by keeping the sitting in the wheelchair. However, stroke patients can maintain a posture due to spasticity when they develop spastic dystonia, whose principal example is elbow flexion posture.

Mini-dictionary of terms

Antagonist muscle produces an opposite movement. Since antagonist muscles produce an opposing joint torque to the agonist muscles, this torque can be used to control the motion.
Antigravity muscle acts to counterbalance the pull of gravity and to maintain an upright posture. Most important antigravity muscles are quadriceps femoris and triceps surae.
Catch is a sudden appearance of increased muscle activity as a response to a fast passive stretch, which provokes an abrupt stop.
Clasp knife phenomenon occurs when there is an initial resistance to passive movement of a joint and this tone reduces suddenly and then the limb can move quite freely through its range of motion.
Clonus is an involuntary rhythmic muscle contraction that can cause distal joint oscillation.
Hypertonia is an involuntary increase in muscle resistance to passive stretching.
Osteotendinous hyperreflexia is an exaggerated muscular response to percussion of the tendons.
Spasms are abrupt, involuntary muscle contractions.
Spinal shock is the temporary loss of spinal reflex activity that appears as an initial phase when SCI starts abruptly (as occurs in traumatic or vascular injuries).
Tonus (muscle tone) is a continuous and passive partial contraction of the muscles that works as preparatory for voluntary movement.

Key facts of "diagnosis of spasticity in spinal cord injury"

When a traumatic SCI is starting, the appearance of spasticity means the ending of the spinal shock.
Spasticity cannot be found in lower motoneuron syndromes. The clinical course of cauda equina or conus medullaris syndromes is like a second motoneuron syndrome, and therefore they never develop spasticity.
When the cause of the SCI is vascular, the duration of spinal shock is usually longer.
The presence of neurogenic bladder or bowel is associated with normal or even flaccid tone but frequent and spontaneous spasms.

We must make a differential diagnosis between spasticity and other tone disorders; resistance to passive movement found in extrapyramidal stiffness, paratonia, or simulation is velocity-independent.

Key facts of "treatment of spasticity in spinal cord injury"

Physical modalities are often considered the mainstay of treatment for spasticity, but the duration of the effect is too short, so these treatments are useless. It may be beneficial to strengthen the muscles antagonistic to the spastic ones.
Although there is only one trial with only six SCI patients that compared oral baclofen with placebo, baclofen has been reported to be effective for reducing spasticity (particularly spasms) and is considered the first-line treatment for spasticity.
Since the proportion of elderly SCI patients is increasing, the dosage of baclofen is becoming more difficult due to its effects on cognitive abilities.
Tizanidine is the drug with the most important and reliable studies but it is usually associated with the treatment of stroke spasticity, where it is the only drug allowed.
Clonazepam has not been supported by any published study (not even observational), but it is found in all spasticity treatment protocols when the clinical features are spasms.

Summary points

Spasticity is defined as a disordered sensorimotor control, resulting from an upper motor neuron injury, presenting as intermittent or sustained involuntary activation of muscles. It occurs in 65% of SCI patients.
Spinal cord damage breaks the connection between the brain and the lower areas, so inhibitory signals are not received, and this causes a release and hyperactivity of segmental reflexes.
Spasticity in spinal cord injuries is characterized by being generalized and very intense.
The diagnosis of spasticity is eminently clinical and is made by confirming the clinical symptoms and signs.
The assessment is carried out by means of the measurements of the tone (Modified Ashworth Scale), dynamic phenomena (Spinal Cord Assessment Tool for Spastic reflexes), and of the functional repercussions.
Treatment is required only if the spasticity causes functional disadvantage and the main point is the education of the patient as to the recognition of the factors that can exacerbate the spasticity and the interventions to reduce its intensity.
Baclofen is the first-choice drug for the treatment of spasticity in spinal cord injuries.

References

Adams, M. M., Ginis, K. A., & Hicks, A. L. (2007). The spinal cord injury spasticity evaluation tool: Development and evaluation. *Archives of Physical Medicine and Rehabilitation*, *88*, 1185–1192.

Adams, H. H., & Hicks, A. L. (2005). Spasticity after spinal cord injury. *Spinal Cord*, *43*, 577–586.

Alcobendas-Maestro, M., Esclarín-Ruz, A., Casado-López, R. M., Muñoz-González, A., Pérez-Mateos, G., González-Valdizán, E., et al. (2012). Lokomat robotic- assisted versus overground training within 3 to 6 months of incomplete spinal cord lesion: Randomized controlled trial. *Neurorehabilitation and Neural Repair*, *26*, 1058–1063.

Alcobendas-Maestro, M., Palazón-García, R., Vargas-Baquero, E., & Esclarin-Ruz, A. (2015). Guía de práctica clínica para el tratamiento de la espasticidad espinal con toxina botulínica. *Rehabilitación (Madr)*, *49*, 38–44.

Baunsgaard, C. B., Nissen, U. V., Christensen, K. B., & Biering-Sørensen, F. (2016). Modified Ashworth scale and spasm frequency scale in spinal cord injury: Reliability and correlation. *Spinal Cord*, *54*, 702–708.

Benz, E. N., Hornby, T. G., Bode, R. K., Scheidt, R. A., & Schmit, B. D. (2005). A physiologically based clinical measure for spastic reflexes in spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *86*, 52–59.

Bohannon, R. W., & Smith, M. B. (1987). Interrater reliability of a modified Ashworth scale of muscle spasticity. *Physical Therapy*, *67*, 206–207.

Burns, A. S., Lanig, I., Grabljevec, K., New, P. W., Bensmail, D., Ertzgaard, P., et al. (2016). Optimizing the management of disabling spasticity following spinal cord damage: The ability network- an international initiative. *Archives of Physical Medicine and Rehabilitation*, *97*, 2222–2228.

Cook, K. F., Teal, C. R., Engebretson, J. C., Hart, K. A., Mahoney, J. S., Robinson-Whelen, S., et al. (2007). Development and validation of patient reported impact of spasticity measure (PRISM). *Journal of Rehabilitation Research and Development*, *44*, 363–371.

Decq, P. (2003). Physiopathologie de la spasticité. *Neurochirurgie*, *49*, 163–184.

Dymarek, R., Ptaszkowski, K., Ptaszkowska, L., Kowal, M., Sopel, M., Taradaj, J., et al. (2020). Shock waves as a treatment modality for spasticity reduction and recovery improvement in post-stroke adults—Current evidence and qualitative systematic review. *Clinical Interventions in Aging*, *15*, 9–28. https://doi.org/10.2147/CIA.S221032.

Ertzgaard, P., Nene, P., Kiekens, C., & Burns, A. S. (2019). A review and evaluation of patient-reported outcome measures for spasticity in persons with spinal cord damage: Recommendations from the ability network—An international initiative. *The Journal of Spinal Cord Medicine*, *13*, 1–11.

Gebler, K. (1990). Physical modalities. In M. B. Glenn, & J. Whyte (Eds.), *The practical management of spasticity in children and adults* (pp. 118–146). Philadelphia: Lea & Febiger.

Hara, T., Abo, M., Hara, H., Kobayashi, K., Shimamoto, Y., Shibata, Y., et al. (2018). Effects of botulinum toxin A therapy and multidisciplinary rehabilitation on lower limb spasticity classified by spastic muscle echo intensity in post-stroke patients. *The International Journal of Neuroscience*, *128*, 412–420.

Harrington, A. L., & Bockenek, W. L. (2011). Spasticity. In D. I. Campagnolo, & S. Kirshblum (Eds.), *Spinal cord medicine* (pp. 265–281). Philadelphia: Lippincott & Williiams.

Holtz, K. A., Szefer, E., Noonan, V. K., & Mills, P. B. (2018). Treatment patterns of in-patient spasticity medication use after traumatic spinal cord injury: A prospective cohort study. *Spinal Cord*, *56*, 1176–1183.

Huang, Y. C., Chen, P. C., Tso, H. H., Yang, Y. C., Ho, T. L., & Leong, C. P. (2019). Effects of kinesio taping on hemiplegic hand in patients with upper limb post-stroke spasticity: A randomized controlled pilot study. *European Journal of Physical and Rehabilitation Medicine*, *55*, 551–557.

Joseph, L. H., Ismail, O. H., Naicker, A. S., Ying, P. P., & Mohammad, A. R. (2009). Three-year study of spinal cord injury outcomes and related secondary complications in a tertiary Centre: A retrospective analysis. *Archives of Medical Science*, *5*, 190–194.

Khan, F., Amatya, B., Bensmail, D., & Yelnik, A. (2019). Non-pharmacological interventions for spasticity in adults: An overview of systematic reviews. *Annals of Physical and Rehabilitation Medicine*, *62*, 265–273.

Khurana, S. R., & Garg, D. S. (2014). Spasticity and the use of intrathecal baclofen in patients with spinal cord injury. *Physical Medicine and Rehabilitation Clinics of North America*, *25*, 655–669.

Kita, M., & Goodkin, D. E. (2000). Drugs used to treat spasticity. *Drugs*, *59*, 487–495.

Korzhova, J., Sinitsyn, D., Chervyakov, A., Poydasheva, A., Zakharova, M., Suponeva, N., et al. (2018). Transcranial and spinal cord magnetic stimulation in treatment of spasticity. A literature review and meta- -analysis. *European Journal of Physical and Rehabilitation Medicine*, *54*, 75–84.

Krause, P., & Straube, A. (2003). Repetitive magnetic and functional electrical stimulation reduce spastic tone increase in patients with spinal cord injury. *Supplements to Clinical Neurophysiology*, *56*, 220–225.

Krause, P., Szecsi, J., & Straube, A. (2008). Changes in spastic muscle tone increase in patients with spinal cord injury using functional electrical stimulation and passive leg movements. *Clinical Rehabilitation*, *22*, 627–634.

Lance, J. W. (1980). Symposium. In R. G. Feldman, R. R. Young, & W. P. Koella (Eds.), *Spasticity: Disordered motor control* (pp. 485–495). Chicago: Year Book Medical Pubs.

McIntyre, A., Mays, R., Mehta, S., Janzen, S., Townson, A., Hsieh, J., et al. (2014). Examining the effectiveness of intrathecal baclofen on spasticity in individuals with chronic spinal cord injury: A systematic review. *The Journal of Spinal Cord Medicine*, *37*, 11–18.

Meseguer-Henarejos, A. B., Sánchez-Meca, J., López-Pina, J. A., & Hernández, R. C. (2018). Inter- and intra-rater reliability of the modified Ashworth scale: A systematic review and meta- analysis. *European Journal of Physical and Rehabilitation Medicine*, *54*, 576–590.

Nene, A. V., Campos, A. R., Grabljevec, K., Lopes, A., Skoog, B., & Burns, A. (2018). Clinical assessment of spasticity in people with spinal cord damage: Recommendations from the ability network, an international initiative. *Archives of Physical Medicine and Rehabilitation*, *99*, 1917–1926.

New, P. W., Rawicki, B., & Bailey, M. J. (2002). Nontraumatic spinal cord injury: Demographic characteristics and complications. *Archives of Physical Medicine and Rehabilitation*, *83*, 996–1001.

Palazón-García, R., Alcobendas-Maestro, M., Esclarin-Ruz, A., & Benavente-Valdepeñas, A. M. (2019). Treatment of spasticity in spinal cord injury with botulinum toxin. *The Journal of Spinal Cord Medicine*, *42*, 281–287.

Phadke, C. P., Balasubramanian, C. K., Ismail, F., & Boulias, C. (2013). Revisiting physiologic and psychologic triggers that increase spasticity. *American Journal of Physical Medicine & Rehabilitation*, *92*, 357–369.

Phadke, C. P., Vierira, L., Mathur, S., Cipriano, G., Ismail, F., & Boulias, C. (2019). Impact of passive leg cycling in persons with spinal cord injury: A systematic review. *Top Spinal Cord Review*, *25*, 83–96.

Rekand, T., Hagen, E. M., & Grønning, M. (2012). Spasticity following spinal cord injury. *Tidsskr Nor Legeforen*, *132*, 970–973.

Richard-Denis, A., Nguyen, B. H., & Mac-Thiong, J. M. (2020). The impact of early spasticity on the intensive functional rehabilitation phase and community reintegration following traumatic spinal cord injury. *The Journal of Spinal Cord Medicine*, *43*, 435–443. https://doi.org/10.1080/10790268.

Roy, R. R., & Edgerton, V. R. (2012). Neurobiological perspective of spasticity as occurs after spinal cord injury. *Experimental Neurology*, *235*, 116–122.

Sadeghi, M., Mclvor, J., Finlayson, H., & Sawatzky, B. (2016). Static standing, dynamic standing and spasticity in individuals with spinal cord injury. *Spinal Cord*, *54*, 376–382.

Stevenson, V. L. (2010). Rehabilitation in practice: Spasticity management. *Clinical Rehabilitation*, *24*, 293–304.

Taricco, M., Pagliacci, M. C., Telaro, E., & Adone, R. (2006). Pharmacological interventions for spasticity following spinal cord injury: Results of a Cochrane systematic review. *Europa Medicophysica*, *42*, 5–15.

Whitlock, J. A. (1990). Neurophysiology of spasticity. In M. B. Glenn, & J. Whyte (Eds.), *The practical management of spasticity in children and adults* (pp. 8–33). Philadelphia: Lea & Febiger.

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Chapter 10

Fall circumstances, consequences, assessments, and interventions to manage fall risk among individuals living with spinal cord injury

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List of abbreviations

10-MWT	10-Meter walking test
6-MWT	6-Minute Walking Test
ADL	activities of daily living
BBS	Berg balance scale
CHIEF	Craig Hospital Inventory of Environmental Factors
FIST	function in sitting test
FOF	fear of falling
FES—I	The Falls Efficacy Scale International
mFRT	modified functional reach test
PEI	photo-elicitation interviews
SCI	spinal cord injury
SCI-FCS	Spinal Cord Injury-Fall Concerns Scale
SCIM III	Spinal Cord Independence Measure III
TAI	transfer assessment instrument
TUG	timed up and go
WISCI II	Walking Index for SCI
WST	Wheelchair Skills Test

Introduction

Falls are a common scenario, among other impairments and conditions, experienced by individuals living with a spinal cord injury (SCI) (see Table 1). Between 31% and 82% of individuals living with SCI will experience at least one fall in a year (Khan et al., 2019). This chapter examines the frequency of falls, circumstances associated with falls, consequences of falls, methods to evaluate fall risk, and intervention programs to manage fall risk.

Fall frequency

Falls are common among people living with SCI who are nonambulatory (use a wheelchair or scooter full time) and those who ambulate. A fall is defined as an event in which an individual unexpectedly makes contact with the ground, floor, or some other lower level (Lamb et al., 2005). Due to differences in functional abilities, it is important to consider differences in fall frequency between those who ambulate and those who do not.

A systematic review and meta-analysis performed by Khan et al. in 2019 found that 34% to 82% of individuals living with SCI who are able to ambulate fell at least once over a 6- to 12-month period, and 31% to 73% of individuals living with SCI who are nonambulatory fell at least once in the same time span (Khan et al., 2019) (see Table 2).

Diagnosis and Treatment of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822498-4.00010-5

TABLE 1 Common impairments, conditions, and scenarios associated with spinal cord injury.

Spinal shock
Paralytic ileus
Deep venous thrombosis and pulmonary embolus
Autonomic dysreflexia
Falls
Pressure ulcers
Spasticity
Postural hypotension
Bladder, bowel, and sexual function
Osteoporosis

A summary is provided of impairments, conditions, and scenarios commonly associated with spinal cord injury.

TABLE 2 Frequency of falls among ambulatory and nonambulatory individuals living with spinal cord injury (Khan et al., 2019).

Frequency	% of Ambulatory individuals with SCI	% of Nonambulatory individuals with SCI
At least 1 fall	34%–82%	31%–73%
Recurrent falls (more than 1 fall)	28%–68%	30%–41%

The frequency of falls among individuals living with Spinal Cord Injury (SCI) who ambulate and nonambulatory individuals are presented along with data on the frequency of the population, both ambulatory and nonambulatory, that sustain recurrent falls.
(Data source: Khan, A., Pujol, C., Laylor, M., Unic, N., Pakosh, M., Dawe, J., et al. (2019). Falls after spinal cord injury: A systematic review and meta-analysis of incidence proportion and contributing factors. *Spinal Cord, 57*(7), 526–539. https://doi.org/10.1038/s41393-019-0274-4).

Ambulatory individuals are more likely to fall compared to individuals who do not ambulate (Jorgensen et al., 2016). The odds of falling for individuals who ambulate are more than 29 times higher compared to individuals who do not ambulate. Jorgensen et al. proposed that falls are less frequent among nonambulatory individuals due to the larger base of support provided by the wheelchair.

Recurrent falls

Among nonambulatory individuals with SCI, Jorgensen et al. reported that men experienced recurrent falls (more than one fall) 3.1 times more often than women within a year. This finding could be explained by the difference in how men and women manage risk. As age increases, the odds of falling more than once among nonambulatory individuals with SCI decreased. The increased odds of falling among younger adults may be due to activity level and involvement in activities in the workplace that increase exposure to more potential fall situations than older adults (Jorgensen et al., 2016).

Between 30% and 41% of nonambulatory individuals had recurrent falls within a 6- to 12-month period (Khan et al., 2019). Recurrent falls were also reported 14% more often among individuals with greater functional mobility independence, likely because more mobile individuals can engage in more intense physical activity and are therefore more likely to fall (Jorgensen et al., 2016).

Most ambulatory individuals with SCI report falling more than once (Wirz & van Hedel, 2018). Within a 6- to 12-month period, 28%–68% of ambulatory individuals with SCI experienced multiple falls (Khan et al., 2019). Jorgensen et al. reported that individuals who could recover by themselves following a fall experienced 4.7 times more recurrent falls than those who could not get up by themselves. The increased frequency could be related to increased confidence in the ability to recover from a fall among those who are able to recover independently. Increased confidence may result in taking greater risks and exposure to more situations that lead to a fall (Jorgensen et al., 2016).

Fall circumstances

The circumstances in which individuals living with SCI are likely to encounter a fall vary widely. Compared with other populations, including older adults, much less is known about fall risk factors among individuals living with SCI (Khan et al., 2019). Further research is needed to comprehensively understand risk factors associated with falls.

To systematically examine the known risk factors associated with falls, the Biological, Behavioral, Social & Economic, and Environmental (BBSE) Model is used to classify fall risk factors and highlight the multi-factorial nature of falls (Institute of Medicine Committee., 2001). Fig. 1 displays a visual representation of the BBSE.

Biological risk factors

Biological contributors of falls among both ambulatory and nonambulatory individuals living with SCI include many factors. The most common contributors include muscle weakness, loss of balance, spasticity, and muscle spasms (Brotherton, Krause, & Nietert, 2007b; Jorgensen et al., 2016; Musselman, Arnold, Pujol, Lynd, & Oosman, 2018; Nelson et al., 2010). Lower levels of functional mobility have also been linked to an increased risk of falling (Wannapakhe, Arayawichanon, Saengsuwan, & Amatachaya, 2014). However, Nelson et al. found that persons with more function are also at greater risk because they have a greater exposure to situations where falls may occur, making them more likely to engage in risk-taking behaviors (Nelson et al., 2010). Other biological factors that may increase the risk of falls summarized by Khan et al. include: male sex (wheelchair users only), an increased number of comorbidities, trunk weakness, fatigue, walking asymmetry, shorter duration since sustaining SCI, narcolepsy, and reduced sensation (Khan et al., 2019). Age can also be a risk factor. Among 94 participants, individuals who reported a high frequency of falls were significantly younger. This may be because these individuals are more active and have greater levels of enthusiasm and energy (Amatachaya, Pramodhyakul, Wattanapan, & Eungpinichpong, 2015). In addition, reports of pain in the 2 months prior to the fall can affect the performance of activities of daily living and increase fall risk (Nelson et al., 2010). Studies have also revealed that individuals living with incomplete spinal cord injury, injuries in which partial sensation and/or motor function persists below the level of injury, experience significantly more falls than individuals with complete injuries (Amatachaya, Wannapakhe, Arrayawichanon, Siritarathiwat, & Wattanapun, 2011).

Behavioral risk factors

In a systematic review and meta-analysis, Khan et al. found that the most commonly reported behavioral attributions associated with falls included inattention or distraction, ambulation, fear of falling, a history of previous falls, and not using the safety features of a wheelchair or walking aid (Khan et al., 2019). Risk-taking behaviors are also associated with falls (Jannings, 2017), which is theorized to be the reason why men are three times more likely to fall than women (Jorgensen et al., 2016). Nelson et al. also found alcohol abuse increased the risk of falls as well as the use of a shorter

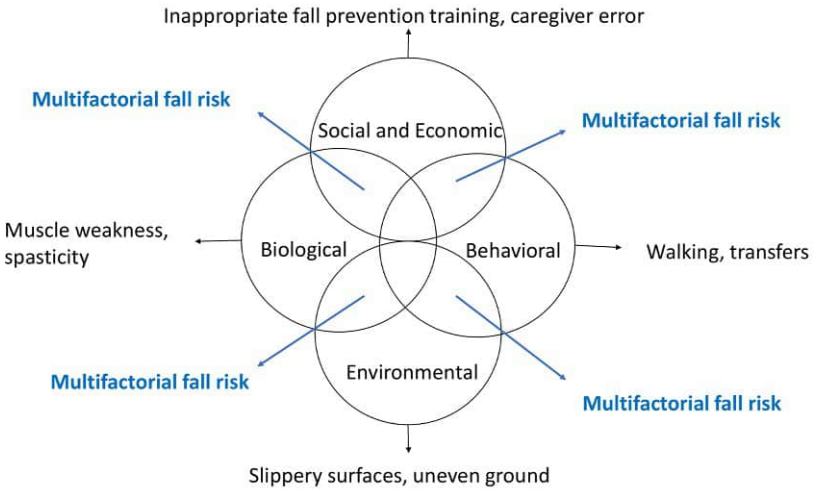

FIG. 1 Biological, Behavioral, Social and Economic, and Environmental Fall Model. The figure provides a visual representation of the biological, behavioral, social and economic, and environmental fall model. The model provides a framework for the classification of circumstances associated with falls. Please note how the various components intersect. This represents the multi-factorial nature of falls and the need to consider various factors when designing programs to manage fall risk. *(Data source: Institute of Medicine (US) Committee on Health and Behavior: Research. (2001). The National Academies Collection: Reports funded by National Institutes of Health. In Health and behavior: The interplay of biological, behavioral, and societal influences. National Academies Press (US) Copyright © 2001, National Academy of Sciences. https://doi.org/10.17226/9838).*

wheelchair. A shorter wheelchair allows for greater maneuverability; however, the design makes the chair less stable overall (Nelson et al., 2010). Finally, individuals with a lower quality of life were found to fall more frequently (Jorgensen et al., 2016).

Environmental risk factors

Environmental contributors to falls exist both within and outside the home. Hazards such as railings, stairs, heavy doors, and slippery floors are identified as increasing the risk of falls (Jorgensen et al., 2016). Among nonambulatory individuals, Sung et al. reported that the bathroom was the most common location for falls to occur, and 43% of falls were associated with pushing or driving the wheelchair on rough surfaces (Sung, Trace, Peterson, Sosnoff, & Rice, 2019). Forslund et al. found that 65% of falls occurred indoors, and 47% of falls occurred between the hours of 9 AM and 6 PM (Forslund et al., 2017).

Social and economic

Social and economic factors were also identified as fall contributors. Nelson et al. found that a higher level of education was associated with falls (Nelson et al., 2003). In addition, lack of fall prevention training (Musselman et al., 2018) and caregiver error (Jannings, 2017) were also found to contribute to falls. Table 3 summarizes fall risk factors according to the BBSE.

Consequences of falls

Falls experienced by individuals living with SCI can result in a variety of physical and psychosocial consequences for the faller, as well as high costs to society at large (see Table 4).

Physical consequences of falls

A systematic review and meta-analysis conducted by Khan et al. (2019) revealed that the frequency of reported falls which resulted in injuries ranged from 6% to 62% in ambulatory individuals with SCI and 13%–38% in nonambulatory individuals with SCI, though the frequency of total falls experienced (both injurious and noninjurious) appears to be similar between ambulatory and nonambulatory individuals with SCI (see Table 5).

While the majority of physical injuries sustained as a result of a fall were considered minor, such as bruises, cuts, or abrasions, approximately 15% of falls result in more severe injury, such as bone fractures (Amatachaya et al., 2011; Brotherton, Krause, & Nietert, 2007a), loss of consciousness (Wannapakhe et al., 2014; Wannapakhe, Arrayawichanon, Saengsuwan, & Amatachaya, 2015), or concussion (Forslund et al., 2017). Other moderate injuries reported as a result

TABLE 3 The top risk factors for falls classified by the biological, behavior, social and economic, and environmental model found in a systematic review and meta-analysis by Khan et al. (2019).

Biological	Behavioral	Environmental	Social and economic factors
• Muscle weakness • Impaired balance • Greater function/ mobility • Muscle spasms/ spasticity • Lower function/ mobility	• Inattention/distraction during movement • Ambulating • Fear of falling • Previous History of Falls • Not using protective straps/safety belt/ wheel locks	• Hazards in environment • Obstacles • Stairs • Uneven ground • Doors	• Higher education levels • Lack of fall prevention training • Caregiver error

The top risk factors for falls, organized using the biological, behavioral, social & economic, and environmental model, as reported by Khan et al. in a 2019 systematic review.
(Data source: Khan, A., Pujol, C., Laylor, M., Unic, N., Pakosh, M., Dawe, J., et al. (2019). Falls after spinal cord injury: A systematic review and meta-analysis of incidence proportion and contributing factors. *Spinal Cord, 57*(7), 526–539. https://doi.org/10.1038/s41393-019-0274-4).

TABLE 4 Consequences of falls experienced by ambulatory and nonambulatory individuals living with spinal cord injury.

Physical injuries consequences	Bruises, cuts, abrasions, bone fractures, concussions, death
Psychosocial consequences	Fear of falling, feelings of embarrassment or frustration; deconditioning, decreased community participation
Societal consequences	Cost to health-care systems, increased dependence on caregivers

A summary is provided of the physical, psychosocial, and societal consequences of falls experienced by both ambulatory and nonambulatory individuals living with spinal cord injury.
(Data source: Amatachaya, S., Wannapakhe, J., Arrayawichanon, P., Siritarathiwat, W., & Wattanapun, P. (2011). Functional abilities, incidences of complications and falls of patients with spinal cord injury 6 months after discharge. *Spinal Cord, 49*(4), 520–524. https://doi.org/10.1038/sc.2010.163; Amatachaya, S., Pramodhyakul, W., Wattanapan, P., & Eungpinichpong, W. (2015). Ability of obstacle crossing is not associated with falls in independent ambulatory patients with spinal cord injury. *Spinal Cord, 53*(8), 598–603. https://doi.org/10.1038/sc.2015.22; Brotherton, S. S., Krause, J. S., & Nietert, P. J. (2007). Falls in individuals with incomplete spinal cord injury. *Spinal Cord, 45*(1), 37–40. https://doi.org/10.1038/sj.sc.3101909; Forslund, E. B., Jorgensen, V., Franzen, E., Opheim, A., Seiger, A., Stahle, A., et al. (2017). High incidence of falls and fall-related injuries in wheelchair users with spinal cord injury: A prospective study of risk indicators. *Journal of Rehabilitation Medicine, 49*(2), 144–151. https://doi.org/10.2340/16501977-2177; Jannings, W. (2017). A quality improvement project to investigate the circumstances of lower limb fractures in non-ambulant persons with spinal cord injury. *Journal of the Australasian Rehabilitation Nurses Association, 20*(August), 14–18.; Musselman, K. E., Arnold, C., Pujol, C., Lynd, K., & Oosman, S. (2018). Falls, mobility, and physical activity after spinal cord injury: An exploratory study using photo-elicitation interviewing. *Spinal Cord Series and Cases, 4*, 39. https://doi.org/10.1038/s41394-018-0072-9; Verma, S. K., Willetts, J. L., Corns, H. L., Marucci-Wellman, H. R., Lombardi, D. A., & Courtney, T. K. (2016). Falls and fall-related injuries among community-dwelling adults in the United States. *PLoS One, 11*(3), e0150939. https://doi.org/10.1371/journal.pone.0150939; Wannapakhe, J., Arayawichanon, P., Saengsuwan, J., & Amatachaya, S. (2014). Changes of functional ability in patients with spinal cord injury with and without falls during 6 months after discharge. *Physical Therapy, 94*(5), 675–681. https://doi.org/10.2522/ptj.20130260).

TABLE 5 Injuries reported among fallers living with SCI (Khan et al., 2019).

Population	Frequency of injuries
Ambulatory individuals	6%–62%
Nonambulatory individuals	13%–38%

A summary is reported of the injuries experienced by individuals living with spinal cord injury, as reported by Khan et al. in a 2019 systematic literature review and meta-analysis. Note the increased reports of injuries among ambulatory individuals.

of a fall sometimes include muscle tears (Amatachaya et al., 2015), sprains, bloody nose, and numbness (Nelson et al., 2010). In severe cases, injuries sustained from a fall can even result in death (Nelson et al., 2010).

Ambulatory individuals with SCI experience a greater number of minor injuries as a result of a fall compared to nonambulatory individuals (Wannapakhe et al., 2015). They also have a greater incidence of fractures as a result of falls compared to healthy older adults (Brotherton et al., 2007a). Ambulatory women with SCI report more injurious falls than men of the same population, similarly to women without SCI compared to their male peers. Ambulatory individuals with SCI who have a history of recurrent falls are also at an increased risk of experiencing an injurious fall compared to those with no such history (Jorgensen et al., 2017).

Psychosocial consequences of falls

Fear of falling

While physical consequences of falling are more easily identified, there also exist psychosocial consequences of falls that heavily influence individuals with SCI.

Many individuals living with SCI who experience a fall, report an increase in fear of falling (Amatachaya et al., 2015; Musselman et al., 2018). Fear of falling (FOF) is defined as an ongoing concern about experiencing a fall which may ultimately limit the performance of daily activities (Legters, 2002). Developing a FOF is a common occurrence after experiencing a fall; however, a FOF can develop even when there is no history of falls. While a moderate amount of FOF may prompt individuals to be more mindful of their environment when performing tasks, FOF often leads individuals to unnecessarily avoid performing activities which they are physically capable of doing (Tinetti, Speechley, & Ginter, 1988). This can result in the deconditioning of the body which may put individuals with SCI at a further increased risk of falling and experiencing more severe consequences of falls when activity by necessity occurs, such as reaching for

an item while getting dressed or transferring to a toilet (Brotherton et al., 2007b). Fear of falling may be caused by post-fall–related experiences, such as injury, or underlying factors that enhance fall risk, such as having poor balance, muscle weakness, and impaired sensation, which may decrease fall-related self-efficacy (Jorgensen et al., 2017).

Fear of falling is also a risk factor for recurrent falls in ambulatory individuals with SCI (Phonthee, Saengsuwan, Siritaratiwat, & Amatachaya, 2013) and has been found to be associated with decreased community participation (Peterson, Cho, & Finlayson, 2007; Tinetti, Speechley, & Ginter, 1988) and lower quality of life (Nelson et al., 2010). Sung et al. found that 65% of nonambulatory individuals with SCI reported a fear of falling. Of those who reported a FOF, 26% also indicated that they limited their activities because of this fear (Sung, Peterson, Shen, Sosnoff & Rice, 2021). Friedman, Munoz, West, Rubin, and Fried (2002) found that there was a "spiraling effect" between increasing fall occurrences, FOF, and functional decline. Ambulatory individuals with SCI who have better balance appear to show less fear of falling (Wirz, Müller, & Bastiaenen, 2010), suggesting that interventions targeted at improving balance may help to decrease FOF.

Negative feelings and decreased community participation

In combination with increased fear of falling, other feelings expressed by individuals with SCI after falling include feelings of embarrassment (Jannings, 2017) and frustration (Musselman et al., 2018), even if they were not physically injured. While these emotions, combined with FOF, may motivate an individual to be more cautious in the future, of great concern is the frequently reported decrease in community participation and social interactions by as many as 45% of fallers with SCI (Musselman et al., 2018).

Societal consequences of falls

In addition to the physical and psychosocial burden of falls, there also exists a significant societal burden. In 2010, among U.S. adults, it was estimated that fall-related injuries cost health-care systems 111 billion dollars (Verma et al., 2016). Saunders, DiPiro, Krause, Brotherton, and Kraft (2013) found that approximately 20% of falls experienced by ambulatory individuals with SCI resulted in the need for medical attention. Fall-related injuries can also lead to an increased dependence on others for assistance with daily activities. This can lead to increased caregiver burden and costs over a lifetime (Forslund et al., 2017).

Assessment of fall risk

The assessment of fall risk among people living with SCI is of high importance to foster management of fall risk. Methods used to assess fall risk include clinical measures (Srisim, Saengsuwan, & Amatachaya, 2015), self-report strategy (Sung et al., 2019), and photo-elicitation techniques (Singh et al., 2020).

It is important to note that fall risk factors in people with SCI have shown to be specific, individualized, and highly dependent on the specific characteristics of the injury including the type of injury (complete or incomplete), chronicity of injury, and the level of injury. Other factors, such as the functional ability of the person with SCI, including personal characteristics and the surrounding environment, also determine the level of risk of falls. Therefore, fall risk assessments differ between ambulatory and nonambulatory people with SCI (see Fig. 2).

Assessment among ambulatory people with SCI

Most studies on fall risk assessment have focused on individuals living with SCI who ambulate (Abou, de Freitas, Palandi, & Ilha, 2018). Previous research indicates that biological factors are the primary risk factors associated with falls among ambulatory people and include level of functional independence, physical fitness, gait velocity, reaction time, limits of stability, and lower extremity muscle strength (Abou et al., 2018). These biological factors are measurable in clinical settings through the performance of clinical measures including the Berg Balance Scale (BBS), the Spinal cord Independence Measure (SCIM) III, and the Timed Up and Go (TUG). Abou, Ilha, Romanini, and Rice (2019) reported that the BBS is the most appropriate clinical balance measure and has the ability to effectively predict future falls among ambulatory people with SCI. However, since falls are multi-factorial, there is no consensus on the relationship between level of mobility and fall risk in this population. Some studies reported a significant relationship between a higher level of mobility and increased risk of falling (Amatachaya et al., 2018; Phonthee, Saengsuwan, & Amatachaya, 2013), while other studies related lower level of mobility to an increased risk of falling (Srisim et al., 2015). Undoubtedly, other biological factors such as sex, type

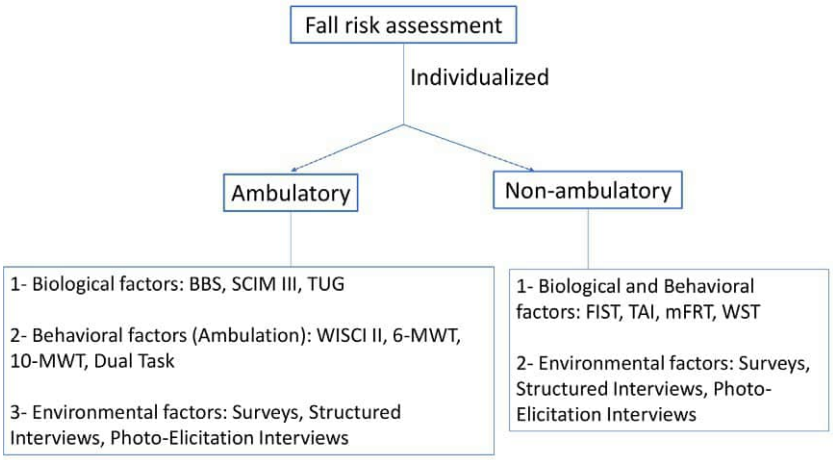

FIG. 2 Summary of fall risk assessments among people living with spinal cord injury. This table depicts the various assessments to examine fall risk among individuals living with spinal cord injury categorized by the primary target area using the biological, behavioral, social and economic, and environmental model. Abbreviations: *6-MWT*: 6-minute walking test, *10-MWT*: 10-meter walking test, *BBS*: Berg balance scale, *FIST*: function in sitting test, *mFRT*: modified functional reach test, *SCIM III*: spinal cord independence measure III, *TUG*: timed up and go, *WISCI II*: Walking Index for SCI*TAI*: transfer assessment instrument, *WST*: Wheelchair Skills Test.

of injury, fatigue, pain, sensorial impairment, time since SCI, trunk weakness, and the presence of comorbidities also contribute to an increased risk of falling.

Ambulating itself has been reported as one of the most common behavioral risks of falling along with inattention or distraction (Khan et al., 2019). This is because ambulating may easily lead to a loss of balance when performing an additional task (i.e., ambulation and a cognitive task) (Amatachaya et al., 2018). In clinical settings, ambulation can be assessed by use of the Walking Index for SCI (WISCI-II), the 6-Minute Walking Test (6-MWT), dual-task obstacle crossing (Amatachaya et al., 2018), and the 10-Meter Walking Test (10-MWT) (Moore et al., 2018). Amatachaya et al. showed that failing to cross an obstacle while performing a color-word Stroop task during the 10-MWT and the TUG is significantly associated with future risk of falls (Amatachaya, Promkeaw, Arayawichanon, Thaweewannakij, & Amatachaya, 2020). However, the relationship between ambulation outcome measures and falls still need to be further explored. Other behavioral factors that increase the risk of falling including a fear of falling, a history of previous falls, and not using a walking aid should be assessed with ambulation (Khan et al., 2019).

Environmental factors that increase the risk of falling both within and outside of the home can be assessed using different techniques. Hazards in the environment such as stairs, ramps or hills, and uneven or slippery surfaces can be assessed using surveys, semistructured interviews, and photo-elicitation interviews (PEI) (Brotherton et al., 2007a; Musselman et al., 2018). The Craig Hospital Inventory of Environmental Factors (CHIEF) is a comprehensive measure to evaluate environmental barriers (Whiteneck et al., 2004). However, compared with surveys and semistructured interviews, PEI provides more details about the environmental factors related to falls. PEI allows participants to take photographs of situations, places, people, hazards in the environment, and obstacles that may lead them to falls. Also, through PEI, participants are actively involved in identifying factors that lead them to falls (Clark-IbáÑez, 2004).

Finally, social and economic fall risk factors should also be considered and need further exploration among ambulatory people with SCI through surveys and interviews. Among other populations, including older adults, the level of education, fall prevention training, caregiver and family training have been associated with falls (Deandrea et al., 2010). These factors should be taken into consideration when evaluating an individual's risk for falls.

Assessment among nonambulatory people with SCI

Few studies have focused on the exploration of fall risk factors among nonambulatory people with SCI (Sung et al., 2019). Performance of activities of daily living constitutes the main behavioral fall risk in this population. The influence of muscle spasticity and poor balance can negatively affect the safe performance of activities of daily living while using a wheelchair (Abou et al., 2018). Activities of daily living including transfers from/to different surfaces, wheelchair propulsion, and reaching for an object are commonly associated with falls (Sung et al., 2019) can be assessed with clinical measures. The Function in Sitting Test (FIST) (Abou, Sung, et al., 2019), Wheelchair Skills Test (Keeler, Kirby, Parker, McLean, & Hayden, 2019), Transfer Assessment Instrument (TAI) (Worobey, Rigot, Hogaboom, Venus, & Boninger, 2018; Worobey, Zigler, et al., 2018), and modified Functional Reach Test (Lynch, Leahy, & Barker, 1998) can be used

to assess sitting balance, wheelchair skills, transfers, and functional reach, respectively, among nonambulatory people with SCI. Additionally, a smartphone-based assessment has been recently developed to assess sitting balance among nonambulatory people with SCI (Frechette, Abou, Rice, & Sosnoff, 2020). However, the relationship between the aforementioned outcome measures and falls still needs to be established.

Similar to ambulatory people with SCI, environmental factors that constitute important fall risk factors among nonambulatory people with SCI can be assessed using surveys, semistructured interviews, and PEI (Brotherton et al., 2007a; Musselman et al., 2018). PEI may foster the identification of environmental factors associated with falls in the bathroom, street, bedroom, living room, and kitchen. In addition, PEI may provide clinicians with more details about environmental conditions including wet and slippery surfaces, low lighting, and uneven ground which were also reported as conditions that increase the risk of falling among nonambulatory people with SCI (Sung et al., 2019).

Assessing fear of falling

Several approaches have been used by researchers to assess FOF in individuals with SCI. While some studies have utilized single-item questions, such as directly asking participants if they are worried or concerned about falling (Jorgensen et al., 2017; Sung et al., 2019), others have used more comprehensive assessment tools to identify levels of concern about falling in relation to specific activities. The Falls Efficacy Scale-International (FES-I) (Yardley, Beyer, Hauer, Kempen, & Piot-Ziegler, 2005) was designed for ambulatory elderly individuals but has been used in studies of other ambulatory individuals including those with SCI (Wirz et al., 2010). Boswell-Ruys, Harvey, Delbaere, and Lord (2010) modified the FES-I to be more appropriate to assess FOF among nonambulatory individuals with SCI, creating the Spinal Cord Injury-Fall Concerns Scale (SCI-FCS). Assessment tools such as the FES-I and SCI-FCS allow for a more comprehensive understanding of FOF and can help in the creation of tailored interventions to address warranted and unwarranted FOF.

Intervention program to manage fall risk

As a result of the high frequency and significant consequences associated with falls among individuals living with SCI, effective management of fall risk is critical for the health and well-being of individuals living with SCI.

Rice, Sung, Keane, Peterson, and Sosnoff (2019) examined the efficacy of a one-time, 1:1, 45-min intervention among 18 full-time manual wheelchair users living with SCI. The intervention focused on the refinement of transfer skills and implementation of an exercise program to improve upper extremity strength and core stability. After the initial education, participants were given an opportunity to practice the skills and discuss individual fall concerns. Participants were then asked to integrate the education at home for a period of 12 weeks. After exposure to the intervention, fall incidence significantly decreased and seated balance significantly improved. Improvements were also seen with regards to quality of life.

Amatachaya et al. (2020) examined the effects of walking training on a walking track with different surfaces, including grass, soft areas, and pebbles, compared to standard overground walking training among individuals living with SCI who ambulate independently, with or without an assistive device. Participants engaged in walking training on the walking track (intervention) or received standard overground walking training (control) 5 days per week, 30 min per day for 4 weeks. In both groups, participants walked at a self-selected speed. Six months after exposure to the intervention fewer participants in the intervention group ($n = 5$, 18%) experienced falls compared to the control group ($n = 12$, 46%).

While the literature is sparse related to specific fall management programs for individuals living with SCI, other peer-reviewed intervention programs have been developed to manage common circumstances associated with falls. The studies presented in Table 6 contain details on intervention programs that target risk factors associated with falls including poor transfer skills (Worobey, Rigot, et al., 2018; Worobey, Zigler, et al., 2018), wheelchair and scooter skills (Keeler et al., 2019), and dynamic balance (Chisholm et al., 2017; Khurana et al., 2017; Qi et al., 2018; Williams et al., 2020).

Application to other areas of neuroscience

In this chapter, we have examined falls among individuals living with SCI. This is an expanding topic of concern that frequently impacts other individuals living with a variety of neurological impairments. For example, falls are also very common among individuals living with Multiple Sclerosis and can result in similarly significant consequences.

When assessing which individuals are at high risk for falls and circumstances associated with falls, it is important to consider that falls are multi-factorial. While some of the information presented in this book chapter can be carried over to other populations of individuals living with neurological impairments, it is important to note the various factors that

TABLE 6 **Intervention programs to manage fall risk among ambulatory and nonambulatory individuals living with spinal cord injury.**

Author	Area of focus	Population	Key intervention components	Outcome
Rice (Rice et al., 2019)	Comprehensive fall management	Full-time manual wheelchair users	Transfer education and exercise to increase upper extremity strength and core stability	After exposure to the intervention: Decreased fall frequency and improved seated balance
Amatachaya (Amatachaya et al., 2020)	Comprehensive fall management	Independent ambulators or individuals who used an assistive device to ambulate	Walking on a track with different surfaces (grass, soft areas, pebbles) vs standard overground walking training	18% of intervention participants experienced a fall vs control group
Worobey (Worobey, Rigot, et al., 2018; Worobey, Zigler, et al., 2018)	Transfer skills	Individuals who perform a sitting pivot transfer	In-person management of individual transfer skill deficits vs online skill management	Improvement seen in transfer quality through both in-person and online education
Keeler (Keeler et al., 2019)	Wheelchair skills	Full-time manual and power wheelchair users	Various instruction methods (1:1, group, peer-led, etc.) to improve wheelchair skill capacity and quality	Various formats studied result in improvements in wheelchair skill capacity and quality among manual and power wheelchair users
Williams (Williams et al., 2020)	Dynamic balance	C6-T12, AIS A-C	Arm crank ergometer training	After exposure to intervention, static sitting balance significantly improved
Qi (Qi et al., 2018)	Balance control and quality of life	C6-L1, AIS B-D	Tai Chi	Individuals who practiced Tai Chi had greater static sitting balance and increased quality of life compared to a control group
Khurana (Khurana, Walia, & Noohu, 2017)	Dynamic balance	T6-T12	Virtual reality game training	Virtual reality game-based training resulted in greater improvements in balance and functional performance compared to real-world, task-specific training
Chisholm (Chisholm, Alamro, Williams, & Lam, 2017)	Dynamic balance	C7-T4, AIS A-B	Robotic training	Overground robotic training resulted in improved postural stability vs treadmill-based robotic gait training

A summary is provided of peer-reviewed intervention programs designed to comprehensively manage fall risk and target risk factors associated with falls. References of individual studies are noted within the table.

influence falls. For example, wheelchair propulsion or driving over rough surfaces is reported as a common circumstance associated with falls among individuals living with SCI. This information will apply to other populations who use wheelchairs and scooters on a full-time basis. However, other factors more specific to SCI, such as the influence of spasticity or lack of sensation, may further increase the individuals' risk of falling. As a result, it is important for a clinician to consider the various factors that influence falls when examining fall risk and developing intervention programs to manage fall risk.

Among both individuals living with SCI and other neurological impairments, research related to this topic is limited. In recent years, research has begun to uncover important points including the frequency of falls and circumstances associated with falls. However, compared to research focused on older adults, the literature is very limited. Most significantly there is limited information regarding appropriate ways to assess fall risk and interventions to manage falls among individuals living with SCI and other populations affected by neurological impairments. It is important to consider that this is an evolving field of study and further research is needed.

Mini-dictionary of terms

Ambulatory: A term referring to individuals who are able to walk by themselves with or without an assistive device, such as a cane or walker.

Balance: A generic term describing the dynamics of body posture to prevent falling. Balance refers to the ability of the body to maintain the center of gravity within the limits of stability as determined by the base of support.

Deconditioning: A decline in the function of body parts and systems as a result of inactivity or lack of use.

Dual-task: A paradigm in experimental neuropsychology that requires an individual to perform two tasks simultaneously. A common dual-task example used in clinical experiments consists of walking and carrying on a conversation.

Fall: An event in which an individual unintentionally makes contact with some lower surface, such as the ground or floor.

Fear of falling: A fear or concern that a fall will occur. Fear of falling may develop as a result of a fall or independent of a fall event. An individual may limit their performance of activities they enjoy doing in their home or community that they remain capable to doing.

Gait training: Strategy to improve ambulation skills focused on restoring the pattern of walking to develop biomechanically efficient gait. Assistive devices may be used.

Nonambulatory: A term referring to individuals who are unable to walk without assistance from another person or a mobile device, such as a wheelchair.

Photo-Elicitation Interviews: An interview strategy in which participants are asked to take photos of areas associated with falls in order to foster a more in-depth discussion.

Quality of life: The degree to which an individual is healthy, comfortable, and able to participate in and enjoy life. This can be challenging to assess because nearly everyone places different values on these measures.

Key facts of fall frequency and fall circumstances

- Falls are a common health concern for individuals living with SCI.
- Between 31% and 82% of individuals living with SCI will experience at least one fall over a 6- to 12-month period of time.
- Individuals who ambulate fall more often compared to individuals who use a wheelchair or scooter.
- A wide variety of factors, such as muscle weakness, being distracted, and pushing or driving a wheelchair on a rough surface contribute to the occurrence of a fall.
- Falls often occur due to a combination of many different factors. For example, a fall may occur as a result of pushing a wheelchair on a rough surface while talking with a friend (being distracted).

Key facts of consequences of falls

- Falls may result in physical injuries and have psychosocial consequences, as well as societal costs.
- Up to 62% of individuals living with SCI may experience an injury as a result of a fall.
- The majority of physical injuries are minor; however, significant injuries, such as fractures or concussions, may occur.
- Fear of falling can lead to a spiraling effect, in which someone who is afraid of falling stops performing activities, leading to deconditioning, which in turn puts them at greater risk of falling in the future.

Summary points

- This chapter examines fall frequency, consequences of falls, fall circumstances, methods to assess fall risk, and interventions to manage fall risk.

- In a 6- to 12-month period, 34%–82% of ambulatory individuals and 31%–73% of nonambulatory individuals living with SCI experience at least one fall.
- Between 28% and 68% of ambulatory and 30% and 41% of nonambulatory individuals will experience recurrent falls.
- The circumstances associated with falls among ambulatory and nonambulatory individuals are diverse; however, some of the most common circumstances include falls due to the influence of muscle weakness or spasticity and inattention or distraction.
- Falls may occur both inside and outside of the home and were more common among individuals who were working or studying.
- Falls can result in significant consequences, including physical injuries, such as bruising, fractures, or head injuries.
- Falls can also result in the development of a fear of falling that can limit engagement in desired activities in the home and community.
- Falls can be evaluated using a combination of clinical assessments, self-report surveys, or photo-elicitation interviews.
- Interventions to manage fall risk show promise; however, additional studies are needed to develop comprehensive intervention programs.

References

Abou, L., de Freitas, G. R., Palandi, J., & Ilha, J. (2018). Clinical instruments for measuring unsupported sitting balance in subjects with spinal cord injury: A systematic review. *Topics in Spinal Cord Injury Rehabilitation*, *24*(2), 177–193. https://doi.org/10.1310/sci17-00027. Spring.

Abou, L., Ilha, J., Romanini, F., & Rice, L. A. (2019). Do clinical balance measures have the ability to predict falls among ambulatory individuals with spinal cord injury? A systematic review and meta-analysis. *Spinal Cord*. https://doi.org/10.1038/s41393-019-0346-5.

Abou, L., Sung, J., Sosnoff, J. J., & Rice, L. A. (2019). Reliability and validity of the function in sitting test among nonambulatory individuals with spinal cord injury. *The Journal of Spinal Cord Medicine*, 1–8. https://doi.org/10.1080/10790268.2019.1605749.

Amatachaya, S., Pramodhyakul, W., Wattanapan, P., & Eungpinichpong, W. (2015). Ability of obstacle crossing is not associated with falls in independent ambulatory patients with spinal cord injury. *Spinal Cord*, *53*(8), 598–603. https://doi.org/10.1038/sc.2015.22.

Amatachaya, S., Promkeaw, D., Arayawichanon, P., Thaweewannakij, T., & Amatachaya, P. (2020). Various surfaces benefited functional outcomes and fall incidence in individuals with spinal cord injury: a randomized controlled trial with prospective data follow-up. *Archives of Physical Medicine and Rehabilitation*. https://doi.org/10.1016/j.apmr.2020.08.009.

Amatachaya, S., Srisim, K., Thaweewannakij, T., Arrayawichanon, P., Amatachaya, P., & Mato, L. (2018). Failures in dual-task obstacle crossing could predict risk of future fall in independent ambulatory individuals with spinal cord injury. *Clinical Rehabilitation*. https://doi.org/10.1177/0269215518788913, 269215518788913.

Amatachaya, S., Wannapakhe, J., Arrayawichanon, P., Siritarathiwat, W., & Wattanapun, P. (2011). Functional abilities, incidences of complications and falls of patients with spinal cord injury 6 months after discharge. *Spinal Cord*, *49*(4), 520–524. https://doi.org/10.1038/sc.2010.163.

Boswell-Ruys, C. L., Harvey, L. A., Delbaere, K., & Lord, S. R. (2010). A falls concern scale for people with spinal cord injury (SCI-FCS). *Spinal Cord*, *48*(9), 704–709.

Brotherton, S. S., Krause, J. S., & Nietert, P. J. (2007). Falls in individuals with incomplete spinal cord injury. *Spinal Cord*, *45*(1), 37–40. https://doi.org/10.1038/sj.sc.3101909.

Brotherton, S. S., Krause, J. S., & Nietert, P. J. (2007b). A pilot study of factors associated with falls in individuals with incomplete spinal cord injury. *The Journal of Spinal Cord Medicine*, *30*(3), 243–250. https://doi.org/10.1080/10790268.2007.11753932.

Chisholm, A. E., Alamro, R. A., Williams, A. M., & Lam, T. (2017). Overground vs treadmill-based robotic gait training to improve seated balance in people with motor-complete spinal cord injury: A case report. *Journal of Neuroengineering and Rehabilitation*, *14*(1), 27. https://doi.org/10.1186/s12984-017-0236-z.

Clark-IbáÑez, M. (2004). Framing the social world with photo-elicitation interviews. *American Behavioral Scientist*, *47*(12), 1507–1527. https://doi.org/10.1177/0002764204266236.

Deandrea, S., Lucenteforte, E., Bravi, F., Foschi, R., La Vecchia, C., & Negri, E. (2010). Risk factors for falls in community-dwelling older people: A systematic review and meta-analysis. *Epidemiology*, *21*(5), 658–668. https://doi.org/10.1097/EDE.0b013e3181e89905.

Forslund, E. B., Jorgensen, V., Franzen, E., Opheim, A., Seiger, A., Stahle, A., et al. (2017). High incidence of falls and fall-related injuries in wheelchair users with spinal cord injury: A prospective study of risk indicators. *Journal of Rehabilitation Medicine*, *49*(2), 144–151. https://doi.org/10.2340/16501977-2177.

Frechette, M. L., Abou, L., Rice, L. A., & Sosnoff, J. J. (2020). The validity, reliability, and sensitivity of a smartphone-based seated postural control assessment in wheelchair users: A pilot study. *Frontiers in Sports and Active Living*. https://doi.org/10.3389/fspor.2020.540930.

Friedman, S. M., Munoz, B., West, S. K., Rubin, G. S., & Fried, L. P. (2002). Falls and fear of falling: Which comes first? A longitudinal prediction model suggests strategies for primary and secondary prevention. *Journal of the American Geriatrics Society*, *50*(8), 1329–1335.

Institute of Medicine (US) Committee on Health and Behavior: Research. (2001). The National Academies Collection: Reports funded by National Institutes of Health. In *Health and behavior: The interplay of biological, behavioral, and societal influences* National Academies Press (US). Copyright © 2001, National Academy of Sciences https://doi.org/10.17226/9838.

Jannings, W. (2017). A quality improvement project to investigate the circumstances of lower limb fractures in non-ambulant persons with spinal cord injury. *Journal of the Australasian Rehabilitation Nurses Association*, *20*(August), 14–18.

Jorgensen, V., Butler Forslund, E., Franzen, E., Opheim, A., Seiger, A., Stahle, A., et al. (2016). Factors associated with recurrent falls in individuals with traumatic spinal cord injury: A multicenter study. *Archives of Physical Medicine and Rehabilitation*, *97*(11), 1908–1916. https://doi.org/10.1016/j.apmr.2016.04.024.

Jorgensen, V., Butler Forslund, E., Opheim, A., Franzen, E., Wahman, K., Hultling, C., et al. (2017). Falls and fear of falling predict future falls and related injuries in ambulatory individuals with spinal cord injury: A longitudinal observational study. *Journal of Physiotherapy*, *63*(2), 108–113. https://doi.org/10.1016/j.jphys.2016.11.010.

Keeler, L., Kirby, R. L., Parker, K., McLean, K. D., & Hayden, J. A. (2019). Effectiveness of the wheelchair skills training program: A systematic review and meta-analysis. *Disability and Rehabilitation. Assistive Technology*, *14*(4), 391–409. https://doi.org/10.1080/17483107.2018.1456566.

Khan, A., Pujol, C., Laylor, M., Unic, N., Pakosh, M., Dawe, J., et al. (2019). Falls after spinal cord injury: A systematic review and meta-analysis of incidence proportion and contributing factors. *Spinal Cord*, *57*(7), 526–539. https://doi.org/10.1038/s41393-019-0274-4.

Khurana, M., Walia, S., & Noohu, M. M. (2017, Summer). Study on the effectiveness of virtual reality game-based training on balance and functional performance in individuals with paraplegia. *Topics in Spinal Cord Injury Rehabilitation*, *23*(3), 263–270. https://doi.org/10.1310/sci16-00003.

Lamb, S. E., Jørstad-Stein, E. C., Hauer, K., Becker, C., & Prevention of Falls Network Europe and Outcomes Consensus Group. (2005). Development of a common outcome data set for fall injury prevention trials: The prevention of falls network Europe consensus. *Journal of the American Geriatrics Society*, *53*(9), 1618–1622. https://doi.org/10.1111/j.1532-5415.2005.53455.x.

Legters, K. (2002). Fear of falling. *Physical Therapy*, *82*(3), 264–272. https://www.ncbi.nlm.nih.gov/pubmed/11869155.

Lynch, S. M., Leahy, P., & Barker, S. P. (1998). Reliability of measurements obtained with a modified functional reach test in subjects with spinal cord injury. *Physical Therapy*, *78*(2), 128–133. http://www.ncbi.nlm.nih.gov/pubmed/9474105.

Moore, J. L., Potter, K., Blankshain, K., Kaplan, S. L., O'Dwyer, L. C., & Sullivan, J. E. (2018). A core set of outcome measures for adults with neurologic conditions undergoing rehabilitation: A CLINICAL PRACTICE GUIDELINE. *Journal of Neurologic Physical Therapy*, *42*(3), 174–220. https://doi.org/10.1097/NPT.0000000000000229.

Musselman, K. E., Arnold, C., Pujol, C., Lynd, K., & Oosman, S. (2018). Falls, mobility, and physical activity after spinal cord injury: An exploratory study using photo-elicitation interviewing. *Spinal Cord Series And Cases*, *4*, 39. https://doi.org/10.1038/s41394-018-0072-9.

Nelson, A., Ahmed, S., Harrow, J., Fitzgerald, S., Sanchez-Anguiano, A., & Gavin-Dreschnack, D. (2003). Fall-related fractures in persons with spinal cord impairment: A descriptive analysis [Research Support, non-U.S. Gov't]. *SCI Nursing*, *20*(1), 30–37. Spring http://www.ncbi.nlm.nih.gov/pubmed/14626016.

Nelson, A. L., Groer, S., Palacios, P., Mitchell, D., Sabharwal, S., Kirby, R. L., et al. (2010, Aug). Wheelchair-related falls in veterans with spinal cord injury residing in the community: A prospective cohort study [multicenter study research support, U.S. Gov't, Non-P.H.S.]. *Archives of Physical Medicine and Rehabilitation*, *91*(8), 1166–1173. https://doi.org/10.1016/j.apmr.2010.05.008.

Peterson, E. W., Cho, C. C., & Finlayson, M. L. (2007). Fear of falling and associated activity curtailment among middle aged and older adults with multiple sclerosis. *Multiple Sclerosis Journal*, *13*(9), 1168–1175.

Phonthee, S., Saengsuwan, J., & Amatachaya, S. (2013). Falls in independent ambulatory patients with spinal cord injury: Incidence, associated factors and levels of ability. *Spinal Cord*, *51*(5), 365–368. https://doi.org/10.1038/sc.2012.147.

Phonthee, S., Saengsuwan, J., Siritaratiwat, W., & Amatachaya, S. (2013). Incidence and factors associated with falls in independent ambulatory individuals with spinal cord injury: A 6-month prospective study. *Physical Therapy*, *93*(8), 1061–1072. https://doi.org/10.2522/ptj.20120467.

Qi, Y., Zhang, X., Zhao, Y., Xie, H., Shen, X., Niu, W., et al. (2018). The effect of wheelchair Tai Chi on balance control and quality of life among survivors of spinal cord injuries: A randomized controlled trial. *Complementary Therapies in Clinical Practice*, *33*, 7–11. https://doi.org/10.1016/j.ctcp.2018.07.004.

Rice, L. A., Sung, J. H., Keane, K., Peterson, E., & Sosnoff, J. J. (2019). A brief fall prevention intervention for manual wheelchair users with spinal cord injuries: A pilot study. *The Journal of Spinal Cord Medicine*, 1–9. https://doi.org/10.1080/10790268.2019.1643070.

Saunders, L., DiPiro, N., Krause, J., Brotherton, S., & Kraft, S. (2013). Risk of fall-related injuries among ambulatory participants with spinal cord injury. *Topics in Spinal Cord Injury Rehabilitation*, *19*, 259–266.

Singh, H., Scovil, C. Y., Yoshida, K., Oosman, S., Kaiser, A., Craven, C., et al. (2020). Factors that influence the risk of falling after spinal cord injury: A qualitative photo-elicitation study with individuals that use a wheelchair as their primary means of mobility. *BMJ Open*, *10*(2). https://doi.org/10.1136/bmjopen-2019-034279, e034279.

Srisim, K., Saengsuwan, J., & Amatachaya, S. (2015). Functional assessments for predicting a risk of multiple falls in independent ambulatory patients with spinal cord injury. *The Journal of Spinal Cord Medicine*, *38*(4), 439–445. https://doi.org/10.1179/2045772313Y.0000000186.

Sung, J., Peterson, E., Shen, S., Sosnoff, J., & Rice, L. A. (2021). Fear of falling, community participation and quality of life among community-dwelling people who use wheelchairs full time. *Archives of Physical Medicine and Rehabilitation*, *102*, 1140–1146.

Sung, J., Trace, Y., Peterson, E. W., Sosnoff, J. J., & Rice, L. A. (2019). Falls among full-time wheelchair users with spinal cord injury and multiple sclerosis: A comparison of characteristics of fallers and circumstances of falls. *Disability and Rehabilitation*, *41*(4), 389–395. https://doi.org/10.1080/09638288.2017.1393111.

Tinetti, M. E., Speechley, M., & Ginter, S. F. (1988). Risk factors for falls among elderly persons living in the community. *New England Journal of Medicine*, *319*(26), 1701–1707.

Verma, S. K., Willetts, J. L., Corns, H. L., Marucci-Wellman, H. R., Lombardi, D. A., & Courtney, T. K. (2016). Falls and fall-related injuries among community-dwelling adults in the United States. *PLoS One*, *11*(3). https://doi.org/10.1371/journal.pone.0150939, e0150939.

Wannapakhe, J., Arayawichanon, P., Saengsuwan, J., & Amatachaya, S. (2014). Changes of functional ability in patients with spinal cord injury with and without falls during 6 months after discharge. *Physical Therapy*, *94*(5), 675–681. https://doi.org/10.2522/ptj.20130260.

Wannapakhe, J., Arrayawichanon, P., Saengsuwan, J., & Amatachaya, S. (2015). Medical complications and falls in patients with spinal cord injury during the immediate phase after completing a rehabilitation program. *The Journal of Spinal Cord Medicine*, *38*(1), 84–90. https://doi.org/10.1179/2045772313y.0000000173.

Whiteneck, G. G., Harrison-Felix, C. L., Mellick, D. C., Brooks, C. A., Charlifue, S. B., & Gerhart, K. A. (2004). Quantifying environmental factors: A measure of physical, attitudinal, service, productivity, and policy barriers. *Archives of Physical Medicine and Rehabilitation*, *85*(8), 1324–1335. https://doi.org/10.1016/j.apmr.2003.09.027.

Williams, A. M. M., Chisholm, A. E., Lynn, A., Malik, R. N., Eginyan, G., & Lam, T. (2020). Arm crank ergometer "spin" training improves seated balance and aerobic capacity in people with spinal cord injury. *Scandinavian Journal of Medicine & Science in Sports*, *30*(2), 361–369. https://doi.org/10.1111/sms.13580.

Wirz, M., Müller, R., & Bastiaenen, C. (2010). Falls in persons with spinal cord injury: Validity and reliability of the berg balance scale. *Neurorehabilitation and Neural Repair*, *24*(1), 70–77.

Wirz, M., & van Hedel, H. J. A. (2018). Balance, gait, and falls in spinal cord injury. *Handbook of Clinical Neurology*, *159*, 367–384. https://doi.org/10.1016/B978-0-444-63916-5.00024-0.

Worobey, L. A., Rigot, S. K., Hogaboom, N. S., Venus, C., & Boninger, M. L. (2018). Investigating the efficacy of web-based transfer training on independent wheelchair transfers through randomized controlled trials. *Archives of Physical Medicine and Rehabilitation*, *99*(1), 9–16. e10 https://doi.org/10.1016/j.apmr.2017.06.025.

Worobey, L. A., Zigler, C. K., Huzinec, R., Rigot, S. K., Sung, J., & Rice, L. A. (2018, Summer). Reliability and validity of the revised transfer assessment instrument. *Topics in Spinal Cord Injury Rehabilitation*, *24*(3), 217–226. https://doi.org/10.1310/sci2403-217.

Yardley, L., Beyer, N., Hauer, K., Kempen, G., & Piot-Ziegler, C. T. (2005). Development and initial validation of the falls efficacy scale international (FES-I). *Age and Ageing*, *34*, 614–619.

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Chapter 11

Infections and spinal cord injury: Covid-19 and beyond

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List of abbreviations

ARDS	acute respiratory distress syndrome
bDMARDs	biological disease-modifying anti-rheumatic drugs
CT	computerized tomography
Covid-19	coronavirus disease 2019
GCs	glucocorticoids
HPA	hypothalamic-pituitary-adrenal
IUC	indwelling urethral catheter
ICU	intensive care unit
ISNCSCI	International Standards for Neurological Classification of the Spinal Cord Injury
JAKi	Janus kinase inhibitors
MRI	magnetic resonance imaging
NICE	National Institute for Clinical Excellence
NE	norepinephrine
PI	pulmonary infections
PEP	positive expiratory pressure
PPE	personal protective equipment
ISC	self-catheterization
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SPC	suprapubic catheter
SCI	spinal cord injury
SCIP	spinal cord-injured patients
SNS	sympathetic nervous system
SPNs	sympathetic preganglionic neurons
UTI	urinary tract infections
WHO	World Health Organization

Introduction

An epidemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) started in Wuhan in December 2019 and quickly spread across the world. The 2019 coronavirus disease (Covid-19) was declared a pandemic on March 11, 2020, by the World Health Organization (WHO). On February 7th, 2021, 105,962,538 cases were confirmed worldwide with 2,313,136 deaths (Johns Hopkins Coronavirus Resource Center, 2020). This new SARS-CoV-2 has brought higher levels

Diagnosis and Treatment of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822498-4.00011-7

of illness, deaths, and fear to our planet than any other virus in current history. In this context, it is mandatory to determine the effect in people with spinal cord injury (SCI).

SCI induces numerous chronic disorders that put these individuals at a high risk of severe Covid-19 prognosis. Specifically, the SCI population presents higher rates of hypertension, SCI-induced immunosuppression, and, if the metameric level is T8 or above, respiratory failure with continuous or episodic hypoxemia due to respiratory muscle weakness. Sympathetic denervation following SCI compromises body temperature regulation, as a result of dysautonomia, which not only complicates the early diagnosis of Covid-19 which places them at risk of a poor prognosis, but also makes it difficult to control infection transmission to other patients and/or healthcare staff.

In general population, clinical symptoms appear after an incubation period of around 5 days (Zhu et al., 2020), presented in order of frequency as: fever (87.9%), dry cough (67.7%), asthenia (38.1%), dyspnea (18.6%), pharyngeal pain and odynophagia (13.9%), headache (13.6%), arthromyalgia (14.8%), chills (11.4%), nausea or vomiting (5%), nasal congestion (4.8%), and anosmia and diarrhea (3.7%). Approximately 80% of patients present as asymptomatic or with few symptoms including dry cough and fever or low-grade fever (Guan et al., 2020), but the remaining 20% of cases develop around the 7th day after the onset, severe hypoxemic respiratory failure that progresses to Acute Respiratory Distress Syndrome (ARDS) (15% of the total) and even to multi-organ failure (5% of the total), requiring mechanical ventilation and admission to an Intensive Care Unit (ICU) (Huang et al., 2020). Up to 18% of patients who request consultation for Covid-19 compatible symptoms do not present radiological alterations. When these appear, the most frequent clinical sign is unilateral or bilateral ground glass opacification with an interstitial pneumonia pattern or bilateral patched consolidation, evident on plain radiography and on chest computerized tomography (CT) examination (56.4%) (Hosseiny et al., 2020; Zu et al., 2020). At diagnosis, more than 80% of patients present lymphopenia (Guan et al., 2020), which is more severe and accompanied by neutrophilia in patients requiring ICU admission (Huang et al., 2020). The main cause of death after Covid-19 infection is respiratory failure and fulminant myocarditis, (Ruan et al., 2020). In these patients, a highly exaggerated inflammatory response has been described known as hyperinflammatory syndrome, with a massive release of cytokines into the bloodstream (Mehta et al., 2020; Ritchie & Singanayagam, 2020) similar to that observed in hemophagocytic syndromes caused by other virosis (Ramos-Casals et al., 2014). A series of clinical factors have been described, associated with symptoms of greater morbidity and mortality: male gender, age above 60 years—especially above 80 years old, where the fatality rate is close to 16%—and the presence of previous comorbidities such as: hypertension, ischemic heart disease, diabetes mellitus, lung disease, and various disease entities that lead to immunosuppression, such as autoimmune diseases or cancer (Zhou et al., 2020). Analytical markers associated with a higher risk of mortality are sustained lymphopenia and elevation of D-dimer, IL-6, ferritin, LDH, and troponin (Zhou et al., 2020).

The aim of this chapter is to analyze the clinical presentation of Covid-19 in spinal cord-injured patients (SCIP). The authors pretend to make pause to understand if this emergent disease, which is deadly hitting our general population, behaves in the same or different way as in these especial patients, in order to understand if the SCI condition is acting as a risk factor for morbidity or not, and why. For this purpose, we believe the immune system plays a significant role in infection, especially from our knowledge of other infections.

Immunosuppression due to spinal cord injury

Among non-specialist the most evident consequences of SCI is loss of mobility and sensibility. However, in spite of their dramatic effect on patient quality of life, this is only the tip of an iceberg compared to the other lifelong neurological and non-neurological sequelae. These patients have an immunodepressed state characterized by changes in the number and function of immune cells that render them highly susceptible to infections (Bracchi-Ricard et al., 2016; Brommer et al., 2016; Kopp et al., 2017). Indeed, these are the leading cause of morbidity and mortality after SCI (Thietje et al., 2011). In this chapter, we review why immunodepression occurs after SCI and how this affects the ability of patients to cope with the current Covid-19 pandemic and other infectious diseases.

Pathophysiology of spinal cord injury-induced immunodepression

The physiological responses to physical or psychological stress are mediated by the coordinated response of the sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal (HPA) axis. Both systems mediate the so-called fly-or-fight responses by setting the whole organism to cope with stressful stimuli at the expenses of arresting functions that are not indispensable for immediate survival. This physiological and evolutionary adapted response may, however, turn into a maladaptive chronic situation. Spinal cord injuries are a source of tremendous physical and psychological stress that unfortunately exemplifies the effect on the immune system of maladaptive SNS and HPA responses.

Dysregulation of the sympathetic nervous system

The main mechanism driving immunodepression after SCI is the dysregulation of the autonomic sympathetic nervous system. The cell bodies of the sympathetic preganglionic neurons (SPNs) are localized in the lateral horn of the spinal cord, in the intermedio-lateral nucleus. Classically, it has been considered as sympathetic the neurons located from T1 to the first lumbar segments (L2 – 3), although recently, the parasympathetic neurons located in the lateral horn of the sacral segments have been shown to have phenotypical and ontogenetic characteristics of SPNs (Espinosa-Medina et al., 2016). In any case, SPNs synapse in sympathetic ganglia majorly with post-ganglionic noradrenergic neurons, which in turn release norepinephrine (NE) in the target organs, though a minority of post-ganglionic sympathetic neurons are cholinergic, as those innervating sweat glands (Dale & Feldberg, 1934). The timing and intensity of SPNs activation is controlled by nuclei located in the brainstem, pons and hypothalamus that project inhibitory descendants into the spinal cord (Dénes et al., 2005). After a severe SCI, these supraspinal projections are interrupted and, thus, SPNs loss their inhibitory inputs. Consequently, when these neurons are activated, it may give raise to an exaggerated or more durable sympathetic response and, thus, to an excessive release of NA in the target organs. In addition, the sublesional spinal circuitry involved in the control of preganglionic neurons undergoes a remodeling process that favors the connectivity between activating interneurons and SPNs (Ueno et al., 2016). Overall, the resultant sympathetic overactivation below the lesion level underlies a plethora of autonomic dysfunctions after SCI, including the suppression of the immune system.

The sympathetic nervous system innervates both the primary and the secondary lymphoid organs, and modulates all the immune processes, from hematopoiesis to immune responses (Jung et al., 2017; Noble, Brennan, & Popovich, 2018). Immune cells sense NE majorly through beta-2-adrenergic receptors, although monocytes/macrophages also express lower levels of alpha-1- and alpha-2-adrenergic receptors (Kavelaars, 2002). The overall effect of adrenergic receptor activation on physiological conditions over innate immune cells is anti-inflammatory (Meltzer et al., 2004; Nance & MacNeil, 2001). On B cells, NE participates in T-cell mediated IgG production (Alaniz et al., 1999; Kohm & Sanders, 2001), while the effects of NE over T lymphocytes is more complex and varies according to the cellular stage of maturation and timing of exposure. Depending on the stage of maturation of T $CD8^+$ cells, exposure to NE may either promote or decrease their cytolytic activity (Nance & Sanders, 2007). Similarly, exposing Th1 cells to NE before their activation decreases the synthesis of IL-2 and IFN-gamma, while exposing them to NE after activation increases the synthesis of IFN-gamma (Nance & Sanders, 2007). In any case, the overall effect of NE over adaptive immune responses is also considered to be anti-inflammatory, inhibiting Th1 cell differentiation and promoting Treg-suppressive activity (Elenkov, Wilder, Chrousos, & Vizi, 2000; Guereschi et al., 2013).

After SCI, immune cells may be subjected to persistent or more intense exposure to NE, which results in immunosuppression (Prass et al., 2003). A factor that may dramatically affect the sympathetic dysregulation-induced immunodepression is the lesion level, being lesions at T5 or above associated to a greater impairment of the immune system both in patients and in experimental animal models (Brommer et al., 2016; Lucin et al., 2007; Lucin et al., 2009). This observation coincides with the fact that most of the sympathetic innervation of immune organs arise from preganglionic neurons located below T5. The innervation of lymph nodes is not resolved, but it is considered to originate from spinal segments close to their location in the body (Nance & Sanders, 2007). Thymus receives most of its innervation from above T5, specifically between T1 and T7 (Trotter et al., 2007). In any case, the sympathetic dysregulation induced by SCI suppresses immune cells in the decentralized lymphoid organs. This statement is supported by direct experimental evidence showing that immune suppression effects depend on beta-2-adrenergic stimulation and may be reverted by receptor antagonists (Table 1). Indirect evidence is further provided by the observation of a relationship between lesion level and extent of immunodepression (Table 2).

TABLE 1 Effects of SCI over immune cells with experimental evidence of dependence on beta-2-adrenergic receptor stimulation.

Cell type	Effect	References
B cells	(1) Impaired primary humoral responses (2) Apoptosis	(1) Lucin et al. (2007), Oropallo et al. (2012) (2) Lucin et al. (2009)
T cells	Apoptosis	Lucin et al. (2009)
$CD8^+$ T cells	T cell exhaustion	Zha et al. (2014)

Experimental evidence shows that SCI-induced immune suppression effects depend on beta-2-adrenergic stimulation and may be reverted by receptor antagonist. *SCI: spinal cord injury.*

TABLE 2 Effects of SCI over immune cells dependent on lesion level.

Cell type	Effect	References
B cells	Decreased number	Lucin et al. (2007), Held, Steward, Blanc, and Lane (2010), Zhang et al. (2013)
T cells	Decreased number	Lucin et al. (2009)
$CD4^+$ T cells	Decreased number	Zhang et al. (2013)
NK cells	Decreased number	Herman et al. (2018)
Dendritic cells	Decreased number	Iversen et al. (2000)

The observation of a relationship between the injury level and severity and the extent of immunodepression highlights the effects of SCI over immune cells. *SCI: spinal cord injury.*

There is evidence of the contribution of sympathetic overactivation to immune depression after SCI results from autonomic dysreflexia crises, potentially triggered by any sustained sensory stimuli entering the spinal cord below the lesion level. This occurs mainly in patients with severe lesions above T5 because these injuries render without inhibitory supraspinal inputs the SPNs that control abdominal circulation (Weaver et al., 2002). As a consequence, SPNs overactivation occurs and results in vasoconstriction and hypertension. As a counteractive measure it is triggered a vagal response that induces vasodilatation (only successful above the lesion level) and bradycardia, which may be life-threatening if derives into a cardiac arrest. It has been experimentally proved that in these crises, the overactive sympathetic response further aggravates immunodepression in animals with high thoracic (T3) SCI (Zhang et al., 2013), which may help to explain why infections result in morbidity and mortality among patients with tetraplegia compared to patients with paraplegia.

Another potential symptom of immunodepression driven by the autonomous nervous system is the "inflammatory reflex" (Pavlov & Tracey, 2017). When the vague nerve is stimulated, spleen macrophages are polarized into an anti-inflammatory profile. Evidence shows that the spleen does not receive parasympathetic innervation. However, the vagus nerve synapses with sympathetic post-ganglionic neurons in the celiac ganglion, eliciting the release of NE in the spleen. In response, T lymphocytes produce acetylcholine, which acting on alpha-7-nicotinic receptors expressed by macrophages inhibits the production of TNF-alpha, IL-1 beta and IL-18 by these cells. The contribution of the inflammatory reflex to SCI-induced immunodepression is not elucidated, but it seems reasonable to believe that it could be triggered by the vague nerve reflex that takes place during autonomic dysreflexia crises.

Dysregulation of the hypothalamic-pituitary-adrenal axis

The activation of the HPA axis after SCI is well documented by the increase of blood serum glucocorticoids (GCs) in patients and in experimental animals. Besides the direct immunosuppressive actions of GCs on immune cells, glucocorticoids (GCs) and NE synergize to modulate immune cell function. GCs increase the affinity and persistence in the cell membrane of beta-2-adrenergic receptors (Davies & Lefkowitz, 1981; Mak et al., 1995) while NE potentiates GCs signaling (Rangarajan, Umesono, & Evans, 1992). As such, when cortisol and the NE analog terbutaline are added together, they synergize to induce apoptosis of B and T cells in vitro (Lucin et al., 2009). Notably, the spleen atrophy and the decrease in the number of splenocytes induced by an experimental SCI in T3 is partially reverted by the join administration of antagonists of beta-2-adrenergic and GC-receptors (Lucin et al., 2009). In addition, it should also be considered that adrenal glands are innervated by the SNS, which induces the release of GCs.

Leading infection diseases in spinal cord-injured patients

Infection is one of the leading complications of inpatients, especially severe for SCIP due to the risk of death when it occurs a progression to a bloodstream infection. These patients have a greater predisposition to suffer infectious diseases because of their required use of medical devices such as intravenous and urinary catheters or ventilators. Special conditions suffered by these patients such as lack of mobility or bladder and respiratory dysfunctions contribute to a higher level of infection (Esclarín de Ruz et al., 2009).

There are two main features that make diagnosis of infection particularly challenging in SCIP. First, their loss of feeling can mask standard symptoms which make its diagnosis more difficult to diagnosis. Second, there are also some other

described conditions that can simulate an infection, but they are really the manifestation of another disease with no infection as it occurs in hyperthermia, abdominal retention, and pulmonary embolism or collapsed lung (Esclarín de Ruz et al., 2009).

In general terms for treatment, it is strongly recommended to use narrow-spectrum and less toxic antibiotics to avoid eliminating patient's native bacterial flora. It is also important to choose an appropriate directed antibiotic therapy to avoid the appearance of resistant bacteria.

The major infections that suffer SCIP are explained below (Table 3).

Urinary tract infections (UTI)

UTI are the most frequent cause of infections (95%) in SCIP. They increase the risk of morbidity and mortality because of interruptions of rehabilitation treatment, required visits to the emergency room, and progression to a sepsis. The latter can make SCIP more likely to develop an immunodeficiency syndrome that facilitates the appearance of recurrent UTI (Craven et al., 2019; Esclarín de Ruz et al., 2009). *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis* are the most frequently involved pathogens causing an UTI (Skelton-Dudley et al., 2019).

Physiopathology and etiology

Neurogenic bladder presents overdistension and high pressure due to the interruption of its voiding process. This produces an ischemia of the bladder's wall, which causes bacteria to invade its submucosal layer, and starts the UTI. If this process repeatedly occurs, collagen forms a scared tissue that replaces muscle fibers from the bladder's wall, which decreases bladder's wall compliance. This leads to increase ischemia of the bladder's wall and bladder's overdistension (Fig. 1) (Linsenmeyer, 2018).

To avoid high intravesical pressure and overdistension of the bladder's wall, more than a 60% of SCIP need a medical device to facilitate their bladder voiding such as an intermittent self-catheterization (ISC), an indwelling urethral catheter (IUC) or a suprapubic catheter (SPC). ISC is the gold standard method because it allows a cyclic emptying and filling of the bladder, comparable to the physiological bladder's functioning. Some studies as Kinnear et al., 2020, suggest that ISC is associated with lower rates of UTI when comparing with other medical devices. Despite that, SCIP who use ISC are likely to suffer UTI when they drink plenty of fluids or they do not practice the voiding method regularly, because of an overdistension of the bladder's wall. It becomes worse when patients have an overactive bladder and/or a decreased bladder function (Kinnear et al., 2020).

TABLE 3 Principle infection features in SCIP.

	UTI	PI	Covid-19
Frequency	It is the most frequent cause of infection (95%) in SCIP	• The 50% of SCIP who suffer acute tetraplegia develop pneumonia during acute hospitalization • PI and respiratory failure are the major causes of death in this population	Unknown but lower than expected
Pathogens	• *Escherichia coli* • *Klebsiella pneumoniae* • *Proteus mirabilis*	• Pneumococcus, Pseudomonas (outpatients) • No data (inpatients)	SARS-CoV-2
Etiology	• Changes due to neurogenic bladder produce an overdistension of the bladder, high intravesical pressure and bladder compliance decrease that can lead to an UTI • Medical devices that are used for facilitating bladder voiding can lead to an UTI as well	• The dysfunction of inspiratory and expiratory muscles, the increased risk of dysphagia disorders and the changes inside lung that produces a neurogenic pulmonary edema can lead to a PI • Medical devices to assist with breathing can lead to a PI as well	• Immunosuppression induced by SCI • Neuromuscular respiratory failure due to respiratory muscles weakness and clearance secretions' decrease in SCI levels of injury above T6–T8

Continued

TABLE 3 Principle infection features in SCIP—cont'd

	UTI	PI	Covid-19
Diagnosis	• It is necessary to differentiate between: - Asymptomatic bacteriuria/ bladder colonization: - $\geq 10^2$ cfu/mL bacteriuria at sediment - or any bacteria detected at sediment when using IUC - no symptoms - [a]UTI: - bacteriuria (with one primary organism detected at culture) - one bladder symptom at least: - hematuria - new/increased incontinence - change in urine odor/clarity - pyuria - one general symptom at least: - fever - acute autonomic dysreflexia - acutely increased spasticity - sepsis - persistent fatigue - vomiting • When symptoms appear, urine and blood cultures are required • When symptoms persist, it may be necessary to carry out additional test as ultrasounds, cystoscopy or kidney scan, to rule out complications (hydronephrosis, vesicoureteral reflux, urinary lithiasis or kidney abscesses) • Blood biomarkers (procalcitonin and interleukin-6) has shown poor evidence in ITU detection	• Clinical symptoms: fever, dyspnea, secretions • Chest X-ray that shows infiltrates within lungs • Alterations in blood gas analysis • Leukocytosis • Culture and sputum Gram stain: – when NOT wearing an artificial airway: Sputum culture (>25 polymorphonuclear leukocytes and < 10 epithelial cells per field) – when wearing an artificial airway: - bronchoalveolar lavage sample: $>10^4$ cfu/mL - tracheal aspiration sample: $>10^6$ cfu/mL	• Mild symptoms of onset: hypoxia, secretion clearance impairment could be the only symptoms of onset; but SCIP can also present fever, dyspnea, fatigue, anosmia, ageusia, arthromyalgias, and headache • Close observation to neurofunctional outcomes, especially with the help of the International Standards for Neurological Classification of the Spinal Cord Injury (ISNCSCI) Worksheet, is needed to know if this infection produces sensory and motor deficits in these patients • Whenever those symptoms are suspected, it is needed to make a RT-PCR SARS-CoV-2 from nasopharyngeal or bronchial aspiration test to confirm the infected condition • Other paraclinical tests: Chest X-ray (to explore infiltrates at lungs), gas blood analysis (to explore ventilation perfusion state), and a blood analysis (to rule out lymphopenia, increase of D-dimer, ferritin and IL-6 • After 7–14 days from the onset of the symptoms, if patient presents a favorable clinical evolution, a serological SARS-CoV-2 should be done to look for IgM and IgG levels
Treatment	• The choice of the most appropriate antibiotic treatment depends on culture results • Long-term antibiotic treatment (from 7 to 14 days) is recommended	• Prompt empirical antibiotic treatment is needed - [b]Community acquired pneumonia - empiric anti-pseudomonal coverage is recommended - optimize secretion mobilization: • Multi-modal treatment • Quad coughing • Mechanical insufflator-exsufflator - [b]Early hospital-acquired pneumonia - empiric antibiotic treatment depends on most common pathogens for each hospital, ICU and anti-microbial susceptibility patterns of each community • It is recommended to use agents from a different antibiotic class than the patient has recently received	• The same as general population • In these patients, respiratory rehabilitation is especially important due to their condition of respiratory muscle weakness (secretions' clearance therapies, lower and upper active-assisted or passive kinesiotherapy, and relaxation exercises, and a positive expiratory pressure exercises with a Threshold PEP device to optimize the alveolar recruitment) • It is mandatory that Physiotherapists use PPE for self-protection

TABLE 3 Principle infection features in SCIP—cont'd

	UTI	PI	Covid-19
Prevention	• Minimize urinary retention: anti-cholinergic medications or onabotulinum toxin A (Botox) injections for overactive bladders • Change bacterial flora of the bladder: - urine acidification (methenamine hippurate) - bacterial interference • Strengthen the host: - probiotics - proanthocyanidins (cranberry extracts) - immune biotherapy • Reduce biofilm formation: - D-mannose - nanoparticles - to cover the catheter with hydrophilic material - bacteriophages	• [b]Outpatients: - annual Influenza and Pneumococcal polysaccharide vaccines - aggressive mobilization of secretions • [b]Inpatients: - standard precautions - hand washing - gloving and gowning - to perform tracheal and nasopharyngeal respiratory techniques and cares under aseptic conditions - to consider non-invasive positive-pressure ventilation instead of invasive ventilation - to perform orotracheal rather than nasotracheal intubation whenever possible - to clear secretions - to avoid saliva or respiratory secretions microaspiration by raising the head of the bed from 30 to 45 degrees - to perform pre-operative breathing exercises and post-operative incentive spirometry - to remove patients out of bed as soon as possible - to prevent hospital-acquired, ventilator associated, and healthcare-associated pneumonia	• Isolation and hygienic measures, the same as in general population. • Caregivers and health workers need to use PPE for self-protection.

Pathogens, frequency, etiology, diagnosis, treatment, and prevention strategies of the main infections that affect SCIP. *Covid-19*: coronavirus disease 2019; *ICU*: intensive care unit; *PEP*: positive expiratory pressure.; *PI*: pulmonary infections; *PPE*: personal protective equipment; *SARS-CoV-2*: severe acute respiratory syndrome coronavirus 2; *SCIP*: spinal cord-injured patients; *UTI*: urinary tract infections.
[a]*Modified from: Craven, B. C., et al. (2019). Conception and development of urinary tract infection indicators to advance the quality of spinal cord injury rehabilitation: SCI-high project.* Journal of Spinal Cord Medicine, 42*(sup1), 205–214.*
[b]*Modified from: Burns, S. P. (2007). Acute respiratory infections in persons with spinal cord injury.* Physical Medicine and Rehabilitation Clinics of North America, 18*(2), 203–16.*

Diagnosis

First, it is important to provide an early UTI detection. For this purpose, it is necessary to differentiate between asymptomatic bacteriuria and symptomatic UTI. The first one appears when there is a count of 10^2 cfu/mL or higher at the urine sediment, and when any bacteria are detected with the use of IUC. In this situation, the patient shows no symptoms, and it is considered a colonization of the bladder. This situation is different from an UTI because colonization does not need to be treated as it may play a protective role to the bladder flora (Kirshblum et al., 2011; Linsenmeyer, 2018). To make the diagnosis of UTI, the Experts in Urohealth and/or UTI recognition and management and the SCI-High Project Team at Craven et al. (2019), propose the following criteria: bacteriuria should be confirmed with at least one germ in the urine culture, at least one bladder symptom (hematuria, change in urine odor and clarity, new or increased incontinence, pyuria) and at least one general symptom (fever, sepsis, acute autonomic dysreflexia, persistent fatigue, acutely increased spasticity, vomiting, etc.).

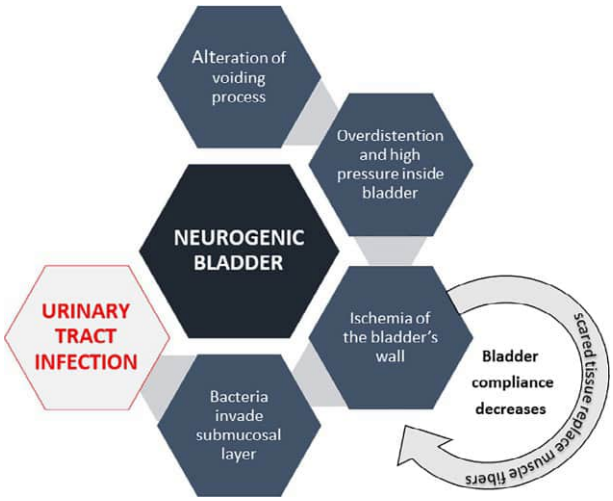

FIG. 1 Physiopathology of urinary tract infections. Step-by-step summary of the sequence of events leading to urinary tract infections (UTI) in SCI neurogenic bladder.

When those symptoms appear, it is necessary to take a urine and a blood culture in order to prescribe an appropriate antibiotic treatment to reduce antibiotic resistance and other associated complications in these patients.

It may be useful to practice a urine sediment because the majority of patients wearing a IUC present leukocyturia (50 leukocytes or more per field). The absence of leukocyturia excludes the diagnosis of UTI. This test has a high negative predictive value. Pyuria is only significant when there is also leukocyturia (Esclarín de Ruz et al., 2009).

If, in spite of an appropriate antibiotic treatment, symptoms persist, it may be necessary to carry out some additional tests such as ultrasound examination, cystoscopy, or kidney scan, to look for a structural cause or a complication being the leading cause of the persistent UTI (hydronephrosis, vesicoureteral reflux, urinary lithiasis, or kidney abscesses).

Blood biomarkers have shown poor evidence in the detection of UTI. Procalcitonin has been described as a biomarker in the diagnosis of UTI and pyelonephritis in pediatric population, but not in adults. IL-6 could help to differentiate between UTI and pyelonephritis, but further validation is needed yet (Skelton-Dudley et al., 2019).

Treatment and prevention

SCIP develop complicated UTI because of the urinary tract dysfunction. Because of this reason, it is necessary to follow a long-term antibiotic treatment from 7 to 14 days. To avoid the increased likelihood of anti-microbial resistance and to reduce the administration of wide spectrum antibiotics, it is necessary to perform a urine culture to select the most appropriate antibiotic treatment (Esclarín de Ruz et al., 2020).

Though some studies advise using prophylactic antibiotics as nitrofurantoin to prevent catheter associated UTI (Chew et al., 2019); the truth is that more consistent evidence is required to make this recommendation in a safe way to compensate the risk of resistances appearance derived from the use of these antibiotics (Skelton-Dudley et al., 2019), because there are some other studies like Morton et al. (2002), which show that using prophylactic antibiotics is worthless as it does not decrease the number of UTI, and even may be harmful, as it reduces asymptomatic bacteriuria while increasing antibiotic resistance.

To prevent recurrent UTI in SCIP it is desirable to improve patients' conditions minimizing urinary retention and optimizing urinary voiding, using anti-cholinergic medications or onabotulinum toxin A (Botox) when they have an overactive bladder. Also, it is important to correct anatomical problems like urethral stricture or bladder calculi (Linsenmeyer, 2018).

There are other prevention strategies for SCIP with recurrent UTI. The most commonly used are: (1) changing the bacterial flora of the bladder with urine acidification; or (2) strengthening the host by administering probiotics, proanthocyanidins such as cranberry extracts or D-mannose (to reduce biofilm formation on the bladder and catheter wall). In the foreseeable future, clinicians will also have nanoparticles capable of inhibiting biofilm formation by *E. coli* and *Staphylococcus aureus*, but this promising strategy is currently in the pre-clinical phase. To cover the catheter with hydrophilic material before its introduction to the bladder delays and decreases the number of UTI in acute SCI (Cardenas et al., 2011) by blocking the biofilm catheter formation. The use of bacteriophages that are responsible for producing a depolymerase

enzyme that breaks the extracellular polysaccharide matrix of the biofilms on urinary catheter, are also useful when the patient has developed antibiotic resistance because, when antibiotic-resistant bacteria become resistant to the phage, in some cases, the bacterial sensitivity to antibiotics is restored. Also, immune biotherapy uses the administration of antigenic components to be recognized as "danger signals" which contribute to activate the innate immune system as a prophylactic method (Linsenmeyer, 2018).

Pulmonary infections (PI)

The 50% of SCIP who suffer acute tetraplegia develop pneumonia during acute hospitalization and rehabilitation (Schilero et al., 2005). PI and respiratory failure are major causes of death in this population (Yong et al., 2012). Review study by Burns (2007) has identified Pneumococcus as the first leading pathogen causing pneumonia in outpatients with SCI, while Pseudomonas is the second one. Conversely, there are no published data on etiologic pathogens that cause pneumonia during acute hospitalization and rehabilitation for these patients. It is assumed that the etiology of a nosocomial pneumonia depends on the type of hospital, ICU, and anti-microbial susceptibility patterns of each community (Díaz, Martín-Loeches, & Vallés, 2013).

Review study by Burns (2007) also shows that in ventilator-dependent patients, more than 90% of patients suffering from pneumonias and requiring hospitalizations have previously developed upper respiratory tract infections.

Physiopathology and etiology

Depending on the level and severity of the SCI, there are different mechanisms that are thought to be involved in causing pneumonia. In complete lesions above C3, the respiratory muscles are paralyzed. In C3–C5 lesions, despite varying degrees of phrenic nerve injury, respiratory neuromuscular activation is preserved but dysfunctional. Lesions below C5 retain some degree of ventilatory function due to intercostal and abdominal muscles, but above all, both diaphragms are preserved. These three situations involve inspiratory and expiratory hypofunction, which leads to dyspnea, decreased vital capacity, ineffective cough and problems with mucociliary clearance (Yong et al., 2012), and also they are more likely to suffer dysphagia disorders, especially due to tracheostomy, rigid fixation and high complete lesions due to the delay of mechanical ventilation weaning (Abel, Ruf, & Spahn, 2004). Apart from that, patients with low thoracic SCI, who retain good muscular respiratory function, may develop neurogenic pulmonary edema due to pulmonary vein constriction, increased pulmonary capillary hydrostatic pressure, alveolar damage and increased capillary permeability due to transient sympathetic discharge, which is underdiagnosed and provides the right environment for developing PI (Yong et al., 2012) (Fig. 2).

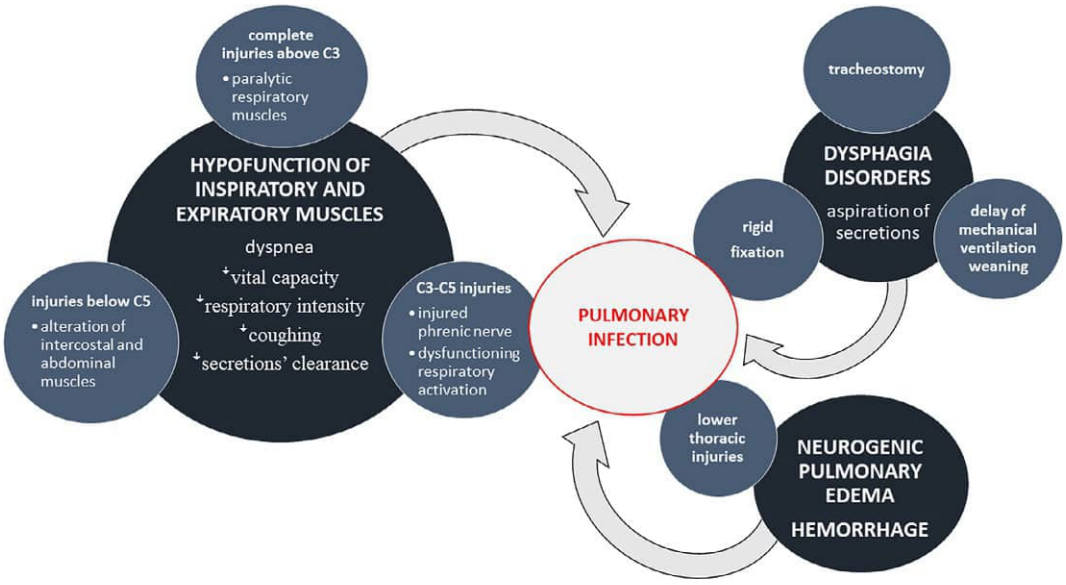

FIG. 2 Physiopathology of pulmonary infections. SCI-induced inspiratory and expiratory muscles hypofunction, dysphagia disorders, and neurogenic pulmonary edema can lead to develop a pulmonary infection in spinal cord-injured patients.

Diagnosis

Fever, respiratory symptoms as dyspnea or secretions, chest X-rays with infiltrates within lungs and alterations in blood gas analysis, and leukocytosis determine a diagnosis of pneumonia. To administrate an appropriate antibiotic treatment, it is necessary to make a culture and a sputum Gram stain.

In cases where a patient is not wearing an artificial airway, it is sufficient to make a sputum culture. A sample of >25 polymorphonuclear leukocytes and <10 epithelial cells per field is considered representative of the lower respiratory tract. In cases where patients are wearing an artificial airway, it is necessary to take a sample by bronchoalveolar lavage or a tracheal aspiration. An infection is diagnosed when there are $>10^4$ cfu/mL in bronchoalveolar lavage sample or $>10^6$ cfu/mL in tracheal aspiration sample (Esclarín de Ruz et al., 2020).

Treatment and prevention

While obtaining a culture, and before administrating a specific antibiotic treatment it is necessary to use a prompt empirical antibiotic treatment for avoiding respiratory infection progression. The choice of empiric antibiotic coverage depends on the most common pathogens for each hospital, ICU and anti-microbial susceptibility patterns of each community.

Burns (2007) recommends the management of community acquired pneumonia to consider empiric anti-pseudomonal coverage. It is also recommended to optimize secretion mobilization by multi-modal treatment, quad coughing or mechanical insufflator-exsufflator. To choose the empiric antibiotic coverage for SCIP with an early hospital-acquired pneumonia, it is recommended to use the same medications used for hospital-acquired pneumonia in patients without SCI, as the etiologic organisms for pneumonia that develop during acute care in SCIP are still undescribed. It is recommended to include agents from a different antibiotic class than the patient has received recently.

To prevent respiratory infections in outpatients with spinal cord injury, Burns (2007) recommends annual Influenza and Pneumococcal polysaccharide vaccines, and aggressive mobilization of secretions. In the case of SCI inpatients, the same author also recommends using the standard precautions (hand washing, use of gloves and gowns), performing the various tracheal and nasopharyngeal respiratory techniques and cares under aseptic conditions, as well as considering non-invasive positive pressure ventilation instead of invasive ventilation, opting for orotracheal instead of nasotracheal intubation whenever possible, clear secretions, avoid saliva or respiratory secretions microaspiration by raising the head of the bed from 30 to 45 degrees, perform pre-operative breathing exercises and post-operative incentive spirometry, and remove patients out of bed as soon as possible, to prevent hospital-acquired, ventilator-associated and healthcare-associated pneumonia.

There are other less frequent but also important infections that can affect SCIP such as pressure ulcer infections, surgery wound infections, intra-abdominal abscesses causing acute abdomen, sepsis… that are not explained here but expert SCI physicians need to know deeply to provide the acutest diagnosis and the best care and treatment to these patients. The latter review of the most frequent infections of SCIP (UTI) and the more severe ones (PI), pretend to help to achieve the greater understanding of the new Covid-19 infection in these patients.

COVID-19 disease: A new infectious normality in spinal cord-injured patients?

As it is well established, SCIP can be quite fragile. When Covid-19 pandemic started, we feared that they would have to face poor evolution and harsh prognosis, because of the presence of immunosuppression and induced autoimmunity, but above all, because of the respiratory muscles' weakness in all those cases with injury levels above T6–T8 (López-Dolado & Gil-Agudo, 2020). In addition, the mortality rate from influenza pneumonia was known to be higher than that of the general population (Soden et al., 2000). However, this grim prognosis does not seem to be confirmed. In fact, it has been reported that SCIP with concomitant Covid-19 infection show mild initial symptoms and better outcomes, even being aged over 60 and/or presenting clinically severe phenotypes (D'Andrea et al., 2020; Rodríguez-Cola et al., 2020), (Table 3). This apparently "indifferent" behavior toward Covid-19 infection has also been described in some autoimmune osteoarthropathies such as rheumatoid arthritis, also in those patients treated with biological disease-modifying anti-rheumatic drugs (bDMARDs) or Janus kinase inhibitors (JAKi) (Stradner et al., 2020). Data regarding Covid-19 and SCI are sparse, and further studies are needed to investigate the course of Covid-19 in SCIP, whether or not they have comorbidities and whether they are acute or chronic, but two simple although important points must be taken into account. First of all, the typical immune response involved in viral infections is sensibly different than in bacterial ones. Viruses are intracellular pathogens while bacteria are extracellular, so the role of CD8s and NK is quite different in both cases (see above). Second, as important as the pathogen in clearing up any infection is the immune system that fights against it, so in this regard, the SCIP cannot be considered as a homogeneous population. Factors such as advanced age, the presence of

comorbidities or long-term SCI chronic stages would negatively influence the immune response and could conditionate different risk levels (Monroe et al., 2019). Finally, with the available data to date, it is not possible to support or reject that Covid-19 infection is less symptomatic or severe in SCIP, since the use of drugs that dampen the local pulmonary inflammatory response is common in this population and the available data mostly come from case reports or at most from case series, valuable work for sure, but with restricted levels of evidence.

Another interesting aspect is the thrombogenic nature of Covid-19 shared by SCI. Using proteomic analysis to look for diagnostic biomarkers of Covid-19 infection in a cohort of SCIP, a specific role of heparin response to Covid-19 infection was found, supported by a significant correlation with proteins implied in coagulation/platelet activation. In this study, SCIP with Covid-19 receive from the moment of diagnosis prophylactic heparin, a common practice with these persons when bedridden is needed to avoid typical thrombotic and embolic complications (Calvo et al., 2020). Interestingly, heparin has demonstrated therapeutic potential against SARS-CoV-2 infection as a competitive inhibitor in general population Covid-19 patients.

It is well established that close to half of the hospitalized Covid-19 patients exhibit neurologic manifestations at the onset of the infection. To the author's knowledge, no study has been found that specifically analyzes this aspect in SCIP, although myalgias, headache, anosmia, and ageusia have frequently been found (Liotta et al., 2020). Sensory and motor deficits, barely been reported in the general population, have not been detected at all in SCIP, which does not mean that they have not appeared, but that we have not been able to detect them. Close observation to the neurofunctional outcome of the Covid-19 SCIP in the near and further future will permit to address this aspect.

The prevalence of Covid-19 infection among acute or chronic SCIP is unknown, but judging by the number of published cases, it seems lower than that of the general population (D'Andrea et al., 2020; López-Dolado & Gil-Agudo, 2020; Rodríguez-Cola e al., 2020). Part of the explanation could lie in the lower number of social contacts experienced by individuals who have reduced mobility and disability, in addition to the hygienic measures usually and constantly taken by their caregivers, which are similar to the measures that protect general population from Covid-19. The risk of transmission for the caregivers is nevertheless, another matter. Because being paucisymptomatic, Covid-19 infection could go unnoticed, turning the SCIP into a reservoir that would substantially increase the risk of contagion their caregivers. Therefore, caregivers and health providers must have access to adequate personal protective equipment (PPE) (Cossarizza et al., 2020). On top of that, both patients and their caregivers have experienced this pandemic, anxiety, loneliness and sadness, emotions that, if not addressed, will have negative impact on the health of all those groups (Taylor et al., 2020). The current pandemic has severely restricted SCIPs' access to health services, either for clinical control and follow-up, or to receive rehabilitative interventions. It is our vocation and obligation to use all the tools at our disposal, like the telemedicine platforms to maintain a safe, economical method of patient care.

Despite the burden of this worldwide disease there is no specific drug available to combat Covid-19. Vaccine efficacy depends largely upon the vaccine target and platform. Generally, the clinical development of a new vaccine requires many years of efforts in this area. However, having the results of previous efforts related to SARS-CoV and MERS vaccine research available, this time it has been possible to develop several vaccines, yet almost ready for their massive use in general population. There are no data to support the preferential vaccination of SCIP if the expressiveness and severity of the Covid-19 infection is taken into account. However, the fact that they can become virus reservoirs, and therefore, a source of transmission, is a compelling reason to recommend its extensive vaccination. Former experiences during previous pandemics, such as H1V1 or influenza, highlighted the need to make every effort not just to get the vaccine but to inform the target population to achieve sufficient vaccination rates. All possible efforts to ensure that accurate and clear information reaches the target SCIP must be done, since it is known that the better the information available on the disease and the vaccine, the higher the vaccination rate (LaVela et al., 2012). The medical community serving SCIP constitutes an exceptional group for quality information on Covid-19 vaccination to permeate (Locatelli et al., 2013). Thus, the current pandemic has shown us that from now on we should include in our health education programs all necessary information to protect SCIP against emerging pathogens and, among them, a better knowledge of available vaccines.

Applications to other areas of neuroscience

In this chapter we have reviewed the implication of the alteration of immune system in spinal cord-injured patients, and how this process leads the different infections that can suffer these patients. We also interlink the role of this immunosuppressed induced condition, with the current SARS-Cov-2 pandemic.

A better understanding about the interaction between the nervous system and the immune system could be reached by comprehending how SARS-Cov-2 virus affects patients with central nervous system diseases, such as in the spinal cord-injured patients, as Covid-19 influences the nervous system functioning and the immunity status as well. Due to its

neurotrophic feature, the deep knowledge of its structure, function, infection mechanism and characteristics, may help to improve the design of the current viral vectors applied at Neuroscience.

It should be an increasingly common requirement at the educational and clinical practice to include the study of the effects on our immune system in order to achieve the acutest and better understanding of every oldest known and new diseases. These diseases develop in a shared territory between neuroscience and immunology, so the deep knowledge of this space "in between" is a challenge, not only for physicians and immunologists, but also for neuroscientists, the spearhead of a successful knowledge in the research of central nervous system diseases and disabilities.

Mini-dictionary of terms

Respiratory syndrome coronavirus 2: Infection disease caused by Coronavirus that originates a severe damage to the lungs that involves a respiratory insufficiency, even in some cases, a breathing failure, requiring artificial ventilation supply.

Immunodepression: State of weakness of the immune system that delays and makes difficult to develop a prompt and active defense response against pathogens that invade human body. It has been demonstrated that spinal cord injury is a systemic disease which precipitates systemic changes that affect the immune system in this way.

Sympathetic nervous system: Part of the autonomic nervous system made up of neurons located from the first thoracic to the first lumbar segments which are presumed to carry out within its multiple functions, to innervate the primary and secondary lymphoid organs and modulate all the immune processes. Any process affecting this sympathetic nervous system, as spinal cord injury, could result in an alteration of the immune response of a patient.

Hypothalamic-pituitary-adrenal axis: Complex hormonal communicating system between the brain and different body glands that participate in different body responses, as the stress responses, energy metabolism, or the modulation of immune responses, as sympathetic nervous system does as well. In addition, adrenal glands, which are part of this axis, are innervated by the sympathetic nervous system. If a patient suffers a spinal cord injury, it will result in an alteration of all those responses by damaging the sympathetic nervous system and by altering this axis as well.

Bloodstream infection: Presence of pathogen organisms in the blood, having come directly from outside or being the spreading of a previously local infection. This is a severe infectious disease that can threat patient's life.

Native bacterial flora: Specific species of bacterial organisms that normally dwell different parts of human body without causing a disease. In fact, the loss of these bacterial organisms could imply the invasion from other pathogens that can lead an infection, so this native bacterial flora usually plays a protective role.

Neurogenic bladder: Dysfunction of the bladder due to a neurological damage that implies an overdistension of the bladder's wall and an increased high pressure inside due to the alteration of its voiding process. Therefore, patient suffers incontinence and urine retention that may need medications and/or medical devices to facilitate and normalize their bladder's voiding.

Recurrent urinary tract infection: Repeated infection of the urinary tract that does not disappear despite adequate anti biotic treatment. In spinal cord-injured patients, it should make consider the presence of a urinary complication as hydronephrosis, vesicoureteral reflux, urinary lithiasis, or kidney abscesses. First, it will be necessary to rule out these disorders to treat the infection successfully, later on.

Biofilm: Adherence of pathogens to the wall of artificial products that are in direct contact to body tissues, such as medical devices, that are able to produce a protective layer that make them resistant to standard antibiotic treatments. When it appears in a catheter and it remains unnoticed, the catheter biofilm becomes a leading cause of recurrent urinary tract infection and appearance of resistant bacterial pathogens.

Dysphagia disorders: Alteration of the deglutition process that implies the risk of passing food through airway by the larynx. It is a leading cause of pneumonia, which is considered to be the severest infection in spinal cord-injured patients because it can threat their life.

Neurogenic pulmonary edema: Fluid invasion of the alveolar spaces from the lungs due to an inflammatory cascade which is thought to be the result of the immune system's damage suffered in severe neurological injured patients. The resulting pulmonary edema could behave as an adequate environment for developing a pulmonary infection in these patients.

Telemedicine and telerehabilitation: Way of supplying a medical attention, or medical, and/or rehabilitation treatment that replace the classic patient's physical attendance at the place of the doctor visit, by a telephone or video consultation, which avoids patients' movements from home or familiar environment. It provides an effective source of access to medical healthcare to chronically affected patients as spinal cord-injured patients, who may find impairments to achieve transportations, especially during pandemic restriction period.

Key facts of "infections and spinal cord injury: Covid-19 and beyond"

Key facts of "immunosuppression due to spinal cord injury"

- Spinal cord injury is a systemic disease.
- Spinal cord injury induces an alteration of the immune system.
- This alteration of the immune system leads patients to suffer from infections.
- The better understanding of the modifications produced by the alteration of the immune system enables physicians and scientists to be able to appreciate the clinical presentations of these diseases, and patient's responses to treatments, as well.

Key facts of "Leading infection diseases in spinal cord-injured patients"

- Infection is one of the leading complications of spinal cord-injured patients because this disease can threat their life.
- Urinary tract infections are the most frequent cause of infection in these patients because they present a neurogenic bladder and they usually need to use medical devices to facilitate their bladder's voiding.
- Its acute diagnosis will be of great importance to establish a long-term and appropriate antibiotic treatment to avoid antimicrobial resistances and further complications.
- Pulmonary infections are the most severe cause of infection in these patients because they can lead to a respiratory insufficiency and breathing failure that can strongly threat patients' life.
- While waiting for etiologic organisms' results and before starting an adequate antibiotic treatment guided by those results, with the only clinical suspicion, physicians need to start an empirical antibiotic treatment, to avoid the progression of the infection.

Key facts of "Covid-19 disease"

- Most of the published studies show a tendency of milder initial symptoms and a less severe evolution of the Covid-19 disease in spinal cord-injured patients, but currently further validation is needed to support or reject that Covid-19 infection is less symptomatic or severe in this population.
- Covid-19 disease has shown a thrombogenic nature in spinal cord-injured patients that must be treated with heparins.
- In spite of coronavirus' neurotropism, it has not been detected a sensory or motor deterioration in spinal cord-injured patients due to Covid-19 disease yet; but close observation to the neurofunctional outcomes should be done to ensure this affirmation.
- As Covid-19 disease could go unnoticed, turning the spinal cord-injured patients into a reservoir that could increase the contagion of their caregivers, medical community serving these patients should do every possible effort to provide appropriate healthcare educational programs with all the information needed to protect them from emerging pathogens that include the better knowledge of the available vaccines.
- Telemedicine has demonstrated to be a useful and effective tool to provide access to medical healthcare to chronically affected patients as spinal cord-injured patients, especially during this pandemic restriction period.

Summary points

- Spinal cord injury induces not only a loss of mobility and sensibility, but also numerous chronic disorders.
- Spinal cord-injured patients suffer a dysregulation of the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis, which causes an alteration of all their immune processes.
- The combination of this situation with other locally impaired conditions provides a suitable environment for developing an infection.
- Urinary tract infections are the most frequent infections in these patients, because of the presence of a neurogenic bladder and the use of catheters to facilitate its voiding.
- Pulmonary infections are the severest ones, because of the respiratory muscle weakness, dysphagia disorders, pulmonary edema, and the use of ventilators to assist with breathing.
- The deep understanding of the physiopathology of these infections should help us to understand its appropriate diagnosis, treatment, and methods of prevention.

- The pandemic Covid-19, which is deadly hitting our general population, seems to show a tendency of milder initial symptoms and a less severe evolution in spinal cord-injured patients, but currently further validation is needed to support or reject it.
- The altered immune response could play a critical role in the clinical presentation of these patients.
- Telemedicine has demonstrated to be a useful and effective tool to provide access to medical healthcare to these chronically affected patients, especially during this pandemic restriction period.

References

Abel, R., Ruf, S., & Spahn, B. (2004). Cervical spinal cord injury and deglutition disorders. *Dysphagia*, *19*(2), 87–94.

Alaniz, R. C., et al. (1999). Dopamine β-hydroxylase deficiency impairs cellular immunity. *Proceedings of the National Academy of Sciences of the United States of America*, *96*(5), 2274–2278.

Bracchi-Ricard, V., et al. (2016). Chronic spinal cord injury attenuates influenza virus-specific antiviral immunity. *Journal of Neuroinflammation*, *13*(1), 1–13.

Brommer, B., et al. (2016). Spinal cord injury-induced immune deficiency syndrome enhances infection susceptibility dependent on lesion level. *Brain*, *139*(3), 692–707.

Burns, S. P. (2007). Acute respiratory infections in persons with spinal cord injury. *Physical Medicine and Rehabilitation Clinics of North America*, *18*(2), 203–216.

Calvo, E., et al. (2020). Why does COVID-19 affect patients with spinal cord injury milder? A case-control study: Results from two observational cohorts. *Journal of Perinatal Medicine*, *10*(4), E182.

Cardenas, D. D., et al. (2011). Intermittent catheterization with a hydrophilic-coated catheter delays urinary tract infections in acute spinal cord injury: A prospective, randomized, multicenter trial. *PM & R : The Journal of Injury, Function, and Rehabilitation*, *3*(5), 408–417.

Chew, A. B., et al. (2019). Long-term prescribing of nitrofurantoin for urinary tract infections (UTI) in veterans with spinal cord injury (SCI). *The Journal of Spinal Cord Medicine*, *42*(4), 485–493.

Cossarizza, A., et al. (2020). Handling and processing of blood specimens from patients with COVID-19 for safe studies on cell phenotype and cytokine storm. *Cytometry. Part A: The Journal of the International Society for Analytical Cytology*, *97*(7), 668–673.

Craven, B. C., et al. (2019). Conception and development of urinary tract infection indicators to advance the quality of spinal cord injury rehabilitation: SCI-high project. *The Journal of Spinal Cord Medicine*, *42*(sup1), 205–214.

D'Andrea, S., et al. (2020). Clinical features and prognosis of COVID-19 in people with spinal cord injury: A case–control study. *Spinal Cord Series And Cases*, *6*(1), 69.

Dale, H. H., & Feldberg, W. (1934). The chemical transmission of secretory impulses to the sweat glands of the cat. *The Journal of Physiology*, *82*(1), 121–128.

Davies, A. O., & Lefkowitz, R. J. (1981). Agonist-promoted high affinity state of the β-adrenergic receptor in human neutrophils: Modulation by corticosteroids. *Journal of Clinical Endocrinology and Metabolism*, *53*(4), 703–708.

Dénes, Á., et al. (2005). Central autonomic control of the bone marrow: Multisynaptic tract tracing by recombinant pseudorabies virus. *Neuroscience*, *134*(3), 947–963.

Díaz, E., Martín-Loeches, I., & Vallés, J. (2013). Neumonía nosocomial [Nosocomial pneumonia]. *Enfermedades Infecciosas y Microbiología Clínica*, *31*(10), 692–698.

Elenkov, I. J., Wilder, R. L., Chrousos, G. P., & Vizi, E. S. (2000). The sympathetic nerve—An integrative interface between two supersystems: The brain and the immune system. *Pharmacological Reviews*, *52*(4), 595–638.

Esclarín de Ruz, A., et al. (2009). *Lesión medular. Enfoque multidisciplinario* (1st ed.). Spain: Panamericana (Chapter 18).

Esclarín de Ruz, A., et al. (2020). *Lesión medular. Enfoque multidisciplinario* (2nd ed.). Spain: Panamericana (Chapter 20).

Espinosa-Medina, I., et al. (2016). The sacral autonomic outflow is sympathetic. *Science*, *354*(6314), 893–897.

Guan, W. J., et al. (2020). China medical treatment expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. *The New England Journal of Medicine*, *382*(18), 1708–1720.

Guereschi, M. G., et al. (2013). Beta2-adrenergic receptor signaling in CD4+ Foxp3+ regulatory T cells enhances their suppressive function in a PKA-dependent manner. *European Journal of Immunology*, *43*(4), 1001–1012.

Held, K. S., Steward, O., Blanc, C., & Lane, T. E. (2010). Impaired immune responses following spinal cord injury lead to reduced ability to control viral infection. *Experimental Neurology*, *226*(1), 242–253.

Herman, P., et al. (2018). Persons with chronic spinal cord injury have decreased natural killer cell and increased toll-like receptor/inflammatory gene expression. *Journal of Neurotrauma*, *35*(15), 1819–1829.

Hosseiny, M., et al. (2020). Radiology perspective of coronavirus disease 2019 (COVID-19): Lessons from severe acute respiratory syndrome and Middle East respiratory syndrome. *AJR. American Journal of Roentgenology*, *214*(5), 1078–1082.

Huang, C., et al. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet (London, England)*, *395*(10223), 497–506.

Iversen, P. O., et al. (2000). Depressed immunity and impaired proliferation of hematopoietic progenitor cells in patients with complete spinal cord injury. *Blood*, *96*(6), 2081–2083.

Johns Hopkins Coronavirus Resource Center. (2020). *Coronavirus COVID-19 Global Cases by the Center for Systems*. Science and Engineering (CSSE) at Johns Hopkins University (JHU). https://www.arcgis.com/apps/opsdashboard/index. html#/bda7594740fd40299423467b48e9ecf6. Accessed the 7th of February, 2021).

Jung, W. C., et al. (2017). It takes nerve to fight back: The significance of neural innervation of the bone marrow and spleen for immune function. *Seminars in Cell and Developmental Biology*, *61*, 60–70.

Kavelaars, A. (2002). Regulated expression of α-1 adrenergic receptors in the immune system. *Brain, Behavior, and Immunity*, *16*(6), 799–807.

Kinnear, N., et al. (2020). The impact of catheter-based bladder drainage method on urinary tract infection risk in spinal cord injury and neurogenic bladder: A systematic review. *Neurourology and Urodynamics*, *39*(2), 854–862.

Kirshblum, S., et al. (2011). *Spinal cord medicine* (2nd ed.). Philadelphia, PA: Lippicott Williams & Wilikins (Chapter 13).

Kohm, A. P., & Sanders, V. M. (2001). Norepinephrine and β2-adrenergic receptor stimulation regulate CD4+ T and B lymphocyte function in vitro and in vivo. *Pharmacological Reviews*, *53*(4), 487–525.

Kopp, M., et al. (2017). Long-term functional outcome in patients with acquired infections after acute spinal cord injury. *Neurology*, *88*(9), 892–900.

LaVela, S. L., et al. (2012). Factors associated with H1N1 influenza vaccine receipt in a high-risk population during the 2009-2010 H1N1 influenza pandemic. *Topics in spinal cord injury rehabilitation*, *18*(4), 306–314.

Linsenmeyer, T. A. (2018). Catheter-associated urinary tract infections in persons with neurogenic bladders. *The Journal of Spinal Cord Medicine*, *41*(2), 132–141.

Liotta, E. M., et al. (2020). Frequent neurologic manifestations and encephalopathy-associated morbidity in Covid-19 patients. *Annals of Clinical Translational Neurology*, *7*(11), 2221–2230.

Locatelli, S. M., et al. (2013). Influenza infection control guidance provided to staff at veterans affairs facilities for veterans with spinal cord injury during a pandemic. *The Journal of Spinal Cord Medicine*, *36*(6), 666–671.

López-Dolado, E., & Gil-Agudo, A. (2020). Lessons learned from the coronavirus disease 2019 (Covid-19) outbreak in a monographic center for spinal cord injury. *Spinal Cord*, *58*(5), 517–519.

Lucin, K., et al. (2007). Impaired antibody synthesis after spinal cord injury is level dependent and is due to sympathetic nervous system dysregulation. *Experimental Neurology*, *207*(1), 75–84.

Lucin, K. M., et al. (2009). Stress hormones collaborate to induce lymphocyte apoptosis after high level spinal cord injury. *Journal of Neurochemistry*, *110*(5), 1409–1421.

Mak, J. C. W., et al. (1995). Protective effects of a glucocorticoid on downregulation of pulmonary β2-adrenergic receptors in vivo. *Journal of Clinical Investigation*, *96*, 99–106.

Mehta, P., et al. (2020). COVID-19: Consider cytokine storm syndromes and immunosuppression. *Lancet*, *395*(10229), 1033–1034.

Meltzer, J. C., et al. (2004). Stress-induced suppression of in vivo splenic cytokine production in the rat by neural and hormonal mechanisms. *Brain, Behavior, and Immunity*, *18*(3), 262–273.

Monroe, D., et al. (2019). Clinical associations with telomere length in chronic spinal cord injury. *Spinal Cord*, *57*(12), 1084–1093.

Morton, S. C., et al. (2002). Antimicrobial prophylaxis for urinary tract infections in persons with spinal cord dysfunction. *Archives of Physical Medicine and Rehabilitation*, *83*(1), 129–138.

Nance, D. M., & MacNeil, B. (2001). *Immunoregulation by the sympathetic nervous system*. Elsevier.

Nance, D. M., & Sanders, V. M. (2007). Autonomic innervation and regulation of the immune system (1987-2007). *Brain, Behavior, and Immunity*, *21*(6), 736–745.

Noble, B. T., Brennan, F. H., & Popovich, P. G. (2018). The spleen as a neuroimmune interface after spinal cord injury. *Journal of Neuroimmunology*, *321*, 1–11.

Oropallo, M. A., et al. (2012). Chronic spinal cord injury impairs primary antibody responses but spares existing humoral immunity in mice. *Journal of Immunology (Baltimore, Md.: 1950)*, *188*(11), 5257–5266.

Pavlov, V. A., & Tracey, K. J. (2017). Neural regulation of immunity: Molecular mechanisms and clinical translation. *Nature Neuroscience*, *20*(2), 156–166.

Prass, K., et al. (2003). Stroke-induced immunodeficiency promotes spontaneous bacterial infections and is mediated by sympathetic activation reversal by Poststroke T helper cell type 1–like Immunostimulation. *The Journal of Experimental Medicine*, *198*(5), 725–736.

Ramos-Casals, M., et al. (2014). Adult haemophagocytic syndrome. *Lancet*, *383*(9927), 1503–1516.

Rangarajan, P. N., Umesono, K., & Evans, R. M. (1992). Modulation of glucocorticoid receptor function by protein kinase a. *Molecular Endocrinology*, *6*(9), 1451–1457.

Ritchie, A. I., & Singanayagam, A. (2020). Immunosuppression for hyperinflammation in COVID-19: A double-edged sword? *Lancet*, *395*(10230), 1111.

Rodríguez-Cola, M., et al. (2020). Clinical features of coronavirus disease 2019 (COVID-19) in a cohort of patients with disability due to spinal cord injury. *Spinal Cord Series and Cases*, *6*(1), 39. https://doi.org/10.1038/s41394-020-0288-3.

Ruan, Q., et al. (2020). Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Medicine*, *46*(5), 846–848.

Schilero, G., et al. (2005). Assessment of airway caliber and bronchodilator responsiveness in subjects with spinal cord injury. *Chest*, *127*(1), 149–155.

Skelton-Dudley, F., et al. (2019). Spinal cord injury creates unique challenges in diagnosis and Management of Catheter-Associated Urinary Tract Infection. *Topics in spinal cord injury rehabilitation*, *25*(4), 331–339. fall.

Soden, R. J., et al. (2000). Causes of death after spinal cord injury. *Spinal Cord*, *38*(10), 604–610.

Stradner, M. H., et al. (2020). Rheumatic musculoskeletal diseases and COVID-19 a review of the first 6 months of the pandemic. *Frontiers in Medicine*, *7*, 562142.

Taylor, S., et al. (2020). Fear and avoidance of healthcare workers: An important, under-recognized form of stigmatization during the COVID-19 pandemic. *Journal of Anxiety Disorders*, *75*, 102289.

Thietje, R., et al. (2011). Mortality in patients with traumatic spinal cord injury: Descriptive analysis of 62 deceased subjects. *The Journal of Spinal Cord Medicine*, *34*(5), 482–487.

Trotter, R. N., et al. (2007). Transneuronal mapping of the CNS network controlling sympathetic outflow to the rat thymus. *Autonomic Neuroscience : Basic & Clinical*, *131*(1–2), 9–20.

Ueno, M., et al. (2016). Silencing spinal interneurons inhibits immune suppressive autonomic reflexes caused by spinal cord injury. *Nature Neuroscience*, *19*(6), 784–787.

Weaver, L. C., et al. (2002). Central mechanisms for autonomic dysreflexia after spinal cord injury. *Progress in Brain Research*, *137*, 83–95.

Yong, T., et al. (2012). Pulmonary edema and hemorrhage, possible causes of pulmonary infection and respiratory failure in the early stage of lower spinal cord injury. *Medical Hypotheses*, *79*(3), 299–301.

Zha, J., et al. (2014). Chronic thoracic spinal cord injury impairs CD8+ T-cell function by up-regulating programmed cell death-1 expression. *Journal of Neuroinflammation*, *11*, 65.

Zhang, Y., et al. (2013). Autonomic Dysreflexia causes chronic immune suppression after spinal cord injury. *Journal of Neuroscience*, *33*(32), 12970–12981.

Zhou, F., et al. (2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. *Lancet*, *395*(10229), 1054–1062.

Zhu, N., et al. (2020). China novel coronavirus investigating and research team. A novel coronavirus from patients with pneumonia in China, 2019. *The New England Journal of Medicine*, *382*(8), 727–733.

Zu, Z. Y., et al. (2020). Coronavirus disease 2019 (COVID-19): A perspective from China. *Radiology*, *296*(2), E15–E25.

Chapter 12

Sleep problems in spinal cord injury

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List of abbreviations

AASM	American association of sleep medicine
AHI	apnea hypopnea index
AQOL	assessment of quality of life
BMI	body mass index
COSAQ	randomized controlled trial of CPAP for OSA in Quadriplegia
CPAP	continuous positive airway pressure
CSA	central sleep apnea
EEG	electroencephalogram
EMG	electromyogram
EOG	electrooculogram
OSA	obstructive sleep apnea
PASAT	paced auditory serial addition task
P_{CRIT}	critical closing pressure of the upper airway during sleep
PLM	periodic leg movement
PLMD	periodic leg movement disorder
RHT	retinohypothalamic tract
RLS	restless leg syndrome
SCI	spinal cord injury
SCN	suprachiasmatic nuclei
SDB	sleep-disordered breathing
3T MRI	3-Tesla magnetic resonance imaging

Introduction

Spinal cord injury (SCI) is a significant global cause of mortality and morbidity. In 2007, the global incidence was estimated to be 23 cases per million per annum, ranging from 15 cases per million in Australia to 29 cases per million in sub-Saharan Africa (Lee, Cripps, Fitzharris, & Wing, 2014).

Most people with SCI sustain their injuries in their second or third decade of life. Because of improvements in both the acute management and long-term supportive care, their life expectancy after injury has increased significantly. As such, secondary diseases and impairments that are a direct consequence of the SCI have significant impacts for many years. Sleep disorders, especially sleep-disordered breathing (SDB), periodic and/or restless leg syndromes (PLM/RLS), and circadian rhythm disorders, are all prevalent disorders after SCI. This chapter focuses on these particular sleep disorders because while insomnia, generalized fatigue, and other sleep-associated disorders affect people living with SCI just as the general population, the increased prevalence and altered pathogenicity due to the spinal lesion per se of SDB, PLMs, and circadian rhythm disorders after SCI deserves special consideration (Sankari, Badr, Martin, Ayas, & Berlowitz, 2019). Population prevalence, known physiological differences in causation, response to therapies, and longer-term consequences of sleep disorders in these sleep disorders after SCI are discussed.

Diagnosis and Treatment of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822498-4.00012-9

Sleep-disordered breathing

Sleep-disordered breathing is an umbrella term that includes obstructive sleep apnea (OSA), central sleep apnea (CSA), and sleep-related hypoventilation. OSA is repeated partial (narrowing/hypopnea) or complete (occlusion/apnea) closure and interruption to ventilation at the level of the upper airway during sleep. The drive to breath is generally maintained during OSA, whereas CSA is characterized by periods of diminished or absent ventilatory drive with associated reductions in ventilation. Both OSA and CSA result in periodic oxygen desaturation and fragmentation of sleep typically resulting excessive daytime sleepiness. Hypoventilation refers to periods during which arterial carbon dioxide homeostasis is not maintained because minute ventilation inadequately matches metabolism. The consequence of hypoventilation is a raised arterial carbon dioxide. All three disorders may exist separately or together in the same person and to various degrees over, and indeed within, sleep periods (Guilleminault, Tilkian, & Dement, 1976). The most common risk factors for OSA in the general population are being male and having a raised body mass index (BMI).

There is very little published research into respiratory sleep disorders in paraplegia. While little data reduces our ability to be certain, it is believed that the pathophysiology, risk factors and prevalence of respiratory sleep disorders in those living with paraplegia is not substantially different to the general population. Conversely, tetraplegia has been studied extensively. Despite substantial overall respiratory muscle weakness, (Berlowitz & Tamplin, 2013) tetraplegia is not routinely associated with hypoventilation, but rather with OSA (Berlowitz et al., 2019). The upper airway muscles derive motor innervation from the cranial nerves, predominantly the hypoglossal, rather than from the spinal segmental nerves. Hence, an injury that disrupts, for example, C6 should not have any effect on the genioglossus. Yet while OSA is highly prevalent (Fig. 1), hypoventilation appears rare at a population level. In a recent large, multi-center randomized controlled trial of continuous positive airway pressure (CPAP) for SDB in acute tetraplegia (Berlowitz et al., 2013), only eight of the 212 otherwise eligible participants (3.8%) were excluded due to hypoventilation ($PaCO_2 > 45$ mmHg) (Berlowitz et al., 2019). Hypoventilation has been reported, particularly at sleep onset in physiological studies (Bascom, Sankari, Goshgarian, & Badr, 2015) and in association with a reduced ventilatory reserve for carbon dioxide

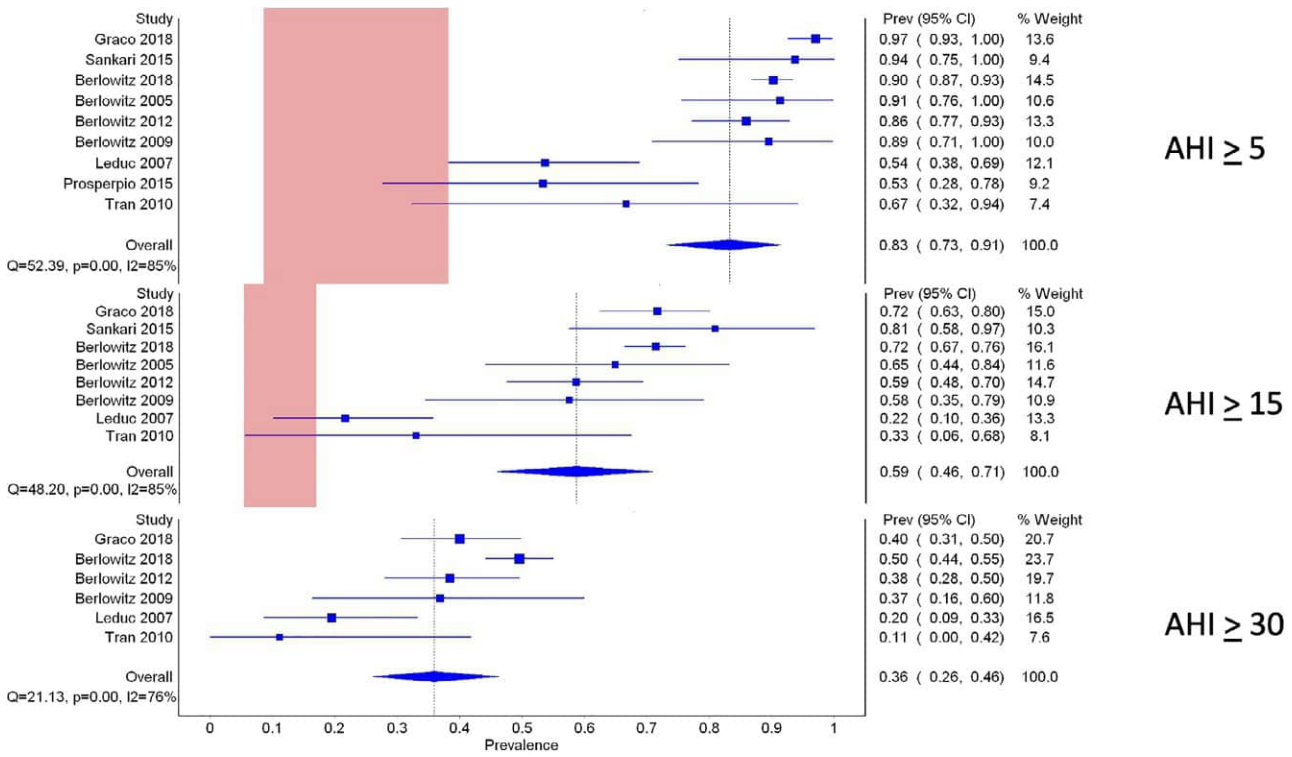

FIG. 1 Prevalence estimates and their relationships to general population data for mild, moderate, and severe sleep-disordered breathing in tetraplegia. Forest plots of individual study data, pooled estimates of prevalence in studies of people with tetraplegia, and ranges of general population estimates at mild (AHI > 5), moderate (AHI > 15), and severe (AHI > 30) levels of SDB severity (Graco, McDonald, Green, Jackson, & Berlowitz, 2021). These graphs illustrate the substantially higher prevalence of sleep-disordered breathing in tetraplegia across all ranges of severity. Solid bands across the mild and moderate data ranges are general population estimates ranges (Senaratna et al., 2017). *AHI* = apnea hypopnea index (measured in events per hour).

(Sankari, Bascom, Chowdhuri, & Badr, 2014), but there is little evidence for increased hypoventilation prevalence across all those living with tetraplegia. Clinically however, if a raised carbon dioxide is detected in a particular patient, this relatively rare sign demands immediate clinical attention.

Prevalence of sleep-disordered breathing after tetraplegia

The prevalence of disordered breathing during sleep is estimated to be between 9% and 38%, and increases with age (Senaratna et al., 2017). In previous cross-sectional population studies of sleep disorders in patients with tetraplegia, the prevalence of SDB has been estimated to be between 27% and 97% (Giannoccaro et al., 2013; Graco et al., 2018). However, a recent meta-analysis of the published population estimates in tetraplegia presented the pooled estimates at various cut-off severities (Graco et al., 2021). Twelve articles across 20 years were included, nine of which presented data amenable to meta-analysis (combined $n = 630$). The reported SDB prevalence rates from the 12 studies ranged from 46% to 97%. Following meta-analysis the mean prevalence of at least mild (apnea hypopnea index AHI $\geq$ 5 events per hour), moderate (AHI $\geq$ 15), and severe (AHI $\geq$ 30) SDB were 83% (95% CI = 73–91), 59% (46–71), and 36% (26–46), respectively. As illustrated in Fig. 1, the prevalence of SDB after cervical SCI is clearly elevated at all levels of severity compared with general population estimates (Senaratna et al., 2017).

Sleep-disordered breathing is an acute and direct consequence of cervical SCI

As noted above, the upper airway is innervated directly from the brain via the cranial nerves, not by the spinal segmental nerves. Notwithstanding this, an acute cervical spinal cord injury appears to directly compromise upper airway patency during sleep within weeks of the injurious event. Berlowitz et al. studied all patients presenting to the specialized SCI unit in Melbourne, Australia, over an 18-month period and undertook full, bedside polysomnography to determine when SDB appeared after injury (Berlowitz, Brown, Campbell, & Pierce, 2005). As illustrated in Fig. 2, approximately 10% of the cohorts were at increased risk of the SDB prior to injury as estimated by a prediction algorithm that incorporates signs and symptoms. Within 2 weeks of injury, the measured prevalence of clinically important disease had increased to 60% and peaked at over 80% 3 months after initial injury. Most people with SDB have an insidious onset of the disorder over a number of years as they age and gain weight. In contrast, tetraplegia appears to be the only model of acute SDB in humans. As such, the pathophysiology in acute tetraplegia is likely different from the general population and is not yet fully understood (Sankari et al., 2019).

Sleep-disordered breathing after tetraplegia has clinically important impacts

Alongside the cardinal SDB signs of nightly intermittent hypoxia, repeated arousals from sleep, and excessive daytime sleepiness, SDB is also associated with increased cardiovascular risk and clinically important degrees of neurocognitive dysfunction. In the general population, numerous reviews have described the deleterious impact of SDB on neuropsychological functioning and demonstrated impairment in the domains of attention, information processing, executive function, memory, and learning (Bucks, Olaithe, & Eastwood, 2013). While SDB in the general population is associated with

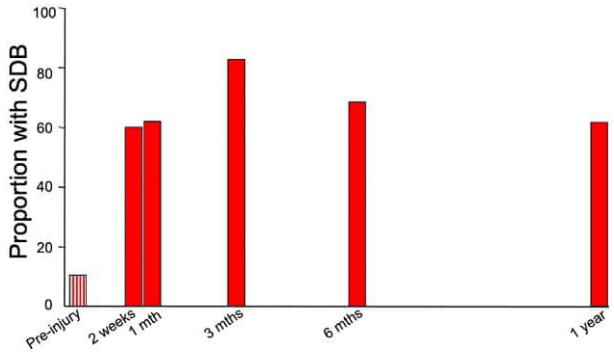

FIG. 2 Proportion of those with sleep-disordered breathing in a prospective, acute cohort study. Solid bar graphs refer to the proportion of the cohort with SDB at each assessment. The pre-injury proportion with an AHI score greater than 10 (vertical striped bar) was estimated using a prediction algorithm that incorporates, age, sex, body mass index and (participant recalled) symptoms to give a likelihood of an AHI > 10 (Berlowitz, Brown, Campbell and Pierce, 2005). *SDB* = sleep-disordered breathing as defined by a respiratory disturbance index (RDI) > 10 events per hour.

hypertension, altered diurnal blood pressure patterns and heart rate variability (HRV), these relationships are not as uniformly observed in those with tetraplegia and SDB. Goh and colleagues demonstrated that tetraplegia is associated with relative nocturnal hypertension and "reverse dipping" or a loss of the usual reduction in blood pressure overnight (Goh et al., 2018). In contrast, Sankari et al. have demonstrated that those with tetraplegia and SDB are also more likely to have diagnosed hypertension and cardiovascular disease (Sankari, Martin, & Badr, 2015). However, Fang et al. were unable to show any difference in the 24-h, night-time, and daytime blood pressure patterns in those with tetraplegia and mild, moderate, severe or no SDB (Fang, Goh, O'callaghan, & Berlowitz, 2018).

SDB has been associated with worse quality of life in tetraplegia. A study investigating the relationships between quality of life and sleep disorders in chronic tetraplegia measured both health-related quality of life (Assessment of Quality of Life) and SDB severity with a full, portable home-based sleep study (Berlowitz, Spong, Gordon, Howard, & Brown, 2012; Spong, Graco, Brown, Schembri, & Berlowitz, 2015). As illustrated in Fig. 3, quality of life and health utility scores were worse in the group with complete lesions compared with incomplete lesions. This single co-morbidity reduces health-utility by an approximately five times the minimally clinically important difference. As such, any effective treatment is likely to have an important impact on those living with both tetraplegia and SDB.

In patients living with chronic SCI, Sajkov et al. (1998) published neuropsychological evaluation data that were performed concurrently with a diagnostic sleep study in 40 people who had been living with tetraplegia for many years (McEvoy et al., 1995). The neuropsychological functions most affected were verbal attention and concentration, immediate and short-term memory, cognitive flexibility, internal scanning and working memory. These impairments are similar to those observed in the able bodied with OSA, which suggested that even if the pathogenesis of SDB is different immediately after SCI, the cognitive consequences of living with SDB for decades appear similar.

As noted earlier, our group recently completed a large, multi-center randomized controlled trial of CPAP for SDB in acute tetraplegia (Berlowitz et al., 2013; Berlowitz et al., 2019). Baseline data from that study was utilized to investigate the relationship between apnea severity and neuropsychological function in patients with acute-onset tetraplegia and SDB dysfunction (Schembri, Spong, Graco, Berlowitz, & Team, 2017). Study enrolment analyses showed more severe sleep apnea was significantly associated with poorer attention, information processing, and immediate recall. Higher pre-injury intelligence and being younger reduced the associations with sleep-disordered breathing; however, these protective factors were insufficient to counter the damage to attention, immediate recall, and information processing associated with the sleep-disordered breathing. As illustrated in Table 1, these deficits in attention and information processing, as measured by the PASAT, were clinically important, being well within the range of values reported in moderate to severe isolated head

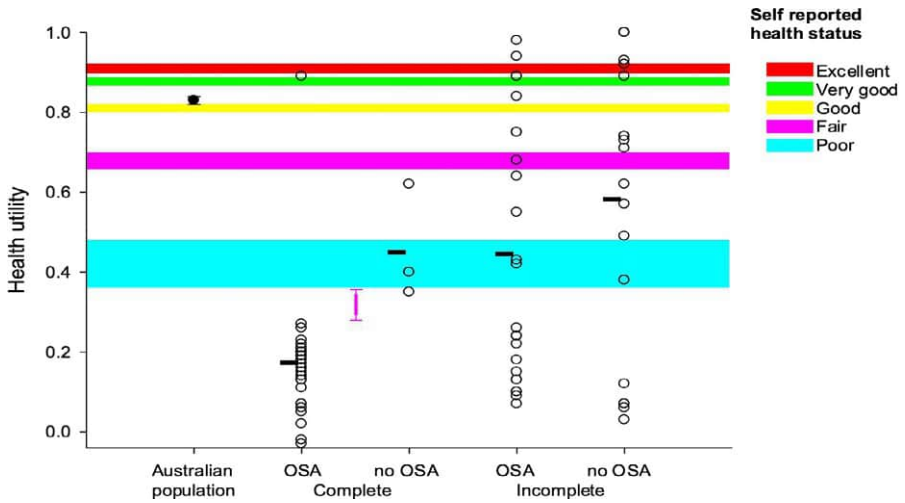

FIG. 3 Tetraplegia severity and obstructive sleep apnea independently modify health status. Colored bands represent the Australian population averages for categories of self-reported health status. Health utility ranges from one (self-rated "perfect health"), through zero (self-rated health state equivalent to death), and down to a health status of −0.04 (self-reported health status that is perceived to be "worse than death"). The Australian population average (95% confidence interval) score is located between "good" and "very good" (Hawthorne & Osbourne, 2005). The pink vertical bar represents the minimal clinically important difference in health status (0.06) and the associated confidence interval of this difference. People with tetraplegia are categorized by the presence or not of sleep apnea and of motor and sensory complete spinal injury (ASIA impairment scale A vs B, C, or D). Open circles represent individual participant scores, and the horizontal bars represent group mean values (Berlowitz et al., 2012). *OSA* = obstructive sleep apnea as defined by an apnea hypopnea index (AHI) > 10 events per hour.

TABLE 1 Attention and Information processing performance as measured by the PASAT performance in acute tetraplegia compared with other patient groups.

Group	PASAT score mean or range of reported means
Healthy controls	56–74
Chronic fatigue syndrome	62
Multiple Sclerosis	45–54
Mild traumatic brain injury	39–57
Moderate to severe traumatic brain injury	19–51
Mild-moderate SDB in acute tetraplegia	*48*
Severe SDB in acute tetraplegia	*33*
Overall baseline COSAQ	*41*
Overall end study COSAQ	*49*

Scores are represented as the percentage of correct responses, and thus higher percentages indicate better performance. Data in italics for SDB in acute tetraplegia are taken from the CPAP for OSA in Quadriplegia (COSAQ) trial (Berlowitz et al., 2013; Berlowitz et al., 2019; Schembri et al., 2017). Comparison values are from a review of the range of values for the PASAT across a number of research study samples (Tombaugh, 2006).

injury (Tombaugh, 2006). Attention and information processing as measured on the PASAT naturally decline as we age, but the reduction seen in those with severe SDB compared with milder SDB was equivalent to an additional 31 years of ageing.

Why do people with tetraplegia have sleep-disordered breathing, predominantly obstructive sleep apnea?

It is apparent that SDB in SCI is not simply due to peri-accident neuroanatomical compromise; however, the exact etiology remains unknown. Obesity, as measured by increased weight, body mass index (BMI), waist, abdominal, and neck girth, is associated with OSA in both SCI and the general population (Berlowitz et al., 2012; Graco et al., 2021). Obesity results in upper airway narrowing in both lateral pharyngeal tissues and the tongue in the general population, as well as those with SCI (Kim et al., 2014; O'donoghue et al., 2018). Truncal obesity reduces lung volume and distal tethering of the trachea which in turn leads to decreased upper airway caliber during sleep (Owens, Malhotra, Eckert, White, & Jordan, 2009). In chronic SCI, several authors have observed associations between OSA prevalence and increasing age, BMI and neck circumference, (Berlowitz et al., 2012; Burns, Kapur, Yin, & Buhrer, 2001; McEvoy et al., 1995; Stockhammer et al., 2002) but these relationships appear weaker in the immediate period after injury (Berlowitz et al., 2005).

Many people living with SCI are prescribed medications (sedatives, muscle relaxants, and narcotics) that can affect breathing, especially during sleep. Loud snoring (a typical OSA sign) has been associated with the use of anti-spasticity medications and obesity in SCI in one cross-sectional study (Ayas et al., 2001). There have been no controlled studies in SCI of the effect of medication provision or withdrawal on SDB severity; however, a smaller proportion of those in the intervention (CPAP treatment for SDB) arm of the COSAQ study were prescribed baclofen at end-study (Berlowitz et al., 2019), and a non-significant reduction in baclofen prescription rates was observed in those whose SDB improved over time in another cohort trial (Berlowitz et al., 2005).

People with tetraplegia and those with lesions above T6, also develop increased nasal and total upper airway resistance due to increased parasympathetic tone. This increased nasal resistance may contribute to upper airway narrowing by increasing negative (collapsing) pressure in the upper airway during inspiration (Gainche et al., 2016; Wijesuriya et al., 2019). While this increased upper airway resistance can be acutely reduced with topical sympathomimetic application, no difference in SDB was observed in a pilot, cross-over randomized controlled trial of topical sympathomimetic application (phenylephrine) in people with tetraplegia and SDB (Wijesuriya et al., 2019).

Our research group in Melbourne, Australia and colleagues in Detroit, USA have undertaken the majority of these physiological sleep studies and both centers have used comparable physiological measures ensuring that our data are complementary. By comparing people with tetraplegia and SDB with control participants (no SCI) that had SDB, a number of putative physiological factors have been examined. The reflex response of genioglossus to negative upper airway pressure was reduced and delayed in people with both OSA and SCI compared to those with OSA but without SCI (Wijesuriya et al.,

2018). This reflex is an important protective response of the upper airway and a reduction predisposes the upper airway to collapse during sleep. The critical closing pressure of the upper airway (P_{CRIT}) is determined by first stabilizing the upper airway during sleep with small amounts of continuous positive airway pressure and then reducing that external pressure until the upper airway collapses. Sankari et al. demonstrated that the P_{CRIT} in tetraplegia and SDB is not different to non-disabled people with SDB (Sankari, Bascom, & Badr, 2014). Data examining arousal responses and muscle recruitment remain equivocal.

The upper airway is a collapsible tube where patency is largely dependent on the surrounding soft tissue, phasic and tonic muscle tone, fat pad volume, and extraluminal tissue pressure from blood, lymph, and extracellular water. A series of magnetic resonance imaging studies in people with SDB and tetraplegia have compared the structure and function of the upper airway with non-disabled controls and observed that while SCI OSA patients have heterogeneous pharyngeal dilator muscle responses to the negative pressures occurring during inspiration, as a group they are more similar to able-bodied OSA patients than healthy controls of similar age and BMI (Hatt et al., 2020; O'donoghue et al., 2018).

Clinical management of sleep-disordered breathing in people with SCI

Despite the high prevalence of SDB and its detrimental effects on health and quality of life, surveys indicate that less than 25% of people with SCI are diagnosed and treated for the disorder (Burns et al., 2001; Sankari et al., 2015). The "gold-standard" method for diagnosing SDB is a Level I, overnight, attended polysomnography (PSG). Clinical practice guidelines recommend PSG for people with SCI and signs and symptoms of SDB (Consortium for Spinal Cord Medicine, 2005). However, access to this test, which requires an overnight stay in a sleep laboratory, is often poor. At least two studies have investigated the use of limited channel studies to detect SDB in SCI with results demonstrating moderate accuracy of this less intensive method (Bauman et al., 2016; Graco et al., 2018). These limited channel sleep studies may provide alternatives to PSG, particularly when access to sleep specialist services is poor.

Treatments for SDB in SCI are essentially the same as for the general population. Continuous positive airway pressure (CPAP) is the first-line treatment for SDB. CPAP provides a continuous positive airway pressure of typically between 4 and 20 mmHg, via a mask, to prevent upper airway collapse during sleep. Our COSAQ study, described earlier, is the first and only controlled trial to investigate the effects of CPAP in people with SCI. It demonstrated that CPAP effectively improved daytime sleepiness in people with acute tetraplegia, although there was no effect of CPAP on neurocognition (Berlowitz et al., 2019). CPAP effectiveness is limited by poor adherence and acceptance of the therapy in both SCI and the general population. When defined as an average of at least 4 h per night, CPAP adherence in people with tetraplegia and SDB has been estimated at approximately 25% (Graco et al., 2019; Graco et al., 2019). A qualitative study seeking to understand the barriers and enablers to CPAP use among people with tetraplegia found that both the burdens and the benefits of using CPAP were substantial, and patients actively weighed these burdens and benefits to decide whether to continue with the therapy (Graco, Green, et al., 2019).

Other potential treatments for SDB in SCI include bi-level positive airway pressure (PAP), mandibular advancement splints (MAS) and positional therapy. Bi-level PAP is a more expensive PAP therapy than CPAP, which delivers a higher inspiratory than expiratory pressure and is commonly used for hypoventilation disorders. Some clinicians prefer to use it to treat SDB in patients with more severe SCI (i.e., high tetraplegia) and greater respiratory compromise, and in those with a predominance of central than obstructive events. However, there is no research evidence to support the use of bi-level PAP over CPAP for treating SDB in SCI, and vice-versa. MAS are commonly prescribed in the general population to those who are unable to tolerate CPAP or as a first-line therapy to treat mild OSA. The mouthguard-like device is worn on the upper and lower jaw and is designed to pull the lower jaw forwards to open the airway while simultaneously increasing tension in the soft tissues and preventing collapse. Research has demonstrated that MAS devices can effectively improve the symptoms of OSA in the general population (Iftikhar et al., 2017). As yet, there have been no published studies investigating MAS in SCI.

Recent qualitative research aiming to describe and understand the management of SDB in SCI rehabilitation centers has identified that the management of SDB is highly varied in SCI (Graco, Berlowitz, & Green, 2019). The most common management pathway for people with SCI suspected of having SDB involves referral from the primary care or rehabilitation doctor to a specialist sleep/respiratory physician for investigation and management (Graco, Berlowitz, & Green, 2019). However, this care model often presents significant access barriers to people with tetraplegia and may contribute to the low rates of detection and treatment seen in this population (Graco, Green, et al., 2019). The same study identified three spinal cord injury (SCI) rehabilitation centers that had developed an "in-house" SDB management model in response to poor access to specialist sleep services. In each center, a multi-disciplinary team provides screening, diagnosis and treatment of uncomplicated SDB using portable equipment and without direct specialist sleep service involvement. This

demonstrates that it is feasible for multi-disciplinary SCI rehabilitation teams to independently manage un-complicated SDB Graco, Berlowitz, & Green, 2019) and further research investigating the safety and effectiveness of SDB management provided by the rehabilitation team is urgently needed.

How does SCI alter the circadian rhythm?

Following a complete cervical SCI, afferent somatic and autonomic fiber pathways below the SCI are disrupted and the efferent sympathetic innervation of the pineal gland via the superior cervical ganglion is interrupted. This anatomical disruption alters the circadian rhythmicity of melatonin regulation and production in tetraplegia and those with paraplegia lesions associated with autonomic dysfunction, typically T6 and higher. Under normal conditions, light striking the retina stimulates afferent pathways through the suprachiasmatic nuclei (SCN) that in turn pass to the superior cervical ganglion and onward to the pineal gland to inhibit melatonin production. Darkness removes this inhibition, and melatonin is produced. The fibers from the SCN travel alongside those from the sympathetic system to exit the spine between the first and sixth thoracic levels. The SCN to pineal pathway then ascends *outside* the spinal canal to the superior cervical ganglion, back into the cortex, and on to innervate the pineal gland. This circuitous pathway exposes melatonin regulation to disruption after SCI (Fig. 4).

In 2000, Zeitzer et al. demonstrated that complete tetraplegia is associated with near abolition of circadian melatonin rhythmicity and a markedly reduction in circulating levels of the hormone (Zeitzer, Ayas, Shea, Brown, & Czeisler, 2000). The same authors also demonstrated that this dysrhythmia was specific to melatonin and did not extend to other circadian modified rhythms such as cortisol or thyroid stimulating hormone. Despite these clear abnormalities of circadian control in SCI and the ready availability of melatonin as a therapeutic, surprisingly little research has explored the clinical utility of exogenous melatonin after SCI. A small pilot study (Spong, Kennedy, Brown, Armstrong, & Berlowitz, 2013) and two small randomized controlled, cross-over trials have demonstrated that exogenous melatonin administration in tetraplegia is safe and appears to be associated with some subjective sleep improvement (Spong et al., 2013; Zeitzer, Ku, Ota, & Kiratli, 2014). Exogenous melatonin administration in tetraplegia has also been shown to normalize clock gene expression in

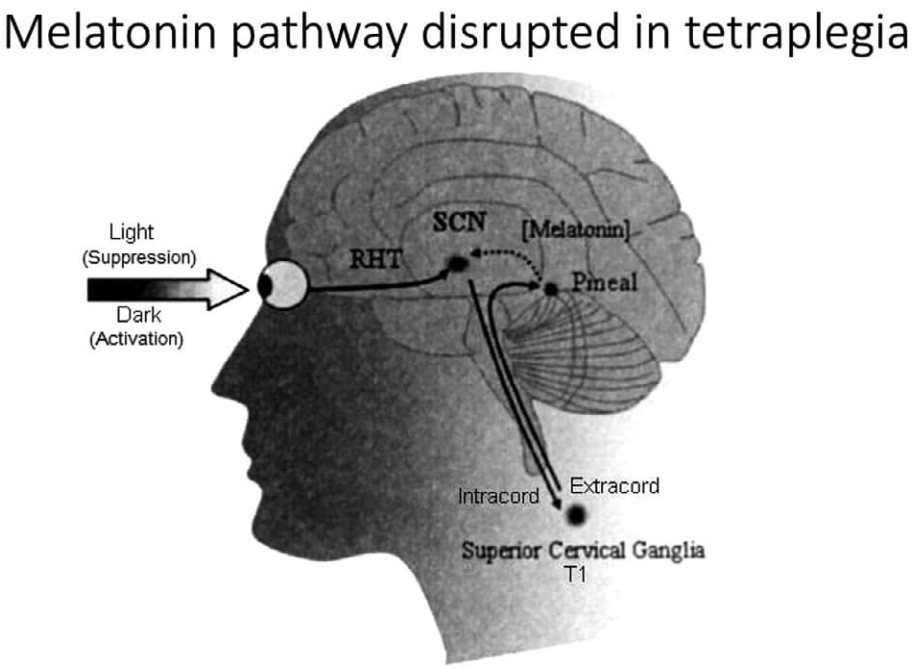

FIG. 4 Tetraplegia-associated interruption of Melatonin secretion. Light striking the retina stimulates the intrinsically photosensitive retinal ganglion cells which project monosynaptically, to the SCN via the optic nerve. The pathway continues to the superior cervical ganglion and onward to the pineal gland to inhibit melatonin production. Darkness removes this inhibition and thus melatonin is produced. The fibers from the SCN exit the spine between the first and sixth thoracic levels. The SCN to Pineal pathway then ascends outside the spinal canal to the superior cervical ganglion, back into the cortex, and on to innervate the pineal gland. A spinal cord injury above the first thoracic level will likely interrupt this pathway. *RHT* = retinohypothalamic tract. *SCN* = suprachiasmatic nuclei.

peripheral blood (Kostovski et al., 2015; Kostovski et al., 2018); however, the clinical significance of these findings is unclear.

Periodic leg movements of sleep in SCI

Periodic leg movements (PLM) are characterized by periodic episodes of repetitive and highly stereotyped limb movements during sleep. The associated restless leg syndrome (RLS) is characterized by uncomfortable leg sensations usually prior to sleep onset that causes an almost irresistible urge to move. Both conditions can result in considerable disruption to sleep quality and are typically associated with excessive daytime sleepiness. Up to 80% of RLS patients also experience PLMS (periodic leg movement syndrome), as defined by five or more PLM events per hour of sleep (Ferri et al., 2015). Periodic leg movement disorder (PLMD) appears to be another distinct sleep disorder that is more common in people living with SCI. The high prevalence of SDB in SCI, particularly in tetraplegia, confounds studies of PLMs because the AASM PLM scoring rules exclude events that occur from 0.5 s prior to or following a scored respiratory event. As such, co-existent SDB would theoretically tend to underestimate the severity of PLM, yet studies examining both SDB and PLM have consistently found an elevated rate of both. For example, Peters et al. reviewed 262 clinical and research sleep studies in people with tetraplegia and reported a SDB prevalence of 88% and a PLMD prevalence of 59% (PLMs per hour >15) (Peters et al., 2018).

While the precise etiology of PLMs in the general population is unclear, evidence of substantia nigra involvement and the clinical effectiveness of dopaminergic agents, has made them the mainstay of therapy and the belief that PLMs are centrally generated is the mainstream view. PLMs are predominantly observed in non-rapid eye movement (NREM) sleep in the general population whereas after SCI PLMs are apparent throughout sleep, including during rapid eye movement (REM) sleep. Indeed, PLMs have even been observed during wake after SCI (Peters et al., 2018). Interventions which alter cortical arousal in SCI do not necessarily result in a reduction in PLMs and similarly, inhibition of PLMs does not reduce sleep disruption (Manconi et al., 2012; Salminen et al., 2013). Taken together, these findings suggest that PLMs after SCI arise peripherally rather than centrally. Regardless of whether PLMs are a central and/or peripheral phenomenon in SCI, dopaminergic agents are still effective. A clinical case series of people with SCI referred for refractory "spasticity" despite maximal anti-spasticity therapy recently demonstrated that most in fact had untreated PLMs (Levy et al., 2018). Sleep studies demonstrated a substantial reduction in PLMs after pramipexole therapy.

Applications to other areas of neuroscience

In this chapter, we reviewed the prevalent sleep disorders in SCI, sleep-disordered breathing, circadian rhythm dysfunction, and periodic leg movements and examined the barriers to effective diagnosis and treatment. While all three disorders are well described in the non-injured population, the pathogenesis of these after SCI provides unique insights into the underlying neuroscience. It appears that tetraplegia is the only model of acute OSA in humans. As such, the comparative upper airway physiology experiments we detailed extend the phenotyping approach to understanding the individual personal determinants of the "end-organ dysfunction" we describe as OSA. In particular, differences in ventilatory control and afferent reflex activation in tetraplegia provide novel opportunities for exploration of neuropathophysiology. Similar to OSA, tetraplegia provides a unique model of disruption to the hypothalamic/melatonin/pineal axis of circadian control. Experiments such as those involving exogenous melatonin administration and light therapy with subsequent assaying of melatonin metabolism and peripheral clock gene expression will undoubtedly provide novel insights into neurohumoral circadian control, including in the non-injured. The periodic leg movement disorder had been characterized as a central dysfunction, with much of therapy focused on cortical dopaminergic augmentation. The high prevalence of PLMD after SCI refutes the "central-only" hypothesis and perhaps similarly to the OSA data, point to PLMD as another form of "end-organ dysfunction" with multiple phenotypic pathways to expression. SCI perhaps reveals pathogenic pathways not readily observable in the non-injured. Lastly, the examination of barriers to symptom recognition, diagnosis, and treatment of sleep disorders in SCI highlights issues that are likely common to other neurological and neuromuscular disorders such as stroke, multiple sclerosis, etc.

Mini-dictionary of terms

Periodic leg movements (PLM). These are periodic episodes of repetitive and highly stereotyped limb movements during sleep.

Restless leg syndrome (RLS). The RLS is associated with PLM and is characterized by uncomfortable leg sensations usually prior to sleep onset that causes an almost irresistible urge to move. Both PLM and RLS can co-exist in the same person and result in considerable disruption to sleep quality and subsequent excessive daytime sleepiness.

Circadian rhythm. The circadian rhythm is the natural, internal process that regulates the sleep–wake cycle, is regulated by the circadian clock and repeats roughly every 24 h.

Sleep-disordered breathing (SDB). SDB is an umbrella term representing a group of sleep disorders involving the respiratory system and characterized by repetitive periods of total or partial cessation of airflow during sleep.

Obstructive sleep apnea (OSA). OSA is a sub-category of SDB, characterized by repetitive periods of complete or partial obstruction of the upper airway during sleep resulting in complete or reduced airflow.

Central sleep apnea (CSA). CSA is another sub-category of SDB, characterized by the absence of respiratory effort at the time of complete/partial reduction in airflow.

Key facts of sleep

- Sleep is composed of four distinct stages. During normal sleep, a person cycles through these stages four to six times.
- We do most of our dreaming in REM (Rapid Eye Movement) sleep, which is Stage 4 sleep. REM sleep makes up between 20% and 25% of total sleep in healthy adults.
- During REM sleep all skeletal muscles, apart from the diaphragm and the ocular muscles, are essentially paralyzed.
- Teenagers move their circadian phase later in the day and need almost as much sleep as toddlers.
- Body temperature during sleep drops by half to one degree during sleep before rising again as we wake.
- The most common sleep disorders in humans are insomnia, sleep apnea, restless less syndrome and narcolepsy. It is estimated that 20%–40% of adults have a sleep disorder.

Summary points

- Acute cervical spinal cord injury results in sleep-disordered breathing.
- Sleep-disordered breathing in tetraplegia is predominately obstructive sleep apnea rather than central sleep apnea or hypoventilation.
- Acutely, obstructive sleep apnea impairs attention and information processing which improves over time; CPAP does not change recovery in neurocognitive function, but it improves sleepiness.
- Sleep-disordered breathing in tetraplegia is highly prevalent (83% mild, 59% moderate, and 36% severe).
- Sleep-disordered breathing in tetraplegia reduces health-related quality of life by approximately 30%.
- Obstructive sleep apnea in tetraplegia is not due to an upper airway that is smaller, more collapsible, or moves abnormally compared.
- The upper airway has a higher resistance in people with tetraplegia and OSA and that can be reduced, but larger studies are needed and phenylepherine is likely not to be the agent of choice.
- Melatonin supplementation may have subjective benefits.
- Translatable, novel treatment models of diagnosis and care for sleep disorders after SCI must be developed and tested for non-inferiority of person-centered outcomes.

References

Ayas, N. T., Epstein, L. J., Lieberman, S. L., Tun, C. G., Larkin, E. K., Brown, R., et al. (2001). Predictors of loud snoring in persons with spinal cord injury. *The Journal of Spinal Cord Medicine*, *24*, 30–34.

Bascom, A. T., Sankari, A., Goshgarian, H. G., & Badr, M. S. (2015). Sleep onset hypoventilation in chronic spinal cord injury. *Physiological Reports*, *3*.

Bauman, K. A., Kurili, A., Schotland, H. M., Rodriguez, G. M., Chiodo, A. E., & Sitrin, R. G. (2016). Simplified approach to diagnosing sleep-disordered breathing and nocturnal hypercapnia in individuals with spinal cord Injury. *Archives of Physical Medicine and Rehabilitation*, *97*, 363–371.

Berlowitz, D. J., Ayas, N., Barnes, M., Brown, D. J., Cistulli, P. A., Geraghty, T., et al. (2013). Auto-titrating continuous positive airway pressure treatment for obstructive sleep apnoea after acute quadriplegia (COSAQ): Study protocol for a randomized controlled trial. *Trials*, *14*, 181.

Berlowitz, D. J., Brown, D. J., Campbell, D. A., & Pierce, R. J. (2005). A longitudinal evaluation of sleep and breathing in the first year after cervical spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *86*, 1193–1199.

Berlowitz, D. J., Schembri, R., Graco, M., Ross, J. M., Ayas, N., Gordon, I., et al. (2019). Positive airway pressure for sleep-disordered breathing in acute quadriplegia: A randomised controlled trial. *Thorax*, *74*, 282–290.

Berlowitz, D. J., Spong, J., Gordon, I., Howard, M. E., & Brown, D. J. (2012). Relationships between objective sleep indices and symptoms in a community sample of people with tetraplegia. *Archives of Physical Medicine and Rehabilitation*, *93*, 1246–1252.

Berlowitz, D. J., & Tamplin, J. (2013). Respiratory muscle training for cervical spinal cord injury. *Cochrane Database of Systematic Reviews*, *7*, CD008507.

Bucks, R. S., Olaithe, M., & Eastwood, P. (2013). Neurocognitive function in obstructive sleep apnoea: A meta-review. *Respirology*, *18*, 61–70.

Burns, S. P., Kapur, V., Yin, K. S., & Buhrer, R. (2001). Factors associated with sleep apnea in men with spinal cord injury: A population-based case-control study. *Spinal Cord*, *39*, 15–22.

Consortium for Spinal Cord Medicine. (2005). Respiratory management following spinal cord injury: A clinical practice guideline for health-care professionals. *The Journal of Spinal Cord Medicine*, *28*, 259–293.

Fang, X., Goh, M. Y., O'callaghan, C., & Berlowitz, D. (2018). Relationship between autonomic cardiovascular control and obstructive sleep apnoea in persons with spinal cord injury: A retrospective study. *Spinal Cord Series And Cases*, *4*, 29.

Ferri, R., Proserpio, P., Rundo, F., Lanza, A., Sambusida, K., Redaelli, T., et al. (2015). Neurophysiological correlates of sleep leg movements in acute spinal cord injury. *Clinical Neurophysiology*, *126*, 333–338.

Gainche, L., Berlowitz, D. J., Leguen, M., Ruehland, W. R., O'donoghue, F. J., Trinder, J., et al. (2016). Nasal resistance is elevated in people with tetraplegia and is reduced by topical sympathomimetic administration. *Journal of Clinical Sleep Medicine*, *12*, 1487–1492.

Giannoccaro, M. P., Moghadam, K. K., Pizza, F., Boriani, S., Maraldi, N. M., Avoni, P., et al. (2013). Sleep disorders in patients with spinal cord injury. *Sleep Medicine Reviews*, *17*, 399–409.

Goh, M. Y., Millard, M. S., Wong, E. C. K., Berlowitz, D. J., Graco, M., Schembri, R. M., et al. (2018). Comparison of diurnal blood pressure and urine production between people with and without chronic spinal cord injury. *Spinal Cord*, *56*, 847–855.

Graco, M., Berlowitz, D. J., & Green, S. E. (2019). Understanding the clinical management of obstructive sleep apnoea in tetraplegia: A qualitative study using the theoretical domains framework. *BMC Health Services Research*, *19*(1), 405.

Graco, M., Green, S. E., Tolson, J., Stevens, B., Barnes, M., Rigoni, A., et al. (2019). Worth the effort? Weighing up the benefit and burden of continuous positive airway pressure therapy for the treatment of obstructive sleep apnoea in chronic tetraplegia. *Spinal Cord*, *57*, 247–254.

Graco, M., McDonald, L., Green, S. E., Jackson, M. L., & Berlowitz, D. J. (2021). Prevalence of sleep-disordered breathing in people with tetraplegia-a systematic review and meta-analysis. *Spinal Cord*, *59*, 474–484.

Graco, M., Schembri, R., Cross, S., Thiyagarajan, C., Shafazand, S., Ayas, N. T., et al. (2018). Diagnostic accuracy of a two-stage model for detecting obstructive sleep apnoea in chronic tetraplegia. *Thorax*, *73*, 864–871.

Graco, M., Schembri, R., Ross, J., Green, S. E., Booker, L., Cistulli, P. A., et al. (2019). Continuous positive airway pressure use for obstructive sleep apnea in acute, traumatic tetraplegia. *Archives of Physical Medicine and Rehabilitation*, *100*, 2276–2282.

Guilleminault, C., Tilkian, A., & Dement, W. (1976). The sleep apnoea syndromes. *Annual Reviews in Medicine*, *27*, 465–484.

Hatt, A., Brown, E., Berlowitz, D. J., O'donoghue, F., Meaklim, H., Connelly, A., et al. (2020). Tetraplegic obstructive sleep apnoea patients dilate the airway similarly to able-bodied obstructive sleep apnoea patients. *The Journal of Spinal Cord Medicine*, 1–11.

Hawthorne, G., & Osbourne, R. (2005). Population norms and meaningful differences for the Assessment of Quality of Life (AQoL) measure. *Australian and New Zealand Journal of Public Health*, *29*, 136–142.

Iftikhar, I. H., Bittencourt, L., Youngstedt, S. D., Ayas, N., Cistulli, P., Schwab, R., et al. (2017). Comparative efficacy of Cpap, MADs, exercise-training, and dietary weight loss for sleep apnea: A network meta-analysis. *Sleep Medicine*, *30*, 7–14.

Kim, A. M., Keenan, B. T., Jackson, N., Chan, E. L., Staley, B., Poptani, H., et al. (2014). Tongue fat and its relationship to obstructive sleep apnea. *Sleep*, *37*, 1639–1648.

Kostovski, E., Dahm, A. E., Mowinckel, M. C., Stranda, A., Skretting, G., Osterud, B., et al. (2015). Circadian rhythms of hemostatic factors in tetraplegia: A double-blind, randomized, placebo-controlled cross-over study of melatonin. *Spinal Cord*, *53*, 285–290.

Kostovski, E., Frigato, E., Savikj, M., Dahm, A., Sandset, P. M., Mowinckel, M. C., et al. (2018). Normalization of disrupted clock gene expression in males with tetraplegia: A crossover randomized placebo-controlled trial of melatonin supplementation. *Spinal Cord*, *56*, 1076–1083.

Lee, B. B., Cripps, R. A., Fitzharris, M., & Wing, P. C. (2014). The global map for traumatic spinal cord injury epidemiology: Update 2011, global incidence rate. *Spinal Cord*, *52*, 110–116.

Levy, J., Hartley, S., Mauruc-Soubirac, E., Leotard, A., Lofaso, F., Quera-Salva, M. A., et al. (2018). Spasticity or periodic limb movements? *European Journal of Physical and Rehabilitation Medicine*, *54*, 698–704.

Manconi, M., Ferri, R., Zucconi, M., Bassetti, C. L., Fulda, S., Aricò, D., et al. (2012). Dissociation of periodic leg movements from arousals in restless legs syndrome. *Annals of Neurology*, *71*, 834–844.

McEvoy, R. D., Mykytyn, I., Sajkov, D., Flavell, H., Marshall, R., Antic, R., et al. (1995). Sleep apnoea in patients with quadriplegia. *Thorax*, *50*, 613–619.

O'donoghue, F. J., Meaklim, H., Bilston, L., Hatt, A., Connelly, A., Jackson, G., et al. (2018). Magnetic resonance imaging of the upper airway in patients with quadriplegia and obstructive sleep apnea. *Journal of Sleep Research*, *27*, e12616.

Owens, R. L., Malhotra, A., Eckert, D. J., White, D. P., & Jordan, A. S. (2009). The influence of end-expiratory lung volume on measurements of pharyngeal collapsibility. *Journal of Applied Physiology*, *00755*, 2009.

Peters, A. E. J., Van Silfhout, L., Graco, M., Schembri, R., Thijssen, D., & Berlowitz, D. J. (2018). Periodic limb movements in tetraplegia. *The Journal of Spinal Cord Medicine*, *41*, 318–325.

Sajkov, D., Marshall, R., Walker, P., Mykytyn, I., Mcevoy, R. D., Wale, J., et al. (1998). Sleep apnoea related hypoxia is associated with cognitive disturbances in patients with tetraplegia. *Spinal Cord*, *36*, 231–239.

Salminen, A. V., Manconi, M., Rimpilä, V., Luoto, T. M., Koskinen, E., Ferri, R., et al. (2013). Disconnection between periodic leg movements and cortical arousals in spinal cord Injury. *Journal of Clinical Sleep Medicine : Jcsm : Official Publication of the American Academy of Sleep Medicine*, *9*, 1207–1209.

Sankari, A., Badr, M. S., Martin, J. L., Ayas, N. T., & Berlowitz, D. J. (2019). Impact of spinal cord Injury on sleep: Current perspectives. *Nature and Science of Sleep*, *11*, 219–229.

Sankari, A., Bascom, A. T., & Badr, M. S. (2014). Upper airway mechanics in chronic spinal cord injury during sleep. *Journal of Applied Physiology (1985)*, *116*, 1390–1395.

Sankari, A., Bascom, A. T., Chowdhuri, S., & Badr, M. S. (2014). Tetraplegia is a risk factor for central sleep apnea. *Journal of Applied Physiology (1985)*, *116*, 345–353.

Sankari, A., Martin, J. L., & Badr, M. (2015). A retrospective review of sleep-disordered breathing, hypertenstion and cardiovascular diseases in spinal cord injury patients. *Spinal Cord*, *53*, 496–497.

Schembri, R., Spong, J., Graco, M., Berlowitz, D. J., & Team, C. S. (2017). Neuropsychological function in patients with acute tetraplegia and sleep disordered breathing. *Sleep*, *40*.

Senaratna, C. V., Perret, J. L., Lodge, C. J., Lowe, A. J., Campbell, B. E., Matheson, M. C., et al. (2017). Prevalence of obstructive sleep apnea in the general population: A systematic review. *Sleep Medicine Reviews*, *34*, 70–81.

Spong, J., Graco, M., Brown, D. J., Schembri, R., & Berlowitz, D. J. (2015). Subjective sleep disturbances and quality of life in chronic tetraplegia. *Spinal Cord*, *53*, 636–640.

Spong, J., Kennedy, G. A., Brown, D. J., Armstrong, S. M., & Berlowitz, D. J. (2013). Melatonin supplementation in patients with complete tetraplegia and poor sleep. *Sleep Disorders*, *2013*, 8.

Stockhammer, E., Tobon, A., Michel, F., Eser, P., Scheuler, W., Bauer, W., et al. (2002). Characteristics of sleep apnea syndrome in tetraplegic patients. *Spinal Cord*, *40*, 286–294.

Tombaugh, T. N. (2006). A comprehensive review of the paced auditory serial addition test (PASAT). *Archives of Clinical Neuropsychology*, *21*, 53–76.

Wijesuriya, N. S., Eckert, D. J., Jordan, A. S., Schembri, R., Lewis, C., Meaklim, H., et al. (2019). A randomised controlled trial of nasal decongestant to treat obstructive sleep apnoea in people with cervical spinal cord injury. *Spinal Cord*, *57*, 579–585.

Wijesuriya, N. S., Gainche, L., Jordan, A. S., Berlowitz, D. J., Leguen, M., Rochford, P. D., et al. (2018). Genioglossus reflex responses to negative upper airway pressure are altered in people with tetraplegia and obstructive sleep apnoea. *The Journal of Physiology*, *596*, 2853–2864.

Zeitzer, J. M., Ayas, N. T., Shea, S. A., Brown, R., & Czeisler, C. A. (2000). Absence of detectable melatonin and preservation of cortisol and thyrotropin rhythms in tetraplegia. *The Journal of Clinical Endocrinology and Metabolism*, *85*, 2189–2196.

Zeitzer, J. M., Ku, B., Ota, D., & Kiratli, B. J. (2014). Randomized controlled trial of pharmacological replacement of melatonin for sleep disruption in individuals with tetraplegia. *The Journal of Spinal Cord Medicine*, *37*, 46–53.

Further reading

Bucks, R. S., Olaithe, M., Rosenzweig, I., & Morrell, M. J. (2017). Reviewing the relationship between OSA and cognition: Where do we go from here? *Respirology*, *22*, 1253–1261.

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Section C

Diagnosis and evaluation

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Chapter 13

Biomarkers in spinal cord injury: A highlight on prognostic insights

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Abbreviations

APRIL	a proliferation-inducing ligand
ASIA	American Spine Injury Association
AZGP	zinc alpha 2 glycoprotein
B2M	β2 microglobulin
BAFF	B-cell activating factor
BCMA	B-cell maturation antigen
BSCB	blood spinal cord barrier
CathD	cathepsin D
CCL2	chemokine ligand 2
CD95L	CD95 (Fas/APO-1)-ligand
CNS	central nervous system
CSF	cerebral spinal fluid
DEmiRNAs	differently expressed miRNAs
EAE	experimental autoimmune encephalomyelitis
ENO2	enolase 2
EV	extracellular vesicle
FGF	fibroblast growth factor
GBM	glioblastoma
GDNF	glial cell-derived neurotrophic factor
GFAP	glial fibrillary-acidic protein
HMGB1	high mobility group 1 box
HP	haptoglobin
IGF	insulin-like growth factor
IL	interleukin
INF	interferon
IP	C-X-C motif chemokine ligand 10
MBP	myelin basic protein
MCP	monocyte chemotactic protein
MIF	macrophage migration inhibitor
miRNAs	microRNAs
MMPs	metalloproteinases
MS	multiple sclerosis
NFL	neurofilaments
NSE	neuron-specific enolase
PEA15	phosphoprotein enriched in astrocytes 15
pNF-H	phosphorylated form of neurofilament heavy chain
S100β	glial-specific calcium-binding β protein
SBDP	spectrin breakdown products
SCI	spinal cord injury
TF	transferrin

Diagnosis and Treatment of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822498-4.00013-0

TGF	growth factor transformer
TPI	triosephosphate isomerase
UCH-L1	ubiquitin carboxy-terminal hydrolase L1
VEGF	vascular endothelial growth factor

Introduction

Spinal cord injury (SCI) is a broad term that includes changeable grades of neurological deficits and is still considered an incurable condition. In spite of substantial advances in surgical and medical treatment, just around 1% of SCI patients experience complete healing. Unfortunately, almost 45% of the them suffer from serious neurological loss, which includes incomplete or complete tetraplegia, with or without respiratory compromise (Spinal Cord Injury (SCI), 2016). Therefore, SCI usually has devastating vocational, social, and physical implications for patients and caregivers (Ahuja et al., 2017).

The patient's outcome after initial SCI is still very difficult to predict, because the tools we have today for both evaluating the gravity of spinal cord tissue destruction and better assessing the recovery of SCI patients are still restricted (Rodrigues, Moura-Neto, & Spohr, 2018). Imaging examinations of the spinal cord cannot accurately predict the prognosis of the disease. Computed tomography shows only fractures or dislocations, while magnetic resonance imaging is not highly sensitive to edema of the spinal cord, be it related or not to SCI. Furthermore, laboratory tests of blood biochemistry such as lactate dehydrogenase and protein kinase C are not specific for SCI, as other non-neurological damage can also cause changes in blood parameters, having, therefore, no clinical application (Ding et al., 2019). There's no doubt that the sooner we evaluate the extent of the lesion and start treating the patient, the better the outcome is. Nowadays, the best predictive value of neurological assessment of the SCI patient is defined by typical clinical neurological examinations during the patient's first evaluation (Rodrigues et al., 2018). So the identification of biomarkers that can predict lesions is crucial to helping assess damage severity, prognosis, and therapeutic outcomes (Rodrigues et al., 2018).

In this chapter, we will highlight the most recent research on the expression of biomarkers in the pathophysiology of the SCI and try to correlate to diagnosis and prognosis.

Pathophysiology of SCI

It is well known that SCI occurs in two mechanisms that progress through three stages. Both mechanisms that lead to acute SCI are now very well characterized and recognized as primary (mechanical) and secondary injuries. The primary injury is caused by the initial mechanical trauma of surrounding tissues, followed by contusion and compression of the spinal cord, which induces damage to nerve cells, blood vessels, and myelin (Rodrigues et al., 2018). The secondary lesion is triggered by the primary lesion and is classified in three phases, namely the acute phase, the sub-acute (or intermediate) phase, and the chronic phase, according to the pathomechanism and post-injury time (Bareyre & Schwab, 2003; Rodrigues et al., 2018).

The acute stage begins with the mechanical injury and extends to the first 48 h after the initial traumatic injury. In this stage, the patient develops some neurological deficits directly associated with the mechanical injury. This is when innumerable pathophysiological processes begin, leading to the initial inflammatory response to the injury and causing patients to develop "spinal shock" (Albayar et al., 2019; Rodrigues et al., 2018). It is well established that, at this stage, crucial events are induced by vascular rupture, ischemia, and hemorrhage by the action of inflammatory growth factors which affects neurons and glial cells, including excessive production of free radicals, ionic dysregulation, inflammatory response, and excitotoxicity, inducing pathological changes (Kwon, Tetzlaff, Grauer, Beiner, & Vaccaro, 2004; Rodrigues et al., 2018). At this stage, primary care should be provided for the patients, including protection of the airways, maintenance of the respiratory function, and use of hemodynamic support (Albayar et al., 2019).

It is, however, often difficult to define the baseline severity of the injury, as the patient is often in an unstable clinical condition due to spinal shock (Hachisuka et al., 2014). In order to reduce inflammation and neurological deficits, some centers use high-dose corticosteroids in the first 8 h after the injury, following the NASCIS II protocol (Witiw & Fehlings, 2015). Nevertheless, damage to glial cells, neurons and oligodendrocytes caused by the presence of excessive amounts of excitatory neurotransmitters (glutamate, aspartate) cannot be prevented. Furthermore, neurons die during all phases of the injury due to necrosis and astrocytes. Neurons and oligodendrocytes also die due to apoptotic mechanisms (Beattie, Hermann, Rogers, & Bresnahan, 2002).

The secondary or sub-acute stage lasts up to 2 weeks after the damage. At this stage, the patient usually recovers from the initial spine shock. However, neurological loss as well as other potential complications associated with the original trauma continue, as nerve cell dysfunction and blood supply problems derived from the acute stage can get even worse

(Albayar et al., 2019). In this phase, reactive gliosis increases both the content of glial fibrillary-acidic protein (GFAP) and the size of astrocytes to form the glial scar, In this phase, an intense inflammatory response begins, whereby phagocytic cells are recruited (Bareyre & Schwab, 2003; Rodrigues et al., 2018). The glial scar, with its firmly fused processes, forms an inhibitory agglomerate in the form of a mesh that plays a fundamental role in interrupting axonal regeneration (Ahuja et al., 2017). However, despite limiting regeneration after an injury to the central nervous system (CNS), the uncontrolled proliferation of reactive astrocytes suppresses the formation of aberrant synapses at the injury site and also contributes to both the restoration of the integrity of the blood spinal cord barrier (BSCB) and the reconstruction of microenvironment homeostasis (Faulkner et al., 2004). This mechanism is important for the removal of edemas, in addition to reducing the infiltration of cells of the immune system, helping, thus to limit the spread of the lesion (Wanner et al., 2013).

The chronic SCI phase, whose characterization requires further investigation, follows the sub-acute SCI phase. At this stage, patients may experience partial neurological recovery, which will depend on the extent of the lesion and the general condition of each patient. In addition, patients may also have maturation of adaptive mechanisms or the onset of more delayed neurological symptoms such as urinary bladder dysfunction, neuropathic pain, lipodystrophy, musculoskeletal atrophy, dysautonomia, and abnormal skeletal postures (Eckert & Martin, 2017). This phase may prolong from days to years after the shock, and is characterized by Wallerian degeneration, apoptosis and scarring that cause functional impairment (Bareyre & Schwab, 2003; Rodrigues et al., 2018). At this stage, it is also normal for patients to develop **syringomyelia*** due to the formation of the glial scar. Therapeutic strategies generally focus on increasing the regeneration of damaged axons and remyelination through different mechanisms, whether through pharmacological methods or cell therapy (Kim, Ha, & Kim, 2017).

Biomarkers of SCI

First, it is important to define the word **biomarker***. Biomarkers, also known as "biological markers," are related to a wide sub-category of medical signs which can be measured with precision and reproducibility. Thus, biomarkers are, for purposes of interpretation, quantifiable results of biological mechanisms (Strimbu & Tavel, 2010). A biomarker of tissue injury should ideally be abundant, preferably (or exclusively) produced in the tissue of interest, and to be naturally present in small concentrations in blood and other body fluids (Laterza et al., 2009; Rodrigues et al., 2018). It is also important to have good biomarkers that can contribute as a measure of valuable therapeutic responses. They are highly valuable in the decision-making process of seeking additional clinical evaluation of a drug, and in helping to define critical parameters such as the intervention time window, drug dose and monitoring schedule for a clinical trial. It is also important to have good biomarkers that are acutely related to biochemical changes made or sustained during all phases of SCI. It is finally very important to validate all the potential biomarkers candidates.

Currently, there are neither drugs for treatment nor specific laboratory tests for the diagnosis of SCI. Therefore, in order to determine the extent of SCI as soon as possible, it is urgent to further the discovery and use of specific biomarkers for SCI. This could help guide doctors and researchers toward the discovery of a new object of intervention that can help prevent and decrease disability resulting from SCI.

SCI in the acute stage

In the acute stage, there is a change in the permeability of the BSCB, due to the formation of glial scarring and the disturbance of endothelial cells. These cells secrete various inflammatory cytokines and some are currently being investigated as potential SCI biomarkers. High concentrations of interleukin-6 (IL-6), interleukin-8 (IL-8), and monocyte chemotactic protein (MCP)-1 (also known as chemokine ligand 2 (CC motif) (CCL2)) have been expressed in CSF. They have been shown to be dependent on the severity of the injury, when patients presented with American Spinal Injury Association grade A (ASIA A) injury had higher levels of these cytokines compared to ASIA B and C patients (Kwon et al., 2010).

Recently, a study with 15 ASIA A and B patients demonstrated that IL-10, IL-1rα, IL-9, IL-16, and IL-18 were positively regulated 24 h after SCI, and that interferon-gamma (INF-γ) and IL-13 have been downregulated (Fernández et al., 2020). Upregulation of the high mobility group 1 box (HMGB1) and the inflammatory cytokine macrophage migration inhibitor (MIF) factor were also identified, both occurring regardless of the degree or severity of injury (Kwon et al., 2019). Several studies also analyzed the transient expression of some proteins during the acute phase. Some structural proteins in glial cells and neurons are usually modulated in the CSF and in the serum of patients with acute SCI. Proteins such as GFAP, Phosphorylated Neurofilament Heavy (pNF-H), light chains of neurofilaments (NFL, 68 kDa), neuron-specific

TABLE 1 Cytokines and proteins highly expressed in the acute stage.

Expression in CSF	Cytokines	Proteins
Upregulated	IL-6, IL-8, IL-10, IL-1rα, IL-9, IL-16, IL-18MCP-1 (CCL2), HMGB1, MIF	GFAP, S100β, NSE, p-NF-H, NFL, UCH-L1, SBDP, MBP
Downregulated	INF-γ, IL-13	

Table based on de Mello Rieder et al. (2019), Du et al. (2018), Fernández et al. (2020), Ghosh and Pal (2019), Kwon et al. (2019, 2010, 2017), Leister et al. (2020), and Moghieb et al. (2016).

enolase (NSE), glial-specific calcium-binding β protein (S100β), tau, ubiquitin carboxy-terminal hydrolase L1 (UCH-L1), αII spectrin breakdown products (SBDP), myelin basic protein (MBP), transferrin, cathepsin D, triosephosphate isomerase-1, and astrocytic phosphoprotein PEA-15 were analyzed in patients with acute SCI (de Mello Rieder et al., 2019; Du et al., 2018; Kwon et al., 2010, 2017; Leister et al., 2020).

GFAP is an astrocyte-specific intermediate filament protein associated with glial scar formation, and astrocyte protein S100β in adults is generally elevated due to damage to the nervous system. It has been shown that both GFAP and S100β are present at higher levels in CSF and serum 24 h after injury, depending on severity, and that both can serve as a prognostic biomarker (Kwon et al., 2017; Leister et al., 2020). Inverse results were observed with the tau protein, which is an intracellular neuron protein involved in the stabilization of microtubules. A negative correlation was observed between CSF and serum tau concentrations and the severity of spinal cord injury 24 h after the injury, suggesting that tau may score as a prognostic biomarker for neurological improvement after acute spinal cord injury (Kwon et al., 2010; Leister et al., 2020).

NSE, p-NF-H, NFL have been found to be elevated in the serum and CSF of patients with acute SCI. However, when p-NF-H decreases to normal values, it allows the prediction of a favorable outcome (Ghosh & Pal, 2019). UCH-L1, SBDP, MBP have also been found to be transiently elevated in the CSF of patients with SCI and show a correlation between severity and recovery (Moghieb et al., 2016) (see Table 1).

SCI in the sub-acute stage

In the sub-acute stage, during the formation of the **glial scar***, astrocytes increase the expression of not only GFAP, but also of nestin and vimentin. It has also been reported that, at this stage, astrocytes also secrete various **cytokines*** and growth factors such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF)-β, glial cell-derived neurotrophic factor (GDNF), and growth factor transformer (TGF)-β, which are speculated to promote in later stages the differentiation, proliferation and migration of oligodendrocyte precursor cells. TGF-β1 is suggested to be implicated in scar formation after spinal cord injury (Kim et al., 2017; Rodrigues et al., 2018).

Recently, a study showed that patients with SCI had a decrease in both serum TGF-β1, an insulin-like growth factor 1 (IGF-1), and in sCD95L, but there was an upregulation 12 weeks after the injury correlated with the absence of neurological recovery (Ferbert et al., 2017).

CD95(Fas/APO-1)-ligand (CD95L) protein during the sub-acute phase is cleaved and a portion of it is released into the peripheral blood. This protein induces apoptosis in CD95-sensitive cells, especially at the sub-acute stages when apoptotic activity increases. This protein has the potential of acting as a biomarker at the sub-acute stage, and mainly of indicating the apoptotic effect destructive to the spinal cord tissue and the consequent neurological loss (Biglari et al., 2013). At this stage, the phagocytic inflammatory cells normally release cytokines that could be used as biomarkers. One of those cytokines is IL-1β, which has shown a significant fall at 1 and 4 weeks post injury in patients who experienced less progress (Biglari et al., 2015). Several metalloproteinases (MMPs) are upregulated during the sub-acute phase, and specially MMP-8 and -9, which have been pointed as a useful indicator for recovery potential (Albayar et al., 2019; Moghaddam et al., 2017). The C-X-C motif chemokine ligand 10 (IP-10) was found increased in serum at 3–6 h after SCI. However, there was a peak after 7 days of trauma at the sub-acute phase (Hassanshahi et al., 2013). Other proteins were pointed as potential biomarkers in the sub-acute phase, among them transferrin (TF), cathepsin D (CathD), triosephosphate isomerase-1 (TPI-1), phosphoprotein enriched in astrocytes 15 (PEA15), zinc alpha 2 glycoprotein (AZGP) and Haptoglobin (HP). They were found in human CSF from SCI patients, whose AZGP and HP protein levels decline in the CSF as the secondary injury process progresses (Moghieb et al., 2016; Sengupta et al., 2014) (see Table 2).

TABLE 2 MMPs, cytokines, proteins and growth factors highly expressed in the sub-acute stage.

Expression in CSF	Metalloproteinase	Proteins	Growth factors	Cytokines
Upregulated	MMP-8 and 9	Nestin, Vimentin, TF, CathD, TPI-1, PEA15	GFAP, VEGF, FGF-β, GDNF, TGF-β 1[a], IGF-1[a], CD95L[a]	IP-10
Downregulated		AZGP, HP		

[a]*Upregulation 12 weeks after the injury is correlated with the absence of neurological recovery.*
Table based on Albayar et al. (2019), Biglari et al. (2013, 2015), Ferbert et al. (2017), Hassanshahi et al. (2013), Kim et al. (2017), Moghaddam et al. (2017), Moghieb et al. (2016), Rodrigues et al. (2018), and Sengupta et al. (2014).

SCI in the chronic stage

During the chronic phase, glial cells and neurons continue to die from apoptosis, compromising the channel and the functions of the receptor, and scarring and demyelination accompany Wallerian degeneration. All of these processes lead to deficits and are signs that the injury has matured (Norenberg, Smith, & Marcillo, 2004; Rodrigues et al., 2018).

It has been shown that two potent pro-inflammatory cytokines, namely macrophage migration inhibiting factor (MIF) and high mobility group box 1 (HMGB1), which are present in large quantities in both types of immune and neuronal cells, were found increased in patients with chronic spinal cord injury, regardless of the severity or level of the injury (Kwon et al., 2019; Papatheodorou et al., 2017; Stein et al., 2013). Studies have also shown that, at this stage, patients have elevated levels of IL-2, tumor necrosis factor alpha (TNFα), C-reactive protein, IL-6 and interleukin-1 receptor antagonist (IL-1RA), the two latter also being related to urinary tract infections, neuropathic pain or comorbidities such as pressure ulcers (Davies, Hayes, & Dekaban, 2007; Frost, Roach, Kushner, & Schreiber, 2005; Kwon et al., 2019).

It has also been shown hat in the chronic phase there is an elevated expression of some autoimmunity-promoting cytokines such as B-cell maturation antigen (BCMA), B-cell activating factor (BAFF), and A proliferation-inducing ligand (APRIL), and that some proteins that were found elevated in acute SCI were also increasingly present in people with chronic SCI such as β2 microglobulin (B2M), enolase 2 (ENO2), and S100A9 (Saltzman et al., 2013; Streijger et al., 2018). These studies demonstrated that some biomarkers could be used as good candidates to evaluate biochemical changes made or sustained during all stages of the SCI in order to help validate the potential impact on the clinical care of patients throughout the treatment (see Table 3).

microRNAs as biomarkers

Recently, microRNAs (**miRNAs***) have been identified as good candidates as biomarker in blood in various pathologies, including in pancreatic adenocarcinomas, Alzheimer's disease, low-grade gliomas, ectopic pregnancy, breast cancer, and ovarian cancer among others (Rodrigues et al., 2018). The advantages of using miRNAs as biomarkers are that they are tissue specific, very stable in fluids, and have a phylogenetic relationship. In addition, they are present in all systems and have specific expression patterns at the developmental- and tissue-specific levels (Farh et al., 2005). MiRNAs downregulate the translation of RNA proteins by binding to the 3′-UTR of their target mRNAs. They are endogenously derived, short (usually 18–22 nucleotides in length), and generally induce mRNA degradation or translational repression (Bartel, 2004). The changes in the expression of miRNAs after SCI can be classified into three groups: (1) decreased miRNAs; (2) increased miRNAs; and (3) bidirectional (decreased or increased) miRNAs. There is little research related to miRNA and SCI in humans. Most of the studies have been conducted in rats, mice, or pigs. Efforts are currently being made to

TABLE 3 Cytokines and proteins highly expressed in the chronic stage.

Expression in CSF	Proteins	Cytokines
Upregulated	B2M, ENO2, S100A9	MIF, HMGB1, IL-2, IL-6,[a] Il-1RA,[a] BCMA, BAFF, APRIL

[a]*Also related to urinary tract infections, neuropathic pain or comorbidities such as pressure ulcers.*
Table based on Davies et al. (2007b), Frost et al. (2005), Kwon et al. (2019), Norenberg et al. (2004), Papatheodorou et al. (2017), Rodrigues et al. (2018), Saltzman et al. (2013), Stein et al. (2013), and Streijger et al. (2018).

validate in humans data that have been observed in animal models. There is no doubt that possible targets for modified miRNAs after SCI include genes that encode components involved in oxidative stress, inflammation, and apoptosis. The problem is that SCI patients represent very heterogeneous groups according to injury mechanism, severity and location, and the age and genetic background of the patients.

Recently, 190 detected miRNAs were found to be differentially expressed in the CSF of patients with all three SCI severities (ASIA A, B, and C). It was also demonstrated that these miRNAs showed changes in CSF and serum depending on the severity of the injury (Tigchelaar et al., 2019) (see Table 4).

Moreover, it was also shown that CSF miRNA expression at 24 h post injury within patients with ASIA A differs between those patients who will, and those who will not convert to ASIA B, and also differs from those that will not convert to C or D at 6 months post injury (Tigchelaar et al., 2019).

TABLE 4 Most differentially expressed miRNAs in cerebrospinal fluid after 24 h of the injury.[a]

miRNA	Regulation	AISA
miR-219a-2-3p	↑	A
miR-9-5p	↑	A
miR-9-3p	↑	A
miR-129-5p	↑	A
miR-219a-5p	↑	B
miR-1246	↑	A
miR-760	↑	A
miR-410-3p	↑	A
miR-485-5p	↑	B
miR-323b-3p	↑	A
miR-124-3p	↑	A
miR-488-3p	↑	A
miR-320b	↑	B
miR-433-3p	↑	B
miR-1298-3p	↑	A
miR-211-5p	↑	B
miR-92b-3p	↑	B
miR-128-3p	↑	A
miR-1910-5p	↑	C
miR-10b-3p	↑	B
miR-3605-3p	↑	B
miR-125b-1-3p	↑	B
miR-584-5p	↑	B
miR-338-5p	↑	B
miR-21-3p	↑	C
miR-1307-5p	↑	C
miR-23b-3p	↓	C
miR-195-5p	↓	C

[a]*Table based on Tigchelaar et al. (2019).*

It was shown that a total of 19 miRNAs were differently expressed in human serum, and that 16 of them were specific only to the ASIA A group. The miRNA miR-133a-3p demonstrated the most significant change in expression, and it is already associated with injury severity. The miRNAs miR-208 and miR-499 associated with skeletal muscle mass regulation were demonstrated not only to be regulated in human serum after the SCI but also to have similar severity-dependent expression patterns (Boon et al., 2015; Tigchelaar et al., 2019).

However, the take-home message of the work from the group of Tigchelaar is that, although 190 miRNAs were detected in the CSF and 19 in serum after evaluating 44 individuals that met one of the three ASIA A, B and C criteria, only one of them, namely miR-423, was shown to be one of the strongest prognosticators of neurologic progress at 6 months post injury in humans (Tigchelaar et al., 2019). It is already known that miR-423 is related to neuronal apoptosis, as it regulates caspase-3 activity (Li et al., 2014).

Exosomes

Although "free circulating" miRNAs can be used as biomarkers, they have low concentration and little stability in other body fluids (Ding et al., 2019). Therefore, the best way to search for miRNAs is in the small extracellular vesicles (EVs) secreted by most of the eukaryotic cells, called exosomes.

Exosomes are EVs derived from the 30 to 120 nm endocytic membrane and are present in many or perhaps in all body fluids. They participate in cell-to-cell communication and distribution of proteins and RNA, as they transport a diversity of proteins, lipids and nucleic acids. Exosomal miRNAs in body fluids have many advantages over free miRNAs. It has already been shown that the molecular components of exosomes, especially exosomal proteins and miRNAs, are promising as new biomarkers for clinical diagnosis (Lin et al., 2015).

Recently, it was shown in a rat model of acute SCI that there were changes in the expression of miRNA in circulating exosomes associated with the pathological mechanism of acute SCI by their target-regulated pathways. Identified serum exosomal miR-130a-3p, miR-125b-5p, and miR-152-3p are distinguishing and easily detectable diagnostic markers in acute SCI. In the same study, other differently expressed miRNAs (DEmiRNAs) and their expression were found to be either up- or downregulated, depending on the activation or inhibition of signaling pathways with response to the injury (Ding et al., 2020) (see Tables 5 and 6).

TABLE 5 miRNAs identified in exosomes in acute SCI.

miRNA	Expression in SCI	Actions already known
miR-152-3p	Increased in the injured area after SCI	• Diagnosis, treatment, and prognosis of tumors • Dengue infection • Type 2 diabetic nephropathy • Alzheimer's disease
miR-130a-3p	Significantly increased in the SCI	• Regulate the insulin sensitivity and hepatic steatosis • Regulate cell migration and invasion in gemcitabine-resistant hepatoma cells • Suppress cell migration and invasion in human gastric carcinoma • Suppress cell viability, proliferation, and invasion in nasopharyngeal carcinoma • Increase cisplatin resistance in non-small-cell lung cancer • Regulate gemcitabine resistance in cholangiocarcinoma • Attenuate activation, and induces apoptosis of hepatic stellate cells
microRNA-125b	SIGNIFICANTLY decreased in the acute phase of SCI	• Significantly upregulated in primary glioblastomas • Highly expressed in mouse models of cardiac hypertrophy and idiopathic end-stage failing human hearts • Decreased in primary neuroblastoma tumors, psoriasis, and atopic eczema • Important negative regulator of p53 and p53-induced apoptosis

Table based on Ding et al. (2019, 2020) and Lin et al. (2015).

TABLE 6 DemiRNA targets that were identified in acute SCI.

Expression	Most enriched pathways of the targets of DEmiRNAs
Upregulated	• Axon guidance • Melanogenesis • Wnt signaling pathway • Long-term potentiation
Downregulated	• ECM receptor interaction • Focal adhesion

Table based on Ding et al. (2019, 2020) and Lin et al. (2015).

Conclusions

SCI can cause permanent disability, and yet, despite advances in clinical management, many patients are left with substantial neurological impairment. Presently, prevention is the only procedure we can take to avoid the primary mechanical damage to the spinal cord (Rodrigues et al., 2018). There is no doubt that these patients need to be correctly diagnosed, but an effective treatment for SCI hasn't been found yet.

The fact is that the sooner patients are treated and the magnitude of their lesion is defined, the better their chance of a good outcome. However, the problem of using proteins as biomarkers is that they should be frequently collected from the CSF in order to characterize the severity of the injury, but collecting CSF through a lumbar puncture is unquestionably invasive (Kwon et al., 2017; Rodrigues et al., 2018). Further bioinformatics analysis and functional research will be of great help in clarifying the role of exosomes, microRNAs and proteins in the pathological process of spinal cord injury and in judging whether they can be used as diagnostic markers (Ding et al., 2019). Unfortunately, the identification of biomarkers to predict SCI prognosis and treatment still needs much more research.

Applications to other areas of neuroscience

The research concerning the use of biomarkers as predictor for the treatment of SCI and several other devastating diseases such as cancer, cardiovascular diseases, Alzheimer's and Parkinson has been increasing since the last decade (Califf, 2018).

Recently, the search for good biomarkers has been focused on exosomal biomarkers, as they support comparable or superior sensitivity and specificity associated to their excellent stability (Lin et al., 2015). Using an animal model, it was demonstrated that urine exosomes may be a specific and sensitive source of miRNA biomarkers for experimental autoimmune encephalomyelitis (EAE) disease and Multiple Sclerosis (MS). It was possible to identify miRNAs in urine, plasma and spinal cord exosomes in a period before the onset of the disease, suggesting their early involvement in the pathology of EAE and MS (Singh, Deshpande, Suhail, Rattan, & Giri, 2016).

In addition to exosomal proteins and RNAs, exosomal lipids have also been shown to have a diagnostic potential. In patients with glioblastoma (GBM), several exosomes and miRNAs have been identified as being useful for diagnostic and/or prognostic biomarkers (Saadatpour et al., 2016). But unfortunately, exosomal biomarkers are still at an early stage of discovery/development and their potential value in clinical diagnosis has not been fully analyzed yet (Lin et al., 2015).

Mini-dictionary of terms

Biomarkers—Biomarkers, also known as "biological markers," are related to a wide sub-category of medical signs, which can be measured with precision and reproducibility. Therefore, biomarkers are often determined and evaluated to examine pathogenic processes, normal biological processes, or pharmacologic responses to a therapeutic intervention. In medicine, they can be used in clinical settings for guiding treatment based on their application: predictive, prognostic, or diagnostic.

Syringomyelia is an illness in which a cyst or cavity forms within the spinal cord. The cyst, also called a syrinx, can grow and become quite large over time, destroying the spinal cord. The damage may result in paralysis, loss of feeling, weakness, and rigidity in the shoulders, back, and extremities. The illness may also induce a loss of the ability to feel extremes of cold or hot, especially in the hands. It may also lead to a cape-like bilateral loss of temperature sensation and pain along the arms and upper chest.

miRNAs are small non-coding RNAs molecules containing about 22 nucleotide which are found in all species including plants, animals and some viruses. MiRNAs function in silencing and post-transcriptional regulation of gene expression, via base-pairing with complementary sequences within mRNA molecules. As a result, these mRNA molecules are silenced by one or more of the subsequent ways (1) cleavage of the mRNA strand into two pieces; (2) destabilization of the mRNA through shortening of its poly(A) tail, and (3) less efficient translation of the mRNA into proteins by ribosomes.

glial scar is formed by reactive astrocytes that proliferate and have processes that are firmly fused, making an inhibitory meshlike bundle that has the valuable task of acting as an obstacle for axonal regeneration, and therefore being considered the main origin for the restricted regeneration after a CNS damage.

Cytokines are a broad category of small proteins (~5–20 kDa) that are very important in cell signaling. They are peptides that cannot cross the lipid bilayer of cells to enter the cytoplasm, so they act through cell surface receptors and are especially important in the immune system. Cytokines can act in an autocrine, paracrine and endocrine fashion way. Cytokines include interleukins, chemokines, lymphokines, interferons, and tumor necrosis factors, but generally not hormones or growth factors (despite some overlap in the terminology). They are produced by a broad range of cells, including immune cells like macrophages, B lymphocytes, T lymphocytes and mast cells, as well as endothelial cells, fibroblasts, and various stromal cells. Cytokines are important in health and disease, specifically in host immune responses to inflammation, infection, cancer, trauma, sepsis, and reproduction.

Key facts of biomarkers spinal cord injury

- Spinal cord injury (SCI) is still considered an incurable condition, resulting in a heterogeneous recovery and an uncertain prognosis.
- The sooner patients are treated and the magnitude of their lesion is defined, the better their chance of a good outcome.
- Biomarkers, also known as "biological markers," are part of the biological response to injury, and are related to a wide sub-category of medical signs which can be measured with precision and reproducibility.
- Identification of biomarkers that can predict lesions is crucial to helping assess damage severity, prognosis, and therapeutic outcomes.
- Good biomarkers that can contribute as a measure of therapeutic responses are highly valuable in the decision-making process of seeking additional clinical evaluation of a drug, and in helping to define critical parameters such as the intervention time window, dose and monitoring schedule for a clinical trial.

Summary points

- Biomarkers are part of the biological response to injury.
- It is important to understand the degree or stage of the injury to focus on treatment.
- The change of proteins in some fluids is consistent, but their distribution in peripheral fluids is not the same.
- Non-invasive examinations with reproducible results are better to assess the injury.
- MiRNAs are tissue specific, very stable in fluids and have a phylogenetic relationship.
- Exosomes participate in cell-to-cell communication and the distribution of proteins and RNA, as they transport a diversity of proteins, nucleic acids and lipids.
- As exosomes are distributed in body fluids, exosomal miRNAs have many advantages over free miRNAs, being thus promising as new biomarkers for clinical diagnosis.

Acknowledgments

This work was supported by the National Institute for Translational Neuroscience (INNT) of the Ministry of Science and Technology; the Brazilian Federal Agency for the Support and Evaluation of Graduate Education (CAPES) of the Ministry of Education; the National Council for Scientific and Technological Development (CNPq); the Carlos Chagas Filho Research Support Foundation (FAPERJ); and the Ary Frauzino Foundation for Cancer Research.

References

Ahuja, C. S., Nori, S., Tetreault, L., Wilson, J., Kwon, B., Harrop, J., et al. (2017). Traumatic spinal cord injury—Repair and regeneration. *Clinical Neurosurgery*, *80*(3), S22–S90.

Ahuja, C. S., Wilson, J. R., Nori, S., Kotter, M. R. N., Druschel, C., Curt, A., et al. (2017). Traumatic spinal cord injury. *Nature Reviews. Disease Primers*, *3*(1), 17018.

Albayar, A. A., Roche, A., Swiatkowski, P., Antar, S., Ouda, N., Emara, E., et al. (2019). Biomarkers in spinal cord injury: Prognostic insights and future potentials. *Frontiers in Neurology*, *10*, 27. https://doi.org/10.3389/fneur.2019.00027. eCollection 2019.

Bareyre, F. M., & Schwab, M. E. (2003). Inflammation, degeneration and regeneration in the injured spinal cord: Insights from DNA microarrays. *Trends in Neurosciences*, *26*(10), 555–563.

Bartel, D. P. (2004). MicroRNAs: Genomics, biogenesis, mechanism, and function. *Cell*, *116*(2), 281–297.

Beattie, M. S., Hermann, G. E., Rogers, R. C., & Bresnahan, J. C. (2002). Cell death in models of spinal cord injury. *Progress in Brain Research*, *137*, 37–47.

Biglari, B., Büchler, A., Swing, T., Biehl, E., Roth, H. J., Bruckner, T., et al. (2013). Increase in soluble CD95L during subacute phases after human spinal cord injury: A potential therapeutic target. *Spinal Cord*. https://doi.org/10.1038/sc.2012.139.

Biglari, B., Swing, T., Child, C., Büchler, A., Westhauser, F., Bruckner, T., et al. (2015). A pilot study on temporal changes in IL-1β and TNF-α serum levels after spinal cord injury the serum level of TNF-α in acute SCI patients as a possible marker for neurological remission. *Spinal Cord*, *53*, 510–514.

Boon, H., Sjögren, R. J. O., Massart, J., Egan, B., Kostovski, E., Iversen, P. O., et al. (2015). MicroRNA-208b progressively declines after spinal cord injury in humans and is inversely related to myostatin expression. *Physiological Reports*, *3*(11), e12622. https://doi.org/10.14814/phy2.12622. Epub 2015 Nov 24.

Califf, R. M. (2018). Biomarker definitions and their applications. *Experimental Biology and Medicine*, *243*(3), 213–221. https://doi.org/10.1177/1535370217750088.

Davies, A. L., Hayes, K. C., & Dekaban, G. A. (2007). Clinical correlates of elevated serum concentrations of cytokines and autoantibodies in patients with spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *88*(11), 1384–1393. https://doi.org/10.1016/j.apmr.2007.08.004. https://doi.org/S0003-9993(07)01342-1 [pii].

de Mello Rieder, M., Oses, J. P., Kutchak, F. M., Sartor, M., Cecchini, A., Rodolphi, M. S., et al. (2019). Serum biomarkers and clinical outcomes in traumatic spinal cord injury: Prospective cohort study. *World Neurosurgery*, *122*, e1028–e1036. https://doi.org/10.1016/j.wneu.2018.10.206. Epub 2018 Nov 7.

Ding, S. Q., Chen, Y. Q., Chen, J., Wang, S. N., Duan, F. X., Shi, Y. J., et al. (2020). Serum exosomal microRNA transcriptome profiling in subacute spinal cord injured rats. *Genomics*, *12*(6), 5086–5100. https://doi.org/10.1016/j.ygeno.2019.09.021. Epub 2020 Sep 9.

Ding, S. Q., Chen, J., Wang, S. N., Duan, F. X., Chen, Y. Q., Shi, Y. J., et al. (2019). Highlight article: Identification of serum exosomal microRNAs in acute spinal cord injured rats. *Experimental Biology and Medicine*, *244*(14), 1149–1161. https://doi.org/10.1177/1535370219872759. Epub 2019 Aug 26.

Du, W., Li, H., Sun, J., Xia, Y., Zhu, R., Zhang, X., et al. (2018). The prognostic value of serum neuron specific enolase (NSE) and s100b level in patients of acute spinal cord injury. *Medical Science Monitor*, *24*, 4510–4515. https://doi.org/10.12659/MSM.907406.

Eckert, M. J., & Martin, M. J. (2017). Trauma: Spinal cord injury. *Surgical Clinics of North America*, *97*(5), 1031–1045. https://doi.org/10.1016/j.suc.2017.06.008.

Farh, K. K., Grimson, A., Jan, C., Lewis, B. P., Johnston, W. K., Lim, L. P., et al. (2005). The widespread impact of mammalian microRNAs on mRNA repression and evolution. *Science*, *310*(5755), 1817–1821.

Faulkner, J. R., Herrmann, J. E., Woo, M. J., Tansey, K. E., Doan, N. B., & Sofroniew, M. V. (2004). Reactive astrocytes protect tissue and preserve function after spinal cord injury. *The Journal of Neuroscience*, *24*(9), 2143–2155.

Ferbert, T., Child, C., Graeser, V., Swing, T., Akbar, M., Heller, R., et al. (2017). Tracking spinal cord injury: Differences in cytokine expression of IGF-1, TGF-B1, and sCD95l can be measured in blood samples and correspond to neurological remission in a 12-week follow-up. *Journal of Neurotrauma*, *34*(3), 607–614.

Fernández, M., Baldassarro, V. A., Capirossi, R., Montevecchi, R., Bonavita, J., Cescatti, M., et al. (2020). Possible strategies to optimize a biomarker discovery approach to correlate with neurological outcome in patients with spinal cord injury: A pilot study. *Journal of Neurotrauma*, *37*(3), 431–440. https://doi.org/10.1089/neu.2018.6362. Epub 2019 Aug 1.

Frost, F., Roach, M. J., Kushner, I., & Schreiber, P. (2005). Inflammatory C-reactive protein and cytokine levels in asymptomatic people with chronic spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *86*(2), 312–317. https://doi.org/10.1016/j.apmr.2004.02.009.

Ghosh, A., & Pal, R. (2019). Spinal cord injury: Point-of-care biomarkers for better prognosis. *Journal of Neurosciences in Rural Practice*, *10*(3), 390–391. https://doi.org/10.1055/s-0039-1698032. Epub 2019 Oct 7.

Hachisuka, S., Kamei, N., Ujigo, S., Miyaki, S., Yasunaga, Y., & Ochi, M. (2014). Circulating microRNAs as biomarkers for evaluating the severity of acute spinal cord injury. *Spinal Cord*, *52*(8), 596–600.

Hassanshahi, G., Amin, M., Shunmugavel, A., Vazirinejad, R., Vakilian, A., Sanji, M., et al. (2013). Temporal expression profile of CXC chemokines in serum of patients with spinal cord injury. *Neurochemistry International*, *63*(5), 363–367. https://doi.org/10.1016/j.neuint.2013.07.012. Epub 2013 Aug 6.

Kim, Y. H., Ha, K. Y., & Kim, S. I. (2017). Spinal cord injury and related clinical trials. *Clinics in Orthopedic Surgery*, *9*(1), 1–9.

Kwon, B. K., Bloom, O., Wanner, I. B., Curt, A., Schwab, J. M., Fawcett, J., et al. (2019). Neurochemical biomarkers in spinal cord injury. *Spinal Cord*, *57*(10), 819–831. https://doi.org/10.1038/s41393-019-0319-8. Epub 2019 Jul 4.

Kwon, B. K., Stammers, A. M., Belanger, L. M., Bernardo, A., Chan, D., Bishop, C. M., et al. (2010). Cerebrospinal fluid inflammatory cytokines and biomarkers of injury severity in acute human spinal cord injury. *Journal of Neurotrauma*, *27*(4), 669–682.

Kwon, B. K., Streijger, F., Fallah, N., Noonan, V. K., Bélanger, L. M., Ritchie, L., et al. (2017). Cerebrospinal fluid biomarkers to stratify injury severity and predict outcome in human traumatic spinal cord injury. *Journal of Neurotrauma*, *34*(3), 567–580.

Kwon, B. K., Tetzlaff, W., Grauer, J. N., Beiner, J., & Vaccaro, A. R. (2004). Pathophysiology and pharmacologic treatment of acute spinal cord injury. *The Spine Journal*, *4*(4), 451–464.

Laterza, O. F., Lim, L., Garrett-Engele, P. W., Vlasakova, K., Muniappa, N., Tanaka, W. K., et al. (2009). Plasma microRNAs as sensitive and specific biomarkers of tissue injury. *Clinical Chemistry*, *55*(11), 1977–1983.

Leister, I., Haider, T., Mattiassich, G., Kramer, J. L. K., Linde, L. D., Pajalic, A., et al. (2020). Biomarkers in traumatic spinal cord injury—Technical and clinical considerations: A systematic review. *Neurorehabilitation and Neural Repair*.

Li, M. M., Jiang, T., Sun, Z., Zhang, Q., Tan, C. C., Yu, J. T., et al. (2014). Genome-wide microRNA expression profiles in hippocampus of rats with chronic temporal lobe epilepsy. *Scientific Reports*, *4*, 4734. https://doi.org/10.1038/srep04734.

Lin, J., Li, J., Huang, B., Liu, J., Chen, X., Chen, X. M., et al. (2015). Exosomes: Novel biomarkers for clinical diagnosis. *Science World Journal*, *2015*, 657086. https://doi.org/10.1155/2015/657086. Epub 2015 Jan 27.

Moghaddam, A., Heller, R., Daniel, V., Swing, T., Akbar, M., Gerner, H. J., et al. (2017). Exploratory study to suggest the possibility of MMP-8 and MMP-9 serum levels as early markers for remission after traumatic spinal cord injury. *Spinal Cord*, *55*(1), 8–15. https://doi.org/10.1038/sc.2016.104. Epub 2016 Jul 5.

Moghieb, A., Bramlett, H. M., Das, J. H., Yang, Z., Selig, T., Yost, R. A., et al. (2016). Differential neuroproteomic and systems biology analysis of spinal cord injury. *Molecular & Cellular Proteomics*, *15*(7), 2379–2395. https://doi.org/10.1074/mcp.M116.058115. Epub 2016 May 5.

Norenberg, M. D., Smith, J., & Marcillo, A. (2004). The pathology of human spinal cord injury: Defining the problems. *Journal of Neurotrauma*, *21*(4), 429–440.

Papatheodorou, A., Stein, A., Bank, M., Sison, C. P., Gibbs, K., Davies, P., et al. (2017). High-mobility group box 1 (HMGB1) is elevated systemically in persons with acute or chronic traumatic spinal cord injury. *Journal of Neurotrauma*, *34*(3), 746–754. https://doi.org/10.1089/neu.2016.4596. Epub 2016 Oct 26.

Rodrigues, L. F., Moura-Neto, V., & Spohr, T. (2018). Biomarkers in spinal cord injury: From prognosis to treatment. *Molecular Neurobiology*, *55*(8), 6436–6448.

Saadatpour, L., Fadaee, E., Fadaei, S., Nassiri Mansour, R., Mohammadi, M., Mousavi, S. M., et al. (2016). Glioblastoma: Exosome and microRNA as novel diagnosis biomarkers. *Cancer Gene Therapy*, *23*(12), 415–418. https://doi.org/10.1038/cgt.2016.48. Epub 2016 Nov 11.

Saltzman, J. W., Battaglino, R. A., Salles, L., Jha, P., Sudhakar, S., Garshick, E., et al. (2013). B-cell maturation antigen, a proliferation-inducing ligand, and B-cell activating factor are candidate mediators of spinal cord injury-induced autoimmunity. *Journal of Neurotrauma*, *30*(6), 434–440. https://doi.org/10.1089/neu.2012.2501. Epub 2013 Mar 28.

Sengupta, M. B., Basu, M., Iswarari, S., Mukhopadhyay, K. K., Sardar, K. P., Acharyya, B., et al. (2014). CSF proteomics of secondary phase spinal cord injury in human subjects: Perturbed molecular pathways post injury. *PLoS One*, *9*(10), e110885. https://doi.org/10.1371/journal.pone.0110885. eCollection 2014.

Singh, J., Deshpande, M., Suhail, H., Rattan, R., & Giri, S. (2016). Targeted stage-specific inflammatory microRNA profiling in urine during disease progression in experimental autoimmune encephalomyelitis: Markers of disease progression and drug response. *Journal of Neuroimmune Pharmacology*, *11*(1), 84–97. https://doi.org/10.1007/s11481-015-9630-0. Epub 2015 Aug 16.

Spinal Cord Injury (SCI). (2016). 2016 facts and figures at a glance. *The Journal of Spinal Cord Medicine*, *39*(4), 493–494. https://doi.org/10.1080/10790268.2016.1210925.

Stein, A., Panjwani, A., Sison, C., Rosen, L., Chugh, R., Metz, C., et al. (2013). Pilot study: Elevated circulating levels of the proinflammatory cytokine macrophage migration inhibitory factor in patients with chronic spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *94*(8), 1498–1507. https://doi.org/10.1016/j.apmr.2013.04.004. Epub 2013 Apr 22.

Streijger, F., So, K., Manouchehri, N., Gheorghe, A., Okon, E. B., Chan, R. M., et al. (2018). A direct comparison between norepinephrine and phenylephrine for augmenting spinal cord perfusion in a porcine model of spinal cord injury. *Journal of Neurotrauma*, *35*(12), 1345–1357. https://doi.org/10.1089/neu.2017.5285. Epub 2018 Mar 28.

Strimbu, K., & Tavel, J. A. (2010). What are biomarkers? *Current Opinion in HIV and AIDS*, *5*(6), 463–466. https://doi.org/10.1097/COH.0b013e32833ed177.

Tigchelaar, S., Gupta, R., Shannon, C. P., Streijger, F., Sinha, S., Flibotte, S., et al. (2019). MicroRNA biomarkers in cerebrospinal fluid and serum reflect injury severity in human acute traumatic spinal cord injury. *Journal of Neurotrauma*, *36*(15), 2358–2371. https://doi.org/10.1089/neu.2018.6256. Epub 2019 May 14.

Wanner, I. B., Anderson, M. A., Song, B., Levine, J., Fernandez, A., Gray-Thompson, Z., et al. (2013). Glial scar borders are formed by newly proliferated, elongated astrocytes that interact to corral inflammatory and fibrotic cells via STAT3-dependent mechanisms after spinal cord injury. *The Journal of Neuroscience*, *33*(31), 12870–12886. https://doi.org/10.1523/JNEUROSCI.2121-13.2013.

Witiw, C. D., & Fehlings, M. G. (2015). Acute spinal cord injury. *Journal of Spinal Disorders and Techniques*, *28*(6), 202–210. https://doi.org/10.1097/BSD.0000000000000287.

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Chapter 14

Quality of life tools for spinal cord–injured people

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Abbreviations

ADL	activities of daily living
ASIA	American Spinal Injury Association
BPI	brief pain inventory
CHART	Craig Handicap Assessment and Reporting Technique
FSFI	female sexual function index
HRQOL	health-related quality of life
ICF	International Classification of Functioning disability and health
IIEF	International Index of Erectile Function
ISCOS	International Spinal Cord Society
LISAT	life satisfaction questionnaire
NIH	National Institutes of Health
ParQOL	Participation and Quality of life toolkit
PRISM	Patient Reported Interference of Spasticity Measure
PROMIS	Patient Reported Outcomes Measurement Information System
QLI	quality of life index
QOL	quality of life
QWB	quality of well-being scale
SCI	spinal cord injury/spinal cord injured
SF-36	Medical Outcomes Study 36-item short form health survey
SWLS	satisfaction with life scale
WHO	World Health Organization
WHOQOL	WHO quality of life instrument

Introduction

From the second half of the last century, advances in the study and medical care aimed to help people with spinal cord injury (SCI) have resulted in greater life expectancy in this population (Hill, Noonan, Sakakibara, & Miller, 2010). SCI sequelae are well known, as well as other specific associated medical problems that these patients have to overcome, which frequently interfere with everyday life. Likewise, people with SCI require specific equipment to enable the integration into their social and home environments and adapt to daily life, i.e., from mobility devices to incontinence products, as well as help from other people for basic activities of daily living (ADL). All these circumstances cause great psychological pressure with which they have to live and result in comorbidities, e.g., anxiety, depression, distortion of body image, self-esteem, sense of failure, etc.

Moreover, there are different barriers that interfere particularly with the quality of life (QOL) of people with disabilities (Bökel et al., 2020). In 2001, after various periods of study and reflection on models for evaluating people with distinct functional capabilities, the World Health Organization (WHO) developed the International Classification of Functioning (ICF) (WHO: https://apps.who.int/iris/handle/10665/42407) that addresses the medical condition from a biopsychosocial perspective and seeks to integrate a person's functional capacity with the execution of activities and social participation (Dijkers, 2005).

Diagnosis and Treatment of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822498-4.00014-2

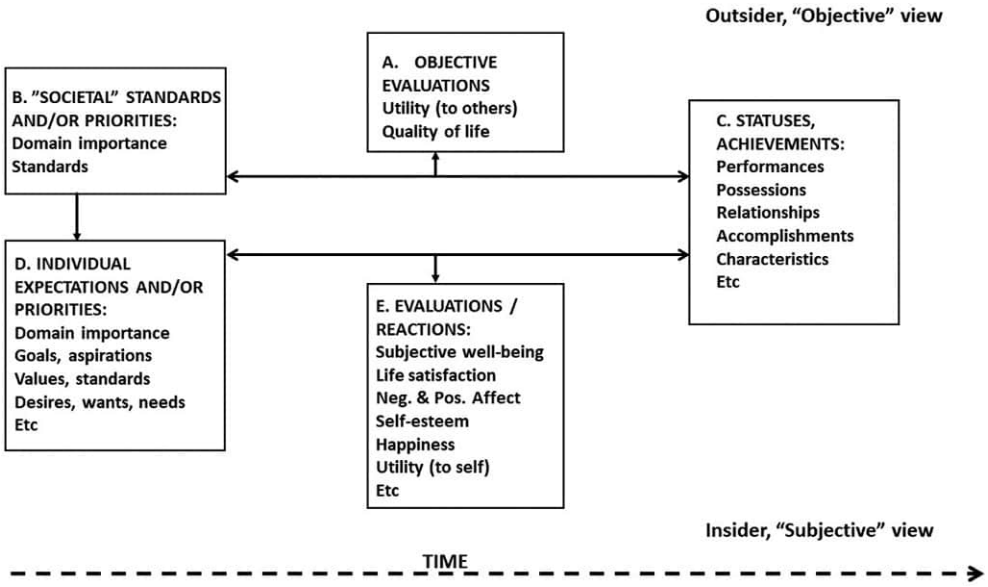

FIG. 1 Dijkers' Model of approach to quality of life. Approach to quality of life according to a "objective" or "Subjective" view, which shows various factors that influence the researcher's perception in their social environment, or the individual's and their subjective standards. *(With permission from: Dijkers MP. (2003) Individualization in quality of life measurement: instruments and approaches. Arch Phys Med Rehabil,84 Suppl 2: Fig. 1, page S4.).*

However, despite the work done, there is no agreement in the scientific literature on the concept of QOL to be studied in handicapped people and/or with chronic diseases, as in the case of this population (Hill et al., 2010; Post, 2014). In their assessment, researchers additionally need to define the concept of health, which affects the daily life of the people subject of study.

Since the establishment of the concept of *health* by the WHO in 1947, "*a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity*", QOL was correlated to states of subjective well-being, although later, some objective aspects were included (Post, 2014).

Thus, the definition of *quality of life* in medicine and in psychology has been the subject of controversy on many occasions. On the one hand, a subjective approach is adopted by the person subject of study, in which there should be a consistency between the person's expectations and achievements to perceive satisfaction in their lives. On the other hand, there is an objective approach in which case the observer establishes certain parameters that characterize a satisfactory QOL from different points of view (Dijkers, 2003) (Fig. 1) one of them being the medical condition considered by the researcher (Hill et al., 2010; Miller et al., 2010).

If we consider the previously exposed ideas, different angles can be used when assessing QOL in people with SCL: subjective assessment of QOL by the person (Moons, Budts, & De Geest, 2006), its interrelation with the social environment in which the person lives, physical components—mainly impairments due to physical sequelae—mood, overall health status, or by specifying the difficulties in the management or assumption of system dysfunction that affect having a satisfactory social life—family-related, work-related, and education.

Definitions: Quality of life and health-related quality of life

QOL is a multi-dimensional concept that includes subjective and objective factors, for which reason it is defined differently in each academic field, social group, or individuals. In fact, the WHO defines QOL as "*individual's perception of their position in life in the context of the culture and value system in which they live and in relation to their goals, expectations, standards, and concerns*" (The WHOQOL Group, 1998). This conveys a subjective view linked to the social context.

For an integrative assessment of QOL, an approach from a variable number of dimensions or *domains* is accepted, each of which refers to an area of vital aspects that differs from the others (Dijkers, 2005). To complete the definition of *health* proposed by the WHO, at least three dimensions are included: physical function, mental state, and ability to have social interactions (Post, 2014), which are usually found in the instruments that measure QOL from a subjective view by the affected person and the objective perspective of the observer.

Thus, approaching QOL in medicine is easily associated with the concept of health-related quality of life (HRQOL), which according to Dijkers is part of an objective view and makes reference to *those components in the person's QOL directly or indirectly affected by the disease, lesions, and treatment side effects* (Dijkers, 1997), for which reason the "medical condition" of the person is included, as pointed out by Post (2014).

On a higher level, the interaction of the health domains with the ability to interact with the surroundings and function of the person is contemplated in the structure of the ICF (Post & Noreau, 2005).

Implementation in the study of quality of life in people with spinal cord injury

Defining the concept of QOL and its assessment from an objective view is subject of discussion and lack of agreement between researches (Tate & Forchheimer, 2014), due to the complexity of SCI physical sequelae, along with the outcome of rehabilitation and evidence that people with SCI may enjoy a full life integrated in their social environment. The instruments are usually developed based on values imposed on the participants, and sometimes there is little relation between the values communicated by the concerned individuals and those believed to be relevant by the researches and even by the caregivers (Fuhrer, Rintala, Hart, Clearman, & Young, 1992). As stated by Tate (Tate, Kalpakjian, & Forchheimer, 2002), subjects affected by SCI distinguish between having spinal cord injury–related sequelae and their health status ("I am healthy").

For this reason, the impact certain sequelae have on various QOL domains is examined in instruments assessing HRQOL in people with SCI-related sequelae, along with the assessment of global QOL, the latter form a subjective view as it can only be determined by the affected person (Moons et al., 2006).

Databases

There are numerous academic institutions and knowledge bases trying to cluster the different instruments for measuring abilities, sequelae, or dysfunctions, and their interaction with the subject's life regarding physical aspects, function, mental, social, and of QOL in general. Concerning SCI, the SCIRE project (Miller et al., 2010; www.scireproject.com) is of great relevance. Revisions of the different fields of action are carried out in the project, and recommendations of different assessment instruments given, with regular updates, reviews on their validity, and diffusion in the medical literature. Likewise, numerous instruments for assessing health conditions secondary to SCI are found in the resources grouped in the Participation and Quality of Life Toolkit (ParQOL; www.parQOL.com), but in this case, they are related with Dijkers's QOL model and provide use and access instructions.

From a perspective focused on the person, the project developed under the auspice of the National Institutes of Health in the United States of America as of 2004, the Patient-Reported Outcomes Measurement Information System (PROMIS: www.healthmeasures.net), groups numerous useful instruments for assessing different elements linked with HRQOL that have shown a correlation with aspects collected by the ICF (Wong et al., 2018). The mission of PROMIS is to create a health model to transmit the health status communicated by the subject (Post, 2014), so that a global assessment on the person that is useful for the observer can be made compatible with the standards of the ICF. Its use in subjects with neurological disorders concentrates in Neuro-QOL (Tulsky et al., 2015). A specific HRQOL for SCI is the SCI-QOL, inside the PROMIS project, that is undergoing validation with a large sample of persons with SCI in United States of America (Tate & Forchheimer, 2014).

However, the use of many instruments is complex in clinical practice, and consequently clinical researches focus on a limited number of them. When choosing a tool, we must consider which is the aspect of QOL we want to assess: the subjective perspective of the person, the relationship with the social and cultural environment, specific health domains, effect of a specific sequelae or dysfunction, comparison or not with other populations—either by cultural setting or different type of disability or function—specific validation for SCI or general, etc. (Geyh, Fellinghauer, Kirchberger, & Post, 2010; Tate & Forchheimer, 2014).

Several reviews of the instruments and methods used for assessing QOL in people with SCI have been done (Hill et al., 2010) (Tables 1 and 2).

Below we discuss the most commonly used instruments in the medical literature, clustering them as global QOL and specific HRQOL for certain SCI-related sequelae tools (Tables 3 and 4). Despite the numerous instruments used in this population, there are no agreed standard measures and some show deficiencies in validity and sensitivity to change in comparative studies.

TABLE 1 Objective QOL Instruments.

Objective tools									
Name	**Description**	**Items**	**Domains (No. of questions)**	**Scoring and response**	**Measurement model**	**Time taken (min)**	**Alternative languages**	**Item bias**	**Interviewer (I) or self-administration**
Patient reported impact of spasticity measure (PRISM)	Addresses negative and positive impact of spasticity on QOL in SCI population	41	Societal avoidance/ anxiety (11); psychological agitation (5); daily activities (6); need for assistance/ positioning (5); impact on activities +/− (4); need for intervention (5); social embarrassment (5)	5-point Likert scale Sub-scale scores are obtained by averaging item scores and dividing by number of items Higher is unhealthier	"Relative to the range of the scale, more persons scored in lower ranges (indicating less impact)"	Not available	None	Developed in SCI population	SA
Quality of well-being questionnaire-SA (QWB-SA)	Point-in-time preference measure designed to measure HRQOL	71	Symptoms and problems (58); mobility, physical activity, social activity (13)	0.0—death to 1.0—optimum health Higher is healthier	No floor and ceiling effects	<20	Various	Face validity supports low bias	SA
Qualiveen	Disease-specific perspective on QOL in SCI for urinary disorders	30	Limitations (9); constraints (8); fears (8); feelings (5)	5-point Likert scales (0–4); total range 0–100 Tabulate total Higher is unhealthier	Minimal	Not available	Various	Developed in SCI population	I or SA
Sickness Impact Profile (SIP68)	Generic health status measure, measures health-related changes in behavior associated with the carrying out of daily activities	68	Somatic autonomy (17); mobility control (12); mobility range (10); social behavior (12); emotional stability (6); psychological autonomy and communication (11)	No = 0, yes = 1; total range 0–68 Yes responses are tabulated; can divide into SIPSOM, SIPPSY, SIPSOC sub-scales Higher is unhealthier	Ceiling effects MR (31.3%), ES (54%), & PAC (53.8%) domains	~15–20	Dutch	Scoring on one question adjusted for SCI	I or SA

Short Form 36 (SF-36)	Addresses basic human values relevant to QOL and well-being through individual domains and two global components	36	Physical functioning (10); role limitations because of physical health problems (4); bodily pain (2); general health (5); vitality (4); social functioning (2); role limitations because of emotional problems (3); mental health (5)	Total range 0–100 Norm-based score is 50, with standard deviation 10. Can be divided into two summary scores: physical and mental, calculated by a system of + and − weights on domain scores Higher is healthier	Floor and ceiling effect PF (12.2%–24.2%; free—29.7%), RLP (28.1%–36.3%; 22.5%–54.4%); ceiling effect SF (free—33.5%), RLE (63.8%–75.3%)	<15	Available in most major languages	Face validity supports low bias	I or SA
Short form 36 veterans/SCI (SF-36 V)	Version of SF-36 designed for use in the disabled population. Physical functioning section has been modified to accommodate SCI population	36	Physical functioning (8)	Each domain converted to range of 0–100 Divided into two summary scores: physical and mental components, are norm based; general population score 50 and standard deviation of 10 Higher is healthier	"Descriptive responses to the items showed a floor effect on many of the items"	Not Available	None	PF domain altered in SCI population	I or SA
Short form 12 (SF-12)	A shortened version of the SF-36, used in population studies	12	Physical functioning (2); role limitations because of physical health problems (2); bodily pain (1); general health (1); vitality (1); social functioning (1); role limitations because of emotional problems (2);	Total range 0–100 Divided into two summary scores: physical and mental components, are norm based; general population score 50 and standard	Summary scores free of floor and ceiling effects	˜2–4	Available in most major languages	Face validity supports low bias	I or SA

Continued

TABLE 1 Objective QOL Instruments—cont'd

Objective tools									
Name	**Description**	**Items**	**Domains (No. of questions)**	**Scoring and response**	**Measurement model**	**Time taken (min)**	**Alternative languages**	**Item bias**	**Interviewer (I) or self-administration**
			general mental health (2)	deviation of 10 Higher is healthier					
Short form 6-disability (SF-6D)	A six-dimensional health state classification based on the SF-36	11	Physical functioning (3); role limitation physical (1); role limitations emotional (1); social functioning (1); pain (2); mental health (2); vitality (1)	0.29 (the worst health state)—1.00 (perfect or full health) Preference-based weights were assigned to each response; negative responses detract from perfect health score Higher is healthier	Floor effect PF (37%); ceiling effect RLP and E (55%), SF (50%), P (36%), MH (35%)	Not available	Available in most major languages	Face validity supports low bias	I or SA

Reproduction of table showing the objective instruments of QOL according to MR Hill. Adapted with permission from: Hill, M., Noonan, V., Sakakibara, B. and the SCIRE research team. (2010). Quality of life instruments and definitions in individuals with spinal cord injury: a systematic review. Spinal Cord, 48, 438–450.

TABLE 2 Subjective QOL Instruments.

Subjective tools									
Name	**Description**	**Items**	**Domains (No. of questions)**	**Scoring and response**	**Measurement model**	**Time taken (min)**	**Alternative languages**	**Item bias**	**Interviewer (I) or self-administration**
Quality of life index (QLI)	Measures subjective QOL in terms of satisfaction	32–37	Health and functioning (8); social and economic (8); psychological and spiritual (8); family (8)	6-point Likert scales for both importance and satisfaction sub-sections Weigh satisfaction (S) scores with corresponding importance (I) scores; 3.5 subtracted from S scores, raw I score used. Total and sub-scale scores tabulated Higher is healthier	None	~10	None for SCI version	SCI version evaluated by SCI patients	I or SA
Quality of life profile for adults with physical disabilities (QOLP-PD)	A holistic approach to QOL that empowers individuals in which elements of QOL are the same for people with and without disabilities, but each may address issues differently; questions address aspects of daily life	102	Being (32): physical, psychological, spiritual; belonging (37): physical, social, community; becoming (33): practical, leisure, growth	5-point Likert item scales 1—not at all satisfied to 5—extremely satisfied and 1—not important to 5—very important Weigh satisfaction and importance scores for each item; three points are subtracted from S scores, raw I scores used Higher is healthier	None reported	Not available	None	Developed in disabled and SCI population	I or SA

Continued

TABLE 2 Subjective QOL Instruments—cont'd

Subjective tools									
Name	**Description**	**Items**	**Domains (No. of questions)**	**Scoring and response**	**Measurement model**	**Time taken (min)**	**Alternative languages**	**Item bias**	**Interviewer (I) or self-administration**
Satisfaction with life survey (SWLS)	Addresses life satisfaction as a whole, reflecting a global perspective of individual's values	5	In most ways my life is close to ideal; the conditions of my life are excellent; I am satisfied with my life; so far I am getting the important things I want in life; if I could live my life over, I would change almost nothing	7-point Likert scale Global score is computed Higher is healthier	Floor effects seen on some items	<5	Various	Face validity supports low bias; some questions	I or SA
Sense of well-being index (SWBI)	Measures subjective QOL for people with disabilities in work rehabilitation	26	Physical well-being and associated feelings about self (6); psychological well-being (7); family and social well-being (6); financial well-being (8)	4-point Likert scale Tabulate total and domain scores Higher is healthier	None reported	"Brief"	None	Altered for and evaluated in SCI population	I or SA
World Health Organization quality of life (WHOQOL-BREF)	Instrument that conceptually fits with the WHO definition of QOL	26	Physical health/capacity (7); psychological health/well-being (6); social relationships (3); environment (8); overall QOL (1); general health (1)	5-point Likert scale Domain scores calculated by multiplying mean of facet scores by four, and transformed onto a scale of 0–100 Higher is healthier	None; floor effect in one item: mobility (29.7%)	Not reported	Available in most major languages	Face validity supports low bias	SA

Reproduction of the continuation of the table showing the subjective instruments of QOL according to MR Hill. Adapted with permission from: Hill, M., Noonan, V., Sakakibara, B. and the SCIRE research team. (2010). Quality of life instruments and definitions in individuals with spinal cord injury: a systematic review. Spinal Cord, 48, 438–450.

TABLE 3 Global instruments.

Instrument	Authorship	Available	Validated SCI	Items global QOL or HRQOL Yes Y (n)/No N	Mainly Subjective S/Objective O
CHART	Whiteneck 1992	http://tbims.org/combi/chart/	Yes	N	O
SF-36	Ware 1992	https://www.rand.org/health-care/surveys_tools/mos/36-item-short-form.html	Yes	N	O
QLI	Ferrans & Powers 1985	http://qli.org.uic.edu/questionaires/questionnairehome.htm	Yes	Y (10%)	S
SWLS	Diener 1985	https://eddiener.com/scales/7	Yes	Y (100%)	S
LISAT-9	Fugl-Meyer 1991	*http://scireproject.com/*	Yes	Y (1)	S
QWB-SA	Andresen 1999	https://hoap.ucsd.edu/qwb-info/	No	N	O
WHOQOL-BREF	WHOQOL Group 1998	https://www.who.int/healthinfo/survey/whoqol-qualityoflife/en/	Yes	Y (2)	S
EQ-5-5 L; EQ-5-3 L	EuroQol Group 1990	https://euroqol.org/support/how-to-obtain-eq-5d/	No	Y (1)	O

Characteristics of global instruments reported in the text. The author that originally reported each one, and on-line resource are shown. The fact that items about global QOL are asked in the questionnaire correlates with subjective view of the instrument.

TABLE 4 Specific instruments for associated conditions in SCI.

Instrument	Measure	Authorship	Available at	Validated for SCI
CHART	Disability	Whiteneck et al., 1992	http://tbims.org/combi/chart/	Yes
PRISM	Spasticity	Cook KF et al., 2007	https://pubmed.ncbi.nlm.nih.gov/18247233/	Yes
SCI-SET	Spasticity	Adams et al., 2007	https://www.archives-pmr.org/action/showPdf?pii=S0003-9993%2807%2900426-1	Yes
BPI	Pain	Cleeland CS, 1994	*Long form:* https://www.mdanderson.org/content/dam/mdanderson/documents/Departments-and-Divisions/Symptom-Research/BPI-Long_English_SAMPLE.pdf *Short form:* https://www.mdanderson.org/content/dam/mdanderson/documents/Departments-and-Divisions/Symptom-Research/BPI-SF_English-24h_Original_SAMPLE.pdf	Yes
MPI	Pain	Widerström-Noga et al., 2002	https://www.archives-pmr.org/article/S0003-9993(02)96227-1/fulltext#secd11784441e1566	Yes

Continued

TABLE 4 Specific instruments for associated conditions in SCI—cont'd

Instrument	Measure	Authorship	Available at	Validated for SCI
MPRCQ2	Pain	Nielson WR et al., 2003	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2758642/pdf/nihms125144.pdf	Yes
WUSPI	Pain	Curtis KA et al., 1995		Yes
NBDS	Neurogenic bowel dysfunction	Krogh K et al. 2005	Long form: https://www.coloplast.ca/Global/3_Bladder%20and%20Bowel/Pictures/Peristeen%20HCP/Peristeen_NBD_Score_Questionaire_A4.pdf	Yes
FIQOL	Fecal incontinence	Rockwood et at, 2000	https://pubmed.ncbi.nlm.nih.gov/10813117/	No
FICQOL	Fecal incontinence and constipation	Nanigian et al., 2008	https://pubmed.ncbi.nlm.nih.gov/18721959/	Yes (Spina Bifida)
Qualiveen-30	Neurogenic bladder dysfunction	Costa, P, 2001	https://pubmed.ncbi.nlm.nih.gov/11173948/	Yes
SF-Qualiveen	Neurogenic bladder dysfunction	Bonniaud,V 2008	https://pubmed.ncbi.nlm.nih.gov/18950816/	Yes
SCI-QOL Bladder Complications	Urinary tract infections	Tulsky,D·S, 2015	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4445020/	Yes
SIAS	Sexuality	Kreuter,M 1994	https://pubmed.ncbi.nlm.nih.gov/7885719/	Yes
FSFI	Sexual function in women	Rosen, R.C. 2000	https://pubmed.ncbi.nlm.nih.gov/10782451/	No
IIEF	Sexual function in males	Rosen,R.C. 1997	https://pubmed.ncbi.nlm.nih.gov/9187685/	No

Specific instruments that are used for measuring the impact of some conditions in the QOL of the person. The author that spread it is displayed. Abbreviations: PRISM, Patient Reported Impact of Spasticity Measure; SCI-SET, Spinal Cord Injury Spasticity Evaluation Tool; BPI, Pain Brief Inventory; MPI, Multi-dimensional Pain Inventory; MPRCQ2, Multi-dimensional Pain Readiness to Change Questionnaire; WUSPI, Wheelchair Users Shoulder Pain Index; NBDS, Neurogenic Bowel Dysfunction Score; FIQOL, Fecal Incontinence Quality of Life Scale; FICQOL, Fecal Incontinence and Constipation Quality of Life; SIAS, Sexual Interest, Activity and Satisfaction; FSFI, Female Sexual Function Index; IIEF, International Index of Erectile Function.

There are also many other tools for evaluating different aspects of people with SCI in relation with their QOL, as measures of health status, physical function, mental function, and participation. We display some examples of tools referenced in the literature that are useful in SCI population studies (Table 5).

Integrative quality of life assessment instruments

The **Medical Outcomes Study 36-Item Short Form Health Survey (SF-36)** was developed in the early 90s (Ware Jr. & Sherbourne, 1992). It is a generic scale that provides a profile of the health status (physical and mental components) and has been useful for assessing HRQOL in the general population and also in people with SCI. This scale has been validated and used in several languages and a short version of the SF-36 has been constructed (SF12) with similar validity (Iorio-Morin et al., 2018). However, all the above-mentioned is not an impediment to point out there are certain difficulties for its use in SCI persons, as some of the items are not easy to apply in this population due to mobility issues (Andresen, Gravitt, Aydelotte, & Podgorski, 1999; Tate et al., 2002) and modifications were done adapted to this objective, either by reformulating the items (Froehlich-Grobe, Andresen, Caburnay, & White, 2008) or adapting new items to the disability (SF-36 V) (Kazis et al., 2004; Luther et al., 2006). Nonetheless, it is one of the most widely used reference instruments,

TABLE 5 General instruments referenced for SCI assessments.

Instrument	Measure	Assessing	Refer to
Sickness Impact Profile	Health status	Person's perception of their health status in six sub-scales with respect to their disease impact.	Bergner M et al. 1981 https://physio-pedia.com/File:SIP.png
Nottingham Health Profile	Health status	Person's perception of emotional, social and physical health problems.	Hunt SM et al. 1981 https://doi.org/10.1016/0271-7123(81)90005-5
CHART	Participation	Ability in six domains with respect to maintain typical community roles	Whiteneck GG et al., 1992 http://tbims.org/combi/chart/
FIM	Disability	Records the severity of disability of rehabilitation patients in six areas	Linacre JM et al. 1994 https://www.physio-pedia.com/File:Functional_Independence_Measure.jpg
SCIM-III	Disability	Independence in ADL, mobility and bladder & bowel function specific for SCI people	Itzkovich M et al. 2007 https://scireproject.com/wp-content/uploads/SCIM_Toolkit_Printable-1.pdf
Neuro-QoL Lower Extremity Function	Function	Ability or difficulty for mobility in different environment	healthmeasures.net https://www.healthmeasures.net/index.php?option=com_instruments&view=search&Itemid=977
Patient Health Questionnaire	Mental function	Diagnostic criteria for major depressive disorder	Kroenke K et al. 2001 https://www.icsi.org/guideline/depression/appendix-a-patient-health-questionnaire-phq-9/
Hospital Depression and Anxiety Scale	Mental function	States of depression and anxiety in the setting of a hospital medical outpatient clinic	Bjelland I et al. 2002 https://www.researchgate.net/figure/The-standard-Hospital-anxiety-and-depression-scale-questionnaire-in-English_fig1_321034906
Brief Symptom Inventory	Mental function	Global psychological distress, covering nine symptom dimensions of depression	Derogatis LR, Melisaratos N. 1983 http://psychcorp.pearsonassessments.com/HAIWEB/Cultures/en-us/Productdetail.htm?Pid=PAbsi
DASS-21	Mental function	Screening for depression, anxiety and stress	Mitchell MC et al. 2008 https://maic.qld.gov.au/wp-content/uploads/2016/07/DASS-21.pdf
SCL CSQ	Mental function & general	Three domains about coping with SCI: acceptance of injury, social reliance and fighting spirit	Elfström ML et al. 2007 http://scireproject.com/wp-content/uploads/Clinician-Summary-v.5.0_SCL_CSQ.pdf

There are several measurement instruments used in combination to QOL scales. Some representative tools are displayed, with the author that spread it. Inside the PROMIS-NEURO-QoL system, there are several measures that are useful in many function and health domains. Healthmeasures.net is referred for obtaining them. Abbreviations: CHART, Craig Handicap Assessment and Reporting Technique; FIM, Functional Independence Measurement; SCIM-III, Spinal Cord Independence Measurement v.III; DASS-21, Depression Anxiety Stress Scale; SCLCSQ, Spinal Cord Lesion-related Coping Strategies Questionnaire.

with high consistency and reproducibility. It measures the following domains: physical, mental, emotional, pain, vitality, social functioning, and health in general.

The **Quality of Life Index** (QLI) has been widely used since its proposal by Ferrans and Powers and has been adapted to SCI (May & Warren, 2002). It allows assessing general QOL with social, spiritual, and economic aspects, and has been applied to SCI populations (Mortenson, Noreau, & Miller, 2010), associated or not to other objective instruments, e.g., assessment of bladder dysfunction (Best, Ethans, Craven, Noreau, & Hitzig, 2017). It is available in numerous languages and thus very useful to evaluate this population, although its psychometric properties have not been completely established in SCI (Miller et al., 2010).

Another known instrument for global assessment is the **Satisfaction with Life Scale** (SWLS) (Pavot & Diener, 1993), validated for people with SCI (Dijkers, 1999) and widely used in different studies in subjects with SCI (Post, van Leeuwen, van Koppenhagen, & de Groot, 2012), including assessment of rehabilitation outcomes (Hicks et al., 2005). This tool is

recommended for its shortness (five items) and easy-to-use in daily clinical practice; it has an acceptable consistency and reliability for comparative studies (Miller et al., 2010). Despite its wide use, larger psychometric studies should be performed in subjects with SCI (Geyh et al., 2010).

The **Life Satisfaction Questionnaire** (LISAT) developed by Fugl-Meyer in 1991, has been applied in several studies, mainly European, in its nine-item version, showing correct validity in relation with other QOL instruments (Post & Noreau, 2005; M. W. Post et al., 2012) and correct internal consistency (Geyh et al., 2010). However, its use in assessment studies with the SCI population is scarce.

The **Quality of Well-Being** (QWB) scale was used in numerous studies since its development by Andresen in 1998. Later, the self-administered version (QWB-SA) was created. However, this is an instrument with a high number of items (71) and there are few references on its validity in people with SCI (Andresen et al., 1999; Whitehurst, Engel, & Bryan, 2014).

During the decade of the 90s the WHO Quality of Life group developed the research of instruments for assessing QOL (The WHOQOL Group, 1998) in people affected by diverse conditions (AIDS, mental disorders, cancer, transplant recipients, etc.). Thus, in 1995 the **WHOQOL-100** questionnaire was created, and later its reduced version—the **WHOQOL-BREF—**was created (https://www.who.int/mental_health/publications/whoqol/en/). It has been applied on people with SCI since 2004 (Jang, Hsieh, Wang, & Wu, 2004) and validated in different languages, together with the 26-item short version. This version (WHOQOL-BREF) has demonstrated good applicability in clinical diagnosis with sufficient psychometric characteristics, although some of its domains (social) have less consistency due to the low number of items (Skevington, Lotfy, & O'Connell, 2004). Many validation studies against other reference instruments such as the SF-36 have been carried out (Lin, Hwang, Chen, & Chiu, 2007), showing lower ceiling and floor percentages. Similarly, in general, its items are better accepted by people with SCI than the SF-36. Its validity for studying global QOL and its relationship with physical, psychological, and relation with the surroundings, makes it interesting for studying the QOL in people with SCI-related sequelae (Salvador-De La Barrera et al., 2018).

In the early 90s, the European EuroQol-Group (1990) developed an instrument for measuring HRQOL. Five assessment domains were established: mobility, daily activities and self-care, psychological functioning, social and role performance, and pain or other health problems. Furthermore, a grading of global QOL was added in the form of a visual analogue scale (VAS) (Devlin & Brooks, 2017). This instrument began to be widely used and two versions were made: the **EQ-5D** and the **EQ-3D** that differentiate in the number of levels that characterize each domain, based on the levels of difficulty or affectation (five or three degrees, respectively). The EuroQol instrument has been widely used, translated into several languages, and applied to people with SCI; however, it has not been sufficiently validated for this population, with the disadvantage that mobility items are drafted incorrectly for wheelchair users (Whitehurst, Noonan, Dvorak, & Bryan, 2012).

Health-related quality of life assessment instruments for conditions resulting from spinal cord injury

Numerous instruments have been proposed to assess the effects the different sequelae and dysfunctions caused by devices have on QOL in people with SCI. Give the diversity of scales and instruments it is not possible to discuss all of them (Table 4). We have selected a sample of the most referenced ones in the medical literature, e.g., assessment of the impact of conditions such as bladder dysfunction, pain, spasticity, or sexual function.

- Assessment of the impact of neurogenic bladder on the quality of life of patients with spinal cord injury

The Qualiveen-30 questionnaire was developed by Costa (Costa et al., 2001) to specifically measure the impact of bladder dysfunction on QOL in spinal cord-injured patients. It is a 30-item subjective questionnaire comprising four domains, each considering different aspects derived from alterations in bladder emptying (limitations, constraints, fears, and feelings).

The validity of the questionnaire in patients with SCI has been tested in many studies (Bonniaud, Bryant, Parratte, & Guyatt, 2008a; Nikfallah et al., 2015) and stands out for its high reproducibility and internal consistency (Nikfallah et al., 2015). Furthermore, the questionnaire has been validated by comparing it to other QOL questionnaires, such as the Kings Health Questionnaire (Karapolat, Akkoç, Eyigör, & Tanıgör, 2018). The use of the Qualiveen-30 questionnaire has been extended to other medical specialties, e.g., multiple sclerosis (Milinis, Tennant, A Young, & Group, 2017).

In 2008, the short version of this questionnaire was developed, the SF-Qualiveen (Bonniaud et al., 2008a), with eight items and four domains.

Recently published reviews recommend Qualiveen-30 and SF-Qualiveen and identify them as the best options to assess the QOL in people suffering from neurogenic bladder after SCI (Best et al., 2017).

- Assessment of the impact of spasticity on the quality of life of people with spinal cord injury

Spasticity is a common impairment associated to SCI and considered a limiting factor by many patients (Levi, Hultling, Nash, & Seiger, 1995). To date, few scales are available for patients with SCI. However, in a systematic review carried out by Balioussis (Balioussis, Hitzig, Flett, Noreau, & Craven, 2014), the authors concluded that the Patient-Reported Impact of Spasticity Measure (PRISM) is superior to the Spasticity Evaluation Tool (SCI-SET), because besides including more psychometric data, PRISM is more sensitive for measuring the impact of spasticity and represents more affective values.

PRISM is a subjective scale developed by Cook (Cook et al., 2007), a 41-item tool divided into seven sub-scales. Currently it is only available in English and Serbian, has good reliability and reproducibility (Hill et al., 2010), and has been validated for patients with multiple sclerosis (Knezevic et al., 2015). Several studies support the usefulness of this measuring tool (Hill et al., 2010; Sweatman, Heinemann, Furbish, & Field-Fote, 2020; Whitehurst et al., 2012).

- Assessment of the impact of pain on the quality of life of patients with spinal cord injury

Although exact prevalence of chronic pain in patients with SCI is variable, this condition is considered a major limiting factor, causing huge impact on QOL (van Gorp, Kessels, Joosten, van Kleef, & Patijn, 2015).

The **Brief Pain Inventory (BPI)** is an instrument designed to assess the severity of pain and its impact on ADL. It was shaped based on McGill's pain questionnaire, translated to several languages, and may be completed as a self-report or interview (Cleeland & Ryan, 1994). This instrument is available in two formats: the BPI short (used for clinical trials and translations to other languages) and long (with additional descriptive items) forms (de Andrés Ares et al., 2015).

There are three modified versions of this inventory for the SCI population (7, 10, and 12 items). Five additional items make up the 12-item scale (self-care, recreational activities, social activities, communication, learning new information) and only the first three ones are used to complete the 10-item scale. Its clinical use has been confirmed in different studies (Dawu et al., 2019; Hand, Velozo, & Krause, 2018).

Regarding its reliability, internal consistency of the BPI is high for the three modified versions and as for the validity, it has high correlation with pain intensity numerical rating scales and with the Short Form-36 (SF-36) scale (Raichle, Osborne, Jensen, & Cardenas, 2006).

- Assessment of the impact on sexual dysfunction

Preserving sexual function is one of the high priority issues of subjects after SCI. Subjective scales were developed at the end of the 80s and early 90s to assess QOL associated to sexual function (The SCIRE Project; https://scireproject.com/outcome-measures/). However, in the systematic review carried out by Abrahmson (Abramson, McBride, Konnyu, Elliott, & Team, 2008) the authors pointed out that none of the scales have the ability to assess the most relevant aspects that define sexual health of this population group. On the same line are the recently published ISCOS guidelines, which establish the recommendations on data collection when analysis of sexual function is done segregated by gender: International SCI Male Sexual Function Basic Data Set and the International SCI Female Sexual and Reproduction Function Basic Data Set (Alexander et al., 2017).

At present, the most widely used sexual function scales in people with SCI are the International Index of Erectile Function (IIEF) and the Female Sexual Function Index (FSFI), although neither one is sufficiently validated in patients with spinal cord injury (S. Elliott & Querée, 2018) and cannot be considered QOL assessment instruments. Recently (2019), a questionnaire within the SCI-High Project has been developed—the SCI-High Sexual Health Patient Questionnaire—and is pending validation (S. Elliott et al., 2019).

Finally, it is important to point out the need for widely used, validated, and accepted instruments, and we support the initiative of the International SCI Data Sets Project of the international societies ASIA and ISCOS (Biering-Sørensen et al., 2006; Tate & Forchheimer, 2014). Although the SCI-QOL-Basic Data Set (QOL-BDS) questionnaire (Charlifue et al., 2012) is not widely distributed and there is scarce experience, it has shown sufficient consistency for its use in studies and data collection databases (Post et al., 2019).

Conclusions

When assessing the QOL of people with SCI-related sequelae, the subjective view of the person must always be taken into consideration, choosing the instrument as per the global or specific aspect to be studied.

Global QOL assessment instruments are the most widely used covering many domains linked to the medical condition of the person. When studying HRQOL, an objective approach is done defining the domains possibly affected by SCI, without putting aside the subjective perspective of the person.

The use of instruments focused on a specific SCI-related condition or sequelae should be based on wide studies. Furthermore, there must be agreements for their validity in many social and cultural environments.

Applications to other areas of neuroscience

Assessment of quality of life (QOL) in handicapped people is part of the rehabilitation and measurement of outcomes. In the case of spinal cord injuries (SCI), sequelae resulting from the lesion or disease affect the person's live and measuring instruments are essential. Simultaneously, the consequences on the person's psychological sphere have an effect on the subjective component. Thus, many of the studies performed to assess these instruments belong to the field of psychology.

On the other hand, major advances have been made on the knowledge and treatment of SCI-related sequelae, although their impact on QOL and acceptance by the affected subject, have not always been sufficiently assessed, e.g., the different alternatives for the management of bladder dysfunction (Best et al., 2017). Thus, the use of instruments that measure health-related QOL, when studying outcomes of new therapeutic methods for chronic sequelae, is of great importance.

Similarly, measuring QOL is recommended after rehabilitation and when using new therapies aimed at motor recovery (Hicks et al., 2005), such as robotic systems for walking and technical help for mobility, whose integration into daily life may affect his/her perspective of QOL. This assessment will also be of great help to show the advances of neurobiological therapies of spinal cord injury.

Usually, global QOL instruments are not specific for SCI and have been adapted to diverse neurological pathologies, which allow their comparison in many populations. Instruments that are specific for SCI are usually validated for subjects with multiple sclerosis (Bonniaud, Bryant, Parratte, & Guyatt, 2008b), among other conditions.

Finally, we reiterate the need of international validation and agreement regarding the instruments (D. Tate & Forchheimer, 2014), as this will allow making comparisons between diverse cultures and conditions.

Dictionary of terms

Quality of life (QOL): Individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns.

Health: a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.

Health-related quality of life (HRQOL): Those aspects of QOL that are affected by the state of physical or mental health.

Disability: an umbrella term, covering impairments, activity limitations and participation restrictions, reflecting an interaction between features of a person's body and features of the society in which he or she lives.

Functioning: is a term that denotes the positive aspects of the interaction between a person's health—body structures and their limitations—and his contextual (environmental and personal) factors.

Domain: is an area of knowledge, emotions, or abilities, which are distinguished from others, being measured or examined by a test.

Spasticity: disordered sensory-motor control, resulting from an upper motor neuron lesion, presenting as intermittent or sustained involuntary activation of muscle.

Neuropathic pain: Pain caused by a lesion or disease of the somatosensory nervous system.

Neurogenic bladder: abnormal or difficult function of the bladder, urethra, sphincter system in mature individuals, in the context of clinically confirmed relevant neurologic disorder.

Validity: ability of the instrument to measure the construct that it intends to measure and for which it was designed.

Key facts of measuring quality of life in sci people

- Quality of life (QOL) is a subjective multi-dimensional concept that may be assessed with instruments not specific for people with spinal cord injuries (SCI).
- There is no universal agreement on the assessment of QOL in this population.
- For assessing the impact of SCI-related sequelae on the person's QOL, instruments aiming objective measures are used (Health-related QOL [HRQOL] instruments).
- Instruments for objective measurements of HRQOL must also include items for a subjective assessment of QOL by the person.
- Multi-center agreements should be reached regarding the numerous HRQOL measuring instruments to achieve greater diffusion.

Summary

- Spinal cord injuries–related sequelae lead to a series of daily difficulties for the affected person that may further hinder his/her quality of life.
- Quality of life (QOL) is a *subjective* concept defined as "*individual's perception of their position in life in the context of the culture and value system in which they live and in relation to their goals, expectations, standards, and concerns*."
- QOL may be viewed from a subjective perspective by the affected person or objective by the observer, then including QOL aspects affected by the disease or lesion (health-related quality of live—HRQOL).
- Global QOL questionnaires, such as WHOQOL, SWLS, QLI, SF-36, and EuroQol, are the most commonly used assessment tools.
- Specific instruments to assess the impact that certain conditions associated to spinal cord injuries (SCI) have on QOL have been developed, e.g., bladder dysfunction, spasticity, as well as others adapted from other populations, such as neuropathic pain and sexual dysfunction.
- It is important to establish international agreements regarding the use of validated instruments that can be compared in diverse populations for measuring different aspects of QOL in people with SCI.

References

Abramson, C. E., McBride, K. E., Konnyu, K. J., Elliott, S. L., & Team, S. R. (2008). Sexual health outcome measures for individuals with a spinal cord injury: A systematic review. *Spinal Cord*, *46*(5), 320–324.

Alexander, M. S., New, P. W., Biering-Sørensen, F., Courtois, F., Popolo, G. D., Elliott, S., et al. (2017). International spinal cord injury male sexual function and female sexual and reproductive function basic data sets-version 2.0. *Spinal Cord Series And Cases*, *3*, 17050.

Andresen, E. M., Gravitt, G. W., Aydelotte, M. E., & Podgorski, C. A. (1999). Limitations of the SF-36 in a sample of nursing home residents. *Age and Ageing*, *28*(6), 562–566.

Balioussis, C., Hitzig, S. L., Flett, H., Noreau, L., & Craven, B. C. (2014). Identifying and classifying quality of life tools for assessing spasticity after spinal cord injury. *Topics in Spinal Cord Injury Rehabilitation*, *20*(3), 208–224.

Best, K. L., Ethans, K., Craven, B. C., Noreau, L., & Hitzig, S. L. (2017). Identifying and classifying quality of life tools for neurogenic bladder function after spinal cord injury: A systematic review. *The Journal of Spinal Cord Medicine*, *40*(5), 505–529.

Biering-Sørensen, F., Charlifue, S., DeVivo, M., Noonan, V., Post, M., Stripling, T., et al. (2006). International spinal cord injury data sets. *Spinal Cord*, *44*(9), 530–534.

Bökel, A., Dierks, M. L., Gutenbrunner, C., Weidner, N., Geng, V., Kalke, Y. B., et al. (2020). Perceived environmental barriers for people with spinal cord injury in Germany and their influence on quality of life. *Journal of Rehabilitation Medicine*, *52*(8), jrm00090.

Bonniaud, V., Bryant, D., Parratte, B., & Guyatt, G. (2008a). Development and validation of the short form of a urinary quality of life questionnaire: SF-Qualiveen. *The Journal of Urology*, *180*(6), 2592–2598.

Bonniaud, V., Bryant, D., Parratte, B., & Guyatt, G. (2008b). Qualiveen, a urinary-disorder specific instrument: 0.5 corresponds to the minimal important difference. *Journal of Clinical Epidemiology*, *61*(5), 505–510.

Charlifue, S., Post, M. W., Biering-Sorensen, F., Catz, A., Dijkers, M., Geyh, S., et al. (2012). International spinal cord injury quality of life basic data set. *Spinal Cord*, *50*(9), 672–675.

Cleeland, C. S., & Ryan, K. M. (1994). Pain assessment: Global use of the brief pain inventory. *Annals of the Academy of Medicine, Singapore*, *23*(2), 129–138.

Cook, K. F., Teal, C. R., Engebretson, J. C., Hart, K. A., Mahoney, J. S., Robinson-Whelen, S., et al. (2007). Development and validation of patient reported impact of spasticity measure (PRISM). *Journal of Rehabilitation Research and Development*, *44*(3), 363–371.

Costa, P., Perrouin-Verbe, B., Colvez, A., Didier, J., Marquis, P., Marrel, A., et al. (2001). Quality of life in spinal cord injury patients with urinary difficulties. Development and validation of qualiveen. *European Urology*, *39*(1), 107–113.

Dawu, W., Chao, H., Kaiting, L., Lan, S., Xiaohua, P., & Dingqun, B. (2019). Pain correlates with social integration in individuals with traumatic spinal cord injury: A cross-sectional survey. *Journal of Rehabilitation Medicine*, *51*(7), 506–512.

de Andrés Ares, J., Cruces Prado, L. M., Canos Verdecho, M. A., Penide Villanueva, L., Del Valle Hoyos, M., Herdman, M., et al. (2015). Validation of the short form of the brief pain inventory (BPI-SF) in Spanish patients with non-cancer-related pain. *Pain Practice*, *15*(7), 643–653.

Devlin, N. J., & Brooks, R. (2017). EQ-5D and the EuroQol group: Past, present and future. *Applied Health Economics and Health Policy*, *15*(2), 127–137.

Dijkers, M. (1997). Quality of life after spinal cord injury: A meta analysis of the effects of disablement components. *Spinal Cord*, *35*(12), 829–840.

Dijkers, M. P. (1999). Correlates of life satisfaction among persons with spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *80*(8), 867–876.

Dijkers, M. P. (2003). Individualization in quality of life measurement: Instruments and approaches. *Archives of Physical Medicine and Rehabilitation*, *84*(4 Suppl 2), S3–14.

Dijkers, M. P. (2005). Quality of life of individuals with spinal cord injury: A review of conceptualization, measurement, and research findings. *Journal of Rehabilitation Research and Development*, *42*(3 Suppl 1), 87–110.

Elliott, S., Jeyathevan, G., Hocaloski, S., O'Connell, C., Gulasingam, S., Mills, S., et al. (2019). Conception and development of sexual health indicators to advance the quality of spinal cord injury rehabilitation: SCI-high project. *The Journal of Spinal Cord Medicine*, *42*(sup1), 68–84.

Elliott, S., & Querée, M. (2018). Sexual and reproductive health following spinal cord injury. In J. J. Eng, R. W. Teasell, W. C. Miller, D. L. Wolfe, A. F. Townson, J. T. C. Hsieh, & M. Querée (Eds.), *Spinal cord injury rehabilitation evidence*. *Version 6.0* (pp. 1–133). Vancouver.

EuroQol-Group. (1990). EuroQol—a new facility fpr the measurement of health-related quality of life. *Health Policy*, *16*(3), 199–208.

Froehlich-Grobe, K., Andresen, E. M., Caburnay, C., & White, G. W. (2008). Measuring health-related quality of life for persons with mobility impairments: An enabled version of the short-form 36 (SF-36E). *Quality of Life Research*, *17*(5), 751–770.

Fuhrer, M. J., Rintala, D. H., Hart, K. A., Clearman, R., & Young, M. E. (1992). Relationship of life satisfaction to impairment, disability, and handicap among persons with spinal cord injury living in the community. *Archives of Physical Medicine and Rehabilitation*, *73*(6), 552–557.

Geyh, S., Fellinghauer, B. A., Kirchberger, I., & Post, M. W. (2010). Cross-cultural validity of four quality of life scales in persons with spinal cord injury. *Health and Quality of Life Outcomes*, *8*, 94.

Hand, B. N., Velozo, C. A., & Krause, J. S. (2018). Measuring the interference of pain on daily life in persons with spinal cord injury: A Rasch-validated subset of items from the brief pain inventory interference scale. *Australian Occupational Therapy Journal*, *65*(5), 405–411.

Hicks, A. L., Adams, M. M., Martin Ginis, K., Giangregorio, L., Latimer, A., Phillips, S. M., et al. (2005). Long-term body-weight-supported treadmill training and subsequent follow-up in persons with chronic SCI: Effects on functional walking ability and measures of subjective well-being. *Spinal Cord*, *43*(5), 291–298.

Hill, M. R., Noonan, V. K., Sakakibara, B. M., & Miller, W. C. (2010). Quality of life instruments and definitions in individuals with spinal cord injury: A systematic review. *Spinal Cord*, *48*(6), 438–450.

Iorio-Morin, C., Noonan, V. K., White, B., Noreau, L., Leblond, J., Dumont, F. S., et al. (2018). Quality of life and health utility scores among Canadians living with traumatic spinal cord injury—a National Cross-Sectional Study. *Spine (Phila Pa 1976)*, *43*(14), 999–1006.

Jang, Y., Hsieh, C. L., Wang, Y. H., & Wu, Y. H. (2004). A validity study of the WHOQOL-BREF assessment in persons with traumatic spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *85*(11), 1890–1895.

Karapolat, H., Akkoç, Y., Eyigör, S., & Tanıgör, G. (2018). Bladder-related quality of life in people with neurological disorders: Reliability and validity of the Turkish version of the King's health questionnaire in people with spinal cord injury. *Turkish Journal of Urology*, *44*(5), 411–417.

Kazis, L. E., Miller, D. R., Clark, J. A., Skinner, K. M., Lee, A., Ren, X. S., et al. (2004). Improving the response choices on the veterans SF-36 health survey role functioning scales: Results from the veterans health study. *The Journal of Ambulatory Care Management*, *27*(3), 263–280.

Knezevic, T., Konstantinovic, L., Rodic, S., Foti, C., Drulovic, J., Dackovic, J., et al. (2015). Validity and reliability of the Serbian version of patient-reported impact of spasticity measure in multiple sclerosis. *International Journal of Rehabilitation Research*, *38*(3), 199–205.

Levi, R., Hultling, C., Nash, M. S., & Seiger, A. (1995). The Stockholm spinal cord injury study: 1. Medical problems in a regional SCI population. *Paraplegia*, *33*(6), 308–315.

Lin, M. R., Hwang, H. F., Chen, C. Y., & Chiu, W. T. (2007). Comparisons of the brief form of the World Health Organization quality of life and short Form-36 for persons with spinal cord injuries. *American Journal of Physical Medicine & Rehabilitation*, *86*(2), 104–113.

Luther, S. L., Kromrey, J., Powell-Cope, G., Rosenberg, D., Nelson, A., Ahmed, S., et al. (2006). A pilot study to modify the SF-36V physical functioning scale for use with veterans with spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *87*(8), 1059–1066.

May, L. A., & Warren, S. (2002). Measuring quality of life of persons with spinal cord injury: External and structural validity. *Spinal Cord*, *40*(7), 341–350.

Milinis, K., Tennant, A., Young, C. A., & TONiC Study Group. (2017). Rasch analysis of SF-Qualiveen in multiple sclerosis. *Neurourology and Urodynamics*, *36*(4), 1161–1166.

Miller, W., Sakakibara, B., Noonan, V., Tawashy, A., Aubut, J., Connolly, S., et al. (2010). Outcome measures. In J. J. Eng, R. W. Teasell, W. C. Miller, D. L. Wolfe, A. F. Townson, J. T. C. Hsieh, & B. M. Sakakibara (Eds.), *Spinal cord injury rehabilitation evidence* (pp. 1–147). Vancouver.

Moons, P., Budts, W., & De Geest, S. (2006). Critique on the conceptualisation of quality of life: A review and evaluation of different conceptual approaches. *International Journal of Nursing Studies*, *43*(7), 891–901.

Mortenson, W. B., Noreau, L., & Miller, W. C. (2010). The relationship between and predictors of quality of life after spinal cord injury at 3 and 15 months after discharge. *Spinal Cord*, *48*(1), 73–79.

Nikfallah, A., Rezaali, S., Mohammadi, N., Abrishamkar, M., Rezaei, E., Sahraian, M. A., et al. (2015). Translation, cultural adaptation and validation of the Qualiveen-30 questionnaire in Persian for patients with spinal cord injury and multiple sclerosis. *Lower Urinary Tract Symptoms*, *7*(1), 42–49.

Pavot, W., & Diener, E. (1993). Review of the satisfaction with life scale. *Psychological Assessment*, *5*, 164–172.

Post, M. W. (2014). Definitions of quality of life: What has happened and how to move on. *Topics in Spinal Cord Injury Rehabilitation*, *20*(3), 167–180.

Post, M. W. M., Forchheimer, M. B., Charlifue, S., D'Andréa Greve, J. M., New, P. W., & Tate, D. G. (2019). Reproducibility of the international spinal cord injury quality of life basic data set: An international psychometric study. *Spinal Cord*, *57*(11), 992–998.

Post, M., & Noreau, L. (2005). Quality of life after spinal cord injury. *Journal of Neurologic Physical Therapy*, *29*(3), 139–146.

Post, M. W., van Leeuwen, C. M., van Koppenhagen, C. F., & de Groot, S. (2012). Validity of the life satisfaction questions, the life satisfaction questionnaire, and the satisfaction with life scale in persons with spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *93*(10), 1832–1837.

Raichle, K. A., Osborne, T. L., Jensen, M. P., & Cardenas, D. (2006). The reliability and validity of pain interference measures in persons with spinal cord injury. *The Journal of Pain*, *7*(3), 179–186.

Salvador-De La Barrera, S., Mora-Boga, R., Ferreiro-Velasco, M. E., Seoane-Pillado, T., Montoto-Marqués, A., Rodríguez-Sotillo, A., et al. (2018). A validity study of the Spanish-World Health Organization quality of life short version instrument in persons with traumatic spinal cord injury. *Spinal Cord*, *56*(10), 971–979.

Skevington, S. M., Lotfy, M., & O'Connell, K. A. (2004). The World Health Organization's WHOQOL-BREF quality of life assessment: Psychometric properties and results of the international field trial. A report from the WHOQOL group. *Quality of Life Research*, *13*(2), 299–310.

Sweatman, W. M., Heinemann, A. W., Furbish, C. L., & Field-Fote, E. C. (2020). Modified PRISM and SCI-SET spasticity measures for persons with traumatic spinal cord injury: Results of a Rasch analyses. *Archives of Physical Medicine and Rehabilitation*, *101*(9), 1570–1579.

Tate, D., & Forchheimer, M. (2014). Review of cross-cultural issues related to quality of life after spinal cord injury. *Topics in Spinal Cord Injury Rehabilitation*, *20*(3), 181–190.

Tate, D. G., Kalpakjian, C. Z., & Forchheimer, M. B. (2002). Quality of life issues in individuals with spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *83*(12 Suppl 2), S18–S25.

The WHOQOL Group. (1998). Development of the World Health Organization WHOQOL-BREF quality of life assessment. *Psychological Medicine*, *28*, 551–558.

Tulsky, D. S., Kisala, P. A., Victorson, D., Choi, S. W., Gershon, R., Heinemann, A. W., et al. (2015). Methodology for the development and calibration of the SCI-QOL item banks. *The Journal of Spinal Cord Medicine*, *38*(3), 270–287.

van Gorp, S., Kessels, A. G., Joosten, E. A., van Kleef, M., & Patijn, J. (2015). Pain prevalence and its determinants after spinal cord injury: A systematic review. *European Journal of Pain*, *19*(1), 5–14.

Ware, J. E., Jr., & Sherbourne, C. D. (1992). The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Medical Care*, *30*(6), 473–483.

Whitehurst, D. G., Engel, L., & Bryan, S. (2014). Short form health surveys and related variants in spinal cord injury research: A systematic review. *The Journal of Spinal Cord Medicine*, *37*(2), 128–138.

Whitehurst, D. G., Noonan, V. K., Dvorak, M. F., & Bryan, S. (2012). A review of preference-based health-related quality of life questionnaires in spinal cord injury research. *Spinal Cord*, *50*(9), 646–654.

Wong, A. W. K., Lau, S. C. L., Fong, M. W. M., Cella, D., Lai, J. S., & Heinemann, A. W. (2018). Conceptual underpinnings of the quality of life in neurological disorders (Neuro-QoL): Comparisons of core sets for stroke, multiple sclerosis, spinal cord injury, and traumatic brain injury. *Archives of Physical Medicine and Rehabilitation*, *99*(9), 1763–1775.

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Chapter 15

S100b in spinal cord injury

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List of abbreviations

CSF cerebrospinal fluid
SCI spinal cord injury
MRI magnetic resonance imaging
CNS central nervous system
MS multiple sclerosis

Introduction

Spinal cord injury (SCI) results in severe social–economic problems, because it is observed mostly among younger adults. The incidence of SCI has been reported at 10.5 cases per 100,000 people (Kumar, Lim, Mekary, et al., 2018). This type of injury occurs in young to middle-aged populations due to road traffic accidents, violence, and contact sports. Unfortunately, only 1% of SCI patients experience injuries that fully resolve. Almost half of cases suffer of severe neurological loss (para/tetraparesis, para/tetraplegia) with or without respiratory disturbances (Albayar, Roche, Swiatkowski, et al., 2019).

Several prognostic factors have been proposed according to the previously published studies. But there is still no consensus on which clinical diagnostic tests could be applied to reliably indicate the sub-clinical neurophysiological changes occurring in the spinal cord during the acute phase, and this affects the prediction of cell death and tissue destruction in SCI. Neurological examination provide a general indication of spinal cord neurological function, but are unreliable, especially during the acute phase (first 24 h) after SCI as a result of spinal shock in many patients (Cao, Yang, Liu, et al., 2008). MRI provides an accurate anatomical diagnosis, but it is impossible to distinguish neuronal tissue necrosis from post-traumatic edema. Most of the medical decisions are targeting the stabilization of the patients and preventing further injury, but no definitive treatment for the present state of the CNS trauma exists (Albayar et al., 2019). In these cases, where the real-time injury is the question in clinical diagnosis and prognosis, serum and CSF biomarker evaluation provides another option. A biomarker must be accurate, sensitive, specific, and provide high predictive value. The most widely used biomarker in such cases is S100b, a protein found in cells of neural crest derivation, which can be measured in the serum after disruption of the blood brain barrier (Wolf, Krall, Pajenda, et al., 2014, b). S100b is implicated in a very broad number of CNS conditions, and as such, it is perhaps one of the strongest candidate markers (Sen and Belli, 2007). In case of a CNS injury, accompanied by a nervous tissue and cellular damage, this structural protein is released from nervous cells and its concentration increase extra-cellularly—including CSF and blood. In these cases, S100b could be a potential biomarker of nervous tissue damage (Hajduková, Sobek, Prchalová, et al., 2015).

S100b characteristics

The S-100 protein family constitutes a sub-group of Ca^{+2}-binding proteins. The term "S-100" was used because this protein was soluble in 100% ammonium sulfate and refers to a mixture of dimeric proteins consisting of two sub-units termed α and β (Sen and Belli, 2007). Three isoforms are known. S100a (αβ) is found in glial cells and melanocytes, S-100b (ββ) is present in high concentrations in glial cells and Schwann cells of the central and peripheral nervous systems as well as in Langerhans cells and cells of the anterior pituitary gland and S-100a0 (αα), which represents 5% of the S-100 protein in the brain (hippocampus, olfactory cells). The last is found outside the nervous system in slow-twitch muscle, heart, and kidney (Donato, 1991). The genes encoding the majority of human S100 proteins are organized in a cluster within the

Diagnosis and Treatment of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822498-4.00015-4

chromosomal region 1q21, while some genes coding individual S100 proteins are located in other chromosomal regions, including 21q22 where, in particular, the gene for the S100b protein is located (Michetti, Corvino, Geloso, et al., 2012).

S100b is primarily an astrocytic protein and it was first detected in CSF at the acute phase of exacerbation of MS (Michetti et al., 2012). The majority of astrocytic S100b is located within the cytoplasm, 5%–7% is membrane bound. At least 80%–90% of the total S100b pool is found within the brain, the remainder being located in other non-neuronal tissues. S100b is thought to be involved in a number of Ca^{+2}-dependent cellular functions, including protein phosphorylation, enzyme activation, cell proliferation and differentiation, cytoskeletal dynamics, intra-cellular Ca^{+2} homeostasis and protection against oxidative injury (Donato, 1991). In a low concentration it seems to have a neurotrophic effect, it stimulates the growth of neurons, and it increases their survival during development and also during an injury. Higher concentrations might be toxic and evoke cell death. S100b is metabolized and excreted by the kidneys and has a half-life of about 30 min. S100b is found at low levels in healthy patients and remains chemically stable for several hours after sampling (Donato, 1991, 2003).

S100b and CNS pathology

S100b was regarded for almost two decades as specific to the nervous system (Michetti et al., 2012). Generally, S100b acts like a damage-associated molecular pattern (DAMP), which is released from damaged or activated cells under conditions of cell stress. Furthermore, a more complex role of S100b in the inflammatory processes has been described (Hajduková, Sobek, Prchalová, et al., 2015).

The concept of brain-specific proteins was first proposed in 1965 when S100 was characterized by Moore as a neuronal protein (Moore, 1965). Many studies followed this conclusion and found a clear role of S100b protein in maintenance and development of CNS. This role of S100b protein could be summarized in the following points (Donato, 1991, 2003):

- Regulation of enzymatic activities
- Interactions with cytoskeleton proteins
- Stimulation of neuronal differentiation, neurite extension activity, and pro-survival effects on neurons
- Protection of p53 from thermal denaturation and aggregation; stimulation of p53-dependent cell growth arrest and apoptosis (tumor-suppressor activity); inhibition of p53-dependent transcription activation (tumor-promoting activity) via disruption of the p53 tetramer
- Stimulation of astrocyte proliferation and apoptosis
- Stimulation of IL-6 secretion by neurons, NO secretion by astrocytes and microglia
- Modulation of synaptic plasticity

Over the years, different studies observed a varied grade of correlation between S100b overexpression in neuropathologic states in vivo and trophic/toxic effects in vitro. For example, overexpression of S100b protein has also been shown in cerebral palsy, Gilles de la Tourette syndrome, Down syndrome, Alzheimer's disease, schizophrenia, cerebral vasospasm after subarachnoid hemorrhage, astrocytomas, after head injury, and Creutzfeldt–Jacob disease (Sen and Belli, 2007). S100b protein could also represent a useful tool for early detection of intra-ventricular hemorrhage in the post-asphyxia period when clinical examination and cranial ultrasound might still be silent. It is reasonable to hypothesize that S100b accumulates in the extracellular space after astrocyte death or due to increased release by activated astrocytes, or after cellular disintegration of the damaged parenchyma. The finding that increased S100b is not accompanied by alterations in other structural markers of neural cell types, such as glial fibrillary acidic protein (GFAP), myelin basic protein (MBP) and neuron-specific enolase (NSE) has been regarded as an indication that S100b is actively released by astrocytes rather than leaked from damaged cells (Michetti et al., 2012). Under these conditions, the increased accumulation of S100b may become toxic due to its stimulatory effects on nitric oxide production by astrocytes and microglia (Sen and Belli, 2007).

S100b is normally present in cells derived from the neural crest but also from chondrocytes, adipocytes, myoepithelial cells, macrophages, Langerhans cells, dendritic cells, and keratinocytes (Benneker, Leitner, Martinolli, et al., 2008). Additionally, many studies have suggested extra-cranial sources of S100b, such as following cardiopulmonary bypass surgery, cardiac arrest, carbon monoxide and benzodiazepine poisoning, small and large bone fractures, abdominal injuries, and in fat tissue (Wolf, Krall, Pajenda, et al., 2014, b). Although in trauma patients larger extra-cranial soft tissue and bone injuries led also to an increase of S100b, confounding the interpretation of results, studies focused only on TBI cases revealed a high negative predictive power of S100b. They have found S100b elevation in CSF and peripheral blood after TBI, which is positively correlated with the severity of injury but negatively correlated with outcome. It was concluded that monitoring of S100b levels could contribute to early detection of patients at risk of secondary rises in intra-cranial pressure and subsequent fatal outcome (Sen and Belli, 2007).

Biomarkers in SCI

The acute phase of SCI is evaluated by neurological examination and MRI study. These patients are classified based on image characteristics, severity and need for surgical intervention. In comparison with MRI, neurological findings are most predictive of outcome. As the degree and localization of injured and spared white matter primarily determine functioning after SCI, MRI has limited success as a prognostic tool (Leister, Haider, Mattiassich, et al., 2020). On the other hand, injury severity alone does not adequately predict the degree of spontaneous neurological recovery.

Spinal cord trauma causes an acute disruption of the spinal cord parenchyma, which is followed by a secondary axonal degeneration and further degeneration or death of nerve cells by either apoptosis or necrosis, processes that may last from days to weeks. As the spinal cord is surrounded by vessels and CSF, damage to the spinal cord releases proteins and metabolites from the nervous tissue into CSF and blood. The implementation of biomarkers in SCI provides a useful tool supporting clinical decision making in acute SCI, especially in severe injured unresponsive patients (Guez, Hildingsson, Rosengren, et al., 2003; Leister et al., 2020).

An ideal prognostic CNS biomarker should have all of the following properties: CNS specificity, rapid and profound release into blood or/and CSF after injury, easily assessed, predictability of serious injury from an early sample, correlation of biomarker value with injury severity, of low cost minimally influenced by other factors and reproducible (Vaage and Anderson, 2001). The most studied biomarkers for SCI patients and their characteristics are summarized in Table 1.

TABLE 1 Characteristics of most studied biomarkers.

Biomarkers	Characteristics
Neurofilament proteins ✓ NF-L (light) ✓ NF-M (medium) ✓ NF-H (heavy)	• Components of neuronal cytoskeleton • Control axonal signaling and transport • Increase extra-cellular concentration upon neurological injuries • NF-L correlated with severity of SCI and neurological outcome
Glia fibrillary protein (GFAP)	• Components of astrocytic cytoskeleton • Development of astrocytic cytoskeleton • Variable CSF levels according to type of spinal injury • Post-traumatic CSF levels correlated with motor improvement
Cleaved Tau protein (C-Tau)	• Axonal microtubules • Stabilization of cytoskeleton • Axonal transport • Doubtful role
S100b protein	• Calcium-binding protein in astrocytes • Homeostatic balance • Regulating calcium levels, cell proliferation and differentiation • Enzymatic and metabolic • Early increase correlated with severity of SCI and outcome
Neuron-specific enolase (NSE)	• Neuronal cytoplasm enzyme • Homeostatic balance • Intra-lesional levels increased in experimental studies • Early increase correlated with severity of SCI and outcome
MAP-2 (microtubule-associated protein 2)	• Cytoskeletal proteins enriched in dendritic cells • Determining and stabilizing neuronal morphology during neuron development • Rapid loss post injury in experimental studies
Myelin basic protein	• Myelin sheath • In rat models post-traumatic detection in regenerated oligodendrocytes and marked increase in CSF, serum and intra-lesionally
Matrix metalloproteinases (MMPs)	• Extra-cellular matrix • Cell migration • CNS repair • Post-traumatic increase, in sub-acute phase correlated with outcome

TABLE 2 Characteristics of most studied inflammatory biomarkers.

Inflammatory biomarkers	Characteristics
Transforming growth factor beta (TGF-β)	• Regulation axonal extension, astrogliosis, and proteoglycans' accumulation • After 12 weeks there was a correlation between the increased levels and the poor neurological improvement
Tumor necrosis factor-alpha (TNF-α)	• Released within a few hours after damage • In 12 weeks post-injury CSF and serum levels correlated with neurological outcome
Insulin-like growth factor (IGF)	• In 12 weeks post-injury higher serum value is correlated with worse neurological improvement
Interleukins (ILs)	• Inflammatory process and glial scar tissue formation after SCI • At first and fourth post-traumatic week decreased serum levels of IL-1B in patients with poorer neurological status
Soluble CD95 ligand (sCD95L)	• Upregulation responsible for apoptosis in oligodendrocytes and spinal cord neurons • Increased serum levels during the sub-acute phase

SCI is a well-known neuroinflammatory process starting with local ischemia and edema. In cellular level, ionic disturbances and mitochondrial dysfunction have been observed. These events lead to neuron death, disruption of blood-brain barrier (BBB), neutrophils and macrophages infiltration and finally scar formation into the spinal cord (Albayar et al., 2019). Based on this concept several inflammatory biomarkers were also studied from several authors as specific predictive tool in cases of SCI (Biglari, Swing, Child, et al., 2015; Ferbert, Child, Graeser, et al., 2017) (Table 2).

S100b and SCI

The last 20 years there are several experimental and in vitro studies about the predictive role of S100b in tissue, serum or CSF after SCI, concluded that this biomarker could be a real-time indicator of early stages of spinal cord involvement (Table 3).

TABLE 3 Studies of the last 20 years about the role of S100b in SCI.

Study	Experimental/ Human	Biological fluid	Results
Ma, Novikov, Karlsson, et al. (2001)	Rats	Serum	At 3, 12, and 72 h after SCI increased levels were identified
Cornefjord, Nyberg, Rosengren, et al. (2004)	Pigs	CSF	Non-significant differences were identified after the induced nerve root injury
Loy, Sroufe, Pelt, et al. (2005)	Rats	Serum	At 6 h after SCI increased levels
Cao et al. (2008)	Rats	Serum, CSF	At 2 h after SCI serum and CSF concentrations were elevated
Schultke, Griebel, and Juurlink (2010)	Rats	Serum	At 6, 12, and 24 h after the trauma S-100b levels were significantly higher in quercetin-treated animals
Kwon, Stammers, Belanger, et al. (2010)	Human	CSF, serum	The highest levels during the first 24 h were included in the final prediction model
Ersahin, Toklu, Erzik, et al. (2011)	Rats	Serum	Significant increase 1 week after SCI induction
Zhang, Huang, Su, et al. (2011)	Pigs	CSF, serum	S-100B was significantly increased in the serum and cerebrospinal fluid 3 h after trauma

TABLE 3 Studies of the last 20 years about the role of S100b in SCI—cont'd

Study	Experimental/ Human	Biological fluid	Results
Pouw, Kwon, Verbeek, et al. (2014)	Human	CSF	The mean S-100β concentration in motor complete patients was significantly higher compared with motor incomplete patients
Wolf, Krall, Pajenda, et al. (2014, 2014b)	Human	Serum	Patients with neurologic deficits had significantly higher S100b levels compared with the patients with vertebral fractures but without neurologic deficits within 24 h after injury
Dalkilic, Fallah, Noonan, et al. (2018)	Human	CSF	Significantly lower in patients, who experienced an improvement within 6 months after injury
Yang, Bramlett, Moghieb, et al. (2017)	Rats	CSF, serum	Significantly elevated levels within 24 h (acute phase)
Kwon, Streijger, Fallah, et al. (2017	Human	CSF	Motor score improvement also was strongly correlated with the 24-h post-injury CSF levels
Du, Li, Sun, et al. (2018)	Human	Serum	Levels rose after the injury and reached a peak on the fourth day of injury, which was followed by a gradual decline 2 weeks after the injury

The initial experimental approaches found high level of S100b in the first 3–6 h in CSF and serum, whereas in some other cases was recorded an increase even at 3–7 days after SCI (Cornefjord et al., 2004; Ersahin et al., 2011; Loy et al., 2005; Ma, Novikov, Karlsson, et al., 2001). An experimental study from Cao, Yang, Liu, et al., 2008 showed significantly elevated serum and CSF levels of S100b and NSE which were then considered to be the most specific biomarkers for the acute phase of SCI (Cao et al., 2008). Their data indicated that NSE and S100b protein level changes are time-dependent and correlated with higher neurological defects and injury severity. A significant increase in NSE and S100b protein levels in serum and CSF was observed at 2 h after injury, and in a stepwise manner they reached maximum levels at 6 h. Serum S100b levels were elevated as well as 24 h after SCI as it was observed from Schultke et al. (2010). In general, S-100b protein levels in animals' serum and CSF elevate following SCI and have diagnostic value. During the initial 6 h of SCI, the level of this protein is very high in CSF and serum, but with time passing, the serum level of this protein decreases and after 24 h, its rate does not differ from animals without SCI (Faridaalee and Khajeh, 2019). Marquardt et al. found that the serum levels of S100b in rats rose rapidly within a short time (24 h) and then declined gradually and reached the normal level around the 10th day of injury, an observation similar to study from Marquardt, Setzer, and Seifert (2006) and Zhang, Underwood, Landfield, et al. (2000).

S100b was studied as a predictor of initial spinal cord damage that reflects directly to the severity of SCI. Kwon et al. studied in vitro the correlation between elevation in IL-6, IL-8, MCP-1, Tau-Protein, S100b, and GFAP and severity of injury (Kwon et al., 2010). Using protein concentrations at 24 h post injury, the model accurately predicted the observed ASIA grade in 89% of patients and furthermore provided a better prediction of segmental motor recovery at 6 months post injury than the patients' baseline ASIA grade. In a CSF study of 16 SCI patients Pouw et al. found that mean levels of S100b were significantly higher in more severely injured patients according to ASIA scale, reinforcing the aforementioned findings of Pouw et al. (2014). Protein levels were comparable between males and females, and not associated with age which gives rise for a more objective assessment despite the heterogeneity in patients with SCI. Marquardt et al. observed also that S100b could have a predictive value in other cases of spinal cord pathology. Patients with epidural empyema and persistently increased S100b levels for a minimum of 3 days after operative decompression had unfavorable functional outcome, as measured by motor function. Patients with spinal metastasis and persistently increased S100b levels for a minimum of 10 days after operative decompression had unfavorable functional outcome, as measured by motor function (Marquardt, Setzer, & Seifert et al., 2004a, 2004b). Marquardt concluded that the only significant biomarker correlation was between S100b serum levels and fractures of the vertebral spine, as well as between S100b serum levels and spinal cord injuries with resulting neurological deficits. Animals with favorable outcome had either always normal levels or levels that were initially increased but normalized within 2 days, when the values of animals with unfavorable outcome were elevated throughout (Marquardt, Setzer, Theisen, et al., 2011). Du et al. found that S100b has a sensitivity of 71.79% and a specificity of 66.67% for the evaluation of neurologic functional recovery (Du et al., 2018). The cut-off value of 29.07 μg/L indicated that patients with more than this value had increased risk of poor prognosis. Serum levels were low

in the well-recovered group but very high in the modest-recovered group. Patients' recovery was mainly associated with the extent of SCI damage at the time of injury. The serum levels of S100b increased after injury and reached a peak on the 4th day of injury. Then, the levels declined gradually, 2 weeks after the injury. Elevated S100b in human CSF after SCI was observed in patients with worse neurological outcome and lower concentration in cases of significant improvement after 6 months in a study from Dalkilic et al., when Kwon et al. reported a strong correlation between motor score improvement and CSF level of S100b in the first 24 h (Dalkilic, Fallah, Noonan, et al., 2018; Kwon et al., 2017). In the same year, an experimental study confirmed that highest levels of S100b in serum and CSF appeared in acute post-traumatic period (Yang et al., 2017).

Significant S100b serum level changes were seen in patients with vertebral spine fractures and spinal cord injury. When spinal fracture occurs, the fractured vertebrae affect the adjacent spinal cord which is a bundle of neurons, and S100b is then released from the injured spinal cord. A percentage of 5%–15% of cases with significant cervical injuries is missed on plain radiographs though were high-risk patients (Pouw, Hosman, van Middendorp, et al., 2009). CT or MRI is recommended in high-energy injuries and in patients with normal plain radiographs but continued symptoms. On the other hand, as it was reported in previous studies, there is a "false positive" range of biomarker elevations because it was observed that patients with a period of aortic clamping and patients with a whiplash trauma may have elevated biomarker levels in CSF without neurologic deficits. S100b can play a significant role in determining whether further evaluation is needed for patients with normal plain radiographs of spine even in absence of neurologic deficits (Pouw et al., 2009). Markedly increased levels of S100b in patients with spinal fracture might be evidence of spinal cord injury (Lee, Kim, Lee, et al., 2010). In a study of 19 patients with isolated vertebral fractures, Benneker detected elevated S100b serum levels, with a mean S100b value of 0.38 μg/L. Benneker concluded that the measurement of S100b serum levels has a high negative predictive power to rule out vertebral fractures (Benneker et al., 2008). In another study from Wolf et al. (S100b) serum levels was significantly higher in patients with vertebral spine fractures and additional presence of neurological deficits was correlated significantly with higher S100b serum levels (Wolf, Krall, Pajenda, et al., 2014, b).

Limitations and perspectives

S100b protein could be a useful tool after SCI for early detection of the degree of spinal cord involvement and the grade of neurological outcome within a 6-month period. The presence of extra-cranial injuries where fat and bone tissue are involved contributes to elevated S100b in serum and may be over interpreted as a reliable positive predictor for injuries to the spine (Albayar et al., 2019; Benneker et al., 2008). Additionally, before the 72 h post-injury period, factors such as spinal shock and medical instability affect the reliability of the neurological examination (Pouw et al., 2014; Zhang et al., 2011). Noteworthy that there is a severe difficulty to obtain CSF sample from SCI patients as it is painful and is associated with a risk of epidural hematoma that may lead to further spinal cord compression.

The most recent study from Leister et al. included series of clinical trials, cohort studies, pilot studies based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement and consists a detailed report for biomarkers in SCI (Leister et al., 2020). The correlation between S100b and severity of spinal cord injury according to neurological outcome could raise considerations for future respective studies such as:

- Correlation with later time imaging findings may reveal new pathways between structural changes and fluctuations of biomarkers (Zhang et al., 2011).
- Biomarkers that could be related with short and long-term complications after SCI, when there are at least 10 times more chronic SCI patients than new SCI cases (Albayar et al., 2019; Yousefifard, Sarveazad, Babahajian, et al., 2019).
- Use the protein not only as a biomarker but also as a potential therapeutic target for treatment of the pathological conditions in which it is involved (Sen and Belli, 2007).
- Increased knowledge about mechanisms of regulation of post-injury S100b release (Donato, 1991, 2003; Michetti et al., 2012).

Applications to other areas of neuroscience

- When the patient suffers from TBI, the blood-brain barrier is disrupted, causing a leakage of proteins from the CSF with subsequent cerebral edema formation.
- The most studied protein biomarker of cerebral damage in TBI is S100b.
- All traumatic cerebral injuries have been shown to have increased S100b in serum, but focal injuries, such as cerebral contusions and subdural hematomas, present higher levels as compared to diffuse injuries.

- Patients without a steady decline of S100b in CSF and serum have been shown to present with worse outcome.
- S100b appears to be an important and useful predictor of functional outcome in moderate-to-severe TBI.

Mini-dictionary of terms

- ***S100 protein***: Family of low-molecular-weight proteins with two calcium-binding sites and are involved in a variety of intra-cellular and extra-cellular functions.
- ***Spinal cord injury***: Traumatic damage to the spinal cord with or without bone and ligament involvement.
- ***Traumatic brain injury***: An alteration in normal brain function caused by an external force.
- ***Biomarker***: A measurable indicator of a medical condition which is evaluated using sample of blood, urine, CSF or soft tissue.
- ***Blood-brain barrier***: A barrier between capillaries (small blood vessels) and other components of brain and spinal cord (parenchyma, meninges, bone) that protects them from pathogens and toxins.

Key facts of calcium-binding proteins

- Calcium in nervous system is involved in functions membrane excitability, signal transduction, neurotransmitters release, synaptic plasticity, cell-cycle regulation, cell migration, and axon growing.
- Calcium-binding proteins react to Ca^{2+} transients and modulate the activity of proteins involved in both maintaining homeostatic conditions.
- Calmodulin, parvalbumin, calbindin, S100 proteins, calpain, and more than 200 proteins belong to this family.
- S100b protein has been measured in CSF and blood of patients with cerebral infarction, transient ischemic attack, hemorrhage, and head injury.
- S100b might be a selective biomarker to estimate the extent of nervous tissue damage and the prognosis of patients after SCI.

Summary points

- Spinal cord injury (SCI) results in severe social-economic problems, because it is observed mostly among younger adults.
- Most of the medical decisions are targeting the stabilization of the patients and preventing further injury, but no definitive treatment for the present state of the CNS trauma exists.
- In these cases, where the real-time injury is the requested in clinical diagnosis and prognosis, serum and CSF biomarker examination provides a quantitative method.
- As the spinal cord is surrounded by vessels and CSF, damage to the spinal cord releases proteins and metabolites from the nervous tissue into CSF and blood. The implementation of biomarkers in SCI provides a useful tool supporting clinical decision making in acute SCI.
- S100b constitutes was regarded for almost two decades as specific to the nervous system.
- The last 20 years there are several experimental and in vitro studies about the predictive role of S100b in tissue, serum or CSF after SCI, concluded that this biomarker could be a real-time indicator of early stages of spinal cord involvement.

References

Albayar, A. A., Roche, A., Swiatkowski, P., et al. (2019). Biomarkers in spinal cord injury: Prognostic insights and future potentials. *Frontiers in Neurology*, *29*, 10. Article 27.

Benneker, L. M., Leitner, C., Martinolli, L., et al. (2008). Isolated vertebral fractures give elevated serum protein S-100B levels. *Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine*, *16*, 13.

Biglari, B., Swing, T., Child, C., et al. (2015). A pilot study on temporal changes in IL-1β and TNF-α serum levels after spinal cord injury: The serum level of TNF-α in acute SCI patients as a possible marker for neurological remission. *Spinal Cord*, *53*, 510–514.

Cao, F., Yang, X. F., Liu, W. G., et al. (2008). Elevation of neuron-specific enolase and S-100beta protein level in experimental acute spinal cord injury. *Journal of Clinical Neuroscience*, *15*(5), 541–544.

Cornefjord, M., Nyberg, F., Rosengren, L., et al. (2004). Cerebrospinal fluid biomarkers in experimental spinal nerve root injury. *Spine*, *29*, 1862–1868.

Dalkilic, T., Fallah, N., Noonan, V. K., et al. (2018). Predicting injury severity and neurological recovery after acute cervical spinal cord injury: A comparison of cerebrospinal fluid and magnetic resonance imaging biomarkers. *Journal of Neurotrauma*, *235*, 435–445.

Donato, R. (1991). Perspectives in S-100 protein biology. Review article. *Cell Calcium*, *12*(10), 713–726.

Donato, R. (2003). Intracellular and extracellular roles of S100 proteins. *Microscopy Research and Technique*, *60*(6), 540–551.
Du, W., Li, H., Sun, J., et al. (2018). The prognostic value of serum neuron specific enolase (NSE) and S100B level in patients of acute spinal cord injury. *Medical Science Monitor*, *24*, 4510–4515.
Ersahin, M., Toklu, H. Z., Erzik, C., et al. (2011). Ghrelin alleviates spinal cord injury in rats via its anti-inflammatory effects. *Turkish Neurosurgery*, *21*(4), 599–605.
Faridaalee, G., & Khajeh, F. K. (2019). Serum and cerebrospinal fluid levels of S-100b. Is a biomarker for spinal cord injury; a systematic review and Meta-analysis. *Archives of Academic Emergency Medicine*, *7*(1), e19.
Ferbert, T., Child, C., Graeser, V., et al. (2017). Tracking spinal cord injury: Differences in cytokine expression of IGF-1, TGF- B1, and sCD95l can be measured in blood samples and correspond to neurological remission in a 12-week follow-up. *Journal of Neurotrauma*, *34*(3), 607–614.
Guez, M., Hildingsson, C., Rosengren, L., et al. (2003). Nervous tissue damage markers in cerebrospinal fluid after cervical spine injuries and whiplash trauma. *Journal of Neurotrauma*, *20*(9), 853–858.
Hajduková, L., Sobek, O., Prchalová, D., et al. (2015). Biomarkers of brain damage: S100B and NSE concentrations in cerebrospinal fluid—A normative study. *BioMed Research International*, *2015*, 379071.
Kumar, R., Lim, J., Mekary, R. A., et al. (2018). Traumatic spinal injury: Global epidemiology and worldwide volume. *World Neurosurgery*, *113*, e345–e363.
Kwon, B. K., Stammers, A. M., Belanger, L. M., et al. (2010). Cerebrospinal fluid inflammatory cytokines and biomarkers of injury severity in acute human spinal cord injury. *Journal of Neurotrauma*, *27*(4), 669–682.
Kwon, B. K., Streijger, F., Fallah, N., et al. (2017). Cerebrospinal fluid biomarkers to stratify injury severity and predict outcome in human traumatic spinal cord injury. *Journal of Neurotrauma*, *34*, 567–580.
Lee, S. J., Kim, C. W., Lee, K. J., et al. (2010). Elevated serum S100b levels in acute spinal fracture without head injury. *Emergency Medicine Journal*, *27*(3), 209–212.
Leister, I., Haider, T., Mattiassich, G., et al. (2020). Biomarkers in traumatic spinal cord injury-technical and clinical considerations: A systematic review. *Neurorehabilitation and Neural Repair*, *34*(2), 95–110.
Loy, D. N., Sroufe, A. E., Pelt, J. L., et al. (2005). Serum biomarkers for experimental acute spinal cord injury: Rapid elevation of NSE and S-100b. *Neurosurgery*, *56*(2), 391–397 (discussion 391–397).
Ma, J., Novikov, L. N., Karlsson, K., et al. (2001). (2001). Plexus avulsion and spinal cord injury increase the serum concentration of S-100 protein: An experimental study in rats. *Scandinavian Journal of Plastic and Reconstructive Surgery and Hand Surgery*, *35*, 355–359.
Marquardt, G., Setzer, M., & Seifert, V. (2004a). Protein S-100b as serum marker for prediction of functional outcome in metastatic spinal cord compression. *Acta Neurochirurgica*, *146*, 449–452.
Marquardt, G., Setzer, M., & Seifert, V. (2004b). Protein S-100b for individual prediction of functional outcome in spinal epidural empyema. *Spine*, *29*, 59–62.
Marquardt, G., Setzer, M., & Seifert, V. (2006). Serum biomarkers for experimental acute spinal cord injury: Rapid elevation of neuron-specific enolase and S-100b. *Neurosurgery*, *58*, E590.
Marquardt, G., Setzer, M., Theisen, A., et al. (2011). Experimental subacute spinal cord compression: Correlation of serial S100B and NSE serum measurements, histopathological changes, and outcome. *Neurological Research*, *33*(4), 421–426.
Michetti, F., Corvino, V., Geloso, M. C., et al. (2012). The S100b protein in biological fluids: More than a lifelong biomarker of brain distress. *Journal of Neurochemistry*, *120*, 644–659.
Moore, B. W. (1965). A soluble protein characteristic of the nervous system. *Biochemical and Biophysical Research Communications*, *19*, 739–744.
Pouw, M. H., Hosman, A. J., van Middendorp, J. J., et al. (2009). Biomarkers in spinal cord injury. *Spinal Cord*, *47*(7), 519–525.
Pouw, M. H., Kwon, B. K., Verbeek, M. M., et al. (2014). Structural biomarkers in the cerebrospinal fluid within 24 h after a traumatic spinal cord injury: A descriptive analysis of 16 subjects. *Spinal Cord*, *52*, 428–433.
Schultke, E., Griebel, R. W., & Juurlink, B. H. (2010). Quercetin administration after spinal cord trauma changes S-100 levels. *The Canadian Journal of Neurological Sciences*, *37*(2), 223–228.
Sen, J., & Belli, A. (2007). S100b in neuropathologic states: The CRP of the brain? *Journal of Neuroscience Research*, *85*(7), 1373–1380.
Vaage, J., & Anderson, R. (2001). Biochemical markers of neurologic injury in cardiac surgery: The rise and fall of S100β. *The Journal of Thoracic and Cardiovascular Surgery*, *122*, 853–855.
Wolf, H., Krall, C., Pajenda, G., et al. (2014). Alterations of the biomarker S-100B and NSE in patients with acute vertebral spine fractures. *The Spine Journal*, *14*, 2918–2922.
Yang, Z., Bramlett, H. M., Moghieb, A., et al. (2017). Temporal profile and severity correlation of a panel of rat spinal cord injury protein biomarkers. *Molecular Neurobiology*, *55*(3), 2174–2184.
Yousefifard, M., Sarveazad, A., Babahajian, A., et al. (2019). Potential diagnosting and prognostic value of serum and CSF biomarkers in traumatic SCI: A systematic review. *Journal of Neurochemistry*, *149*, 317–330.
Zhang, B., Huang, Y., Su, Z., et al. (2011). Neurological, functional, and biomechanical characteristics after high-velocity behind armor blunt trauma of the spine. *Journal of Trauma*, *71*(6), 1680–1688.
Zhang, S. X., Underwood, M., Landfield, A., et al. (2000). Cytoskeletal disruption following contusion injury to the rat spinal cord. *Journal of Neuropathology & Experimental Neurology*, *59*(4), 287–296.

Chapter 16

Assessment of postural control after spinal cord injury or disease: A narrative review

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List of abbreviations

ABC Scale	Activities-specific Balance Confidence Scale
AIS	American Spinal Injury Association Impairment Scale
BBS	Berg Balance Scale
CB&M Scale	Community Balance and Mobility Scale
COM	center of mass
COP	center of pressure
FRT	Functional Reach Test
IMU	inertial measurement units
KAFO	knee ankle foot orthoses
L/E	lower extremity
mini-BESTest	mini-Balance Evaluation Systems Test
mFRT	modified Functional Reach Test
MMT	manual muscle testing
SCI/D	spinal cord injury or disease
SWAT	Standing and Walking Assessment Tool
WheelCon	Wheelchair Use Confidence Scale v.3

Introduction

Following spinal cord injury or disease (SCI/D), physical rehabilitation is focused on regaining independence for community living and maximizing quality of life. The multi-disciplinary rehabilitation team facilitates the retraining of daily activities (e.g., bathing, feeding) and mobility (e.g., walking, wheeling, transferring), and assists with the reintegration of vocational and recreational activities. The priorities of rehabilitation are also informed by people living with SCI/D, who have identified improving upper limb and trunk strength, sexual function, bowel and bladder function, and walking ability as being most important for life satisfaction (Anderson, 2004). Common to the safe and successful completion of all of these tasks is the requirement of postural control. Without postural control, movement is limited and independence compromised.

The term postural control is often used interchangeably with the terms balance or balance control. Indeed, these are similar and inter-related constructs. Postural control refers to one's ability to maintain, achieve, or restore a state of balance at any given time (Pollock, Durward, Rowe, & Paul, 2000). From a biomechanical perspective, balance refers to the relationship between one's center of mass and one's base of support (Maki & McIlroy, 1997). When the vertical projection of one's center of mass moves outside of one's base of support, muscle activity is required to change the base of support or reposition the center of mass within the base of support. Without this corrective muscle activity, a fall would result. Achieving a state of balance, or postural control, is required when maintaining a posture (e.g., sitting or standing), moving voluntarily, or reacting to an external perturbation (e.g., trip, push) (Pollock et al., 2000).

For many individuals living with SCI/D, postural control is an ongoing challenge due to the sensorimotor deficits associated with their injury. Falling is common after SCI/D; 78% (95% confidence interval: 73%–83%) of ambulators fall each year, while 69% (95% confidence interval: 60%–76%) of wheelchair users fall (Khan et al., 2019). Falls have a significant

Diagnosis and Treatment of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822498-4.00016-6

detrimental impact on those living with SCI/D (Musselman, Arnold, Pujol, Lynd, & Oosman, 2018; Singh et al., 2020). Up to 62% of ambulators and 38% of wheelchair users have reported a physical injury from a fall, with most injuries being minor in nature (i.e., cuts, bruises) (Khan et al., 2019). The most common serious injuries include fractures and head trauma with a loss of consciousness (Khan et al., 2019). More than 50% of chronic wheelchair users with SCI/D experience osteoporosis (Jensen et al., 2013); hence, these individuals are at high risk of sustaining a fall-related fracture (Jannings, 2017).

In addition to physical injury, those who fall or who have a high fall risk may develop a fear of falling, defined as an enduring concern about falling that causes one to avoid activities despite being physically able to perform them (Brouwer, Musselman, & Culham, 2004). About 47% to 63% of people living with SCI/D report a fear of falling (Butler Forslund, Roaldsen, Hultling, Wahman, & Franzén, 2016; Chan et al., 2020). This fear often leads to a "post-fall syndrome" characterized by dependence, loss of autonomy, depression, anxiety, reduced mobility and restricted participation in daily activities (World Health Organization, 2007). Individuals living with SCI/D describe the harmful psychosocial impact of falls, including feelings of vulnerability and embarrassment, lost work productivity, interference with parenting, and a restriction of meaningful recreational activities (Singh et al., 2020). The constant threat of falling, and fear of the potential consequences of a fall, can have a significant impact on quality of life (Singh et al., 2020).

Chapter objectives

Postural control is inherent to our ability to move and function safely, but is commonly impaired following SCI/D. Hence, improving postural control is a target of rehabilitation assessment and intervention across the continuum of care (i.e., from acute care to community rehabilitation). Regardless of neurological level of injury, severity of the SCI/D (i.e., as indicated by the American Spinal Injury Association Impairment Scale (AIS)), time since injury or mobility status, an evaluation of postural control is warranted for all individuals living with SCI/D. Yet, clinicians and researchers lack guidance on how to approach the assessment of postural control after SCI/D, especially given the heterogeneity in clinical presentation of this population. The primary aim of this narrative review is to outline an individualized and comprehensive approach to the assessment of postural control after SCI/D. The secondary aims are to: (1) describe common impairments in postural control following SCI/D, and (2) describe the current state of postural control assessment for individuals with SCI/D.

Comprehensive assessment of postural control

More than 30 measures of postural control have been used in research studies with the SCI/D population (Arora, Oates, Lynd, & Musselman, 2020). Hence, the challenge of postural control assessment post-SCI/D is not the availability of measures, but rather deciding which measure(s) to use. In their systematic review, Arora, Oates, et al. (2020) considered the psychometric properties, clinical utility and comprehensiveness of each measure. A measure's comprehensiveness is a relatively new concept that reflects the complexity of postural control. Postural control requires the complex interaction of numerous musculoskeletal and neurophysiological mechanisms, which are effectively outlined in the Systems Framework for Postural Control (Horak, 2006; Sibley, Beauchamp, Van Ooteghem, Straus, & Jaglal, 2015). In the original framework, Horak (2006) described six systems that contribute to postural control and suggested that appropriate evaluation of each system would enable identification of an individual's specific impairments and compensations, promoting individualized treatments. In 2015, Sibley and colleagues led a revision of the Framework, resulting in the identification of nine contributing systems (see Table 1); functional stability limits, underlying motor systems, static stability, verticality, reactive postural control, anticipatory postural control, dynamic stability, sensory integration, and cognitive influences. This revised Systems Framework for Postural Control provides a basis for a comprehensive assessment of postural control for individuals with SCI/D.

Following SCI/D, impairments in postural control are expected. The spinal cord contains numerous descending motor spinal pathways that are involved in the regulation of postural control through activation of postural synergies (Beloozerova, Sirota, Orlovsky, & Deliagina, 2005; Zelenin, Beloozerova, Sirota, Orlovsky, & Deliagina, 2010). There are also a number of ascending pathways, which carry somatosensory information to the brain and allow the adaptation of postural control to the environment (Chiba, Takakusaki, Ota, Yozu, & Haga, 2016). The extent of the impairments in postural control due to the SCI/D depends on the neurological level and severity of injury. The resulting impairments are more pronounced in a sub-set of the postural control systems (see Table 1 and Fig. 1). All individuals with SCI/D are likely to experience impairments in functional stability limits, underlying motor systems (e.g., muscle strength and coordination), static stability and sensory integration. Research involving individuals with motor incomplete SCI/D (i.e., AIS C and D) demonstrated deficits in reactive postural control (Arora, Musselman, et al., 2020; Chan et al., 2020) and cognitive influences (Lemay et al., 2020; Tse et al., 2017). For dynamic stability, the overall findings are variable. Individuals with

TABLE 1 Ten components of a comprehensive assessment of postural control.

(1) **Functional Stability Limits** (Horak, 2006; Sibley et al., 2015)	
Definition:	• The ability to move the COM within the base of support (base of support includes mobility aid, wheelchair).
Example Activities:	• Reaching in sitting or standing. • Reaching for the armrest when transferring. • Leaning for pressure relief in sitting.
Impact of SCI/D:	• Impaired Decreased control over COM resulting in longer path to stability limit and smaller functional boundaries in sitting (AIS A, C, D) (Shin & Sosnoff, 2013) and standing (AIS C, D) (Houston, Unger, Lee, Masani, & Musselman, 2020; Lemay et al., 2014).
(2) **Underlying Motor Systems** (Horak, 2006; Sibley et al., 2015)	
Definition:	• Muscular and neuromuscular properties contributing to strength and coordination.
Example Activities:	• Leg and trunk strength and/or sequence of muscle activation to transfer from sitting to standing, climb stairs, take a step, etc. • Trunk strength and/or sequence of muscle activation to lean in sitting.
Impact of SCI/D:	• Impaired Varying degrees of decreased strength below level of SCI/D. Reduced trunk-leg movement coordination in standing (AIS C, D) (Noamani, Lemay, Musselman, & Rouhani, 2020). Role of trunk strength on postural control in sitting after SCI/D is unclear (AIS A) (Chen et al., 2003).
(3) **Static Stability** (Horak, 2006; Sibley et al., 2015)	
Definition:	• The ability to control the COM within a static base of support during sitting and standing.
Example Activities:	• Independent sitting without trunk or upper limb support. • Independent standing without upper limb support.
Impact of SCI/D:	• Impaired Increased postural sway in sitting (AIS A, B, C) (Milosevic, Gagnon, Gourdou, & Nakazawa, 2017) and standing with greater deficits without vision (AIS D) (Lemay et al., 2013).
(4) **Verticality** (Horak, 2006; Sibley et al., 2015)	
Definition:	• The ability to align the body with respect to gravity.
Example Activities:	• Standing, sitting or walking on an incline or decline.
Impact of SCI/D:	• Minimal Increased variability in perception of vertical; however, reliance on visual and vestibular inputs compensates for decreased somatosensation (AIS A) (Joassin, Bonniaud, Barra, Marquer, & Perennou, 2010).
(5) **Reactive Postural Control** (Horak, 2006; Sibley et al., 2015)	
Definition:	• The ability to return the COM within the base of support after an external perturbation using corrective motor strategies (e.g., ankle and hip strategies, reactive stepping).
Example Activities:	• Taking step(s) to recover from a slip on ice. • Flexing/extending at the hips when balance has been lost posteriorly/anteriorly on a fixed base of support (e.g., balance beam, crowded subway platform).
Impact of SCI/D:	• Impaired Decreased ability to execute single step responses during a forward fall in standing (AIS C, D) (Chan et al., 2020). Able to maintain state of balance in standing during unexpected surface perturbations (AIS D) (Thigpen et al., 2009). Decreased ability to increase margin of stability in response to a slip while walking (AIS D) (Arora et al., 2020).
(6) **Anticipatory Postural Control** (Horak, 2006; Sibley et al., 2015)	
Definition:	• The ability to shift the COM appropriately prior to discrete movements.
Example Activities:	• When turning the head to look behind the body, shifting body weight toward the direction of the turn. • Walking with decreased speed, shorter step length, wider step width and a flatter foot-floor angle when on a slippery surface.

Continued

TABLE 1 Ten components of a comprehensive assessment of postural control—cont'd

Impact of SCI/D:	• Likely impaired with more severe SCI/D • Minimal for less severe SCI/D Able to modulate timing and amplitude of muscle activity in lower limb muscles in response to expected surface perturbations (AIS D) (Thigpen et al., 2009). Able to use anticipatory strategies in a similar manner to individuals without SCI/D when walking on known slippery surface (AIS D) (Bone et al., 2021).
(7) **Dynamic Stability** (Horak, 2006; Sibley et al., 2015)	
Definition:	• The ability to control the COM while the base of support is changing (e.g., during walking).
Example Activities:	• Walking, transferring.
Impact of SCI/D:	• Likely impaired with more severe SCI/D • Variable findings for less severe SCI/D Increased inter-stride variability of gait parameters (e.g., cadence, gait cycle time) (AIS D) (Lemay et al., 2020). Increased foot placement variability during treadmill walking (AIS D) (Day, Kautz, Wu, Suter, & Behrman, 2011). Stabilizing and destabilizing forces during single support phase of gait suggest increased stability (AIS D) (Lemay, Duclos, Nadeau, Gagnon, & Desrosiers, 2014). Increased stability during walking (i.e., decreased speed, shorter steps, greater percentage of time in double support) (Arora et al., 2019).
(8) **Sensory Integration** (Horak, 2006; Sibley et al., 2015)	
Definition:	• The ability to combine sensory input from multiple sources and re-weight when input is altered.
Example Activities:	• Transitioning between different surfaces when walking (e.g., pavement to sand). • Transitioning between environments with varying degrees of light (e.g., bright theatre lobby to dark theatre).
Impact of SCI/D:	• Impaired Increased reliance on visual input (i.e., decreased ability to re-weight sensory input) during standing (AIS D) (Lemay et al., 2013; Noamani, Lemay, Musselman, & Rouhani, 2021) and walking (AIS D) (Lemay et al., 2020) under different sensory conditions.
(9) **Cognitive Influences** (Horak, 2006; Sibley et al., 2015)	
Definition:	• The ability to maintain postural control while responding to commands during a task or attending to additional tasks (i.e., dual tasking).
Example Activities:	• Responding to an instruction to increase speed while walking. • Attending to a cognitive load (e.g., conversing, mental math) while sitting, standing or walking.
Impact of SCI/D:	• Impaired Cognitive dual-task decreased standing time (AIS C, D) (Tse, Carpenter, Liu-Ambrose, Chisholm, & Lam, 2017) and increased inter-stride variability of cadence when walking (AIS D) (Lemay et al., 2020).
(10) **Balance Confidence** (Hatch, Gill-Body, & Portney, 2003)	
Definition:	• The level of perceived confidence in the ability to maintain a state of balance while performing daily activities.
Example Activities:	• Having confidence to complete daily activities (e.g., get onto an escalator, reach for something on tiptoes, and walk on an uneven surface) without losing balance.
Impact of SCI/D:	• Impaired Decreased balance confidence during standing and walking activities (AIS C, D) (Shah, Oates, Arora, Lanovaz, & Musselman, 2017). Greater balance confidence associated with decreased velocity of COP in standing (AIS C, D) (Shah et al., 2017). Decreased falls self-efficacy associated with increased postural sway in standing with bilateral KAFO (AIS A) (John, Cherian, & Babu, 2010).

An original table providing the definition of each component of postural control along with example activities. A description of the observed impact of spinal cord injury or disease (SCI/D) on each component is summarized. *COM*, center of mass; *AIS*, American Spinal Injury Association Impairment Scale; *COP*, center of pressure; *KAFO*, knee ankle foot orthoses.

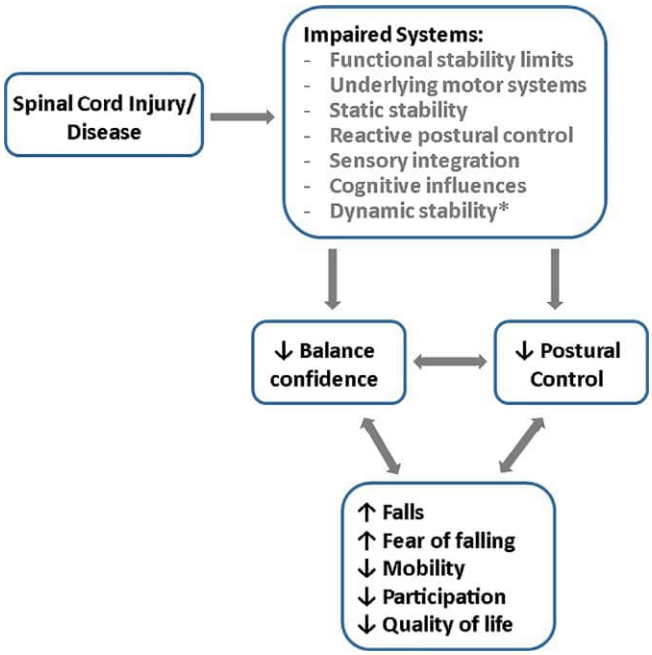

FIG. 1 Effect of spinal cord injury/disease on the systems of postural control. An original figure summarizing the systems of postural control that are negatively affected by spinal cord injury or disease (*conflicting research findings concerning dynamic stability). These impaired systems result in reduced postural control and balance confidence, with these two constructs influencing one another. Reduced postural control and balance confidence can negatively impact the occurrence and fear of falls, mobility, participation and quality of life, resulting in a cycle of decline whereby falls and decreased mobility/participation result in further decreases in postural control and confidence.

AIS D SCI/D show variability in gait parameters, suggesting compromised dynamic stability (Day et al., 2011; Lemay et al., 2020); however, they also show markers of greater stability during walking than age- and sex-matched able-bodied adults (Arora et al., 2019; Lemay, Duclos, et al., 2014). Arora et al. (2019) proposed that increased stability when walking may be a compensatory strategy to avoid losing balance and having to rely on an impaired reactive postural control system to prevent a fall. There do not appear to be impairments in anticipatory postural control for those individuals with the least severe SCI/D (i.e., AIS D) (Bone et al., 2021; Thigpen et al., 2009), but deficits may be evident in those with greater sensorimotor deficits. Lastly, SCI/D does not affect verticality (Joassin et al., 2010), although deficits may occur in individuals with a relevant co-morbidity, such as a vestibular disorder or brain injury.

Not only do the above-mentioned physiological factors influence postural control, but so do psychological factors, such as balance confidence (Carpenter, Adkin, Brawley, & Frank, 2006). Balance confidence or self-efficacy refers to an individual's perceived self-confidence in maintaining a state of balance during relatively non-hazardous activities (Hatch et al., 2003). The Systems Framework for Postural Control does not account for the effect of this psychological construct on postural control. However, due to the associations between balance confidence and postural control after SCI/D (John et al., 2010; Shah et al., 2017) (see Table 1 and Fig. 1), a measure of balance confidence should be included as the tenth component of a comprehensive assessment of postural control (see Fig. 2). This inclusion allows the clinician or researcher to evaluate the alignment between an individual's perceived balance confidence and physical abilities. For example,

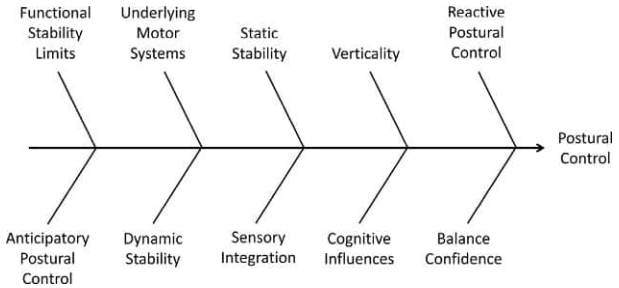

FIG. 2 Fishbone diagram of postural control after spinal cord injury/disease. An original figure highlighting ten components that impact postural control.

perceived balance confidence may be high while the physical ability to maintain a state of balance is low. These findings may suggest an individual lacks insight into his/her postural control deficits, resulting in a high fall risk due to an increased likelihood of risk-taking behaviors. Conversely, someone with low balance confidence, but capable of maintaining a state of balance during daily activities, may needlessly restrict their mobility and participation due to an exaggerated concern about falling. Hence, balance confidence adds a unique dimension to the comprehensive assessment of postural control.

Current state of postural control assessment in clinical settings

Survey studies involving more than 400 Canadian physical therapists have shed light on the postural control assessment practices for adult populations (Oates et al., 2017; Sibley, Straus, Inness, Salbach, & Jaglal, 2011). While the researchers reported variation in how postural control was assessed clinically, they noted that several postural control systems were regularly evaluated (i.e., by >80% of respondents): static stability, dynamic stability and underlying motor systems (Sibley et al., 2011). In contrast, reactive postural control was evaluated by only 41% of respondents (Sibley et al., 2011). The most commonly used measures of postural control included movement observation, the Berg Balance Scale and the single-leg stance test (Oates et al., 2017; Sibley et al., 2011). In another survey by Sibley, Straus, Inness, Salbach, and Jaglal (2013), 94% of physical therapists agreed that quantifying impairments in postural control was critical for patient care; however, only 43% of respondents agreed that existing measures of postural control were adequate for clinical practice. Moreover, even fewer (21%) indicated that these measures evaluated postural control in a comprehensive way (Sibley et al., 2013), highlighting a key gap in current approaches to the assessment of postural control.

Several organizations have produced clinical recommendations regarding the assessment of postural control. The American Physical Therapy Association and the Academy of Neurological Physical Therapy supported the development of a core set of outcome measures for adults with neurological conditions (Moore et al., 2018). The recommended measures of postural control include the Berg Balance Scale for static and dynamic sitting and standing, the Functional Gait Assessment for dynamic balance, and the Activities-specific Balance Confidence (ABC) Scale for balance confidence. More specific to the SCI/D population, the Canadian Standing and Walking Module Group produced the Standing and Walking Assessment Tool (SWAT) (Musselman et al., 2019). The SWAT is a SCI/D-specific, staged approach to the standardized assessment of standing and walking ability post-SCI/D. Within the SWAT, the Berg Balance Scale is recommended for the majority of individuals with SCI/D (i.e., those who have at minimum the ability to stand with assistance) while the ABC Scale is recommended for those who ambulate, whether therapeutically with assistance or independently in the community (Musselman, Lemay, et al., 2019). In sum, these two practice guidelines are aligned and highlight appropriate measures of postural control for the SCI/D population. However, as outlined below, the Berg Balance Scale and ABC Scale on their own do not fulfill the requirement of a comprehensive and individualized approach to the assessment of postural control after SCI/D.

Arora, Oates, et al. (2020) concluded their systematic review with recommendations for the clinical assessment of postural control after SCI/D. They concluded that of the >30 measures reviewed "no single measure had high clinical utility, strong psychometric properties and comprehensiveness" (Arora, Oates, et al., 2020). The Berg Balance Scale and Functional Reach Test were highlighted for their well-established psychometric properties in the SCI/D population, while the mini-Balance Evaluation Systems Test (mini-BESTest) was identified as the most comprehensive measure that has been used with individuals with SCI/D. The mini-BESTest was developed from the original Systems Framework of Postural Control, and is one of the only clinical measures that evaluates reactive postural control (Arora, Oates, et al., 2020; Horak, Wrisley, & Frank, 2009). Since Arora, Oates, et al. (2020) completed the database searching for their review, the mini-BESTest has been shown to be a valid and reliable measure of postural control for individuals with motor incomplete SCI/D (Chan et al., 2019; Jørgensen, Opheim, Halvarsson, Franzén, & Roaldsen, 2017). Given the comprehensiveness, strong psychometric properties and high clinical utility of the mini-BESTest, its use among the SCI/D population is expected to increase.

Instrumented assessments of postural control

In addition to the above-mentioned clinical measures, there are instrumented assessments of postural control involving force plates and inertial measurement units (IMU) that have primarily been used in research settings. These instruments can be adapted to facilitate assessment of the components of postural control, with the exception of balance confidence. In their review, Arora, Oates, et al. (2020) highlighted the use of instrumented assessments of postural control among the SCI/D population. Center of pressure-based measures of postural sway, quantified with force plates, were most commonly used (Arora, Oates, et al., 2020). Force plates consist of a rigid surface instrumented with multiple force transducers allowing the measurement of forces in three dimensions. Force plate-based measures of postural sway are considered the gold standard measure of postural control in standing (Ghislieri, Gastaldi, Pastorelli, Tadano, & Agostini, 2019). They are a valid and

reliable tool for the evaluation of standing postural control among individuals with incomplete SCI/D (Tamburella, Scivoletto, Iosa, & Molinari, 2014). More specifically, force plates have been used to quantify the performance of functional stability limits (Houston et al., 2020; Lemay, Gagnon, et al., 2014), underlying motor systems (Lee et al., 2021), static stability (Lemay et al., 2013), anticipatory postural control (Arora et al., 2019), dynamic stability (Arora et al., 2019), sensory integration (Lemay et al., 2013) and cognitive influences (Tse et al., 2017). More recently, force plates have been used to assist with the identification of spatiotemporal deficits in reactive postural control (Chan et al., 2020), with some metrics showing adequate validity and reliability (Unger et al., 2020).

IMU are being increasingly used to quantify postural control during sitting (Perez-SanPablo, Quinzanos-Fresnedo, Lopez-Romero, & Quinones-Uriostegui, 2018), standing (Noamani et al., 2020, 2021) and walking (Lemay et al., 2020). IMU typically include accelerometers to measure linear acceleration and gyroscopes to measure angular velocity, and may include magnetometers to measure the amplitude and direction of magnetic fields (Ghislieri et al., 2019). Information characterizing postural control in static standing can be collected with a single IMU (Noamani et al., 2021); however, multiple sensors are needed to extract information about more complex and dynamic postural tasks (Lemay et al., 2020; Noamani et al., 2020). Their reliability and/or validity for use during sitting, standing and walking with individuals with SCI/D have been established (Lemay et al., 2020; Noamani et al., 2020; Perez-SanPablo et al., 2018). IMU can be used in a variety of contexts and for a variety of tasks, and therefore address a number of the components of postural control. For example, among the SCI/D population, IMU have been used to quantify underlying motor systems (Noamani et al., 2020), static stability (Noamani et al., 2020), dynamic stability (Lemay et al., 2020), sensory integration (Lemay et al., 2020; Noamani et al., 2021) and cognitive influences (Lemay et al., 2020).

Although IMU and force plates can facilitate a comprehensive assessment of postural control, these tools tend to have low clinical utility due to their high cost, high level of skill required to administer and interpret the measure, and in the case of force plates, their low portability (Arora, Oates, et al., 2020). As low-cost alternatives to these instrumented tools are developed, their use in clinical settings is likely to increase.

Individualized and comprehensive assessment of postural control after SCI/D

When an individual with SCI/D begins a rehabilitation program, whether during the acute, sub-acute or chronic phase of recovery, a comprehensive and individualized approach to the assessment of postural control is warranted. Evaluation of the ten components of postural control (see Table 1 and Fig. 2) will ensure the initial assessment is comprehensive. A comprehensive approach will allow the identification of an individual's unique impairments in postural control, thereby identifying the components that should be addressed in therapy and monitored throughout the rehabilitation process at subsequent assessments.

In addition to being comprehensive, the assessment of postural control should be individualized to a person's level of mobility and function. The majority of clinical measures are not applicable to all levels of SCI/D severity. For example, the Berg Balance Scale has a ceiling effect for individuals with AIS D SCI/D (Chan et al., 2017; Jørgensen et al., 2017; Lemay & Nadeau, 2010). To select the measures of postural control most appropriate for an individual, mobility status should be considered. The above-mentioned SWAT is a standardized approach to the staging of mobility status after SCI/D that has been used at Canadian rehabilitation hospitals since 2015 (Musselman, Lemay, et al., 2019). The SWAT stages span all possible levels of mobility and postural control, from Non-independent Sitting Capacity (Stage 0) to Full Walking Capacity (Stage 4) (see Fig. 2). Stage 1 (Standing Capacity), Stage 2 (Therapeutic Walking Capacity (indoors)) and Stage 3 (Functional Walking (outdoors)) are each further divided into three stages, resulting in 12 stages that span the continuum of standing and walking ability. Definitions for each stage are provided to assist physical therapists with the staging process (see Table 2). The SWAT links these stages of mobility with well-established, clinical measures of gait (i.e., 10-m walk test, 6-min walk test) and balance (i.e., Berg Balance Scale, ABC Scale), aiding physical therapists in their selection of appropriate measures to use with an individual (Musselman, Lemay, et al., 2019). The validity and responsiveness of the SWAT stages have been established (Musselman et al., 2019; Musselman, Lemay, et al., 2019).

The SWAT can be used to determine which clinical measures to include in an individual's assessment of postural control. The recommended measures change as the SWAT stages progress from minimal sitting capacity to full community ambulation (see Fig. 3). The selection of clinical measures was guided by the above-mentioned, pre-existing recommendations of the Canadian SCI Standing and Walking Module Group, the American Physical Therapy Association and the Academy of Neurological Physical Therapy, as well as by the review completed by Arora, Oates, et al. (2020). The selected measures have high clinical utility, strong psychometric properties in the SCI/D population and are freely available. The following sections include descriptions of each measure along with an explanation of how the measure fits into a comprehensive assessment of postural control. The sections are organized according to three groupings of SWAT stages (Bayley

TABLE 2 Standing and walking assessment tool stages of walking recovery.

SWAT stage	Classification		Definition
0.0	Non-independent sitting capacity		Individual is unable to sit independently of a seating system on a firm surface with hips and knees at 90 degrees and feet on the floor for 60 s without using arms to stabilize.
0.5	Independent sitting capacity		Individual is able to sit independently of a seating system on a solid surface with hips and knees at 90 degrees and feet on the floor for 60 s without using arms to stabilize.
1	Standing capacity		Individual cannot ambulate but may be able to stand with assistance
	1A	Trace L/E movement	Unable to stand without total assistance of gait aid and/or orthoses and/or therapist(s). No voluntary L/E functional movement. (L/E MMT ≤ grade 1 in tibialis anterior, soleus, quads, and gluteus.)
	1B	Voluntary Non-Functional L/E movement	Unable to stand independently/needs partial assistance of gait aid and/or orthoses (except bilateral KAFO) and/or therapist(s) to stand. The use of bilateral KAFO is not allowed. Voluntary L/E Movement (L/E MMT of grade 1 +/2- to grade 3- in anti-gravity muscles).
	1C	Voluntary Functional L/E movement	Able to stand independently with minimal assistance of gait aid for limited amount of time (<30 s). Orthoses are allowed except for bilateral KAFO. Voluntary L/E Movement. (L/E MMT of grade 3 or higher in most anti-gravity muscles except grade 1 tibialis anterior with an orthosis would fit this group.)
2	Therapeutic walking capacity (indoors)		Individual is starting to ambulate with therapist assistance and gait aids/orthoses and progresses toward minimal assistance.
	2A	Maximal assistance	Ability to stand and initiate reciprocal steps through voluntary L/E movement but requires maximal physical assistance (>50% of total effort) of at least one person and may include use of assistive devices and/or orthoses with the exception of bilateral KAFO.
	2B	Moderate assistance	Ability to stand and initiate reciprocal steps through voluntary L/E movement but requires moderate physical assistance (25%–50% of total effort) of one person and may include use of assistive devices and/or orthoses with the exception of the bilateral KAFO.
	2C	Minimal assistance	Ability to stand and initiate reciprocal steps through voluntary L/E movement but requires minimal physical assistance (<25% of total effort) of one person and may include use of assistive devices and/or orthoses with the exception of the bilateral KAFO.
3	Functional walking (outdoors)		Individual is starting to ambulate without therapist assistance, but still requires gait aids/orthoses. Individual progresses to ambulating in the community.
	3A	Supervised household ambulator	Ability to ambulate daily using reciprocal steps over ground for short distances (10–100 m) with supervision. Individual may use assistive devices and/or orthoses with the exception of bilateral KAFO.
	3B	Independent household ambulator	Ability to ambulate daily using reciprocal steps over ground for short distances (10–100 m) independently. Individual may use assistive devices and/or orthoses with the exception of the bilateral KAFO.
	3C	Community ambulator	Ability to ambulate daily using reciprocal steps over ground for long distances (>100 m) independently. Individual may use assistive devices and/or orthoses with the exception of the bilateral KAFO.
4	Full walking capacity		Individual ambulates independently without therapist assistance or gait aids/orthoses. Independent ambulator—ability to ambulate full time daily at home and in the community without assistive devices, orthoses, or physical assistance.

Classification and definition for each stage of the Standing and Walking Assessment Tool (SWAT). *SCI*, spinal cord injury; *L/E*, lower extremity; *MMT*, manual muscle testing; *KAFO*, knee ankle foot orthoses.

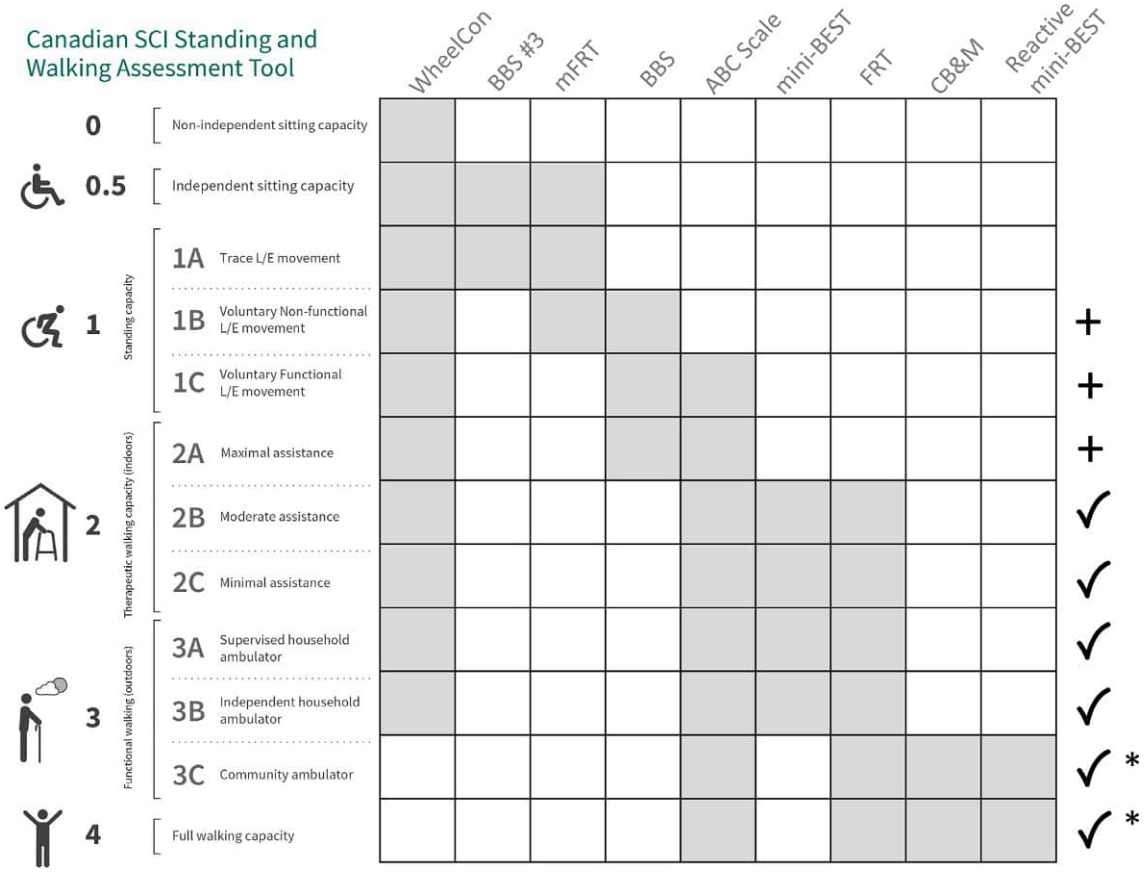

FIG. 3 Individualized and comprehensive approach to postural control assessment. The stages of the Standing and Walking Assessment Tool (left, reproduced with permission from the Canadian SCI Standing and Walking Module Group) are used to identify which clinical measures of postural control are appropriate for each stage. +Additional non-standardized measures of reactive postural control, cognitive influences and verticality in sitting could be added to increase comprehensiveness. √ All components of postural control assessed by recommended measures. √*All components of postural control, with the exception of verticality, assessed by recommended measures. *BBS #3*, third item on the Berg Balance Scale (BBS); *Reactive mini-BEST*, Reactive sub-scale of the mini-Balance Evaluation Systems Test (mini-BESTest); *SCI*, spinal cord injury; *L/E*, lower extremity; *WheelCon*, Wheelchair Use Confidence Scale v.3; *mFRT*, modified Functional Reach Test; *ABC Scale*, Activities-specific Balance Confidence Scale; *FRT*, Functional Reach Test; *CB&M*, Community Balance and Mobility Scale.

et al., 2019): (1) wheelchair users with varying degrees of independence in sitting and standing (i.e., Stages 0 through 2A); (2) part-time ambulators who also use a wheelchair for mobility (i.e., Stages 2B through 3B); and (3) full-time community ambulators (i.e., Stages 3C and 4).

Wheelchair users: Assessment of postural control

For individuals with SCI/D who are at a Stage 0 through 2A on the SWAT, the assessment of postural control is focused on sitting and standing activities, as appropriate for the individual's level of function (see Table 2). The clinical measures recommended for these SWAT stages address some, but not all, of the components of postural control (see Fig. 3 and Table 3).

Stage 0

A meaningful postural control assessment for individuals lacking independent sitting capacity is limited to an evaluation of balance confidence. To gauge balance confidence in a wheelchair user, the Wheelchair Use Confidence Scale v.3 (WheelCon) can be used, with separate versions available for manual and power wheelchair users (Rushton, Miller, Kirby, Eng, & Yip, 2011). The questionnaire measures one's confidence in using a wheelchair according to six wheelchair-related topics: wheelchair activities, negotiating the physical environment, knowledge and problem solving,

TABLE 3 Comprehensiveness of recommended clinical measures.

Clinical measure	Components of postural control									
	Functional stability limits	Underlying motor systems	Static stability	Verticality	Reactive postural control	Anticipatory postural control	Dynamic stability	Sensory integration	Cognitive influences	Balance confidence
WheelCon										✓
BBS #3			✓							
mFRT	✓	✓				✓				
BBS	✓	✓	✓			✓	✓	✓		
ABC Scale										✓
Mini-BESTest		✓	✓	✓	✓	✓	✓	✓	✓	
FRT	✓	✓				✓				
CB&M Scale		✓	✓			✓	✓	✓	✓	
Reactive mini-BESTest					✓					

Clinical measures recommended for a comprehensive and individualized approach to postural control assessment after spinal cord injury or disease are listed (left). √The component of postural control is assessed by the clinical measure (Arora, Oates, et al., 2020; Sibley et al., 2015). *BBS #3*, third item on the Berg Balance Scale (BBS); *Reactive mini-BEST*, Reactive sub-scale of the mini-Balance Evaluation Systems Test (mini-BESTest); *WheelCon*, Wheelchair Use Confidence Scale v.3; *mFRT*, modified Functional Reach Test; *ABC Scale*, Activities-specific Balance Confidence Scale; *FRT*, Functional Reach Test; *CB&M*, Community Balance and Mobility Scale.

advocacy, managing emotions and managing social situations (Rushton et al., 2011). The WheelCon was shown to have excellent reliability, validity and responsiveness in a group of wheelchair users, 60% of whom had SCI/D (Rushton, Miller, Kirby, & Eng, 2013).

Stages 0.5 and 1A

For those individuals with no standing capacity, but independent sitting capacity, the assessment of postural control is focused on a few appropriate components: (1) balance confidence related to wheelchair use, as measured with the WheelCon; (2) static stability in sitting, as measured with item three on the Berg Balance Scale, "Sitting with Back Unsupported but Feet Supported on Floor or on Stool" (Berg, Wood-Dauphinee, Williams, & Gayton, 1989); and, (3) functional stability limits, underlying motor systems and anticipatory postural control in sitting, as measured by the modified Functional Reach Test. The modified Functional Reach Test measures the maximum distance one can reach in a seated position. It has validity and reliability in both the motor complete (Lynch, Leahy, & Barker, 1998) and motor incomplete SCI/D (Field-Fote & Ray, 2010) populations.

Stages 1B, 1C, and 2A

For individuals with minimal ability to step, a greater number of the components of postural control can be evaluated through inclusion of the entire Berg Balance Scale. The Berg Balance Scale evaluates balance control during 14 sitting and standing tasks, such as chair-to-chair transfers and reaching forward in standing (Berg et al., 1989). It is a valid and reliable measure of balance for the SCI/D population (Wirz, Muller, & Bastiaenen, 2010). Although the Berg Balance Scale increases the comprehensiveness of the assessment for wheelchair users, several components of postural control are missing from this clinical measure: reactive postural control, cognitive influences and verticality (Arora, Oates, et al., 2020). To address these gaps in assessment, non-standardized evaluations of reactive postural control and dual tasking in sitting could be added. If an individual presents with a co-morbid condition known to affect verticality, then a non-standardized evaluation of this postural control system in sitting could be included.

To evaluate balance confidence, the WheelCon is recommended for individuals staged at 1B through 2A. However, for individuals who are beginning to stand (i.e., Stages 1C and 2A), the ABC Scale should also be included to gauge balance confidence during upright activities. The ABC Scale asks individuals to rate their confidence, from 0% to 100%, in their ability to maintain balance while performing 16 standing and walking tasks (Powell & Myers, 1995). The ABC Scale has validity and reliability among individuals with chronic incomplete SCI/D (Shah et al., 2017).

Part-time ambulators: Assessment of postural control

At Stages 2B through 3B, individuals with SCI/D can stand, but have varying degrees of ambulatory ability and are likely using a wheelchair to meet some of their mobility needs (see Table 2). At these SWAT stages, an assessment including all 10 components of postural control is achieved by combining two clinical scales (i.e., the mini-BESTest and the Functional Reach Test) and two questionnaires that query balance confidence (i.e., the WheelCon and the ABC Scale) (see Fig. 3 and Table 3).

For part-time ambulators, the mini-BESTest is the clinical measure of choice. The mini-BEST is the most comprehensive measure of postural control that has been used with the SCI/D population (Arora, Oates, et al., 2020). It is also known to have less of a ceiling effect than the Berg Balance Scale (Jørgensen et al., 2017). The mini-BESTest assesses four balance control systems: anticipatory, reactive postural control, sensory orientation and dynamic gait (Franchignoni, Horak, Godi, Nardone, & Giordano, 2010). The mini-BESTest and its sub-scales have validity and reliability among the chronic incomplete SCI/D population (Chan et al., 2019; Jørgensen et al., 2017). As the mini-BESTest evaluates all systems outlined in the modified Systems Framework for Postural Control with the exception of functional stability limits (Arora, Oates, et al., 2020), it is recommended that the Functional Reach Test is used as well for part-time ambulators. The Functional Reach Test is similar to the modified Functional Reach Test, except it is performed in standing.

Full-time ambulators: Assessment of postural control

A comprehensive assessment of postural control that is appropriate for the high level of function of Stages 3C and 4 (see Table 2) is possible by combining a questionnaire of balance confidence (i.e., the ABC Scale) with three clinical measures (see Fig. 3 and Table 3). First, to evaluate functional stability limits, the Functional Reach Test is recommended. Second, to

evaluate reactive postural control, the Reactive sub-scale of the mini-BEST may be used. Third, to evaluate the remaining components of postural control, with the exception of verticality, the Community Balance and Mobility Scale is recommended. The Community Balance and Mobility Scale is a 19-item scale that evaluates performance on challenging balance tasks requiring speed and accuracy; for example, tandem walking, hopping forward, and running with a controlled stop (Inness et al., 2011). The tasks are completed without any assistance or gait aid. It is valid and reliable measure among inpatients with primarily AIS D SCI/D (Chan et al., 2017). Lastly, if an evaluation of verticality is indicated based on an individual's medical history, item 9 on the mini-BESTest (i.e., "Incline—Eyes Closed") (Franchignoni et al., 2010) could be included in the assessment.

Summary

Postural control assessment is a valued part of the rehabilitation of individuals living with SCI/D. Yet current approaches in clinical practice are unstandardized and rarely target all ten components of postural control. New measures are not needed to address these gaps; currently available clinical measures and questionnaires can be combined to create a comprehensive assessment of postural control. Instrumented tools, such as force plates and IMU, can be applied in a variety of contexts and tasks, contributing to a comprehensive assessment. The stages of the SWAT can be used to individualize the assessment to the individual's mobility status, providing clinicians and researchers with a standardized approach to the selection of clinical measures.

Applications to other areas of neuroscience

An assessment of postural control is a critical part of the rehabilitation for individuals with spinal cord injury or disease, as well as individuals living with other neurological conditions, such as stroke, Multiple Sclerosis, Parkinson's disease, and cerebral palsy. Despite differences in the nature and location of neurological damage across conditions, the principles of comprehensiveness and individualization apply to the postural control assessment for all. Each neurological condition will have a unique clinical presentation that can be characterized through standardized assessment of all components of postural control.

Similarly, the measures recommended for the assessment of postural control (see Fig. 3) are not specific to spinal cord injury or disease; many of these measures were developed and validated for other clinical populations. Only the stages of the Standing and Walking Assessment Tool are specific to spinal cord injury; however, these stages were developed from classification systems used with other neurological populations, such as the Functional Ambulation Categories. Moreover, the broad categories of mobility status presented here (i.e., wheelchair users, part-time ambulators, full-time ambulators) have applicability to other neurological conditions.

Mini-dictionary of terms

- **Anticipatory postural control**: The ability to shift one's center of mass appropriately prior to discrete movements.
- **Balance**: The term that describes the relationship between one's center of mass and one's base of support.
- **Balance confidence**: The level of perceived confidence in one's ability to maintain a state of balance while performing daily activities.
- **Cognitive influences**: The ability to maintain postural control while responding to commands during a task or attending to additional tasks (i.e., dual tasking).
- **Dynamic stability**: The ability to control one's center of mass while the base of support is changing (e.g., during walking).
- **Functional stability limits**: The ability to move one's center of mass within one's base of support.
- **Postural control**: One's ability to maintain, achieve or restore a state of balance when maintaining a posture, moving voluntarily, or reacting to an external perturbation.
- **Reactive postural control**: The ability to return one's center of mass within one's base of support after an external perturbation using corrective motor strategies (e.g., ankle and hip strategies, reactive stepping).
- **Sensory integration**: The ability to combine sensory input from multiple sources and re-weight when input is altered.
- **Static stability**: The ability to control one's center of mass within a static base of support during sitting and standing.
- **Underlying motor systems**: The muscular and neuromuscular properties that contribute to strength and coordination.
- **Verticality**: The ability to align one's body with respect to gravity.

Key facts of postural control

- Postural control is the ability to maintain, achieve or restore a state of balance when maintaining a posture (e.g., sitting, standing), moving (e.g., walking) or reacting to a perturbation (e.g., slip, trip), thereby preventing a fall.
- Physiological factors, such as muscle strength and coordination, and psychological factors, such as balance confidence, influence postural control.
- Impairments in postural control are experienced by most individuals living with spinal cord injury or disease, resulting in frequent falls.
- Clinicians view assessment of postural control as important for patient care.
- Movement observation, standardized clinical scales and instrumented measures, such as force plates and inertial measurement units, can be used to evaluate postural control.

Summary points

- Individuals with spinal cord injury or disease have impairments in postural control regardless of the neurological level or severity of injury.
- Following damage to the spinal cord, impairments in functional stability limits, underlying motor systems, static stability, sensory integration, reactive postural control, cognitive influences, dynamic stability and balance confidence are common.
- Clinicians and researchers lack a standardized and comprehensive approach to the assessment of postural control in individuals with spinal cord injury or disease.
- A comprehensive and individualized approach to the assessment of postural control is needed to tailor rehabilitation for each unique individual.
- A comprehensive assessment of postural control includes evaluation of ten components based on the Systems Framework of Postural Control combined with balance confidence.
- Instrumented measures, such as force plates and inertial measurement units, can contribute to comprehensive assessments of postural control.
- An individualized assessment is achieved by considering an individual's mobility status as outlined in the Stages of the Standing and Walking Assessment Tool.
- Based on an individual's Standing and Walking Assessment Tool Stage, clinical measures are combined to create a comprehensive assessment of postural control.

References

Anderson, K. D. (2004). Targeting recovery: Priorities of the spinal cord-injured population. *Journal of Neurotrauma*, *21*, 1371–1383.

Arora, T., Musselman, K. E., Lanovaz, J., Linassi, G., Arnold, C., Milosavljevic, S., et al. (2020). Reactive balance responses to an unexpected slip perturbation in individuals with incomplete spinal cord injury. *Clinical biomechanics*, *78*, 105099.

Arora, T., Musselman, K. E., Lanovaz, J., Linassi, G., Arnold, C., Milosavljevic, S., et al. (2019). Walking stability during normal walking and its association with slip intensity among individuals with incomplete spinal cord injury. *Physical Medicine & Rehabilitation*, *11*, 270–277.

Arora, T., Oates, A., Lynd, K., & Musselman, K. E. (2020). Current state of balance assessment during transferring, sitting, standing and walking activities for the spinal cord injured population: A systematic review. *Journal of Spinal Cord Medicine*, *43*, 10–23.

Bayley, M. T., Kirby, R. L., Farahani, F., Titus, L., Smith, C., Routhier, F., et al. (2019). Development of wheeled mobility indicators to advance the quality of spinal cord injury rehabilitation: SCI-high project. *Journal of Spinal Cord Medicine*, *42*(Suppl 1), S130–S140.

Beloozerova, I. N., Sirota, M. G., Orlovsky, G. N., & Deliagina, T. G. (2005). Activity of pyramidal tract neurons in the cat during postural corrections. *Journal of Neurophysiology*, *93*, 1831–1844.

Berg, K., Wood-Dauphinee, S., Williams, J., & Gayton, D. (1989). Measuring balance in the elderly: Preliminary development of an instrument. *Physiotherapy Canada*, *41*, 304–311.

Bone, M. D., Arora, T., Musselman, K. E., Lanovaz, J. L., Linassi, G. A., & Oates, A. R. (2021). Investigating proactive balance control in individuals with incomplete spinal cord injury while walking on a known slippery surface. *Neuroscience Letters*, *749*, 135744.

Brouwer, B., Musselman, K., & Culham, E. (2004). Physical function and health status among seniors with and without a fear of falling. *Gerontology*, *6*, 135–141.

Butler Forslund, E., Roaldsen, K. S., Hultling, C., Wahman, K., & Franzén, E. (2016). Concerns about falling in wheelchair users with spinal cord injury – Validation of the Swedish version of the spinal cord injury falls concern scale. *Spinal Cord*, *54*, 115–119.

Carpenter, M. G., Adkin, A. L., Brawley, L. R., & Frank, J. S. (2006). Postural, physiological and psychological reactions to challenging balance: Does age make a difference? *Age and Ageing*, *35*, 298–303.

Chan, K., Guy, K., Shah, G., Golla, J., Flett, H., Williams, J., et al. (2017). Measuring balance in high-functioning individuals with incomplete spinal cord injury: The community balance and mobility scale. *Spinal Cord*, *55*, 294–299.

Chan, K., Lee, J. W., Unger, J., Yoo, J., Masani, K., & Musselman, K. E. (2020). Reactive stepping after a forward fall in people living with incomplete spinal cord injury or disease. *Spinal Cord*, *58*, 185–193.

Chan, K., Unger, J., Lee, J. W., Johnston, G., Constand, M., Masani, K., et al. (2019). Quantifying balance control after spinal cord injury: Reliability and validity of the mini-BESTest. *Journal of Spinal Cord Medicine*, *42*(Sup 1), 141–148.

Chen, C. L., Yeung, K. T., Bih, L. I., Wang, C. H., Chen, M. I., & Chien, J. C. (2003). The relationship between siting stability and functional performance in patients with paraplegia. *Archives of Physical Medicine and Rehabilitation*, *84*, 1276–1281.

Chiba, R., Takakusaki, K., Ota, J., Yozu, A., & Haga, N. (2016). Human upright posture control models based on multisensory inputs; in fast and slow dynamics. *Neuroscience Research*, *2014*, 96–104.

Day, K. V., Kautz, S. A., Wu, S. S., Suter, S. P., & Behrman, A. L. (2011). Foot placement variability as a walking balance mechanism post-spinal cord injury. *Clinical biomechanics*, *13*, 13.

Field-Fote, E. C., & Ray, S. S. (2010). Seated reach distance and trunk excursion accurately reflect dynamic postural control in individuals with motor-incomplete spinal cord injury. *Spinal Cord*, *48*, 745–749.

Franchignoni, F., Horak, F., Godi, M., Nardone, A., & Giordano, A. (2010). Using psychometric techniques to improve the balance evaluation system's test: The mini-BESTest. *Journal of Rehabilitation Medicine*, *42*, 323–331.

Ghislieri, M., Gastaldi, L., Pastorelli, S., Tadano, S., & Agostini, V. (2019). Wearable inertial sensors to assess standing balance: A systematic review. *Sensors (Basel)*, *19*, 4075.

Hatch, J., Gill-Body, K. M., & Portney, L. G. (2003). Determinants of balance confidence in community-dwelling elderly people. *Physical Therapy*, *83*, 1072–1079.

Horak, F. B. (2006). Postural orientation and equilibrium: What do we need to know about neural control of balance to prevent falls? *Age and Ageing*, *35* (Suppl_2), ii7–ii11.

Horak, F. B., Wrisley, D. M., & Frank, J. (2009). The balance evaluation systems test (BESTest) to differentiate balance deficits. *Physical Therapy*, *89*, 484–498.

Houston, D., Unger, J., Lee, J. W., Masani, K., & Musselman, K. E. (2020). Functional electrical stimulation plus visual feedback balance training for standing balance performance among individuals with incomplete spinal cord injury: A case series. *Frontiers in Neurology—Neurorehabilitation*, *11*, 680.

Inness, E. L., Howe, J., Niechwiej-Szwedo, E., Jaglal, S. B., McIlroy, W. E., & Verrier, M. C. (2011). Measuring balance and mobility after traumatic brain injury: Validation of the community balance and mobility scale (CB&M). *Physiotherapy Canada*, *63*, 199–208.

Jannings, W. (2017). A quality improvement project to investigate the circumstances of lower limb fractures in non-ambulant persons with spinal cord injury. *Journal of the Australasian Rehabilitation Nurses Association*, *20*, 14–18.

Jensen, M. P., Truitt, A. R., Schomer, K. G., Yorkston, K. M., Baylor, C., & Molton, I. R. (2013). Frequency and age effects of secondary health conditions in individuals with spinal cord injury: A scoping review. *Spinal Cord*, *51*, 882–892.

Joassin, R., Bonniaud, V., Barra, J., Marquer, A., & Perennou, D. (2010). Somaesthetic perception of the vertical in spinal cord injured patients: A clinical study. *Annals of Physical and Rehabilitation Medicine*, *53*, 568–574.

John, L. T., Cherian, B., & Babu, A. (2010). Postural control and fear of falling in persons with low-level paraplegia. *Journal of Rehabilitation Research & Development*, *47*, 497–502.

Jørgensen, V., Opheim, A., Halvarsson, A., Franzén, E., & Roaldsen, K. S. (2017). Comparison of the berg balance scale and the mini-BESTest for assessing balance in ambulatory people with spinal cord injury: Validation study. *Physical Therapy*, *97*, 677–687.

Khan, A., Pujol, C., Laylor, M., Unic, N., Pakosh, M., Dawe, J., et al. (2019). Falls after spinal cord injury: A systematic review and meta-analysis of incidence proportion and contributing factors. *Spinal Cord*, *57*, 526–539.

Lee, J. W., Chan, K., Unger, J., Yoo, J., Musselman, K. E., & Masani, K. (2021). Inter-joint coordination between the ankle and hip joints during quiet standing in individuals with incomplete spinal cord injury. *Journal of Neurophysiology*, *125*, 1681–1689.

Lemay, J. F., Duclos, C., Nadeau, S., Gagnon, D., & Desrosiers, É. (2014). Postural and dynamic balance while walking in adults with incomplete spinal cord injury. *Journal of Electromyography and Kinesiology*, *24*, 739–746.

Lemay, J. F., Gagnon, D., Duclos, C., Grangeon, M., Gauthier, C., & Nadeau, S. (2013). Influence of visual inputs on quasi-static standing postural steadiness in individuals with spinal cord injury. *Gait & Posture*, *38*, 357–360.

Lemay, J. F., Gagnon, D. H., Nadeau, S., Grangeon, M., Gauthier, C., & Duclos, C. (2014). Center-of-pressure total trajectory length is a complementary measure to maximum excursion to better differentiate multidirectional standing limits of stability between individuals with incomplete spinal cord injury and able-bodied individuals. *Journal of Neuroengineering and Rehabilitation*, *11*, 8.

Lemay, J. F., & Nadeau, S. (2010). Standing balance assessment in AISA D paraplegic and tetraplegic participants: Concurrent validity of the berg balance scale. *Spinal Cord*, *48*, 245–250.

Lemay, J. F., Noamani, A., Unger, J., Houston, D. J., Rouhani, H., & Musselman, K. E. (2020). Using wearable sensors to characterize gait after spinal cord injury: Evaluation of test–retest reliability and construct validity. *Spinal Cord*, *59*, 1–9.

Lynch, S. M., Leahy, P., & Barker, S. P. (1998). Reliability of measurements obtained with a modified functional reach test in subjects with spinal cord injury. *Physical Therapy*, *78*, 128–133.

Maki, B. E., & McIlroy, W. E. (1997). The role of limb movements in maintaining upright stance: The 'change-in support' strategy. *Physical Therapy*, *77*, 488–507.

Milosevic, M., Gagnon, D. H., Gourdou, P., & Nakazawa, K. (2017). Postural regulatory strategies during quiet sitting are affected in individuals with thoracic spinal cord injury. *Gait & Posture*, *58*, 446–452.

Moore, J. L., Potter, K., Blankshain, K., Kaplan, S. L., O'Dwyer, L. C., & Sullivan, J. E. (2018). A core set of outcome measures for adults with neurologic conditions undergoing rehabilitation. *Journal of Neurologic Physical Therapy*, *42*, 174–220.

Musselman, K. E., Arnold, C., Pujol, C., Lynd, K., & Oosman, S. (2018). Falls, mobility and physical activity after spinal cord injury: An exploratory study using photo-elicitation interviewing. *Spinal Cord Series And Cases*, *4*, 39.

Musselman, K. E., Chan, K., Lemay, J. F., Walden, K., Verrier, M., & Gagnon, D. (2019). Responsiveness of the standing and walking assessment tool in inpatients with spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *100*, E198–E199.

Musselman, K. E., Lemay, J. F., Walden, K., Harris, A., Gagnon, D., & Verrier, M. (2019). The standing and walking assessment tool for individuals with spinal cord injury: A qualitative study of validity and clinical use. *Journal of Spinal Cord Medicine*, *42*(Sup1), 108–118.

Noamani, A., Lemay, J. F., Musselman, K. E., & Rouhani, H. (2020). Postural control strategy after incomplete spinal cord injury: Effect of sensory inputs on trunk-leg movement coordination. *Journal of Neuroengineering and Rehabilitation*, *17*, 141.

Noamani, A., Lemay, J. F., Musselman, K. E., & Rouhani, H. (2021). Characterization of standing balance after incomplete spinal cord injury: Alteration in integration of sensory information in ambulatory individuals. *Gait & Posture*, *83*, 152–159.

Oates, A., Arnold, C., Walker-Johnston, J., Van Ooteghem, K., Oliver, A., Yausie, J., et al. (2017). Balance assessment practices of Saskatchewan physiotherapists: A brief report of survey findings. *Physiotherapy Canada*, *69*, 217–225.

Perez-SanPablo, A. S., Quinzanos-Fresnedo, J., Lopez-Romero, J. C., & Quinones-Uriostegui, I. (2018). Reliability of posturographic measures obtained during instrumental assessment of trunk control using inertial sensors in individuals with spinal cord injury. *Annals of Physical and Rehabilitation Medicine*, *61*(Suppl), e84.

Pollock, A. S., Durward, B. R., Rowe, P. J., & Paul, J. P. (2000). What is balance? *Clinical Rehabilitation*, *14*, 402–406.

Powell, L. E., & Myers, A. M. (1995). The activities-specific balance confidence (ABC) scale. *Journal of Gerontology Series A Biological Sciences & Medical Sciences*, *50*, M28–M34.

Rushton, P. W., Miller, W. C., Kirby, R. L., & Eng, J. J. (2013). Measure for the assessment of confidence with manual wheelchair use (WheelCon-M) version 2.1: Reliability and validity. *Journal of Rehabilitation Medicine*, *45*, 61–67.

Rushton, P. W., Miller, W. C., Kirby, R. L., Eng, J. J., & Yip, J. (2011). Development and content validation of the wheelchair use confidence scale: A mixed-methods study. *Disability and Rehabilitation: Assistive Technology*, *6*, 57–66.

Shah, G., Oates, A. R., Arora, T., Lanovaz, J. L., & Musselman, K. E. (2017). Measuring balance confidence after spinal cord injury: The validity and reliability of the activities-specific balance confidence scale. *Journal of Spinal Cord Medicine*, *40*, 768–776.

Shin, S., & Sosnoff, J. J. (2013). Spinal cord injury and time to instability in seated posture. *Archives of Physical Medicine and Rehabilitation*, *94*, 1615–1620.

Sibley, K. M., Beauchamp, M. K., Van Ooteghem, K., Straus, S. E., & Jaglal, S. B. (2015). Using the systems framework for postural control to analyze the components of balance evaluated in standardized balance measures: A scoping review. *Archives of Physical Medicine and Rehabilitation*, *96*, 122–132.

Sibley, K. M., Straus, S. E., Inness, E. L., Salbach, N. M., & Jaglal, S. B. (2011). Balance assessment practices and use of standardized balance measures among Ontario physical therapists. *Physical Therapy*, *91*, 1583–1591.

Sibley, K. M., Straus, S. E., Inness, E. L., Salbach, N. M., & Jaglal, S. B. (2013). Clinical balance assessment: Perceptions of commonly-used standardized measures and current practices among physiotherapists in Ontario, Canada. *Implementation Science*, *8*, 33.

Singh, H., Scovil, C., Yoshida, K., Oosman, S., Kaiser, A., Jaglal, S. B., et al. (2020). Capturing the psychosocial impacts of falls from the perspectives of wheelchair users with spinal cord injury through photo-elicitation. *Disability and Rehabilitation*, *43*(19), 2680–2689.

Tamburella, F., Scivoletto, G., Iosa, M., & Molinari, M. (2014). Reliability, validity, and effectiveness of center of pressure parameters in assessing stabilometric platform in subjects with incomplete spinal cord injury: A serial cross-sectional study. *Journal of Neuroengineering and Rehabilitation*, *11*, 86.

Thigpen, M. T., Cauraugh, J., Creel, G., Day, K., Flynn, S., Fritz, S., et al. (2009). Adaptation of postural responses during different standing perturbation conditions in individuals with incomplete spinal cord injury. *Gait & Posture*, *29*, 113–118.

Tse, C. M., Carpenter, M. G., Liu-Ambrose, T., Chisholm, A. E., & Lam, T. (2017). Attentional requirements of postural control in people with spinal cord injury: The effect of dual task. *Spinal Cord*, *55*, 915–920.

Unger, J., Oates, A. R., Lanovaz, J., Chan, K., Lee, J. W., Theventhiran, P., et al. (2020). The measurement properties of the Lean-and-Release test in people with incomplete spinal cord injury or disease. *Journal of Spinal Cord Medicine*, 1–10. https://doi.org/10.1080/10790268.2020.1847562.

Wirz, M., Muller, R., & Bastiaenen, C. (2010). Falls in persons with spinal cord injury: Validity and reliability of the Berg Balance Scale. *Neurorehabilitation and Neural Repair*, *24*, 70–77.

World Health Organization. (2007). *WHO Global report on falls prevention in older age*. https://www.who.int/ageing/publications/Falls_prevention7March.pdf.

Zelenin, P. V., Beloozerova, I. N., Sirota, M. G., Orlovsky, G. N., & Deliagina, T. G. (2010). Activity of red nucleus neurons in the cat during postural corrections. *Journal of Neuroscience*, *30*, 14533–14542.

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Section D

Treatments: Experimental and clinical

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Chapter 17

Surgical management of acute spinal cord injury in emergency setting

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List of abbreviations

AIS	ASIA Impairment Scale
ASIA score	American Spinal Injury Association score
CCS	Central Cord Syndrome
CES	Cauda Equina Syndrome
CMS	Conus Medullary Syndrome
CRHSCIR	Canadian Rick Hansen Spinal Cord Injury Registry
CSM	cervical spondylotic myelopathy
ESD	early surgical decompression
NACTN	North American Clinical Trials Network for SCI
SCI	spinal cord injury
SCIM	spinal cord independence measure
SD	surgical decompression
SDSF	surgical decompression and segment fixation
STACSIS study	Surgical Timing in Acute Spinal Cord Injury study

Introduction

Historically, closed reduction with external immobilization was the milestone of treatment for acute SCI and only few cases were reserved for surgical management. However, in the last 2 decades, spine surgeons emphasized early surgical management of SCI (Hawryluk, Rowland, Kwon, & Fehlings, 2008; Rowland, Hawryluk, Kwon, & Fehlings, 2008; Wilson & Fehlings, 2011).

Preclinical studies suggested that persistent compression of spinal cord after primary injury is responsible for an additional secondary damage which might be avoided reducing tissue damage as soon as possible and improving outcomes (Dimar, Glassman, Raque, Zhang, & Shields, 1999; Fehlings & Perrin, 2006).

SDSF allows stabilization of vertebral column and decompression of spinal cord. Moreover, stabilization prevents any further trauma on spinal cord and allows early rehabilitation (Wilson et al., 2017).

Since vascular mechanisms of secondary injury after SCI were already discovered in the past, the practice of ESD has now biological support (Ahuja et al., 2017; Tator & Fehlings, 1991).

Removing spinal cord compression and restoring blood supply should reduce the biochemical process induced by ischemia due to local compression (Dolan, Tator, & Endrenyi, 1980; Guha, Tator, Endrenyi, & Piper, 1987; Rivlin & Tator, 1978).

Despite the increasing literature, there are still some unanswered questions about the optimal methods for ESD. We still don't know if all patients are going to benefit from ESD or if there are subgroups which are more likely to benefit than others

Diagnosis and Treatment of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822498-4.00017-8

TABLE 1 SCI severity.

Classification of spinal cord injury (SCI) severity			
Normal neurological condition	**Incomplete SCI**	**Complete SCI**	**Clinical syndromes**
ASIA scale E	ASIA scale B, C or D	ASIA scale A	– Central Cord – Anterior Cord – Conus Medullaris – Cauda Equina – Brown-Sequard

ASIA scale scores are paired with normal neurological status or incomplete or complete SCI. In the fourth column all special clinical syndromes related to SCI are reported.

(Table 1). We still don't know the appropriate time for surgical intervention balancing key priorities of efficacy and clinical feasibility.

In this narrative review, we will highlight the situation of last 20 years literature about ESD in patients with acute SCI focusing to which subgroups of SCI will benefit from ESD and the time of surgical intervention.

Natural history of patients with acute cervical SCI

Approximately, one third of patients with cervical SCI has a complete injury. However, the incidence is double in patients with associated polytrauma (Stephan et al., 2015).

At 1 year from injury, 70% of patients with an initial ASIA (Table 2) score A injury will remain A, while about 30% of them will show some signs of improvement. Around 14% will improve to B, 9.5% to C, 6.5% to D, while none will improve to ASIA E (Wiberg & Hauge, 1988; Zariffa, Curt, & Steeves, 2012). On the other hand, patients with incomplete SCI have a much higher spontaneous recovery (Kirshblum, Millis, McKinley, & Tulsky, 2004).

Unfortunately, at 1 year after time of injury, patients with complete cervical SCI had a mean recovery ranging from 9.0 to 14 motor score points(Marino et al., 2011), calculating as motor score (ranging from 0 to 5 per muscle group), the strength for each muscle group below the lesion level (Maynard et al., 1997).

Neurological improvement will typically show within the first 3 months and then it will enter a steady state (Fawcett et al., 2007); even if in a little percentage of patients (about 9%) some little improvement can be showed even 5 years after injury (Ter Wengel, De Haan, Feller, Oner, & Vandertop, 2020).

Natural history of patients with thoracic or thoracolumbar SCI

A complete neurological injury is reported ranging from 16.2% to 73.0% of patients with acute thoracic SCI (Nijendijk, Post, & Van Asbeck, 2014) and it is more frequent in patients with polytrauma (Stephan et al., 2015) (Fig. 1).

TABLE 2 ASIA scale classification of neurological impairment.

ASIA scale	Description
A	COMPLETE. No motor or sensory function is preserved in the sacral segments S4-S5
B	INCOMPLETE. Sensory but not motor functions preserved under the level of lesion. It includes S4-S5
C	INCOMPLETE. Motor function is preserved below the neurological level and more than 50% of key muscles below the neurological level have a muscle grade less than 3
D	INCOMPLETE. Motor function is preserved below the neurological level and at least 50% of key muscles below the neurological level have a muscle grade greater than or equal to 3
E	NORMAL. Motor and sensory function are normal

ASIA scale scores are reported on the left and paired with the accurate description of signs and symptoms.

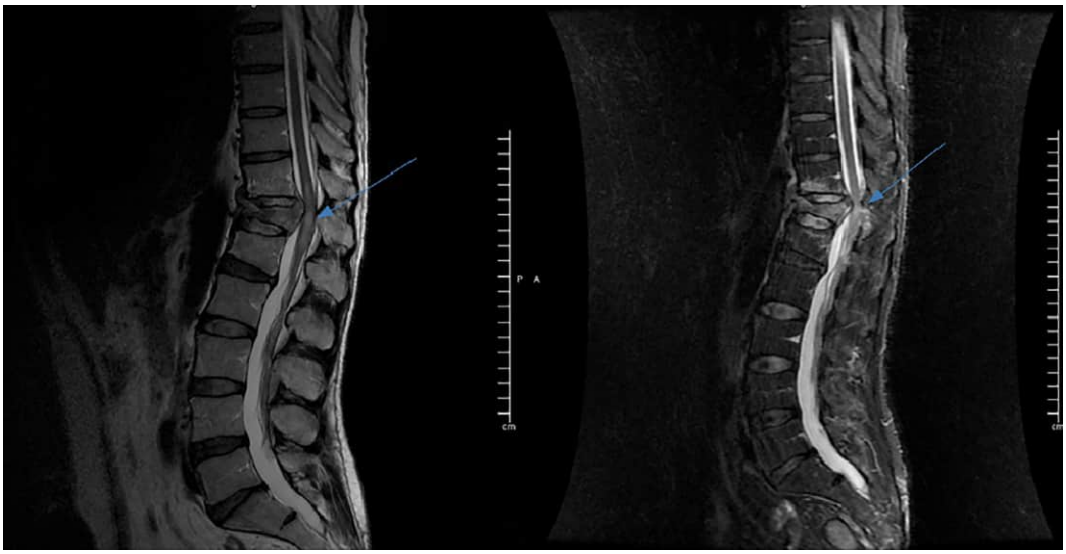

FIG. 1 Magnetic resonance imaging (MRI) about T12 fracture causing complete SCI. In this picture T2 *(left)* and STIR *(right)* MRI sequences of a SCI clinical case. The patient (46 years old, man) arrived after trauma occurred at home. On the left and on the right, marked by the *blue arrows*, hyperintensity can be seen (SCI lesion causing paraplegia).

At 1 year from injury, about 85% of patients with initial ASIA A will not improve, while about 15% of them will show 1 or more ASIA grade improvement. In patients with initial ASIA B, more than 80% of them will show some improvement (Fawcett et al., 2007; Zariffa et al., 2012).

Substantially, acute thoracic SCI will improve less than cervical or thoracolumbar SCI (Zariffa et al., 2011). In only 3.6% of patients with ASIA A grade at 1 year after injury, some minor neurological recovery can be recorded up till 5 years (Kirshblum et al., 2004).

Thoracolumbar fractures can be associated with conus medullary injury (fractures from T8-L2) and cauda equina injury (fractures below L1-L2) (Brouwers et al., 2017).

Both syndromes are difficult to be distinguished one by the other. CMS is often characterized by a symmetric sensory deficits, bladder and bowel disfunction, and mild lower extremity weakness. CES is often defined by asymmetric sensory and motor deficits. In 20% of patients a complete lack of sensory and motor function will be present below the level of injury (Pickett et al., 2006).

Thoracolumbar SCI will show the same rate of neurological recovery of complete cervical SCI (Zariffa et al., 2011) After 1 year from trauma, patients will experience a mean recovery of 4.5 motor score points below injury level (Dvorak et al., 2014).

Surgical procedures

SCI are a wide spectrum of injuries, ranging from less to more severe spinal cord damage. For this reason, a singular approach to the spine is not correct and surgical choice should be individualized to each patient (Gargiulo et al., 2019; Girardo et al., 2018). The main goals of treatment are fixation of instability and decompression of the spinal cord (Fig. 2) and the choice of the correct surgical procedure is based on severity, level and mechanism of injury; location and extension of compression and surgeon preference.

Surgical approaches to the spine are classified as anterior or posterior. With both approaches stabilization and decompression can be achieved, but in more severe cases where a circumferential arthrodesis is needed, both approaches are combined together (staged or in single setting) (Bose, Osterholm, Northrup, & Cotler, 1985).

In cervical SCI, anterior approach is the most widely used allowing easily a ventral decompression and corpectomy, while a posterior approach is more appropriate for the thoracolumbar spine, where chest and abdomen represent an anatomical barrier.

In most cases, due to complex injury with disruption of anterior and posterior elements, anterior and posterior approach where combined together to perform a 360° arthrodesis.

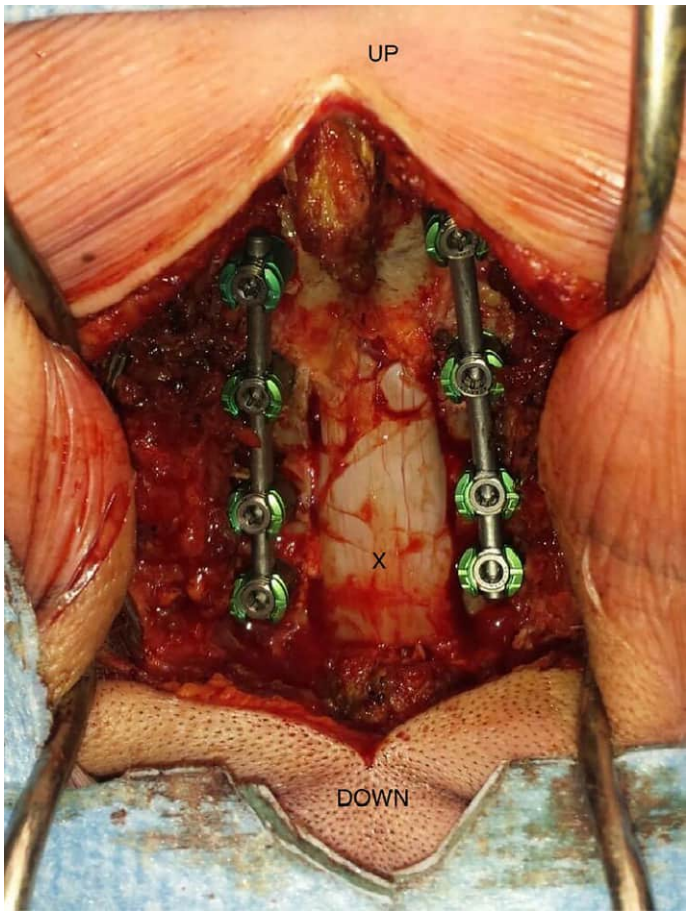

FIG. 2 Intraoperative picture about surgical decompression and fixation with screws and bars. In this picture the medulla (marked with "X") was decompressed and the cervical column was stabilized with screws and bars. "UP" and "DOWN" are referred to the patient head position.

Most common instrumentation devices used are pedicle screws with or without cement augmentation for thoracolumbar spine and pedicle or lateral masses screws for cervical spine. Usually, in acute traumatic SCI only one or two vertebral segments are involved and short segment stabilization is always preferred if possible. In flexion type injuries, posterior approach is usually preferred in the most of thoracolumbar injuries. In most cases, laminectomy, assure quick spinal decompression and also reduction with ligamentotaxis for thoracolumbar fractures (Feuchtbaum, Buchowski, & Zebala, 2016; Girardo et al., 2018) (Fig. 3).

How to define early versus late surgery post SCI?

Several articles have examined a different post injury range of time thresholds to define early versus late surgery. However, how much time can be considered "early" in not already clearly established. To recommend one of these thresholds and to choose the most favorable moment, two main principles must be considered (Fehlings & Sekhon, 2001; Wilson et al., 2017):

(1) efficacy (the extent of time in which surgery results in better outcomes).
(2) feasibility (the extent of time in which it is possible to perform surgery before the said limit taking into account the practical realities of the prehospital and hospital environment).

Which is the most efficacious threshold?

The theoretical objective of surgery is to begin a neuroprotective therapy performing a post injury treatment as soon as possible, preventing a secondary injury and favoring better recovery.

According to literature (Wilson et al., 2020), three common time thresholds can be found:

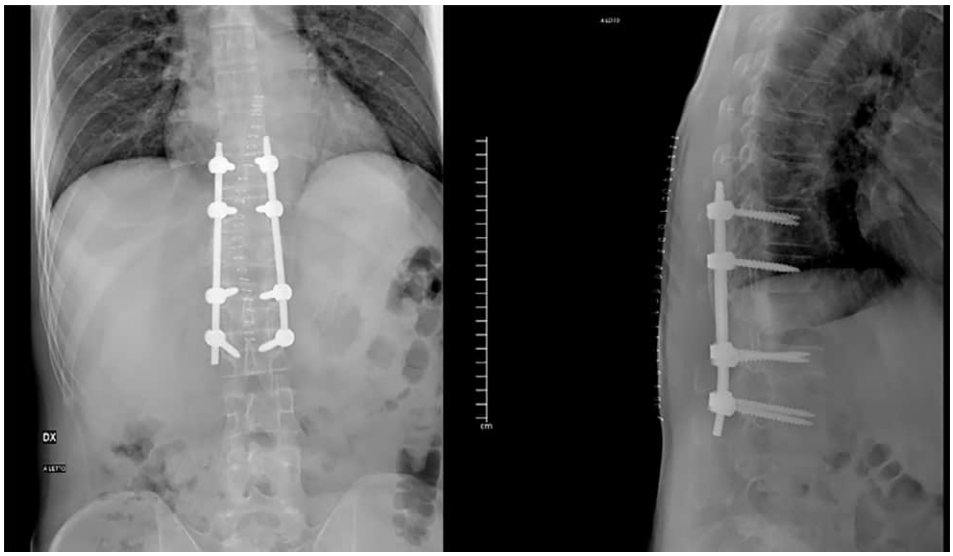

FIG. 3 X-rays about surgical treatment of SCI. About the same case of Fig. 1. The patient underwent ultra ESD with T10-L2 fixation with screws and bars.

(1) ultra-early threshold (8–12 h post SCI).
(2) early threshold (24 h post SCI).
(3) late threshold (48–72 h post SCI).

Ultra-early threshold (8–12 h post SCI)

Jug et al. evaluated the neurological outcomes of 48 patients who underwent surgery before 8 h and between 8 and 24 h post-injury. After 6 months from injury, patients treated <8-h showed a greater median improvement in ASIA motor score and a higher likelihood of improve of at least 2 AIS grade (Jug et al., 2015).

Grassner et al. evaluated the impact of surgery on functional outcomes in 70 patients who underwent SD prior to 8 h at 1 year follow up. The Authors analysis showed that patients receiving surgery prior to 8 h had superior scores and better motor outcomes at follow-up (Grassner et al., 2016).

In another study, 48 patients were retrospectively categorized into three groups depending on the timing of surgery: ultra-early (<12 h), early (12–24 h), and late (>24 h). Authors found a mean significant improvement of 1.3 AIS grade in ultra-early surgery group as compared with the mean improvement of 0.5 of patients who underwent early surgery (Burke et al., 2019).

Early threshold (24 h post SCI)

STACSIS highlight the role of early surgery in cervical SCI, showing greater neurological recovery, with 2 AIS grade improvement at 6 months of follow up (Van Middendorp, Hosman, & Doi, 2013). On another study focused on thoraco-lumbar SCI, Rahimi-Movaghar et al. didn't reach the same conclusion. In fact, despite the study lack some power, the difference between early and late surgery were not statistically significant (Rahimi-Movaghar et al., 2009).

In the comprehensive study of Dvorak et al., early surgery for all anatomical level reached significantly greater motor recovery. However, the same effect was not demonstrated in complete SCI (Dvorak et al., 2015).

In the Ontario-based cohort study, early surgery showed a higher likelihood of a 2 AIS grade improvement with a trend of additional improvement in motor recovery (Wilson et al., 2012).

It must be acknowledged that the 24 h cut-off is biologically arbitrary and it has been proposed for practical purpose; nothing changes between 23 and 25 h. So, when interpreting literature, it is important to remind that surgery is more effective when performed earlier but 24 h is only a threshold.

Late threshold (48–72 h post SCI)

Vaccaro et al. evaluated 64 SCI patients who received SD before 72 h after SCI or later than 5 days. At 1 year of follow up, the two groups didn't show any statistically difference in AIS grade conversion and motor score recovery (Vaccaro et al., 1997).

McKinley et al., reported the result of a study with a large sample of 779 patients from Model SCI Systems database and divided patients on the basis of SD prior or post 72 h. Authors found shorter hospital stay and reduced respiratory complications in patients who underwent SD before 72 h; however, no difference was found for neurological recovery (McKinley, Meade, Kirshblum, & Barnard, 2004).

Clohisy et al. evaluated 20 patients with thoracolumbar junction SCI. They found that patients surgically treated before 48 h showed grater improvements in neurological recovery than patients treated later. However, in this study patients who receive later surgery were treated about 2 months after injury (Clohisy, Akbarnia, Bucholz, Kenneth Burkus, & Backer, 1992).

What threshold is feasible?

Despite the common objective is to promote early treatment, the reality of daily life trauma care, from prehospital support to emergency department access, carry on several barriers.

For many reasons, including hospital transport, patient stability and diagnostic delays, only 50% of patients would be eligible to undergo SD before 24 h while other 50% of patients, in most cases underwent SD between 24 and 48 h (Tator, Fehlings, Thorpe, & Taylor, 1999).

The analysis of the CRHSCIR reported that in only 39% of cervical SCI and 45% of thoracic SCI, spine surgeons were able to perform SD before 24 h from trauma. Some Authors suggested that to improve early surgery rate, it is necessary to reduce barriers to early surgery in order to optimize patient outcomes (Dvorak et al., 2015).

Despite about 90% of patients arrived at the site of definitive treatment within 6 h of trauma, only 50% of them are able to undergo surgical treatment within 24 h. Older age and intermediate stop in peripheral health centers, prior to arrival in specialized center, were important factors for delay of surgery (Wilson et al., 2016) (Battistuzzo et al., 2016).

To support this findings, Furlan et al. reported that those patients who receive an early treatment (<24 h) spent less time in intermediate center before the arrival to definitive center (Furlan, Tung, & Fehlings, 2013).

In common practice, when patients access emergency department, they should be screened for any life threatened pathology, which must be treated first, since SCI is commonly associated with high energy trauma. For that reason, it is difficult to believe that most surgeries could be performed before 24 h from injury.

Does ESD offers the same benefit for all acute SCI?

SCI offers a wide spectrum of neurological impairment, from minimally to significant disabling, with a wide variability due to injury severity and neurological level of injury.

We will evaluate the current evidences about the efficacy of ESD in acute SCI based on level and severity of injury and time of surgical intervention.

Complete versus incomplete SCI

In literature, only few studies have examined the role of ESD in complete and incomplete SCI. Dvorak et al. evaluated 888 patients recruited in the CRHSCIR. In this study, attention was focused on the significant role of early surgery (<24 h post SCI) on motor recovery and the Authors concluded as ESD was not associated with significant improvements in motor function. However, considering only patients with incomplete SCI graded as ASIA B-D, ESD was associated with an improvement of 6.3 points in motor score recovery at 6 months follow-up. As expected, no significant effect for ESD was observed in grade A patients (Dvorak et al., 2015).

Bourassa-Moreau et al. examined a cohort of SCI. He found a 34% of AIS improvement of ESD (<24 h) and 13% of improvement in late surgery (>24 h), with even a higher difference for cervical SCI (64% versus 36%). Moreover, they didn't observe any conversion in AIS grade for complete SCI between early and late surgery (Bourassa-Moreau et al., 2016).

More recently, Ma et al. analysed in their meta-analysis the effects of ultra ESD (<8 h) on patients with acute SCI. He found more significant improvement in AIS score than in patients treated with early (8–24 h) or late (>24 h) surgery.

Patients had more benefits in neurological recovery from ultra ESD with no difference in hospital stay and rate of complications (Ma et al., 2020).

On the other hand, ESD (<24 h after injury) reduced hospital stay, especially for patients with complete SCI (Dvorak et al., 2015).

All studies were in accordance regarding the benefits of ESD also for what concern the length of hospital stay for patients with complete SCI, while no other study support the benefit of ESD for incomplete SCI (Bourassa-Moreau, Mac-Thiong, Feldman, Thompson, & Parent, 2013; Mac-Thiong, Feldman, Thompson, Bourassa-Moreau, & Parent, 2012).

Unfortunately, there are no large prospective studies that confirmed the superior effects of ESD on neurological outcomes for incomplete versus complete SCI. These findings are supported by the hypothesis that for incomplete SCI, the primary energy of injury is not so powerful to cause a complete SCI, and there may be greater potential for neuroprotection (Dvorak et al., 2015) (Bourassa-Moreau et al., 2016).

Effects of ESD on different neurological level of injury

One of the most important factors in patients with SCI is the neurological level of injury, which can influence patients' potential recovery (Wilson et al., 2012).

However, there are no many studies focused on specific neurological level and the effect of early or late surgery on neurological recovery. Commonly, cervical and thoracolumbar SCI are reported together and data are difficult to be extracted for each neurological level.

Effect of SD in patients with cervical SCI

STASCIS is the largest study involving patients with only cervical SCI (Fehlings et al., 2012). Authors of this study analysed several cervical SCI undergoing either early (<24 h) or late (>24 h) SD and compared AIS grade changes at 6 months follow up. Both groups underwent at least 1 grade; however, patients treated with early surgery are more likely to improve AIS of 2 grade or more (odds ratio 2.57; $P = .01$), than patients who underwent late surgery. No differences between groups were found in term of complications, despite the trend is in favor of ESD (24% versus 30% respectively) (Van Middendorp, 2012).

More recently, Aarabi et al. evaluated 72 patients with traumatic cervical SCI with AIS grade A, B or C. Patients were stratified on the basis of ultra-early (<12 h), early (<24 h) and late (>24 h) surgery. Improvement of one grade or more was present in 55.6% of grade A, 60.9% of grade B, and 86.4% of grade C patients, but not in a significant manner. Authors also found other crucial predictive factors that could be more likely associated with injury recovery such as admission motor score and intramedullary lesion length (Aarabi et al., 2020).

Effect of SD in patients with thoracic and thoracolumbar SCI

Rahimi-Movaghar et al. evaluated 35 patients with thoracic and thoracolumbar (T1-L1) SCI. Some underwent early (<24 h) while other late (>24 h) surgery. There was no difference between motor score recovery at 12 months of follow up, considering both complete and incomplete SCI (Rahimi-Movaghar et al., 2009).

In the NACTN for SCI, researchers evaluated 86 patients with SCI and neurological injury between T1 and L1. Early surgery (<24 h) was associated with additional seven points of ASIA motor recovery and a reduction of 60% in pulmonary complications (Wilson et al., 2018).

Effect of SD on miscellaneous SCI

Some studies reported cervical, thoracic and thoracolumbar SCI as a unique entity; we report them in this section since it is not possible to revise the results and divide them in anatomical region.

In the study of Bourassa-Moreau et al., patients treated with early surgical decompression (<24 h) showed improved rates of AIS conversion among cervical AIS grade A, while the same was not reported for thoracolumbar trauma (Bourassa-Moreau et al., 2016).

The Ontario-based cohort study involved 84 patients with all levels of SCI. Patients treated surgically prior to 24 h didn't show a significant increasing trend in motor recovery at rehabilitation discharge. Authors found the level of injury to be a significant predicting factor for neurological recovery, but they didn't investigate if the effects of ESD vary with level of injury (Wilson et al., 2012).

In the study of Dvorak et al., despite the impact of surgery was not analysed, it appears that patients with incomplete SCI from all anatomical level benefit from ESD (Dvorak et al., 2015).

The special case of Central Cord Syndrome

Central Cord Syndrome (CCS), the most frequent type of incomplete SCI, was first described by Schneider in 1954; it is characterized by involvement of the four limbs but with greater motor and sensitive deficits in upper extremities. Commonly, it is often secondary to low energy trauma especially in elderly patients where a pre-existing spinal stenosis (Schneider & Knighton, 1959; Schneider, Thompson, & Bebin, 1958) (Fig. 4).

The natural history of neurological recovery for CCS has been generally favorable. Most of patients well able to walk independently, without supports, with normal sphincteric function at long term follow-up (Dahdaleh et al., 2013). For that reason, conservative treatment had been historically the gold standard in CCS, while early operative intervention might derail this otherwise favorable natural history. This concerns find their foundation in Schneider's original description of CSS, where one patient had a worsening of neurologic injury after acute surgical treatment (Schneider, Cherry, & Pantek, 1954).

Despite early surgery is gaining popularity as the preferred approach for treatment of SCI, practices surrounding the time of surgery remains undefined. Currently, many surgeons continue to adhere to historical practice (Fehlings, Rabin, Sears, Cadotte, & Aarabi, 2010). In fact, in a recent survey, only 44% of attendants preferred to operate within the first 24 h from injury (Ter Wengel et al., 2018).

Currently, despite only few high-quality studies are about this topic, the best evidence found in international literature support the practice of early surgery.

Lenehan et al. evaluated the impact of surgical timing on clinical outcomes in patients with CCS. Patients were divided in early and late surgical group according to surgical intervention time, prior or post 24 h from injury. Patients treated early, experienced 6.3 points more of motor recovery and had about three times more of AIS grade conversion than late surgery. The same was observed for patients who underwent ESD with no significant perioperative morbidity (Lenehan et al., 2010).

Despite the huge historical significance, the surgical approach of Schneider, who performed a posterior direct intradural approach to cervical disc, would not be acceptable today. With better and improved surgical techniques and technologies, surgery can be performed effectively and safely.

Although natural history of CCS is favorable for ambulation, motor recovery and sphincter function, it must be acknowledge that some patients could suffer from neuropathic pain, ongoing spasticity and impairments in hand dexterity (Dvorak et al., 2005).

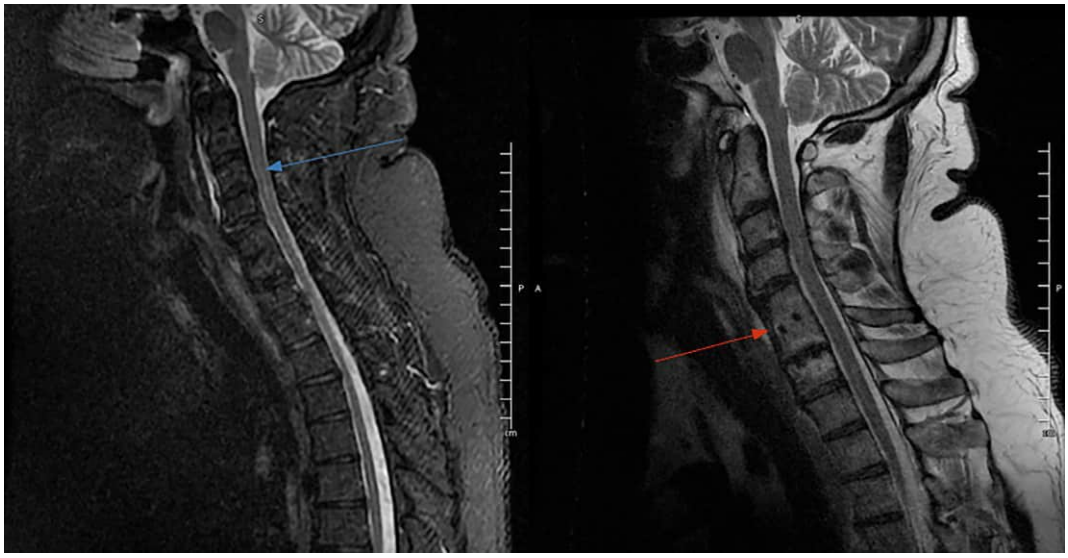

FIG. 4 Clinical case of Central Cord Syndrome (CCS). In this picture STIR *(left)* and T2 *(right)* MRI sequences of a CCS clinical case. The patient (50 years old; man) arrived after a motorcycle accident. On the left, marked by the *blue arrow*, hyperintensity can be seen (Central Cord Syndrome lesion). In this specific case the lesion occurred over a rigid cervical spine segment marked by the *red arrow* (previous arthrodesis).

Conclusions

Surgical treatment of SCI is important to avoid the secondary mechanism of injury related with vascular impairment and ischemic damage. Natural history of complete cervical SCI is characterized by an absence of improvement for the majority of cases, while in patients with incomplete SCI, the chance of natural neurological improvement is significant higher. Complete thoracic SCI shares the same rate of improvement of complete cervical SCI; however, thoracolumbar SCI has lower motor score recovery than cervical SCI.

Surgical treatment is performed through SDSF; anterior, posterior or combined approach depends of the level of injury, extension of compression and surgeon preference.

According to literature, surgical treatment can be performed ultra-early, early or late, depending of time passed from injury. At the moment early treatments offers superior results.

Despite earlier is better, it's extremely difficult to undergo surgical intervention before 8 h from trauma. This difficulty is connected to transport from place of injury to reference center for spinal injury, injury assessment, patient stability and other life-threatening pathologies. For this reason, the most suitable and realistic time of intervention balancing surgical risks and better outcomes should be set before 24 h.

Applications to other areas of neuroscience

In this chapter, we have reported a review about efficacy and effectiveness of SD for the treatment of SCI. This kind of surgery also has an important role for the treatment of CSM caused by spondylosis or ossification of the posterior longitudinal ligament (Boogaarts & Bartels, 2015). This pathology usually affects people aged over 50 years old causing progressive dysfunction and disability. The principal symptoms that may be found are weakness in upper and lower body, numbness, clumsiness, and difficulty handling. Posterior decompression is the most accepted treatment for CSM and it plays a crucial role like decompression for SCI (Singrakhia, Malewar, Singrakhia, & Deshmukh, 2017). The treatment aims to reduce stress and forces that attack spinal cord and medulla driving to ischemic troubles and lesions. Unlike decompression for SCI, the CSM one is usually performed posteriorly and may be performed with or without segment fixation. In fact, despite the indication of posterior decompression surgery without segment fixation is rarely performed; some Authors reported this technique as a valuable, easier and faster surgical approach in patients strictly selected on the base of preoperative cervical alignment or segmental stability (Gargiulo et al., 2019). However, the correct indication about fixing or not fixing is actually debated in literature.

Mini-dictionary of terms

- Spinal Cord Injury: A damage to the spinal cord.
- Complete spinal cord injury: Damage to the spinal cord in which the nerves below the level of injury cannot communicate with the brain anymore
- Incomplete spinal cord injury: Damage to the spinal cord in which the nerves below the level of injury can still sent some signals along the spinal cord. The clinical pattern of movement and sensation may vary a lot among patients
- Tetraplegia: Also known as quadriplegia, it is the paralysis that results in the partial or total loss of use of all four limbs.
- Paraplegia: Paralysis that results in the partial or total loss of use of the lower limbs.
- Central Cord Syndrome: Most common form of SCI; characterized by loss of motion and sensation in arms while the lower limbs result to be normal
- Anterior Cord Syndrome: It is caused by ischemia of the anterior spinal artery that lead to the complete loss of function of the anterior spinal cord with motor function loss associated to loss of pain and temperature sensation.
- Cauda Equina Syndrome: Serious neurologic condition characterized by low back pain that radiates down the leg associated with numbness around anus and loss of bladder and anus control. This condition affects only lower motor neurons.
- Conus Medullaris Syndrome: It is a subset of SCI caused by injuries that involve the tract between T12 an L2. Very similar to Cauda Equina Syndrome (CES), but unlike CES a combined involvement of upper and lower motor neuron may be found.
- Brown-Sequard Syndrome: Rare neurological condition characterized by hemiplegia and hemianesthesia affecting two opposite side of the body

- Surgical Decompression: Surgical procedure that is usually performed to alleviate pain caused by pinched nerves. In case of SCI, surgeons may perform this procedure to alleviate the compression forces that damage the spinal cord.
- Posterior stabilization: Surgical procedure that consists in stabilize the spine through a posterior surgical access. The hardware most used are screws and bars.
- ASIA scale: Universal classification tool for spinal cord injuries based on standardized sensory and motor assessment.

Key facts of surgical treatment of spinal cord injury

- Wait and see approach is not recommended
- SD granted oedema reduction, compression removal, blood supplies improvement and neuronal apoptosis inhibition
- ESD (<24 h) of SCI improved neurological symptoms
- Ultra ESD (<6 h) ensure better chance of spinal cord recovery; however, no later than 24 h decompression is recommended, since life treating condition could delay SD
- SD of Central Cord Syndrome is still controversial; the more recent literature support early surgical decompression

Summary points

- In SCI the persistent compression derived by the first injury may inexorably drive to a second injury.
- Low ASIA scale scores at injury are related with worse prognosis. Approximately 85% of ASIA scale grade A patients at injury will not improve their neurological status at 1 year of follow up.
- Thoracic SCI improve less than cervical and lumbar ones.
- Surgery has two main objectives: to fix and to decompress.
- Three common time thresholds are described in literature: ultra-early threshold (8–12 h post SCI), early threshold (24 h post SCI) and late threshold (48–72 h post SCI).
- Anterior and posterior approaches to the spine may be adopted. Posterior ones are preferred in thoracolumbar spine.
- Earlier decompression surgery may guarantee better rate of neurological improvement.
- In CCS patients, decompression efficacy is debated.

References

Aarabi, B., et al. (2020). Efficacy of ultra-early (<12 h), early (12-24 h), and late (>24-138.5 h) surgery with magnetic resonance imaging-confirmed decompression in American spinal injury association impairment scale grades A, B, and C cervical spinal cord injury. *Journal of Neurotrauma*, *37*(3), 448–457.

Ahuja, C. S., et al. (2017). Traumatic spinal cord injury. *Nature Reviews. Disease Primers*, *3*, 17018 (Nature Publishing Group).

Battistuzzo, C. R., et al. (2016). Early decompression following cervical spinal cord injury: Examining the process of care from accident scene to surgery. *Journal of Neurotrauma*, *33*(12), 1161–1169.

Boogaarts, H. D., & Bartels, R. H. M. A. (2015). Prevalence of cervical spondylotic myelopathy. *European Spine Journal*, *24*(Suppl 2), 139–141.

Bose, B., Osterholm, J. L., Northrup, B. E., & Cotler, J. M. (1985). Management of lumbar translocation injuries: Case reports. *Neurosurgery*, *17*(6), 958–961.

Bourassa-Moreau, É., Mac-Thiong, J. M., Feldman, D. E., Thompson, C., & Parent, S. (2013). Non-neurological outcomes after complete traumatic spinal cord injury: The impact of surgical timing. *Journal of Neurotrauma*, *30*(18), 1596–1601.

Bourassa-Moreau, É., et al. (2016). Do patients with complete spinal cord injury benefit from early surgical decompression? Analysis of neurological improvement in a prospective cohort study. *Journal of Neurotrauma*, *33*(3), 301–306.

Brouwers, E., Van De Meent, H., Curt, A., Starremans, B., Hosman, A., & Bartels, R. (2017). Definitions of traumatic conus medullaris and cauda equina syndrome: A systematic literature review. *Spinal Cord*, *55*(10), 886–890.

Burke, J. F., et al. (2019). Ultra-early (<12 hours) surgery correlates with higher rate of American spinal injury association impairment scale conversion after cervical spinal cord injury. *Neurosurgery*, *85*(2), 199–203.

Clohisy, J. C., Akbarnia, B. A., Bucholz, R. D., Kenneth Burkus, J., & Backer, R. J. (1992). Neurologic recovery associated with: Anterior decompression of spine fractures at the thoracolumbar junction (t12-l1). *Spine*, *17*(8 Suppl), 325–330.

Dahdaleh, N. S., et al. (2013). Evidence-based management of central cord syndrome. *Neurosurgical Focus*, *35*(1), E6.

Dimar, J. R., Glassman, S. D., Raque, G. H., Zhang, Y. P., & Shields, C. B. (1999). The influence of spinal canal narrowing and timing of decompression on neurologic recovery after spinal cord contusion in a rat model. *Spine*, *24*(16), 1623–1633.

Dolan, E. J., Tator, C. H., & Endrenyi, L. (1980). The value of decompression for acute experimental spinal cord compression injury. *Journal of Neurosurgery*, *53*(6), 749–755.

Dvorak, M. F., et al. (2005, October 15). Factors predicting motor recovery and functional outcome after traumatic central cord syndrome: A long-term follow-up. *Spine (Phila Pa 1976)*, *30*(20), 2303–2311.

Dvorak, M. F., et al. (2014). Minimizing errors in acute traumatic spinal cord injury trials by acknowledging the heterogeneity of spinal cord anatomy and injury severity: An observational Canadian cohort analysis. *Journal of Neurotrauma*, *31*(18), 1540–1547.

Dvorak, M. F., et al. (2015). The influence of time from injury to surgery on motor recovery and length of hospital stay in acute traumatic spinal cord injury: An observational Canadian cohort study. *Journal of Neurotrauma*, *32*(9), 645–654.

Fawcett, J. W., et al. (2007). Guidelines for the conduct of clinical trials for spinal cord injury as developed by the ICCP panel: Spontaneous recovery after spinal cord injury and statistical power needed for therapeutic clinical trials. *Spinal Cord*, *45*, 190–205.

Fehlings, M. G., Rabin, D., Sears, W., Cadotte, D. W., & Aarabi, B. (2010). Current practice in the timing of surgical intervention in spinal cord injury. *Spine*, *35*(21 Suppl), S166–S173.

Fehlings, M. G., & Sekhon, L. H. (2001). Acute interventions in spinal cord injury: What do we know, what should we do? *Clinical Neurosurgery*, *48*, 226–242.

Fehlings, M. G., et al. (2012). Early versus delayed decompression for traumatic cervical spinal cord injury: Results of the surgical timing in acute spinal cord injury study (STASCIS). *PLoS One*, *7*(2), e32037.

Fehlings, M. G., & Perrin, R. G. (2006). The timing of surgical intervention in the treatment of spinal cord injury: A systematic review of recent clinical evidence. *Spine (Phila Pa 1976)*, *31*, S28–S35.

Feuchtbaum, E., Buchowski, J., & Zebala, L. (2016). Subaxial cervical spine trauma. *Current Reviews in Musculoskeletal Medicine*, *9*(4), 496–504 (Humana Press Inc).

Furlan, J. C., Tung, K., & Fehlings, M. G. (2013). Process benchmarking appraisal of surgical decompression of spinal cord following traumatic cervical spinal cord injury: Opportunities to reduce delays in surgical management. *Journal of Neurotrauma*, *30*(6), 487–491.

Gargiulo, G., et al. (2019). Clinical comparison between simple laminectomy and laminectomy plus posterior instrumentation in surgical treatment of cervical myelopathy. *European Journal of Orthopaedic Surgery and Traumatology*, *29*(5), 975–982.

Girardo, M., Rava, A., Fusini, F., Gargiulo, G., Coniglio, A., & Cinnella, P. (2018). Different pedicle osteosynthesis for thoracolumbar vertebral fractures in elderly patients. *European Spine Journal*, *27*(Suppl 2), 198–205.

Grassner, L., et al. (2016). Early decompression (< 8 h) after traumatic cervical spinal cord injury improves functional outcome as assessed by spinal cord independence measure after one year. *Journal of Neurotrauma*, *33*(18), 1658–1666.

Guha, A., Tator, C. H., Endrenyi, L., & Piper, I. (1987). Decompression of the spinal cord improves recovery after acute experimental spinal cord compression injury. *Paraplegia*, *25*(4), 324–339.

Hawryluk, G. W. J., Rowland, J., Kwon, B. K., & Fehlings, M. G. (2008). Protection and repair of the injured spinal cord: A review of completed, ongoing, and planned clinical trials for acute spinal cord injury. *Neurosurgical Focus*, *25*(5), E14.

Jug, M., et al. (2015). Neurological recovery after traumatic cervical spinal cord injury is superior if surgical decompression and instrumented fusion are performed within 8 hours versus 8 to 24 hours after injury: A single center experience. *Journal of Neurotrauma*, *32*(18), 1385–1392.

Kirshblum, S., Millis, S., McKinley, W., & Tulsky, D. (2004). Late neurologic recovery after traumatic spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *85*(11), 1811–1817.

Lenehan, B., Fisher, C. G., Vaccaro, A., Fehlings, M., Aarabi, B., & Dvorak, M. F. (2010). The urgency of surgical decompression in acute central cord injuries with spondylosis and without instability. *Spine*, *35*(21 Suppl), S180–S186.

Ma, Y., Zhu, Y., Zhang, B., Wu, Y., Liu, X., & Zhu, Q. (2020). The impact of urgent (<8 hours) decompression on neurologic recovery in traumatic spinal cord injury: A meta-analysis. *World Neurosurgery*, *140*, e185–e194.

Mac-Thiong, J. M., Feldman, D. E., Thompson, C., Bourassa-Moreau, E., & Parent, S. (2012). Does timing of surgery affect hospitalization costs and length of stay for acute care following a traumatic spinal cord injury? *Journal of Neurotrauma*, *29*(18), 2816–2822.

Marino, R. J., Burns, S., Graves, D. E., Leiby, B. E., Kirshblum, S., & Lammertse, D. P. (2011). Upper- and lower-extremity motor recovery after traumatic cervical spinal cord injury: An update from the national spinal cord injury database. *Archives of Physical Medicine and Rehabilitation*, *92*(3), 369–375.

Maynard, F. M., et al. (1997). International standards for neurological and functional classification of spinal cord injury. *Spinal Cord*, *35*(5), 266–274.

McKinley, W., Meade, M. A., Kirshblum, S., & Barnard, B. (2004). Outcomes of early surgical management versus late or no surgical intervention after acute spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *85*(11), 1818–1825.

Nijendijk, J. H. B., Post, M. W. M., & Van Asbeck, F. W. A. (2014). Epidemiology of traumatic spinal cord injuries in the Netherlands in 2010. *Spinal Cord*, *52*(4), 258–263.

Pickett, G. E., et al. (2006). Epidemiology of traumatic spinal cord injury in Canada. *Spine (Phila Pa 1976)*, *31*, 799–805.

Rahimi-Movaghar, V., et al. (2009). The efficacy of surgical decompression before 24 hours versus 24 to 72 hours in patients with spinal cord injury from T1 to L1 – With specific consideration on ethics: A randomized controlled trial. *Trials*, *10*, 77.

Rivlin, A. S., & Tator, C. H. (1978). Effect of duration of acute spinal cord compression in a new acute cord injury model in the rat. *Surgical Neurology*, *10*(1), 39–43.

Rowland, J. W., Hawryluk, G. W. J., Kwon, B., & Fehlings, M. G. (2008). Current status of acute spinal cord injury pathophysiology and emerging therapies: Promise on the horizon. *Neurosurgical Focus*, *25*(5), E2.

Schneider, R. C., Cherry, G., & Pantek, H. (1954). The syndrome of acute central cervical spinal cord injury; with special reference to the mechanisms involved in hyperextension injuries of cervical spine. *Journal of Neurosurgery*, *11*(6), 546–577.

Schneider, R. C., & Knighton, R. (1959). Chronic neurological sequelae of acute trauma to the spine and spinal cord. III. The syndrome of chronic injury to the cervical spinal cord in the region of the central canal. *The Journal of Bone and Joint Surgery. American Volume*, *41-A*(5), 905–919.

Schneider, R. C., Thompson, J. M., & Bebin, J. (1958). The syndrome of acute central cervical spinal cord injury. *Journal of Neurology, Neurosurgery, and Psychiatry*, *21*(3), 216–227.

Singrakhia, M. D., Malewar, N. R., Singrakhia, S. M., & Deshmukh, S. S. (2017). Cervical laminectomy with lateral mass screw fixation in cervical spondylotic myelopathy: Neurological and sagittal alignment outcome: Do we need lateral mass screws at each segment? *Indian Journal of Orthopaedics*, *51*, 658–665.

Stephan, K., et al. (2015). Spinal cord injury - incidence, prognosis, and outcome: An analysis of the TraumaRegister DGU. *The Spine Journal*, *15*(9), 1994–2001.

Tator, C. H., & Fehlings, M. G. (1991). Review of the secondary injury theory of acute spinal cord trauma with emphasis on vascular mechanisms. *Journal of Neurosurgery*, *75*(1), 15–26.

Tator, C. H., Fehlings, M. G., Thorpe, K., & Taylor, W. (1999). Current use and timing of spinal surgery for management of acute spinal cord injury in North America: Results of a retrospective multicenter study. *Journal of Neurosurgery*, *91*(1 Suppl), 12–18.

Ter Wengel, P. V., De Haan, Y., Feller, R. E., Oner, F. C., & Vandertop, W. P. (2020). Complete traumatic spinal cord injury: Current insights regarding timing of surgery and level of injury. *Global Spine Journal*, *10*(3), 324–331 (SAGE Publications Ltd).

Ter Wengel, P. V., et al. (2018). Timing of surgery in traumatic spinal cord injury: A national, multidisciplinary survey. *European Spine Journal*, *27*(8), 1831–1838.

Vaccaro, A. R., et al. (1997). Neurologic outcome of early versus late surgery for cervical spinal cord injury. *Spine (Phila Pa 1976)*, *22*, 2609–2613.

Van Middendorp, J. J. (2012). Letter to the editor regarding: Early versus delayed decompression for traumatic cervical spinal cord injury: Results of the Surgical Timing in Acute Spinal Cord Injury Study (STASCIS). *The Spine Journal*, *12*(6), 540.

Van Middendorp, J. J., Hosman, A. J. F., & Doi, S. A. R. (2013). The effects of the timing of spinal surgery after traumatic spinal cord injury: A systematic review and meta-analysis. *Journal of Neurotrauma*, *30*(21), 1781–1794.

Wiberg, J., & Hauge, H. N. (1988). Neurological outcome after surgery for thoracic and lumbar spine injuries. *Acta Neurochirurgica*, *91*(3–4), 106–112.

Wilson, J. R., & Fehlings, M. G. (2011). Emerging approaches to the surgical management of acute traumatic spinal cord injury. *Neurotherapeutics*, *8*(2), 187–194.

Wilson, J. R., Voth, J., Singh, A., Middleton, J., Jaglal, S. B., Singh, J. M., … Fehlings, M. G. (2016). Defining the pathway to definitive care and surgical decompression after traumatic spinal cord injury: Results of a Canadian population-based cohort study. *Journal of Neurotrauma*, *33*(10), 963–971.

Wilson, J. R., Witiw, C. D., Badhiwala, J., Kwon, B. K., Fehlings, M. G., & Harrop, J. S. (2020). Early surgery for traumatic spinal cord injury: Where are we now? *Global Spine Journal*, *10*(1 Suppl), 84S–91S.

Wilson, J. R., et al. (2012). Early versus late surgery for traumatic spinal cord injury: The results of a prospective Canadian cohort study. *Spinal Cord*, *50*(11), 840–843.

Wilson, J. R., et al. (2017). Timing of decompression in patients with acute spinal cord injury: A systematic review. *Global Spine Journal*, *7*(3 Suppl), 95S–115S (SAGE Publications Ltd).

Wilson, J. R., et al. (2018). Natural history, predictors of outcome, and effects of treatment in thoracic spinal cord injury: A multi-center cohort study from the north American clinical trials network. *Journal of Neurotrauma*, *35*(21), 2554–2560.

Zariffa, J., Curt, A., & Steeves, J. D. (2012). Functional motor preservation below the level of injury in subjects with American spinal injury association impairment scale grade a spinal cord injuries. *Archives of Physical Medicine and Rehabilitation*, *93*(5), 905–907.

Zariffa, J., Kramer, J. L. K., Fawcett, J. W., Lammertse, D. P., Blight, A. R., Guest, J., … Steeves, J. D. (2011). Characterization of neurological recovery following traumatic sensorimotor complete thoracic spinal cord injury. *Spinal Cord*, *49*(3), 463–471.

Chapter 18

Spinal cord epidural stimulation for autonomic nervous system control: A focus on improving bladder, bowel, and cardiovascular function

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List of abbreviations

AD	autonomic dysreflexia
AIS	American Spinal Injury Association Impairment Scale
FDA	Food and Drug Administration
IDE	Investigational Device Exemption
L	lumbar (referring to spinal cord level)
scES	spinal cord epidural stimulation
SCI	spinal cord injury
T	thoracic (referring to spinal cord level)
S	sacral (referring to spinal cord level)

Introduction

Spinal cord injury (SCI) affects nearly 2 million people in the United States (Reeve Foundation Paralysis Resource, 2021) and results in profound neurologic impairment with widespread deficits to sensorimotor and autonomic systems. While the lack of ambulation is most widely recognized, there are many internal systems that are disrupted after SCI due to the critical role of the spinal cord in coordinating bodily functions. As a result, individuals with SCI endure a myriad of complications that result in increased mortality, morbidity, hospitalization, high burden of care and health care costs, and a drastically lowered quality of life (Merritt, Taylor, Yelton, & Ray, 2019).

The autonomic nervous system serves to provide essential regulatory communication between the brain and internal organs, vascular supply, and numerous glands in order to maintain dynamic equilibrium and homeostasis of all systems. Sympathetic and parasympathetic systems (including the enteric system for the gastrointestinal tract) function to integrate complex reflex pathways between the target organ and integration centers within the nervous system (Gibbins, 2013). Thus, autonomic disruption extends across multiple systems and drastically impacts overall health and quality of life. Alterations of urogenital and bowel dysfunctions are consistently rated as top consumer priorities for recovery post-SCI (Anderson, 2004; Ditunno, Patrick, Stineman, & Ditunno, 2008; Simpson et al., 2012). Acutely post-SCI, bladder dysfunction often manifests as "flaccid paralysis," resulting in urinary retention necessitating bladder catheterization. Overtime, bladder dysfunction progresses into detrusor hyperreflexia and detrusor-sphincter dyssynergia, resulting in incontinence and incomplete emptying. Gastrointestinal disruptions after SCI are highly prevalent and include a wide-range of symptoms, including delayed gastric emptying, diminished propulsive transit, abdominal distention, pain, constipation, anal fissures, hemorrhoids, rectal prolapse, and sphincter/defecation disturbances (Krogh et al., 1997). Cardiovascular dysfunction associated with autonomic dysregulation contributes to increased morbidity and is the leading cause of mortality in acute and chronic SCI (Devivo, Krause, & Lammertse, 1999). The disruption of supraspinal control over sympathetic pathways

Diagnosis and Treatment of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822498-4.00018-X

results in decreased sympathetic tone below the level of injury and impaired autonomic function and blood pressure regulation (Koh, Brown, Beightol, Ha, & Eckberg, 1994). One critical complication that occurs in individuals with lesions above T6 is autonomic dysreflexia (AD), an exaggerated sympathetic nervous system response to a noxious stimulus below the level of injury, including bladder/bowel distention, urinary tract infections, fecal impaction, and orgasms (Karlsson, 1999). As a result, increased cardiovascular dysregulation has a profound effect on the body as a whole and significantly interferes with motor and autonomic recovery post-injury.

Bladder dysfunction after SCI

Long-term deficits in bladder function after SCI manifest as detrusor hyperreflexia (bladder contractions at low volumes, causing incontinence and smooth muscle hypertrophy), detrusor-sphincter dyssynergia (uncoordinated bladder and external urethral sphincter contractions, causing inefficient emptying and smooth muscle hypertrophy), decreased compliance (unable to store urine under appropriately low pressures) and loss of continence (Fig. 1) requiring lifelong management, maintenance, and health care visits (Stover, Devivo, & Go, 1999). Major urological concerns contributing to increased morbidity and mortality include repeated lower urinary tract infections that can lead to sepsis, chronic vesico-ureteral reflux and hydronephrosis with progression to renal failure as a result of high-intravesical pressures, and inter-related cardiovascular complications such as AD (Hagen, Faerestrand, Hoff, Rekand, & Gronning, 2011) that

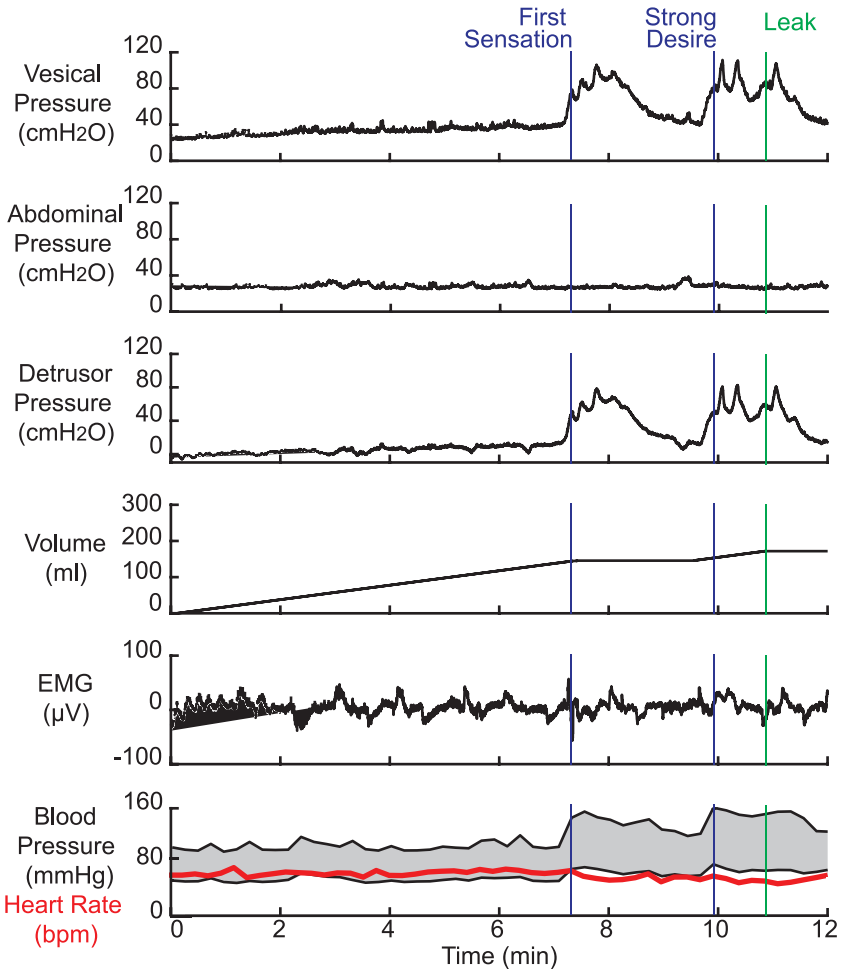

FIG. 1 Neurogenic bladder dysfunction. Representative cystometry recording, including vesical pressure (cmH_2O), abdominal pressure (cmH_2O), detrusor pressure (cmH_2O), volume of infused saline (Ml), surface electromyography (EMG, μV) of the external anal sphincter, continuous blood pressure (mmHg), and heart rate (red, bpm) responses in a 26-year-old male (C4, AIS B), who performs intermittent catheterization for bladder emptying. Multiple detrusor contractions are present, resulting in incontinence at 171 ml with detrusor leak point pressure of 58 cmH_2O. The rise in blood pressure was timed with the rise in detrusor pressure.

limits bladder storage (Hubscher et al., 2018). Current therapies to improve the efficiency of bladder voiding, management and continence after SCI include catheterization, pharmacologic and surgical interventions, functional electrical stimulation, as well as urethral stents. In particular, neurogenic detrusor overactivity and detrusor sphincter dyssynergia are commonly managed with anti-muscarinic drugs and Botox injections, and while these pharmacotherapy agents do not prevent or reverse the changes, they primarily focus on improving storage outcomes and do not address the emptying phase. Furthermore, anti-muscarinic agents can have unpleasant side effects such as dry mouth and constipation, exacerbating existing bowel dysfunction. The primary goal in managing neurogenic bladder is to protect the upper urinary tract and reduce the incidence of infections, followed by achieving continence. As such, when conservative management fails, surgeries to reduce high bladder pressures and chronic urinary incontinence include urinary diversion and lower urinary tract reconstruction approaches (Biers, Venn, & Greenwell, 2012). As urinary complications continue to impact long-term morbidity in this population, additional therapeutic and rehabilitative approaches are needed that aim to improve function by targeting the recovery of underlying impairments.

Bowel dysfunction after SCI

Complications with bowel storage and evacuation are highly prevalent after SCI, with 95% of patients reporting issues with constipation (Glickman & Kamm, 1996). Also, 75% report episodes of fecal incontinence with 30% considering bowel disorders more burdensome than bladder (Krogh et al., 1997) and having a substantial negative impact on quality of life, social integration, and overall independence (Emmanuel, 2010). Neurogenic bowel dysfunction can be characterized by the presence of increased colonic wall and anal tone along with weak abdominal musculature, resulting in fecal retention and constipation. A significant risk of incontinence can occur from an inability to adequately engage the external anal sphincter and pelvic floor musculature (Stiens, Bergman, & Goetz, 1997). While gastrointestinal transit is primarily influenced by local enteric reflexes, motility patterns can be modulated by extrinsic innervation derived from sympathetic, parasympathetic and vagal inputs. Due to difficulties with elimination, prolonged colonic transit time, and impaired motor dexterity (Longo, Ballantyne, & Modlin, 1989), large amounts of time are devoted to bowel care programs (for some, up to 2 h) (Glickman & Kamm, 1996; Hubscher et al., 2018). Many individuals with SCI are also dependent on caregiver assistance. As a result, many choose to conduct their programs every other day (Kirshblum, Gulati, O'connor, & Voorman, 1998), which may increase the risk of constipation, fecal impaction, colorectal distension, and episodes of AD. Conservative bowel regimen approaches include the use of laxatives and stool softeners to obtain a desired consistency, followed by rectal stimulation with either suppositories, enemas, or digital stimulation. Digital stimulation involves rectal pressure with a gloved finger to activate the recto-colic reflex, generating coordinated colonic peristaltic activity and increased motility (Shafik, 1996). Consequently, there is tremendous interest to use neuromodulatory strategies to achieve same or better effects.

Cardiovascular dysfunction and interactions with other autonomic systems after SCI

Cardiovascular diseases are the leading causes of morbidity and mortality among the SCI population (Wecht et al., 2020). Hemodynamic and metabolic cardiovascular effects occur in both the acute and chronic phases of SCI. Disruptions of sympathetic pathways to the heart and vasculature cause autonomic dysfunction and baroreflex impairment resulting in a reduced ability of cardiovascular system to maintain stable blood pressure after SCI. Dysregulation leads to persistent hypotension, bradycardia, orthostatic hypotension, and episodes of AD which drastically impacts quality of life by affecting health and disrupting engagement in daily activities (Krassioukov, Eng, Warburton, & Teasell, 2009). Combinations of sympathetic agonists and venous compression devices are the primary measures currently used for symptomatic management. Manifestations of the reduced quality of life experienced is evidenced by reductions in peripheral blood flow, resulting in an increased risk of pressure ulcers, parasympathetic imbalance increasing vasovagal syncope, fatigue and cognitive dysfunction, and symptomatic orthostasis (Wecht & Bauman, 2018). With time, post-injury blood pressure instability becomes more prominent and persists in many individuals with SCI for the rest of their lives (Katzelnick et al., 2019). AD, characterized by episodes of acute hypertension, is generated by unmodulated sympathetic reflexes below the injury level, and is typically accompanied by compensatory baroreceptor-mediated bradycardia (Karlsson, 1999). Distention or contraction of hollow organs, such as bladder and bowel, are the most common triggers of AD (Lindan, Joiner, Freehafer, & Hazel, 1980). Such below-level peripheral afferent stimuli reach the isolated spinal cord and activate a massive unmodulated sympathetic reflex causing widespread vasoconstriction, presenting as severe hypertension. With high-level SCI, the additional interruption of descending modulatory autonomic pathways that normally inhibit sympathetic preganglionic neurons during hypertension allows AD to persist until the stimulus is removed (Rabchevsky, 2006) (Fig. 2). Management

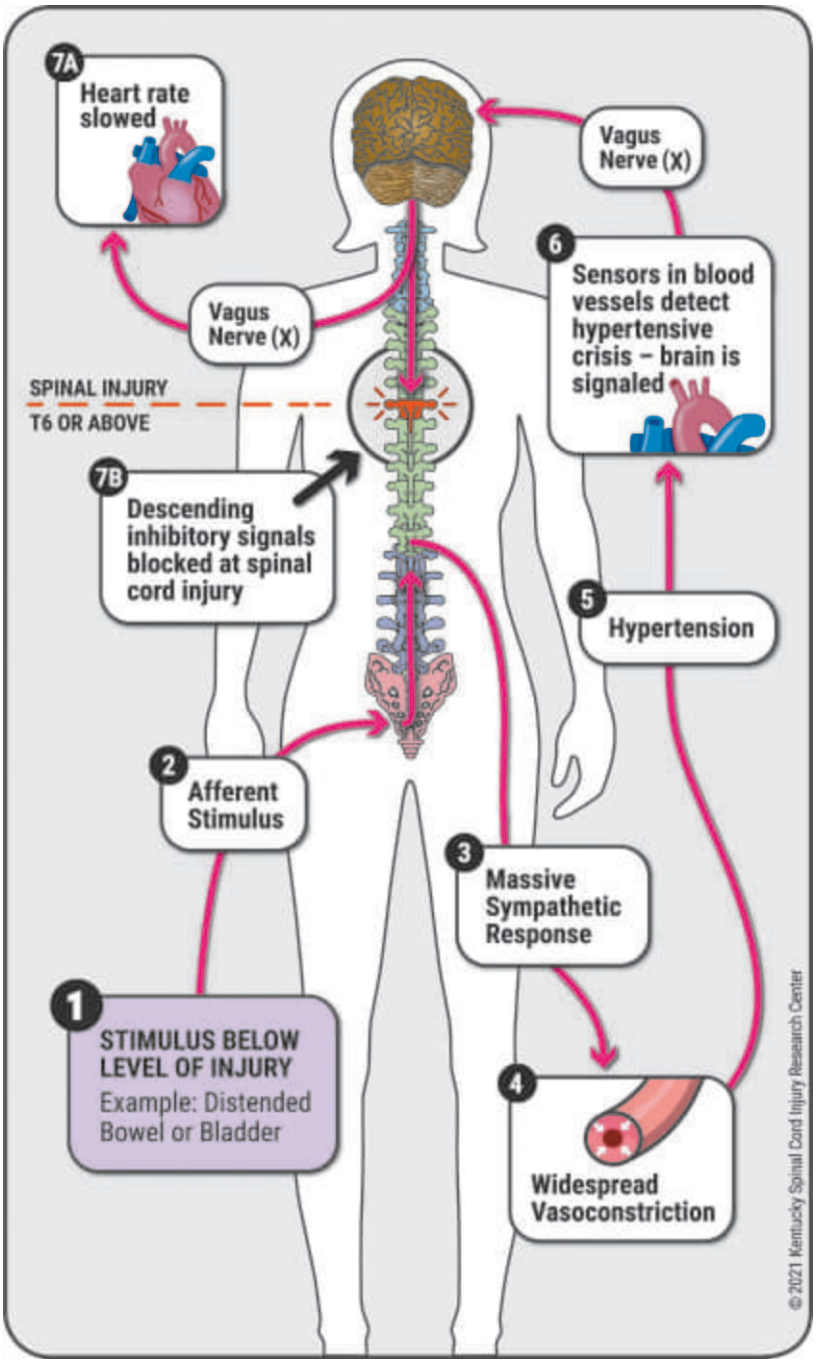

FIG. 2 Autonomic Dysreflexia after SCI. Cartoon diagram outlining the cascade of events leading up autonomic dysreflexia. Primary precipitating stimuli for autonomic dysreflexia include bladder and/or bowel distention.

and mitigation of unstable blood pressure is therefore a high consumer priority in SCI care; however, therapies available that have demonstrated the ability to resolve chronic cardiovascular dysfunction are lacking (Wecht et al., 2020; Wecht, Cirnigliaro, Azarelo, Bauman, & Kirshblum, 2015). With time, post-injury episodes of AD become more prominent and persist long-term. The ability to recover bladder function such as, increasing bladder capacity, minimizing detrusor instability and improving bladder pressure and emptying, is limited by such severe fluctuations in blood pressure. Furthermore, improvements in bowel function are challenged by regular occurrences of AD symptoms during bowel programs, evoked by distention (Inskip, Lucci, McGrath, Willms, & Claydon, 2018) (Fig. 3). The extreme dysregulation of the cardiovascular system underscores the importance of addressing these multi-faceted autonomic complications.

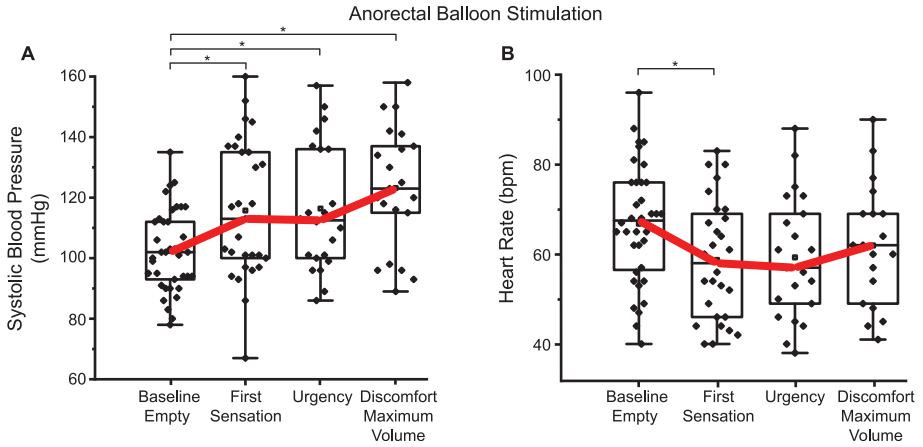

FIG. 3 Blood pressure responses to anorectal distention. Participants ($n = 37$) were asked to respond to sensations of rectal fullness associated with gradual inflation of a balloon catheter during anorectal manometry. Relative to baseline (prior to inflation), mean systolic blood pressure *(red line)* was significantly greater at first sensation ($n = 30$, $P < .01$), urgency ($n = 22$, $P < .05$), and maximum volume ($n = 21$, $P < .01$) (A), while mean heart rate *(red line)* was significantly lower at first sensation ($n = 30$, $P < .01$) relative to baseline (B). Note, while data are normally distributed, not every participant reported each sensation. The normative ranges for volume (mL) at which first, urgency, and maximum sensations of fullness occur are 10–60 mL, 10–100 mL, and 100–200 mL, respectively.

Introduction of spinal cord stimulation

Melzack and Wall's publication of the Gate Theory (Melzack & Wall, 1965) transformed our understanding of pain mechanisms and the associated clinical management, leading to the realization that pain was the result of complex dynamic processes in the nervous system and not simply the result of activity in a hard-wired system. The concept that damage to the nervous system can itself result in chronic pain led to a gradual shift from ablative and destructive surgical approaches, such as cutting nerves, toward reversible neuromodulatory strategies such as therapeutic electrical stimulation of the dorsal spinal cord. The theory that nociceptive impulses, carried by Aδ and C fibers, could be inhibited by electrical stimulation of thick myelinated Aβ fibers provided the first scientific basis for the use of stimulation for pain. At that time, implanted electrode-induced electrical stimulation of the dorsal columns was initially introduced in 1967 in an effort to treat chronic intractable pain (Shealy, Mortimer, & Reswick, 1967). Its use was expanded to treat a wide variety of pain disorders following improvements in sensorimotor function in the multiple sclerosis population (Cook & Weinstein, 1973) and was first used to treat neuropathic pain in SCI in the early 1970s (Nashold Jr. & Friedman, 1972; Shealy, Mortimer, & Hagfors, 1970). Subsequently, the US Food and Drug Administration (FDA) approved the use of spinal cord stimulation in 1989 for the treatment of chronic intractable pain of the trunk or limbs and now accounts for the majority of all neuromodulation interventions (Barolat & Sharan, 2000).

Initial applications of spinal cord epidural stimulation (scES), which served to clinically control severe spasticity in SCI (Dimitrijevic, Illis, Nakajima, Sharkey, & Sherwood, 1986), led to the examination of whether scES had the capacity to drive locomotor capabilities through excitation of the lumbosacral motor circuitry (Waltz, Andreesen, & Hunt, 1987). By activating sophisticated spinal networks below the level of injury, scES functions by reactivating spared neural pathways and bridging supraspinal connectivity across the lesion with the goal of improving recovery after SCI. In persons with motor complete SCI, rhythmic, locomotor-like EMG activity and tonic motor patterns of the lower limbs from the supine position (in the absence of afferent input) were induced with scES (Dimitrijevic, Gerasimenko, & Pinter, 1998). Harkema and colleagues then demonstrated that a critical level of excitability, provided by scES and coupled with intense training that provides appropriate task-specific sensory cues, was necessary to facilitate standing and stepping, as well as intentional movement in clinically motor complete SCI (Angeli, Edgerton, Gerasimenko, & Harkema, 2014; Harkema et al., 2011). The combination of locomotor training (stepping and standing) plus scES not only enhanced coordinated and controlled voluntary motor behavior, but was also reported by individuals to improve physiologic outcomes such as bladder, bowel, and sexual function (Darrow et al., 2019; Harkema et al., 2011; Herrity et al., 2020), as depicted in Fig. 4. A summary of spinal cord stimulation approaches is provided in Table 1.

Neuromodulation to improve bladder function

Many current and past neuromodulatory procedures have had variable success at sustained improvements of bladder function after SCI (McGee, Amundsen, & Grill, 2015; Wheeler et al., 2018). The Finetech-Brindley device (marketed

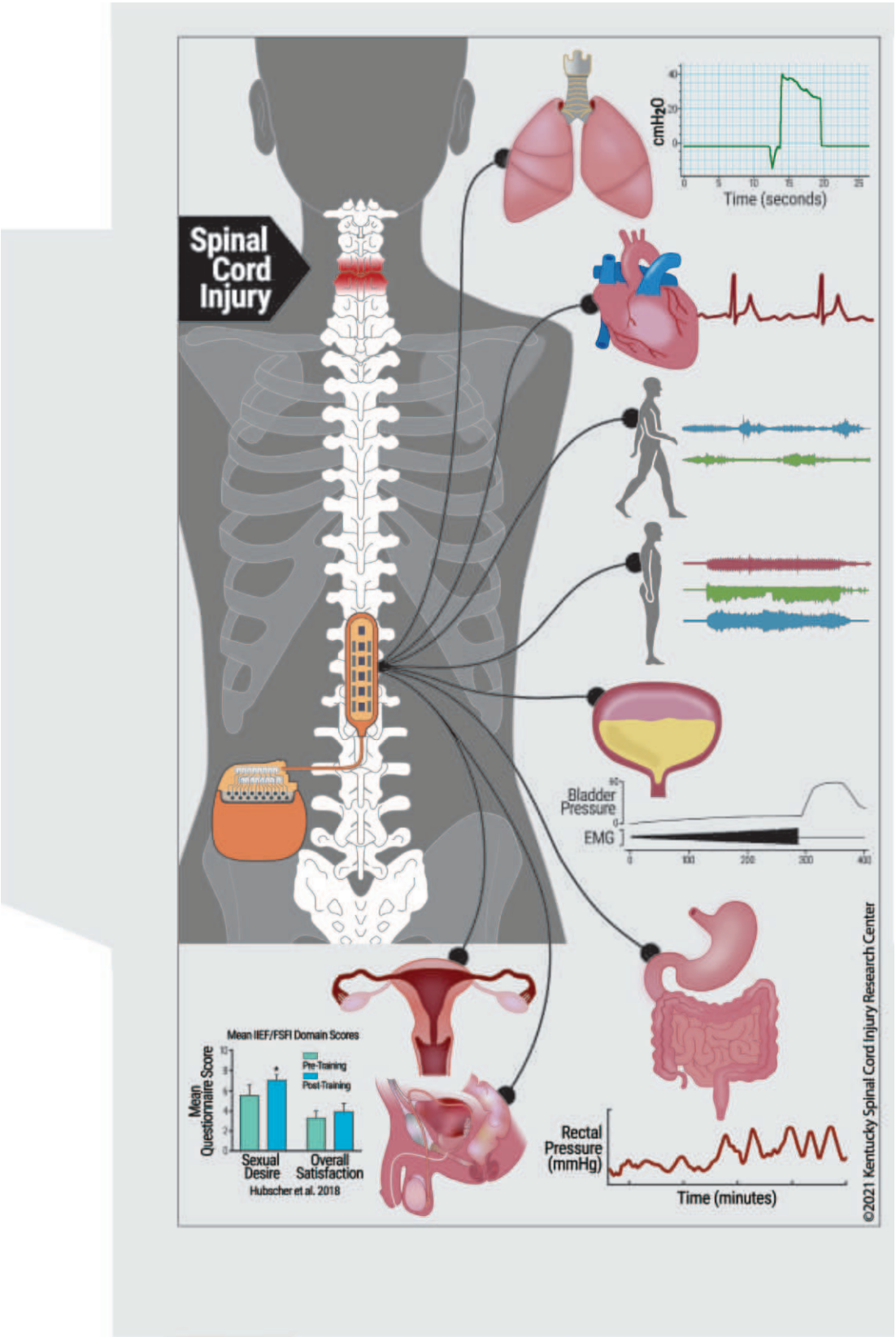

FIG. 4 Restoration of motor and autonomic function using scES. Cartoon illustration depicting some of the body systems targeted by scES. Device implantation in individuals with SCI currently involves placement of an electrode array at the lumbosacral segment of the spinal cord between L1 to S1. The location of the stimulation paddle electrode is guided by intra-operative fluoroscopy and electrophysiology mapping to identify segments of the spinal cord that respond to electrical stimulation. Following surgery, additional neurophysiological spatiotemporal mapping of various electrode configurations is performed.

TABLE 1 Spinal cord stimulation approaches in pre-clinical and clinical studies targeting autonomic function after spinal cord injury.

STIM type	Visceral target	Study model	Author/date	Journal
Epidural	Bladder	Rats	Gad et al. (2014)	PLOS One
		Rats	Gad et al. (2016)	Exp Neurol
		Rats[a]	Chang et al. (2018)	Exp Neurol
		Rats	Sysoev et al. (2020)	Front Sys Neurosci
		Rats	Hoey et al. (2021)	Sci Reports
		Rats[a]	Yousefpour and Erfanian (2021)	Sci Reports
		Pigs[a]	Guiho et al. (2018)	IEEE Trans Neural Syst Rehabil Eng
		Human	Meglio, Cioni, Amico, Ronzoni, and Rossi (1980)	Acta Neurochir (Wien)
		Human	Loubser (1997)	J Pain Symptom manage
		Human	Herrity et al. (2018)	Sci Reports
		Human	Walter et al. (2018)	Front Physiol
		Human	Schieferdecker, Neudorfer, El Majdoub, and Maarouf (2019)	Oper Neurosurg
		Human	Darrow et al. (2019)	J Neurotrauma
		Human	Herrity et al. (2020)	Front Sys Neurosci
	Bowel	Rats	Hoey et al. (2021)	Sci Reports
		Pigs[a]	Guiho et al. (2018)	IEEE Trans Neural Syst Rehabil Eng
		Human	Walter et al. (2018)	Front Physiol
		Human	Darrow et al. (2019)	J Neurotrauma
	Cardiovascular	Rats, Rhesus Macaques	Squair et al. (2021)	Nature
		Human	Richardson et al. (1979)	Neurosurgery
		Human	Harkema, Wang, et al. (2018)	Front Human Neurosci
		Human	Harkema, Legg Ditterline, et al. (2018)	JAMA Neurol
		Human	Aslan et al. (2018)	Front Physiol
		Human	West et al. (2018)	JAMA Neurol
		Human	Legg Ditterline et al. (2020)	Clinical Auton Res
		Human	Legg Ditterline et al. (2020)	Exp Physiol
		Human	Legg Ditterline et al. (2020)	Front Neurosci
		Human	Bloom et al. (2020)	Front Sys Neurosci
		Human	Darrow et al. (2019)	J Neurotrauma
		Human	Squair et al. (2021)	Nature

Continued

TABLE 1 Spinal cord stimulation approaches in pre-clinical and clinical studies targeting autonomic function after spinal cord injury—cont'd

STIM type	Visceral target	Study model	Author/date	Journal
Intra-spinal	Bladder	Mice	Abud et al. (2015)	AJP, Renal Physiology
		Rats[a]	Blok and Holstege (1997)	Neurosci Lett
		Cats[a]	Grill, Wang, Hadziefendic, and Haxhiu (1998)	Brain Res
		Cats[a]	Fedirchuk and Shefchyk (1991)	Exp Br Res
		Cats	Tai, Booth, de Groat, and Roppolo (2004)	Exp Neurol
		Cats	Pikov et al. (2007)	J Neural Eng
		Cats	Pikov et al. (2007)	J Neural Eng
		Dogs	Walter, Robinson, Khan, Wheeler, and Wurster (1989)	Stereotact Funct Neurosurg
		Human	Nashold Jr. and Friedman (1972)	Arch Surg
		Human	Carlsson and Fall (1984)	Paraplegia
	Cardiovascular	Rats[a]	(Qin, Farber, Linderoth, Shahid, & Foreman, 2008)	Journal of Pain
	Bowel	Cats[a]	Tai, Booth, de Groat, and Roppolo (2001)	Brain Res
Transcutaneous	Bladder	Mice	Ahmed (2017) (trans-spinal)	J Neural Eng
		Rhesus Macaques[a]	Havton, Christe, Edgerton, and Gad (2019)	Exp Neurol
		Human	Gad, Kreydin, Zhong, Latack, and Edgerton (2018)	J Neurotrauma
		Human	Gad et al. (2018)	Front Neurosci
		Human	Niu, Bennett, Keller, Leiter, and Lu (2018)	Sci Reports
		Human	Kreydin et al. (2020)	Front Sys Neurosci
	Bowel	Human	Tsai et al. (2009) (magnetic)	J Rehab Medicine
		Human	Lin et al. (2001) (magnetic)	Arch Phys Med Rehab
	Cardiovascular	Rats	Sachdeva et al. (2021)	Neurotherapeutics
		Human	Phillips et al. (2018)	J Neurotrauma

[a]*Denotes non-SCI model.*

in the United States as VOCARE Bladder System), designed to stimulate the anterior sacral roots (S2–S4), was used to aid voiding via intermittent stimulation bursts that maintained constant bladder pressure while periodically relaxing the urethral sphincter, allowing urine to flow in between stimulus intervals (post-stimulus voiding) (Brindley, 1994). Despite the clinical improvements in bladder emptying, one of the major accompanying limitations of the device stems from the irreversibility of ablating intact neural roots. Thus, a shift toward continuous or conditional neuromodulation was proposed in order to preserve the potential for future treatment options in patients with SCI (Hansen et al., 2005). Continuous sacral neuromodulation (applied most commonly over the S3 nerve root) is now a widely accepted stimulation modality for patients with refractory non-neurogenic lower urinary tract dysfunction, including, non-obstructive chronic urinary retention, urgency-frequency syndrome, and urge incontinence (Kessler et al., 2007). Initially, its use was not intended for those with neurogenic bladder dysfunction, but has shown some benefit for reducing detrusor hyperreflexia in those with incomplete SCI (Kessler et al., 2010). Note that peripheral nerves have also served as promising, minimally invasive

targets to modulate the bladder circuitry after SCI, especially for those who may not be appropriate candidates for sacral neuromodulation. However, the stimulation site is distant from the central nervous system and involves repeated applications that may limit long-term durability in the SCI population (Gaziev et al., 2013).

Lumbosacral scES may be an effective approach which mechanistically may involve indirect activation of the same neural networks for bladder function. Several pre-clinical studies have demonstrated that electrical stimulation at select spinal locations can modulate both reflex detrusor and external urethral sphincter activity to induce micturition in different conditions: non-injured rats (Sysoev et al., 2020), nerve crush injuries (Chang, Yeh, Ichiyama, Rodriguez, & Havton, 2018), and following SCI in rats (Abud, Ichiyama, Havton, & Chang, 2015; Hoey et al., 2021) and cats (Pikov, Bullara, & Mccreery, 2007). In the context of human studies using scES, unanticipated gains in bladder function were achieved following locomotor training, where stimulation was optimized for improving standing and stepping (Harkema et al., 2011). The effects of activity-dependent scES on bladder function was further tested in 10 participants enrolled in scES training studies relative to participants in usual care ($n = 10$) who continued their typical daily lives without any study-related change in routine (no intervention), which resulted in improved bladder storage outcomes (increased bladder capacity and compliance and reduced detrusor pressure) at the post-training time point. Even though scES parameters were not targeted to the urinary system and scES was not "on" during bladder testing, long-term gains in bladder capacity persisted a year after training (Herrity et al., 2020), indicating the existence of integrated locomotor and autonomic networks.

When stimulation was targeted for bladder function, key parameters were identified through scES configuration mapping at the caudal end of the array that improved reflexive voiding efficiency in a participant characterized with motor complete SCI (Herrity, Williams, Angeli, Harkema, & Hubscher, 2018). This configuration was also re-tested in four additional individuals (3 AIS A, 1 AIS B), improving bladder emptying in each one, using the same frequency found effective in the initial participant. In these examples, it is possible that sufficient excitation of the lumbosacral circuitry through scES can enable activation of both autonomic and motor spinal cord circuits that control the lower urinary tract, permitting timed detrusor contraction with adequate relaxation of the sphincters and pelvic floor to facilitate more efficient emptying. One important advantage of scES is its capability to simultaneously target multiple systems. Given the heterogeneous nature of neurogenic lower urinary tract dysfunction, it is likely that parameters may vary from participant to participant and configurations found effective for bladder storage may differ from those that improve bladder emptying. Use of multi-electrode scES arrays has the advantage of targeting cardiovascular-specific parameters to control blood pressure in response to bladder distention in susceptible individuals (those with injuries above T6) (Fig. 5), in addition to other patient-specific urological needs (i.e., those using indwelling suprapubic catheters vs. those performing intermittent catheterization).

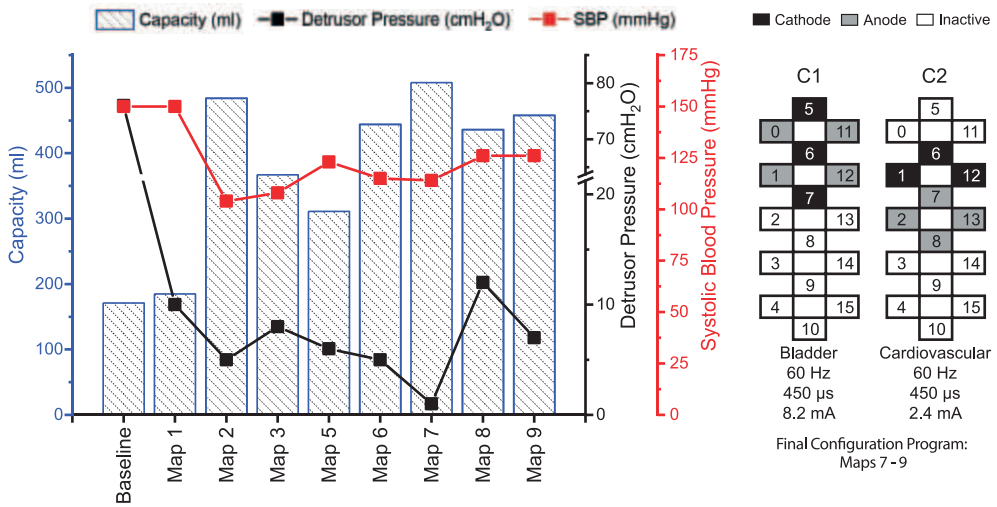

FIG. 5 Inter-system scES improves bladder function. Bladder mapping was conducted during urodynamics to identify specific stimulation parameters effective for bladder storage, which included maintaining bladder capacity *(blue)* within normative ranges established by the International Continence Society (300–600 mL) and maximum detrusor pressure < 40 cmH_2O *(black line)* (C1, cohort 1). Note the integration of a second cohort (C2), used to stabilize blood pressure *(red line)* in response to bladder filling.

Neuromodulation to improve bowel function

It has been demonstrated that electrical neuromodulation of gastrointestinal and autonomic networks can increase peristaltic activity to improve bowel motility and reduce constipation using a wide range of approaches including sacral nerve stimulation and wireless implanted stimulators within the GI system (Deng et al., 2018; Schiano Di Visconte et al., 2019). Vagal nerve stimulation of autonomic networks has also been shown to increase peristaltic activity and reduce inflammation in patients with inflammatory bowel disorders (Frøkjaer et al., 2016). Experimental pre-clinical studies evaluating the use of scES have demonstrated a role in reducing hypersensitivity associated with irritable bowel syndrome (Greenwood-Van Meerveld, Johnson, Foreman, & Linderoth, 2005) and modulating peristaltic activity in a rodent model of SCI (Hoey et al., 2021). In clinical studies with the Finetech-Brindley device, while stimulation of sacral anterior roots increased peristaltic activity in the distal colon and rectum, it also caused concomitant external anal sphincter contraction which prevented emptying during stimulation (Varma, Binnie, Smith, Creasey, & Edmond, 1986). Sacral nerve stimulation has primarily shown benefits in decreasing symptoms of constipation associated with neurogenic bowel dysfunction and decreasing episodes of incontinence in incomplete SCI (Lombardi & Del Popolo, 2009). In patients with gastroparesis, who have symptoms and pathophysiologic similarities to those with SCI (constipation, delayed emptying, prolonged transit time, autonomic dysfunction, abnormal inflammation, dysbiosis, metabolic abnormalities), direct gastric electrical stimulation improved symptoms of nausea and vomiting, constipation, decreased inflammation, and improved gastric motility (Abell et al., 2019). Compared to a conventional bowel routine, a 55%-fold reduction in bowel management time and a reduction in the neurogenic bowel dysfunction score from 15 (severe) to 8 (minor) was demonstrated using scES (preprogrammed for lower extremity and trunk activation) in a case report of one individual with motor complete SCI (Walter, Lee, Kavanagh, Phillips, & Krassioukov, 2018). A reduction in the time required to complete one's bowel program in one participant following the use of scES targeted for voluntary movement was also reported (Darrow et al., 2019). Despite these improvements, much remains unknown about the potential of and how best to target scES to improve bowel function after SCI. Further development of the parameters of stimulation and programming strategies for specifically targeting motility, maintaining continence and promoting evacuation are needed. Importantly, bowel distention is another main trigger of AD after SCI, and therefore, it is likely that stimulation will need to consider parameters to control blood pressure (similar to bladder) when scES is used to promote emptying during one's bowel program.

Neuromodulation to improve cardiovascular function

Cardiovascular autonomic regulation is also a complex interplay of sympathetic and parasympathetic stimulation which is mediated by the spinal cord as the key integrator of complex signals including baroreceptors from the periphery and from supraspinal centers in the brainstem. In spinally intact individuals, lumbosacral scES can promote increased peripheral blood flow in those with peripheral vascular disease (Huber, Vaglienti, & Huber, 2000) and increase blood pressure in a model of central baroreflex failure (Yamasaki et al., 2006). Early evidence of the benefit of spinal stimulation for cardiovascular function in SCI is demonstrated in a study examining the use of percutaneous epidural stimulation to reduce spasticity in 5 subjects, which subsequently resolved AD in four of five individuals (Richardson, Cerullo, & Meyer, 1979). Our recent work has demonstrated that scES in the absence of descending input can modify the excitability of relevant spinal interneuron pools allowing them to respond to peripheral autonomic input and approximate normal cardiovascular control (Harkema et al., 2018). In the context of human locomotor studies in SCI, scES used to facilitate motor activity in individuals undergoing stand training also increased arterial blood pressure, mitigating orthostatic intolerance and stabilizing blood pressure for the duration of standing (Aslan et al., 2018). By stimulating the lumbosacral spinal cord with individual-specific cardiovascular scES configurations, blood pressure can be effectively and safely elevated and maintained within normative ranges from a chronic hypotensive state, without activation of lower limb skeletal muscles, in individuals with severe SCI (Harkema et al., 2018; Legg Ditterline et al., 2020; West et al., 2018). Daily training with scES parameters for cardiovascular function has also been shown to acutely alleviate orthostatic hypotension during orthostatic stress testing, demonstrating an immediate cardiovascular responsiveness to scES (Harkema, Legg Ditterline, et al., 2018).

Future directions with scES and applications to other areas of neuroscience

Restoration of standing and stepping function as well as the regulation of autonomic function in chronic motor complete SCI has been achieved using the existing scES technology. However, the technology remains limited for full independent use in the home and community. The scES devices that are already FDA-approved (for use in chronic pain in non-SCI individuals), and IDE-approved for SCI, are not specifically designed to meet the complex needs

of the SCI population. Upgrading the stimulator's programming and wireless communication platforms to generate a more seamless system capable of delivering multiple training paradigms across multiple physiological systems is needed. The current gap that places the burden on the user to adjust and monitor stimulation and physiological parameters remains one of the most important limiting factors in the effective utilization of this technology outside the laboratory. Thus, to improve long-term adaptations and recovery of autonomic function, integrating use of the technology in the natural environment is key.

From a clinical perspective, identifying those individuals who will potentially benefit from scES, including those with other neurological disorders such as multiple sclerosis (Abbate, Cook, & Atallah, 1977), as well as establishing clear guidelines and protocols regarding the optimization and long-term adjustments of stimulation paradigms, have also been identified as critical areas to advancing the technology (Solinsky, Specker-Sullivan, & Wexler, 2020). Also, given the invasive nature of the scES approach, use of transcutaneous stimulation may be effective in identifying those individuals who respond to scES should device implantation be a future option, as well as testing and determining the optimal spinal locations for different autonomic functions. For example, pilot studies with transcutaneous stimulation applied over interspinous segments of T11 and L1 during urodynamics indicate improvements in bladder storage and emptying in individuals with motor/sensory complete through motor incomplete SCI (Gad et al., 2018; Kreydin et al., 2020).

Mini-dictionary of terms

- **Autonomic Dysreflexia (AD)**: A potentially dangerous syndrome that develops in individuals with cervical or upper thoracic spinal cord injury, resulting in acute, uncontrolled hypertension. AD is typically triggered by noxious or non-noxious peripheral or visceral stimulation below the level of SCI. The most common triggers of AD are from bladder and/or bowel distention.
- **Baroreflex:** a homeostatic response mechanism in which an elevation in blood pressure reflexively causes the heart rate to decrease and blood pressure to decrease.
- **Bowel program**: a regularly scheduled time dedicated to bowel emptying. The process usually begins with stimulating the anorectal region, typically using a suppository, enema, or by digital stimulation.
- **Detrusor-sphincter dyssynergia:** term used to describe a detrusor (bladder muscle) contraction with concomitant involuntary urethral sphincter activation, visualized during urodynamics, and typically present in individuals with neurologically induced bladder dysfunction.
- **Detrusor hyperreflexia:** characterized by the presence of involuntary uninhibited involuntary detrusor contractions, resulting in symptoms of urgency, frequency, and oftentimes, incontinence.
- **Gastroparesis:** impaired breakdown of food in the stomach and slowed gastric emptying resulting in primary symptoms of nausea, vomiting, and abdominal pain.
- **Hydronephrosis:** a condition characterized by excess fluid in a kidney due to the backup of urine, which can cause the kidney to swell.
- **Spinal cord epidural stimulation:** a neurostimulation device that delivers electrical signals through a lead implanted in the epidural space.
- **Urodynamics:** is an assessment of lower urinary tract function to objectively measure, explain and categorize how well the bladder, sphincters, and urethra are storing and releasing urine.
- **Vesico-ureteral reflux**: abnormal retrograde flow (reflux) of urine from the bladder up through one or more of the ureters and sometimes reaching the kidney.

Key facts of autonomic dysfunction after SCI

- Regulation of autonomic function requires an intact neural axis between supraspinal centers and spinal cord autonomic pre-ganglionic neurons.
- Disruption in autonomic nervous system control after SCI results in multi-organ system dysfunction and a loss of overall bodily homeostasis.
- The recovery of bladder and bowel dysfunction may be challenged by interactions from the cardiovascular system, especially in individuals with higher level injuries (above T6) experiencing multiple episodes of AD.
- Autonomic dysfunction has a major impact on the health, well-being, and quality of life in individuals with SCI.

Key facts of scES after SCI

- While initially focused on the motor system, the application of scES in motor complete SCI has more recently been shown to result in meaningful clinical improvements in autonomic function.
- The process of examining scES effects on bladder, bowel, and cardiovascular function begins with identifying specific stimulation parameters (location, rate, intensity, pulse width) during functional mapping that produce the desired outcome.
- Optimal improvements in autonomic function may necessitate the use of inter-system stimulation approaches in which an integration of configurations for multiple systems will enhance coordinated control (i.e., bladder storage and voiding with cardiovascular regulation).

Summary points

- This chapter discusses the widespread impact of SCI on autonomic function and how scES can be used to enhance recovery of bladder, bowel, and cardiovascular function.
- Autonomic dysfunction negatively impacts heath, well-being, and overall quality of life in individuals with SCI.
- Initial applications of scES in the SCI population focused on treating severe spasticity, which subsequently led to the examination of whether scES had the capacity to drive locomotor capabilities through excitation of the lumbosacral motor circuitry.
- Numerous pre-clinical and human studies have demonstrated that scES can also be used to drive meaningful gains in bladder, bowel, and cardiovascular function after SCI.
- Activity-dependent recovery training in combination with scES can facilitate functional reorganization of lumbosacral networks, strengthening residual connections between supraspinal axons and the spinal circuitry involved in autonomic regulation.

References

Abbate, A. D., Cook, A. W., & Atallah, M. (1977). Effect of electrical stimulation of the thoracic spinal cord on the function of the bladder in multiple sclerosis. *The Journal of Urology*, *117*, 285–288.

Abell, T. L., Kedar, A., Stocker, A., Beatty, K., Mcelmurray, L., Hughes, M., et al. (2019). Gastroparesis syndromes: Response to electrical stimulation. *Neurogastroenterology and Motility*, *31*, e13534.

Abud, E. M., Ichiyama, R. M., Havton, L. A., & Chang, H. H. (2015). Spinal stimulation of the upper lumbar spinal cord modulates urethral sphincter activity in rats after spinal cord injury. *American Journal of Physiology. Renal Physiology*, *308*, F1032–F1040.

Ahmed, Z. (2017). Effects of cathodal trans-spinal direct current stimulation on lower urinary tract function in normal and spinal cord injury mice with overactive bladder. *Journal of Neural Engineering*, *14*, 056002.

Anderson, K. D. (2004). Targeting recovery: Priorities of the spinal cord-injured population. *Journal of Neurotrauma*, *21*, 1371–1383.

Angeli, C. A., Edgerton, V. R., Gerasimenko, Y. P., & Harkema, S. J. (2014). Altering spinal cord excitability enables voluntary movements after chronic complete paralysis in humans. *Brain*, *137*, 1394–1409.

Aslan, S. C., Legg Ditterline, B. E., Park, M. C., Angeli, C. A., Rejc, E., Chen, Y., et al. (2018). Epidural spinal cord stimulation of lumbosacral networks modulates arterial blood pressure in individuals with spinal cord injury-induced cardiovascular deficits. *Frontiers in Physiology*, *9*, 565.

Barolat, G., & Sharan, A. D. (2000). Future trends in spinal cord stimulation. *Neurological Research*, *22*, 279–284.

Biers, S. M., Venn, S. N., & Greenwell, T. J. (2012). The past, present and future of augmentation cystoplasty. *BJU International*, *109*, 1280–1293.

Blok, B. F. M., & Holstege, G. (1997). Ultrastructural evidence for a direct pathway from the pontine micturition center to the parasympathetic preganglionic motoneurons of the bladder of the cat. *Neuroscience Letters*, *222*, 195–198.

Bloom, O., Wecht, J. M., Legg Ditterline, B. E., Wang, S., Ovechkin, A. V., Angeli, C. A., … Harkema, S. J. (2020). Prolonged targeted cardiovascular epidural stimulation improves immunological molecular profile: A case report in chronic severe spinal cord injury. *Frontiers in Systems Neuroscience*, *14*. 571011–571011.

Brindley, G. S. (1994). The first 500 patients with sacral anterior root stimulator implants: General description. *Paraplegia*, *32*, 795–805.

Carlsson, C. A., & Fall, M. (1984). Electrical stimulation of the conus medullaris for bladder emptying in a paraplegic. *Paraplegia*, *22*, 87–91.

Chang, H. H., Yeh, J. C., Ichiyama, R. M., Rodriguez, L. V., & Havton, L. A. (2018). Mapping and neuromodulation of lower urinary tract function using spinal cord stimulation in female rats. *Experimental Neurology*, *305*, 26–32.

Cook, A. W., & Weinstein, S. P. (1973). Chronic dorsal column stimulation in multiple sclerosis. Preliminary report. *New York State Journal of Medicine*, *73*, 2868–2872.

Darrow, D., Balser, D., Netoff, T. I., Krassioukov, A., Phillips, A., Parr, A., et al. (2019). Epidural spinal cord stimulation facilitates immediate restoration of dormant motor and autonomic supraspinal pathways after chronic neurologically complete spinal cord injury. *Journal of Neurotrauma*, *36*, 2325–2336.

Deng, Y., Dong, Y., Liu, Y., Zhang, Q., Guan, X., Chen, X., et al. (2018). A systematic review of clinical studies on electrical stimulation therapy for patients with neurogenic bowel dysfunction after spinal cord injury. *Medicine (Baltimore)*, *97*, e12778.

Devivo, M. J., Krause, J. S., & Lammertse, D. P. (1999). Recent trends in mortality and causes of death among persons with spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *80*, 1411–1419.

Dimitrijevic, M. R., Gerasimenko, Y., & Pinter, M. M. (1998). Evidence for a spinal central pattern generator in humans. *Annals of the New York Academy of Sciences*, *860*, 360–376.

Dimitrijevic, M. R., Illis, L. S., Nakajima, K., Sharkey, P. C., & Sherwood, A. M. (1986). Spinal cord stimulation for the control of spasticity in patients with chronic spinal cord injury: II. Neurophysiologic observations. *Central Nervous System Trauma*, *3*, 145–152.

Ditunno, P. L., Patrick, M., Stineman, M., & Ditunno, J. F. (2008). Who wants to walk? Preferences for recovery after SCI: A longitudinal and cross-sectional study. *Spinal Cord*, *46*, 500–506.

Emmanuel, A. (2010). Managing neurogenic bowel dysfunction. *Clinical Rehabilitation*, *24*, 483–488.

Fedirchuk, B., & Shefchyk, S. J. (1991). Effects of electrical stimulation of the thoracic spinal cord on bladder and external urethral sphincter activity in the decerebrate cat. *Experimental Brain Research*, *84*, 635–642.

Frøkjaer, J. B., Bergmann, S., Brock, C., Madzak, A., Farmer, A. D., Ellrich, J., et al. (2016). Modulation of vagal tone enhances gastroduodenal motility and reduces somatic pain sensitivity. *Neurogastroenterology and Motility*, *28*, 592–598.

Gad, P. N., Kreydin, E., Zhong, H., Latack, K., & Edgerton, V. R. (2018). Non-invasive neuromodulation of spinal cord restores lower urinary tract function after paralysis. *Frontiers in Neuroscience*, *12*, 432.

Gad, P. N., Roy, R. R., Zhong, H., Gerasimenko, Y. P., Taccola, G., & Edgerton, V. R. (2016). Neuromodulation of the neural circuits controlling the lower urinary tract. *Experimental neurology*, *285*, 182–189.

Gad, P. N., Roy, R. R., Zhong, H., Lu, D. C., Gerasimenko, Y. P., & Edgerton, V. R. (2014). Initiation of bladder voiding with epidural stimulation in paralyzed, step trained rats. *PLOS One*, *9*, e108184.

Gaziev, G., Topazio, L., Iacovelli, V., Asimakopoulos, A., Di Santo, A., De Nunzio, C., et al. (2013). Percutaneous Tibial nerve stimulation (PTNS) efficacy in the treatment of lower urinary tract dysfunctions: A systematic review. *BMC Urology*, *13*, 61.

Gibbins, I. (2013). Functional organization of autonomic neural pathways. *Organogenesis*, *9*, 169–175.

Glickman, S., & Kamm, M. A. (1996). Bowel dysfunction in spinal-cord-injury patients. *Lancet*, *347*, 1651–1653.

Greenwood-Van Meerveld, B., Johnson, A. C., Foreman, R. D., & Linderoth, B. (2005). Spinal cord stimulation attenuates visceromotor reflexes in a rat model of post-inflammatory colonic hypersensitivity. *Autonomic Neuroscience*, *122*, 69–76.

Grill, W. M., Wang, B., Hadziefendic, S., & Haxhiu, M. A. (1998). Identification of the spinal neural network involved in coordination of micturition in the male cat. *Brain Research*, *796*, 150–160.

Guiho, T., Delleci, C., Azevedo-Coste, C., Fattal, C., Guiraud, D., Vignes, J. R., & Bauchet, L. (2018). Impact of direct epispinal stimulation on bladder and bowel functions in pigs: A feasibility study. *Neurourology and Urodynamics*, *37*, 138–147.

Hagen, E. M., Faerestrand, S., Hoff, J. M., Rekand, T., & Gronning, M. (2011). Cardiovascular and urological dysfunction in spinal cord injury. *Acta Neurologica Scandinavica. Supplementum*, *124*, 71–78.

Hansen, J., Media, S., NØhr, M., Biering-SØrensen, F., Sinkjær, T., & Rijkhoff, N. J. M. (2005). Treatment of neurogenic detrusor overactivity in spinal cord injured patients by conditional electrical stimulation. *Journal of Urology*, *173*, 2035–2039.

Harkema, S., Gerasimenko, Y., Hodes, J., Burdick, J., Angeli, C., Chen, Y., et al. (2011). Effect of epidural stimulation of the lumbosacral spinal cord on voluntary movement, standing, and assisted stepping after motor complete paraplegia: A case study. *Lancet*, *377*, 1938–1947.

Harkema, S. J., Legg Ditterline, B., Wang, S., Aslan, S., Angeli, C. A., Ovechkin, A., et al. (2018). Epidural spinal cord stimulation training and sustained recovery of cardiovascular function in individuals with chronic cervical spinal cord injury. *JAMA Neurology*, *75*, 1569–1571.

Harkema, S. J., Wang, S., Angeli, C. A., Chen, Y., Boakye, M., Ugiliweneza, B., et al. (2018). Normalization of blood pressure with spinal cord epidural stimulation after severe spinal cord injury. *Frontiers in Human Neuroscience*, *12*, 83.

Havton, L. A., Christe, K. L., Edgerton, V. R., & Gad, P. N. (2019). Noninvasive spinal neuromodulation to map and augment lower urinary tract function in rhesus macaques. *Experimental Neurology*, *322*, 113033.

Herrity, A. N., Aslan, S. C., Ugiliweneza, B., Mohamed, A. Z., Hubscher, C. H., & Harkema, S. J. (2020). Improvements in bladder function following activity-based recovery training with epidural stimulation after chronic spinal cord injury. *Frontiers in Systems Neuroscience*, *14*, 614691.

Herrity, A. N., Williams, C. S., Angeli, C. A., Harkema, S. J., & Hubscher, C. H. (2018). Lumbosacral spinal cord epidural stimulation improves voiding function after human spinal cord injury. *Scientific Reports*, *8*, 8688.

Hoey, R. F., Medina-Aguiñaga, D., Khalifa, F., Ugiliweneza, B., Zdunowski, S., Fell, J., et al. (2021). Bladder and bowel responses to lumbosacral epidural stimulation in uninjured and transected anesthetized rats. *Scientific Reports*, *11*, 3268.

Huber, S. J., Vaglienti, R. M., & Huber, J. S. (2000). Spinal cord stimulation in severe, inoperable peripheral vascular disease. *Neuromodulation*, *3*, 131–143.

Hubscher, C. H., Herrity, A. N., Williams, C. S., Montgomery, L. R., Willhite, A. M., Angeli, C. A., et al. (2018). Improvements in bladder, bowel and sexual outcomes following task-specific locomotor training in human spinal cord injury. *PLoS One*, *13*, e0190998.

Inskip, J. A., Lucci, V. M., McGrath, M. S., Willms, R., & Claydon, V. E. (2018). A community perspective on bowel management and quality of life after spinal cord injury: The influence of autonomic dysreflexia. *Journal of Neurotrauma*, *35*, 1091–1105.

Karlsson, A. K. (1999). Autonomic dysreflexia. *Spinal Cord*, *37*, 383–391.

Katzelnick, C. G., Weir, J. P., Jones, A., Galea, M., Dyson-Hudson, T. A., Kirshblum, S. C., et al. (2019). Blood pressure instability in persons with SCI: Evidence from a 30-day home monitoring observation. *American Journal of Hypertension*, *32*, 938–944.

Kessler, T. M., Buchser, E., Meyer, S., Engeler, D. S., Al-Khodairy, A.-W., Bersch, U., et al. (2007). Sacral neuromodulation for refractory lower urinary tract dysfunction: Results of a Nationwide Registry in Switzerland. *European Urology*, *51*, 1357–1363.

Kessler, T. M., La Framboise, D., Trelle, S., Fowler, C. J., Kiss, G., Pannek, J., et al. (2010). Sacral neuromodulation for neurogenic lower urinary tract dysfunction: Systematic review and Meta-analysis. *European Urology*, *58*, 865–874.

Kirshblum, S. C., Gulati, M., O'connor, K. C., & Voorman, S. J. (1998). Bowel care practices in chronic spinal cord injury patients. *Archives of Physical Medicine and Rehabilitation*, *79*, 20–23.

Koh, J., Brown, T. E., Beightol, L. A., Ha, C. Y., & Eckberg, D. L. (1994). Human autonomic rhythms: Vagal cardiac mechanisms in tetraplegic subjects. *The Journal of Physiology*, *474*, 483–495.

Krassioukov, A., Eng, J. J., Warburton, D. E., & Teasell, R. (2009). A systematic review of the management of orthostatic hypotension after spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *90*, 876–885.

Kreydin, E., Zhong, H., Latack, K., Ye, S., Edgerton, V. R., & Gad, P. (2020). Transcutaneous electrical spinal cord neuromodulator (TESCoN) improves symptoms of overactive bladder. *Frontiers in Systems Neuroscience*, *14*, 1.

Krogh, K., Nielsen, J., Djurhuus, J. C., Mosdal, C., Sabroe, S., & Laurberg, S. (1997). Colorectal function in patients with spinal cord lesions. *Diseases of the Colon and Rectum*, *40*, 1233–1239.

Legg Ditterline, B. E., Aslan, S. C., Wang, S., Ugiliweneza, B., Hirsch, G. A., Wecht, J. M., et al. (2020). Restoration of autonomic cardiovascular regulation in spinal cord injury with epidural stimulation: A case series. *Clinical Autonomic Research*, *31*, 317–320.

Lin, V. W., Nino-Murcia, M., Frost, F., Wolfe, V., Hsiao, I., & Perkash, I. (2001). Functional magnetic stimulation of the colon in persons with spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *82*, 167–173.

Lindan, R., Joiner, E., Freehafer, A. A., & Hazel, C. (1980). Incidence and clinical features of autonomic dysreflexia in patients with spinal cord injury. *Paraplegia*, *18*, 285–292.

Lombardi, G., & Del Popolo, G. (2009). Clinical outcome of sacral neuromodulation in incomplete spinal cord injured patients suffering from neurogenic lower urinary tract symptoms. *Spinal Cord*, *47*, 486–491.

Longo, W. E., Ballantyne, G. H., & Modlin, I. M. (1989). The colon, anorectum, and spinal cord patient. A review of the functional alterations of the denervated hindgut. *Diseases of the Colon and Rectum*, *32*, 261–267.

Loubser, P. G. (1997). Adverse effects of epidural spinal cord stimulation on bladder function in a patient with chronic spinal cord injury pain. *Journal of Pain and Symptom Management*, *13*, 251–252.

McGee, M. J., Amundsen, C. L., & Grill, W. M. (2015). Electrical stimulation for the treatment of lower urinary tract dysfunction after spinal cord injury. *The Journal of Spinal Cord Medicine*, *38*, 135–146.

Meglio, M., Cioni, B., Amico, E. D., Ronzoni, G., & Rossi, G. F. (1980). Epidural spinal cord stimulation for the treatment of neurogenic bladder. *Acta Neurochirurgica*, *54*, 191–199.

Melzack, R., & Wall, P. D. (1965). Pain mechanisms: A new theory. *Science*, *150*, 971–979.

Merritt, C. H., Taylor, M. A., Yelton, C. J., & Ray, S. K. (2019). Economic impact of traumatic spinal cord injuries in the United States. *Neuroimmunology and Neuroinflammation*, *6*, 9.

Nashold, B. S., Jr., & Friedman, H. (1972). Dorsal column stimulation for control of pain. Preliminary report on 30 patients. *Journal of Neurosurgery*, *36*, 590–597.

Niu, T., Bennett, C. J., Keller, T. L., Leiter, J. C., & Lu, D. C. (2018). A proof-of-concept study of transcutaneous magnetic spinal cord stimulation for neurogenic bladder. *Scientific Reports*, *8*, 12549.

Phillips, A. A., Squair, J. W., Sayenko, D. G., Edgerton, V. R., Gerasimenko, Y., & Krassioukov, A. V. (2018). An autonomic neuroprosthesis: noninvasive electrical spinal cord stimulation restores autonomic cardiovascular function in individuals with spinal cord injury. *Journal of Neurotrauma*, *35*, 446–451.

Pikov, V., Bullara, L., & Mccreery, D. B. (2007). Intraspinal stimulation for bladder voiding in cats before and after chronic spinal cord injury. *Journal of Neural Engineering*, *4*, 356–368.

Qin, C., Farber, J. P., Linderoth, B., Shahid, A., & Foreman, R. D. (2008). Neuromodulation of thoracic intraspinal viscereroceptive transmission by electrical stimulation of spinal dorsal column and somatic afferents in rats. *The Journal of Pain*, *9*, 71–78.

Rabchevsky, A. G. (2006). Segmental organization of spinal reflexes mediating autonomic dysreflexia after spinal cord injury. In L. C. Weaver, & C. Polosa (Eds.), *Progress in brain research* Elsevier.

Reeve Foundation Paralysis Resource, C. (2021). *One degree of separation: Paralysis and spinal cord injury in the United States*. Christopher & Dana Reeve Foundation. http://www.christopherreeve.org/site/c.mtKZKgMWKwG/b.5184189/k.5587/Paralysis_Facts__Figures.htm.

Richardson, R. R., Cerullo, L. J., & Meyer, P. R. (1979). Autonomic hyper-reflexia modulated by percutaneous epidural neurostimulation: A preliminary report. *Neurosurgery*, *4*, 517–520.

Sachdeva, R., Nightingale, T. E., Pawar, K., Kalimullina, T., Mesa, A., Marwaha, A., et al.…. (2021). Noninvasive neuroprosthesis promotes cardiovascular recovery after spinal cord injury. *Neurotherapeutics*, *18*, 1244–1256.

Schiano Di Visconte, M., Pasquali, A., Cipolat Mis, T., Brusciano, L., Docimo, L., & Bellio, G. (2019). Sacral nerve stimulation in slow-transit constipation: Effectiveness at 5-year follow-up. *International Journal of Colorectal Disease*, *34*, 1529–1540.

Schieferdecker, S., Neudorfer, C., El Majdoub, F., & Maarouf, M. (2019). A retrospective case series of high-frequency spinal cord stimulation (HF10-SCS) in neurogenic bladder incontinence. *Operative Neurosurgery (Hagerstown)*, *17*, 14–20.

Shafik, A. (1996). Recto-colic reflex: Role in the defecation mechanism. *International Surgery*, *81*, 292–294.

Shealy, C. N., Mortimer, J. T., & Hagfors, N. R. (1970). Dorsal column electroanalgesia. *Journal of Neurosurgery*, *32*, 560–564.

Shealy, C. N., Mortimer, J. T., & Reswick, J. B. (1967). Electrical inhibition of pain by stimulation of the dorsal columns: Preliminary clinical report. *Anesthesia and Analgesia*, *46*, 489–491.

Simpson, L. A., Eng, J. J., Hsieh, J. T. C., Wolfe, D. L., & Spinal Cord Injury Rehabilitation Evidence Scire Research, T. (2012). The health and life priorities of individuals with spinal cord injury: A systematic review. *Journal of Neurotrauma*, *29*, 1548–1555.

Solinsky, R., Specker-Sullivan, L., & Wexler, A. (2020). Current barriers and ethical considerations for clinical implementation of epidural stimulation for functional improvement after spinal cord injury. *The Journal of Spinal Cord Medicine*, *43*, 653–656.

Squair, J. W., Gautier, M., Mahe, L., Soriano, J. E., Rowald, A., Bichat, A., et al.…. (2021). Neuroprosthetic baroreflex controls haemodynamics after spinal cord injury. *Nature*, *590*, 308–314.

Stiens, S. A., Bergman, S. B., & Goetz, L. L. (1997). Neurogenic bowel dysfunction after spinal cord injury: Clinical evaluation and rehabilitative management. *Archives of Physical Medicine and Rehabilitation*, *78*, S86–102.

Stover, S. L., Devivo, M. J., & Go, B. K. (1999). History, implementation, and current status of the national spinal cord injury database. *Archives of Physical Medicine and Rehabilitation*, *80*, 1365–1371.

Sysoev, Y., Bazhenova, E., Lyakhovetskii, V., Kovalev, G., Shkorbatova, P., Islamova, R., et al. (2020). Site-specific neuromodulation of detrusor and external urethral sphincter by epidural spinal cord stimulation. *Frontiers in Systems Neuroscience*, *14*, 47.

Tai, C., Booth, A. M., de Groat, W. C., & Roppolo, J. R. (2001). Colon and anal sphincter contractions evoked by microstimulation of the sacral spinal cord in cats. *Brain Research*, *889*, 38–48.

Tai, C., Booth, A. M., de Groat, W. C., & Roppolo, J. R. (2004). Bladder and urethral sphincter responses evoked by microstimulation of S2 sacral spinal cord in spinal cord intact and chronic spinal cord injured cats. *Experimental Neurology*, *190*, 171–183.

Tsai, P. Y., Wang, C. P., Chiu, F. Y., Tsai, Y. A., Chang, Y. C., & Chuang, T. Y. (2009). Efficacy of functional magnetic stimulation in neurogenic bowel dysfunction after spinal cord injury. *Journal of Rehabilitation Medicine*, *41*, 41–47.

Varma, J. S., Binnie, N., Smith, A. N., Creasey, G. H., & Edmond, P. (1986). Differential effects of sacral anterior root stimulation on anal sphincter and colorectal motility in spinally injured man. *BJS (British Journal of Surgery)*, *73*, 478–482.

Walter, J. S., Robinson, C. J., Khan, T., Wheeler, J. S., & Wurster, R. D. (1989). Sacral epidural electrodes for voiding in the chronic spinal dog. *Stereotactic and Functional Neurosurgery*, *53*, 113–124.

Walter, M., Lee, A. H. X., Kavanagh, A., Phillips, A. A., & Krassioukov, A. V. (2018). Epidural spinal cord stimulation acutely modulates lower urinary tract and bowel function following spinal cord injury: A case report. *Frontiers in Physiology*, *9*, 1816.

Waltz, J. M., Andreesen, W. H., & Hunt, D. P. (1987). Spinal cord stimulation and motor disorders. *Pacing and Clinical Electrophysiology*, *10*, 180–204.

Wecht, J. M., & Bauman, W. A. (2018). Implication of altered autonomic control for orthostatic tolerance in SCI. *Autonomic Neuroscience*, *209*, 51–58.

Wecht, J. M., Cirnigliaro, C. M., Azarelo, F., Bauman, W. A., & Kirshblum, S. C. (2015). Orthostatic responses to anticholinesterase inhibition in spinal cord injury. *Clinical Autonomic Research*, *25*, 179–187.

Wecht, J. M., Harel, N. Y., Guest, J., Kirshblum, S. C., Forrest, G. F., Bloom, O., et al. (2020). Cardiovascular autonomic dysfunction in spinal cord injury: Epidemiology, diagnosis, and management. *Seminars in Neurology*, *40*, 550–559.

Wecht, J. M., Weir, J. P., Katzelnick, C. G., Chiaravalloti, N. D., Kirshblum, S. C., Dyson-Hudson, T. A., et al. (2020). Double-blinded, placebo-controlled crossover trial to determine the effects of midodrine on blood pressure during cognitive testing in persons with SCI. *Spinal Cord*, *58*, 959–969.

West, C. R., Phillips, A. A., Squair, J. W., Williams, A. M., Walter, M., Lam, T., et al. (2018). Association of epidural stimulation with cardiovascular function in an individual with spinal cord injury. *JAMA Neurology*, *75*, 630–632.

Wheeler, T. L., De Groat, W., Eisner, K., Emmanuel, A., French, J., Grill, W., et al. (2018). Translating promising strategies for bowel and bladder management in spinal cord injury. *Experimental Neurology*, *306*, 169–176.

Yamasaki, F., Ushida, T., Yokoyama, T., Ando, M., Yamashita, K., & Sato, T. (2006). Artificial baroreflex: Clinical application of a bionic baroreflex system. *Circulation*, *113*, 634–639.

Yousefpour, A., & Erfanian, A. (2021). A general framework for automatic closed-loop control of bladder voiding induced by intraspinal microstimulation in rats. *Scientific Reports*, *11*, 3424.

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Chapter 19

Treating spinal cord injury with implanted spinal cord stimulators

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Abbreviations

AIS	American Spinal Injury Association Impairment Scale
CRPS	complex regional pain syndrome
EES	epidural electrical stimulation
EMG	electromyography
FBSS	failed back surgery syndrome
IPG	implantable pulse generator
MRI	magnetic resonance imaging
SCI	spinal cord injury
SCS	spinal cord stimulation
SCSr	spinal cord stimulator

Introduction

Spinal cord injury

Spinal cord injury (SCI), which literally means damage to the spinal cord, is a devastating and debilitating neurological condition, affecting millions of people worldwide. Traumatic SCI caused by external impacts accounts for the majority of all SCI cases and always accompanies a secondary injury that causes the further death of neurons and glial cells, leading to long-term neurological defects and paralysis. It can significantly harm the spinal cord's functions and burden patients, their families, and friends with substantial personal and socio-economic pressures. According to the 2020 SCI datasheet reported by the National Spinal Cord Injury Statistical Center, approximately 294,000 persons are living with SCI in the United States, with about 17,810 new cases every year, while the World Health Organization (WHO) had estimated that 250,000–500,000 people suffer an SCI each year around the world (Alam et al., 2020; Courtine & Sofroniew, 2019). Clearly, SCI has caused a significant burden on the healthcare system all over the globe.

Etiologically, SCI can be categorized into two types: traumatic SCI and non-traumatic SCI. Traumatic SCI is caused by external physical impacts such as vehicle accidents, sports injuries, violence, or falls. In a traumatic SCI, the external impact firstly causes bone, blood vessel, and ligament damage of the spine, then the debris and dislocation subsequently hurt and rip the spinal cord tissue, initiating the primary injury. After that, it leads to a secondary injury cascade (Fig. 1), resulting in the death of glial cells and neurons, and a long-term neurological defect (Ahuja et al., 2017). Differently, non-traumatic SCI is usually caused by other chronic or degenerative disorders such as tumors or infection, which however can induce a similar level of neurological deficit to a traumatic one. Despite its existence, non-traumatic SCI rarely happens compared with the traumatic SCI that accounts for over 90% of all SCI cases (Alizadeh, Dyck, & Karimi-Abdolrezaee, 2019).

With the improvement in emergency healthcare and medical services, many patients can survive from traumatic SCI and usually live up to a very optimistic life expectancy, however, frequently accompanied by terribly devastating disabilities. The injury cascade leads to complications such as inflammation, ischemia, and subsequently ruin in organization and structure of the spinal cord. Indeed, the clinical outcome is also heavily subject to the location and severity of the injury, since the patients may be partially or wholly paralyzed—depending on the lesion intensity—lose the sensory and motor functions below the level of the lesion, resulting in different extents of disability such as paraplegia and quadriplegia. If the

Diagnosis and Treatment of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822498-4.00019-1

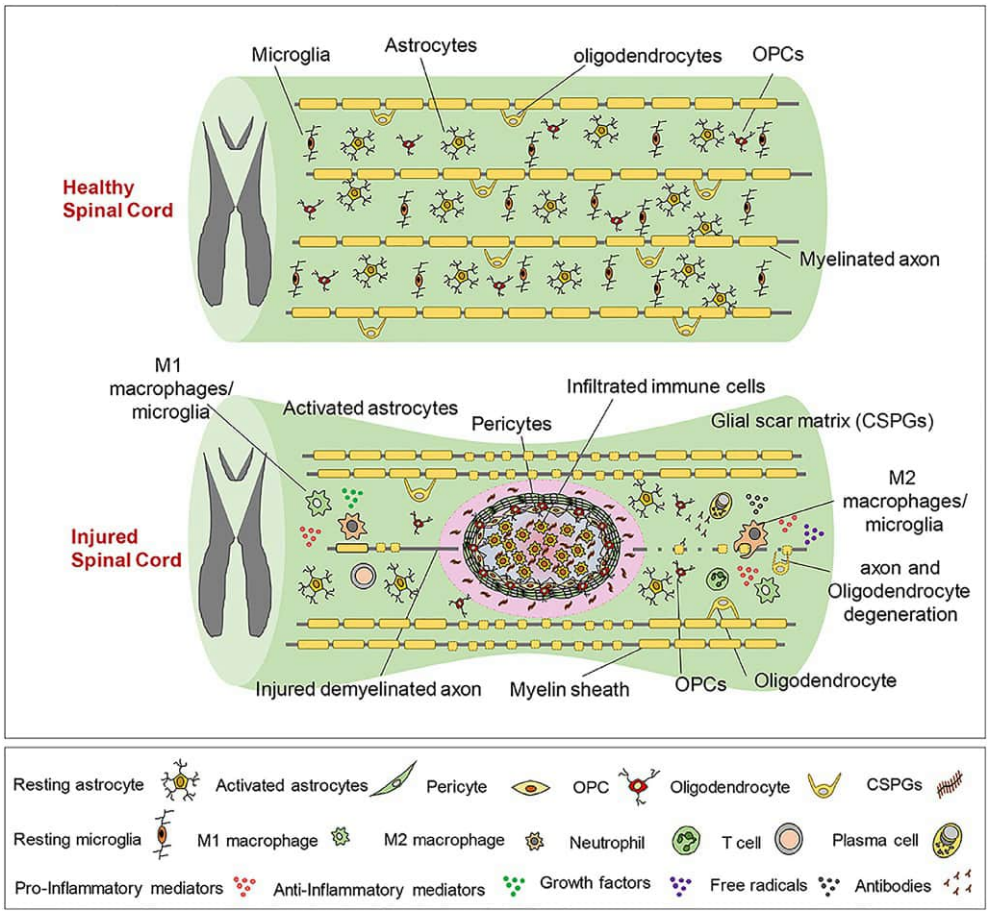


FIG. 1 Pathophysiology of traumatic spinal cord injury. In the healthy spinal cord, axons remain intact, are supported and protected by glia, astrocytes, or other components. After traumatic SCI, a secondary injury following the primary injury leads to the death of glial cells and neurons, initiating a series of devastating responses leading to motor and sensory function loss. *(Reprinted with permission from Alizadeh, A., Dyck, S. M., & Karimi-Abdolrezaee, S. (2019). Traumatic spinal cord injury: An overview of pathophysiology, models and acute injury mechanisms [review]. Frontiers in Neurology, 10(282). https://doi.org/10.3389/fneur.2019.00282.)*

sensory and motor function is totally lost below the injury level, it is clinically defined as a complete SCI; but if there is still any spare function left, it is called an incomplete SCI (Gaber & Brown, 2020). Regardless of different levels of disability, the loss of independence and ability returning to a job and daily life causes immense difficulties, extra works, and costs in caring for SCI patient's daily living. The lifetime cost for each SCI patient is estimated to be US$2.35 million (Alizadeh et al., 2019), which is definitely a considerable amount for many families, especially under the circumstance that the patient themselves cannot often work in their regular jobs anymore. Besides the loss of sensorimotor functions, chronic pain is another common problem, which frequently happens after SCI, with a rate of about 30%–80% and strikingly one third of which suffer from severe pain (Dijkers, Bryce, & Zanca, 2009; Widerström-Noga et al., 2008). Consequently, understanding SCI's pathophysiological mechanism and developing effective treatment to this condition is critical and highly significant.

Treatments for SCI

Over the years, although substantial research and efforts have been contributed to study the SCI, there is still no known method to reverse or cure the damage of SCI at present. Fortunately, different strategies have been found to improve the lost sensorimotor functions, self-independence, and life quality of SCI patients; and other promising treatments are also in progress. Currently, available treatments for SCI are mainly in three aspects: intervention shortly after the injury happens (acute stage), compensatory strategies, and functional recovery in sub-acute and chronic stages (Roy, Harkema, & Edgerton, 2012). The primary purpose of interventions after acute SCI is to decompress the spinal cord and minimize

secondary injury. The typical early intervention approach includes surgical and pharmacological interventions. Though applications on animal models had suggested beneficial outcomes of surgical interventions, its effect on human trials remains unclear (Silva, Sousa, Reis, & Salgado, 2014). Also, despite some successful cases, the ability of pharmacological interventions to improve neurological function remains controversial at present and requires more demonstrations in patients (del Popolo, Mencarini, Nelli, & Lazzeri, 2012). The compensatory strategies usually help improve functions by utilizing assistive devices or training modalities to shift the tasks to unaffected body parts. Compensatory strategies are commonly employed to complete SCI, which has relatively limited restoring capability of the spinal cord functions (Alam & He, 2014; Alam & Zheng, 2017). On the other hand, functional recovery strategies attempt to restore the functions after SCI by means such as stimulations or neurorehabilitation training. These strategies normally show better outcomes for less severe SCI since incomplete SCI has a higher chance of functional recovery; however, stimulation-induced motor function recovery after complete SCI is also heavily investigated (Dietz & Fouad, 2014; Gaber & Brown, 2020). A promising rehabilitative strategy to SCI in recent years is spinal cord stimulation (SCS), which has shown encouraging outcomes in not only functional recovery but also SCI pain relief even in patients who did not expect to improve any function with classical interventions (James, McMahon, Field-Fote, & Bradbury, 2018). In this chapter, we have discussed the principles behind the SCS-mediated rehabilitation of sensorimotor functions after SCI, introduced several notable spinal cord stimulators, and illustrated the procedures of their clinical application.

Spinal cord stimulation

Principles of SCS

SCS has been used to treat neuropathic pains for over 50 years. It is often applied to alleviate chronic pain for which conventional treatments have failed, such as congenital or acquired chronic low back and leg pains, complex regional pain syndrome (CRPS), failed back surgery syndrome (FBSS), and post-SCI pains, etc. (Giugno et al., 2017). SCS blocks pain but not cures it. SCS relieves pain by generating electric pulses at the spinal cord. Its working principle to block pain is the gate control theory of pain (Fig. 2). Gate control theory indicates that other inputs will shut the "nerve gate" for the painful input in the spinal cord, preventing pain signals from reaching the brain so that one does not feel the pain (Ireland, 2010). Based on this theory, the stimulator produces electrical pulses on the spinal cord's dorsal surface, which closes the "nerve gate" to pain signals, prevents them from being received by the brain, thus masks the neuropathic pains (Mammis, 2016).

Besides, SCS starts to serve as a promising tool for movement restoration after SCI. Both invasive and non-invasive SCS could be a powerful tool. The exact principle underlying the motor function improvement by SCS is largely unknown at present. Some findings suggest that even isolated from the brain the spinal circuitry is still able to generate locomotor activity driven by the externally applied stimulation (Courtine et al., 2009; Dimitrijevic, Gerasimenko, & Pinter, 1998; Shah et al., 2016). According to this principle, the SCS replaces the brain to generate stimuli for triggering locomotor-like activity for the paralyzed. So SCS with different patterns, amplitudes, frequencies, pulse widths at different locations may result in different locomotor activities. Theoretically, these motion activities could happen only if SCS is applied to the patient sustainedly. However, another explanation suggests that instead of replacing the brain, the SCS enables the brain

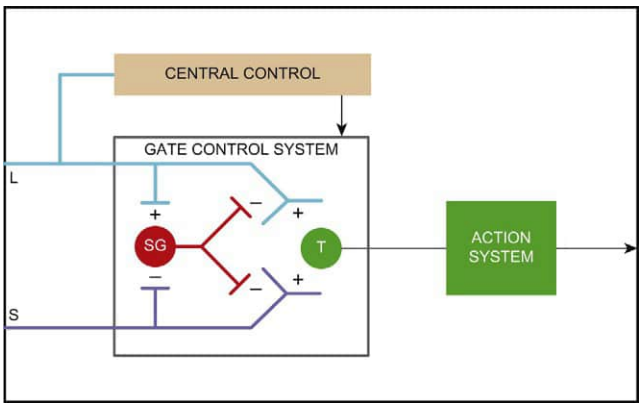


FIG. 2 The gate control theory of pain. The inhibitory neurons in substantia gelatinosa (SG, lamina II) are excited by the non-nociceptive input (L) and thus close the pain gate. *(Reprinted with permission from Braz, J., Solorzano, C., Wang, X., & Basbaum, A. I. (2014). Transmitting pain and itch messages: A contemporary view of the spinal cord circuits that generate gate control. Neuron, 82(3), 522–536. https://doi.org/10.1016/j.neuron.2014.01.018.)*

to recruit the spared and functionally silent nerves residue in SCI, so the reorganization of the residual neural pathway by the SCS promotes and improves locomotor functions (van den Brand et al., 2012). In this theory, the brain is still the command center of the limb movement, and the role of SCS is just to activate the residual neural pathway important for locomotion. So, it is possible that after a period of SCS, the locomotor improvement became long-term and sustained even after the SCS is removed.

Functional rehabilitation with SCS

Though the detailed mechanisms remain largely unclear, many studies found that SCS has benefits on motor function recovery after incomplete or complete SCI, notably in patients' voluntary movement, standing, and stepping recovery as well as cardiovascular and bowel functions management (Table 1). Harkema et al. (2011) propose that tonic SCS could modulate spinal cord circuitry and enable patients with paralysis after SCI to undertake tasks such as standing and stepping. They reported a case in 2011 that a paraplegic patient was able to undergo a full-weight bearing standing and some leg movements during task-specific SCS (Harkema et al., 2011). The subject in the study had a clinically complete loss of voluntary motor function but incomplete sensory SCI, so the regain of some voluntary functions in this study is interpreted by that the residual but silent neuropathway was reactivated or the neuroplasticity was promoted by the SCS (Edgerton & Harkema, 2011). However, in a later study reported in 2014, they found that even for the patients diagnosed with a complete motor and sensory SCI, SCS can still help to proceed detectable leg movements after the paralysis for years (Angeli et al., 2014). This finding uncovers that SCS could be a potential rehabilitative tool for diagnostically complete SCI even a long time after the injury happens. These previous studies apply a relatively low stimulation frequency—usually below 30 Hz—for SCS, and patients still need some external assistance to stand. In 2015, they also reported that two motor-complete but sensory-incomplete SCI patients were able to process full-body weight standing without using any external assistance (Rejc et al., 2015). In this study, a higher stimulation frequency (25–60 Hz) relative to that in previous studies (<30 Hz) lends to an EMG pattern more effective for patients to stand. Also, a body weight-bearing sensory input could remarkably increase the EMG activity to sufficient for standing, while very little EMG activity was generated by lower limb muscles during epidural SCS. The research by Sayenko et al. also demonstrated that the stimulation parameters and sensory conditions significantly influence the SCS outcomes, showing different stimulation responses between standing and supination (Sayenko, Angeli, Harkema, Edgerton, & Gerasimenko, 2014). Besides lower limb movement recovery, SCS at the cervical level was also successfully applied to improve upper limb motor functions and promote voluntary hand movements for patients with tetraplegia (Lu et al., 2016; Qian, Ling, Zhong, Zheng, & Alam, 2020).

In the studies mentioned earlier, the efficacy of SCS on SCI motor function recovery has been witnessed; nonetheless, volitional movements were generated only if real-time task-specific SCS is being provided. Rejc et al. (2017) had progressively found the reemergence of muscle activation pattern sufficient for the standing of complete SCI patients without any real-time SCS after they underwent long-term task-specific motor training with SCS (Rejc et al., 2017). After then, a number of recent studies also showed that a period of SCS motor training enabled SCI patients to conduct independent standing and stepping over the ground (Angeli et al., 2018; Gill et al., 2018; Wagner et al., 2018). These achievements reveal that SCS could stimulate real-time motor activation and be a promising training tool to recover the independent motor functions for patients with complete chronic SCI (Fig. 3) (Cho, Squair, Bloch, & Courtine, 2019).

Spinal cord stimulators

Current spinal cord stimulators

There are currently various kinds of spinal cord stimulators on the market. This section briefly discussed several typical products and compared their properties and features (Table 2). Precision Spectra is an SCSr designed by Boston Scientific Corporation. Its function mainly focuses on pain relief. This product's working principle is similar to what was mentioned previously: generating impulses to mask the pain signals before they could reach the brain. Precision Spectra is featured with more coverage, high flexibility, and advanced control. It is a safe, drug-free, approved by the Food and Drug Administration (FDA) of the United States, and paresthesia-free pain management therapy that is clinically proven to help reduce chronic pains. The Spectra can be personalized for every individual's unique pain and can deliver more than one type of stimulation simultaneously, even at multiple areas, to find the optimum treatment for a particular pain. Firstly, Spectra introduces the world's first implantable pulse generator (IPG) with 32 contacts and a dedicated power source, providing more excellent coverage and more precise targeting to the spinal cord but not increasing the product size. Secondly, Spectra presents an unprecedented level of flexibility. The combination of the four-port design and the broad lead portfolio enables

TABLE 1 The application of implanted SCSrs for SCI.

Paper	*n*	Motor complete/ incomplete (AIS)	Spinal cord stimulator	Trainings	Therapy duration (months)	Therapy intensity (sessions/ week)	Total number of training sessions	Training outcomes or the improvement in ISNCSCI Motor Score: mean (range)
DiMarco, Geertman, Tabbaa, Nemunaitis, & Kowalski, (2020))	5	Complete (A)	Finetech Medical's cough stimulation system + Ardiem Medical's wire lead electrodes	Bowel management (cough restore) training	5.25	14–21	294–441	Restore cough and improve bowel management
Darrow et al. (2019)	2	Complete (A)	Abbott's Tripole and Proclaim Elite + 16-electrode paddle array	Simultaneous stimulation and assessment	No training period	No training period	No training period	Restore some supraspinal control over motor function below the level of injury: volitional motor control, cardiovascular function, bowel-bladder synergy
Harkema et al. (2018)	4	Complete (A/B)	Medtronic's Restore ADVANCED + 16-electrode array	Spinal cord epidural stimulation for cardiovascular function	0.5	2.5	5	Activate mechanisms to elevate blood pressures to normal ranges from a chronic hypotensive state in SCI
Wagner et al. (2018)	3	Incomplete (C/D)	Medtronic's Activa RC + 16-electrode paddle array	Cycling + locomotor training	5	5	108	10.3 (4–16)
Angeli et al. (2018)	4	Complete (A/B)	Medtronic's epidural arrays + neurostimulators + programming devices	Locomotor training	Range 6–20	7	168–560	0.25 (0–1)
Grahn et al. (2017)	1	Complete (A)	Medtronic's RestoreSensor SureScan MRI + 5–6-5 Specify 16-electrode array	Locomotor training	0.5	4	8	Enable volitional control of task-specific muscle activity, rhythmic muscle activity to produce step-like movements while side-lying, independent standing
Rejc, Angeli, Atkinson, and Harkema (2017)	1	Complete (B)	Medtronic's Restore ADVANCED + 5–6-5 Specify 16-electrode array	Activity-based training/task-specific training	16	5	80	From no volitional muscle activation to standing, stepping, volitional leg movement

Continued

TABLE 1 The application of implanted SCSrs for SCI—cont'd

Paper	*n*	Motor complete/ incomplete (AIS)	Spinal cord stimulator	Trainings	Therapy duration (months)	Therapy intensity (sessions/ week)	Total number of training sessions	Training outcomes or the improvement in ISNCSCI Motor Score: mean (range)
Lu et al. (2016)	3	Complete (B)	Boston Scientific's Precision Plus + Artisan 16-electrode epidural array	Volitional hand function	24	1–7	96–672	19.5 (16–23)
Rejc, Angeli, and Harkema (2015)	4	Complete (A/B)	Medtronic's Restore ADVANCED +5–6-5 Specify 16-electrode array	Stand training	16	5	80	Stand over-ground bearing full body weight without any external assistance
Angeli, Edgerton, Gerasimenko, and Harkema (2014)	4	Complete (A/B)	Medtronic's Restore ADVANCED + 16-electrode array	Locomotor training	3–7	7	21–49	Able to generate EMG activity and movement during ankle dorsiflexion in the presence of epidural stimulation
Possover (2014)	4	Complete/ incomplete (B/C)	Medtronics Restore ADVANCED + four 4-array fine wire electrodes	Locomotor training	12	3–5	156–260	12.8 (1 – 21)
Harkema et al. (2011)	1	Complete (B)	Medtronic's Restore ADVANCED + 16-electrode array	Standing + locomotor training	7	1.7	170	Full weight-bearing standing for 4.25 min, supraspinal control of some leg movements
Carhart, Jiping, Herman, Luzansky, and Willis (2004)	1	Incomplete (C)	X-trel 3470 implanted receiver + implanted quadripolar electrode leads (PISCES-Quad Plus, Model 3888) + external transmitter (X-trel, Model 3425)	Locomotor training	7	5	140	Reduction in sense of effort for over ground walking from 8/10 to 3/10 (Borg scale), and was able to double his walking speed reached maximum walking speeds of 0.35 m/s, and was able to ambulate over 325 m

AIS, American Spinal Injury Association Impairment Scale.
The treatment regimens used experimentally in laboratory models or clinically in patients with spinal cord injury of which implanted spinal cord stimulators were applied: subject number (*n*), diagnosis, stimulators, training parameters, and outcomes.

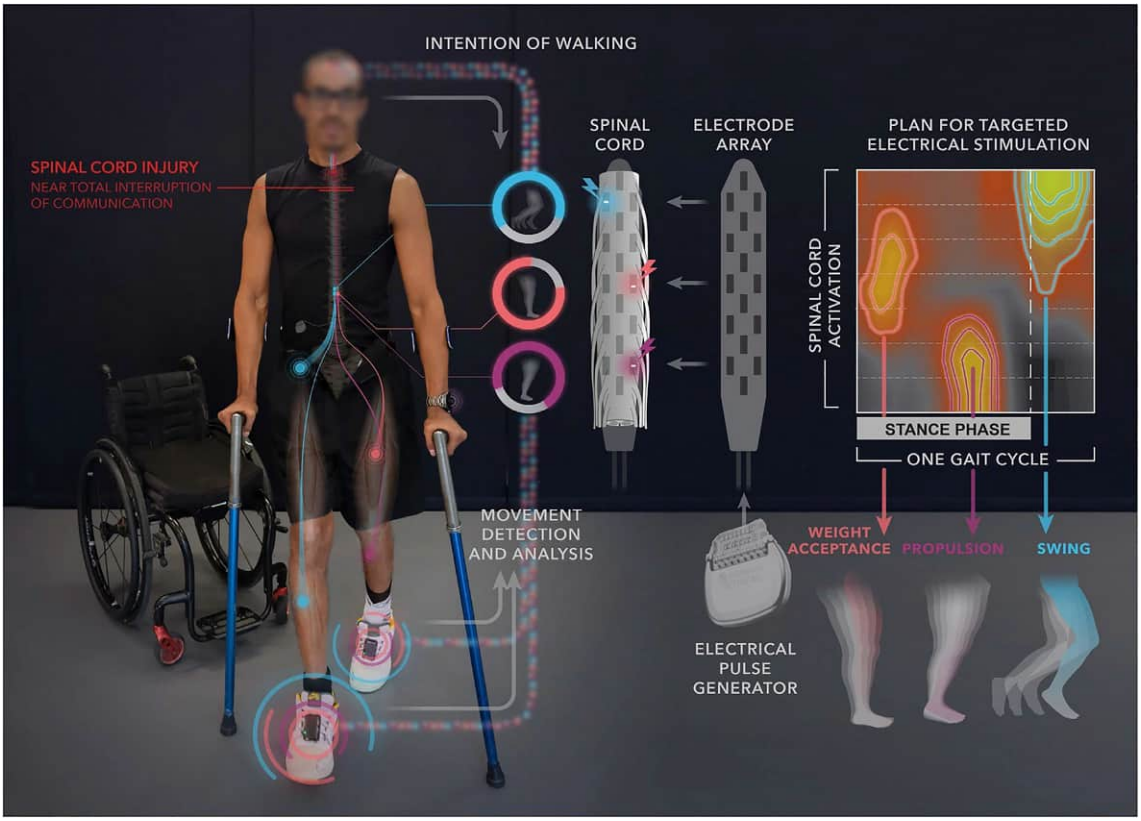


FIG. 3 Enabling over-ground walking with SCS in SCI patients. Stimulation bursts matching the spatial and temporal dynamics of the neural network reproduces natural activation of the spinal cord and enables locomotion in SCI. The spinal cord activation map was reconstructed based on the projection of electromyographic signals on an estimated location of the neural circuit in the spinal cord. *(Reprinted with permission from Cho, N., Squair, J. W., Bloch, J., & Courtine, G. (2019). Neurorestorative interventions involving bioelectronic implants after spinal cord injury. Bioelectronic Medicine, 5(1), 10. https://doi.org/10.1186/s42234-019-0027-x.)*

unmatched flexibility of lead configuration to adapt the possible change of the pain patterns in the future. Besides, Spectra also provides a series of advanced control technologies.

Proclaim XR is a recharge-free SCS system developed by Abbott Laboratories. A long-lasting battery of up to 10 years is a highlight in this SCSr. The battery longevity without any recharging is achieved by delivering low-dose stimulation. Proclaim XR applies BurstDR stimulation therapy, also known as burst stimulation, which imitates natural firing patterns of the human central nervous system to have better pain relief than tonic stimulation and potential benefits to various mechanisms of action (Kirketeig, Schultheis, Zuidema, Hunter, & Deer, 2019). BoldXR dosing protocol is used for patient-specific stimulation to ensure the optimal dose to have the best outcome and prevent the side effects of over-stimulation.

Restore by Medtronic is a family of FDA-approved SCSr that allows the patients to have an MRI scan. There are three IPGs with little differences under this series. Restoresensor Surescan stimulator features a customized pain management pattern and an automatic adjustment between low and high doses to achieve the optimal stimulation setting at the proper position. Restoreadvanced Surescan MRI stimulator specifically features the longest battery endurance among all Medtronic stimulators through a low dose programming. RestoreUltra SureScan allows safe access to the MRI scan, which is FDA-approved for 1.5-Tesla anywhere on the patient's body.

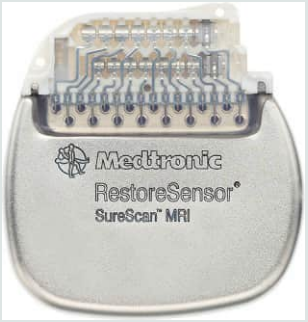
Omnia is a next-generation SCSr launched by Nevro Corporation. The selling point of Omnia is maximum versatility, able to deliver and combine all approved frequencies from 2 to 10,000 Hz, and claimed to have the broadest range of stimulation solution. It provides both direct neural pain inhabitation with a 10 kHz—high frequency (HF10) therapy and dorsal column stimulation at traditionally low frequency; or it can even pair high frequency with low frequency, HF10 with a burst to generate various blending waveforms for different individuals. Also, Omnia is claimed to have the fastest charging rate in SCSrs and is labeled with a full-body conditional MRI scan.

TABLE 2 A comparison of commercial SCSrs.

Boston Scientific
Precision Spectra
Wider pain coverage with 32 contacts and 32 power sources. Flexible configurations realized by 4 ports and various leads

Abbott Laboratories
Proclaim XR
Low energy burst stimulation to prevent overstimulation. Long-lasting battery which can run up to 10 years without any recharging

Medical use: Pain relief *Max. freq.*: 1200 Hz *Max. pulse wid.*: 1000 μs	Customized stim. 4 ports | 32 electrodes 1.5 T MRI head only	*Medical use*: Pain relief *Max. freq.*: 1200 Hz *Max. pulse wid.*: 1000 μs	BurstDR + tonic stim. 2 ports | 16 electrodes 1.5 T head and extremity



Medtronic
Restoresensor Surescan MRI
FDA approved full-body MRI scan eligibility. AdaptiveStim technology providing personalized pain management

Nevro
Omnia
All approved frequencies are available. Various waveforms, dual mechanisms available for more flexible therapy to relieve pain

Medical use: Pain relief *Max. freq.*: 1.2 kHz *Max. pulse wid.*: 1 ms	Low + high dose stim. 2 ports | 16 electrodes 1.5 T MRI whole body	*Medial use*: Pain relief *Max. freq.*: 10 kHz *Max. pulse wid.*: no info.	HF10 + Burst + Tonic stim. No info. about electrodes 1.5-T MRI full body

Four common commercial SCSrs and their basic information: Precision Spectra by Boston Scientific; Proclaim XR by Abbott Laboratories; Restoresensor Surescan MRI by Medtronic; and Omnia by Nevro.

Surgical implantation of neurostimulators

For chronic use, an SCSr is needed to be implanted into the body, which is an invasive procedure that commonly requires surgery. Hence, SCS usually requires candidate evaluation before implantation. Usually, a patient receiving more than 50% pain relief in the trial with all other criteria reached is regarded as a suitable candidate; otherwise, they are not good candidates for the stimulator implantation (Mammis, 2016). In this section, different components of SCSr implantation procedures are introduced.

As mentioned in the previous section, an SCSr commonly have three main components: the leads, an implantable pulse generator (IPG), and an external wireless programmer (Fig. 4). There are also three main types of pulse generators: the conventional one requires another surgery to replace the battery once it runs out, the rechargeable one with a battery that can be recharged without any surgery, and the radiofrequency one with a battery outside the body.

In the trial stimulation, the injection site is first given a local anesthetic. Then insulated leads are inserted through a needle into the epidural space of the spinal cord, guided by fluoroscopy. The electrodes on the lead terminal are then

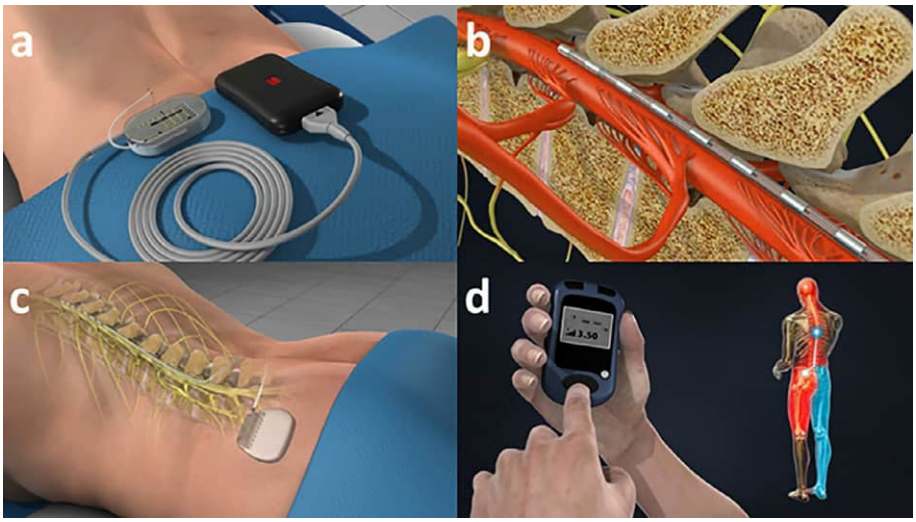


FIG. 4 Surgical steps of a spinal cord stimulation system. (A) Trial stimulation with a temporary SCSr. (B) Insertion of the lead electrodes into the epidural space. (C) Implantation of the IPG at the buttock. (D) Using a wireless programmer for operating the stimulator. *(Printed with permission from ViewMedica.)*

intermittently activated to generate electrical impulses to block the pain signals. During this procedure, the patient gives feedback to help the physician determine the best placement of the electrodes. The lead is then linked to an external trial stimulator for a trial lasting for about 1 week to evaluate SCS efficacy. If the SCS shows an acceptable result during the trial period, permanent implantation may be conducted. The trial leads are removed, and similarly, the patient is anesthetized, and the permanent leads are inserted into the epidural space. A small incision is then created, and the implantable pulses generator (IPG) is implanted in the buttocks. The leads are connected to the IPG. Finally, the external programmer can be used to turn on or off the generator and adjust the stimulation power level and other settings.

Significance of SCS

Motor function deficit and chronic back and leg pain remain critical problems in spinal disorders, affecting millions of patients worldwide. They severely affect patients' self-independences and life qualities, yet traditional medical treatments such as pharmaceutical and surgical interventions often fail to achieve satisfactory results. In contrast, SCS shows significant performance in treating neuropathic pains for which conservative treatments have failed and promising efficacy on motor function improvement after clinically complete or incomplete SCI. The application of SCS on pain relief has been relatively mature, with many studies proving its effectiveness and various kinds of products available on the market. Furthermore, as the functional mechanism is well understood, emerging stimulations with different frequencies, waveforms, and patterns are used to achieve user-specific and more effective therapies.

SCS also demonstrates its significance in motor function restoration. In previous studies, SCS has been used to improve animal models and humans' motor function after an SCI (Wenger et al., 2016). The paraplegic patients were able to conduct voluntary leg movements such as standing, stepping over the ground, or bladder control via SCS. Closed-loop neurostimulation has also shown promises for optimal micturition for SCI (Peh et al., 2018). Sufficient muscle activities related to these motions could be measured during the SCS. Furthermore, after a period of task-specific training with SCS, the patients presented an improvement in standing and stepping independently, even when the SCS was removed. This indicates that the motor function restoration can persist beyond the SCS period. Neuroplasticity plays a significant role in these permanent recoveries (Alam, Rodrigues, Pham, & Thakor, 2016; Ling, Alam, & Zheng, 2019). Based on breakthroughs in the existed studies, SCS is promising to be developed into effective tools for functional restoration following SCI, as the functional mechanism behind them is currently being investigated more deeply.

Current limitations of the neurostimulators

There has already been a wide variety of SCSrs available on the market at present. As mentioned in the previous section, companies such as Boston Scientific, Abbott Laboratories, Medtronic, and Nevro have offered their own SCSr with unique features. These stimulators present various characteristics, such as large pain coverage, long-lasting battery, MRI

compatibility, flexible therapy, etc. However, the current stimulators still have some limitations (Alam et al., 2019; Li et al., 2020). One of them is the invasiveness of the stimulator implantation via surgery, implicating the risks of bleeding, allergic response, infection, etc. The trial stimulations indicate extra implantation; meanwhile, the change of patient's pain condition needs stimulation adjustment and might require additional surgeries for new stimulator implantations, especially for those stimulators unable to provide designable stimulation patterns. Another problem is the device-related problem such as lead migration, connection failure, or damage during use.

A more critical problem of all existed stimulators on the market is their application scope, designing purposely for pain relief. It means that the stimulation pattern, frequency, or waveform of the stimulators are not designed for functional restoration. Hence, SCSrs' application in SCI patients is mostly limited since the pain relief is more likely the emphasis in treating SCI compared with the restoration of function.

Advanced neurostimulators

Besides the current SCSr mentioned above, a recently developed injectable stimulator developed by Stimwave Technologies, Freedom-8A, is a futuristic SCS system, which may overcome some limitations of the existed SCSrs (Billet, Wynendaele, & Vanquathem, 2018). Unlike traditional stimulators requiring bulky implantation, Freedom-8A is a wireless system with only one micro-size component to inject into the epidural space. Without a battery and wires accompanied, Freedom-8A is much smaller and does not require an IPG, which makes it less invasive and reduces the implants' paresthesia. Meanwhile, Freedom-8A can provide up to 64 electrode contacts, twofold of Precision Spectra mentioned previously, and 3.0 T full-body MRI compatibility. It also provides programmable stimulation with a frequency of up to 10 kHz. By integrating features of existed stimulators with its own novelties, Freedom-8A is offering a minimally invasive all-in-one SCS solution for SCI patients. A large clinical outcome of this stimulator is, however, yet to be reported.

GTX Medical, a newly founded spin-off from the Swiss federal institute of technology Lausanne (EPFL), is developing a new generation SCSr for targeted epidural SCS therapy to promote recovery of motor functions and neurologic control in adults with SCI and paralysis based on the recent research findings (Wagner et al., 2018). Their implantable Go-2 system, which is designed to deliver targeted epidural SCS therapy, has recently (June 2020) granted United States Food and Drug Administration (FDA) breakthrough device designation. The Company anticipates the first clinical trial for the complete Go-2 system in patients to take place in 2021.

Prospects of the stimulation for spinal cord injury rehabilitation

A non-invasive SCS could be the solution to the problems that arise from the invasiveness of the SCSrs. Some studies found that besides the epidural SCS, transcutaneous SCS, which is non-invasive without requiring any surgeries, could also enable mobility after SCI and may confer similar outcomes to epidural SCS if suitable parameters are adopted (Gerasimenko, Kozlovskaya, & Edgerton, 2016; Ievins & Moritz, 2017). If the non-invasive transcutaneous SCS could achieve comparable efficacy on motor function improvement to the epidural SCS and even replace it in the future, a great number of complications caused by surgery will be readily solved.

Until today, most commercially available SCSrs are working on pain relief when the application on motor function restoration after SCI is still at the experimental stage. Although many previous results have demonstrated the improvement of motor function for paralysis following SCI during the stimulation period, the preferable breakthrough in the future may be that the SCS training could achieve sustained and unrelenting motion improvement, which means after a period of training the patients could persist the mobility even beyond the period of stimulation (Ievins & Moritz, 2017). More investigations on the mechanism behind SCS induced functional improvement are needed to achieve this goal. Also, the efficacy of SCS on the recovery of more complex movements, such as dexterity control, continued walking, balance, requires further research study and clinical trial (García, Serrano-Muñoz, Taylor, Avendaño-Coy, & Gómez-Soriano, 2019). Lastly, combining SCS with pharmaceutic and cellular interventions may also lead to effective treatment to improve voluntary movement after SCI in the future.

Applications to other areas of neuroscience

In this chapter, we have reviewed the application of SCS by the SCSrs on improving motor functions and relieving chronic pain caused by SCI. We also discussed the advancements and limitations of the existing stimulators and then prospected on the futuristic stimulators in these processes.

The application of SCS also demonstrates high efficacy for pain relief in other neurological or spinal disorders, especially those that fail the conventional treatment approaches. These include failed back surgery syndrome (FBSS), complex regional pain syndrome (CRPS), others such as arachnoiditis, heart pain, nerve-related pain, peripheral vascular diseases, post-amputation pain, and visceral abdominal pain and perineal pain. Indeed, the sources of pain in the above disorders could be very different from the pain of the SCI. However, due to the nature of SCS pain relief, blocking the pain signals from reaching the brain by generating electric pulse, it is reasonable that SCS can be used for other chronic pain relief.

A recent study assessed a group of type I CRPS patients on pain relief and their life qualities after SCS implantation. The result shows that pain relief occurs in most subjects after SCS (Mammis, 2016). While another review on 80 cases of SCS treatments shows that at a 12 months follow-up, 40% of patients did not require medication anymore, while the rest claimed that the pain became manageable accompanied by using a first-line analgesic (Gopal, Fitzgerald, & McCrory, 2016). Similarly, various studies have shown evidence that SCS has clinical effectiveness on FBSS pain relief. One trial applies traditional SCS surgery, which is low-frequency SCS, for a group of subjects who have suffered from unrelenting post-spinal-surgery back pain for more than 3 months. The results collected over more than 2.5 years show about 50% pain relief for 50% of patients (Kumar et al., 2005; Kumar et al., 2007; North, Kidd, Farrokhi, & Piantadosi, 2005).

Mini-dictionary of terms

Spinal cord injury: The damage to the spinal cord. It is often caused by trauma, and the severe one can result in paralysis.
Neuromodulation: The alteration of nerve activity via a certain stimulus such as electrical stimulation, electromagnetic stimulation, and chemical agents.
Spinal cord stimulation: The use of electric impulses to stimulate the region of the spinal cord for a certain purpose. Spinal cord stimulation can be either invasive or non-invasive.
Spinal cord stimulator: The device that delivers spinal cord stimulation.
Complete SCI: The spinal cord injury causing the total loss of communication between the brain and nerves below the point of the injury. It implicates paralysis.
Incomplete SCI: The spinal cord injury in which there is still residual motor or sensory communication between the brain and nerves below the point of the injury. It implicates a paresis.
Neuropathway: The connection formed by axons to enable signals to be sent from one region to another in the nervous system.
Paresthesia: An abnormal sensation. The cause of paresthesia could be various.
Epidural space: The space between the dura mater and the vertebral wall, just above the dural sac.
Chronic pain: The pain lasting for over 3 months, usually coming and going without clearly know reasons.

Key facts of spinal cord injury

- Millions of patients are currently suffering from spinal cord injury (SCI) worldwide, and an estimated 768,473 new cases occur every year.
- There are mainly two types of SCI: traumatic and non-traumatic SCI, when over 90% are traumatic SCI.
- Primary and secondary injury cascades in traumatic SCI cause the death of neurons and glial cells, resulting in long-term neurological defects.
- SCI can cause disabilities: paraplegia and quadriplegia are commonly seen depending on the injury level, sometimes accompanied by pains.
- Complete SCI features the complete loss of sensory or motor functions below the injury site when incomplete SCI has limited function through the residual connection between the brain and nerves below the injury.

Summary points

- Spinal cord injury causes paralysis and chronic pain, affecting millions of patients' self-independence and life quality worldwide.
- Therapeutic and surgical interventions show limited efficacy in restoring patients' functions after SCI.
- Spinal cord stimulation presents a stunning performance in treating chronic back or leg pain and promising effectiveness in improving motor functions after SCI.
- In some studies, patients with motor complete SCI were able to conduct locomotor functions such as weight-bearing standing and stepping over the ground during SCS.

- There are various kinds of spinal cord stimulators on the market targeting chronic pain relief. These stimulators possess large pain coverage, flexible and customized therapy, high-frequency stimulation, and MRI compatibility to achieve a better outcome and user experience.
- There are few spinal cord stimulators specially designed for motor function improvement on the market yet. Further understanding of the mechanism behind SCS will be needed to develop safe and effective stimulators for improving motor functions for SCI.

References

Ahuja, C. S., Wilson, J. R., Nori, S., Kotter, M. R. N., Druschel, C., Curt, A., et al. (2017). Traumatic spinal cord injury. *Nature Reviews Disease Primers*, *3* (1), 17018. https://doi.org/10.1038/nrdp.2017.18.

Alam, M., & He, J. (2014). Lower-limb neuroprostheses: Restoring walking after spinal cord injury. In G. R. Naik, & Y. Guo (Eds.), *Emerging theory and practice in neuroprosthetics* (pp. 153–180). IGI Global. https://doi.org/10.4018/978-1-4666-6094-6.ch009.

Alam, M., Li, S., Ahmed, R. U., Yam, Y. M., Thakur, S., Wang, X.-Y., et al. (2019). Development of a battery-free ultrasonically powered functional electrical stimulator for movement restoration after paralyzing spinal cord injury. *Journal of Neuro Engineering and Rehabilitation*, *16*(1), 36. https://doi.org/10.1186/s12984-019-0501-4.

Alam, M., Ling, Y. T., Wong, A. Y. L., Zhong, H., Edgerton, V. R., & Zheng, Y.-P. (2020). Reversing 21 years of chronic paralysis via non-invasive spinal cord neuromodulation: A case study. *Annals of Clinical and Translational Neurology*, *7*(5), 829–838. https://doi.org/10.1002/acn3.51051.

Alam, M., Rodrigues, W., Pham, B. N., & Thakor, N. V. (2016). Brain-machine interface facilitated neurorehabilitation via spinal stimulation after spinal cord injury: Recent progress and future perspectives. *Brain Research*, *1646*, 25–33. https://doi.org/10.1016/j.brainres.2016.05.039.

Alam, M., & Zheng, Y.-P. (2017). Motor neuroprosthesis for injured spinal cord: Who is an ideal candidate? *Neural Regeneration Research*, *12*(11), 1809–1810. https://doi.org/10.4103/1673-5374.219041.

Alizadeh, A., Dyck, S. M., & Karimi-Abdolrezaee, S. (2019). Traumatic spinal cord injury: An overview of pathophysiology, models and acute injury mechanisms [review]. *Frontiers in Neurology*, *10*(282). https://doi.org/10.3389/fneur.2019.00282.

Angeli, C. A., Boakye, M., Morton, R. A., Vogt, J., Benton, K., Chen, Y., et al. (2018). Recovery of over-ground walking after chronic motor complete spinal cord injury. *New England Journal of Medicine*, *379*(13), 1244–1250. https://doi.org/10.1056/NEJMoa1803588.

Angeli, C. A., Edgerton, V. R., Gerasimenko, Y. P., & Harkema, S. J. (2014). Altering spinal cord excitability enables voluntary movements after chronic complete paralysis in humans. *Brain*, *137*(5), 1394–1409. https://doi.org/10.1093/brain/awu038.

Billet, B., Wynendaele, R., & Vanquathem, N. E. (2018). A novel minimally invasive wireless technology for neuromodulation via percutaneous intercostal nerve stimulation for post-herpetic neuralgia: A case report with short-term follow-up. *Pain Practice*, *18*(3), 374–379. https://doi.org/10.1111/papr.12607.

Carhart, M. R., Jiping, H., Herman, R., Luzansky, S. D., & Willis, W. T. (2004). Epidural spinal-cord stimulation facilitates recovery of functional walking following incomplete spinal-cord injury. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, *12*(1), 32–42. https://doi.org/10.1109/TNSRE.2003.822763.

Cho, N., Squair, J. W., Bloch, J., & Courtine, G. (2019). Neurorestorative interventions involving bioelectronic implants after spinal cord injury. *Bioelectronic Medicine*, *5*(1), 10. https://doi.org/10.1186/s42234-019-0027-x.

Courtine, G., Gerasimenko, Y., van den Brand, R., Yew, A., Musienko, P., Zhong, H., et al. (2009). Transformation of nonfunctional spinal circuits into functional states after the loss of brain input. *Nature Neuroscience*, *12*(10), 1333–1342. https://doi.org/10.1038/nn.2401.

Courtine, G., & Sofroniew, M. V. (2019). Spinal cord repair: Advances in biology and technology. *Nature Medicine*, *25*(6), 898–908. https://doi.org/10.1038/s41591-019-0475-6.

Darrow, D., Balser, D., Netoff, T. I., Krassioukov, A., Phillips, A., Parr, A., et al. (2019). Epidural spinal cord stimulation facilitates immediate restoration of dormant motor and autonomic supraspinal pathways after chronic neurologically complete spinal cord injury. *Journal of Neurotrauma*, *36*(15), 2325–2336. https://doi.org/10.1089/neu.2018.6006.

del Popolo, G., Mencarini, M., Nelli, F., & Lazzeri, M. (2012). Controversy over the pharmacological treatments of storage symptoms in spinal cord injury patients: A literature overview. *Spinal Cord*, *50*(1), 8–13. https://doi.org/10.1038/sc.2011.110.

Dietz, V., & Fouad, K. (2014). Restoration of sensorimotor functions after spinal cord injury. *Brain*, *137*(Pt 3), 654–667. https://doi.org/10.1093/brain/awt262.

Dijkers, M., Bryce, T., & Zanca, J. (2009). Prevalence of chronic pain after traumatic spinal cord injury: A systematic review. *Journal of Rehabilitation Research and Development*, *46*(1), 13–29. https://doi.org/10.1682/JRRD.2008.04.0053.

DiMarco, A. F., Geertman, R. T., Tabbaa, K., Nemunaitis, G. A., & Kowalski, K. E. (2020). Effects of lower thoracic spinal cord stimulation on bowel management in individuals with spinal cord injury. *Archives of Physical Medicine and Rehabilitation*. https://doi.org/10.1016/j.apmr.2020.09.394.

Dimitrijevic, M. R., Gerasimenko, Y., & Pinter, M. M. (1998). Evidence for a spinal central pattern generator in humans. *Annals of the New York Academy of Sciences*, *860*, 360–376. https://doi.org/10.1111/j.1749-6632.1998.tb09062.x.

Edgerton, V. R., & Harkema, S. (2011). Epidural stimulation of the spinal cord in spinal cord injury: Current status and future challenges. *Expert Review of Neurotherapeutics*, *11*(10), 1351–1353. https://doi.org/10.1586/ern.11.129.

Gaber, T., & Brown, M. (2020). Recent advances in neuromodulation for spinal cord injuries. *Progress in Neurology and Psychiatry*, *24*(1), 4–8. https://doi.org/10.1002/pnp.554.

García, A., Serrano-Muñoz, D., Taylor, J., Avendaño-Coy, J., & Gómez-Soriano, J. (2019). Transcutaneous spinal cord stimulation and motor rehabilitation in spinal cord injury: A systematic review. *Neurorehabilitation and Neural Repair*, *34*. https://doi.org/10.1177/1545968319893298, 154596831989329.

Gerasimenko, Y., Kozlovskaya, I., & Edgerton, V. R. (2016). Sensorimotor regulation of movements: Novel strategies for the recovery of mobility. *Human Physiology*, *42*(1), 90–102. https://doi.org/10.1134/S0362119716010096.

Gill, M. L., Grahn, P. J., Calvert, J. S., Linde, M. B., Lavrov, I. A., Strommen, J. A., et al. (2018). Neuromodulation of lumbosacral spinal networks enables independent stepping after complete paraplegia. *Nature Medicine*, *24*(11), 1677–1682. https://doi.org/10.1038/s41591-018-0175-7.

Giugno, A., Gulì, C., Basile, L., Graziano, F., Maugeri, R., Visocchi, M., et al. (2017). Spinal cord stimulation: An alternative concept of rehabilitation? *Acta Neurochirurgica. Supplement*, *124*, 15–18. https://doi.org/10.1007/978-3-319-39546-3_3.

Gopal, H., Fitzgerald, J., & McCrory, C. (2016). Spinal cord stimulation for FBSS and CRPS: A review of 80 cases with on-table trial of stimulation. *Journal of Back and Musculoskeletal Rehabilitation*, *29*, 7–13. https://doi.org/10.3233/BMR-150608.

Grahn, P. J., Lavrov, I. A., Sayenko, D. G., Van Straaten, M. G., Gill, M. L., Strommen, J. A., et al. (2017). Enabling task-specific volitional motor functions via spinal cord neuromodulation in a human with paraplegia. *Mayo Clinic Proceedings*, *92*(4), 544–554. https://doi.org/10.1016/j.mayocp.2017.02.014.

Harkema, S., Gerasimenko, Y., Hodes, J., Burdick, J., Angeli, C., Chen, Y., et al. (2011). Effect of epidural stimulation of the lumbosacral spinal cord on voluntary movement, standing, and assisted stepping after motor complete paraplegia: A case study. *Lancet (London, England)*, *377*(9781), 1938–1947. https://doi.org/10.1016/S0140-6736(11)60547-3.

Harkema, S. J., Wang, S., Angeli, C. A., Chen, Y., Boakye, M., Ugiliweneza, B., et al. (2018). Normalization of blood pressure with spinal cord epidural stimulation after severe spinal cord injury [original research]. *Frontiers in Human Neuroscience*, *12*(83). https://doi.org/10.3389/fnhum.2018.00083.

Ievins, A., & Moritz, C. T. (2017). Therapeutic stimulation for restoration of function after spinal cord injury. *Physiology*, *32*(5), 391–398. https://doi.org/10.1152/physiol.00010.2017.

Ireland, R. (2010). *A dictionary of dentistry*. Oxford University Press. https://doi.org/10.1093/acref/9780199533015.001.0001.

James, N., McMahon, S., Field-Fote, E., & Bradbury, E. (2018). Neuromodulation in the restoration of function after spinal cord injury. *Lancet Neurology*, *17*, 905–917. https://doi.org/10.1016/S1474-4422(18)30287-4.

Kirketeig, T., Schultheis, C., Zuidema, X., Hunter, C. W., & Deer, T. (2019). Burst spinal cord stimulation: A clinical review. *Pain Medicine*, *20*(Suppl. 1), S31–s40. https://doi.org/10.1093/pm/pnz003.

Kumar, K., North, R., Taylor, R., Sculpher, M., Van den Abeele, C., Gehring, M., et al. (2005). Spinal cord stimulation vs. conventional medical management: A prospective, randomized, controlled, multicenter study of patients with failed back surgery syndrome (PROCESS study). *Neuromodulation: Technology at the Neural Interface*, *8*(4), 213–218. https://doi.org/10.1111/j.1525-1403.2005.00027.x.

Kumar, K., Taylor, R. S., Jacques, L., Eldabe, S., Meglio, M., Molet, J., et al. (2007, Nov). Spinal cord stimulation versus conventional medical management for neuropathic pain: A multicentre randomised controlled trial in patients with failed back surgery syndrome. *Pain*, *132*(1–2), 179–188. https://doi.org/10.1016/j.pain.2007.07.028.

Li, S., Alam, M., Ahmed, R. U., Zhong, H., Wang, X.-Y., Ng, S., et al. (2020). Ultrasound-driven piezoelectric current activates spinal cord neurocircuits and restores locomotion in rats with spinal cord injury. *Bioelectronic Medicine*, *6*(1), 13. https://doi.org/10.1186/s42234-020-00048-2.

Ling, Y. T., Alam, M., & Zheng, Y. P. (2019). Spinal cord injury: Lessons about neuroplasticity from paired associative stimulation. *Neuroscientist*, *26*(3), 266–277. https://doi.org/10.1177/1073858419895461.

Lu, D. C., Edgerton, V. R., Modaber, M., AuYong, N., Morikawa, E., Zdunowski, S., et al. (2016). Engaging cervical spinal cord networks to reenable volitional control of hand function in tetraplegic patients. *Neurorehabilitation and Neural Repair*, *30*(10), 951–962. https://doi.org/10.1177/1545968316644344.

Mammis, A. (2016). *Spinal cord stimulation: Principles and practice*. Nova Science Publishers, Incorporated. https://books.google.com.hk/books?id=QSCFjgEACAAJ.

North, R. B., Kidd, D. H., Farrokhi, F., & Piantadosi, S. A. (2005). Spinal cord stimulation versus repeated lumbosacral spine surgery for chronic pain: A randomized, controlled trial. *Neurosurgery*, *56*(1), 98–106. discussion 106–107 https://doi.org/10.1227/01.neu.0000144839.65524.e0.

Peh, W. Y. X., Raczkowska, M. N., Teh, Y., Alam, M., Thakor, N. V., & Yen, S.-C. (2018). Closed-loop stimulation of the pelvic nerve for optimal micturition. *Journal of Neural Engineering*, *15*(6). https://doi.org/10.1088/1741-2552/aadee9, 066009.

Possover, M. (2014). Recovery of sensory and supraspinal control of leg movement in people with chronic paraplegia: A case series. *Archives of Physical Medicine and Rehabilitation*, *95*(4), 610–614. https://doi.org/10.1016/j.apmr.2013.10.030.

Qian, Q., Ling, Y. T., Zhong, H., Zheng, Y.-P., & Alam, M. (2020). Restoration of arm and hand functions via noninvasive cervical cord neuromodulation after traumatic brain injury: A case study. *Brain Injury*, *34*(13–14), 1771–1780. https://doi.org/10.1080/02699052.2020.1850864.

Rejc, E., Angeli, C. A., Atkinson, D., & Harkema, S. J. (2017). Motor recovery after activity-based training with spinal cord epidural stimulation in a chronic motor complete paraplegic. *Scientific Reports*, *7*(1), 13476. https://doi.org/10.1038/s41598-017-14003-w.

Rejc, E., Angeli, C., & Harkema, S. (2015). Effects of lumbosacral spinal cord epidural stimulation for standing after chronic complete paralysis in humans. *PLoS One*, *10*(7). https://doi.org/10.1371/journal.pone.0133998, e0133998.

Roy, R. R., Harkema, S. J., & Edgerton, V. R. (2012). Basic concepts of activity-based interventions for improved recovery of motor function after spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *93*(9), 1487–1497. https://doi.org/10.1016/j.apmr.2012.04.034.

Sayenko, D. G., Angeli, C., Harkema, S. J., Edgerton, V. R., & Gerasimenko, Y. P. (2014). Neuromodulation of evoked muscle potentials induced by epidural spinal-cord stimulation in paralyzed individuals. *Journal of Neurophysiology*, *111*(5), 1088–1099. https://doi.org/10.1152/jn.00489.2013.

Shah, P. K., Sureddi, S., Alam, M., Zhong, H., Roy, R. R., Edgerton, V. R., et al. (2016). Unique spatiotemporal neuromodulation of the lumbosacral circuitry shapes locomotor success after spinal cord injury. *Journal of Neurotrauma*, *33*(18), 1709–1723. https://doi.org/10.1089/neu.2015.4256.

Silva, N. A., Sousa, N., Reis, R. L., & Salgado, A. J. (2014). From basics to clinical: A comprehensive review on spinal cord injury. *Progress in Neurobiology*, *114*, 25–57. https://doi.org/10.1016/j.pneurobio.2013.11.002.

van den Brand, R., Heutschi, J., Barraud, Q., DiGiovanna, J., Bartholdi, K., Huerlimann, M., et al. (2012). Restoring voluntary control of locomotion after paralyzing spinal cord injury. *Science*, *336*(6085), 1182–1185. https://doi.org/10.1126/science.1217416.

Wagner, F. B., Mignardot, J. B., Le Goff-Mignardot, C. G., Demesmaeker, R., Komi, S., Capogrosso, M., et al. (2018). Targeted neurotechnology restores walking in humans with spinal cord injury. *Nature*, *563*(7729), 65–71. https://doi.org/10.1038/s41586-018-0649-2.

Wenger, N., Moraud, E. M., Gandar, J., Musienko, P., Capogrosso, M., Baud, L., et al. (2016). Spatiotemporal neuromodulation therapies engaging muscle synergies improve motor control after spinal cord injury. *Nature Medicine*, *22*(2), 138–145. https://doi.org/10.1038/nm.4025.

Widerström-Noga, E., Biering-Sørensen, F., Bryce, T., Cardenas, D. D., Finnerup, N. B., Jensen, M. P., et al. (2008). The international spinal cord injury pain basic data set. *Spinal Cord*, *46*(12), 818–823. https://doi.org/10.1038/sc.2008.64.

Chapter 20

Bowel dysfunction in spinal cord injury

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Abbreviations

AD	autonomic dysreflexia
BC	bowel care
CTT	colonic transit time
NBD	neurogenic bowel dysfunction
DRF	digital removal of feces
DRS	digital rectal stimulation
EAS	external anal sphincter
ENS	enteric nervous system
LMN	lower motor neuron
NB	neurogenic bowel
SARS	sacral anterior root stimulation
SC	spinal cord
SCI	spinal cord injury
UMN	upper motor neuron

Introduction

Spinal cord injury (SCI) results in loss of motor, sensory and autonomic functions, causing dysfunction of practically all body systems leading to long-term complications (Table 1). Neurogenic bowel (NB) is one of these main impairments after spinal cord injury. It occurs because of changes in innervation of the colon and rectum, as well as the loss of voluntary control of the anal sphincter, affecting colonic motility and defecation maneuvers. Between 80% and 97% of people with SCI suffer at least one NB-related symptom (Correa & Rotter, 2000; Ozisler, Koklu, Ozel, & Unsal-Delialioglu, 2015), mostly constipation and/or fecal incontinence, but also a prolonged and difficult defecation, sense of incomplete emptying, abdominal pain and distension, autonomic dysreflexia (AD), hemorrhoids, and rectal prolapse. Twenty-seven percent of the subjects considers that bowel dysfunction is a greater problem than bladder or sexual dysfunction, and 38% perceive it limits their quality of life (QoL) or social activities (Faaborg, Christensen, Finnerup, Laurberg, & Krogh, 2008).

The level of injury, severity, and presence or absence of sacral reflexes influences NB clinical manifestations and its management. Constipation and incontinence tend to become chronic and are stubborn toward currently available treatments, being a relevant source of complications. This, and the amount of time people with spinal injury spend on their bowel care, causes neurogenic bowel dysfunction (NBD) to have a very negative effect on QoL.

Characteristics of neurogenic bowel in spinal cord injury

Nervous control of the colon is done through the enteric, autonomic, and central nervous systems (Chung & Emmanuel, 2006; Lynch, Antony, Dobbs, & Frizelle, 2001). The enteric nervous system (ENS) is key for generating colonic propulsive activity. It functions independently, but is modulated by the spinal cord (SC) through the sympathetic fibers arising in the intermediolateral column of T5 to L3 and parasympathetic fibers that originate in segments S2 to S4. Sympathetic fibers inhibit colon motility, while parasympathetic fibers enable the contraction of the left colon, sigmoid, and rectum. The motor neurons in S2–S4 innervate the external anal sphincter (EAS), the puborectalis muscle, and the muscles of the pelvic floor;

Diagnosis and Treatment of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822498-4.00020-8

TABLE 1 Principal medical issues after spinal cord injury.

Respiratory complications[a] Atelectasis, pneumonia and respiratory failure
Cardiovascular complications[b] Orthostatic hypotension, autonomic dysreflexia, bradycardia
Neurogenic bladder
Neurogenic bowel
Sexual and fertility dysfunction
Spasticity[c]
Chronic pain Nociceptive pain Neuropathic pain: Above the level, at the level or below the level of injury
Secondary immunodeficiency[d] Increased susceptibility to infections
Osteoporosis Increased risk of low impact fractures
Neurogenic heterotopic ossification[e]
Pressure sores

[a]*Due to paralysis of the phrenic nerve, intercostal muscles and/or abdominal muscles leaving to reduced lung capacity and ineffective cough.*
[b]*Due to loss of supraspinal sympathetic control in patients with injury at T6 and above.*
[c]*Velocity-dependent increase in muscle tone with exaggerated deep tendon reflexes that results from injury to upper motor neurons.*
[d]*Systemic dysfunction of macrophages, T cells, B cells, and natural killer cells due to disruption of central nervous system input to immune organs.*
[e]*Ectopic bone formation in the connective tissue around joints.*

they receive voluntary control from motor neurons of the cerebral cortex and sensitive information from mechanoreceptors of the pelvic floor. SCI causes disturbances in autonomic and central innervation, and consequently loss of voluntary control of defecation, and changes in intestinal motility and sphincter tone. Various studies report a slowing of total and/or segmental colonic transit (Correa & Rotter, 2000; Vallès, Vidal, Clavé, & Mearin, 2006), increased colonic wall tone, changes in rectal compliance (Trivedi, Kumar, & Emmanuel, 2016) and in sphincter tone and sensitivity, as well as lack of relaxation of the anal sphincter in response to rectal distension (Lynch, Anthony, Dobbs, & Frizelle, 2000). Although the function of the ENS remains, it has been shown there is loss of neurons and decrease of nerve fiber density in the myenteric plexus (den Braber-Ymker, Lammens, van Putten, & Nagtegaal, 2017) after SCI. The inflammatory process and changes of extrinsic innervation may alter neuromuscular structures of the colon and contribute to decrease bowel function (White & Holmes, 2019). Not much research has been carried out on the changes of gut microbiota; however, it may well be a contributing factor and thus a target of study for the development of new treatments (Zhang et al., 2018).

Based on the level of SCI, two bowel dysfunction patterns may be distinguished. Lesions over the medullary cone cause upper motor neuron NB syndrome or *hyperreflexic bowel*, in which case there is loss of supraspinal control, but reflex coordination and stool propulsion are preserved. This syndrome is characterized by the increase in the tone of colonic and anal wall, the sphincter remains its tone or it becomes hypertonic, and spasticity of pelvic floor muscles may occur. It associates with constipation and fecal retention; incontinence due to overflow or reflex relaxation of the anal sphincter may also develop. Lesions in the medullary cone and cauda equina cause lower motor neuron NB syndrome or *areflexic bowel*, in which case there is loss of supraspinal control, reflex activity mediated by the spinal cord, and the sphincter is hypotonic. Colonic peristalsis occurs only because of the activity of the ENS, which results in an increase of colonic transit time (CTT). The areflexic bowel is associated to constipation, less difficulty during defecation, and high risk of incontinence due to EAS atony.

Clinical manifestations

Constipation, fecal incontinence, pain, and abdominal distension are the main symptoms of NB in people with SCI. *Constipation* is associated with slowing colonic transit, failure to increase intra-abdominal pressure during defecation, absence

of anal relaxation during the defecation, and increase of rectal and sigmoid compliance (Trivedi et al., 2016; Vallès & Mearin, 2009). Immobility and use of drugs such as opioids or anti-cholinergics, also favor constipation (Paily, Preziosi, Trivedi, & Emmanuel, 2019). Mean time for stool evacuation is longer, with 35% of SCI patients requiring more than an hour (Engkasan & Sudin, 2013; Inskip, Lucci, McGrath, Willms, & Claydon, 2018). *Fecal incontinence* is associated with the loss of voluntary control of the anal sphincter, atonic or hypotonic sphincter, low rectal compliance, low anal pressure at rest, and uninhibited rectal contractions (Lynch et al., 2001; Trivedi et al., 2016; Vallès & Mearin, 2009). It has been more frequently reported in subjects with lower motor neuron NB than in upper motor neuron NB (Inskip et al., 2018). Inadequate bowel management and use of laxatives also favor incontinence.

Abdominal pain is a frequent symptom, emerging later than neuropathic pain (in average 4.2 years after the injury) (Siddall, McClelland, Rutkowski, & Cousins, 2003). Its prevalence is over 30% in chronic SCIs (Nielsen, Faaborg, Christensen, Krogh, & Finnerup, 2017). It characterizes for being diffuse; some patients describe it as a prick, itch, warmth, or burning. It is closely associated with constipation, it worsens or improves with bowel movement.

Abdominal distension and flatulence are symptoms linked with constipation and fecal impaction. *Pathologies of the rectum and anus*, such as hemorrhoids, prolapse, anal fissures, rectal ulcers, and rectal bleeding, are favored by digital rectal stimulation (DRS), manual rectal evacuation (MRE), and the use of suppositories and enemas. Fecal impaction, anal fissures, and defecation routine per se are stimuli that trigger *autonomic dysreflexia* (Faaborg et al., 2014). Arterial hypertension may occur without accompanying symptoms that alert of AD (silent AD) (Kirshblum, House, & O'connor, 2002). The relevance of this lies on the fact that recurrent AD episodes associate with immunosuppression, involvement of cardiac mechanics, cerebrovascular changes, and cognitive impairment after SCI (Eldahan & Rabchevsky, 2018).

It is easy to understand that NBD due to its clinical manifestations and complications, negatively affect physical and psychological well-being, with a significant association between NBD severity and impact on QoL (Pires et al., 2018).

Diagnosis

The *medical history* is key to know the symptoms and their severity, patients' pathological background, and the medication being received. It must include the presence of sensation of defecation, diet, physical activity, frequency of bowel movements, stool consistency, and tested strategies for bowel management. The Bristol scale is a useful instrument to assess stool consistency in a fast and simple way (Lewis & Heaton, 1997). The time spent in bowel toileting is particularly relevant; reducing this time is one of the aims of treatment. Recording a diary of defecation by de patient will allow knowing the response to therapeutic measures. Uniformity in data collection is important when comparing results. The International SCI Bowel Function Basic Data Set (Krogh et al., 2017) gathers the basic data on bowel function following SCI that may be used in clinical practice.

Physical examination includes general, neurological, and abdominal inspection, as well as of the anorectal area. Other aspects to assess are the functional ability, balance in sitting position, and presence of spasticity. *Examination of the anorectal area* allows assessing the sensitivity, anal sphincter tone, and voluntary contraction. The presence of anal and bulbocavernosus sacral reflexes are indicative of anorectal reflex activity.

General *blood tests* are very useful to assess patients' general condition, detect warning signs, or endocrine and metabolic disorders that may contribute to bowel dysfunction.

Plain abdominal X-ray is useful to assess the amount and distribution of stools in the colon and detect megacolon, fecal impaction, and volvulus.

Colonoscopy has the same indication as for the general population, although it requires a more intensive gut preparation than in subjects who are neurologically intact (Song, Svircev, Teng, Dominitz, & Burns, 2018).

Other tests not used routinely are the *measurement of CTT* (total and segmental) and *anorectal manometry*, which may help identify the primary physiopathological mechanism of the symptoms.

Assessment scales

Multiple scales allow measuring the symptoms in bowel dysfunction, primarily constipation and incontinence, as well as the impact it has on QoL, although few have been validated for the SCI population. The Cleveland Clinic Constipation Scoring System (Agachan, Chen, Pfeifer, Reissman, & Wexner, 1996) and the Wexner Continence Grading Scale (Jorge & Wexner, 1993), are frequently used in studies with SCI patients. The 36-Item Short Form Survey (Ware & Sherbourne, 1992) and the Fecal Incontinence Quality of Life questionnaire (Rockwood et al., 2000) are widely used instruments in QoL studies.

The Neurogenic Bowel Dysfunction Score (Table 2) is a scale developed and validated specifically for adult SCI patients (Krogh, Christensen, Sabroe, & Laurberg, 2006). It allows scoring the clinical symptoms of colorectal and anal

TABLE 2 Neurogenic bowel dysfunction score.

Items	Points
(1) Frequency of defecation	
Daily (0) Two to six times every week (1) Less than once a week (6)	
(2) Time used for each defecation	
0–30 min (0) 31–60 min (3) More than 1 h (7)	
(3) Uneasiness, headache, or perspiration during defecation	
No (0) Yes (2)	
(4) Regular use of tablets against constipation	
No (0) Yes (2)	
(5) Regular use of drops against constipation	
No (0) Yes (2)	
(6) Digital stimulation or evacuation of the anorectum	
Less than once every week (0) Once or more every week (6)	
(7) Frequency of fecal incontinence	
Less than once every month (0) One to four times every month (6) One to six times every week (7) Daily (13)	
(8) Medication against fecal incontinence	
No (0) Yes (4)	
(9) Flatus incontinence	
No (0) Yes (2)	
(10) Perianal skin problems	
No (0) Yes (3)	
Total NBD score (range 0–47)	
NBD score	**Bowel dysfunction**
0–6	Very minor
7–9	Minor
10–13	Moderate
14 or more	Severe

10-Item score scale. A score of 0–47, the higher score indicates more severe bowel symptoms.
Modified from Krogh, K., Christensen, P., Sabroe, S., & Laurberg, S. (2006). Neurogenic bowel dysfunction score. *Spinal Cord, 44*(10), 625–631.

dysfunction; the importance of each item was established based on the strength of its association with self-perceived QoL. The greater the scoring, the greater the impact on QoL (Adriaansen, van Asbeck, van Kuppevelt, Snoek, & Post, 2015).

Conservative treatment of the neurogenic bowel

General recommendations

First, it is convenient to check the medications the patient is taking and make adjustments on those that might be contributing to the symptoms. Analgesics, anti-cholinergics, anti-depressants, and anti-psychotics, as well as iron supplements and aluminum compounds, which favor constipation. Excessive use of laxatives favors fecal incontinence, abdominal pain, and flatulence. Assessing the eating habits of the patient is also important.

Diet

Stool volume and consistency can be regulated through diet. Low *fluid* intake increases the probability of suffering constipation. On the other hand, high intake (>2 L/day), may be associated with prolonged bowel care (Engkasan & Sudin, 2013). Recommendation on fluid intake should be tailored and balanced with the type of bladder management.

Fiber helps increase fecal mass and its capacity to retain water. Consequently, colonic transit is accelerated and feces become softer. Although there are no accepted recommendations for SCI, an initial daily intake of 15 g of dietary fiber is suggested, monitoring the effect, and if necessary, increase the amount of fiber slowly and gradually, taking into account that high-fiber diets (30 g/day) may increase CTT in these patients (Cameron, Nyulasi, Collier, & Brown, 1996).

Physical exercise

Regular *physical exercise* may improve constipation symptoms, as it affects bowel motility, speeding up the colonic and gut transit time, and stimulates abdominal muscles helping move fecal matter toward the rectum (Gao et al., 2019). In people with SCI, standing seems to improve bowel function, although this has not been demonstrated in clinical trials (Kwok et al., 2015).

Abdominal massage

The mechanisms suggested to explain the effect of abdominal massage on the bowel are the increase of abdominal pressure and improvement of peristalsis. It may be performed during bowel routine to help pass stool. Fifteen minutes of *abdominal massage* following digital stimulation, decreases CTT, abdominal distension and fecal incontinence, and increases the frequency of defecation (Ayaş, Leblebici, Sözay, Bayramoğlu, & Niron, 2006). Similarly, *electrical stimulation of the abdominal muscles* during the bowel care program shortens the time until the feces come out and total time of bowel care (Korsten et al., 2004).

Mechanical techniques to ease bowel movements

Digital rectal stimulation (DRS) dilates the anal canal relaxing the puborectalis muscle, which reduces the resistance of stool to come out, triggers rectal contraction, and increases contractile activity of the descending and sigmoid colon (Korsten et al., 2007). ***Manual rectal evacuation*** (MRE) of feces is the most frequent form of bowel evacuation in some series (Coggrave, Norton, & Wilson-Barnett, 2009; Savic, Frankel, Jamous, Soni, & Charlifue, 2018). It is often the only effective way to empty the bowel in patients with areflexic bowel. In subjects with reflex function, MRE may be necessary to complete the emptying process (Coggrave et al., 2009) (Table 3).

Pharmacological treatment

Drugs that act on the colon are primarily used, aiming to increase its motility or change the texture of the stools (Table 4). Rectal administration of medication is used to ease defecation.

TABLE 3 Interventions for defecation.

Mechanical interventions			
Digital rectal stimulation			
Manual evacuation (digital removal of feces)			
Pharmacological interventions			
	Presentation	**Mechanism of action**	**Characteristics**
Glycerine	Suppositories, microenemas (5–10 mL)	Stimulant and osmotic laxative	Effective in 15–30 min Side effects: Irritation, stinging, anal itching
Bisacodyl (with a polyethylene glycol base or a hydrogenated vegetable oil base)	Suppositories	Stimulant laxative	Effective in 10–30 min Side effects: Abdominal pain and diarrhea
Docusate sodium or calcium	Microenemas (5–10 mL)	Stool softener	Effective in 2–15 min
Sodium citrate, sodium lauryl sulfoacetate, sorbitol	Microenemas (5–10 mL)	Osmotic laxative	Effective in 5–15 min Side effects: Abdominal pain and diarrhea
Sodium phosphate	Enemas (80, 140, 250 mL)	Saline laxative	Effective in 1–5 min Side effects: Abdominal bloating and pain, vomiting, renal impairment

Mechanical and pharmacological techniques to trigger defecation. Unpublished.

TABLE 4 Pharmacological treatment of neurogenic bowel.

	Mechanism of action	Active principle	Onset of action	Side effects
Oral laxatives				
Bulk-forming laxatives	Retain fluid in the stool increasing its weight and consistency, stimulate peristalsis and soften fecal matter	Psyllium Methylcellulose	24–72 h	Abdominal bloating, and flatulence
Stool softeners laxatives	Tensioactive agents which soften and lubricate fecal matter	Docusate sodium	24–72 h	Inhibition of gallbladder secretion, gastric mucosal lesions, anorexia, nausea and vomiting
		Liquid paraffin	6–8 h	Irritation of rectal mucosa, aspiration pneumonitis
Osmotic laxatives	Create an osmotic gradient drawing fluid into the intestinal lumen and promoting peristalsis and stool propulsion	Lactitol Lactulose	1–3 days	Cramping, abdominal bloating, and flatulence
		Polyethylene glycol (macrogol)	1–4 days	Diarrhea, nausea, abdominal bloating and pain, flatulence
		Magnesium and sodium salts	0.5–3 h	Electrolyte imbalance
Stimulant laxatives	Stimulate intestinal mucosal, decrease fluid and electrolyte absorption	Bisacodyl	6–12 h	Cramping, electrolyte imbalance with chronic use
		Sodium picosulfate	6–9 h	
		Sennosides A and B	8–12 h	Cramping, nausea, abdominal bloating and pain

TABLE 4 Pharmacological treatment of neurogenic bowel—cont'd

	Mechanism of action	Active principle	Onset of action	Side effects
Prokinetic agents				
	Highly-selective serotonin 5-HT4 receptor agonist	Prucalopride		Peak plasma concentration achieved in 2–3 h Requires dose adjustment in renal failure Side effects: headache, nausea, diarrhea, abdominal pain
	Inhibits the hydrolysis of acetylcholine by competing with acetylcholine for attaching to acetylcholinesterase	Neostigmine		Bradycardia, bronchoconstriction

Main oral laxative and prokinetic drugs for the treatment of constipation, including its active principle, mechanism and starting action, and the most frequent side effects. Unpublished.

Rectal laxatives

Suppositories or micro-enemas, alone or in combination with DRS and MRE, are used to trigger defecation. Patients whose rectal-anal reflexes are preserved respond to pharmacological stimulation, although the effectiveness and response time may vary greatly. The most commonly used chemical stimulants are *bisacodyl* and *glycerin*. Large-volume *phosphate enemas* are not routinely used for the chronic management of constipation in SCI patients, although they may be useful in cases of fecal impaction (Table 3).

Oral laxatives

Although they have been used for a long time, there is limited available evidence on their effectiveness and safety (Coggrave, Norton, & Cody, 2014). Bulk-forming and non-saline osmotic are the most commonly used oral laxatives. The choice depends on several factors such as its mechanism of action, speed of onset and duration of effect.

Prokinetics

Prokinetics promote bowel transit by reducing the passage time of stools through the bowel. *Metoclopramide* and *erythromycin* have no effect on colonic motility. They are frequently used for treating gastric dilatation and paralytic ileus, characteristic of the spinal shock phase.

Reduction in CTT has been shown with *prucalopride*, as well as improvement in the frequency of bowel evacuations in SCI patients. No significant improvement was shown for the duration of bowel care, episodes of fecal incontinence, or need for digital evacuation (Krogh et al., 2002).

In people with SCI, *neostigmine* given with glycopyrrolate improves the evacuation and reduces the time of bowel care (Korsten et al., 2005; Rosman et al., 2008). Their cardiovascular and pulmonary adverse effects and parenteral administration limit a chronic use of these types of medication. Recently, good results were reported with transdermal delivery by iontophoresis (Korsten et al., 2018).

Other drugs

Fampridine increases the days of bowel movements in patients with incomplete SCI (Cardenas et al., 2007). *Oxymetazoline* topical gel may help treating fecal incontinence (Barak, Gecse, & Takács, 2019). Other drugs such as *botulinum toxin, colchicine, lubiprostone, and linaclotide* have shown to be effective in chronic constipation and NB of different etiology, although it has not been studied in SCI patients.

Bowel program

The establishment of an early routine bowel program is considered the best practice for SCI patients (Qi, Middleton, & Malcolm, 2018; Stoffel, Van der Aa, Wittmann, Yande, & Elliott, 2018). The aim is to achieve regular, predictable, effective evacuation, as well as to eliminate or minimize incontinence episodes and other secondary complications of NB. Between 56% and 84.8% of the patients will achieve a satisfactory bowel management with the program (Adriaansen et al., 2015; Correa & Rotter, 2000; Engkasan & Sudin, 2013).

The bowel program is the establishment of an evacuation routine following a scheme that sets the moment during the day and frequency at which the routine is going to be carried out. Furthermore, it includes dietary recommendations, oral laxatives, and use of rectal stimulation and/or manual bowel evacuation. The program is different for each patient based on the main symptom, the characteristics of the SCI and presence or absence of sacral reflexes. Most patients will require more than one intervention to reach an effective bowel management. The key for a successful program lies largely on education and training.

The first recommendation is to schedule a regular *frequency and time*. In general, it is advisable to empty the bowel every 48 h to achieve a minimum of three bowel movement every week (Coggrave, Burrows, & Durand, 2006; Correa & Rotter, 2000). A lower frequency or irregular care contributes to constipation and impaction episodes. Patients with areflexic NB, with high risk of incontinence, may need to empty their bowel on a daily basis or even twice a day.

The patient has to establish the time based on his/her needs. Routine is a key element in the program and must be repeated at the same time. It is recommended to perform it 20–30 min after the main meal to take advantage of bowel's increased physiological motility after a meal (gastrocolic reflex) (Suttor et al., 2009).

The patient should preferably be in a sitting position in the toilet and an adapted environment is essential. The need of technical aids will be assessed, i.e., a bathtub stool, side handles, and a toilet seat riser. When the patient has a fragile equilibrium, the program will be carried out in the bed, preferably in the left lateral decubitus position (Ozisler et al., 2015).

For optimum stool consistency and to promote colonic transit, dietary adjustments or an oral laxative may be necessary.

For the act of defecation, a triggering stimulus is usually needed (DRS, suppositories, or micro-enema) (Table 3). MRE may also be necessary as the only emptying method, before the administration of a suppository or DRS, or subsequently, to complete the emptying. Some physical activity can be recommended before the programmed bowel movement, as well as abdominal massage during the process.

There are some differences in the program between reflex and areflexic NB patients (Table 5). Thus, in subjects with reflex NB bowel movement may be achieved with chemical rectal stimulants, DRS, or a combination of both. In some cases, taking a stimulant laxative before the program may be of help, although it is not advisable to do this as a routine. In patients in which sacral reflexes are not preserved, digital rectal and pharmacological stimulation are ineffective and MRE should be used. Stools should be firm in these patients to facilitate manual evacuation and decrease the risk of incontinence in cases of sphincter hypotony or atony. Anal plugs may be effective when there is fluid or gas loss in small volumes.

A well-established program must achieve the shortest possible time spend in bowel care. If it takes more than an hour, it must be assessed to identify which elements need to be corrected. Patients must know how SCI affects the function of their bowel. NBD must be part of the regular follow-up during SCI chronic phase.

TABLE 5 Bowel care in neurogenic bowel.

	Hyperreflexic neurogenic bowel	Areflexic neurogenic bowel
	Presence of sacral reflexes Injury above the medullary cone	Absence of sacral reflexes Injury in medullary cone and cauda equina
Frequency	Daily or alternate days	Daily or twice a day
Consistency of feces	Soft, Bristol 4	Hard, Bristol 3
Defecation	DRS, suppository, microenema	Manual rectal evacuation
Supporting measures	After meals, exercise, abdominal massage	After meals, exercise, abdominal massage

Outline bowel care program according to hyperreflexic vs areflexic neurogenic bowel. *DRS,* digital rectal stimulation. Unpublished.

Anorectal biofeedback

Biofeedback is a reeducation technique through feedback of bowel movement and continence. This treatment modality is scarcely use in NBD, but may be beneficial in people with incomplete motor SCI (Mazor, Jones, Andrews, Kellow, & Malcolm, 2016).

Transanal irrigation

Transanal irrigation (TAI) allows performing a programmed defecation and is a technique for treating bowel dysfunction in SCI patients. Some studies show that it improves constipation, incontinence, shortens the time spent in bowel care, reduces the intake of medications, and improves QoL (Christensen et al., 2006; Faaborg et al., 2009). Good results have been reported in 68% and 63% of patients with incontinence and constipation, respectively (Del Popolo et al., 2008).

The most used systems are cones or rectal balloon catheters, a recipient for water and an infusion set-up. The *infusion* may be carried out through manual pumping (Fig. 1A) or using an electronic control unit (Fig. 1B) in which the volume of water to be infused, the speed of the infusion, and the size of the balloon are programed.

The *irrigation fluid* is usually warm tap water (36–38°C). The instilled volume may vary, generally starting with 500 mL and increased up to 1000 mL.

As with the classical bowel care program, stool consistency should be optimized if necessary. The recommendations to establish a routine at a specific time of the day and perform the irrigation 20–20 min after the meal are maintained. Initially, it is advisable to carry out this on a daily basis and reduce the frequency considering the preferences and needs of the patient.

Absolute *contraindications* for TAI include anal or rectal stenosis, colorectal cancer, inflammatory bowel disease, and recent colonic surgery (Emmanuel et al., 2013). Up to 48% of subjects my suffer *adverse effects* such as abdominal pain or discomfort, rectal bleeding, fatigue, general malaise, sweating, perianal discomfort, nauseas, tremors, headache, and facial redness (Faaborg et al., 2009). Rectum perforation is rare, although it is a potential risk (Christensen et al., 2016; Faaborg et al., 2009). TAI is also a trigger of AD.

Surgical treatment of the neurogenic bowel

Electrical stimulation

Both, neurostimulation and neuromodulation, have been investigated for the treatment of NBD. The goal of ***sacral neuromodulation*** is to adjust and reestablish the balance between the inhibitory and facilitatory reflexes that control the functional activity of the pelvic floor. Some studies suggest this therapy improves bowel function in patients with incomplete SCI (Chen & Liao, 2015; Lombardi, Del Popolo, Cecconi, Surrenti, & Macchiarella, 2010). To date, a widespread use cannot be recommended. The effect on bowel function of ***stimulating the pudendal nerve*** has also been assessed in patients with complete cauda equina lesions (George et al., 2014). Short-term results seem encouraging, showing improvement of constipation and incontinence. ***Sacral anterior root stimulation*** requires a sacral dorsal root rhizotomy with subsequent implantation of a stimulator in the anterior sacral roots S2–S4. Although this system was designed for treating neurogenic bladder in SCI, some patients use it as a method for bowel emptying with reported good results (Rasmussen et al., 2015; Vallès, Rodríguez, Borau, & Mearin, 2009).

Antegrade continence enema

A continence tube is created, generally an appendicostomy, which allows intermittent catheterization for colonic irrigation. This procedure has been used in SCI patients, showing improvement of QoL associated to fecal incontinence (Smith & Decter, 2015).

Colostomy and ileostomy

An invasive procedure, not exempt from complications, which should be indicated to selected patients when other more conservative treatment methods fail.

The most common indications are constipation and unmanageable fecal incontinence, extended bowel care time, AD or pain during defecation; it is also performed to facilitate the healing of pressure sores or infections in the perineum or abdomen. Left-side colostomies maintain better the colonic surface and prevent excessive loss of water, facilitate stoma care, and there is much lower risk of leakage (Safadi, Rosito, Nino-Murcia, Wolfe, & Perkash, 2003). With right-side

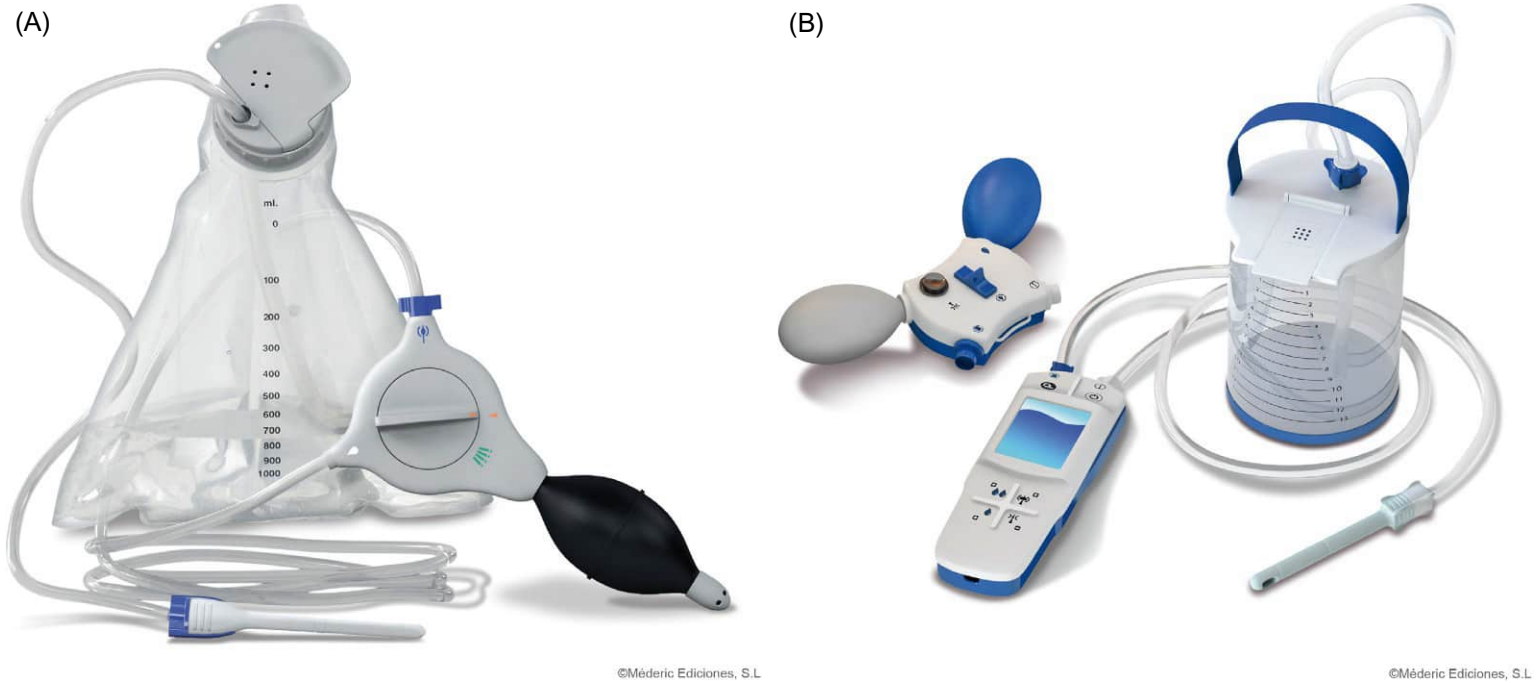

FIG. 1 Transanal irrigation devices. (A) Transanal irrigation device with manual pumping; (B) transanal irrigation device using an electronic control unit. *(With permission of Mederic Ediciones S. L.)*

ileostomies or colostomies, there is less emptying problems. Results from different studies report that they simplify and reduce bowel care time, decrease the number of bowel dysfunction-related hospitalizations, and provide equal or better QoL (Rosito, Nino-Murcia, Wolfe, Kiratli, & Perkash, 2002). Patients are usually satisfied with the surgery and a high percentage communicates that he/she would have undergone surgery earlier (Safadi et al., 2003). Despite the good results, this method is scarcely used; between 2.4% and 8% have undergone a colostomy aimed at bowel care (Adriaansen et al., 2015; Coggrave et al., 2009; Pardee, Bricker, Rundquist, MacRae, & Tebben, 2012).

Conclusions

With the current knowledge on NBD, its therapeutic management remains empirical, based on a step-up approach going from conservative to more invasive options (Fig. 2). It can be predicted that advances in pharmacological research and control of nervous system function through electrical stimulation will provide in-between treatment options.

Applications to other areas of neuroscience

Bowel disturbance is one of the sequelae of spinal cord injury that most affects the life of these patients; however, it is possibly the less studied condition. Advancement in developing successful treatments for neurogenic bowel dysfunction has been slow in part due to the absence of reliable and validated tools to assess neurogenic bowel dysfunction-related symptoms and complications, both from the perspective of the patient and the physician. Therefore, the standardization of validated scales aimed at this group of patients and the further development of quality of life measurement tools specifically associated with intestinal dysfunction will help advance the evaluation, research and better management of neurogenic bowel dysfunction.

On the other hand, it is necessary to develop and improve tools such as colonic transit time, manometry and others, that provide more objective assessment, needed in therapeutic decision-making and in research studies on new treatment approaches.

Although spinal cord injury is the condition most frequently associated with neurogenic bowel dysfunction, any patient suffering from central nervous system disease may experience symptoms of intestinal dysfunction. Neurological conditions such as multiple sclerosis, cerebral palsy, stroke, or Parkinson's disease, placing the individual at risk for constipation and incontinence. Although the presentation of intestinal dysfunction in these conditions can vary, the underlying cause is also the damage to the nervous control of the bowel. Advances in the knowledge of physiopathology and management of bowel dysfunction in SCI may help improve bowel care in other neurological pathologies causing neurogenic bowel dysfunction.

Finally, accurate spinal cord injury bowel dysfunction understanding, and improvement of diagnostic methods may contribute, without doubt, to the assessment of new therapeutic approaches for the treatment of spinal cord injury currently being developed, such as cell therapies or medullary stimulation.

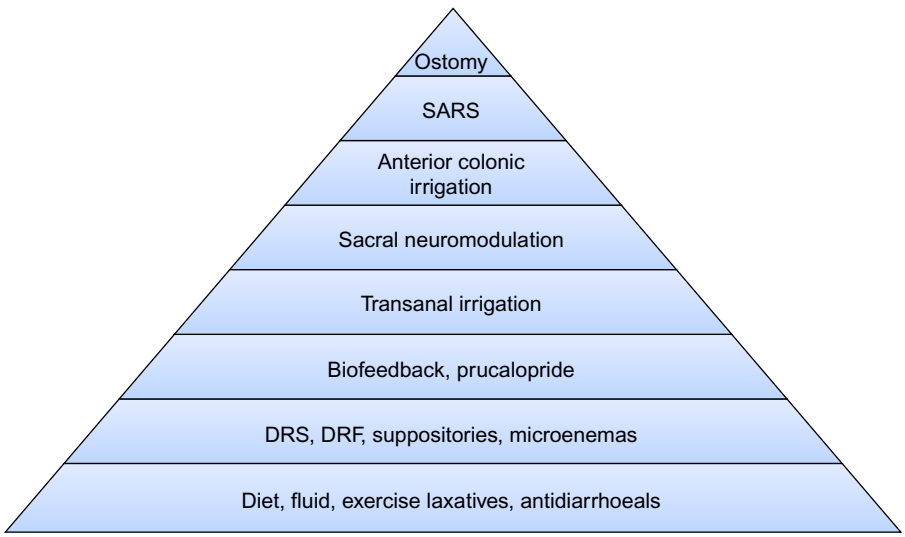

FIG. 2 Treatment options in neurogenic bowel dysfunction management. The pyramid represents a stepwise treatment from conservative measures to more invasive measures. *SARS*, sacral anterior root stimulation; *DRS*, digital rectal stimulation; *DRF*, digital removal of feces. Unpublished.

Dictionary of terms

Abdominal massage: Massage applied to the abdomen in a clockwise direction using the hand.
Anal reflex: Visible contraction of anus in response to pinprick of surrounding skin.
Autonomic dysreflexia: Abnormal sympathetic nervous system response to a noxious stimulus below the level of injury in individuals with spinal cord injury above the seven thoracic levels. The guiding symptom is arterial hypertension.
Bowel care: Number of different interventions combined in a bowel routine to promote effective and timely fecal evacuation.
Bulbocavernosus reflex: Contraction of anus in response to pressure on glans penis or clitoris.
Colonic transit time: Time it takes for stool to pass through the colon.
Dietary fiber: Carbohydrate polymers with 10 or more monomeric units, which are not hydrolyzed by the endogenous enzymes in the small intestine of humans.
Digital rectal stimulation: Technique performed by inserting lubricated finger through the anal canal into the rectum and slowly rotating the finger in a circular movement maintaining contact with rectal mucosa.
Digital removal of feces: Technique performed by insertion of a single gloved, lubricated finger into the rectum to break up or remove stool.
Neurogenic bowel or neurogenic bowel dysfunction: Colonic dysfunction as result of central neurological disease or damage.
Transanal irrigation: Procedure that involves introducing water into de colon through the anus to evacuate the distal colon and rectum.

Key facts of neurogenic bowel dysfunction

- Neurogenic bowel affects to a greater or lower degree most spinal cord injured patients; around 50% perceive restrictions in their quality of live or social activities.
- Spinal cord injury causes colon and rectum innervation changes that lead to loss of voluntary control of defecation, bowel motility impairments, and changes in sphincter tone.
- Fecal incontinence, constipation, and a combination of both are the primary manifestations.
- Based on the level of spinal cord injury, two neurogenic bowel dysfunction patterns are distinguished: hyperreflexic and areflexic.
- The diagnostic assessment is mainly clinical. Assessment scales allow estimating the seriousness of the symptoms and response to treatment.
- Neurogenic bowel dysfunction treatment is largely empirical.

Summary points

- Slower colonic transit, increased colonic tone, changes in rectal compliance, of the tone and sensitivity of the sphincter, and lack of relaxation of the sphincter, are the mechanisms responsible of neurogenic bowel symptoms in spinal cord injury.
- Secondary disturbances in enteric nervous system, colonic neuromuscular structures, and bowel microbiota may be contributing factors.
- Establishing a bowel emptying routine together with a technique that triggers defecation, remains the treatment of choice.
- Optimizing stool consistency through diet and/or a bulk-forming or osmotic laxative may be necessary.
- Transanal irrigation is a treatment modality for effective bowel emptying in cases in which control is not achieved with the bowel program.
- Invasive treatments are an option in selected cases. Colostomy may improve the quality of life in these patients.

References

Adriaansen, J. J., van Asbeck, F. W., van Kuppevelt, D., Snoek, G. J., & Post, M. W. (2015). Outcomes of neurogenic bowel management in individuals living with a spinal cord injury for at least 10 years. *Archives of Physical Medicine and Rehabilitation*, *96*(5), 905–912.

Agachan, F., Chen, T., Pfeifer, J., Reissman, P., & Wexner, S. D. (1996). A constipation scoring system to simplify evaluation and management of constipated patients. *Diseases of the Colon and Rectum*, *39*(6), 681–685.

Ayaş, S., Leblebici, B., Sözay, S., Bayramoğlu, M., & Niron, E. A. (2006). The effect of abdominal massage on bowel function in patients with spinal cord injury. *American Journal of Physical Medicine & Rehabilitation*, *85*(12), 951–955.

Barak, N., Gecse, K. B., & Takács, I. (2019). Topical oxymetazoline for fecal incontinence in patients with spinal cord injury: A double-blind randomized controlled crossover study. *Diseases of the Colon and Rectum*, *62*(2), 234–240.

Cameron, K. J., Nyulasi, I. B., Collier, G. R., & Brown, D. J. (1996). Assessment of the effect of increased dietary fibre intake on bowel function in patients with spinal cord injury. *Spinal Cord*, *34*(5), 277–283.

Cardenas, D. D., Ditunno, J., Graziani, V., Jackson, A. B., Lammertse, D., Potter, P., et al. (2007). Phase 2 trial of sustained-release fampridine in chronic spinal cord injury. *Spinal Cord*, *45*(2), 158–168.

Chen, G., & Liao, L. (2015). Sacral neuromodulation for neurogenic bladder and bowel dysfunction with multiple symptoms secondary to spinal cord disease. *Spinal Cord*, *53*(3), 204–208.

Christensen, P., Bazzocchi, G., Coggrave, M., Abel, R., Hultling, C., Krogh, K., et al. (2006). A randomized, controlled trial of transanal irrigation versus conservative bowel management in spinal cord-injured patients. *Gastroenterology*, *131*(3), 738–747.

Christensen, P., Krogh, K., Perrouin-Verbe, B., Leder, D., Bazzocchi, G., Petersen Jakobsen, B., et al. (2016). Global audit on bowel perforations related to transanal irrigation. *Techniques in Coloproctology*, *20*(2), 109–115.

Chung, E. A., & Emmanuel, A. V. (2006). Gastrointestinal symptoms related to autonomic dysfunction following spinal cord injury. *Progress in Brain Research*, *152*, 317–333.

Coggrave, M., Burrows, D., & Durand, M. A. (2006). Progressive protocol in the bowel management of spinal cord injuries. *British Journal of Nursing*, *15* (20), 1108–1113.

Coggrave, M., Norton, C., & Cody, J. D. (2014). Management of faecal incontinence and constipation in adults with central neurological diseases. *Cochrane Database of Systematic Reviews*, (1), CD002115.

Coggrave, M., Norton, C., & Wilson-Barnett, J. (2009). Management of neurogenic bowel dysfunction in the community after spinal cord injury: A postal survey in the United Kingdom. *Spinal Cord*, *47*(4), 323–330. quiz 331–323.

Correa, G. I., & Rotter, K. P. (2000). Clinical evaluation and management of neurogenic bowel after spinal cord injury. *Spinal Cord*, *38*(5), 301–308.

Del Popolo, G., Mosiello, G., Pilati, C., Lamartina, M., Battaglino, F., Buffa, P., et al. (2008). Treatment of neurogenic bowel dysfunction using transanal irrigation: A multicenter Italian study. *Spinal Cord*, *46*(7), 517–522.

den Braber-Ymker, M., Lammens, M., van Putten, M. J., & Nagtegaal, I. D. (2017). The enteric nervous system and the musculature of the colon are altered in patients with spina bifida and spinal cord injury. *Virchows Archiv*, *470*(2), 175–184.

Eldahan, K. C., & Rabchevsky, A. G. (2018). Autonomic dysreflexia after spinal cord injury: Systemic pathophysiology and methods of management. *Autonomic Neuroscience*, *209*, 59–70.

Emmanuel, A. V., Krogh, K., Bazzocchi, G., Leroi, A. M., Bremers, A., Leder, D., et al. (2013). Consensus review of best practice of transanal irrigation in adults. *Spinal Cord*, *51*(10), 732–738.

Engkasan, J. P., & Sudin, S. S. (2013). Neurogenic bowel management after spinal cord injury: Malaysian experience. *Journal of Rehabilitation Medicine*, *45*(2), 141–144.

Faaborg, P. M., Christensen, P., Finnerup, N., Laurberg, S., & Krogh, K. (2008). The pattern of colorectal dysfunction changes with time since spinal cord injury. *Spinal Cord*, *46*(3), 234–238.

Faaborg, P. M., Christensen, P., Krassioukov, A., Laurberg, S., Frandsen, E., & Krogh, K. (2014). Autonomic dysreflexia during bowel evacuation procedures and bladder filling in subjects with spinal cord injury. *Spinal Cord*, *52*(6), 494–498.

Faaborg, P. M., Christensen, P., Kvitsau, B., Buntzen, S., Laurberg, S., & Krogh, K. (2009). Long-term outcome and safety of transanal colonic irrigation for neurogenic bowel dysfunction. *Spinal Cord*, *47*(7), 545–549.

Gao, R., Tao, Y., Zhou, C., Li, J., Wang, X., Chen, L., et al. (2019). Exercise therapy in patients with constipation: A systematic review and meta-analysis of randomized controlled trials. *Scandinavian Journal of Gastroenterology*, *54*(2), 169–177.

George, A. T., Dudding, T. C., Gurmany, S., Kamm, M. A., Nicholls, R. J., & Vaizey, C. J. (2014). Pudendal nerve stimulation for bowel dysfunction in complete cauda equina syndrome. *Annals of Surgery*, *259*(3), 502–507.

Inskip, J. A., Lucci, V. M., McGrath, M. S., Willms, R., & Claydon, V. E. (2018). A community perspective on bowel management and quality of life after spinal cord injury: The influence of autonomic dysreflexia. *Journal of Neurotrauma*, *35*(9), 1091–1105.

Jorge, J. M., & Wexner, S. D. (1993). Etiology and management of fecal incontinence. *Diseases of the Colon and Rectum*, *36*(1), 77–97.

Kirshblum, S. C., House, J. G., & O'connor, K. C. (2002). Silent autonomic dysreflexia during a routine bowel program in persons with traumatic spinal cord injury: A preliminary study. *Archives of Physical Medicine and Rehabilitation*, *83*(12), 1774–1776.

Korsten, M. A., Fajardo, N. R., Rosman, A. S., Creasey, G. H., Spungen, A. M., & Bauman, W. A. (2004). Difficulty with evacuation after spinal cord injury: Colonic motility during sleep and effects of abdominal wall stimulation. *Journal of Rehabilitation Research and Development*, *41*(1), 95–100.

Korsten, M. A., Lyons, B. L., Radulovic, M., Cummings, T. M., Sikka, G., Singh, K., et al. (2018). Delivery of neostigmine and glycopyrrolate by iontophoresis: A nonrandomized study in individuals with spinal cord injury. *Spinal Cord*, *56*(3), 212–217.

Korsten, M. A., Rosman, A. S., Ng, A., Cavusoglu, E., Spungen, A. M., Radulovic, M., et al. (2005). Infusion of neostigmine-glycopyrrolate for bowel evacuation in persons with spinal cord injury. *American Journal of Gastroenterology*, *100*(7), 1560–1565.

Korsten, M. A., Singal, A. K., Monga, A., Chaparala, G., Khan, A. M., Palmon, R., et al. (2007). Anorectal stimulation causes increased colonic motor activity in subjects with spinal cord injury. *Journal of Spinal Cord Medicine*, *30*(1), 31–35.

Krogh, K., Christensen, P., Sabroe, S., & Laurberg, S. (2006). Neurogenic bowel dysfunction score. *Spinal Cord*, *44*(10), 625–631.

Krogh, K., Emmanuel, A., Perrouin-Verbe, B., Korsten, M. A., Mulcahey, M. J., & Biering-Sørensen, F. (2017). International spinal cord injury bowel function basic data set (version 2.0). *Spinal Cord*, *55*(7), 692–698.

Krogh, K., Jensen, M. B., Gandrup, P., Laurberg, S., Nilsson, J., Kerstens, R., et al. (2002). Efficacy and tolerability of prucalopride in patients with constipation due to spinal cord injury. *Scandinavian Journal of Gastroenterology*, *37*(4), 431–436.

Kwok, S., Harvey, L., Glinsky, J., Bowden, J. L., Coggrave, M., & Tussler, D. (2015). Does regular standing improve bowel function in people with spinal cord injury? A randomised crossover trial. *Spinal Cord*, *53*(1), 36–41.

Lewis, S. J., & Heaton, K. W. (1997). Stool form scale as a useful guide to intestinal transit time. *Scandinavian Journal of Gastroenterology*, *32*(9), 920–924.

Lombardi, G., Del Popolo, G., Cecconi, F., Surrenti, E., & Macchiarella, A. (2010). Clinical outcome of sacral neuromodulation in incomplete spinal cord-injured patients suffering from neurogenic bowel dysfunctions. *Spinal Cord*, *48*(2), 154–159.

Lynch, A. C., Anthony, A., Dobbs, B. R., & Frizelle, F. A. (2000). Anorectal physiology following spinal cord injury. *Spinal Cord*, *38*(10), 573–580.

Lynch, A. C., Antony, A., Dobbs, B. R., & Frizelle, F. A. (2001). Bowel dysfunction following spinal cord injury. *Spinal Cord*, *39*(4), 193–203.

Mazor, Y., Jones, M., Andrews, A., Kellow, J. E., & Malcolm, A. (2016). Anorectal biofeedback for neurogenic bowel dysfunction in incomplete spinal cord injury. *Spinal Cord*, *54*(12), 1132–1138.

Nielsen, S. D., Faaborg, P. M., Christensen, P., Krogh, K., & Finnerup, N. B. (2017). Chronic abdominal pain in long-term spinal cord injury: A follow-up study. *Spinal Cord*, *55*(3), 290–293.

Ozisler, Z., Koklu, K., Ozel, S., & Unsal-Delialioglu, S. (2015). Outcomes of bowel program in spinal cord injury patients with neurogenic bowel dysfunction. *Neural Regeneration Research*, *10*(7), 1153–1158.

Paily, A., Preziosi, G., Trivedi, P., & Emmanuel, A. (2019). Anti-muscarinic drugs increase rectal compliance and exacerbate constipation in chronic spinal cord injury: Anti-muscarinic drug effect on neurogenic bowel. *Spinal Cord*, *57*, 662–668.

Pardee, C., Bricker, D., Rundquist, J., MacRae, C., & Tebben, C. (2012). Characteristics of neurogenic bowel in spinal cord injury and perceived quality of life. *Rehabilitation Nursing*, *37*(3), 128–135.

Pires, J. M., Ferreira, A. M., Rocha, F., Andrade, L. G., Campos, I., Margalho, P., et al. (2018). Assessment of neurogenic bowel dysfunction impact after spinal cord injury using the International Classification of Functioning, Disability and Health. *European Journal of Physical and Rehabilitation Medicine*, *54*(6), 873–879.

Qi, Z., Middleton, J. W., & Malcolm, A. (2018). Bowel dysfunction in spinal cord injury. *Current Gastroenterology Reports*, *20*(10), 47.

Rasmussen, M. M., Kutzenberger, J., Krogh, K., Zepke, F., Bodin, C., Domurath, B., et al. (2015). Sacral anterior root stimulation improves bowel function in subjects with spinal cord injury. *Spinal Cord*, *53*(4), 297–301.

Rockwood, T. H., Church, J. M., Fleshman, J. W., Kane, R. L., Mavrantonis, C., Thorson, A. G., et al. (2000). Fecal Incontinence Quality of Life Scale: Quality of life instrument for patients with fecal incontinence. *Diseases of the Colon and Rectum*, *43*(1), 9–16. discussion 16–17.

Rosito, O., Nino-Murcia, M., Wolfe, V. A., Kiratli, B. J., & Perkash, I. (2002). The effects of colostomy on the quality of life in patients with spinal cord injury: A retrospective analysis. *Journal of Spinal Cord Medicine*, *25*(3), 174–183.

Rosman, A. S., Chaparala, G., Monga, A., Spungen, A. M., Bauman, W. A., & Korsten, M. A. (2008). Intramuscular neostigmine and glycopyrrolate safely accelerated bowel evacuation in patients with spinal cord injury and defecatory disorders. *Digestive Diseases and Sciences*, *53*(10), 2710–2713.

Safadi, B. Y., Rosito, O., Nino-Murcia, M., Wolfe, V. A., & Perkash, I. (2003). Which stoma works better for colonic dysmotility in the spinal cord injured patient? *American Journal of Surgery*, *186*(5), 437–442.

Savic, G., Frankel, H. L., Jamous, M. A., Soni, B. M., & Charlifue, S. (2018). Long-term bladder and bowel management after spinal cord injury: A 20-year longitudinal study. *Spinal Cord*, *56*(6), 575–581.

Siddall, P. J., McClelland, J. M., Rutkowski, S. B., & Cousins, M. J. (2003). A longitudinal study of the prevalence and characteristics of pain in the first 5 years following spinal cord injury. *Pain*, *103*(3), 249–257.

Smith, P. H., & Decter, R. M. (2015). Antegrade continence enema procedure: Impact on quality of life in patients with spinal cord injury. *Spinal Cord*, *53*(3), 213–215.

Song, S. H., Svircev, J. N., Teng, B. J., Dominitz, J. A., & Burns, S. P. (2018). A safe and effective multi-day colonoscopy bowel preparation for individuals with spinal cord injuries. *Journal of Spinal Cord Medicine*, *41*(2), 149–156.

Stoffel, J. T., Van der Aa, F., Wittmann, D., Yande, S., & Elliott, S. (2018). Neurogenic bowel management for the adult spinal cord injury patient. *World Journal of Urology*, *36*(10), 1587–1592.

Suttor, V. P., Ng, C., Rutkowski, S., Hansen, R. D., Kellow, J. E., & Malcolm, A. (2009). Colorectal responses to distension and feeding in patients with spinal cord injury. *American Journal of Physiology. Gastrointestinal and Liver Physiology*, *296*(6), G1344–G1349.

Trivedi, P. M., Kumar, L., & Emmanuel, A. V. (2016). Altered colorectal compliance and anorectal physiology in upper and lower motor neurone spinal injury may explain bowel symptom pattern. *American Journal of Gastroenterology*, *111*(4), 552–560.

Vallès, M., & Mearin, F. (2009). Pathophysiology of bowel dysfunction in patients with motor incomplete spinal cord injury: Comparison with patients with motor complete spinal cord injury. *Diseases of the Colon and Rectum*, *52*(9), 1589–1597.

Vallès, M., Rodríguez, A., Borau, A., & Mearin, F. (2009). Effect of sacral anterior root stimulator on bowel dysfunction in patients with spinal cord injury. *Diseases of the Colon and Rectum*, *52*(5), 986–992.

Vallès, M., Vidal, J., Clavé, P., & Mearin, F. (2006). Bowel dysfunction in patients with motor complete spinal cord injury: Clinical, neurological, and pathophysiological associations. *American Journal of Gastroenterology*, *101*(10), 2290–2299.

Ware, J. E., & Sherbourne, C. D. (1992). The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Medical Care*, *30*(6), 473–483.

White, A. R., & Holmes, G. M. (2019). Investigating neurogenic bowel in experimental spinal cord injury: Where to begin? *Neural Regeneration Research*, *14*(2), 222–226.

Zhang, C., Zhang, W., Zhang, J., Jing, Y., Yang, M., Du, L., et al. (2018). Gut microbiota dysbiosis in male patients with chronic traumatic complete spinal cord injury. *Journal of Translational Medicine*, *16*(1), 353.

Chapter 21

Management of neurogenic lower urinary tract dysfunction due to spinal cord injury

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Abbreviations

AC	augmentation cystoplasty
AD	autonomic dysreflexia
AUS	artificial urinary sphincter
BNR	bladder neck reconstruction
BNS	bladder neck sling
BOO	bladder outlet obstruction
BoNT-A	type A botulinum toxin
CIC	clean intermittent catheterization
DO	detrusor overactivity
DSD	detrusor sphincter dyssynergia
DU	detrusor underactivity
FVC	frequency volume chart
HCC	hydrophilic-coated catheter
LUT	lower urinary tract
NLUTD	neurogenic lower urinary tract dysfunction
PAG	periaqueductal gray
PMC	pontine micturition center
PVR	postvoid residual
QOL	quality of life
PVC	polyvinyl catheter
SARS	sacral anterior root stimulation
SCI	spinal cord injury
SNM	sacral neuromodulation
UI	urinary incontinence
UTI	urinary tract infection
UUT	upper urinary tract
VUDS	video-urodynamic study

Introduction

Since Sir Ludwig Guttmann introduced sterile intermittent catheterization in the 1940s at Stoke Mandeville Hospital (Guttmann & Frankel, 1966), management of lower urinary tract (LUT) dysfunction has been an important part of the clinical practice of patients with spinal cord injury (SCI). This chapter begins with a brief overview of normal LUT function and pathophysiological aspects of neurogenic LUT dysfunction (NLUTD) due to SCI. Then, it outlines the key points of assessment as well as treatment of LUT dysfunction according to the pathway of management of patients with NLUTD due to SCI, as shown in Fig. 1.

Diagnosis and Treatment of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822498-4.00021-X

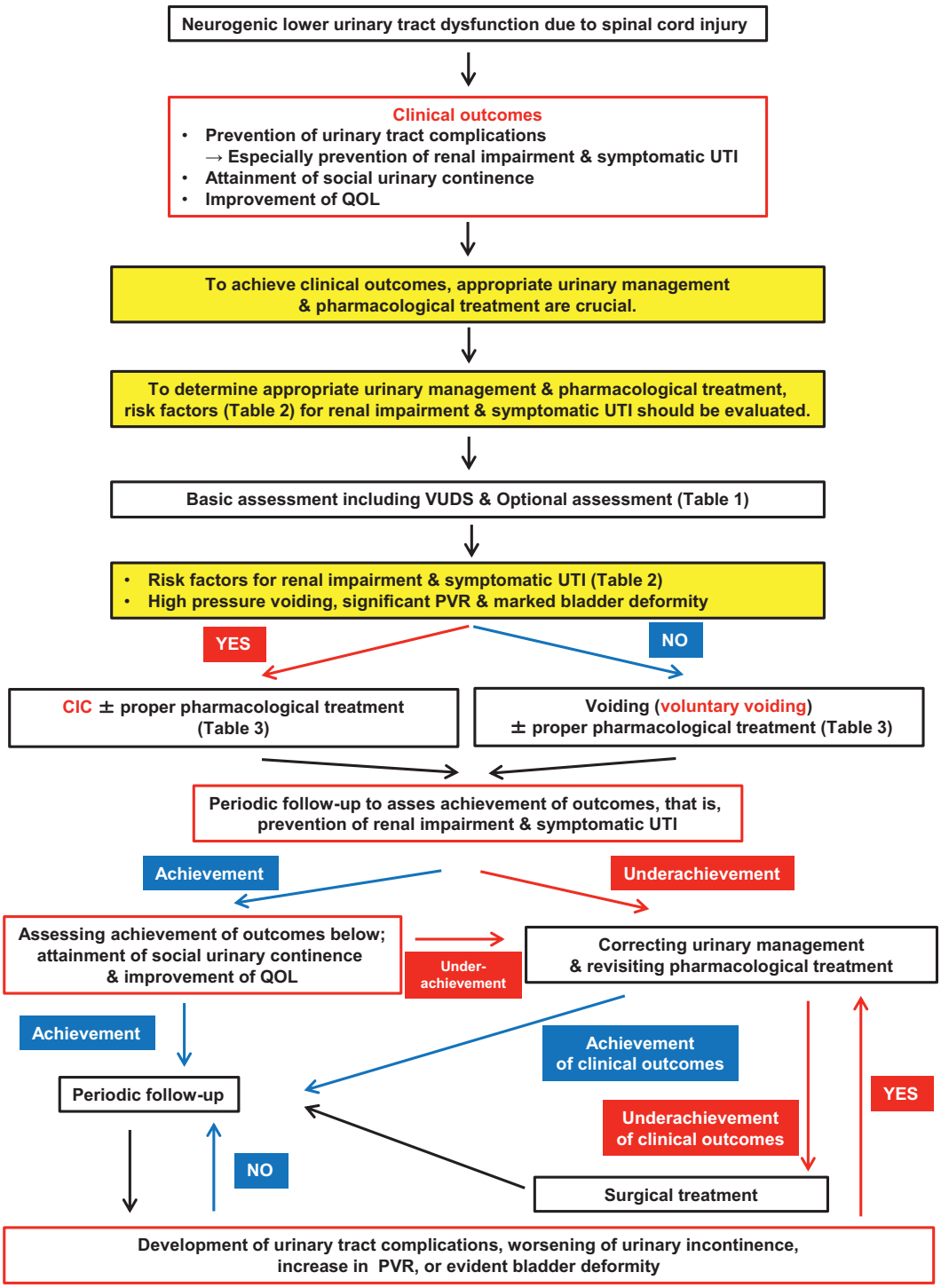

FIG. 1 Clinical pathway of management of patients with neurogenic lower urinary tract dysfunction due to spinal cord injury. Please see "Pathway of NLUTD management" section for details. To achieve the prevention of renal impairment and symptomatic UTI, proper urinary management and pharmacological treatment are determined, based on the basic and optional assessment. Then, further treatment will be considered if these outcomes are not achieved, or obtaining social urinary continence is warranted. *CIC*, clean intermittent catheterization; *PVR*, postvoid residual; *QOL*, quality of life; *UTI*, urinary tract infection; *VUDS*, video-urodynamic study.

Physiology of storage and emptying

The urinary tract consists of the upper urinary tract (UUT) and LUT. While UUT includes the kidneys and ureters, LUT includes the urinary bladder and urethra with the external urethral sphincter. During the storage phase, the bladder gradually distends, which activates myelinated A-delta afferent fibers mainly entering S2 to S4 (de Groat, Griffiths, & Yoshimura, 2015). Then, information about bladder filling ascends the spinal cord and stimulate sympathetic nerves innervating the LUT as well as the pudendal nerve innervating the external urethral sphincter, while eventually reaching the periaqueductal gray (PAG), from which the information is relayed to the relevant areas of the brain (Griffiths, 2015). Ultimately, the medial prefrontal cortex probably determines urine storage or bladder emptying (Griffiths). Once a decision is made to empty the bladder, the medial prefrontal cortex activates the pontine micturition center (PMC) via PAG (Griffiths).

In terms of the peripheral nervous system during the storage phase, the sympathetic nerves from T10 to L1 relax the detrusor via β3-adrenoceptors and contract smooth muscle from bladder neck to proximal urethra via α1-adrenoceptors (de Groat et al., 2015). In addition, the pudendal nerve from S2 to S4 (Onuf's nucleus) controls external urethral sphincter activity (de Groat et al., 2015). These nerve activities result in urine storage at low pressure and of sufficient volume without urinary incontinence (UI). During the emptying phase, once PMC is activated, the parasympathetic nerves from S2 to S4 contract the detrusor via muscarinic receptors (M3 receptors), while sympathetic and pudendal nerves are inhibited, resulting in residual-free voiding with good urinary flow without high pressure (de Groat et al., 2015). The coordination between the detrusor and external urethral sphincter during the emptying phase requires intact neural pathways between PMC and the sacral cord.

Pathophysiology of NLUTD due to SCI

Classification of NLUTD due to SCI

NLUTD due to SCI is divided into two types: supra-sacral NLUTD due to damage above the sacral cord, and sacral NLUTD due to damage to the sacral cord (Sekido et al., 2020). During the acute phase of SCI (spinal shock phase), LUT in the supra-sacral NLUTD reveals an acontractile detrusor with a closed bladder outlet, which lasts about for a few weeks to 3 months. However, a recent report warned that unfavorable urodynamic findings leading to high intravesical pressure were found in two-thirds of patients even during the spinal shock phase (Bywater, Tornic, Mehnert, & Kessler, 2018). In the chronic phase, the supra-sacral NLUTD is characterized by detrusor overactivity (DO) with a discordant external urethral sphincter (detrusor sphincter dyssynergia, DSD), resulting in high-pressure storage as well as emptying. DO can causes reflex UI. In addition, besides DSD during the emptying phase, detrusor underactivity (DU) due to disruption of signal transmission from supra-spinal centers to the sacral cord may contribute to emptying dysfunction (Osman et al., 2014). The sacral NLUTD is characterized by impaired detrusor contractility (DU or acontractile detrusor) with an incompetent urethral closure mechanism (intrinsic sphincter deficiency, ISD) during storage and inadequate urethral relaxation (nonrelaxing sphincter) during emptying, resulting in refractory stress UI as well as incomplete bladder emptying. The bladder sensation is reduced or absent regardless of the level of injury.

Association between neurological level of SCI and NLUTD

The neurological level of SCI is represented by the lowest segment of the cord with residual function, which corresponds to the upper limit of the extent of SCI. On the other hand, as described above, NLUTD is classified according to whether the lower limit of SCI involves the sacral cord. Therefore, it is difficult to accurately predict the NLUTD condition based on the neurological level of SCI regardless of its completeness of SCI, and a video-urodynamic study (VUDS) is required for the assessment of the status of NLUTD after the end of the spinal shock phase (see "Basic and Optional assessments" section).

Elderly SCI

Elderly SCI is characterized by incomplete cervical SCI without bone injury, and central cord syndrome (Chan et al., 2018). Central cervical SCI damages the function of the upper extremities much more than the lower extremities, and the patients often recover well except for impaired hand dexterity. Theresultant impairment in hand dexterity poses serious problems for implementing clean intermittent self-catheterization. While the incidence of LUT dysfunction was reported to be low (Merriam, Taylor, Ruff, & McPhail, 1986), unfavorable urodynamic findings such as DSD were higher than previously reported, and some patients manifested urinary tract complications (Smith, Kraus, Nickell, & Boone, 2000). Therefore, in patients with NLUTD due to central cord injury, VUDS should be performed to assess NLUTD, and regular urological

surveillance is mandatory. Moreover, it should be noted that aging in SCI patients worsens their daily life activities, and eventually converts clean intermittent self-catheterization to indwelling catheterization (Chan et al., 2018). Besides this, renal impairment due to NLUTD or diseases other than NLUTD, urolithiasis, and cognitive impairment due to an excessive anti-cholinergic load should be carefully monitored in these patients (Chan et al., 2018; Welk & McArthur, 2020).

Overview of management of patients with NLUTD due to SCI

Clinical outcomes of management of NLUTD

The critical clinical outcomes or goals of the clinical practice in NLUTD due to SCI are prevention of urinary tract complications [e.g., renal impairment (renal dysfunction/UUT deterioration), symptomatic urinary tract infection (UTI), urolithiasis, gross hematuria, urethral stricture, urethrocutaneous fistula, bladder cancer, and catheter obstruction], attainment of social urinary continence, and improvement of quality of life (QOL) (Sekido et al., 2020).

Pathway of NLUTD management

Recently, patient-reported outcomes have become more important in the field of NLUTD than before, and QOL has been increasingly included in clinical outcomes of treatment for NLUTD (Adriaansen et al., 2017). Even though improvement of QOL is crucial, prevention of urinary tract complications, some of which are closely related to the patient's survival, remains the most important clinical outcome to be achieved in patients with NLUTD due to SCI. Therefore, as shown in Fig. 1, in order to prevent urinary tract complications, the first step is to determine the appropriate urinary management and pharmacological treatment aimed at preventing urinary tract complications, especially renal impairment and symptomatic UTI. Once the appropriate urinary management and pharmacological treatment has been determined, periodic follow-up assesses whether this outcome has been achieved. If the clinical outcomes of prevention of renal impairment and symptomatic UTI are not achieved, correcting urinary management as well as revisiting pharmacological treatment should be considered. If these outcomes are achieved, obtaining social urinary continence and enhancing QOL are the subsequent important clinical outcomes. To this end, urinary management and pharmacological treatment should be optimized without compromising the outcomes of prevention of renal impairment and symptomatic UTI. Because UI is associated with poor QOL, strategies to attain social continence should be actively addressed with careful consideration of the individual patient's preference, characteristics, and social environment. When maximum conservative treatment fails to achieve the above outcomes, surgical intervention becomes an option in carefully selected patients.

Basic and optional assessments

All the patients with NLUTD due to SCI should be assessed by basic assessment (Table 1) (Sekido et al., 2020). The basic assessment includes a history taking (Zlatev, Shem, & Elliott, 2018), assessment of QOL (Costa et al., 2001; Pinder et al., 2012; Welk et al., 2018), focused physical and neurological findings (Sekido et al., 2020), a frequency volume chart (FVC) or a bladder diary, urinalysis, blood tests to screen for renal dysfunction (Goto, Kawasaki, Takemoto, Abe, & Namima, 2018), a morphological evaluation of the urinary tract usually assessed by abdominal ultrasound, measurement of postvoid residual (PVR) and uroflow in patients with voiding (Sekido et al., 2020), and VUDS (Kreydin et al., 2018; Sekido et al., 2020). In addition to the basic assessment, optional assessment may be performed, which includes static and/or dynamic renal scintigrams in cases of renal dysfunction or vesico-ureteral reflux, and cystourethroscopy in cases of suspicious of urethral pathology, anatomical bladder outlet obstruction (BOO), bladder stones, or bladder cancer (Sekido et al., 2020). VUDS and cystourethroscopy should be performed with caution against developing autonomic dysreflexia (AD) during examinations (Liu, Zhou, Biering-Sørensen, & Krassioukov, 2017). Performing the basic as well as optional assessment identifies the presence or absence of risk factors for renal impairment, symptomatic UTI, UI, and QOL (Table 2) (Sekido et al., 2020). In addition, the presence or absence of high-pressure voiding due to functional BOO, significant PVR (>100 mL) due to BOO or DU/acontractile detrusor, and marked bladder deformity defined as grade 2 (bladder having mild pseudodiverticula) or higher by Ogawa's classification should be noted (Sekido et al., 2020).

TABLE 1 Basic assessment.

Evaluations	Comments
History taking	• The level of injury: neurological findings due to SCI are essential in determining urinary management, as residual upper extremity function and the ability to hold a sitting position or open the legs are important factors for clean intermittent self-catheterization. • Urinary management during and after the acute phase • The presence or absence of symptomatic UTI, urinary incontinence, AD • Concomitant medications • The status of anorectal and sexual function • Current co-morbid diseases • Past medical and surgical histories
Assessment of QOL	• Qualiveen 30 • The Neurogenic Bladder Symptom Score • Intermittent Self-Catheterization Questionnaire
Focused physical and neurological examinations of the lumbosacral region	• Sensation in the perianal area • Ability to voluntarily contract the external anal sphincter • The presence or absence of anal reflex (S2–S5) and bulbospongiosus reflex (S2–S4)
Frequency volume chart (or bladder diary)	Useful for • Evaluating bladder storage function • Detecting nocturnal polyuria • Confirming proper frequency/interval of CIC • Measuring treatment outcomes
Urinalysis	Also need urine bacteriology in case of suspected symptomatic UTI
Blood chemistry	• Serum creatinine or cystatin C • For early detection of renal impairment, cystatin C is more useful than serum creatinine • Prostate-specific antigen for middle-aged or older male patients, if indicated
Transabdominal ultrasonography	Screening test for upper and lower urinary tract abnormalities, such as • Hydroureteronephrosis • Bladder wall thickening/trabeculation • Urolithiasis • Prostatic enlargement
Postvoid residual and uroflowmetry[a] in patients with voiding	• Screening test for lower urinary tract dysfunction in patients managed with voiding
Video-urodynamic study	• Indispensable functional examination for NLUTD due to SCI, regardless of complete or incomplete injury, because neurological levels of injury do not always predict the nature of NLUTD • Identification of risk factors for renal impairment, symptomatic UTI, and UI to provide convincing evidence for urinary management and pharmacological treatment • Assessment of AD during the micturition cycle • "As low as reasonably achievable (ALARA)" should be kept in mind

The basic assessment provides clues for the optional assessment and evidence for urinary management and pharmacological treatment.
AD, autonomic dysreflexia; *CIC*, clean intermittent catheterization; *NLUTD*, neurogenic lower urinary tract dysfunction; *QOL*, quality of life; *SCI*, spinal cord injury; *UTI*, urinary tract infection.
[a]*Only patients enabled to urinate on a uroflowmeter.*

Urinary management (Table 3)

Urinary management during acute phase

During an acute phase, an indwelling catheterization should be changed to CIC as soon as the general condition of the patient becomes stable and urine output decreases to approximately 1.5 to 2.0 L per day, because long-term indwelling catheterization will cause catheter-associated complications (Welk et al., 2018).

TABLE 2 Risk factors for clinical outcomes.

	Risk factors
Renal impairment (renal dysfunction[a]/upper urinary tract deterioration[b])	• Video-urodynamic findings: decreased maximal bladder capacity, high pressure, and/or sustained detrusor overactivity, detrusor sphincter dyssynergia, decreased bladder compliance, high detrusor leak point pressure • Urinary management: indwelling urethral catheterization, bladder reflex triggering • Level and severity of the injury: tetraplegia, complete paralysis
Symptomatic urinary tract infection[c]	• Video-urodynamic findings: vesico-ureteral reflux secondary to lower urinary tract dysfunction, that is, decreased maximal bladder capacity, detrusor overactivity, detrusor sphincter dyssynergia, decreased bladder compliance, high detrusor leak point pressure • Urinary management: indwelling urethral catheterization • Level and severity of injury: cervical cord injury, A or B on American Spinal Injury Association impairment scale
Urinary incontinence	• Video-urodynamic findings: detrusor overactivity, decreased bladder compliance, intrinsic sphincter deficiency
Quality of life	• Negative impact: indwelling catheterization, clean intermittent catheterization by attendants • Positive impact: fewer worries about and fewer restrictions arising from urinary incontinence, less concerns about urinary tract infection as well as deterioration of bladder function

The presence or absence of risk factors is relevant to management of lower urinary tract dysfunction.
[a]*Renal dysfunction: increased serum creatinine level, decreased glomerular filtration rate, or renal scarring on renal scintigraphy.*
[b]*Upper urinary tract deterioration: hydroureteronephrosis, vesico-ureteral reflux, febrile upper urinary tract infection, or upper urinary tract stones.*
[c]*Symptomatic urinary tract infection: significant bacteriuria, pyuria, and symptoms suggestive of urinary tract infection, such as discomfort and/or pain in renal or supra-pubic area in incomplete injury, cloudiness of urine, worsening of urine odor, development or worsening of urinary incontinence or leakage around the catheter, pain on micturition, worsening of spasticity discomfort/lethargy/anorexia, autonomic dysreflexia, and fever or chills, without any obvious causes for those findings and symptoms.*

Urinary management during chronic phase

The appropriate urinary management is guided by the presence or absence of risk factors for renal impairment and symptomatic UTI, as well as high-pressure voiding, significant PVR, and marked bladder deformity.

CIC

Patients who have risk factors and/or high-pressure voiding, PVR, or bladder deformity should be managed with CIC (Romo et al., 2018). Based on the VUDS findings, the physician should determine the frequency, timing, and interval of CIC. Proper education and instruction with adequate follow-up are of paramount importance in the long-term compliance and persistence of CIC as well as avoiding complications such as urethral trauma and stricture in male patients, gross hematuria, and symptomatic UTI (Biardeau & Corcos, 2016). In addition, clean intermittent self-catheterization is preferred to CIC by caregivers in terms of maintaining QOL (Adriaansen et al., 2017). In patients managed with CIC, treatment for asymptomatic pyuria/bacteriuria (asymptomatic UTI) with antibiotics is not recommended because there is a dearth of clear evidence supporting the use of antibiotics for prevention of symptomatic UTI and the emergence of drug-resistant bacteria is a major concern (Sekido et al., 2020). There are several different types of catheters available for CIC (Jeong & Oh, 2019; Li et al., 2013; McClurg et al., 2017; Sun, Comiter, & Elliott, 2018) and please see "Key Facts of Catheters for Clean Intermittent Catheterization."

Voiding

Patients who do not have the above hostile findings and can void voluntarily can be managed with voluntary voiding, which means that patients are able to store an adequate volume of urine at low pressure and to void without bladder reflex triggering or bladder expression (Sekido et al., 2020). Voiding with bladder reflex triggering is indicated only in carefully selected male cervical cord injured patients with good reflex bladder contractility who cannot be managed with CIC due to the patient's disabilities and/or the lack of caregiver supports (Romo et al., 2018; Sekido et al., 2020). Transurethral

TABLE 3 Urinary management.

Urinary management	Descriptions
Voiding	• Transurethral bladder emptying without any catheterization
Voluntary (spontaneous) voiding	• Coordinated physiologic voluntary voiding, that is, voluntary detrusor contraction simultaneously with voluntary urethral relaxation • No need of triggering or Crede/Valsalva maneuvers
Bladder reflex triggering	• Need of triggers such as percussion on supra-pubic area to induce micturition reflex • Often concomitant sphincterotomy to overcome DSD
Bladder expression	• Need of Crede and/or Valsalva maneuvers to empty bladder • Preferable to be replaced by CIC
CIC	• Usually per urethra but, in carefully selected patients unable to perform transurethral catheterization, per abdominal continent catheterizable channel • Low pressure and residual-free bladder emptying within low-pressure storage, if properly performed • Need of adherence to appropriate frequency/interval as well as individualized fluid intake to avoid bladder over-distension or high storage pressure • May be performed even by male and female patients with cervical cord injury at the level of C5B and C6B, respectively, with great difficulty, but in practice more residual functions are necessary.
Indwelling catheterization	• Long term bladder drainage method with indwelling catheters • The last resort due to risk of a variety of catheter-associated complications
Indwelling urethral catheterization	• Transurethral catheter drainage • 14–16 Fr caliber catheters with 5–10 mL balloon replaced every 2–6 weeks
Indwelling supra-pubic catheterization	• Percutaneous catheter drainage • Frequent need of spinal or general anesthesia and supra-pubic cystotomy at catheter insertion • Optional urinary management in patients with high cervical SCI • Avoidance of urethral complications • Use of larger (18–22 Fr) caliber catheters with short tips, resulting in less incidence of catheter blockage than indwelling urethral catheterization

This table describes the key urinary management for patients with spinal cord injury.
CIC, clean intermittent catheterization; *DSD*, detrusor sphincter dyssynergia.

sphincterotomy is often needed to achieve low-pressure storage as well as voiding without significant PVR and to prevent UUT deterioration (Takahashi, Kimoto, & Eto, 2018). Bladder expression with manual compression of the supra-pubic area (Crede maneuver) or straining (Valsalva maneuver) is not recommended as voiding because bladder expression is potentially urodynamically unsafe for the urinary tract due to the presence of a nonrelaxing urethral sphincter and should be replaced by CIC (Sekido et al., 2020).

Indwelling catheterization

Generally speaking, indwelling catheterization is not recommended for urinary management of patients with SCI due to a constellation of unavoidable catheter-associated complications, such as symptomatic UTI, urolithiasis, catheter blockage/obstruction, AD, and bladder cancer (Igawa, Wyndaele, & Nishizawa, 2008; Sekido et al., 2020). This type of urinary management is mainly indicated for patients with cervical SCI who cannot be managed with CIC (Sorokin & De, 2015). Supra-pubic catheterization may be better than urethral catheterization in terms of freedom from urethral or genital complications such as urethral trauma, urethral diverticula, urethrocutaneous fistula, epididymitis, or intrascrotal abscess (Feifer & Corcos, 2008; Hunter, Bharmal, & Moore, 2013; Igawa, et al., 2008). On the other hand, the intermittent (temporary) use of an indwelling urethral catheter is an option for patients with nocturnal polyuria and/or difficulty in performing CIC away from home (Ozawa et al., 2005; Sekido et al., 2020; Sturm, Cantrell, Durbin-Johnson, & Kurzrock, 2020). For example, a specialized indwelling catheter for this purpose (Fig. 2) has been approved in Japan, and it is recommended that indwelling time should be kept to a minimum, up to half a day at the most (Sekido et al., 2020). For this reason, proper patient education, including the fact that it is not an alternative to CIC, is essential.

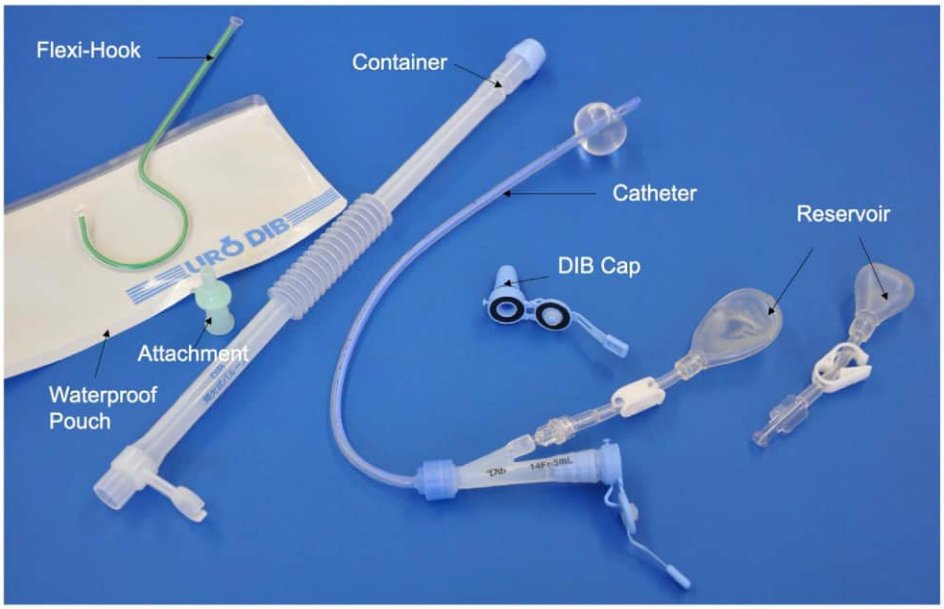

FIG. 2 Specialized indwelling catheter for intermittent (temporary) use approved in Japan. To inflate and indwell the balloon in bladder, sterile water from the reservoir to the balloon is sent. To contract the balloon and remove the catheter, the sterile water in the balloon is sent back to the reservoir. DIB Cap is used for intermittent drainage, especially away from home. Kindly provided by courtesy of DIB International Co., Ltd., Tokyo, JAPAN.

Pharmacological treatment

To facilitate urine storage

Anti-cholinergic drugs, β3-adrenoceptor agonist, or a combination of these drugs suppresses DO and increases bladder compliance and bladder capacity, which ameliorates bladder storage dysfunction (Han, Cho, Jung, Jang, & Lee, 2019; Sekido et al., 2020; Stothers, Tsang, Nigro, Lazare, & Macnab, 2016). Therefore, these drugs are recommended for patients who have the risk factors for renal impairment and symptomatic UTI or UI (Sekido et al., 2020).

To facilitate bladder emptying

α1-Adrenernoceptor antagonists may reduce the resistance at the bladder outlet (Yasuda, Yamanishi, Kawabe, Ohshima, & Morita, 1996). Therefore, these drugs may be used in patients managed by (voluntary) voiding for their potential to improve voiding efficiency despite the lack of robust evidence of these drugs.

The use of parasympathomimetic drugs [muscarinic receptor agonists (e.g., bethanechol) and peripheral cholinesterase inhibitors (e.g., distigmine)] that may improve bladder contractility are not recommended because there is a dearth of evidence on these drugs for patients with NLUTD due to SCI and a possibility of worsening of functional BOO (Barendrecht, Oelke, Laguma, & Michel, 2007).

Assessment of clinical outcomes (periodic follow-up)

Proposal for follow-up protocol

Periodic follow-up is needed to ensure that clinical outcomes are achieved; it includes a medical interview and urinalysis every 3 to 6 months, combined with FVC or the bladder diary especially in patients with CIC, and transabdominal ultrasonography to evaluate the urinary tract annually (Kreydin et al., 2018; Sekido et al., 2020). Follow-up protocols of measurement of PVR and uroflow, and VUDS have not been established; however, these examinations should be performed within 3 to 6 months if urinary management and/or pharmacological treatments are changed. Moreover, these examinations should be promptly performed if urinary tract complications develop, UI is worsened, PVR increases, or bladder deformity becomes evident (Kreydin et al., 2018; Sekido et al., 2020). VUDS can tailor urodynamic study without fluoroscopy to the individual patient's condition.

Proposal for repeated urodynamic study

Regarding urodynamic study, The International Continence Society Urodynamic Committee proposed that "The panel recommends performing the first exam as soon as possible after the end of spinal shock phase and to perform another urodynamic testing at 6 and 12 months after the injury (level of evidence 4, expert opinions). Then, a yearly exam is preferable in SCI patients with cervical and thoracic injury for the first 5 years, deferring it to one in 2 years after attaining a low-pressure reservoir with continence and complete emptying. In case of lumbar injury, urodynamics could be done yearly for the first 2 years and once in 2 years thereafter (level of evidence 4, expert opinions)" (Schurch et al., 2018). In addition, the Committee emphasized that "Maximal attention should be paid to patients with incomplete suppression of detrusor overactivity, in those who empty their bladders by reflex voiding, to poor bladder compliance and in the presence of detrusor sphincter dyssynergia" (Schurch et al., 2018).

Proposal for surveillance for bladder cancer

Although the development of bladder cancer associated with long-term indwelling catheterization is a serious problem, recent reports suggest that the incidence of bladder cancer is not as high as previously thought (Elliott, 2015), and routine screening for bladder cancer using cystourethroscopy or urine cytology in asymptomatic patients is not recommended (Gui-Zhong & Li-Bo, 2017). On the other hand, it should be kept in mind that early detection of bladder cancer in patients with NLUTD is difficult and cancer-specific survival rates are low (Welk, McIntyre, Teasell, Potter, & Loh, 2013). Therefore, not only in patients under long-term indwelling catheterization, but also in all patients with NLUTD due to SCI, it is essential to try to investigate each case on an individual basis, without underestimating the suspicious signs of bladder cancer, such as gross hematuria, worsening of AD, refractory recurrent UTI, and abnormal thickening of the bladder wall on transabdominal ultrasound (Sekido et al., 2020).

Surgical treatment

Transurethral intra-detrusor injection of type A botulinum toxin (BoNT-A)

Several good quality randomized controlled trials have demonstrated the efficacy and safety of transurethral intra-detrusor injection of BoNT-A, thus establishing this minimally invasive treatment as an excellent option for refractory DO (Cruz et al., 2011; Ginsberg et al., 2012). BoNT-A hampers the fusion between a synaptic vesicle containing acetylcholine and a presynaptic membrane, leading to suppression of DO. BoNT-A decreases the number of UI episodes and detrusor pressure as well as increases bladder capacity and bladder compliance. The most frequent complications are symptomatic UTI and, in patients managed with voiding, increased PVR requiring CIC.

Other surgical treatments

The surgical therapies dealt with below should be performed by experienced neurourologists in the specialized centers for NLUTD. In addition, robot-assisted laparoscopic techniques for augmentation cystoplasty (AC), bladder neck surgery, and urinary diversion in patients with NLUTD are still considered to be in their infancy, but they show promise in terms of reducing the invasiveness of the procedures (Cohen, Pariser, Anderson, Pearce, & Gundeti, 2015; Gargollo, 2015).

AC

When all the maximum conservative and minimally invasive treatments fail, AC remains an important option for the improvement of progressive UUT deterioration, recurrent symptomatic UTI, and intractable UI that are attributed to refractory DO and low bladder compliance (Hoen et al., 2017). Usually, the bladder is augmented by a detubularized intestinal segment (enterocystoplasty) with the most commonly used segment being ileum (ileocystoplasty). The major problems with AC are the various frequently occurring peri- and postoperative complications. Peri-operative complications include prolonged ileus, wound infection, thromboembolism, and hemorrhage (Hoen et al., 2017). Long-term postoperative complications include urolithiasis, bowel dysfunction, electrolyte-metabolic disturbances, bladder perforation, and malignant neoplasm (Hoen et al., 2017). AC without the use of an intestinal segment is called auto-augmentation (detrusor myectomy), in which significant area of the detrusor is resected, leaving the mucosal layer intact. Although less invasive than enterocystoplasty, in terms of creating a low-pressure and high-volume environment for urine storage, auto-augmentation generally has poorer outcomes than enterocystoplasty (Wyndaele et al., 2018).

Anti-incontinence surgery

As surgical treatments for ISD in patients with NLUTD, bladder neck reconstruction (BNR), bladder neck sling (BNS), artificial urinary sphincter (AUS), and bladder neck closure with an abdominal continent catheterizable channel have been reported, although optimal surgical procedures remain controversial (Myers et al., 2016; Phé et al., 2017; Wyndaele et al., 2018). BNR is often selected for ISD associated with congenital anomalies, such as bladder exstrophy, and there have been few reports on the efficacy and safety for ISD associated with SCI (Myers et al., 2016). BNS can be conducted in both male and female patients, but the majority of reports are of a pubovaginal sling in female patients with some established efficacy and safety (Myers et al., 2016; Wyndaele et al., 2018). Not only in female patients but also in male patients with NLUTD, AUS is preferably placed at the bladder neck to probable decrease erosion rates (Myers et al., 2016; Wyndaele et al., 2018). Bladder neck closure is the last resort in cases of intractable UI resulting from severe ISD that would be difficult to treat with other anti-incontinence procedures, or in cases where previous anti-incontinence procedures have failed (Wyndaele et al., 2018). Moreover, mid-urethral synthetic sling procedures such as tension-free vaginal tape and transobturator tape in female patients as well as a perineal mesh sling in male patients with NLUTD have recently been reported (El-Azab & El-Nashar, 2015; Myers et al., 2016; Pannek & Wöllner, 2017). The postoperative complications include persistent UI, difficulty in catheterization, urolithiasis, device malfunction and device infection in AUS, vesico-cutaneous fistula and stomal stenosis in bladder neck closure with an abdominal continent catheterizable channel, and tape or mesh erosion in procedures using synthetic materials (Wyndaele et al., 2018).

Urinary diversion

Incontinent urinary diversion as well as a continent urinary reservoir is regarded as the last resort for carefully selected patients with NLUTD (Sekido et al., 2020). Although preservation of renal function, decreased incidence of symptomatic UTI, and attainment of social continence are achieved, a variety of peri- and postoperative complications may be encountered, which needs to be appropriately addressed (Sekido et al., 2020).

Sacral neuromodulation (SNM)

SNM may be a treatment of choice for carefully selected patients with incomplete SCI with refractory overactive bladder as well as nonobstructive urinary retention (Kessler et al., 2010). Electrode(s) for stimulation are usually inserted into the S3 foramen unilaterally or bilaterally, and stimulation to somatic afferents may bring reorganization of neural pathways to the central nervous system, resulting in suppression as well as enhancement of the micturition reflex. Moreover, recent studies indicated that implementing SNM during the acute phase of SCI above T12 may inhibit development of DO and DSD in the chronic phase (Sievert et al., 2010). Adverse events include new pain/undesirable change in stimulation, pain at the implantable pulse generator site, and adverse change in bowel function (Kessler et al., 2010).

Sacral anterior root stimulation (SARS)

SARS with dorsal rhizotomy may be a treatment of choice to attain voiding and urinary continence in extremely carefully selected patients with supra-sacral NLUTD due to complete SCI (Wyndaele et al., 2018). Although stimulation of S2 to S4 anterior roots excites both detrusor and the external urethral sphincter, once the stimulation is turned off, the external sphincter relaxes, while detrusor contraction continues, which means that voiding occurs after stimulation (poststimulus voiding). SARS not only reestablishes voiding, but also ameliorates UI, decreases the frequency of symptomatic UTI and AD, and prevents UUT deterioration through inhibition of DO due to dorsal rhizotomy (Wyndaele et al., 2018). Adverse events include device malfunction and leakage of cerebrospinal fluid (Wyndaele et al., 2018).

Transurethral sphincterotomy and others

As mentioned in "Urinary management" section, sphincterotomy for DSD is often performed to improve voiding efficiency and to prevent UUT deterioration in patients managed by bladder reflex triggering. Complications include insufficient relief of DSD leading to repeated procedures, hemorrhage, and urethrocutaneous fistula (Sekido et al., 2020; Wyndaele et al., 2018). Less invasive procedures such as urethral stents and intra-sphincteric injection of type A botulinum toxin, which is an off-label use, have been reported (Chancellor et al., 1999; Mehta et al., 2012), but have not become widespread yet.

Applications to other areas of neuroscience

Management for NLUTD due to spinal cord injury is the basis for all NLUTDs or non-NLUTDs (Groen et al., 2016). In terms of urinary management, CIC become the standard urinary tract management for NLUTD in which voluntary voiding is not urodynamically safe. For pharmacological treatment, anti-cholinergics and β3 adrenoreceptor agonists are used to ameliorate the neurogenic overactive bladder associated with stroke and Parkinson's disease. BoNT-A has established efficacy and safety in the treatment of refractory DO due to multiple sclerosis (Cruz et al., 2011; Ginsberg et al., 2012).

Moreover, a plenty of basic research using the SCI model has played a major role in elucidating the nervous system involved in LUT function. In normal animals, myelinated A-delta afferent fibers activate the micturition reflex, whereas in chronic SCI animals, micturition is induced by unmyelinated C afferent fibers, resulting in development of DO (de Groat et al., 2015). This contrasts with the pathophysiology of supra-spinal DO seen in stroke and Parkinson's disease, which is caused by loss of forebrain inhibition and/or enhancement of forebrain activation to PAG and PMC (de Groat et al., 2015). Recently, it was reported that transurethral intra-detrusor injection of BoNT-A reduced transient receptor potential vanilloid receptor 1 receptors and purinergic subtype 2X receptors on C fibers, which is considered to be a contributing factor for ameliorating DO (de Groat et al., 2015).

Mini-dictionary of terms

Bladder compliance: An index of the distensibility of the bladder during the storage phase. The normal bladder has very good distensibility, ensuring urine storage at low pressure and of sufficient capacity.

Detrusor: Smooth muscle of the bladder, which relaxes during the storage phase but contracts during the emptying phase.

Detrusor leak point pressure: The lowest detrusor pressure at leakage without detrusor contraction or increased abdominal pressure.

Detrusor overactivity: Involuntary detrusor contraction during the storage phase, which can be phasic or sustained.

Detrusor sphincter dyssynergia: Involuntary external urethral sphincter contraction concomitant with detrusor overactivity during the storage phase or voiding detrusor contraction during the emptying phase in patients with relevant neurological disorders.

Detrusor underactivity: Inadequate detrusor contractile strength and/or duration.

Frequency volume chart: A chart describing the time and volume of each micturition by voiding or clean intermittent catheterization. If relevant information such as the fluid intake, frequency and degree of, and circumstances at urinary incontinence, is also included, the chart is called a "Bladder diary."

Intrinsic sphincter deficiency: Incompetent urethral closure mechanism, which usually caused by anatomical or functional abnormality of the urethral smooth muscle and/or external urethral sphincter.

Neurogenic lower urinary tract dysfunction: Lower urinary tract dysfunction caused by relevant neurological disorders.

Nonrelaxing urethral sphincter: During the emptying phase, the external urethral sphincter is not relaxed but obstructed, resulting in reduced urinary flow.

Postvoid residual: Urine volume left in the bladder after voiding.

Urodynamic study: Examination for precise assessment of lower urinary tract function during storage and emptying, which simultaneously measures intravesical and abdominal pressure, infused volume of fluid, and often electromyography of external urethral sphincter, concomitant with uroflowmetry during the emptying phase. Detrusor pressure is calculated by subtracting abdominal pressure from intravesical pressure.

Uroflowmetry: Measurement of urine volume (mL) excreted per unit of time (s) using a specific device called a uroflowmeter.

Video-urodynamic study: Performing a urodynamic study under fluoroscopy, which enables functional as well as morphological evaluation.

Key facts of catheters for clean intermittent catheterization

Catheter for clean intermittent catheterization (CIC) is divided into two types: disposable and reusable.

The disposable catheter is popular worldwide and is divided into two types: polyvinyl (PVC) and hydrophilic-coated (HCC), although disposable catheters are frequently reused.

At CIC, PVC requires a lubricant for smooth catheterization, while HCC does not, which increases patient convenience.

HCC decreases the incidence of urinary tract infection and gross hematuria (surrogate for urethral trauma), improves the quality of life, and is cost-effective, although long-term outcomes remain controversial.

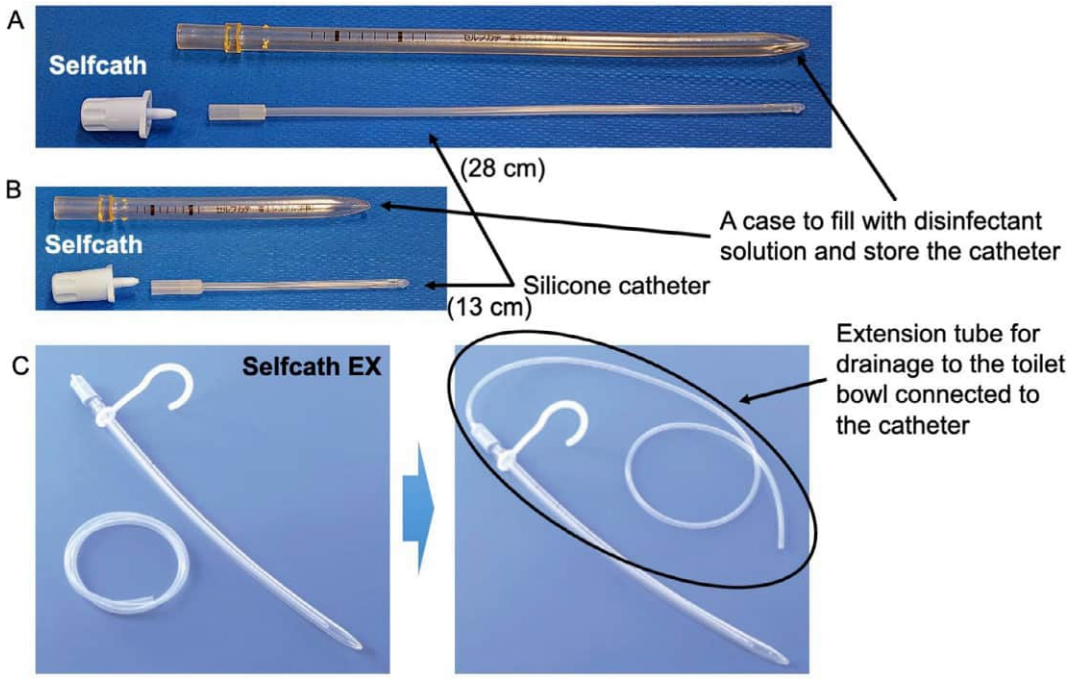

FIG. 3 Examples of reusable silicone catheters approved in Japan. The patients carry the reusable silicone catheter in a case filled with disinfectant solution. (A) for males; (B) for females; (C) for wheelchair patients. Kindly provided by courtesy of Fuji Systems Corporation, Tokyo, Japan.

The cost of HCC is an obstacle to its widespread use, especially in developing countries.

Disposable catheter waste may become an issue in the future in terms of environmental impact.

A reusable catheter is available in some countries, for example in Japan, and some patients use a reusable catheter at home, while using a disposable catheter away from home.

In Japan, several kinds of reusable silicon catheters (Fig. 3) have been approved and widely used for many years, but they should be changed monthly according to the product description, and is stored in a glycerine solution containing 0.025% benzalkonium chloride that is changed daily.

Some reusable catheters are designed to be more convenient for wheelchair patients (Fig. 3).

Summary points

- Management of lower urinary tract dysfunction is an important part of the clinical practice of patients with spinal cord injury.
- The critical clinical outcomes to be achieved are prevention of urinary tract complications, especially renal impairment and symptomatic urinary tract infection, attainment of social urinary continence, and improvement of quality of life.
- Video-urodynamic study plays an important role in identifying risk factors for renal impairment, symptomatic urinary tract infection, and urinary incontinence.
- Appropriate urinary management and pharmacological treatment aimed at preventing renal impairment and symptomatic urinary tract infection are determined depending on the presence or absence of risk factors for these urinary tract complications.
- If these outcomes are achieved, urinary management and pharmacological treatment to obtain social urinary continence and enhance the quality of life should be optimized without compromising the outcomes of prevention of renal impairment and symptomatic urinary tract infection.
- If maximum conservative treatment fails to achieve the above outcomes, surgical treatment becomes an option.

References

Adriaansen, J. J., van Asbeck, F. W., Tepper, M., Faber, W. X., Visser-Meily, J. M., de Kort, L. M., et al. (2017). Bladder-emptying methods, neurogenic lower urinary tract dysfunction and impact on quality of life in people with long-term spinal cord injury. *The Journal of Spinal Cord Medicine*, *40*, 43–53.

Barendrecht, M. M., Oelke, M., Laguma, M. P., & Michel, M. C. (2007). Is the use of parasympathomimetics for treating an underactive urinary bladder evidence-based? *BJU International*, *99*, 749–752.

Biardeau, X., & Corcos, J. (2016). Intermittent catheterization in neurologic patients: Update on genitourinary tract infection and urethral trauma. *Annals of Physical and Rehabilitation Medicine*, *59*, 125–129.

Bywater, M., Tornic, J., Mehnert, U., & Kessler, T. M. (2018). Detrusor acontractility after acute spinal cord injury-myth or reality? *The Journal of Urology*, *199*, 1565–1570.

Chan, L. W., Griebling, T. L., Arnold, E. P., Chu, P. S., New, P. W., & Wagg, A. (2018). Special considerations in the urological management of the older spinal cord injury patient. *World Journal of Urology*, *36*, 1603–1611.

Chancellor, M. B., Bennett, C., Simoneau, A. R., Finocchiaro, M. V., Kline, C., Bennett, J. K., et al. (1999). Sphincteric stent versus external sphincterotomy in spinal cord injured men: Prospective randomized multicenter trial. *The Journal of Urology*, *161*, 1893–1898.

Cohen, A. J., Pariser, J. J., Anderson, B. B., Pearce, S. M., & Gundeti, M. S. (2015). The robotic appendicovesicostomy and bladder augmentation: The next frontier in robotics, are we there? *The Urologic Clinics of North America*, *42*, 121–130.

Costa, P., Perrouin-Verbe, B., Colvez, A., Didier, J., Marquis, P., Marrel, A., et al. (2001). Quality of life in spinal cord injury patients with urinary difficulties. Development and validation of qualiveen. *European Urology*, *39*, 107–113.

Cruz, F., Herschorn, S., Aliotta, P., Brin, M., Thompson, C., Lam, W., et al. (2011). Efficacy and safety of onabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity: A randomized, double-blind, placebo-controlled trial. *European Urology*, *60*, 742–750.

de Groat, W. C., Griffiths, D., & Yoshimura, N. (2015). Neural control of the lower urinary tract. *Comprehensive Physiology*, *5*, 327–396.

El-Azab, A. S., & El-Nashar, S. A. (2015). Midurethral slings versus the standard pubovaginal slings for women with neurogenic stress urinary incontinence. *International Urogynecology Journal*, *26*, 427–432.

Elliott, S. P. (2015). Screening for bladder cancer in individuals with spinal cord injury. *The Journal of Urology*, *193*, 1880–1881.

Feifer, A., & Corcos, J. (2008). Contemporary role of suprapubic cystostomy in treatment of neuropathic bladder dysfunction in spinal cord injured patients. *Neurourology and Urodynamics*, *27*, 475–479.

Gargollo, P. C. (2015). Robotic-assisted bladder neck repair: Feasibility and outcomes. *The Urologic Clinics of North America*, *42*, 111–120.

Ginsberg, D., Gousse, A., Keppenne, V., Sievert, K. D., Thompson, C., Lam, W., et al. (2012). Phase 3 efficacy and tolerability study of onabotulinumtoxinA for urinary incontinence from neurogenic detrusor overactivity. *The Journal of Urology*, *187*, 2131–2139.

Goto, T., Kawasaki, Y., Takemoto, J., Abe, Y., & Namima, T. (2018). Evaluating estimated glomerular filtration rates of creatinine and cystatin C for male patients with chronic spinal cord injury. *Spinal Cord*, *56*, 447–452.

Griffiths, D. (2015). Neural control of micturition in humans: A working model. *Nature Reviews. Urology*, *12*, 695–705.

Groen, J., Pannek, J., Castro Diaz, D., Del Popolo, G., Gross, T., Hamid, R., et al. (2016). Summary of European Association of Urology (EAU) guidelines on neuro-urology. *European Urology*, *69*, 324–333.

Gui-Zhong, L., & Li-Bo, M. (2017). Bladder cancer in individuals with spinal cord injuries: A meta-analysis. *Spinal Cord*, *55*, 340–345.

Guttmann, L., & Frankel, H. (1966). The value of intermittent catheterisation in the early management of traumatic paraplegia and tetraplegia. *Paraplegia*, *4*, 63–84.

Han, S. H., Cho, I. K., Jung, J. H., Jang, S. H., & Lee, B. S. (2019). Long-term efficacy of mirabegron add-on therapy to antimuscarinic agents in patients with spinal cord injury. *Annals of Rehabilitation Medicine*, *43*, 54–61.

Hoen, L., Ecclestone, H., Blok, B. F. M., Karsenty, G., Phé, V., Bossier, R., et al. (2017). Long-term effectiveness and complication rates of bladder augmentation in patients with neurogenic bladder dysfunction: A systematic review. *Neurourology and Urodynamics*, *36*, 1685–1702.

Hunter, K. F., Bharmal, A., & Moore, K. N. (2013). Long-term bladder drainage: Suprapubic catheter versus other methods: A scoping review. *Neurourology and Urodynamics*, *32*, 944–951.

Igawa, Y., Wyndaele, J. J., & Nishizawa, O. (2008). Catheterization: Possible complications and their prevention and treatment. *International Journal of Urology*, *15*, 481–485.

Jeong, S. J., & Oh, S. J. (2019). Recent updates in urinary catheter products for the neurogenic bladder patients with spinal cord injury. *Korean Journal of Neurotrauma*, *15*, 77–87.

Kessler, T. M., Framboise, D. L., Trelle, S., Fowler, C. J., Kiss, G., Pannek, J., et al. (2010). Sacral neuromodulation for neurogenic lower urinary tract dysfunction: Systematic review and meta-analysis. *European Urology*, *58*, 865–874.

Kreydin, E., Welk, B., Chung, D., Clemens, Q., Yang, C., Danforth, T., et al. (2018). Surveillance and management of urologic complications after spinal cord injury. *World Journal of Urology*, *36*, 1545–1553.

Li, L., Ye, W., Ruan, H., Yang, B., Zhang, S., & Li, L. (2013). Impact of hydrophilic catheters on urinary tract infections in people with spinal cord injury: Systematic review and meta-analysis of randomized controlled trials. *Archives of Physical Medicine and Rehabilitation*, *94*, 782–787.

Liu, N., Zhou, M. W., Biering-Sørensen, F., & Krassioukov, A. V. (2017). Cardiovascular response during urodynamics in individuals with spinal cord injury. *Spinal Cord*, *55*, 279–284.

McClurg, D., Coyle, J., Long, A., Moore, K., Cottenden, A., May, C., et al. (2017). A two phased study on health care professionals' perceptions of single or multi-use of intermittent catheters. *International Journal of Nursing Studies*, *72*, 83–90.

Mehta, S., Hill, D., Foley, N., Hsieh, J., Ethans, K., Potter, P., et al. (2012). A meta-analysis of botulinum toxin sphincteric injections in the treatment of incomplete voiding after spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *93*, 597–603.

Merriam, W. F., Taylor, T. K., Ruff, S. J., & McPhail, M. J. (1986). A reappraisal of acute traumatic central cord syndrome. *Journal of Bone and Joint Surgery. British Volume (London)*, *68*, 708–713.

Myers, J. B., Mayer, E. N., Lenherr, S., & Neurogenic Bladder Research Group (NBRG.org). (2016). Management options for sphincteric deficiency in adults with neurogenic bladder. *Translational Andrology and Urology*, *5*, 145–157.

Osman, N. I., Chapple, C. R., Abrams, P., Dmochowski, R., Haab, F., Nitti, V., et al. (2014). Detrusor underactivity and the underactive bladder: A new clinical entity? A review of current terminology, definitions, epidemiology, aetiology, and diagnosis. *European Urology*, *65*, 389–398.

Ozawa, H., Uematsu, K., Ohmori, H., Kondo, A., Iwatsubo, E., & Takasaka, S. (2005). Long-term usefulness and safety of the contemporary balloon catheter. *Nihon Hinyokika Gakkai Zasshi*, *96*, 541–547.

Pannek, J., & Wöllner, J. (2017). Treatment of stress urinary incontinence in men with spinal cord injury: Minimally invasive = minimally effective? *Spinal Cord*, *55*, 739–742.

Phé, V., Boissier, R., Blok, B. F. M., Del Popolo, G., Musco, S., Castro-Diaz, D., et al. (2017). Continent catheterizable tubes/stomas in adult neuro-urological patients: A systematic review. *Neurourology and Urodynamics*, *36*, 1711–1722.

Pinder, B., Lloyd, A. J., Elwick, H., Denys, P., Marley, J., & Bonniaud, V. (2012). Development and psychometric validation of the intermittent self-catheterization questionnaire. *Clinical Therapeutics*, *34*, 2302–2313.

Romo, P. G. B., Smith, C. P., Cox, A., Averbeck, M. A., Dowling, C., Beckford, C., et al. (2018). Non-surgical urologic management of neurogenic bladder after spinal cord injury. *World Journal of Urology*, *36*, 1555–1556.

Schurch, B., Iacovelli, V., Averbeck, M. A., Stefano, C., Altaweel, W., & Finazzi, A. (2018). Urodynamics in patients with spinal cord injury: A clinical review and best practice paper by a working group of The International Continence Society Urodynamics Committee. *Neurourology and Urodynamics*, *37*, 581–591.

Sekido, N., Igawa, Y., Kakizaki, H., Kitta, T., Sengoku, A., Takahashi, S., et al. (2020). Clinical guidelines for the diagnosis and treatment of lower urinary tract dysfunction in patients with spinal cord injury. *International Journal of Urology*, *7*, 276–288.

Sievert, K. D., Amend, B., Gakis, G., Toomey, P., Badke, A., Kaps, H. P., et al. (2010). Early sacral neuromodulation prevents urinary incontinence after complete spinal cord injury. *Annals of Neurology*, *67*, 74–84.

Smith, C. P., Kraus, S. R., Nickell, K. G., & Boone, T. B. (2000). Video urodynamic findings in men with the central cord syndrome. *The Journal of Urology*, *164*, 2014–2017.

Sorokin, I., & De, E. (2015). Options for independent bladder management in patients with spinal cord injury and hand function prohibiting intermittent catheterization. *Neurourology and Urodynamics*, *34*, 167–176.

Stothers, L., Tsang, B., Nigro, M., Lazare, D., & Macnab, A. (2016). An integrative review of standardized clinical evaluation tool utilization in anticholinergic drug trials for neurogenic lower urinary tract dysfunction. *Spinal Cord*, *54*, 1114–1120.

Sturm, R. M., Cantrell, A. B., Durbin-Johnson, B., & Kurzrock, E. A. (2020). Use of a closed diurnal indwelling catheter for patients with spinal cord disorders: A pilot study. *Urology*, *142*, 237–242. https://doi.org/10.1016/j.urology.2020.04.033. Epub 2020 Apr 19 32320790.

Sun, A. J., Comiter, C. V., & Elliott, C. S. (2018). The cost of a catheter: An environmental perspective on single use clean intermittent catheterization. *Neurourology and Urodynamics*, *37*, 2204–2208.

Takahashi, R., Kimoto, Y., & Eto, M. (2018). Long-term urodynamic follow-up after external sphincterotomy in patients with spinal cord injury. *Neurourology and Urodynamics*, *37*, 2625–2631.

Welk, B., Lenherr, S., Elliott, S., Stoffel, J., Presson, A. P., Zhang, C., et al. (2018). The neurogenic bladder symptom score (NBSS): A secondary assessment of its validity, reliability among people with a spinal cord injury. *Spinal Cord*, *56*, 259–264.

Welk, B., & McArthur, E. (2020). Increased risk of dementia among patients with overactive bladder treated with an anticholinergic medication compared to a beta-3 agonist: A population-based cohort study. *BJU International*, *126*, 183–190.

Welk, B., McIntyre, A., Teasell, R., Potter, P., & Loh, E. (2013). Bladder cancer in individuals with spinal cord injuries. *Spinal Cord*, *51*, 516–523.

Welk, B., Schneider, M. P., Thavaseelan, J., Traini, L. R., Curt, A., & Kessler, T. M. (2018). Early urological care of patients with spinal cord injury. *World Journal of Urology*, *36*, 1537–1544.

Wyndaele, J. J., Birch, B., Borau, A., Burks, F., Castro-Diaz, D., Chartier-Kastler, E., et al. (2018). Surgical management of the neurogenic bladder after spinal cord injury. *World Journal of Urology*, *36*, 1569–1576. 2018.

Yasuda, K., Yamanishi, T., Kawabe, K., Ohshima, H., & Morita, T. (1996). The effect of urapidil on neurogenic bladder: A placebo controlled double-blind study. *The Journal of Urology*, *156*, 1125–1130.

Zlatev, D. V., Shem, K., & Elliott, C. S. (2018). Predictors of long-term bladder management in spinal cord injury patients-upper extremity function may matter most. *Neurourology and Urodynamics*, *37*, 1106–1112.

Chapter 22

Bed support surfaces for preventing pressure injuries after spinal cord injury

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List of abbreviations

NPIAP	National pressure injury advisory panel
PI	Pressure injury
SCI	Spinal cord injury

Introduction

After a spinal cord injury (SCI), individuals often remain with limitations that will impede mobility and functional independence. Presence and severity of the neurological deficits associated with SCI represent important risks for developing pressure injuries (PI). During hospitalization, pain, associated injuries, medical complications, spasticity, joint contractures, and surgical interventions may further lead to prolonged bed rest and contribute to increased occurrence of PI. Achieving an optimal plan for preventing PI can be difficult in practice, particularly for individuals requiring total assistance for mobilization and repositioning in bed. The selection of a specialized support surface is thus a critical component of a comprehensive plan for PI prevention and treatment. Support surface refers to "a specialized device for pressure redistribution designed for management of tissue loads, micro-climate, and/or other therapeutic functions" as defined by the National Pressure Injury Advisory Panel (NPIAP S31, 2007). In this document, support surface pertains to bed, mattress, overlay, and integrated bed system. At the end of this chapter, the reader will be able to:

(1) Describe the different forces that are involved in the pathogenesis of PI in the SCI population.
(2) Provide an overview of the main types and features of support surfaces to prevent and/or treat PI.
(3) Propose a simple decision table for guiding healthcare providers to select a support surface for the prevention and treatment of PI in hospitalized SCI patients.

Pressure injuries (PI): Definition, epidemiology and impacts

Defined by the National Pressure Injury Advisory Panel (NPIAP) as a "localized damage to the skin and/or underlying tissue over a bony prominence," pressure injuries (PI) (also called bedsores, decubitus ulcers, pressure sores) represent one of the most common medical complications experienced by hospitalized patients (NPIAP, 2021). No other preventable event occurs as frequently as PI, occurring at a rate of 2%–40% of all acute care hospitalization in the United States and Canada (NPIAP, 2021; Cullum, McInnes, Bell-Syer, & Legood, 2004). PI can occur throughout the continuum of care, with a prevalence of 9.7%, 11.8%, and 12.0% for all patients hospitalized in acute care, in patient rehabilitation, and long-term care (nursing home), respectively (NPIAP, 2021).

In the lying position, PIs usually develop at the sacrum (17%–27%), heel (9%–18%), malleoli (4.6%), trochanters (1.4%), and scapulae or occiput (<5%) areas (Bhattacharya & Mishra, 2015; Kruger, Pires, Ngann, Sterling, & Rubayi, 2013; Talley Group, 2021). It is however proposed that prevention and management of heel PIs may be best managed independently from the bed support surface (Norton, Coutts, & Sibbald, 2011). The occurrence of PI is

Diagnosis and Treatment of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822498-4.00022-1

particularly concerning for individuals with SCI as it interferes with rehabilitative care, community reintegration, and quality of life (Consortium for Spinal Cord Medicine, 2014; Cullum et al., 2004; McInnes et al., 2015). PIs are associated with higher morbidity and mortality and represent an enormous growing financial burden for healthcare systems, with a patient care cost per PI of 20,900 US$ to 151,700 US$, totalizing 26.8 billion US$ in 2019 (Chan et al., 2013; NPIAP, 2021). Individuals with SCI are among the most vulnerable populations for PI, occurring in more than 95% of them during their lifetime (Cowan et al., 2019). Recent literature estimates that hospital-acquired PI among SCI patients ranges from 29.7% to 49.2% (Tran, McLaughlin, Li, & Philips, 2016). According to Fuhrer, Garber, Rintala, Clearman, and Hart (1993), the risk to develop PI is higher for individuals with severe spinal cord injury.

Pathogenesis of pressure injuries following spinal cord injury

The pathophysiology of PI involves different extrinsic factors, paralleling the severity of the neurological impairments related to the SCI. Pressure is acknowledged to be the main factor and is defined as the amount of force applied *perpendicular* to a surface per unit area of application (International Review, 2010). In addition, shearing and friction represent stresses that are exerted *parallel* to the area of application and significantly contribute to the capillary damage (Agrawal & Chauhan, 2012; International Review, 2010) (Fig. 1). The resultant reduction in blood flow reduces the oxygen and nutrients being delivered to the tissues, while simultaneously limiting the removal of metabolic waste products (Agrawal & Chauhan, 2012; Bhattacharya & Mishra, 2015). Neurological impairments associated with severe SCI also lead to difficulties in identifying painful stimulus associated with prolonged and/or excessive compression, to which must be added the difficulty to make independent postural adjustments necessary to restore tissue perfusion (Bhattacharya & Mishra, 2015; Grey & Harding, 2006). Without the relief of compression on soft tissues, ischemia persisting for more than 2 hours may lead to necrosis of subcutaneous tissues (Kuffler, 2015). Inadequate maneuvers while transferring, repositioning, and positioning in bed may also lead to excessive shearing and friction stresses to the skin, further contributing to the development of PI (Agrawal & Chauhan, 2012). Immobility is also associated with the build-up of temperature at the interface, increasing local inflammation biomarkers, associated with PI occurrence (Yoshimura et al., 2015).

Dysfunction of the autonomic nervous system may also contribute the pathophysiology of PI following SCI, by altering the micro-vascular response below the level of the injury. Blood flow regulation relies on the rhythmic alteration of blood vessels constriction controlled by central neurogenic, local myogenic and metabolic mechanisms, which can be altered following SCI (Brienza, Geyer, & Jan, 2005). Impaired myogenic and neurogenic responses of the vascular smooth muscle due to chronic denervation also lead to an inappropriate local blood flow and metabolic responses to pressure load and unload. This phenomenon may be exacerbated in individuals with endothelial dysfunction (for instance, caused by smoking) and in the elderly, for which the loss of elastin and degradation of the collagen matrix put the skin at further risk of deformation of the blood vessels under loading pressure (Phillips, Ainslie, Krassioukov, & Warburton, 2013).

Moreover, 70%–84% of individuals with SCI experience sphincter dysfunction (neurogenic bladder & bowel), which may lead to higher moisture and irritation of the skin, fostering the development of PI (Agrawal & Chauhan, 2012). Nutrition status, comorbidities and body weight should also be assessed following SCI. Obesity and diabetes may reduce the skin ability to dissipate local heat and cutaneous temperature regulation under loading. On the other hand, muscle atrophy associated with SCI may make bony prominences to emerge, leading to increased local pressure and friction/shear in bed. Spasms and joint contractures associated with SCI should also be assessed, as a potential cause of excessive friction and shear and hindrance for proper positioning and repositioning in bed (increased pressure).

Support surfaces: An approach for prevention and treatment of pressure injuries

Biomechanical properties of support surfaces during loading

Support surfaces use three main mechanisms to prevent PI during loading: (1) pressure redistribution; (2) micro-climate, and (3) horizontal stiffness management. Their performance levels on these important features allow differentiating between the variety of available products and help in selecting a proper support surface that matches patient's needs. During loading, the pressure at a specific location will decrease as the contact area increases. Based on this concept, support surfaces aim to redistribute the pressure by using two basic principles (Consortium for Spinal Cord Medicine, 2014; International Review, 2010; McInnes et al., 2015; NPIAP, 2021) (Fig. 2):

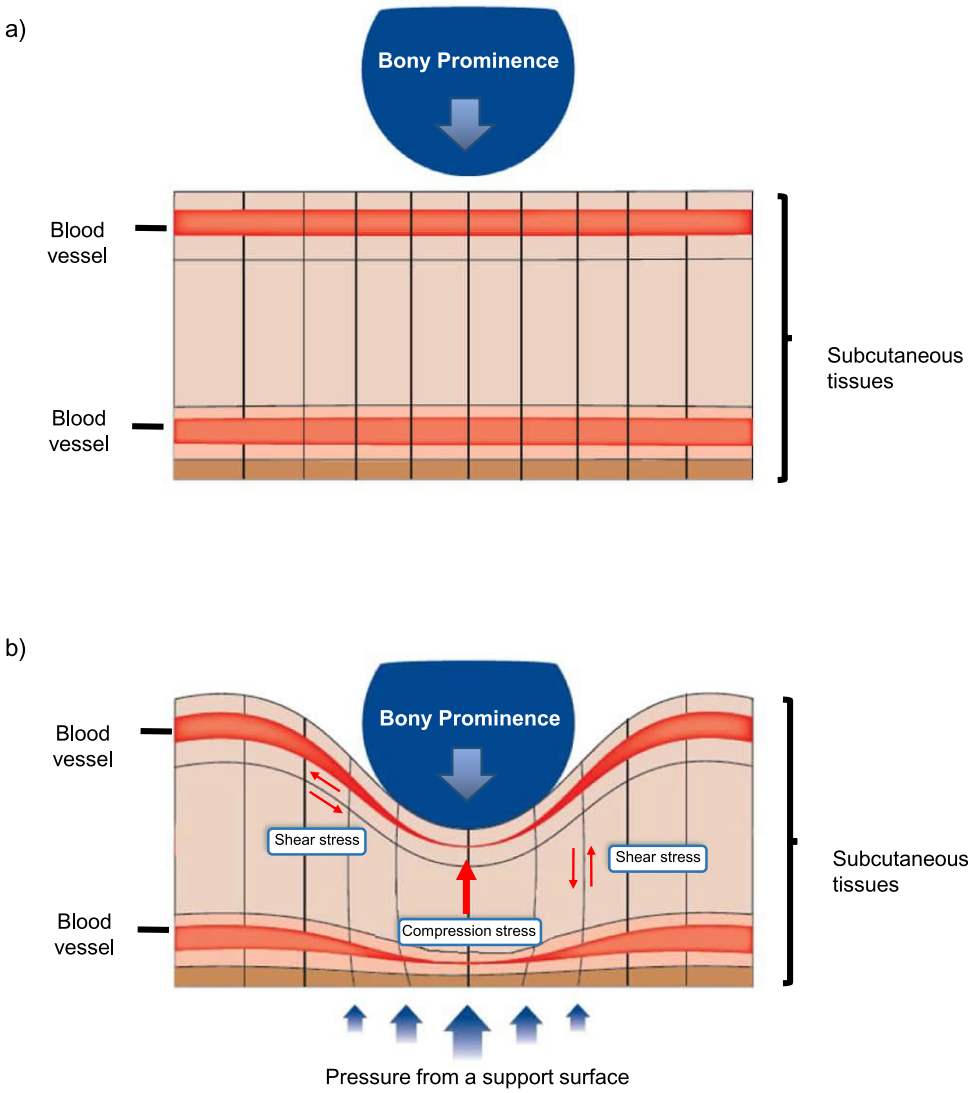


FIG. 1 Compression and shear stresses resulting from an even pressure distribution. (A) Forces applied by the bony prominences, (B) exerted compression and shear stress to subcutaneous tissues that contribute to their damage. *(Adapted from Wounds International (Pressure ulcer prevention: pressure, shear, friction, and micro-climate in context. A consensus document.))*

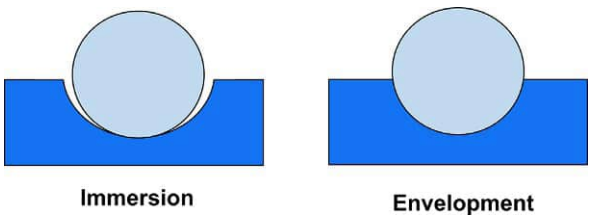


FIG. 2 Illustration of pressure mode distribution. This figure illustrates the ability of a support surface to let the body sink (immersion) or mold its contour (envelopment) to redistribute pressure.

(1) *Envelopment*, referring to the ability of a support surface to conform, so to fit and mold around irregularities in the body. It is generally measured in laboratories by indenter tests providing average pressures on each depth level (mm Hg).
(2) *Immersion*, referring to the penetration (sinking) of the body into a support surface, measured by the depth of penetration (mm).

A higher envelopment and immersion performance of a support surface is associated with greater pressure redistribution, but at the expense of higher instability of the surface making it more difficult for a patient to reposition and/or get out of bed (NPIAP, 2021).

The *micro-climate* is defined as the temperature and humidity at the body interface with the support surface and plays an important role in the development of PI, independently of the average peak pressure (Yoshimura et al., 2015). High skin temperature leads to an increased cutaneous stiffness under loading, higher inflammation, and metabolic activity, further leading to tissue damage (Reger, Adams, Maklebust, & Sahgal, 2001). Moisture can accumulate on the skin increasing the coefficient of friction at the interface while diluting the skin acidity, which was shown to reduce its antibacterial properties (Reger et al., 2001; Tomova-Simitchieva, Lichterfeld-Kottner, Blume-Peytavi, & Kottner, 2018). Micro-climate is measured in laboratories using the local temperature, relative humidity, evaporative capacity and/or dissipating properties of the support surface. However, support surfaces that provide great micro-climate management may also cause patients to feel cold or dehydrate.

The *horizontal stiffness* refers to shear and friction stresses that are generated when the gravity pulls the body down on a support surface, which reacts by pushing back. Horizontal stiffness is measured and reported in Newtons of force. A stiff support surface exerts high resisting forces on the tissues in response to a given amount of displacement, while this force is lower for softer support surfaces. However, the latter can contribute to sliding down in the bed and even to falls (NPIAP, 2021).

Main configurations and classification of support surfaces

Support surfaces are commercially available in three main configurations: (1) mattress, (2) mattress overlay (on top of the patient's mattress), and (3) integrated bed system (combining bed frame and a support surface into a single unit). Individuals with SCI with limited mobility may particularly benefit from specialized bedframes (manual, semi-electric, and electric), which allow adjustments of height and head/foot elevation. These adjustments may promote functional independence, enhance sleep quality, and manage different medical conditions associated with SCI (e.g., autonomic dysreflexia, orthostatic hypotension, and/or spasticity).

Support surfaces can be classified into two main groups (reactive or active) based on the technology used (Hougton et al., 2013; International Review, 2010). Costs related to the different types of support surface technologies are important to consider, as the most expensive does not necessarily signify the "best" mattress for a given patient. Specific properties and performances should be analyzed based on a holistic assessment of the patient's characteristics.

Reactive support surfaces

Reactive support surfaces are powered or non-powered surfaces with the ability to adjust its load distribution properties solely in response to an applied load (Hougton et al., 2013; NPIAP, 2021). Thus, reactive support surfaces do not independently change its load distribution. Consequently, reactive support surfaces provide a constant pressure at the interface, unless the patient actually moves. Different types of reactive support surfaces are available, differing by their structure and material used, providing different properties.

Non-powered reactive support surface

Foam

In its simplest form, a non-powered reactive support surface consists of a single block of foam covered by a plastic or nylon cover. Foam has a flexible, cellular material structure, which may be available in different densities. Foam mattress work reactively to provide pressure redistribution by spreading the load across the whole interface surface area (NPIAP, 2021). However, their capacity to immerse and envelop the body is limited by their stiffness and density (Hougton et al., 2013). Due to its low cost, foam mattresses are widely used in hospitals (Berthe, Bustillo, Mélot, & de Fontaine, 2007). Within this type of support surface, high specification foam may incorporate multiple constructs and/or be compartmentalized into different sections with distinct properties (Hougton et al., 2013; International Review, 2010; NPIAP, 2021). Softer foam mattresses will provide higher level of immersion as compared to stiffer foams, but necessarily need to be thick enough to avoid "bottoming out," referring to the deformation beyond critical immersion whereby the effective pressure redistribution is lost (International Review, 2010; NPIAP, 2021). Foam mattresses can progressively degrade and lose their capability of returning to its original forms or thickness, typically wearing out after 3 years (Brienza et al., 2005; Consortium for Spinal Cord Medicine, 2014). Cullum et al. (2004) suggested that high specification foam mattresses were more effective than

"standard" hospital foam mattresses in moderate to high-risk patients in terms of pressure relief. Bueno de Camargo et al. (2018) suggested that the use of a viscoelastic support surface reduced the incidence of PI (stage 2) in critically ill patients when compared to standard mattress. Moreover, when non-air reactive mattresses are used, the use of contoured postural management components may enhance its pressure redistribution properties (Hosking, 2017).

Gel

Gel mattresses consist of a semi-solid system of solid aggregates, colloidal dispersion or polymers exhibiting elastic properties (NPIAP, 2021). Gel mattresses can range from hard to soft, providing distinctive immersion, envelopment, and horizontal properties. Gel mattresses are generally easy to clean up; however, they may be heavy. Temperature and moisture control may be challenging with the use of non-air non-powered reactive support surfaces, due to their lack of aeration and poor heat conduction properties (Brienza et al., 2005). Tomova-Simitcheva et al. showed in 2017 that a reactive gel support surface (featuring a breathable cover and an open gel column) may exhibit similar effectiveness with an alternating pressure mattress (with low-air-loss function) on the transepidermal water loss, temperature, and erythema at the sacral and heel skin, both being superior as compared to a basic foam mattress.

Air-filled

The use of reactive air-filled mattress overlay is an alternative in patients at some risk of PI development. Indeed, Conner and Clack (1993) suggested that air mattress overlay plus three-inch foam increases its area of contact and reduced tissue shear when compared with foam overlays, using in vivo measurements derived from pelvic CT scans. Matsuo et al. (2011) demonstrated that in air support surfaces, the internal pressure adjustment (inflation level) significantly influenced pressure redistribution properties, with a lower internal pressure resulting in greater immersion and contact area, resulting in a decreased maximum interface pressure. Similarly, Higer and James (2016) demonstrated that the reactive air support surface was the most effective pressure-redistributing material for pediatric occipital pressure, displaying the lowest interface pressure and the most homogeneous pressure distribution compared to foam, fluidized and gel surfaces.

Powered reactive support surface

In a more complex form, reactive support surfaces use a powered flow of air to assist in the management of temperature and humidity of the skin (NPIAP, 2021). Low-air-loss support surfaces are composed of multiple air chambers throughout. However, in contrast to alternating air pressure support (discussed below), low-air-loss surface displays tiny holes at its top surface continually blowing air out, while maintaining a specific inflation level in the chambers (Fig. 3) (Brienza et al., 2005; Hougton et al., 2013; International Review, 2010; McInnes et al., 2015). The pressure at which the support surface must be inflated, and the rate for blowing out the air, is based on the individual's height and weight (Brienza et al.,

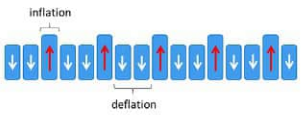
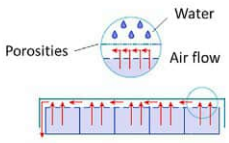
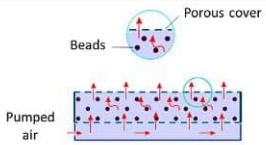
High / Active Technologies	Mechanism of action	Effect on properties during loading
Alternating air pressure		- Pressure redistribution via powered cyclic changes in loading and unloading characterized by specific parameters - Immersion and envelopment
Low-air-loss		- Immersion and envelopment - Microclimate management
Air fluidized		- Immersion and envelopment - Microclimate management

FIG. 3 Description of active support surface technologies. This figure aims to summarize the active technologies and illustrates their mechanisms of action. *PR*, pressure redistribution; *SR*, shear reduction; *MC*, microclimate management; *T*, impact on self-transferring ability. *(Adapted from Wounds International (Pressure ulcer prevention: pressure, shear, friction and microclimate in context. A consensus document.))*

2005), and is adjusted to provide the desired level of immersion/envelopment. Temperature and moisture control at the skin surface is also improved, as compared to alternating air pressure system and non-powered support surfaces, most likely due to the evaporation effect caused by air circulating from the permeable cover (International Review, 2010; Reger et al., 2001). However, the optimal skin temperature and moisture level for PI prevention is still unknown, and this technology represents higher costs compared to non-powered systems (Reger et al., 2001).

A comparison cohort study by Black et al. in 2012 has suggested that critically ill patients placed on low-air-loss mattresses with micro-climate management in surgical intensive care unit had lower PI (stage 2) incidence than those placed on an integrated power air pressure redistribution beds (air alternating pressure) (Black, Berke, & Urzendowski, 2012). Lippodolt et al. in 2014 showed that low-air-loss technology significantly reduced the interface pressure at 0, 10, 30, and 45 degrees of backrest elevation in comparison with foam and air suspension support surfaces (air fluidized). It was thus suggested that low-air-loss technology could be an additional useful tool to help prevent skin breakdown at the sacrum as a compromise between seemingly incompatible demands of skin integrity and prevention of ventilator-associated pneumonia (Lippoldt, Pernicka, & Staudiner, 2014). However, this study did not assess horizontal stiffness.

Reger et al. also suggested in 2001 that measurements of support interface climate change might allow for selective grouping of low-air-loss surfaces according to their rate of moisture evaporation and resulting temperature reduction. Combined, these characteristics can effectively describe the performance of any low-air-loss support system and may be used to define standards of performance (Reger et al., 2001). A meta-analysis completed by Shi, Dumville, and Cullum (2018) suggested that hybrid low-air-loss air surfaces may have the highest probability of being the most effective intervention for PI prevention. However, the authors remain uncertain as to the true ranking of the different support surfaces because the certainty of evidence was very low (Shi et al., 2018). It was also suggested that the performance of low-air-loss support surfaces may also be influenced by their age and should thus be assessed in the quality assessment of these technologies (Black et al., 2012).

Active support surfaces

In opposition to reactive support surfaces, active support surfaces are powered support surface that have the ability to periodically change the load distribution regardless of the applied load (individual's position or movement) (McInnes et al., 2015). This technology mostly rely on its ability to provide pressure redistribution via cyclic changes in loading and unloading as characterized by frequency, duration, amplitude and rate of change parameters (Cullum et al., 2004; McInnes et al., 2015; NPIAP, 2021). Because of this feature, powered support surfaces are generally beneficial to individuals with low mobility. Furthermore, the inflation level can be adjusted to provide the desired level of immersion/envelopment and horizontal stiffness with the body. As illustrated in Fig. 3, active support surfaces can be stratified into two groups according to their mechanism of action (alternating air pressure and air fluidized).

Alternating air pressure

Alternating air pressure support surfaces are composed of multiple air chambers throughout, in which the air is pumped alternately to inflate and deflate the chambers (Fig. 3) (Brienza et al., 2005; Consortium for Spinal Cord Medicine, 2014; Hougton et al., 2013; McInnes et al., 2015). As a result, the pressure is periodically relieved and redistributed by changing the location of the contact areas between the individual's body and the support surface (Brienza et al., 2005; Hougton et al., 2013; McInnes et al., 2015). Cyclic redistribution of loading helps to restore blood flow and re-establish blood supply to the soft tissues (Vanderwee, Grypdonck, & Defloor, 2007). However, it was recently hypothesized that unloading may be associated with reperfusion-induced inflammatory process (Xiao, Wu, & Mak, 2014). Accordingly, the main limitation of air alternating support surfaces remain the lack of evidence pertaining to the ideal frequency, duration and amplitude of cell's inflation/deflation for preventing and treating (Cullum et al., 2004; McInnes et al., 2015). However, a study by Rithalia and Gonsalkorale (1998) showed that the maximum contact pressure on the sacrum were significantly lower on devices for which inflation pressure was adjusted according to the body mass of the subject.

Hickerson, Slugocki, Thaker, Dunkan, and Bishop (2004) investigated the pressure-relieving ability of three specialized support surfaces (low-air-loss, air fluidized, pegasus airwave (air alternating pressure)) compared to a standard foam hospital mattress, by measuring the total body tissue interface pressure. The air alternating pressure surface outperformed the other tested support surfaces by decreasing the overall pressure (Hickerson et al., 2004). A meta-analysis completed by Shi et al. in 2018 suggested a moderate certainty evidence that powered active (alternating) air surfaces and powered hybrid air surfaces (offering both reactive and active pressure redistribution modes) probably reduce PI incidence compared with standard hospital surfaces by 58% and 78% on average, respectively.

An interesting study was completed by Jan, Brienza, Boninger, and Brenes (2011), aiming to guide the selection of parameters of commercial alternating pressure support surfaces for the prevention of PI in the SCI population. In this study, sacral skin response (using laser Doppler flowmetry) was compared for different pressure interface in alternating air pressure and continuous (reactive) air systems. Results showed that alternating pressure (at a low-interface pressure at 0 mmHg and high-interface pressure at 60 mmHg with a cycle time of 5 min) enhanced skin perfusion of weight bearing tissues as compared with constant pressure (with an interface pressure of 30 mmHg) in people with SCI.

Air fluidized

Air fluidized is a feature of a support surface that provides pressure redistribution by forcing air through a granular medium (e.g., beads) producing a fluid state (NPIAP, 2021; Reddy, Gill, & Rochon, 2006). This high-technology (also called high-air-loss) may provide the greatest level of immersion and envelopment of any support surfaces (Brienza et al., 2005; International Review, 2010; McInnes et al., 2015). According to Holzapfel (1993), almost two-third of the body is immersed using this type of support surface, which represents a large contact surface distribution (Holzapfel, 1993). In addition to its high-pressure redistribution quality, air fluidized support surfaces also provide an effective micro-climate management, by letting warm air escape from the top surface (Brienza et al., 2005; International Review, 2010). Rothenberg et al. examined in 2014 the heel blood flow between standard hospital foam mattress bed, viscoelastic foam mattress and an air-fluidized bed. Authors reported that only the air-fluidized bed resulted in a maintained blood circulation (Rothenberg et al., 2014). Previous randomized controlled studies have shown the benefit of this system for individuals with stage III and IV PI in comparison with other non-fluidized support surfaces (International Review, 2010). However, it also showed its risk of dehydration and dry skin (also indirectly associated with PI). One systematic review reported significant reductions in PI size (of any stage and any setting) with air-fluidized devices (McInnes, Jammali-Blasi, Bell-Syer, & Leung, 2018). Authors however concluded that there was a limited evidence for the effectiveness of air-fluidized as opposed to "low-tech" devices in the treatment of existing PI. While the body of evidence was qualified as "good" by Cullum, Deeks, Sheldon, Song, and Fletcher (2000), it was deemed as low quality by McInnes (McInnes et al., 2018). Air fluidized technology is also one of the most expensive support surface system.

Emerging technologies

Adjustable rotational beds consist in integrated bed systems featuring computerized lateral rotation (tilting) of the support surface for assisting patients for periodical repositioning in bed. In addition to promoting functional independence, these systems may also facilitate caregiver interventions (e.g., turning and transferring individuals, examining the skin, assisting in bedding equipment changes, and providing physical/respiratory therapies). Different tilting options can be provided, such as rotational beds and lateral rotating beds. On the other hand, these systems are expensive. Moreover, while pressure redistribution in this system mainly relies on the repositioning of the patient, these systems may potentially generate higher shear and friction stresses than conventional technologies. However, this remains to be defined in the clinical and laboratory settings.

Positioning, surface material and bed making

Positioning of the bed and surface materials are important factors to consider as they influence support surfaces performance during loading. A recent study by Boyle et al. (2020) identified, using a computational model of the weight-bearing pelvis that applying a sufficient supporting lateral pressure may counteract the under-body pressure. Although this study was completed in seated individuals, this strategy is yet to be determined in the lying position (support surfaces) (Boyle et al., 2020). Tran et al. in 2016 investigated the impact of the repositioning frequency on shear stress and overall healthcare cost by decreased utilization of medical personnel. The authors concluded that the traditional repositioning frequency of every 2 hours may be equal in effectiveness to a frequency of 4 hours, and it was suggested that the frequency of repositioning be individualized based on the patient's risk factors, needs and support surface utilized (Tran et al., 2016). Current literature doesn't show that any method of positioning is preferred, and therefore, 30-degree tilted side-lying position, the prone position, and the 30-degree semi-Fowler position, are all considered acceptable (Tran et al., 2016).

Current evidence suggests that surface material impacts on micro-climate, temperature, and humidity at the interface. Posada-Moreno et al. (2011) observed that temperatures were lower in all risk areas that had no support surface protector and were greater when the surfaces were in contact with protector material, with increases up to 2.13°C. Recent studies suggest that silk-like fabrics may be effective in reducing shear and subsequent PI when compared with cotton or cotton-

blend fabrics (Tran et al., 2016). Iuchi et al. (2014) showed that friction and bed making method do not significantly reduce maximum interface pressure, although the hammock effect (forces generated by tension along the loaded interface) can be reduced through the use of stretchable bed sheets on the support surface (Iuchi et al., 2014). Another study proposed by Williamson et al. (2013) concluded that putting additional linens or underpads on low-air-loss surfaces may adversely affect skin temperature and moisture, thereby reducing the PI prevention potential of these surfaces.

Global evidence on the effectiveness of support surfaces

Globally, studies assessing support surfaces are heterogeneous in terms of settings, participants' baseline skin status, and follow-up durations. Moreover, over half of the studies have serious or very serious study limitations, reflecting the global uncertainty of evidence pertaining to the efficacy of support surfaces technologies to prevent and treat PI. It was also reported that most studies assessing support surfaces in PI prevention mostly involved participants aged over 55 years old, suggesting that the current evidence may generally apply for the older population (Shi et al., 2018). Overall, with the current state of evidence, it is thus impossible to determine the most effective support surface for either prevention or treatment. Thorough assessment of the patient's characteristics is required for selecting a support surface that will best serve the patient's needs.

Decision-making for selecting proper support surfaces

Proper risk assessment and implementation of prevention strategies for PI are crucial to providing comprehensive care in the SCI population while reducing healthcare costs (Tran et al., 2016). The following section aims to propose a simple algorithm to identify an appropriate support surface for patients with SCI in hospital settings. This section considers recommendations of the S31 NPIAP committee for "using standards to choose wisely" (NPIAP, 2021), suggesting these important steps:

- *Carefully consider the patient population and needs*

  SCI individuals may be highly vulnerable to PI occurrence, according to their level and severity of the injury, which is particularly true in hospitals setting. Accordingly, particular attention should be given to the following characteristics at admission: presence and severity of motor and sensory function, risk of sphincter incontinence, current or past PI, presence of obesity or bony prominence(s), comorbidities, age, smoking status, and nutritional status. The current mobility (transfer and repositioning) and functional status are also crucial to assess. Secondary conditions related to the SCI and medical complications should also be identified, as they may limit proper positioning and/or repositioning of the patient in bed (orthostatic hypotension, dysphagia, mechanical ventilation, spasticity, joint contractures, etc.).

  Individuals with severe (motor-complete) tetraplegia (or high paraplegia) may be at risk of autonomic dysreflexia and poikilothermia (defined as the ability to regulate core body temperature due to the SCI), leading to variability of the body temperature and higher risk of elevated temperature/moisture. The authors thus recommend that the temperature of low-air-loss and air fluidized support surfaces be carefully monitored in individuals with SCI at risk of poikilothermia. Finally, as suggested by Norton et al. (2011), heels will be excluded of the proposed decision table, as the prevention and management of PI at this location may be best managed independently from the support surface.
- *Determine the type of support surface that will be evaluated and request relevant testing data for the chosen surface from manufacturers*

  After determining the patient's profile and needs, selection of the support surface's type can be completed by matching their specific properties (ability of immersion, envelopment, horizontal stiffness, and to manage microclimate) during loading. Table 1 (adapted from Norton et al., 2011) provides a simple decision table to guide the multi-disciplinary team to select a support surface's type based on relevant characteristics of the SCI population in a hospital context (for prevention or treatment of PI). One can also refer to the manufacturer's data and current literature to compile support surface's performance characteristics on pressure redistribution and micro-climate properties to provide an overall ranking for the most appropriate support surface type, considering costs and hospital resources. Finally, collaborate with the hospital's administration regarding procurement of recommended support surface, keeping in mind that PIs are a common and resource-intensive challenge for hospitals worldwide and prevention strategies are significantly less costly than treatment regimen.

TABLE 1 Decision table for selecting an appropriate support surface type in the SCI population based on the patient's mobility level in bed (vertically) and important risk factors of PI development during hospitalization (horizontally).

		PI risk assessment (sphincter incontinence, level and severity of sensory and motor dysfunction, etc.)			
		Prevention		Treatment	
		No other risk factors No PI	Other risk factors + No PI	PI +	Severe/refractory/ multiple PI or cannot be positioned off
Ability to change position in bed	Total assist	Non-powered reactive or active (APA)	Active (APA)	Powered reactive or active (APA)	Powered reactive or active (AF to consider)
	Moderate assist	Non-powered reactive	Reactive or active (APA)	Powered reactive or active (APA)	Powered reactive or active (AF to consider)
	Independent with or without device	Regular hospital mattress[a]	Non-powered reactive	Reactive	Powered reactive or active (AF to consider)

[a]*Only category where standard hospital mattress may be acceptable.*
This table serves as a guidance to the multi-disciplinary team with experience in SCI care *to select a support surface's type based on relevant characteristics of the SCI population in a hospital context for prevention or treatment of PI.* PI*, pressure injury;* APA*, air pressure alternating;* AF*, air fluidized; Powered reactive (low-air-loss feature); Non-powered reactive (gel, air-filled).*
Adapted from Norton, L., Coutts, P., & Sibbald, R.G. (2011). Beds: Practical pressure management for surfaces and mattresses. *Advances in Skin & Wound Care, 24* (7), 324–32.

Conclusion

Despite advances in the prevention and management of pressure injury (PI) in the last years, PIs remain a severe and frequent medical complication associated to SCI. Support surface is a critical part of the comprehensive plan for the prevention and treatment of PI. Various types of support surfaces have emerged over the years, this chapter aimed at providing information to guide healthcare professionals in selecting an appropriate support surface based on the patient's characteristics and needs following a spinal cord injury (SCI) in hospital settings.

Applications to other areas of neuroscience

Pressure injuries (PI) are preventable medical complications involving all populations with limited mobility and/or independence. Individuals with spinal cord injury (SCI) represent one of the most vulnerable populations for PI throughout the continuum of care and particularly during hospitalization. Similarly, individuals affected by any neurological condition (e.g., traumatic brain injury, stroke, neurocognitive disorder, etc.) affecting their mobility will have an increased risk of developing PI. The level of mobility, neurological status, comorbidities, history of PI and multiple other factors (such as the presence of humidity due to bladder/bowel dysfunction and nutrition level) are important to consider when assessing patient's risk factors of PI. Selection of an appropriate support surface is one of the cornerstones of the comprehensive plan for the prevention and treatment of PI. In this chapter, we have reviewed the epidemiology and pathogenesis of pressure injury as well as its global impact for the spinal cord injury population, particularly in the hospital context. The effects of support surfaces on skin properties (envelopment, immersion, horizontal stiffness and micro-climate management) during loading were also discussed. The main configuration and classification of support surfaces (types, technologies and features) were described and discussed in a clinical context, based on the current clinical and biomechanical studies. Specific characteristics, limitations, and effectiveness of each support surface are also presented. Strategies in the positioning, repositioning in bed, surface material and bed making were also discussed as they may influence the support surface's properties. Along with providing an overview of the main types and features of support surfaces available for the prevention and treatment of PI, this chapter proposes a simple and comprehensive algorithm for the selection an appropriate support surface for the prevention and treatment of PI specific to the SCI population in a clinical context.

Mini-dictionary of terms

The following terms and definitions are provided based on the National Pressure Injury Advisory Panel Support Surface Initiation (S31) "Terms and definitions related to support surfaces" Ver. 01/29/2007, revised 12/27/2018; 11/19/2019. Retrieved at: https://npiap.com/page/S3I.

Active support surface: A powered support surface, with the capability to change its load distribution properties, with or without applied load.
Mechanical load: Force distribution acting on a surface.
Pressure redistribution: The ability of a support surface to distribute load over the contact areas of the human body.
Reactive support surface: A powered or non-powered support surface with the capability to change its load distribution properties only in response to applied load.
Support surface: A specialized device for pressure redistribution designed for management of tissue loads, microclimate, and/or other therapeutic functions. Support surfaces include but are not limited to mattresses, integrated bed systems, mattress replacements or overlays, or seat cushions and seat cushion overlays.

Key facts of pressure injuries after spinal cord injury

- Individuals with spinal cord injuries represent a population highly vulnerable for pressure injuries, which represent one of the leading causes for unplanned re-hospitalizations (Chen, Devivo, & Jackson, 2005).
- Although pressure injuries are evitable, they represent a major public health problem, as their occurrence is associated with severe comorbidities and enormous costs of care (as much as 25% of the total direct costs of care) for the spinal cord injury population.
- There are several choices of surfaces using various technologies, as a crucial part of the strategy for prevention and treatment of pressure injuries following a spinal cord injury.
- The selection of a bed and mattress in individuals at risk of pressure injury development should be based on a multidisciplinary approach, including the patient, considering specific risk factors of pressure injuries.
- Further research is essential to improve pressure redistribution effectiveness and aid in the decision-making process. These achievements may represent important steps for the treatment and prevention of pressure injuries.

Summary points

- Pressure injuries (PI) are of a main concern for individuals with spinal cord injury (SCI). No other preventable event occurs as frequently, occurring at a rate of 2%–40% of all acute care hospitalization in United States and Canada. The recent literature estimates that hospital-acquired PI among SCI patients ranges from 29.7% to 49.2%, which represent enormous costs for healthcare systems.
- The selection of a support surface is a critical component of a comprehensive plan for PI prevention and treatment. There are two main groups of pressure-redistribution support surfaces for the prevention and treatment of PI: (1) reactive and (2) active, which are then stratified based on their mechanism of action and features.
- Overall, with the current state of evidence, it is impossible to determine the most effective support surface for either prevention or treatment. It is thus suggested to assess patient's characteristics in a holistic way before selecting a support surface based on its various properties during loading.
- Selection of support surface may be managed by a multi-disciplinary team, ideally including the patient (if possible), and must take into account many factors, such as the level of mobility, medical status previous or current pressure injuries, and other specific risk factors of pressure injuries.
- Despites the efforts devoted to the development of emerging technologies, further research is warranted in both clinical and fundamental context, to better determine and improve the efficiency of pressure redistributing technologies for prevention and treatment of pressure injuries.

References

Agrawal, K., & Chauhan, N. (2012). Pressure ulcers: Back to the basics. *Indian Journal of Plastic Surgery*, *45*(2), 244–254.
Berthe, J. V., Bustillo, A., Mélot, C., & de Fontaine, S. (2007). *Acta Chirurgica Belgica*, *107*(2), 155–161.
Bhattacharya, S., & Mishra, R. K. (2015). Pressure ulcers: Current understanding and newer modalities of treatment. *Indian Journal of Plastic Surgery*, *48*(1), 4–16.

Black, J., Berke, C., & Urzendowski, G. (2012). Pressure ulcer incidence and progression in critically ill subjects: Influence of low air loss mattress versus powered air pressure redistribution mattress. *Journal of Wound, Ostomy, and Continence Nursing*, *39*(3), 267–273.

Boyle, C. J., Carpanen, D., Pandelani, T., Higgins, C. A., Masen, M. A., & Masouros, S. D. (2020). Lateral pressure equalisation as a principle for designing support surfaces to prevent deep tissue pressure ulcers. *PLoS One*, *15*(1), e0227064.

Brienza, D. M., Geyer, M. J., & Jan, Y.-K. (2005). A comparison of changes in rhythms of sacral skin blood flow in response to heating and indentation. *Archives of Physical Medicine and Rehabilitation*, *86*(6), 1245–1251.

Bueno de Camargo, W. H., Pereira, R. D., Tanita, M. T., Heko, L., Grion, I. C., Festi, J., et al. (2018). The effect of support surfaces on the incidence of pressure injuries in critically ill patients: A randomized controlled trial. *Critical Care Research and Practice*, *2018*, 3712067.

Chan, B. C., Nanwa, N., Mittmann, N., Bryant, D., Coyte, P. C., & Hougton, P. E. (2013). The average cost of pressure ulcer management in a community dwelling spinal cord injury population. *International Wound Journal*, *10*(4), 431–440.

Chen, Y., Devivo, M., & Jackson, A. B. (2005). Pressure ulcer prevalence in people with spinal cord injury: Age-period-duration effects. *Archives of Physical Medicine Rehabilitation*, *86*(6), 1208–1213.

Conner, L. M., & Clack, J. W. (1993). In vivo (CT scan) comparison of vertical shear in human tissue caused by various support surfaces. *Decubitus*, *6*(2), 20–23. 26-8.

Consortium for Spinal Cord Medicine. (2014). *Presssure ulcer prevention and treatment following spinal cord injury: A clinical practice guideline for health-care professionals (second edition)*. Paralyzed Veterans of America. (March 1st 2021). Retrieved at: https://pva.org/research-resources/publications/clinical-practice-guidelines/.

Cowan, L. J., Ahn, H., Flores, M., Yarrow, J., Barks, L. S., Garvan, C., et al. (2019). Pressure ulcer prevalence by level of paralysis in patients with spinal cord injury in lon-term care. *Advances in Skin & Wound Care*, *32*(3), 122–130.

Cullum, N., Deeks, J., Sheldon, T. A., Song, F., & Fletcher, A. W. (2000). Beds, mattresses and cushions for pressure sore prevention and treatment. *Cochrane Database of Systematic Reviews*, (2), CD001735.

Cullum, N., McInnes, E., Bell-Syer, S. E. M., & Legood, R. (2004). Support surfaces for pressure ulcer prevention. *Cochrane Database of Systematic Reviews*, *3*, CD001735.

Fuhrer, M. J., Garber, S. L., Rintala, D. H., Clearman, R., & Hart, K. A. (1993). Pressure ulcer in community-resident persons with spinal cord injury: Prevalence and risk factors. *Archives of Physical Medicine and Rehabilitation*, *74*(11), 1172–1177.

Grey, J. E., & Harding, K. G. (2006). Pressure ulcers. *BMJ*, *332*(7539), 472–475.

Hickerson, W. L., Slugocki, M., Thaker, R. L., Dunkan, R., & Bishop, J. F. (2004). Comparison of total body tissue interface pressure of specialized pressure-relieving mattresses. *Journal of Long-Term Effects of Medical Implants*, *14*(2), 81–94.

Higer, S., & James, T. (2016). Interface pressure mapping pilot study to select surfaces that effectively redistribute pediatric occipital pressure. *Journal of Tissue Viability*, *25*(1), 41–49.

Holzapfel, S. K. (1993). Support surfaces and their use in the prevention and treatment of pressure ulcers. *Journal of ET Nursing*, *20*(6), 251–260.

Hosking, J. (2017). A pilot study comparing custom contoured and planal support surfaces for pressure ulcer risk over the heels for night time postural management using interface pressure mapping and disconfort scores. *Journal of Tissue Viability*, *26*(3), 189–195.

Hougton, P., Campbell, K., & CPG Panel. (2013). *Canadian best practice guidelines for the prevention and management of pressure ulcers in spinal cord injury. A resource handbook for Clinicians*. (March 1st 2021), Retrieved at: http://www.onf.org.

International Review. (2010). *Pressure ulcer prevention: Pressure, shear, friction and microclimate in control*. England: Wounds International Ltd. (march 1st 2021), Retrieved at: https://www.woundsinternational.com/resources/details/international-review-pressure-ulcer-prevention-pressure-shear-friction-and-microclimate-context.

Iuchi, T., Nakajima, Y., Fukuda, M., Matsuo, J., Okamoto, H., Sanada, H., et al. (2014). Using an extreme bony prominence anatomical model to examine the influence of bed sheet materials and bed making methods on the distribution of pressure on the support surface. *Journal of Tissue Viability*, *23*, 60–68.

Jan, Y.-K., Brienza, D. M., Boninger, M. L., & Brenes, G. (2011). Comparison of skin perfusion response with alternating and constant pressures in people with spinal cord injury. *Spinal Cord*, *49*(1), 136–141.

Kruger, E. A., Pires, M., Ngann, Y., Sterling, M., & Rubayi, S. (2013). Comprehensive management of pressure ulcers in spinal cord injury: Current concepts and future trends. *The Journal of Spinal Cord Medicine*, *36*(6), 572–585.

Kuffler, D. P. (2015). Improving the ability to eliminate wounds and pressure ulcers. *Wound Repair and Regeneration*, *23*(3), 312–317.

Lippoldt, J., Pernicka, E., & Staudiner, T. (2014). Interface pressure at different degrees of backrest elevation with various types of pressure-redistribution surfaces. *American Journal of Critical Care*, *23*(2), 119–126.

Matsuo, J., Sugama, J., Sanada, H., Okuwa, M., Nakatani, T., Konya, C., et al. (2011). Development and validity of a new model for assessing pressure redistribution properties of support surfaces. *Journal of Tissue Viability*, *20*(2), 55–66.

McInnes, E., Jammali-Blasi, A., Bell-Syer, S. E. M., Dumville, J. C., Middleton, V., & Cullum, N. (2015). Support surfaces for pressure ulcer prevention. *Cochrane Database of Systematic Reviews*, *9*, CD001735.

McInnes, E., Jammali-Blasi, A., Bell-Syer, S. E. M., & Leung, V. (2018). Support surfaces for treating pressure ulcers. *Cochrane Database of Systematic Reviews*, *10*(10), CD009490.

National Pressure Injury Advisory Panel (NPIAP). (2021). (March 1st 2021). Retrieved at: https://npiap.com/.

National Pressure Injury Advisory Panel (NPIAP) Support Surface Standards Initiative (S31). (2007). *Terms and definitions related to support surfaces*. NPIAP. (March 1st 2020). Retrieved at: https://npiap.com/page/S3I.

Norton, L., Coutts, P., & Sibbald, R. G. (2011). Beds: Practical pressure management for surfaces and mattresses. *Advances in Skin & Wound Care*, *24*(7), 324–332.

Phillips, A. A., Ainslie, P. N., Krassioukov, A. V., & Warburton, D. E. R. (2013). Regulation of cerebral blood flow after spinal cord injury. *Journal of Neurotrauma*, *30*(18), 1551–1563.

Posada-Moreno, P., Losa Igesias, M. E., Becerro de Bengoa Vallejo, R., Soriano, I. O., Zaragoza-Garcia, I., & Martinez-Rincon, C. (2011). Influence of different bed support surface covers on skin temperature. *Contemporary Nurse*, *39*(2), 206–220.

Reddy, M., Gill, S. S., & Rochon, P. A. (2006). Preventing pressure ulcers: A systematic review. *JAMA*, *293*(8), 974–984.

Reger, S. I., Adams, T. C., Maklebust, J. A., & Sahgal, V. (2001). Validation test for climate control on air-loss supports. *Archives of Physical Medicine and Rehabilitation*, *82*(5), 597–603.

Rithalia, S. V., & Gonsalkorale, M. (1998). Assessment of alternating air mattress using a time-based interface pressure threshold technique. *Journal of Rehabilitation Research and Development*, *35*(2), 225–230.

Rothenberg, J., Krauss, S., Held, M., Bender, D., Schaller, H.-E., Rahmanian-Schwarz, A., et al. (2014). A quantitative analysis of microcirculation in sore-prone pressure areas on conventional and pressure relief hospital mattresses using laser Doppler flowmetry and tissus spectropotometry. *Journal of Tissue Viability*, *23*(4), 129–136.

Shi, C., Dumville, J. C., & Cullum, N. (2018). Support surfaces for pressure ulcer prevention: A network meta-analysis. *PLoS One*, *13*(2), e0192707.

Talley Group. (2021). *The role of support surfaces in pressure ulcer prevention and treatment*. Retrieved at: https://www.talleygroup.com.

Tomova-Simitchieva, T., Lichterfeld-Kottner, A., Blume-Peytavi, U., & Kottner, J. (2018). Comparing the effects of 3 different pressure ulcer prevention support surfaces on the structure and function of heel and sacral skin: An exploratory cross-over trial. *International Wound Journal*, *15*(3), 429–437.

Tran, J. P., McLaughlin, J. M., Li, R. T., & Philips, L. G. (2016). Prevention of pressure ulcers in the acute care setting: New innovations and technologies. *Plastic and Reconstructive Surgery*, *138*, 232S. Journal of Biomechanics, 47(7), 1658–64.

Vanderwee, K., Grypdonck, M., & Defloor, T. (2007). Alternating pressure air mattresses as prevention for pressure ulcers: A literature review. *International Journal of Nursing Studies*, *45*(5), 784–801.

Williamson, R., Lachenbruch, C., & VanGilder. (2013). A laboratory study examining the impact of linen use on low-air-loss support surface heat and water vaporisation transmission rates. *Ostomy/Wound Management*, *59*(8), 32–41.

Xiao, D. Z. T., Wu, S. Y. Q., & Mak, A. F. T. (2014). *Accumulation of loading damage and unloading reperfusion injury—Modeling of the propagation of deep tissue ulcers*.

Yoshimura, M., Nakagami, G., Lizaka, S., Yoshida, M., Uehata, Y., Kohna, M., et al. (2015). Microclimate is an independent risk factor for the development of intraoperatively acquired pressure ulcers in the park-bench position: A prospective observational study. *Wound Repair and Regeneration*, *23*(6), 939–947.

Chapter 23

Nerve and tendon transfers in tetraplegia: A new narrative

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List of abbreviations

SCI	spinal cord injury
ICSHT	international classification of surgery for the hand in tetraplegia
PIN	posterior interosseous nerve
AIN	anterior interosseous nerve
ECRL	extensor carpi radialis longus
ECRB	extensor carpi radialis brevis
BR	brachioradialis
FDS	flexor digitorum superficialis
FDP	flexor digitorum profundus
FLP	flexor pollicis longus
EPL	extensor pollicis longus
ECD	extensor communis digitorum
PT	pronator teres
CMC	carpometacarpal
IP	interphalangeal
EPI	extensor proprius indicis
EDM	extensor digitorum minimi
FCU	flexor carpi ulnaris
FP	flexor pollicis
MP	metacarpophalangeal

Introduction

The most common causes of spinal cord injury (SCI) are road accidents and falls from a height, with a prevalence for male patients between 16 and 30 years old (Titolo et al., 2019) and an incidence between 10 and 80 new cases per millions of people annually worldwide (Kumar, Osman, & Chowdhury, 2017).

More than 50% of all spinal cord injuries involve cervical spine leading tetraplegia as main clinical feature, with loss of effective upper-limb function.

The lack of hand function is the sequela which mostly affected the quality of life in patients with tetraplegia and always requires support in their daily-life activities and mobility from other people (Anderson, 2004; Bednar & Woodside, 2018; Waters, Sie, Gellman, & Tognella, 1996). Furthermore, it is reported as more desired than bowel, bladder and sexual function, standing and pain control (Anderson, 2004; Brown, 2011). In this scenario, tendon transposition is a reliable surgical technique able to restore active movement and strength of a damaged anatomical segment; however, the shortage of functional muscles above the segment lesion available for transfer is the main problem treating cervical SCI (Titolo et al.,

Diagnosis and Treatment of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822498-4.00023-3

2019). Similarly, nerve transfer required the adjustment of a healthy donor nerve to a denervated anatomical district to restore function nerve-target, but this means to sacrifice a potential useful nervous structure (Limthongthang, Bachoura, Songcharoen, & Osterman, 2013).

In our review, we are going to illustrate the current available techniques of tendon and nervous transfer in order to restore hand and forearm function combining nerve and tendon transfer in patients with tetraplegia.

Classifications

The most useful and accepted classification for upper-limb lesion in tetraplegia is the:

The Classification for Surgery of the Hand in Tetraplegia (ICSHT), where, the most common patterns of injuries are classified following the number of functional muscles existing below the elbow.

A functional muscle is described as muscle graded 4 or more according to the Muscle Grading System (James, 2007) (Table 1), and the ICSHT principles are reported in the literature as the "gold standard" to choose the most appropriate reconstructive technique mainly based on tendon transfer and tenodesis procedure (Table 2).

It's important to select the most appropriate donor muscle in order to preserve function of anatomical region without creating another functional deficit after tendon transfer which can be used alone or in combination with tenodesis and arthrodesis showing interesting and reproducible results (Bednar & Woodside, 2018).

TABLE 1 International Classification for Surgery of the Hand in Tetraplegia (ICSHT).

Motor GROUP	Characteristics	Function
0	No muscle below elbow suitable for transfer	
1	BR	Flexion and supination of the elbow
2	ECRL	Extension of the wrist
3	ECRB	Extension of the wrist
4	PT	Pronation of the wrist
5	FCR	Flexion of the wrist
6	Finger extensors	Extrinsic extension of the fingers
7	Thumb extensor	Extrinsic extension of the thumb
8	Partial digital flexors	Extrinsic flexion of the fingers
9	Lacks only intrinsics	
10	Exceptions	

BR brachioradialis, ECRL extensor carpi radialis longus, ECRB extensor carpi radialis brevis, PT pronator teres, FCR flexor carpi radialis.

TABLE 2 Muscle Grading System of the British Medical Research Council, muscle function ranged from 0 (no contraction) to 5 (normal power).

GROUPS	Description
0	No contraction
1	Flicker or trace of contraction
2	Active movement with gravity eliminated
3	Active movement against gravity
4	Active movement against gravity and resistance
5	Normal power

According to function importance, a priority order to choose the correct sequence of donor muscles (Limthongthang et al., 2013; Zlotolow, 2011) is well established:

(1) wrist extension recovery,
(2) pinch recovery,
(3) grasp recovery,
(4) finger and thumb extension recovery,
(5) intrinsic muscles function recovery.

When transfer options are ended, the remaining functions are reached using tenodesis and arthrodesis (Titolo et al., 2019).

In the setting of arm dysfunction, nerve transfer is also a successful surgical procedure approaching proximal brachial plexus injury with avulsion of nerve roots or more peripheral nerve injuries. Nerve transfers are commonly used where anatomic repair of original motor nerve is not possible as well as where it's possible to rapidly restore function by rerouting expendable donor nerves (de Mendonça Cardoso, Gepp, Lima, & Gushiken, 2020). Recently, some Authors introduced nerve transfers in tetraplegia, reporting interesting outcomes (Mooney, Hewitt, & Hahn, 2020; Titolo et al., 2019). According to our previous work (Titolo et al., 2019), the current authors propose a new surgical strategy based on classical tendon transfer surgery combined with nerve transfer techniques (Table 3). The use of both surgical approaches allows avoiding a frequent concern about the use of nerve transfer in reconstructive surgery: the risk of using sources of "predictable" results for "unpredictable" results.

In this proposed technique, the choice of the most appropriate nerve donor site is crucial in order to avoid the subtraction of useful muscles; in this way, it is always possible to perform a second stage surgery according to classical tenodesis or tendon transfer surgeries.

Indications and timing

The standard patient candidate to combined nerves and tendons transfer is a patient with cervical spine injury, with incomplete or partial paralysis of the upper limb and a stabilized upper extremity motor function.

Their general condition should be considered stable, with good pain control, no spasticity and infection free. The passive range of motion could be almost complete and they should be very motivated for the long postoperative rehabilitation (Fox et al., 2019).

Patients should be correctly informed before surgery, especially about the difference in terms of recovery time: nerve transfer needs a long time before they can show their results, and often they need a second stage procedure to achieve the set objectives. Great motivation and realistic objectives are strongly requested to obtain good improvement in hand function (Gohritz et al., 2007).

Conversely, contraindications for nerve and tendon transfer surgery which could lead to poor results, are (Lee & Wolfe, 2012) spasticity contractures, chronic pain problems, psychological instability with unrealistic expectations and insufficient motivation.

However, there is no consensus about timing of nerve transfers in tetraplegia. Unfortunately, within the year from injury, all possible spontaneous recovery has already occurred; for this reason, it is recommended to perform tendon transfer after 1 year from SCI. Nevertheless, the neurological recovery usually occurs in the first 6 months from trauma (Lee & Wolfe, 2012).

It is usually accepted that terminal muscular atrophy is established after 1 year of denervation, with no possibility of function restoration (Fu & Gordon, 1995a, 1995b). According to these premises, Lamb and Chan observed that if a muscle is completely paralyzed during the initial assessment and it will remain paralyzed 1 month later, it will be rare to observe any significant improvement, even 1 year later (Lamb & Chan, 1983). On the contrary, Bertelli et al. reported functional muscle reinnervation after distal nerve transfers performed 18 months after SCI (Bertelli & Ghizoni, 2013).

Furthermore, Fox et al. described two type of lesions with different indications about the appropriate surgical time for intervention (Fox, 2016) (Fig. 1).

First, time-independent lesions: clear-cut SCI with a little zone of cell damage located at the anterior horn of the spinal cord. Peripheral nerve transfer can restore segment movement by reconnecting functional motor unit to brain. This transfer switches the motor control from an expendable donor to a muscle group distal to lesion level, bypassing the site of lesion. It can be done at any time after trauma.

Second, time-dependent lesions: injury site is more extensive; roots can be involved as a peripheral nerve lesion. To restore the voluntary control or to reinnervate muscles that would become atrophic nerve transfer should be used.

TABLE 3 Combining Nerve and Tendon Strategy in tetraplegia.

Group 0		
Primary procedure	**Positive outcome?**	**Secondary procedure**
• Teres minor to triceps nerve transfer • Brachialis to ECRL nerve transfer	NO	Posterior deltoid to triceps tendon transfer
	YES	Flexor pollicis longus tenodesis + Moberg key pinch procedure
Group 1 (BR → M 4)		
Primary procedure	**Positive outcome?**	**Secondary procedure**
• Teres minor to triceps nerve transfer	NO	Posterior deltoid to triceps tendon transfer
• Brachialis to AIN/FDS nerve transfer	YES	Extensor digitorum communis tenodesis + Extensor pollicis longus tenodesis
	NO	Flexor pollicis longus tenodesis + Moberg key pinch procedure
• BR to ECRB tendon transfer		
Group 2 (ERCL → M 4)		
Primary procedure	**Positive outcome?**	**Secondary procedure**
• Teres minor to triceps nerve transfer	NO	Posterior deltoid to triceps tendon transfer
• Supinator to PIN nerve transfer	NO	Extensor digitorum communis tenodesis + Extensor pollicis longus tenodesis
• Brachialis to AIN/FDS nerve transfer	YES	BR to opposition
	NO	BR to FPL tendon transfer
Group 3 (ECRB → M 4)		
Primary procedure	**Positive outcome?**	**Secondary procedure**
• Teres minor to triceps nerve transfer	NO	Posterior deltoid to triceps tendon transfer
• Supinator to PIN nerve transfer	NO	Extensor digitorum communis tenodesis + Extensor pollicis longus tenodesis
• Brachialis to AIN/FDS nerve transfer	YES	BR to opposition
	NO	BR to FPL tendon transfer + Tenodesis FDP 2° to FDP 3°-4°-5°
• ECRL to FDP (3°-4°-5° finger) tendon transfer		
Group 4 (PT → M 4)		
Primary procedure	**Positive outcome?**	**Secondary procedure**
• Supinator to PIN nerve transfer	NO	Extensor digitorum communis tenodesis + Extensor pollicis longus tenodesis
• Brachialis to AIN/FDS nerve transfer	YES	BR to opposition
	NO	BR to FPL tendon transfer + Tenodesis FDP 2° to FDP 3°-4°-5°
• ECRL to FDP (3°-4°-5° finger) tendon transfer		

TABLE 3 Combining Nerve and Tendon Strategy in tetraplegia—cont'd

Group 0		
Primary procedure	**Positive outcome?**	**Secondary procedure**
Group 5 (FRC → M 4)		
Primary procedure	**Positive outcome?**	**Secondary procedure**
• Supinator to PIN nerve transfer	NO	Extensor digitorum communis tenodesis + Extensor pollicis longus tenodesis
• Brachialis to AIN/FDS nerve transfer	YES	BR to opposition
	NO	BR to FPL tendon transfer + Tenodesis FDP 2° to FDP 3°-4°-5°
• ECRL to FDP (3°-4°-5° finger) tendon transfer		
Group 6 (EDC → M 4)		
Primary procedure	**Positive outcome?**	**Secondary procedure**
• Brachialis to AIN/FDS nerve transfer	YES	BR to opposition
	NO	BR to FPL tendon transfer + Tenodesis FDP 2° to FDP 3°-4°-5°
• ECRL to FDP (3°-4°-5° finger) tendon transfer		
• EPL tenodesis		
Group 7 (EPL → M 4)		
Primary procedure	**Positive outcome?**	**Secondary procedure**
• Brachialis to AIN/FDS nerve transfer	YES	EDM to APB or EIP to APB
	NO	BR to FPL tendon transfer + Tenodesis FDP 2° to FDP 3°-4°-5° + EDM to APB or EIP to APB
• ECRL to FDP (3°-4°-5° finger) tendon transfer		
Group 8 (partial finger flexion)		
Primary procedure	**Positive outcome?**	**Secondary procedure**
• ECRB to AIN nerve transfer	YES	EPI/EDM to opposition
	NO	BR to FPL tendon transfer + Tenodesis FDP 2° to FDP 3°-4°-5° + EPI/EDM to opposition
Group 9 (intrinsic deficit)		
Primary procedure	**Positive outcomes**	**Secondary procedure**
• Intrinsic reconstruction (Zancolli lasso/ house intrinsic procedure) • Opponensplasty	YES	None
	NO	

A new proposal of surgical treatment based on ICSHT group. In case of failure of the proposed treatment, a salvage procedure (actual treatment) is always possible.

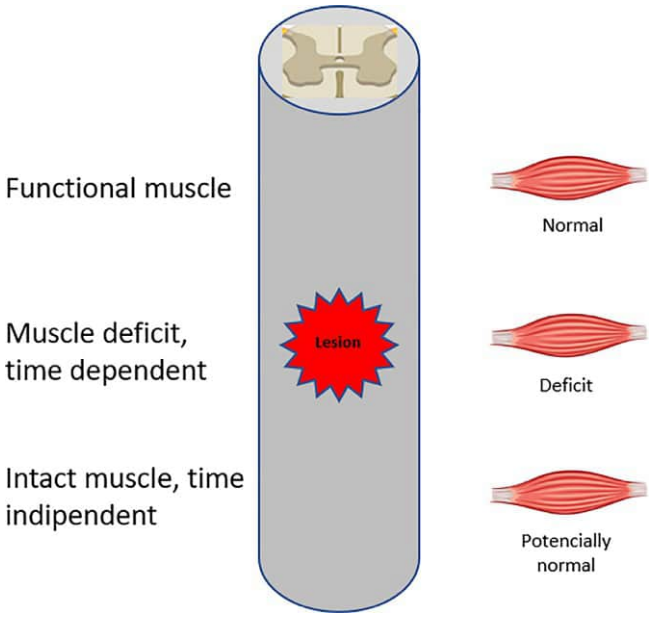

FIG. 1 Time-dependent and time-independent injury based on the level of spinal cord lesion.

Denervated muscles might benefit from early surgery before the onset of muscular atrophy, while paralyzed muscles leave more time for surgery (Cain, Gohritz, Fridén, & van Zyl, 2015; Fox et al., 2018).

Taking into account all these factors, an ideal time for surgery should be performed between 6 and 12 months from trauma, before the onset of irreversible muscle atrophy. Procedures could be anticipated only if muscles denervation is recorded by electromyography (EMG) (Bertelli, Ghizoni, & Tacca, 2011).

In the following paragraphs, we will describe primary and secondary procedures for each group of ICSHT classification (Table 3).

Group 0

Neurological level of injury: C5.

Residual motor function: no muscle of grade 4 below the elbow.

Current reconstructive strategy: In this group, tendon transfer procedures can be performed to restore elbow extension:

- Moberg's procedure based on posterior deltoid to triceps transfer.
- Zancolli's procedure based on biceps to triceps transfer (Arnet, Muzykewicz, Fridén, & Lieber, 2013; Moberg, 1990; Muzykewicz, Arnet, Lieber, & Fridén, 2013). Conventional surgery considers useless any tendons transfers to restore wrist and hand function in this group. The restoration of wrist extension is really important, since tenodesis can allow thumb-to-index key pinch, due to wrist motion. It is also important because it increases patient autonomy, and it improves some daily life activities such as eating, personal care and wheelchair propulsion.

In one larger series, groups 0 and 1 are often together and represent almost 30% of the lesions (Lee & Wolfe, 2012).

Our proposal: It is possible to treat this condition with nerve transfer:

- teres minor to triceps nerve transfer.
- brachialis to extensor carpi radialis longus nerve transfer.

The transfer of teres minor motor branch to triceps long head motor branch allows patients to restore elbow extension without any deficit to the donor site area (Bertelli et al., 2011). Infraspinatus muscle is able to compensate external rotation deficit due to the teres minor nerve transposition. Moreover, teres minor transfer is not typically used in tetraplegia since this transfer doesn't preclude Moberg's procedure as a second surgery in case of failure or to improve a partial recovery.

Bertelli also proposed the use of the posterior division of the axillary nerve to the triceps long and medial head nerve (Bertelli & Ghizoni, 2013); however, if this procedure fails, it is not possible to use posterior deltoid tendon transfer to triceps (Moberg procedure) as salvage procedure.

It is extremely important to fully evaluate shoulder function and to explore any partial deficit of deltoid or teres minor muscle function, since if a deficit is present, it is not possible to use deltoid to restore elbow extension.

Fridén suggested the selective nerve transfer of brachialis to extensor carpi radialis longus (ECRL) to restore wrist extension (Fridén & Gohritz, 2012). Brachialis muscle is primarily innervated by a single branch of the musculocutaneous nerve deriving from the spinal roots C5/6; if biceps is working, this branch can be used as a donor. However, this will not allow a secondary Zancolli's procedure to restore elbow extension.

If brachialis transfer will have positive outcome, the lesion will upgrade from type 0 to type 1 and it is possible to perform flexor pollicis longus tenodesis and Moberg procedure for passive key pinch reconstruction (Wolfe et al., n.d.).

Group 1

Neurological level of injury: C5.

Residual motor function: only brachioradialis (BR) is graded as 4 or more. Elbow flection is still possible since brachioradialis and biceps are functioning.

Current reconstructive strategy: As for group 0, Moberg or Zancolli's procedure can be used to restore elbow extension. The transfer of BR tendon to radial wrist extensors is able to provide enough strength to extend wrist against resistance.

Our proposal: It is possible to transfer:

- Teres minor to triceps nerve.
- Brachialis to anterior interosseous nerve (AIN) and flexor digitorum superficialis (FDS) nerve transfer.
- BR to extensor carpi radialis brevis (ECRB) tendon transfer.
- BR to ECRB tendon transfer is able to restore active wrist extension and passive key pinch reconstruction thanks to flexor pollicis longus (FLP) tenodesis with some tricks (Hentz, House, McDowell, & Moberg, 1992; House, Gwathmey, & Lundsgaard, 1976; Johanson, 2016).

About 10 years ago, Mackinnon described the brachialis to AIN transfer in patients with spinal cord injury (Mackinnon, Yee, & Ray, 2012). In this way, it is possible to improve intrinsic hand muscles function, which are very important to increase grip strength and ability, allowing patients to self-feeding (van Zyl et al., 2014).

If it is possible to partially restore flexor pollicis longus function, this will improve tenodesis effects grasp and provide extra strength and holding power as described by Fox et al. They used brachialis to AIN and FDS nerve transfer for this purpose (Fox et al., 2015a, 2015b, 2018).

If these procedures have good results, with restoration of pinch function, a second stage procedure can be planned to increase grip strength. ECD and EPL can improve hand opening and grasp function. In case of failure, FLP tenodesis can be performed anyway at any time.

Group 2

Neurological level of injury: C6.

Residual motor function: both BR and ECRL graded 4 or more; however, it is difficult to discriminate the differential strength between ECRL (group 2) and ECRB (group 3). It is possible to discriminate between the two groups with different tests, but none of them seems to be really effective:

- Bean's sign (Mohammed, Rothwell, Sinclair, Willems, & Bean, 1992).
- Surgical exploration (Hentz et al., 1992; Moberg, 1990).
- Pronator Teres (PT) as marker of function (Allieu, 2002).

Current reconstructive strategy: surgery aims to obtain an effective key-grip thumb function, and it is usually obtained with House one-stage active key-pinch reconstruction. This technique involves:

- BR to FLP tendon transfer.
- FLP split and arthrodesis of IP joint of the thumb (Henz procedure).
- Carpometacarpal (CMC) fusion.
- Tenodesis of EPL to balance the flection tendency (House, Comadoll, & Dahl, 1992).

Other authors preferred to perform ECRL tendon transfer, only if ECRB has normal strength, while they suggest to avoid this procedure if strength is graded 4 or less (Hentz et al., 1992).

Our proposal: The purpose of nerve transfer in this group is to obtain a functional and effective pinch to allow and active fingers flexion and extension, along with elbow extension:

- Teres minor to triceps nerve transfer.
- Supinator to posterior interosseous nerve (PIN) transfer.
- Brachialis to AIN transfer.
- FDS nerve transfer.

Motor branches for supinator come out from PIN, which is the distal motor division of radial nerve for the forearm. When the lesion is at C6 level, some muscles innervated from radial nerve are still functioning. Supinator is innervated from neuronal cell above the site of lesion and it could be used to partially restore fingers and thumb extension.

Supinator is always functional when there are strong wrist extensors, and a sacrifice of supinator will not affects supination function since it will be allowed by biceps (Bertelli, Tacca, Ghizoni, Kechele, & Santos, 2010).

The objective of nerve transfers is to allow reinnervation of ECD, EPL, abductor pollicis longus and extensor pollicis brevis, in order to preserve trapeziometacarpal joint mobility and avoid tenodesis of abductor pollicis longus. Moreover, the reinnervation of extensor carpi ulnaris allows a secondary transfer to flexor carpi ulnaris to stabilize the wrist during finger extension (Bertelli et al., 2010).

In long time tetraplegia with no response of PIN from electric stimulation, Bertelli also proposed a free gracilis muscle transfer for thumb and finger extension with innervation supplied by supinator (Bertelli & Ghizoni, 2016).

- In case of failure of teres minor motor branch to triceps long head motor branch, it is possible to perform a secondary salvage procedure with posterior deltoid tendon to triceps transfer (Moberg procedure).
- In case of failure of supinator to PIN transfer, it is possible to undertake a salvage procedure with ECD and EPL tenodesis
- If nerve branch of brachialis to AIN transfer reached good functions, the procedure could be completed by BR tendon transfer with a tendinous graft in order to strength thumb opposition (House et al., 1976).

In case of failure, it is always possible to perform the House one-stage active key pinch reconstruction to restore key-pinch.

Group 3

Neurological level of injury: C6.

Residual motor function: both ECRL and ECRB are graded 4 or more.

Current reconstructive strategy: it is based on Zancolli's procedure (Zancolli, 1979), which consists of two steps:

(1) restoration of extension function
(2) restoration of flexion function

For the first stage it is suggested to perform an extensor tenodesis (ECD and EPL), a "lasso procedure" and a thumb IP joint fusion. The Zancolli's "lasso procedure" aimed to prevent MP joint hyperextension and clawing of the fingers during extension; FDS is used to perform MP joint flexion (Wolfe et al., n.d.).

In the second stage, ECRL to FDP and BR to FLP tendon transfer could be performed.

Some author prefer to treat this group of lesions as group 2 in order to prevent the loss of wrist strength using House's one stage active key pinch reconstruction along with a "lasso procedure" if the index finger doesn't flex enough to allow the key pinch (Mohindra, Gogna, Sangwan, Gaba, & Kundu, 2017).

Our proposal: combination of nerve and tendon transfer:

- teres minor to triceps nerve transfer,
- supinator to PIN nerve transfer,
- brachialis to AIN and FDS nerve transfer,
- ECRL tendon to FDP tendon transfer for 3-4-5 finger.

In case of failure of teres minor nerve transfer, the salvage procedure consists in Moberg procedure, while if supinator to PIN nerve transfer fails, to restore thumb and finger extension it is possible to perform ECD and EPL tenodesis.

It also possible to transfer ECRB nerve to AIN, as described by Bertelli, and if it fails, a salvage procedure with brachioradialis and brachialis tendon transfer for finger flexion (Bertelli, 2015).

Recently, experiments on ECRB nerve to AIN transfer, showed recovery of fingers flexion. This could be related to intermuscular nerve connections between AIN and ulnar nerve (Bertelli & Ghizoni, 2017).

We prefer to spare ERCB for secondary tendon transfer, and we prefer to perform brachialis nerve to AIN transfer, since ERCB tendon transfer is a very reliable and suitable technique to obtain finger flexion.

While waiting for extension function recovery (due to supinator to PIN transfer), finger flection imbalance can be temporarily managed with a radial nerve palsy splint, or, in case of nerve transfer failure, with extensor tenodesis as secondary procedure.

According to our experience, if the brachialis nerve to AIN transfer has a good outcome, an independent index finger pinch function could be obtained without the need to primarily transfer ECRL to FDP. Thumb opposition can be improved with BR tendon transfer (House et al., 1976).

If brachialis nerve to AIN transfer fails, it is possible to perform tenodesis of index finger FDP to other fingers (3rd–4th–5th). Moreover, it is possible to perform additional procedures, depending on secondary recovery:

- FLP splint.
- arthrodesis of IP joint.
- CMC fusion.

Group 4

Neurological level of injury: C7.

Residual motor function: PT strength with grade 4 or more.

PT could be considered for tendon transfer, but it is necessary to pay attention to its important role in wheelchair propulsion.

Current reconstructive strategy: House reconstructive strategy of a two-stage reconstruction of grasp and release function.

Extensor phase is performed first and consists in three surgical steps:

– CMC fusion and ELP tenodesis.
– ECD tenodesis to the distal radius or BR to ECD transfer.
– Intrinsic tenodesis using a free tendon graft routed to the lumbrical canals (House et al., 1976).

Flexion phase is performed later and it is divided into 2 different steps:

(1) BR or PT transfer to FLP
(2) ECRL to FDP

It is also possible to improve opposition with BR or PT with FDS graft.

If PT instead of BR is used for FLP tendon transfer, BR could be used to restore adduction—opponens function, using paralyzed FDS, which can be considered an "in situ tendon graft"(Wolfe et al., n.d.).

Our proposal: same as group 3, but in this case, it is not necessary to transfer teres minor to triceps since in this group triceps strength is normal.

In alternative, it is possible to perform PT to FDS nerve transfer (Titolo et al., 2019).

Two branches of the median nerve innervate the PT and the transfer of 1 branch to ECRL in high radial nerve palsy is able to restore almost complete wrist extension (grade 4), preserving at least a grade 4 pronation strength (García-López, Navarro, Martinez, & Rojas, 2014).

It is possible to perform:

– supinator nerve to PIN transfer.
– brachialis nerve to AIN and FDS nerve transfer.
– tendon transfer of ECRL to FDP of the 3rd–4th–5th finger.

Since the lesion is more caudal, BR, ECRL and PT are available for tendon transfer. Usually, ECRB should be preserve in order to stabilize wrist joint (Lee & Wolfe, 2012; Wolfe et al., n.d.).

In radial nerve palsy, pronation of the forearm can be achieved by pronator quadratus, FCR, FDP, and FDS contraction. For that reason, it is difficult to retrieve which is the real pronation deficit in group 4.

In normal hand, complete pronosupination movement can be achieved with BR, extensor carpi ulnaris and EDM (Bertelli & Ghizoni, 2017; Bertelli, Ghizoni, & Tacca, 2016); however, in this group only brachioradialis would still

produce a partial pronation in case of deficit of PT. Since PT is fundamental for wheelchair propulsion, we suggest to avoid PT or FDS nerve transfer. It is possible to perform a secondary House intrinsic procedure.

Group 5

Neurological level of injury: C7.

Residual motor function: FRC graded 4 or more.

It is possible to transfer supinator to PIN nerve, brachialis nerve to AIN and FDS, while it is possible to transfer the tendon of ECRL to FDP of the 3rd–4th–5th finger.

Current reconstructive strategy: same of group 4.

Our proposal: same of group 4. FRC can be transferred to PIN or AIN (García-López et al., 2014), but in our practice, we prefer to spare FRC in place to preserve the maximal wrist control possible (House et al., 1992).

Group 6

Neurological level of injury: C7.

Residual motor function: ECD graded 4 or more. Extensor phase is not necessary in this type of patients and surgery is focused on flexor phase only.

Patients have a "flat hand" because digital extension is not opposed by antagonist muscles, with lack of active grasp. Since the lesion is at C7 level and not above, patients have a perfect control on shoulder, elbow and wrist to control the position of the hand in space, so they will benefit from grasp and reconstructive surgery.

Current reconstructive strategy: same of flexion phase of previous two groups.

Our proposal:

- Brachialis to AIN and FDS nerve transfer.
- EPL tenodesis and ECRL to FDP of the 3rd–4th–5th finger tendon transfer.

The EPL is very weak or totally absent, while finger active extension is strong. For this reason, it is useful to perform a tenodesis of EPL or a transfer to EDC to improve thumb extension.

Some authors proposed to transfer ECRB (extensor carpi radialis brevis) terminal motor branch to FLP (flexor pollicis longus) nerve to reconstruct thumb flexion and brachialis tendon transfer with graft to restore fingers flexion (Bertelli et al., 2012; Bourrel, 1974; Mangus, 1973; Zancolli, 1979).

We suggest to spare ECRL nerve and to use a tendon transfer to obtain fingers flexion. It is also possible to perform a House intrinsic procedure to complete the surgical procedure.

Group 7

Neurological level of injury: C8.

Residual motor function: EPL graded as 4 or more. Fingers and thumb extensors are complete functioning and only flexor phase reconstruction is needed.

Current reconstructive strategy:

- ECRL to FDP tendon transfer.
- BR or PT to FLP tendon transfer to restore active pinch as for the previous group.

A possible alternative is based on Brachialis to AIN and FDS nerve transfer and ECRL to FDP of the 3rd–4th–5th finger tendon transfer.

Thumb control can be improved with CMC fusion and opponens plasty depending on thumb control and patient's preference. A Lasso procedure can be also performed to improve digital grasp (Gupta, Consul, & Swamy, 2015).

Our proposal: same steps of group 6 but avoiding EPL tenodesis. Moreover, we perform also Extensor Indicis Proprius (EPI) or EDM opponens plasty. A further intrinsic reconstruction procedures as suggested by Zancolli (Zancolli, 1979) and Bourrel (Bourrel, 1974) can be added to achieve the desired results.

Group 8

Neurological level of injury: C8 level.

Residual motor function: intact FCU and partial FDP. The flexors of 4th and 5th fingers are usually stronger than those of first three fingers.

Current reconstructive strategy: aim of surgical intervention is to restore fingers flexion using Zancolli's two stage reconstruction: extrinsic transfers and intrinsic reconstruction.

- Extrinsic transfer:
  - side to side suture of the four profundus tendons and half of the index FDP is woven together with other tendons to ensure right tension;
  - a secondary additional part is the BR or PT to FLP transfer.
- Intrinsic reconstruction:
  - Zancolli lasso technique,
  - opponensplasty with EPI or EDM plus CMC fusion or intrinsic tenodesis as described by House et al., 1976.

To achieve an independent flexion of the index it is possible to perform ECRB to FP of the 2nd digit tendon transfer. Intrinsic function reconstruction may always be performed as a second step procedure.

Our proposal: ECRB nerve branch pro AIN nerve transfer (Allieu, 2002; House et al., 1992).

If the procedure fails, House's one-stage active pinch reconstruction can be performed anyway along with Henz procedures. The flexion tendency will be balanced by CMC fusion and EPL tenodesis, while complete hand function will be restored through tenodesis of FDP of second finger to 3rd–4th–5th finger FDP.

Group 9

Neurological level of injury: C8-T1.

Residual motor function: FDS and other extrinsic muscle for fingers and thumb flexion, with lack of intrinsic muscle function.

Current reconstructive strategy and our proposal: surgical intervention aim to restore intrinsic nerve function. Opponensplasty and intrinsic reconstructions can be performed according to the intrinsic imbalance present (Titolo et al., 2019).

A resulting claw deformity of fingers with hyperextension of MP joints can be treated with Zancolli passive or active lasso procedure (Gupta et al., 2015; Zancolli, 1979), while House intrinsic tenodesis can be used to treat PIP flexion deformity (House et al., 1992).

Conclusions

Thanks to new advances in the field of nerve transfer, it is possible to fuse the old concepts of tenodesis and tendon transfer for tetraplegic patients with the new approaches based on nerve surgery to improve upper-limb function.

The fusion between old and new approaches could widen therapeutic choices for this kind of patients, sparing some tendon transfers as salvage procedure which could always be useful in case of combined approach failure.

Applications to other areas of neuroscience

Nerve and tendon transfers are a new surgical approach based on the combination of both techniques. Each technique has some indication and contraindication, which can preclude the chance to get the best result. The principle of tendon transfer is based on the transposition of an expendable tendon to achieve a primary function; however, this is not always possible since higher is the medullary lesion, less functional muscle-nerve unit you have. On the other hand, nerve transfer offers the chance to reinnervate muscle distal to the site of lesion; however, there is no guarantee of success.

Despite recovery of hand function being the most important goal for patients with tetraplegia, combined nerve and tendon transfer can also offer some choice of treatment in patients with lower-limb nerve injury (Park & Casale, 2020).

The recovery of leg motor function due to a combination of nerve and tendon transfer could represent a new perspective in the recovery of walking and standing function (Crowe, Mosca, Osorio, Lewis, & Tse, 2020).

Mini-dictionary of terms

Spinal Cord Injury. Lesion of the central nervous system with loss of function below the level of injury.

Cervical Spine. Upper region of the spine deputy to control of motor function of the upper limb.

Complete Spinal Cord Injury. Lesion involving whole spinal cord with complete loss of function.
Incomplete Spine Cord Injury. Lesion involving a part of spinal cord with preservation of some function.
Tetraplegia. Loss of function of whole body below the level of injury with loss of function in both upper and lower limbs.
Paraplegia. Loss of function of whole body below the level of injury with conservation of function in upper limbs.
Tendon Transfer. Surgical procedure where the tendon insertion is moved, while the origin remains in the same location. It involves redistribution of muscle power, and generally, tendons are transferred from lesser to more important functions.
Nerve transfer. Surgical procedure used in nerve injury with complete loss of muscle function. It involves sacrificing nerve with less important function or redundant branches of a nerve and using it to innervate a target muscle.
Tenodesis. Surgical procedure of fixation of the distal end of a tendon to a bone.
Arthrodesis. Surgical procedure of fusion of a joint with loss of mobility but increase of stability.
Salvage procedure. Procedure to achieve an acceptable result in case of failure of other surgical procedure.

Key facts of nerve and tendon transfers in tetraplegia: A new narrative

Key facts of nerve and tendon transfer

Restore motor function of upper limb in patients suffering from tetraplegia is very important to gain some level of autonomy.
In time-independent lesion, surgery can be performed at any time.
In time-dependent lesion, surgery should be performed as earlier as possible.
Generally, surgery should be performed between 6 and 12 months from injury.
Tendon transfer is the current surgical strategy used to treat tetraplegic upper limb, with fast recovery of function, but with some limitation.
Nerve transfer is a new surgical approach to restore motor function; however, the results are less fast and certain.
Combination of nerve and tendon transfer can overcome the limits of each technique, assuring better recovery of function.
In case of failure, a conventional surgical approach is always possible as salvage procedure.

Summary points

- Usually, SCI occurs after major trauma due to fall from height or motor vehicle accident.
- The restoration of upper-limb function offers patients with tetraplegia some kind of daily living autonomy.
- More distal is the level of injury, more muscles are spared and can be used for tendon and nerve transfer, and more functions are achieved.
- Usually, surgery should be performed between 6 and 12 months from injury for both time-dependent and -independent injury.
- Combination of nerve and tendon transfer is able to overcome the limits of each technique.
- Arthrodesis procedure should be considered to complete nerve and tendon transfer procedures to achieve the best results.
- In case of failure, the current approach of tendon transfer and tenodesis could always be performed as a salvage procedure.

References

Allieu, Y. (2002). General indications for functional surgery of the hand in tetraplegic patients. *Hand Clinics*, *18*(3), 413–421.
Anderson, K. D. (2004). Targeting recovery: Priorities of the spinal cord-injured population. *Journal of Neurotrauma*, *21*(10), 1371–1383. https://doi.org/10.1089/neu.2004.21.1371.
Arnet, U., Muzykewicz, D. A., Fridén, J., & Lieber, R. L. (2013). Intrinsic hand muscle function, part 1: Creating a functional grasp. *The Journal of Hand Surgery*, *38*(11), 2093–2099. https://doi.org/10.1016/j.jhsa.2013.08.099.
Bednar, M. S., & Woodside, J. C. (2018). Management of Upper Extremities in tetraplegia. *Journal of the American Academy of Orthopaedic Surgeons*, *26*(16), e333–e341. https://doi.org/10.5435/JAAOS-D-15-00465.

Bertelli, J. A. (2015). Transfer of the radial nerve branch to the extensor carpi radialis brevis to the anterior interosseous nerve to reconstruct thumb and finger flexion. *The Journal of Hand Surgery*, *40*(2), 323–328.e2. https://doi.org/10.1016/j.jhsa.2014.10.060.

Bertelli, J. A., & Ghizoni, M. F. (2013). Single-stage surgery combining nerve and tendon transfers for bilateral upper limb reconstruction in a tetraplegic patient: Case report. *The Journal of Hand Surgery*, *38*(7), 1366–1369. https://doi.org/10.1016/j.jhsa.2013.03.056.

Bertelli, J. A., & Ghizoni, M. F. (2016). Nerve and free Gracilis muscle transfers for thumb and finger extension reconstruction in long-standing tetraplegia. *The Journal of Hand Surgery*, *41*(11), e411–e416. https://doi.org/10.1016/j.jhsa.2016.08.003.

Bertelli, J. A., & Ghizoni, M. F. (2017). Nerve transfers for restoration of finger flexion in patients with tetraplegia. *Journal of Neurosurgery: Spine*, *26*(1), 55–61. https://doi.org/10.3171/2016.5.SPINE151544.

Bertelli, J. A., Ghizoni, M. F., & Tacca, C. P. (2011). Transfer of the teres minor motor branch for triceps reinnervation in tetraplegia. *Journal of Neurosurgery*, *114*(5), 1457–1460. https://doi.org/10.3171/2010.12.JNS101519.

Bertelli, J. A., Ghizoni, M. F., & Tacca, C. P. (2016). Results of wrist extension reconstruction in C5–8 brachial plexus palsy by transferring the pronator quadratus motor branch to the extensor carpi radialis brevis muscle. *Journal of Neurosurgery*, *124*(5), 1442–1449. https://doi.org/10.3171/2015.3.JNS142428.

Bertelli, J. A., Mendes Lehm, V. L., Tacca, C. P., Winkelmann Duarte, E. C., Ghizoni, M. F., & Duarte, H. (2012). Transfer of the distal terminal motor branch of the extensor carpi radialis brevis to the nerve of the flexor pollicis longus: An anatomic study and clinical application in a tetraplegic patient. *Neurosurgery*, *70*(4), 1011–1016. discussion 1016 https://doi.org/10.1227/NEU.0b013e3182367642.

Bertelli, J. A., Tacca, C. P., Ghizoni, M. F., Kechele, P. R., & Santos, M. A. (2010). Transfer of supinator motor branches to the posterior interosseous nerve to reconstruct thumb and finger extension in tetraplegia: Case report. *The Journal of Hand Surgery*, *35*(10), 1647–1651. https://doi.org/10.1016/j.jhsa.2010.07.012.

Bourrel, P. (1974). Restoration of opposition of the thumb. Apropos of 52 cases. *Annales de Chirurgie*, *28*(4), 309–317.

Brown, J. (2011). Nerve transfers in tetraplegia I: Background and technique. *Surgical Neurology International*, *2*(1), 121. https://doi.org/10.4103/2152-7806.84392.

Cain, S., Gohritz, A., Fridén, J., & van Zyl, N. (2015). Review of upper extremity nerve transfer in cervical spinal cord injury. *Journal of Brachial Plexus and Peripheral Nerve Injury*, *10*(01), e34–e42. https://doi.org/10.1055/s-0035-1558427.

Crowe, C. S., Mosca, V. S., Osorio, M. B., Lewis, S. P., & Tse, R. W. (2020). Partial tibial nerve transfer for foot drop from deep peroneal palsy: Lessons from three pediatric cases. *Microsurgery*. https://doi.org/10.1002/micr.30650.

de Mendonça Cardoso, M., Gepp, R., Lima, F. L., & Gushiken, A. (2020). Intercostal to musculocutaneous nerve transfer in patients with complete traumatic brachial plexus injuries: Case series. *Acta Neurochirurgica*. https://doi.org/10.1007/s00701-020-04433-3.

Fox, I. K. (2016). Nerve transfers in tetraplegia. *Hand Clinics*, *32*(2), 227–242. https://doi.org/10.1016/j.hcl.2015.12.013.

Fox, I. K., Davidge, K. M., Novak, C. B., Hoben, G., Kahn, L. C., Juknis, N., … Mackinnon, S. E. (2015a). Nerve transfers to restore upper extremity function in cervical spinal cord injury: Update and preliminary outcomes. *Plastic and Reconstructive Surgery*, *136*(4), 780–792. https://doi.org/10.1097/PRS.0000000000001641.

Fox, I. K., Davidge, K. M., Novak, C. B., Hoben, G., Kahn, L. C., Juknis, N., … Mackinnon, S. E. (2015b). Use of peripheral nerve transfers in tetraplegia: Evaluation of feasibility and morbidity. *Hand (New York, N.Y.)*, *10*(1), 60–67. https://doi.org/10.1007/s11552-014-9677-z.

Fox, I., Hoben, G., Komaie, G., Novak, C., Hamm, R., Kahn, L., … James, A. (2019). Nerve transfer surgery in cervical spinal cord injury: A qualitative study exploring surgical and caregiver participant experiences. *Disability and Rehabilitation*. https://doi.org/10.1080/09638288.2019.1669225.

Fox, I. K., Novak, C. B., Krauss, E. M., Hoben, G. M., Zaidman, C., Ruvinskaya, R., … Mackinnon, S. E. (2018). The use of nerve transfers to restore upper extremity function in cervical spinal cord injury. *PM & R: The Journal of Injury, Function, and Rehabilitation*. https://doi.org/10.1016/j.pmrj.2018.03.013.

Fridén, J., & Gohritz, A. (2012). Brachialis-to-extensor carpi radialis longus selective nerve transfer to restore wrist extension in tetraplegia: Case report. *The Journal of Hand Surgery*, *37*(8), 1606–1608. https://doi.org/10.1016/j.jhsa.2012.05.005.

Fu, S. Y., & Gordon, T. (1995a). Contributing factors to poor functional recovery after delayed nerve repair: Prolonged axotomy. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *15*(5 Pt 2), 3876–3885. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7751952.

Fu, S. Y., & Gordon, T. (1995b). Contributing factors to poor functional recovery after delayed nerve repair: Prolonged denervation. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *15*(5 Pt 2), 3886–3895. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7751953.

García-López, A., Navarro, R., Martinez, F., & Rojas, A. (2014). Nerve transfers from branches to the flexor carpi radialis and pronator teres to reconstruct the radial nerve. *The Journal of Hand Surgery*, *39*(1), 50–56. https://doi.org/10.1016/j.jhsa.2013.10.011.

Gohritz, A., Fridén, J., Herold, C., Aust, M., Spies, M., & Vogt, P. M. (2007). Ersatzoperationen bei Ausfall motorischer Funktionen an der Hand. *Der Unfallchirurg*, *110*(9), 759–776. https://doi.org/10.1007/s00113-007-1322-7.

Gupta, V., Consul, A., & Swamy, M. (2015). Zancolli lasso procedure for correction of paralytic claw hands. *Journal of Orthopaedic Surgery*, *23*(1), 15–18. https://doi.org/10.1177/230949901502300104.

Hentz, V. R., House, J., McDowell, C., & Moberg, E. (1992). Rehabilitation and surgical reconstruction of the upper limb in tetraplegia: An update. *The Journal of Hand Surgery*, *17*(5), 964–967.

House, J. H., Comadoll, J., & Dahl, A. L. (1992). One-stage key pinch and release with thumb carpal-metacarpal fusion in tetraplegia. *The Journal of Hand Surgery*, *17*(3), 530–538.

House, J. H., Gwathmey, F. W., & Lundsgaard, D. K. (1976). Restoration of strong grasp and lateral pinch in tetraplegia due to cervical spinal cord injury. *The Journal of Hand Surgery*, *1*(2), 152–159.

James, M. A. (2007). Use of the Medical Research Council muscle strength grading system in the upper extremity. *The Journal of Hand Surgery*, *32*(2), 154–156. https://doi.org/10.1016/j.jhsa.2006.11.008.

Johanson, M. E. (2016). Rehabilitation after surgical reconstruction to restore function to the upper limb in tetraplegia: A changing landscape. *Archives of Physical Medicine and Rehabilitation*, *97*(6), S71–S74. https://doi.org/10.1016/j.apmr.2016.03.015.

Kumar, N., Osman, A., & Chowdhury, J. R. (2017). Traumatic spinal cord injuries. *Journal of Clinical Orthopaedics and Trauma*, *8*(2), 116–124. https://doi.org/10.1016/j.jcot.2017.06.022.

Lamb, D. W., & Chan, K. M. (1983). Surgical reconstruction of the upper limb in traumatic tetraplegia. A review of 41 patients. *The Journal of Bone and Joint Surgery*, *65*(3), 291–298.

Lee, S. K., & Wolfe, S. W. (2012). Nerve transfers for the upper extremity: New horizons in nerve reconstruction. *The Journal of the American Academy of Orthopaedic Surgeons*, *20*(8), 506–517. https://doi.org/10.5435/JAAOS-20-08-506.

Limthongthang, R., Bachoura, A., Songcharoen, P., & Osterman, A. L. (2013). Adult brachial plexus injury. *Orthopedic Clinics of North America*, *44*(4), 591–603. https://doi.org/10.1016/j.ocl.2013.06.011.

Mackinnon, S. E., Yee, A., & Ray, W. Z. (2012). Nerve transfers for the restoration of hand function after spinal cord injury. *Journal of Neurosurgery*, *117*(1), 176–185. https://doi.org/10.3171/2012.3.JNS12328.

Mangus, D. J. (1973). Flexor pollicis longus tendon transfer for restoration of opposition of the thumb. *Plastic and Reconstructive Surgery*, *52*(2), 155–159.

Moberg, E. (1990). Surgical rehabilitation of the upper limb in tetraplegia. *Spinal Cord*, *28*(5), 330–334. https://doi.org/10.1038/sc.1990.43.

Mohammed, K. D., Rothwell, A. G., Sinclair, S. W., Willems, S. M., & Bean, A. R. (1992). Upper-limb surgery for tetraplegia. *The Journal of Bone and Joint Surgery*, *74*(6), 873–879.

Mohindra, M., Gogna, P., Sangwan, S. S., Gaba, S., & Kundu, Z. S. (2017). The scope of upper limb surgery for tetraplegics: Role of tendon transfers and universal cuff. *Acta Orthopaedica et Traumatologica Turcica*, *51*(5), 367–371. https://doi.org/10.1016/j.aott.2017.06.002.

Mooney, A., Hewitt, A. E., & Hahn, J. (2020). Nothing to lose: A phenomenological study of upper limb nerve transfer surgery for individuals with tetraplegia. *Disability and Rehabilitation*. https://doi.org/10.1080/09638288.2020.1750716.

Muzykewicz, D. A., Arnet, U., Lieber, R. L., & Fridén, J. (2013). Intrinsic hand muscle function, part 2: Kinematic comparison of 2 reconstructive procedures. *The Journal of Hand Surgery*, *38*(11), 2100–2105.e1. https://doi.org/10.1016/j.jhsa.2013.08.098.

Park, J. S., & Casale, M. J. (2020). Posterior Tibial tendon transfer for common peroneal nerve injury. *Clinics in Sports Medicine*. https://doi.org/10.1016/j.csm.2020.07.003. W.B. Saunders.

Titolo, P., Fusini, F., Arrigoni, C., Isoardo, G., Conforti, L., Artiaco, S., … Battiston, B. (2019, April 9). Combining nerve and tendon transfers in tetraplegia: A proposal of a new surgical strategy based on literature review. *European Journal of Orthopaedic Surgery and Traumatology*. https://doi.org/10.1007/s00590-018-2352-2. Springer-Verlag France.

van Zyl, N., Hahn, J. B., Cooper, C. A., Weymouth, M. D., Flood, S. J., & Galea, M. P. (2014). Upper limb reinnervation in C6 tetraplegia using a triple nerve transfer: Case report. *The Journal of Hand Surgery*, *39*(9), 1779–1783. https://doi.org/10.1016/j.jhsa.2014.06.017.

Wolfe, S. W., Hotchkiss, R. N., Pederson, W. C., Kozin, S. H., Cohen, M. S., & Revision of: Green, D. P (n.d.). Green's operative hand surgery.

Waters, R. L., Sie, I. H., Gellman, H., & Tognella, M. (1996). Functional hand surgery following tetraplegia. *Archives of Physical Medicine and Rehabilitation*, *77*(1), 86–94.

Zancolli, E. (1979). *Structural and dynamic bases of hand surgery*. Lippincott.

Zlotolow, D. A. (2011). The role of the upper extremity surgeon in the Management of Tetraplegia. *The Journal of Hand Surgery*, *36*(5), 929–935. https://doi.org/10.1016/j.jhsa.2011.03.001.

Chapter 24

GEMINI-supported spinal cord transplantation for the treatment of chronic spinal paralysis: Overview and initial clinical translation

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Introduction

There is at present no biological cure for chronic paralysis following spinal cord injury (SCI). A medley of experimental approaches have been tried over the years, and, despite some improvement in some patients, no full recovery has been observed (Ren, Kim, & Canavero, 2019). As underscored by Illis,

> *"it would be difficult to find any other branch of science with over a century of such sterile endeavour. In effect, there has been repetition of the same idea, albeit with different techniques, that is, looking at the lesion site. Are we sentenced to repeating the same experiments in the hope of expecting a different result?"*
>
> (Illis, 2012).

Work conducted mainly by US neurosurgeon L. Walter Freeman more than half a century ago suggests that a permanent, biological cure is possible, at least in several cases of chronic SCI, by removing *en bloc* the "*lesion site*," i.e., the most damaged portion of the spinal cord, and connecting the two free undamaged ends, after spinal (vertebral) shortening (Freeman, 1963; see also Canavero & Ren, 2016a). Transplantation of a healthy segment of cord is an alternative (see below).

In both scenarios, a technology that allows the functional reconnection of the severed ends is necessary. In 2013, the GEMINI spinal cord fusion (SCF) protocol was proposed with this goal in mind (Canavero, 2013, 2015).

Here, we will briefly review the GEMINI SCF protocol and lay out the various alternatives for its ongoing deployment in the clinical setting.

The GEMINI spinal cord fusion protocol: Overview

The GEMINI spinal cord fusion protocol is predicated on four pillars (Canavero, 2015; Canavero & Ren, 2020; Canavero, Ren, Kim, & Rosati, 2016):

1. Sharp severance of the spinal cord with an ultra-thin blade, with its attendant minimal tissue damage, as compared to clinical SCI (<10 N vs 26,000 N)
2. Exploitation of the gray matter internuncial sensori-motor "highway" (so-called cortico-trunco-reticulo-propiospinal pathway; C-TRPS) re-bridged by sprouting connections between the two re-apposed cord stumps. This "highway" runs in parallel to corticospinal descending fibers and is co-responsible for sensori-motor transmission through the cord (see also Kostyuk & Vasilenko, 1979; Shik, 1983).
3. Application of "fusogens/sealants": these "seal" the thin layer of injured cells in the gray matter, both neuronal, glial and vascular; simultaneously they fuse a certain number of axons in the white matter. The pro-regenerative early scar is not inhibited, but necrosis/cavitation is.

Diagnosis and Treatment of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822498-4.00024-5

4. Acceleration of axonal outgrowth by electrical spinal cord stimulation straddling the fusion point and concomitant motor cortex stimulation.

We will briefly review the technology involved. An in-depth discussion can be found elsewhere (Canavero et al., 2016; Canavero & Ren, 2020).

GEMINI: Fusogens

Cell fusion is the process by which the membranes and intracellular contents of any two cells are permanently fused. There are multiple situations where this occurs naturally—fertilization is one very fundamental example, but there is also increasing evidence that cell fusion can be induced for clinical benefit. The most striking clinical application of this is the potential for reconstitution of axon integrity and electrical conductivity through the fusion of axon membranes; this can be performed in order to reconnect the two cut ends of a severed axon, or to create membranous continuity between the ends of two axons that have been newly placed in apposition (such as in a allogeneic transplant). While close spatial proximity is required, and usually achieved through some sort of physical (often micro-surgical) manipulation, the scale at which this occurs is small and relies on a chemical manipulation to complete the fusion at the level of the cellular membrane. The substances that are capable of performing this function are heterogeneous in composition and function, and often referred to as "fusogens" (Ryan & Henderson, 2020).

Axon membrane fusion is valuable in any attempt to manage nerve injury because it allows for the possibility of immediate reconstitution of electrical conductivity and therefore nerve function. An outcome on such a timeline is impossible given the current standard methods for managing nerve injury (approximation via epineurial repair), which accept distal Wallerian degeneration and the need to wait for axon regeneration from the point of injury to the end organ (which is traditionally thought to progress at the rate of approximately 1 mm per day). Therefore, fusogens represent a quantum leap in the way that nerves are managed, as they allow for the possibility of true axon *repair*, as opposed to the traditional methods, which at best harness axon *regeneration* (and accordingly the outcomes after this treatment approach are partial at best, and measured on the order of months to years).

There are two general mechanisms by which fusogens are thought to function: cell aggregation and membrane modification (Ryan & Henderson, 2020). Substances that function only via cell aggregation lead to increasingly closer apposition of the two axon ends (often by extraction of intervening water molecules). This group includes chitosan, dextran sulfate, small organic molecules, and lipids. Substances that function only via membrane modification alter membrane charges to create a more favorable electrochemical environment for apposition and ultimately fusion to occur. This group includes cations such as Ca^{2+} and Mg^{2+}, sodium nitrate, and H-alpha-7. Polyethylene glycol (PEG) is a substance that is thought to function by a combination of both mechanisms, and for that reason is it is the fusogen that, to date, has been used most widely and most successfully in both research and clinical settings.

PEG is a hydrophilic polymer that is inexpensive and commonly encountered, as it has proven to play a role in many different medical, biological, and industrial scenarios. Its potential utility as a means of promoting cellular fusion, however, was first recognized in the 1970s after it was shown to be able to induce immortalized hybridoma cells and fused mammalian erythrocytes (Ren et al., 2019). The ability to induce axon membrane fusion (either in repair of cut ends of the same axon, or the fusion to ends of a different axons) was first realized and progressively tested beginning in the 1980s, starting with invertebrate models (Bittner, Sengelaub, Trevino, et al., 2016), and gradually progressing into rodents and then large mammals (fully reviewed in Canavero & Ren, 2020). It has successfully restored complete digital nerve function after traumatic injury in small human studies (Bamba, Waitayawinyu, Nookala, et al., 2016; see also De Medinaceli & Merle, 1991) and has been effective at restoring neurologic function at the level of the spinal cord in multiple animal models (Ren et al., 2019; fully reviewed in Canavero & Ren, 2020).

In addition to the cell fusion mechanisms of cell aggregation and membrane modification, PEG has been shown to have other effects that are beneficial for maximizing nerve function. First, it is neuroprotective due to its ability to inhibit the formation of the mitochondrial permeability transition pore; second, it may reduce the neuronal membrane tension and thereby improve membrane fluidity; third, it causes the release of neurotrophin-3, which attracts neural stem cells and promotes their differentiation into axons. However, PEG does not lead to the fusion or repair of connective tissue and therefore does not provide any structural strength and in very rare cases may be associated with allergic reactions (see references in Ren et al., 2019).

GEMINI: Electrical stimulation

The GEMINI SCF protocol includes the positioning of an extradural stimulating 16-contact paddle straddling the point(s) of fusion followed by continuous stimulation (15–60 Hz, 5–9 V) during the entire rehabilitation period (Canavero, 2015;

Canavero et al., 2016; Canavero & Ren, 2020). Spinal cord stimulation (SCS) is paired to non-invasive transcranial magnetic stimulation (TMS) of the motor cortex (M1) (Canavero & Ren, 2016a, 2016b).

Electrical stimulation (ES) serves two primary purposes:

1. Promotion/Acceleration of axonal outgrowth and plasticity across the fusion interface. Shirres first emphasized the ability of electricity to stimulate spinal cord regeneration (see full details in Ren et al., 2019). ES has been shown to accelerate axonal outgrowth (neural sprouting) at sites of injury, including the cord, in animal studies (e.g., Thornton, Mehta, Morad, et al., 2018; see also Jack, Hurd, Martin, & Fouad, 2020, Ju, Park, Kim, Kim, et al., 2020). Of note, ES is co-additive to PEG in SCI (Wang et al., 2016).
2. Activation/Facilitation of propriospinal neurons caudal to the fusion interface.

Following complete spinal transection in man, the neuronal networks responsible for locomotion (i.e., central pattern generators, CPG) residing in the spinal cord are intact, but fail to produce limb movements: the excitability of the spinal cord is too depressed to enable the coordinated recruitment of motor neuron pools. Consequently, enabling robust levels of activity during rehabilitation is critical to steer activity-dependent plasticity in the trained circuitry. This is achieved by ES. ES replaces missing sources of excitation to reactivate spinal circuits, and thus enable motor control. In particular, following chemical fusion, sprouting across the fusional interface restarts the flow of electrical transmission between the fused cords. ES amplifies voluntary commands from the brain and thus supports their propagation to the CPGs at cervical and lumbar levels (Canavero & Ren, 2016a, 2016b; Canavero & Ren, 2020; Minassian & Hofstoetter, 2016). In turn, these integrate supraspinal and sensory information into the execution of purposeful movements.

Over the past 20 years, on the heels of Dimitrijevic's pioneering work in the last decades of the XX century (Dimitrijevic, 1983), multiple independent laboratories have shown that the delivery of continuous electrical stimulation (tonic) over the lumbar spinal cord immediately reestablishes intentional control over the activity of previously paralyzed leg muscles, even more than a decade after the occurrence of the SCI. Continuous ES also restores full weight-bearing standing and facilitates stepping (see reviews in James, McMahon, Field-Fote, & Bradbury, 2018; Calvert, Grahn, Zhao, & Lee, 2019; Cho, Squair, Bloch, & Courtine, 2019; Jack et al., 2020; see also chapters in this volume). ES of the spinal cord (SCS) is known to elicit activity locally and rostrally up to the cortex (as shown in chronic pain: see Canavero & Bonicalzi, 2018, pp. 465–474).

Spatiotemporal SCS protocols have been touted as an improvement over continuous stimulation (reviewed in Cho et al., 2019). However, no trials exist that compare continuous with spatiotemporal stimulation in homogeneous patients. Serotonergic agonists may further potentiate the effects of ES (Calvert et al., 2019; Cho et al., 2019).

ES can be employed in conjunction with specialized multidirectional robotic body weight support systems to steer activity-dependent plasticity in response to training (Cho et al., 2019).

Although clinical experience is limited to ES of the lumbar CPG, similar results are expected for the cervical cord (Canavero & Ren, 2016a, 2016b; Sunshine et al., 2013).

Importantly, since recovery of supraspinal control over limb movements is *directly correlated with the amount of spared tissues*, ES in the present context can only be deployed *after* chemical fusion.

As mentioned, M1 is concomitantly stimulated to promote corticospinal tract axonal outgrowth and plasticity; timing of paired stimuli is leveraged to produce plasticity during the rehabilitative phase (Canavero & Ren, 2016a, 2016b; Jack et al., 2020; Song, Amer, Ryan, & Martin, 2015; Zareen, Shinozaki, Ryan, et al., 2017). Stimulation of M1 can be carried out both invasively and noninvasively (Canavero, 2009, 2014). In the present context, noninvasive cortical stimulation (NICS) by means of TMS is the preferred modality. M1 ES promotes sprouting of corticofugal fibers and modulates post-injury neuroplasticity (Canavero, 2009; Canavero & Ren, 2016a, 2016b). M1 orchestrates recovery after SCI, developing new routes through the C-TRPS (Canavero & Ren, 2020; see also Cho et al., 2019).

Clinical translation

Based on experimental evidence (reviewed in Ren et al., 2019), PEG turns out to be the fusogen of choice: it is most effective when applied locally and acutely after cord transection and stump apposition. Cord necrosis and cavitation are greatly reduced or curbed. Studies show that the molecular weight of PEG greatly affects the final outcome, with PEG 600 and PEG1500 as the ones evincing the best results in animal models of cord transection (see in Canavero & Ren, 2020).

Gemini hydrogelation

In the simplest approach, the damaged cord segment (or at least half of it) is removed, up to its border with rostral and caudal healthy tissue and the gap is filled with a PEG hydrogel. PEG can be cross-linked to form porous hydrogels, which can serve

as biocompatible matrices that can closely mimic the Extra-Cellular Matrix. PEG hydrogels possess both high water content/porosity and solidity. Injectable PEG, by in situ gelling, can conform geometrically to the defect (see Ren et al., 2019). Regenerating propriospinal fibers course through this hydrogel "superhighway," as demonstrated in rodent studies after many months (Estrada, Brazda, Schmitz, et al., 2014). Certainly, the use of PEG alone cannot completely mimic the three-dimensional porous structure of the spinal cord and would allow the upper and lower fiber bundles to grow in mismatched or even misplaced channels or pores, which is not the case with the next two approaches (see next section). Moreover, this approach would need many months for recovery. However, microspheres loaded with neurotrophins (e.g., BDNF and GDNF) could be embedded for slow release to accelerate this regrowth (see Ren et al., 2019).

Resection-apposition (Freeman-GEMINI approach)

As mentioned, Walter Freeman suggested the severance-reapposition approach to chronic SCI: he surgically removed the damaged segment of the cord in dogs creating a gap, performed a complete *en bloc* vertebrectomy thus shortening the spine, brought the two fresh cord stumps in contact with fresh plasma and sutured the dura tightly: walking animals resulted after several months (Freeman, 1963; see also Heimburger, 2005, 2006). Notably, he observed direct electrophysiological conductance across the apposed stumps and provided histological evidence of axonal regeneration across the sectional interface (see also Beneš, Druga, Rokyta, & Stastný, 1991 and De Medinaceli & Wyatt, 1993; review in Ren et al., 2019). There is experimental evidence that the transected spinal cord in rabbits too can regenerate with concomitant return of motor, sensory and sphincter function when adequate apposition is obtained (Murray, Ugray, & Graves, 1965). Others carried out Freeman's surgery in dogs either immediately (Derlon, Roy-Camille, Saillant, Poirier, & Pichon, 1978) or 7 days after full section of the cord (Lumb & Nornes, 1983). However, Street (1967) carried out Freeman's procedure in paraplegic patients without success.

Spine-shortening vertebral osteotomy (a.k.a. vertebral column resection) is a surgical technique for correcting severe spinal deformities, treating congenital spinal anomalies, e.g., cord tethering, traumatic spine dislocations, and spine tumors at both cervical and thoraco-lumbar levels (Aoun, Elguindy, Barrie, et al., 2018; Hsieh, Stapleton, Moldavskiy, et al., 2010; Mody, Bravo Iñiguez, Armstrong, et al., 2016; Qiu, Yang, Ma, et al., 2015; Steinberg, Wali, Martin, et al., 2017). In the Freeman-GEMINI variant (Canavero & Ren, 2016a, 2016b; Ren et al., 2019), section of the damaged segment of the cord is performed at the moment of removing the vertebral body; the two ends are further trimmed so that no undue pressure is exerted on either stump by pressure vectors (too much as opposed to modest-pressure would lead to squeezing and local ischemia, jeopardizing the result). PEG is applied at this moment. The vertebra is removed and stabilization carried out simultaneously. The two spinal cord ends can be kept in apposition by some kind of micro-connector system: one incorporating a micro-channel system, through which PEG circulates, has been proposed (Brazda, Voss, Estrada, et al., 2013). Systems like this allow a tension-free, precise apposition of sharply transected nerve spinal cord stumps, as required by GEMINI. Spinal cord stimulators are epidurally positioned.

Spinal cord transplantation (Shirres-GEMINI approach)

In 1905, Shirres reported his attempt to graft a segment of healthy canine cord in a human paraplegic patient: clear signs of neuroregeneration were observed on autoptic material, with initial sensory recuperation at 3 months; autopsy showed signs of neuroregeneration (see Ren et al., 2019). Forty years later, Woolsey, Minckler, Rezende, and Klemme (1944) operated on a 16-year-old male with complete loss of motor and sensory function after he was shot in his right shoulder with the bullet reaching the superior border of T4. Following laminectomy, the injured spinal cord was completely transected and replaced with a cadaveric spinal cord that had been fixed in 10% formalin for 12 days, and cleaned and sterilized with running and distilled water and 70% alcohol. No improvement in the patient's condition was noted, and the patient died almost 4 months after the surgery. Autopsy showed exceptional preservation of the transplanted graft, although with restricted regeneration and limited tissue reaction. The preservation was attributed to the preoperative use of formalin, and no explanations or related conclusion on the microscopic findings could be made.

Today, human cord grafts/transplants are once again a consideration given the availability of an effective spinal fusion protocol, i.e., GEMINI, which would be key to interfacing the donor segment with the recipient's cord stumps (Canavero, Ren, & Kim, 2021). In this variant, PEG would neuroprotect the graft/transplant until vascularization from the healthy ends of the patient. PEG hydrogels support the formation of vascularized tissue in vivo and PEG has been shown to promote angiogenesis in an SCI model (see Ren et al., 2019). The donor segment is harvested from a brain-dead organ donor at the same level of injury. All the roots would be reanastomosed (a process akin to reimplantation of avulsed nerve roots:

Carlstedt, James, & Risling, 2017, see (Canavero et al., 2021)). However, until tolerogenic protocols are developed for this contingency, immunosuppressants would be likely needed and this adds toxicity.

Depending on the length of the segment, surgical restoration of the vascular supply on one side may be required, but remains challenging with current techniques (Canavero et al., 2021).

Alternatively, a vascularized segment of the anatomically undamaged healthy cord caudal or rostral to the injury epicenter represents a suitable, interim alternative to fill the gap, as are bundles of peripheral nerves, as suggested by past animal experiments (Derlon, Roy-Camille, Lechevalier, Bisserie, & Coston, 1983; Sugar & Gerald, 1940) (modified Shirres-GEMINI variant).

Three points should be emphasized:

1. the hemicord used as a bridge in chronic SCI has undergone years of plastic readjustments (as the entire CNS: Isa, 2017), some maladaptive (e.g., in the case of cord central pain: Canavero & Bonicalzi, 2018). This might interfere with the process of recovery in some cases. However, it is well known that so-called entrenched plasticity is in fact reversible (discussed in Canavero & Bonicalzi, 2011).
2. Roots from the hemigraft have to be cut, which causes sensorimotor disruption in their respective territories of innervation. Studies of dorsal rhizotomies in human chronic pain patients verify that nearby roots take over and compensate for the resulting deficits (discussed in Canavero & Bonicalzi, 2007). Motor deficits would affect chest and abdominal wall muscles in a limited area.
3. The entire anatomical layout is disrupted. However, as mentioned (see above), it is the gray matter that supports locomotor recovery, even if white matter bundles are misaligned and not in continuity. This bridging segment is basically a gray matter bridge through which sensorimotor transmission is restored.

In all cases, PEG and electrical stimulation are deployed. PEG alone leads to remarkable recovery, but this is expected to be boosted by spinal cord and motor cortex stimulation (see above; reviewed in Canavero et al., 2016; Canavero & Ren, 2020).

Current human trial

CANINE TRIAL: A preliminary canine study of the modified Shirres-GEMINI approach has been conducted on four female Beagles in China. In this proof-of-principle canine trial, paralysis following removal of an entire 3 cm long segment of the cord was at least partially reversed by a pedicled autograft of the animal's hemicord treated with PEG at the contact interfaces (Fig. 1). At 6 months the final average motor score (canine 0–19 Basso-Bresnahan-Beatty scale, cBBB) was roughly in line with our previous canine PEG studies of a complete spinal cord transection (medians: respectively 11.5 vs 11: Table 1) (reviewed in Ren et al., 2019). The main differences were a slower onset of symptom reversal (17 days vs 3 days) and lower final top scores (12 vs 18). This is likely due to the need for re-growing fibers to cross two, instead of one, sectional levels and more prolonged neuroplastic rearrangement than a simple section. Sphincter control was not regained at 6 months. DTI and histology data verified a vigorous regrowth of fibers across the lesional interfaces (Figs. 2 and 3).

HUMAN TRIAL: On the heels of the above study, a clinical trial was approved by the Medical Ethics Committee of Ruikang Hospital Affiliated to Guangxi University of Traditional Chinese Medicine. Inclusion criteria are: (1) Age < 50 - years old; (2) Thoracic or thoraco-lumbar traumatic-only SCI; (3) Interval from injury >12 months; (4) Absence of neuropsychiatric conditions; (5) Normal cardiopulmonary function. Surgical removal of any fixation devices was carried out in consenting patients. All patients were then submitted to Magnetic Resonance Imaging (MRI), Diffusion Tensor Imaging (DTI), Computerized Tomography (CT), Somatosensory Evoked Potential (SEP), and Motor Evoked Potential (MEP). Initial enrollment included 13 paraplegic patients (9 men, 3 women) classified as American Spinal Injury Association (ASIA) grade A. The goal of this study was to test the two arms (chemical and electrical) of the GEMINI SCF protocol singly (chemical only) or combined and compare long-term results and speed of recovery of both cord autografts and peripheral nerve bridges. Ten male (age range: 14–46 years) and three female (age range: 26–47) patients received the surgery in 2020. Eight underwent cord autotransplants (SCI levels: T2 up to T11) and five peripheral nerve grafting (SCI levels: T10–L2).

PROCEDURE: After positioning the patients in the prone position, general anesthesia was induced. The skin and muscles overlying the thoracic and lumbar spinal column were incised. A laminectomy was performed at spinal cord injury level with a cutting ultrasonic scalpel (BoneScalpel®, Misonix, USA) to expose the dura mater, which was then cut open to expose the spinal cord. The cord autotransplant was performed (see Fig. 1A and 4(1/2)). The SCI epicenter was removed leaving a gap between two fresh spinal cord stumps and sent out for histological assessment. After measuring the gap, a hemicord segment of equal length along with the spared posterior spinal artery (PSA) was gently split from the rest of the cord either rostrally or caudally (depending on the level of SCI) and turned over to bridge the gap. The PSA ensured

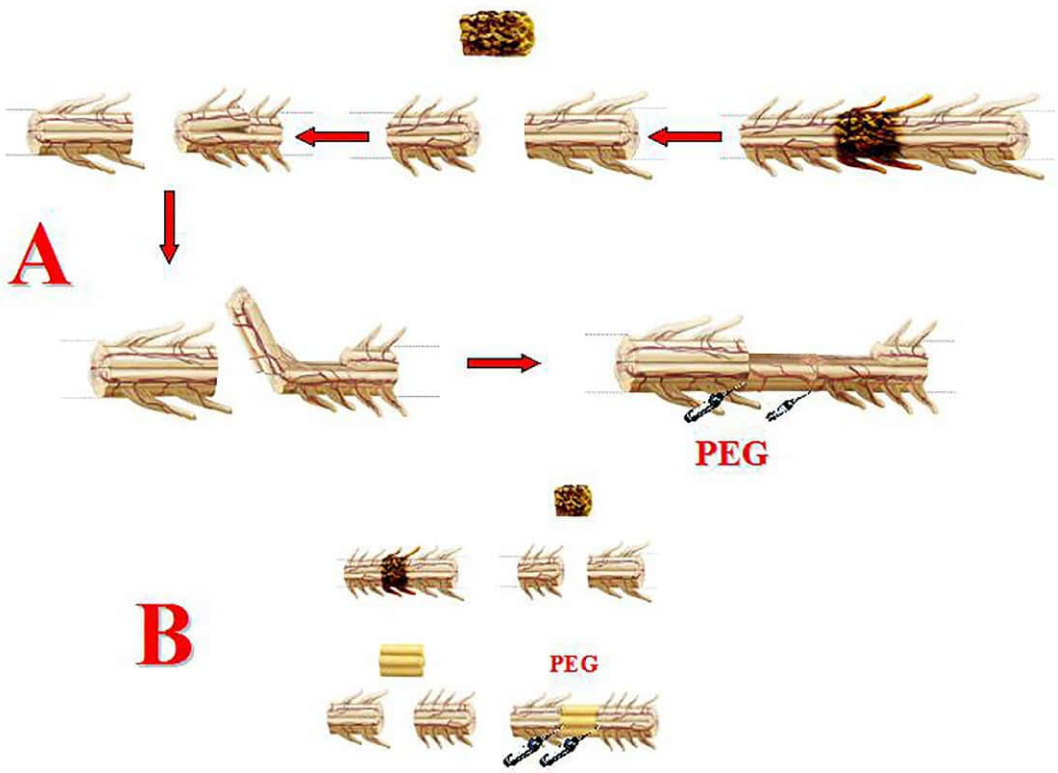

FIG. 1 (A) Modified Shirres-GEMINI protocol: surgical technique. The spinal injury epicenter, as assessed radiologically and then visually during surgery, is removed *en bloc*, leaving a gap bordered by undamaged cord ends. A pedicled (vascularized) hemicord of adequate length is split along the sagittal plane and subsequently turned over to fill the gap. PEG is applied at this moment at both ends. After dural closure with a graft, electrical stimulators are stitched onto the dura. (B) Whenever an autograft is not possible, a bundle of segments from the patient's own sural nerve is positioned inside the gap.

continual vascularization of the cord bridge. At the points of contact between the cord transplant and the stumps PEG600 (10 mL, Sigma-Aldrich/Merck, Germany) was topically injected. Finally, the dura mater was sutured with an artificial dural patch (Guanhao Biotech, China). A 3-hole silicone drainage tube was placed into the wound, and the wound was sutured by layers.

Whenever a cord autograft was not feasible (distal thoracic and lumbar), *free sural nerve transplantation (FSNT)* was performed. The skin and subcutaneous fat overlying the sural nerve of one leg were incised and the sural nerve excised and split into several segments of the same length, which were then assembled into one bundle. The spinal cord was exposed and treated similarly to the PCAT protocol (Fig. 1B). The sural nerve bundle was inserted into the gap and sutured under the operating microscope with 7–0 threads; PEG600 (10 mL) Sigma-Aldrich/Merck, Germany) was topically applied at the two bridge-stump interfaces.

Spinal cord stimulation employed four MEDTRONIC (USA) Model 3778 Pisces-Octad electrodes positioned to cover the two fusional interfaces (Fig. 4(3)). These were initially positioned in the last patients of this series and will be installed in all future patients.

The entire operation (both versions) took about 4 h to complete. Somatosensory evoked potentials (SEP) and motor evoked potentials (MEP) were recorded at preoperatively and 5 min, 1, 2, 3, 4 weeks postoperatively and analyzed with NIM-ECLIPSE® System (Medtronic, USA). All patients were scanned with MRI and DTI using a 1.5 T MRI system in the supine position preoperatively and at 4 weeks postoperatively. Post-operative spinal angiography is a consideration to assess graft vascularization, but possible toxicity from the contrast medium limits its use to selected cases.

Two weeks after surgery, rehabilitation began employing either an assistive robotic exoskeleton (AiWalker, Beijing Ai-Robotics Technology Co. Ltd., China) 30 min *bid*, or an intelligent auxiliary mobile robot (BangBang, Shanghai Bangbang Robot Co. Ltd., China) or a paraplegic standing frame, 40 min *bid*, or a rehabilitation bicycle 1 h *bid*.

PRELIMINARY RESULTS: The postoperative period was uneventful in all cases (no fever, incisional infections, or cerebrospinal fluid leaks). No adverse reaction of any kind to PEG600 was observed. Immunohistochemistry evinced complete

TABLE 1 cBBB scores of four female Beagles submitted to the modified Shirres-GEMINI variant.

Days	Transplant +PEG				Mean
−1	19	19	19	19	19
0	0	0	0	0	0
3	0	0	0	0	0
10	0	0	0	0	0
17	0	0	1	1	0.5
21	0	0	3	4	1.75
25	1	1	4	6	3
29	4	4	5	6	4.75
32	7	6	6	6	6.25
37	9	8	7	9	8.25
45	10	8	9	10	9.25
53	12	8	10	11	10.25
59	12	9	10	12	10.75
180	12	11	10	12	11.25

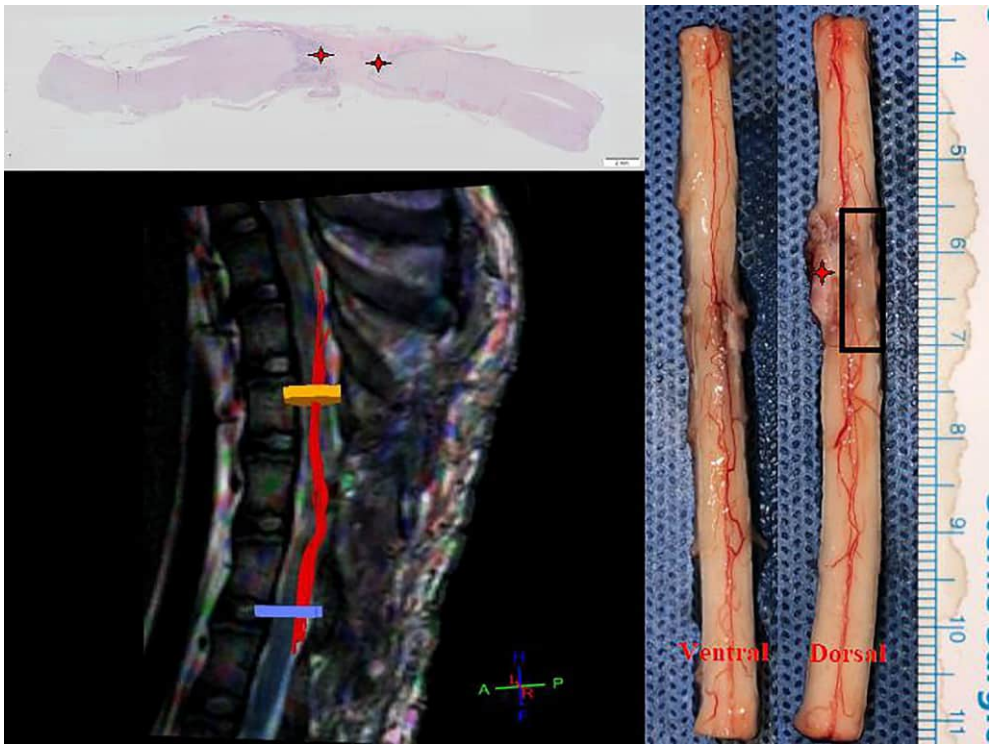

FIG. 2 Canine trial of the modified Shirres-GEMINI variant. Left upper half: sagittal view of the grafted cord (H&E staining): notice the absence of cysts at the points of fusion (stars). Right half: autoptic view of the cords: notice the graft perfectly enmeshed with the healthy cords (black rectangle); on the side, the hemigap is filled by scar. Left lower half: Diffusion Tensor Imaging (DTI) image at 6 months: new fibers extend beyond the fusional interfaces of the graft.

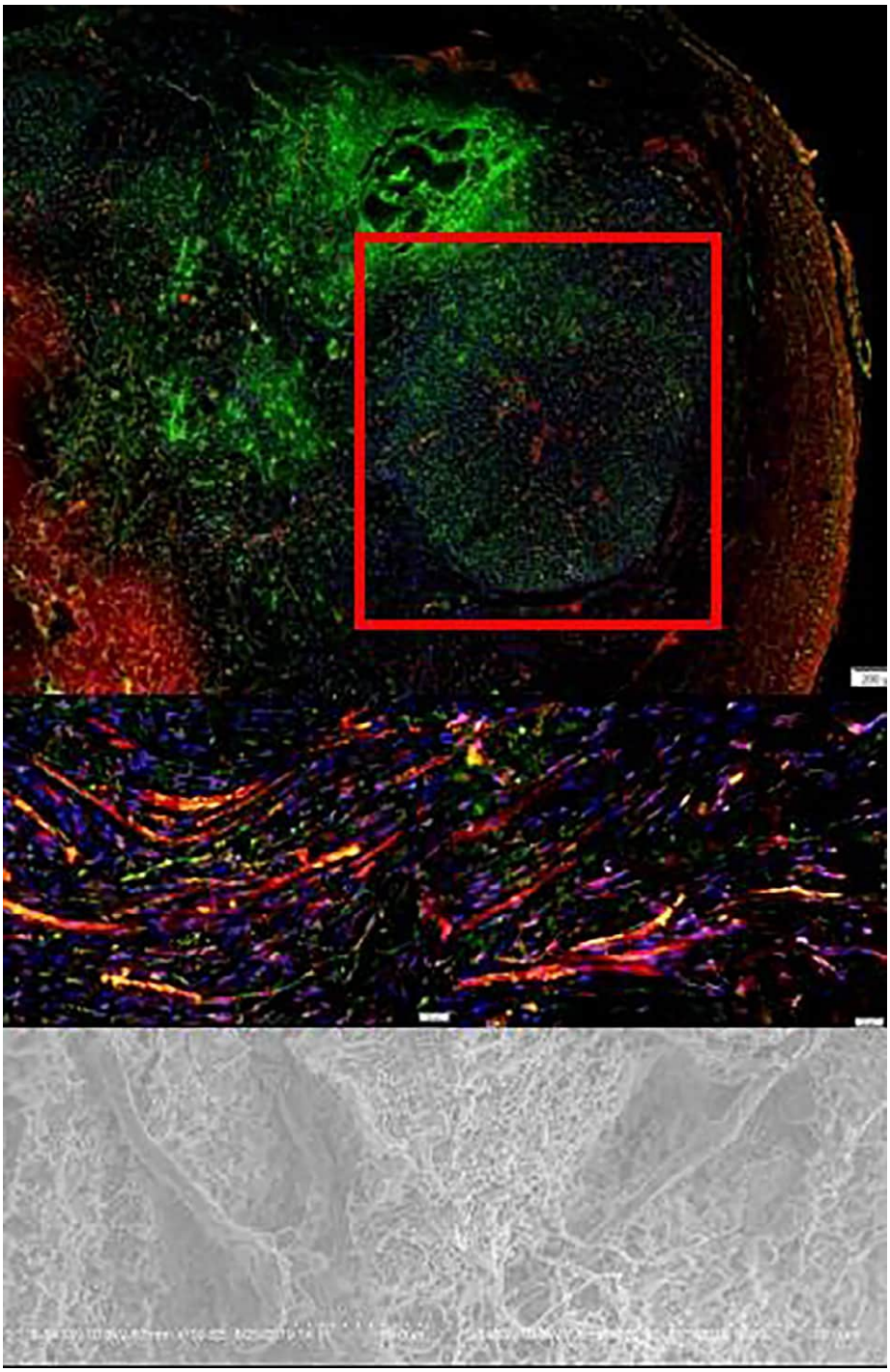

FIG. 3 Canine trial of the modified Shirres-GEMINI variant. Neurofilament immunofluorescence of the graft (red square) and fusional interfaces (middle): notice profuseness of fiber regrowth. Lower third: Scanning Electron Microscope images of sprouting fibers across the fusional interfaces.

absence of surviving fibers in the removed injured segment and correct removal of all damaged tissues. In line with the canine study, no sign of motor recovery was evinced for several days after the surgery. In patients treated with PEG only, the first signs of recovery were visible at 2 weeks, as one cord-transplant patient was able to move the knee, ankle and toe joints of both lower extremities voluntarily; a nerve-bridge patient did the same at 3 weeks. By month 4, several patients displayed voluntary control of the legs; initial supported ambulation was observed in some cases (Fig. 5). DTI and MEPs showed anatomical and physiological recovery (Fig. 5).

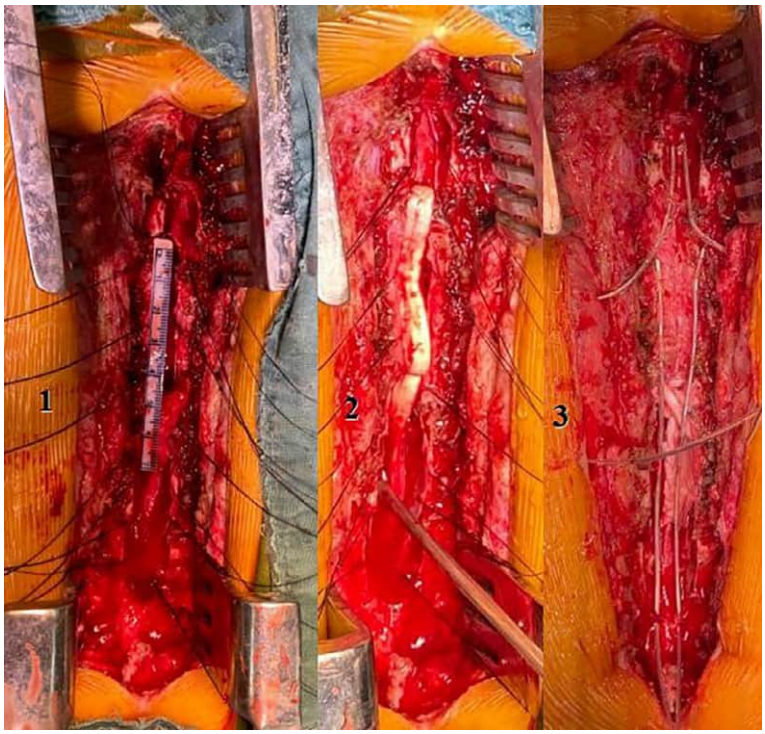

FIG. 4 Shirres-GEMINI operative view in a patient. Post-resection gap (T6–7), length: 5 cm (1); pedicled hemisegment in place (2); four MEDTRONIC octopolar leads are positioned on the dural graft (3).

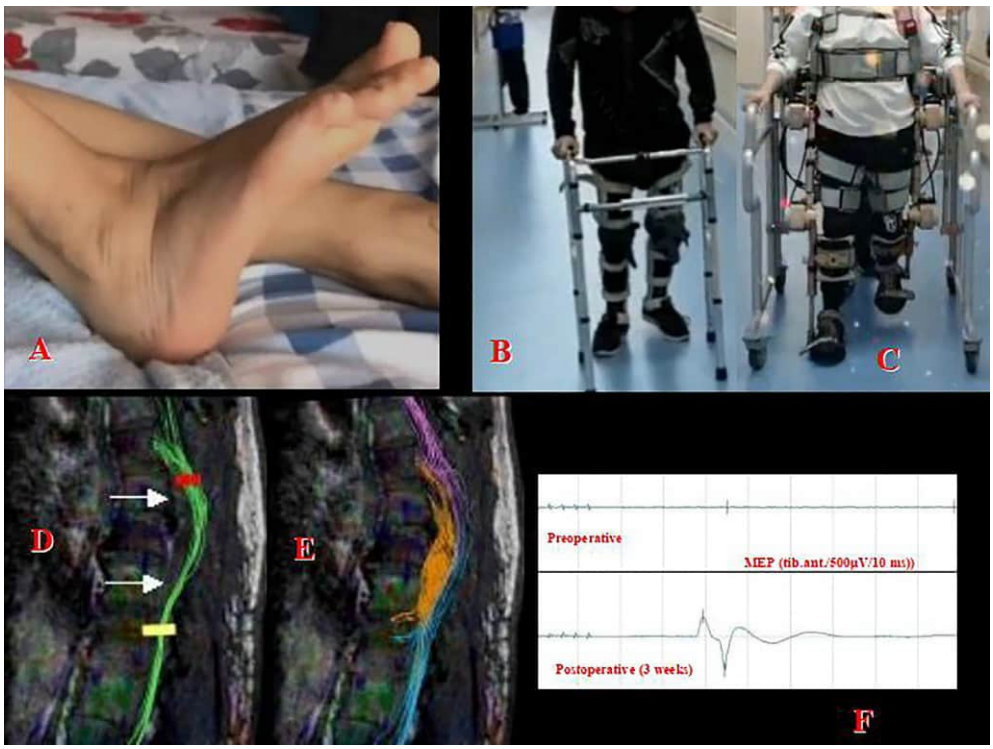

FIG. 5 Evidence of motor recovery in patients. (A) At 1 month, lower limbs can be flexed voluntarily. (B) At 2 months, patients can take the first steps with assistance. (C) Patient undergoing rehabilitation inside a robotic harness. (D and E) DTI showing fiber regrowth across the cord autograft. (F) Recovery of motor evoked potentials.

Spinal cord stimulation was conducted by stimulating with either the upper or the lower electrodes or combined. After a few weeks, stimulation with the upper electrodes could elicit motor activity in the legs, proving the viability of the anatomical bridge; patients experienced voluntary control over the legs at high voltage (5–9 V). As expected, stimulation with the lower electrodes activated leg movements immediately after the surgery, again at high voltages. Combination stimulation was carried out at low voltage (3 V) cranially and high voltage caudally (max 9 V). Frequencies assessed ranged from low (20 Hz) to moderately high (60 Hz); pulse widths were tested between 60 and 450 μs. Preliminary observations suggest that electrical stimulation does indeed accelerate recovery.

Conclusion

The decades-old idea that SCI can be cured by removing the most heavily damaged segment of a cord and bringing the healthy tissue above and below the epicenter in direct—or indirect contact, through a viable graft/transplant (either cord or peripheral nerve segments)—is now being translated clinically on the heels of the introduction of the GEMINI spinal cord fusion protocol in 2013. The initial results of the first clinical trial of GEMINI-powered spinal cord autografting are promising.

Applications to other areas of neuroscience

In this chapter, we have reviewed the GEMINI spinal cord fusion protocol in its translation to spinal cord injury. The GEMINI protocol exploits fusogens such as polyethylene glycol (PEG) and spinal electrical stimulation to re-start nerve conduction across transected spinal cords. Animal studies including in rodents, canines, and primates confirmed its efficacy. The GEMINI protocol has been developed to enable head and brain transplants. Head transplants are now been assessed in man, while brain transplants are in the experimental phase. Both have been developed primarily for life extension, and once tolerogenic protocols that avoid immunosuppression become available, they will revolutionize human society as we know it. Cosmetic body transplants will also become an option. The GEMINI protocol can theoretically be applied to several neuroconditions, e.g., multiple sclerosis, in which focal damage in the cord is primarily responsible for motor disability. Transplanting segments of healthy cords could reverse arm and gait impairment. The availability of a powerful nerve function restoration protocol can actually be envisioned as a treatment for several brain ailments. For instance, a possible scenario deals with transplantation of segments of healthy brain (from donor, fresh cadavers, or organoids) as replacement of diseased brain tissue, e.g., after stroke or major trauma, including prolonged unconsciousness states.

Mini-dictionary of terms

1. PEG: Polyethylene Glycol is a widely used chemical with membrane fusogenic properties. Once applied, it leads to the reconstitution of damaged cell membranes.
2. Spinal Cord Electrical Stimulation: this is a widely employed technique to control chronic pain, with the additional benefit of kick-starting depressed neural activity in the cord movement generating centers after spinal injury.
3. GEMINI: this is the technology that re-establishes anatomophysiologic continuity of a transected spinal cord. It combines fusogens and electrical stimulation of the nervous system.
4. Shirres-GEMINI approach: this surgery combines *en bloc* removal of the most injured segment of the cord, replacement with a pedicled hemicord segment from above or below the extirpation area and application of the GEMINI spinal cord fusion protocol at both ends of the grafted segment.
5. Freeman-GEMINI approach: this surgery combines en bloc removal of the most injured segment of the cord, shortening of the vertebral column and direct fusion of the stumps under GEMINI conditions.

Key facts of the GEMINI spinal cord fusion protocol for spinal cord injury

1. GEMINI was introduced with the goal of enabling head and brain transplants in 2013
2. GEMINI exploits special substances called fusogens, such as polyethylene glycol (PEG) combined with spinal electrical stimulation to force two ends of a transected cord to re-establish communication.
3. Fusogens have the ability to refuse damaged cell membranes, including neuronal and axonal membranes.

4. Electricity stimulates nerve fiber regrowth and "powers up" depressed neuronal circuits after spinal cord injury.
5. The GEMINI spinal cord fusion (SCF) protocol has been shown to reverse motor paralysis after spinal cord transection in rodents, canines and primates

Summary points

1. There is at present no biological cure for chronic paralysis following spinal cord injury (SCI). Chronic disability after spinal cord injury remains challenge.
2. Many experimental treatments including stem cells have not led to a long-sought cure
3. In the 1940s to 1950s, surgeons believed that the first step toward a cure would require the extirpation of the most damaged segment of the cord. The result would be the creation of two undamaged stumps whose ends would have to be connected somehow.
4. The GEMINI spinal cord fusion protocol was introduced in 2013 to mend transected spinal cords in the context of head/brain transplants
5. By combining 3 and 4, a permanent, biological cure becomes: after removing the most damaged portion of the spinal cord *en bloc*, the two ends of the cord can be brought together after spinal (vertebral) shortening (Freeman-GEMINI approach) or alternatively, the post-extirpation gap is filled with a segment of normal cord (Shirres-GEMINI approach)
6. We describe these two approaches and report the preliminary results of the first clinical trial testing autologous cord grafting in chronic SCI patients.

References

Aoun, S. G., Elguindy, M., Barrie, U., et al. (2018). Four-level vertebrectomy for en bloc resection of a cervical chordoma. *World Neurosurgery*, *118*, 316–323.

Bamba, R., Waitayawinyu, T., Nookala, R., et al. (2016). A novel therapy to promote axonal fusion in human digital nerves. *Journal of Trauma and Acute Care Surgery*, *81*, S2177.

Beneš, V., Jr., Druga, R., Rokyta, R., & Stastný, J. (1991). Vertebrectomy and its possible use in repair of spinal cord injuries by neural transplantation. *Restorative Neurology and Neuroscience*, *2*, 255–260.

Bittner, G. D., Sengelaub, D. R., Trevino, R. C., et al. (2016). The curious ability of polyethyne glycol fusion technologies to restore lost behaviors after nerve severance. *Journal of Neuroscience Research*, *94*, 207–230.

Brazda, N., Voss, C., Estrada, V., et al. (2013). A mechanical microconnector system for restoration of tissue continuity and long-term drug application into the injured spinal cord. *Biomaterials*, *34*, 10056–10064.

Calvert, J. S., Grahn, P. J., Zhao, K. D., & Lee, K. H. (2019). Emergence of epidural electrical stimulation to facilitate sensorimotor network functionality after spinal cord injury. *Neuromodulation*, *22*, 244–252.

Canavero, S. (Ed.). (2009). Textbook of therapeutic cortical stimulation. In New York: Nova Science Pub. Co.

Canavero, S. (2013). HEAVEN: The head anastomosis venture project outline for the first human head transplantation with spinal linkage (GEMINI). *Surgical Neurology International*, *4*, S335–S342.

Canavero, S. (Ed.). (2014). *Textbook of cortical brain stimulation*. Berlin: DeGruyter Open.

Canavero, S. (2015). The "Gemini" spinal cord fusion protocol: Reloaded. *Surgical Neurology International*, *6*, 18.

Canavero, S., & Bonicalzi, V. (2007). *Central pain syndrome*. New York: Cambridge University Press.

Canavero, S., & Bonicalzi, V. (2011). *Central pain syndrome* (2nd ed.). Cambridge: Cambridge University Press.

Canavero, S., & Bonicalzi, V. (2018). *Central pain syndrome* (3rd ed.). Springer-Nature.

Canavero, S., & Ren, X. (2016a). Houston, GEMINI has landed: Spinal cord fusion achieved. *Surgical Neurology International*, *7*, S626–S628.

Canavero, S., & Ren, X. P. (2016b). The spark of life: Engaging the cortico-truncoreticulo-propriospinal pathway by electrical stimulation. *CNS Neuroscience & Therapeutics*, *22*, 260–261.

Canavero, S., & Ren, X. P. (Eds.). (2020). *The technology of head transplantation*. New York: NOVA Science Pub. Co.

Canavero, S., Ren, X., & Kim, C.-Y. (2021). Heterologous spinal cord transplantation in man. *Surgical Neurology International*, *12*, 295.

Canavero, S., Ren, X., Kim, C. Y., & Rosati, E. (2016). Neurologic foundations of spinal cord fusion (GEMINI). *Surgery*, *160*, 11–19.

Carlstedt, T., James, N., & Risling, M. (2017). Surgical reconstruction of spinal cord circuit provides functional return in humans. *Neural Regeneration Research*, *12*, 1960–1963.

Cho, N., Squair, J. W., Bloch, J., & Courtine, G. (2019). Neurorestorative interventions involving bioelectronic implants after spinal cord injury. *Bioelectronic Medicine*, *5*, 10.

De Medinaceli, L., & Merle, M. (1991). Applying "cell surgery" to nerve repair: A preliminary report on the first ten human cases. *Journal of Hand Surgery (British)*, *16*, 499–504.

De Medinaceli, L., & Wyatt, R. J. (1993). A method for shortening of the rat spine and its neurologic consequences. *Journal of Neural Transplantation & Plasticity*, *4*, 39–52.

Derlon, J. M., Roy-Camille, R., Lechevalier, B., Bisserie, M., & Coston, A. (1983). Delayed spinal cord anastomosis. In C. C. Kao, R. P. Bunge, & P. J. Reier (Eds.), *Spinal cord reconstruction* (pp. 223–234). New York: Raven Press.

Derlon, J. M., Roy-Camille, R., Saillant, G., Poirier, J., & Pichon, F. (1978). Experimental transection of the spinal cord. *Neurochirurgie*, *24*, 103–111.

Dimitrijevic, M. R. (1983). Neurophysiological evaluation and epidural stimulation in chronic spinal cord injury patients. In C. C. Kao, R. P. Bunge, & P. J. Reier (Eds.), *Spinal cord reconstruction* (pp. 465–474). New York: Raven Press.

Estrada, V., Brazda, N., Schmitz, C., et al. (2014). Long-lasting significant functional improvement in chronic severe spinal cord injury following scar resection and polyethylene glycol implantation. *Neurobiology of Disease*, *67*, 165–179.

Freeman, L. W. (1963). Observation on the regeneration of spinal axons in mammals. In *Proceedings, X congreso latinoamericano de neurochirurgia* (pp. 135–144). Brazil: Editorial Don Bosco.

Heimburger, R. F. (2005). Return of function after spinal cord transection. *Spinal Cord*, *43*, 438–440.

Heimburger, R. F. (2006). Is there hope for return of function in lower extremities paralyzed by spinal cord injury? *Journal of the American College of Surgeons*, *202*, 1001–1004.

Hsieh, P. C., Stapleton, C. J., Moldavskiy, P., et al. (2010). Posterior vertebral column subtraction osteotomy for the treatment of tethered cord syndrome: Review of the literature and clinical outcomes of all cases reported to date. *Neurosurgical Focus*, *29*, E6.

Illis, L. S. (2012). Central nervous system regeneration does not occur. *Spinal Cord*, *50*, 259–263.

Isa, T. (2017). The brain is needed to cure spinal cord injury. *Trends in Neurosciences*, *40*, 625–636.

Jack, A., Hurd, C., Martin, J. H., & Fouad, K. (2020). Electrical stimulation as a tool to promote plasticity of the injured spinal cord. *Journal of Neurotrauma*, *37*, 1933–1953.

James, N. D., McMahon, S. B., Field-Fote, E. C., & Bradbury, E. J. (2018). Neuromodulation in the restoration of function after spinal cord injury. *Lancet Neurology*, *17*, 905–917.

Ju, C., Park, E., Kim, T., Kim, T., et al. (2020). Effectiveness of electrical stimulation on nerve regeneration after crush injury: Comparison between invasive and non-invasive stimulation. *PLoS One*, *15*, e0233531.

Kostyuk, P. G., & Vasilenko, D. A. (1979). Spinal interneurons. *Annual Review of Physiology*, *41*, 115–126.

Lumb, W. V., & Nornes, H. O. (1983). Vertebral resection and spinal cord reapposition. In C. C. Kao, R. P. Bunge, & P. J. Reier (Eds.), *Spinal cord reconstruction* (pp. 209–222). New York: Raven Press.

Minassian, K., & Hofstoetter, U. S. (2016). Spinal cord stimulation and augmentative control strategies for leg movement after spinal paralysis in humans. *CNS Neuroscience & Therapeutics*, *22*, 262–270.

Mody, G. N., Bravo Iñiguez, C., Armstrong, K., et al. (2016). Early surgical outcomes of en bloc resection requiring vertebrectomy for malignancy invading the thoracic spine. *The Annals of Thoracic Surgery*, *101*, 231–236.

Murray, G., Ugray, E, & Graves, A. (1965). Regeneration in injured spinal cord. *American Journal of Surgery*, *109*, 406–409.

Qiu, F., Yang, J. C., Ma, X. Y., et al. (2015). Relationship between spinal cord volume and spinal cord injury due to spinal shortening. *PLoS One*, *10*, e0127624.

Ren, X., Kim, C., & Canavero, S. (2019). Bridging the gap: Spinal cord fusion as a treatment of chronic spinal cord injury. *Surgical Neurology International*, *10*, 51.

Ryan, I., & Henderson, P. W. (2020). Gemini: Overview of fusogens. In S. Canavero, & X. P. Ren (Eds.), *The technology of head transplantation*. New York: Nova Science Publishers (Chapter 4).

Shik, M. L. (1983). Action of the brainstem locomotor region on spinal stepping generators via propriospinal pathways. In C. C. Kao, R. P. Bunge, & P. J. Reier (Eds.), *Spinal cord reconstruction* (pp. 421–434). New York: Raven Press.

Song, W., Amer, A., Ryan, D., & Martin, J. H. (2015). Combined motor cortex and spinal cord neuromodulation promotes corticospinal system functional and structural plasticity and motor function after injury. *Experimental Neurology*, *277*, 46–57.

Steinberg, J. A., Wali, A. R., Martin, J., et al. (2017). Spinal shortening for recurrent tethered cord syndrome via a lateral retropleural approach: A novel operative technique. *Cureus*, *9*, e1632.

Street, D. M. (1967). Traumatic paraplegia treated by vertebral resection, excision of spinal cord lesion, suture of the spinal cord and interbody fusion. In *Proceedings of the annual clinical spinal cord injury conference (Long Beach, CA, USA), 16* (pp. 92–103).

Sugar, O., & Gerald, R. W. (1940). Spinal cord regeneration in the rat. *Journal of Neurophysiology*, *3*, 1–19.

Sunshine, M. D., Cho, F. S., Lockwood, D. R., Fechko, A. S., Kasten, M. R., & Moritz, C. T. (2013). Cervical intraspinal microstimulation evokes robust forelimb movements before and after injury. *Journal of Neural Engineering*, *10*, 036001.

Thornton, M. A., Mehta, M. D., Morad, T. T., et al. (2018). Evidence of axon connectivity across a spinal cord transection in rats treated with epidural stimulation and motor training combined with olfactory ensheathing cell transplantation. *Experimental Neurology*, *309*, 119–133.

Wang, A., Zhang, G., Xiaochen, W., Zhang, C., Tao, S., & Huo, X. (2016). Combination of applied electric field and polyethylene glycol effectively enhance functional recovery in acute spinal cord injury of rats. In *Paper presented at: 2016 Asia-Pacific international symposium on electromagnetic compatibility (APEMC)* (pp. 17–21).

Woolsey, D., Minckler, J., Rezende, N., & Klemme, R. (1944). Human spinal cord transplantation. *Experimental Medicine and Surgery*, *2*, 93–102.

Zareen, N., Shinozaki, M., Ryan, D., et al. (2017). Motor cortex and spinal cord neuromodulation promote corticospinal tract axonal outgrowth and motor recovery after cervical contusion spinal cord injury. *Experimental Neurology*, *297*, 179–189.

Chapter 25

Chondroitinase ABC I as a novel candidate for reducing damage in spinal cord injury

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Abbreviations

cABC I	chondroitinase ABC I
CNS	central nervous system
CS	chondroitin sulfate
CSPG	chondroitin sulfate proteoglycan
CSPGs	chondroitin sulfate proteoglycans
DS	dermatan sulfate
DSPG	dermatan sulfate proteoglycan
ECM	extracellular matrix
GAGs	glycosaminoglycans
GBM	glioblastoma
HA	hyaluronic acid
Hep	heparin
HepS	heparan sulfate
HS	heparin sulfate
KS	keratan sulfate
PEG	polyethylene glycol (PEG)
SCI	spinal cord injury

Molecular perspectives

Glycosaminoglycans and proteoglycans

Extracellular matrices (ECMs) and cell surfaces of the mammalian tissues contain repeating disaccharide units known as glycosaminoglycans (GAGs). These linear polysaccharides can be sulfated in various positions to obtain a negatively charged nature that is essential for molecular recognition and binding. The corresponding reactions are catalyzed by the enzymes of the sulfotransferase family. Based on the type of disaccharide units, GAGs are categorized into several groups, including hyaluronic acid (HA), chondroitin sulfate/dermatan sulfate (CS/DS), heparin/heparin sulfate (Hep/HS), and keratan sulfate (KS) (Gandhi & Mancera, 2008).

A typical chondroitin sulfate disaccharide unit in human, chondroitin-6-sulfate (C6S) with the primary configuration containing a uronic acid (Glucuronic acid) and amino sugar (Galactosamine) is shown in Fig. 1A. As shown in Fig. 1B; GAG chains can covalently bind at their reducing ends to a serine or asparagine residue of a target protein, forming a proteoglycan (Jackson, Busch, & Cardin, 1991). On a higher level, a biopolymer such as hyaluronic acid acts as a backbone structure to assemble similar or various types of proteoglycans (Fig. 1C).

These macromolecules are synthesized in all mammalian cells and based on the type and function; they may be secreted into the ECM, localized into the plasma membrane, or stored in secretory vesicles (Couchman, 2010; Dick, Akslen-Hoel, Grøndahl, Kjos, & Prydz, 2012; Iozzo & Schaefer, 2015; Yanagishita, 1993). Due to the wide variety of functions, any

Diagnosis and Treatment of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822498-4.00025-7

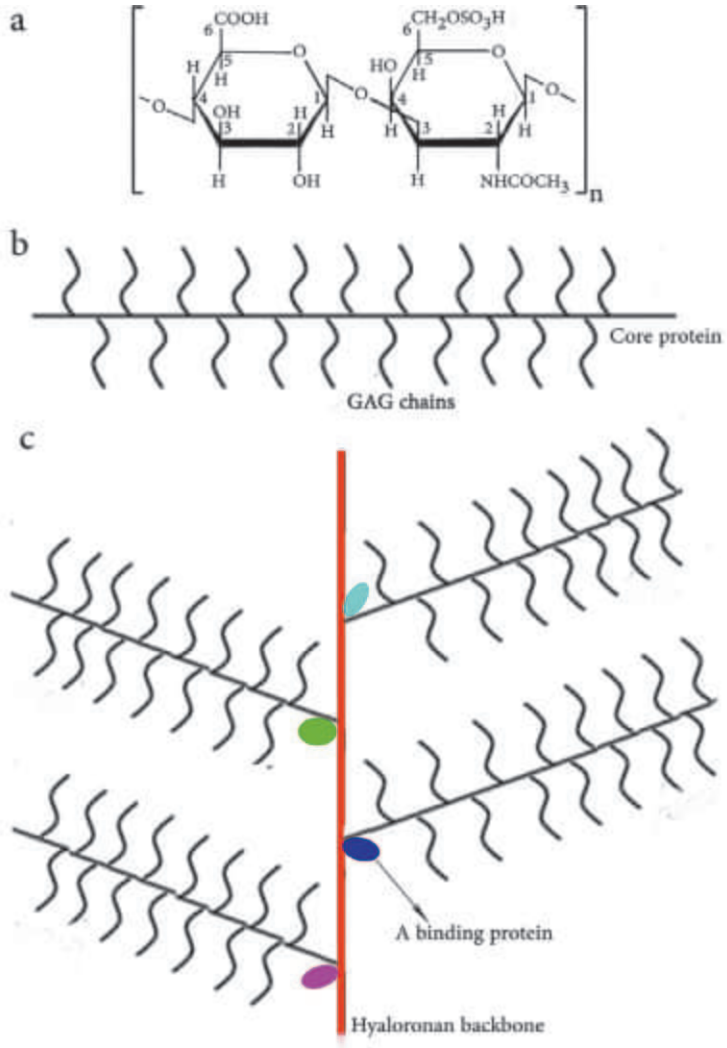

FIG. 1 Structural organization of Glycosaminoglycans and Proteoglycans. (A) The structure of a disaccharide unite in chondroitin-6-sulfate (C6S). D-glucuronic acid has a β1–3 linkage to *N*-acetyl-β-D-galactosamine. The connection between disaccharide units in the polymerized GAG is β1–4. Galactosamine can be variously sulfated at either 4 or 6 positions to give C4S or C6S, respectively. (B) The polymerized GAG chains are attached to the target protein forming a proteoglycan. The GAG chains may be the same or of other types. (C) The hyaluronic acid serves as a backbone to assemble similar or different types of proteoglycans. Specific proteins, such as growth factors and cytokines, can reversibly bind to this macromolecule.

defects in the synthesis and processing of proteoglycans have important clinical manifestations (Schwartz & Domowicz, 2018). Regarding the protein binding affinity and biocompatibility of GAGs, they are proposed as a tool for localized drug-delivery, using enzymes as drug (Hachim, Whittaker, Kim, & Stevens, 2019).

Distribution and functions of GAGs and proteoglycans

The GAGs play essential roles in fundamental biological processes, and wide distribution of these biopolymers in animals demonstrates that they have conserved functions in organisms (DeAngelis, 2002). In the normal state, individual tissues of the human body contain a defined combination of GAGs, some of which are tissue-specific, and others may be temporally observe during growth, development, and pathogenic conditions.

The ability to absorb water molecules and their spatial structure enables GAGs and proteoglycans to provide a suitable scaffold that is essential to maintain the shape, cohesive properties, and mechanical features of tissues (Beldowski, Mazurkiewicz, Topoliński, & Małek, 2019). Accordingly, in tissue-based diseases, damage to the structure of proteoglycan is a central event (Hardingham & Bayliss, 1990). Some of the GAGs can bind into several specific proteins such as

cytokines, chemokines, growth factors, morphogens, etc., to form biologically effective types of macromolecules (Imberty, Lortat-Jacob, & Pérez, 2007). These interactions are crucial in regulating of some critical biological processes, including cell migration (Merle, Durussel, Delmas, & Clézardin, 1999), regulation of blood coagulation and homeostasis (Bourin & Lindahl, 1993; Lasne, Jude, & Susen, 2006), growth factor control (Lander & Selleck, 2000), cell adhesion, and signaling (Werz & Schachner, 1988), inflammation (Gill, Wight, & Frevert, 2010), and pathogens attachment (García et al., 2016). They are involved in multicellular processes and have critical roles in development.

The GAGs are also involved in the inhibition of smooth muscle cell proliferation (Clowes & Karnowsky, 1977). It has been reported that proteoglycans may have essential roles in normal glomerular cell function and progressive renal disease (Templeton, 1992). They are considered as the first defensive line at the bladder's luminal surface against urinary tract infections, that created by pathogenic *Escherichia coli* among postmenopausal women (Anand et al., 2012). It has postulated that the accumulation of specific GAGs may form a physical barrier to the passage of immunocompetent cells from the mother to the fetus (Calatroni & di Ferrante, 1969). The changes in the composition and molecular structure of placental GAGs during pregnancy could alter the molecular transport rate through placental connective tissue and affect the rate of fetal growth (Lee, Jamieson, & Schafer, 1973). It has been reported that GAGs are involved in tumor development, angiogenesis and metastasis in certain types of cancers (Muir, De Winter, Verhaagen, & Fawcett, 2019).

CSPGs in the nervous system

It has revealed that CSPGs and DSPGs are dominant proteoglycans in CNS-ECM (Iozzo & Schaefer, 2015). Chondroitin sulfate proteoglycans (CSPGs) are those CS-GAGs that are covalently linked to a core protein (Imberty et al., 2007). The GAG side chains in CSPGs are of different lengths, and the disaccharide units of CSPGs have either *N*-acetylglucosamine or *N*-acetylgalactosamine as well as uronic acid (see Fig. 1). Hence, depending on the length and the type of disaccharide unit and the position of sulfate moiety (positions 4 or 6), different types of CSPGs have identified, some of them have important tasks in CNS (Quraishe, Forbes, & Andrews, 2018). In CNS-ECM, various types of CSPGs bind to linear non-sulfated polysaccharides such as hyaluronan to produce a specific combination of proteoglycans, which is collectively known as lectican family proteoglycans. They include Neurocan, Brevican, Aggrecan, Perlecan, Testican, Versican, and Biglycan (Jones, Margolis, & Tuszynski, 2003; Siebert, Conta Steencken, & Osterhout, 2014). Some of the GAGs are attached to the transmembrane proteins and form the transmembrane family of proteoglycans. A schematic representation

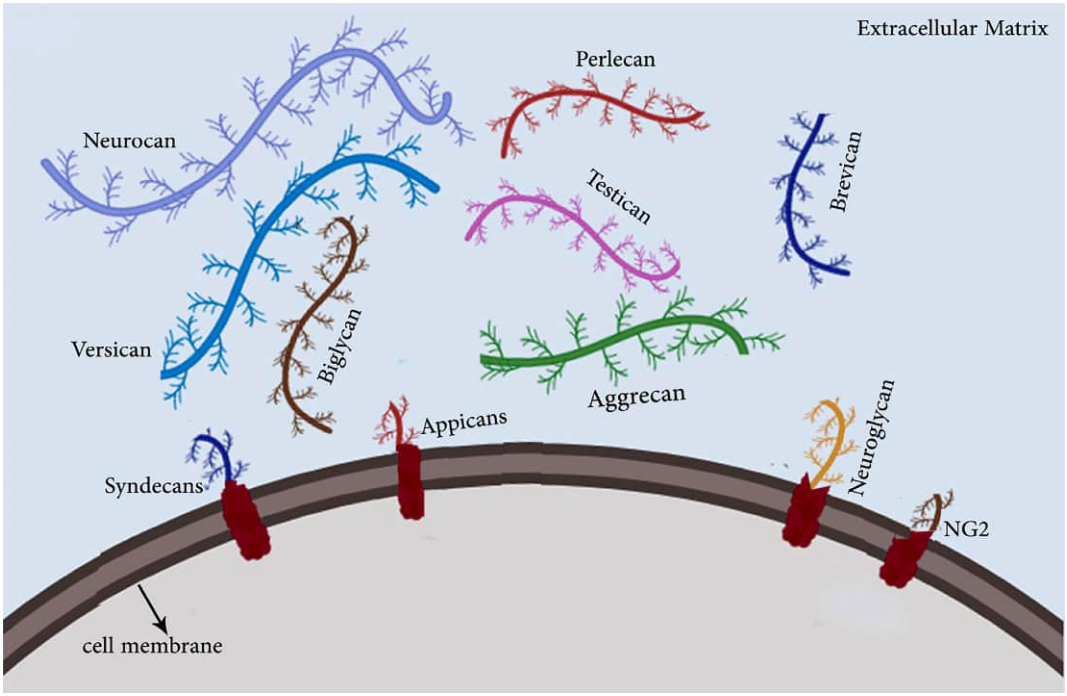

FIG. 2 A schematic representation of the proteoglycan families found in the extracellular environment and the membrane of the central nervous system. The proteoglycans in the extracellular matrix of central nervous system (CNS) including, Aggrecan, Versican, Neurocan, and Brevican, are members of the Lectican family. Members of syndecan family along with Apican, Neuroglycan, and NG2 are transmembrane proteoglycans.

of various proteoglycans in the cell surface and ECM of nervous tissues is provided in Fig. 2 (Schwartz & Domowicz, 2018). Structurally, the CNS-ECM proteoglycans provide the viscoelastic properties, maintain ions and water content and normal osmotic pressure, and dictate proper tissue organization. It has shown that the development of the nervous system in mammals involves coordinated cellular interactions, such as patterning and routing of migrating neural cells, axon pathfinding, and synapse formation, that is due to the proper organization of the nervous ECM (Silver & Silver, 2014; Tessier-Lavigne & Goodman, 1996). Hence, the time-dependent concentration of CSPGs relative to other adhesive matrix molecules at the various developmental stage, define the normal state of the CNS-ECM (Galtrey & Fawcett, 2007).

Implication of CSPGs in pathogen conditions

It has been reported that CSPGs have implications in the processes of tumor metastasis by affecting endothelial migration and adhesion (Denholm, Lin, & Silver, 2001). In the case of brain cancer, changing the pattern of interaction of CS with ligands, growth factor receptors, extracellular matrix components, and structural proteins is accompanied by the progress of Glioblastoma (GBM) (Wade et al., 2013). It has also revealed that neurodegenerative disorders are related to defects in the synthesis/degradation of proteoglycans that affect the structural integrity of nervous tissues (DeWitt, Richey, Praprotnik, Silver, & Perry, 1994). Genome-wide association studies have shown that mental disorders such as bipolar character and depression are related to unbalance in CNS-ECM constituents (Cichon et al., 2011; Shi et al., 2011).

One of the important clinical manifestations after SCI includes the rapid increasing of various types of CSPGs in ECM. It is believed that this event is a defensive mechanism that seals off the injury to prevent bacterial penetration. The corresponding injury response in damaged CNS is called reactive gliosis or glial scarring (Fawcett & Asher, 1999). The glial scar also has other positive effects such as reducing the inflammation area, modulating immune activity, and helping to restore the blood–brain barrier (Lin, Kwok, Crespo, & Fawcett, 2008; Rolls, Shechter, & Schwartz, 2009; Tuinstra, Ducommun, Briley, & Shea, 2013). However, despite these positive impacts, the glial scar as a physical barrier reveals a negative role in axonal regrowth, sprouting, and synaptic reorganization following SCI (Cregg et al., 2014; Siebert et al., 2014). Production of CSPGs occurs after the cute phase in approximately 48 h following SCI (Katoh, Yokota, & Fehlings, 2019). It also prevents oligodendrocyte maturation and remyelination (Karus et al., 2016). Accordingly, medical intervention to control the concentration of CSPGs and limit the scar size in CNS-ECM has become central to the treatment of spinal cord injuries, and management of the CSPGs concentration during this period can result in the successful treatment of SCI in subsequent phases. There are numerous reports that carbohydrate and proteoglycan degrading enzymes can be used as a therapeutic drug to prevent CSPGs chains from accumulating in the site of SCI (Bradbury et al., 2002; García-Alías, Barkhuysen, Buckle, & Fawcett, 2009; Rosenzweig et al., 2019; Tauchi et al., 2012).

Glycosaminoglycan degrading enzymes: A brief description

Regarding the various functions of GAG-proteoglycans, it is evident that creating a delicate balance between the biosynthesis and degradation of heteropolysaccharides is crucial in maintaining the normal health conditions of tissues. As mentioned in Implication of CSPGs in pathogen conditions section, the formation of proteoglycan-rich glial scar around traumatic injury of SCI inhibits long-term axonal recovery predominantly by CSPGs moieties, and degrading enzymes is considered as therapeutic drugs to overcome this medicinal challenge. Two types of enzymes can depolymerize GAG chains including lyases (EC 4.2.2.-) and hydrolases (EC 3-2-1.-). The lyases degrade GAGs by eliminative cleavage, while hydrolases-based degradation is carried out by hydrolytic cleavage. Based on the position of the cutting site, the pattern of enzymatic action is exolytic or endolytic mode (Linhardt, 2001) (Ernst, Langer, Cooney, & Sasisekharan, 1995). In vivo degradation of GAGs is carried out by corresponding hydrolases such as keratinase, hyaluronic acid hydrolase, and heparin hydrolase. The GAG degrading lyases have mainly bacterial sources, and are categorized into three main groups, including heparinases, chondroitinases, and hyaluronidases.

Structural features of chondroitinase ABC I

According to CAZy (Carbohydrate-Active enZYmes Database), the tertiary structure of cABC I include $(\alpha/\alpha)_6$ toroid + anti-parallel β-sheet. As shown in Fig. 3, it is composed of three distinctive domains, including N- and C-terminals, that are symmetrically attached to the central (catalytic) domain (Huang et al., 2003). The catalytic residues are located in the central domain, and include His-501, Tyr-508, Arg-560, and Glu-653 (Prabhakar et al., 2005). The peripheral domains are mainly made up of well-defined organized β-sheets, and the central domain has mainly helix conformation. The movement of N- and C-terminal domains around the catalytic region leads to the creation of open and closed conformation that is

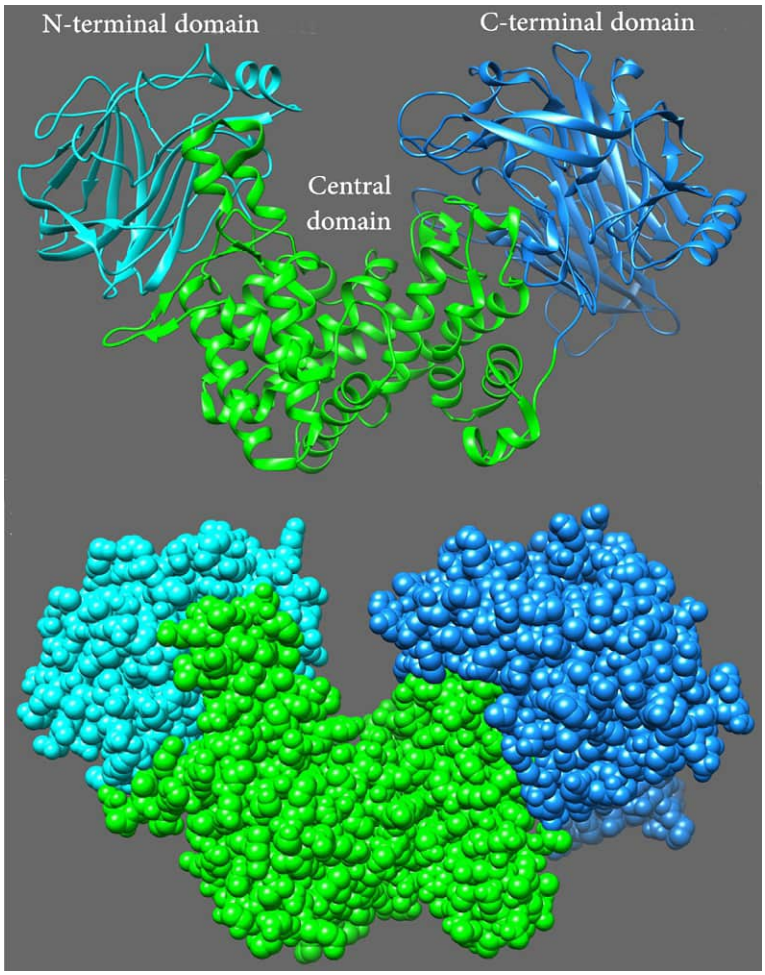

FIG. 3 The Tertiary structure of chondroitinase ABC I. Ribbon (Upper panel) and sphere (lower panel) representation of cABC I. The structure was depicted by the UCSF Chimera program using the crystal structure of cABC I (PDB ID:1HN0).

essential for the catalytic activity of the enzyme. The enzyme cleaves its substrates at the glycosidic bond via β-elimination of 1,4-hexosaminidic bonds to produce Δ4,5-unsaturated disaccharides, and a reducing end polysaccharide. Spectroscopically, product formation can be monitored as an increase in absorbance at 232 nm as a function of time.

Chondroitinase ABC I and spinal cord injury

By convention, A, B, and C in chondroitinase ABC (cABC) nomenclature, refers to chondroitin 4-sulfate, dermatan sulfate, and chondroitin 6-sulfate, respectively. According to BRENDA—The Comprehensive Enzyme Information database (www.brenda-enzymes.org), cABC I from *Proteus vulgaris* (EC 4.2.2.20) is a broad specific endolytic enzyme that degrades a variety of glycosaminoglycans of the chondroitin-sulfate- and dermatan-sulfate type. It can also acts on hyaluronan at a much lower rate. Fortunately, these substrates are the main constituents of CNS GAGs that are formed by activated astrocytes following SCI. Hence, the broad specificity of cABC I toward a combination of GAGs can be considered as a positive feature to degrade the GAG chains and can restore the right condition for nerve regeneration following SCI.

In vivo delivery of cABC I to reduce the size of glial scar and removing the inhibitory environment for the treatment of SCI was first reported by Lemons et al. in 1999 (Lemons, Howland, & Anderson, 1999). Four years later, research groups from the University of Cambridge and the University of London delivered cABC to the lesioned dorsal columns of adult rats and observed a marked functional recovery of injured CNS (Bradbury et al., 2002). To analyze the effects of cABC on axon regeneration, Lin and co-workers made unilateral nigrostriatal lesions in adult rats and found that injection of cABC can

digest hyaluronan and reduce neurocan in a limited area around the injection region. At the same time, the majority of GAGs are inaccessible to cABC digestion. They suggest that a single injection of cABC can produce an environment conducive to CNS repair for a long-term over 10 days (Lin et al., 2008). In 2011, Fawcett et al. showed that using cABC combined with rehabilitation is effective in functional recovery of forelimb function in rats with chronic SCI. They used cABC I 4 weeks after SCI (Wang, Ichiyama, Zhao, Andrews, & Fawcett, 2011). These studies, together with other investigations, have confirmed the ability of cABC I to help axon regeneration following SCI (Kasinathan, Volety, & Josyula, 2016; Muir et al., 2019).

Chondroitinase ABC I for enzyme therapy: Challenges and perspectives

Proteus Vulgaris as the bacterial source of cABC I presents in soil and intestinal tract of the human body. It uses acidic polysaccharides along with epithelial cells in the intestinal lumen as its nutrient source. Accordingly, its optimum temperature for the activity is in accordance with the normal temperature of the human body. However, the time-dependent concentration of cABC I in *P. vulgaris* is low, which is essential for its solubility. In other words, protein aggregation is an entropy-dependent process, and increasing the concentration of the enzyme molecules for practical uses, particularly at 37 °C, leads to protein aggregation due to the higher probability of effective molecular collisions (Mohammadyari, Shirdel, Jafarian, & Khalifeh, 2019). Additionally, the enzyme adaptation has been occurred not only on the temperature but also on the other environmental factors of *P. vulgaris* such as pH and ionic strengths that are different from those found in the new therapeutic environment. Accordingly, changing the environmental conditions for the enzyme is accompanied by decreasing its half-life and lower catalytic efficiency due to its low conformational stability. So, more concentration of the enzyme is needed to have efficient catalysis. Nonetheless, as mentioned above, there is a critical concentration of the enzyme above that it undergoes molecular aggregation. Moreover, using a high concentration of the recombinant enzyme per injection or increasing the number of enzyme injections at the site of SCI for more efficient catalysis may have immunogenicity responses (Muir et al., 2019). Considering the instability of cABC I due to protein aggregation and decreased half-life as well as medical challenges following repeatedly administer of the recombinant enzyme, various enzyme stabilization and enzyme delivery methods, should be developed to efficient use of the enzyme for SCI treatment. Furthermore, the formulation of the enzyme appropriate for long-term storage permits the clinicians to access the enzyme in the shortest time and a usable form.

Protein engineering strategies toward functional drug delivery

The enzyme can be synthesized, extracted, and purified with the enzyme technology methods. The classical procedures for enhancing the enzyme stability involve setting up right environmental conditions using suitable solvents containing various types of osmolytes and additives as stabilizers. It was shown that chemical modification of the recombinant enzymes with Polyethylene glycol (PEG) could increase the protein half-life and reduces the possibility of immunological side effects due to its bacterial origin (Greenwald, 2001). Additionally, site-directed mutagenesis has intensively used to logically replace critical amino acids on the structure of the protein with new residues to improve the functional and structural features of the enzyme. For example, it was revealed that increasing the repulsive electrostatic interactions between enzyme molecules via changing of surface-exposed residues by site-directed mutagenesis can reduce aggregation (Mohammadyari et al., 2019). Shoichet et al. used PEG-chemical modification procedure and site-directed mutagenesis strategy to produce improved engineered enzyme for SCI treatment. They demonstrated that representative PEGylated mutants of cABC could be locally delivered at the site of SCI in a more stabilized form (Hettiaratchi et al., 2019). Drug nano-carriers such as nano-structured lipid carriers (NLCs) are also potential candidates for the efficiently deliver of the enzyme toward its target. Enzyme immobilization using biocompatible nano-structures can protect the enzyme molecules from biodegradation and leads to the gradual release of the enzyme (Xia et al., 2015; Zuidema, Gilbert, & Osterhout, 2016). These are only examples of ongoing research studies on the humanization and methodological setting for using cABC I as a drug. Details of such studies have been reviewed elsewhere (Kasinathan et al., 2016; Muir et al., 2019).

Combinatorial therapy with chondroitinase ABC I

It is worth mentioning that SCI is accompanied by several events including proliferation of astrocytes, accumulation of macrophages and microglia, production of growth-inhibitory matrix around SCI region, abnormality in signal transduction, etc. These phenomena result in multiple clinical consequences. Therefore, SCI should be simultaneously targeted with various medical interventions (Rolls et al., 2009). In other words, cABC I should be used besides other therapeutic agents

to achieve a satisfactory outcome. Efficient delivery of cABC as a drug requires the determination of the therapeutic window of enzyme utilization during treatment time. As well as timing, the threshold of enzyme concentration influences the efficacy of enzyme therapy. It was shown that the expression of corresponding proteins increases following SCI within the first 24 h, and the maximum level of CSPGs is generally observed approximately 2 weeks after SCI. However, the gradual increase of CSPGs over time is occurred with different rates according to the type of proteoglycan (Jones et al., 2003). Finally, locomotor recovery depends on optimized drug-based treatments combined with rehabilitation.

Applications to other areas of neuroscience

Regarding the diverse roles of CSPGs in the physiological and pathological conditions of the CNS-ECM, cABC I can be used to control the right composition of the CSPGs according to the abnormal states of the nervous tissue. It had demonstrated that the efficiency of nerve recovery through peripheral nerve graft (PNG) increased in combined with cABC I and acidic fibroblast growth factor usage (DePaul, Lin, Silver, & Lee, 2015). The enzyme can also be used to eliminate the inhibitory function of CSPGs on the remyelination, which is essential in the treatment of multiple sclerosis (Lau et al., 2012). Investigating the experimental models has revealed that cABC I offers the opportunity to improve the outcome of Alzheimer's disease treatment via restoration of extracellular matrix plasticity in the synaptic region of hippocampal (Végh et al., 2014). It would be beneficial in the case of Parkinson's disease and for patients that are involved in phobias and anxiety (Moon, Asher, Rhodes, & Fawcett, 2001; Thompson et al., 2018). There are pieces of evidence that cABC I is helpful in the treatment of glioblastoma through sensitizing the glioblastoma cells to cancer drugs and enhancing the spread of oncolytic viruses as well as changing the pattern of the interaction of CSPGs with specific proteins (Dmitrieva et al., 2011; Jaime-Ramirez et al., 2017; Wade et al., 2013).

Mini-dictionary of terms

Glycosaminoglycan: Linear polysaccharide made up of repeating disaccharide units. Based on the type of sugar building blocks, various glycosaminoglycans are found in extracellular matrices of tissues.

Proteoglycan: A highly glycosylated protein produced by attachment of a given glycosaminoglycan to a given target protein. A combination of various types of proteoglycans is found in extracellular matrices. The time-dependent concentration of proteoglycans is changed due to the developmental stage or pathogenic conditions of the cells and tissues.

Chondroitin sulfate proteoglycans: Specific types of proteoglycans that are sulfated in representative positions of their sugar moiety. They are one of the main constituents of the extracellular matrix of the nervous system.

CAZy: stands for "Carbohydrate-Active enZYmes Database." It is the specialized database that describes the families of structurally-related enzymes and carbohydrate-binding modules that are involved in the breakdown, biosynthesis, or modification of carbohydrates and glycoconjugates. It can be found at http://www.cazy.org/

BRENDA: It is a bioinformatics database containing the functional and structural information of the known enzymes. It can be found at www.brenda-enzymes.org

Glioblastoma: A type of cancer originated from the proliferation of astrocytes in the brain or spinal cord.

Conformational stability: In statistical thermodynamics, the conformational stability of a given enzyme refers to the ratio of the population of the native structure to denature states of the enzyme molecules at equilibrium condition. When a single molecule is considered, it is the structural integrity of an enzyme molecule that is the difference energy of the unfolded and folded states of an enzyme molecule. In both paradigms, increasing conformational stability leads to the activity improvement of the enzyme.

Catalytic efficiency: The minimum concentration of the substrate molecule required for an enzyme to reach its maximum catalysis capacity.

Half-life: The time required for an enzyme to lose 50% of its original activity. Increasing the conformational stability leads to increasing the half-life of an enzyme.

Protein Aggregation: is a process in which protein molecules accumulate and form molecular aggregates. Upon aggregation, the protein loses its activity. It occurred by attractive intermolecular interactions, mainly the hydrophobic one, between surface-exposed hydrophobic patches. Based on the identity of hydrophobic interaction, protein aggregation depends on the molecular collisions, which enhance by increasing the temperature and the concentration of the protein molecule. Proteins with surfaced-exposed hydrophobic patches are more prone to aggregation.

Domain: In protein science, domain is defined as distinct structural unite in the three dimensional structure of proteins. In the simplest form, the whole structure of a small and compact protein is considered as a domain. Some proteins have two

or more domains. Domains are responsible for the structural integrity and stability of proteins. They are also involved in the functional features of the proteins.

Recombinant DNA technology: Recombinant DNA technology includes insertion of a given DNA sequence from an organism to the other one. In protein engineering studies, the host organism may be an engineered bacterium that is used for the expression of a recombinant protein which is of value to biotechnology.

Key facts of chondroitinase ABC I

Chondroitinase ABC I is a non-hydrolytic degrading enzyme that cleaves the glycosidic bonds of polysaccharides.

- It has three distinctive domains, where the peripheral ones are symmetrically arranged around the central catalytic domain.
- Naturally, this enzyme is expressed in *Proteus Vulgaris*. This bacterium is found in soil and intestinal tract of the human body.
- The enzyme and its mutated variants can be produced by recombinant DNA technology, and using engineered bacteria as protein express systems.
- Chondroitinase ABC I as a polysaccharide lyase has broad substrate specificity.
- Its substrates constitute the main glycosaminoglycans of extracellular matrix of the central nervous system.

Key facts of the therapeutic potential of chondroitinase ABC I

- The concentration of corresponding substrates of chondroitinase ABC I increases in the extracellular matrix upon spinal cord injury, which acts as inhibitors against axon regeneration.
- The enzyme can be used to degrade the glycosaminoglycans around the traumatic region of the spinal cord.
- Its conformational stability and half-life reduce in the environmental conditions around the region of SCI.
- To use as a drug, the conformational stability, and biocompatibility of the enzyme should be increased via protein engineering strategies.
- Appropriate drug delivery methods should be developed to efficient use of chondroitinase ABC I at the site of spinal cord damage.

Summary points

- The extracellular matrix of the central nervous system contains various types of glycosaminoglycans in the form of proteoglycans.
- A fine balance between the concentrations of different proteoglycans is established in normal physiological conditions.
- Glial scar is proposed as the main inhibitor for axon regeneration following spinal cord injury.
- Glial scar is composed of various types of concentrated glycosaminoglycans in the region of spinal cord damage.
- Degradation of glycosaminoglycans at the site of spinal cord damage combined with other therapeutic strategies can help axons to recover.
- The broad substrate specificity of cABC I in accord with the composition of glial scar makes the enzyme a suitable therapeutic drug to restore tissue plasticity and axon regeneration.
- Using a high concentration of the enzyme per injection leads to molecular aggregation.
- Increasing the number of injection of the enzyme may results in immunological side effects.
- Protein engineering and drug delivery procedures are needed to produce, store, and therapeutically use of chondroitinase ABC I.
- Enzyme therapy should be used in predefined periods of time.
- Combinatorial approaches and other medical interventions along with intensive rehabilitation are being developed for locomotor recovery.

References

Anand, M., Wang, C., French, J., Isaacson-Schmid, M., Wall, L. L., & Mysorekar, I. U. (2012). Estrogen affects the glycosaminoglycan layer of the murine bladder. *Female Pelvic Medicine & Reconstructive Surgery*, *18*(3), 148–152. https://doi.org/10.1097/SPV.0b013e31824b76bd.

Beldowski, P., Mazurkiewicz, A., Topoliński, T., & Małek, T. (2019). Hydrogen and water bonding between glycosaminoglycans and phospholipids in the synovial fluid: Molecular dynamics study. *Materials (Basel)*, *12*(2060), 1–11. https://doi.org/10.3390/ma12132060.

Bourin, M., & Lindahl, U. (1993). Glycosaminoglycans and the regulation of blood coagulation. *Biochemical Journal*, *289*(2), 313–330. https://doi.org/10.1042/bj2890313.

Bradbury, E. J., Moon, L. D. F., Popat, R. J., King, V. R., Bennett, G. S., Patel, P. N., … McMahon, S. B. (2002). Chondroitinase ABC promotes functional recovery after spinal cord injury. *Nature*, *416*, 636–640. https://doi.org/10.1038/416636a.

Calatroni, A., & di Ferrante, N. (1969). The glycosaminoglycans of human term placenta. *Carbohydrate Research*, *10*(4), 535–548. https://doi.org/10.1016/S0008-6215(00)80122-6.

Cichon, S., Mühleisen, T. W., Degenhardt, F. A., Mattheisen, M., Miró, X., Strohmaier, J., … Nöthen, M. M. (2011). Genome-wide association study identifies genetic variation in neurocan as a susceptibility factor for bipolar disorder. *American Journal of Human Genetics*, *88*, 372–381. https://doi.org/10.1016/j.ajhg.2011.01.017.

Clowes, A. W., & Karnowsky, M. J. (1977). Suppression by heparin of smooth muscle cell proliferation in injured arteries. *Nature*, *265*(5595), 625–626. https://doi.org/10.1038/265625a0.

Couchman, J. R. (2010). Transmembrane signaling proteoglycans. *Annual Review of Cell and Developmental Biology*, *26*, 89–114. https://doi.org/10.1146/annurev-cellbio-100109-104126.

Cregg, J. M., DePaul, M. A., Filous, A. R., Lang, B. T., Tran, A., & Silver, J. (2014). Functional regeneration beyond the glial scar. *Experimental Neurology*, 197–207. https://doi.org/10.1016/j.expneurol.2013.12.024.

DeAngelis, P. L. (2002). Evolution of glycosaminoglycans and their glycosyltransferases: Implications for the extracellular matrices of animals and the capsules of pathogenic bacteria. *Anatomical Record*, *268*(3), 317–326. https://doi.org/10.1002/ar.10163.

Denholm, E. M., Lin, Y. Q., & Silver, P. J. (2001). Anti-tumor activities of chondroitinase AC and chondroitinase B: Inhibition of angiogenesis, proliferation and invasion. *European Journal of Pharmacology*, *416*(3), 213–221. https://doi.org/10.1016/S0014-2999(01)00884-6.

DePaul, M. A., Lin, C. Y., Silver, J., & Lee, Y. S. (2015). Peripheral nerve transplantation combined with acidic fibroblast growth factor and chondroitinase induces regeneration and improves urinary function in complete spinal cord transected adult mice. *PLoS One*, *10*. https://doi.org/10.1371/journal.pone.0139335, e0139335.

DeWitt, D. A., Richey, P. L., Praprotnik, D., Silver, J., & Perry, G. (1994). Chondroitin sulfate proteoglycans are a common component of neuronal inclusions and astrocytic reaction in neurodegenerative diseases. *Brain Research*, *656*(1), 205–209. https://doi.org/10.1016/0006-8993(94)91386-2.

Dick, G., Akslen-Hoel, L. K., Grøndahl, F., Kjos, I., & Prydz, K. (2012). Proteoglycan synthesis and Golgi Organization in polarized epithelial cells. *Journal of Histochemistry and Cytochemistry*, *60*(12), 936–965. https://doi.org/10.1369/0022155412461256.

Dmitrieva, N., Yu, L., Viapiano, M., Cripe, T. P., Chiocca, E. A., Glorioso, J. C., & Kaur, B. (2011). Chondroitinase ABC I-mediated enhancement of oncolytic virus spread and antitumor efficacy. *Clinical Cancer Research*, *17*, 1362–1372. https://doi.org/10.1158/1078-0432.CCR-10-2213.

Ernst, S., Langer, R., Cooney, C. L., & Sasisekharan, R. (1995). Enzymatic degradation of glycosaminogliycans. *Critical Reviews in Biochemistry and Molecular Biology*, *30*(5), 387–444.

Fawcett, J. W., & Asher, R. A. (1999). The glial scar and central nervous system repair. *Brain Research Bulletin*, *49*(6), 377–391. https://doi.org/10.1016/S0361-9230(99)00072-6.

Galtrey, C. M., & Fawcett, J. W. (2007). The role of chondroitin sulfate proteoglycans in regeneration and plasticity in the central nervous system. *Brain Research Reviews*, *54*, 1–18. https://doi.org/10.1016/j.brainresrev.2006.09.006.

Gandhi, N. S., & Mancera, R. L. (2008). The structure of glycosaminoglycans and their interactions with proteins. *Chemical Biology and Drug Design*, *72*, 455–482. https://doi.org/10.1111/j.1747-0285.2008.00741.x.

García, B., Merayo-Lloves, J., Martin, C., Alcalde, I., Quirós, L. M., & Vazquez, F. (2016). Surface proteoglycans as mediators in bacterial pathogens infections. *Frontiers in Microbiology*, *7*(220), 1–11. https://doi.org/10.3389/fmicb.2016.00220.

García-Alías, G., Barkhuysen, S., Buckle, M., & Fawcett, J. W. (2009). Chondroitinase ABC treatment opens a window of opportunity for task-specific rehabilitation. *Nature Neuroscience*, *12*(9), 1145–1151. https://doi.org/10.1038/nn.2377.

Gill, S., Wight, T. N., & Frevert, C. W. (2010). Proteoglycans: Key regulators of pulmonary inflammation and the innate immune response to lung infection. *Anatomical Record*, *293*(6), 968–981. https://doi.org/10.1002/ar.21094.

Greenwald, R. B. (2001). PEG drugs: An overview. *Journal of Controlled Release*, *74*(1–3), 159–171. https://doi.org/10.1016/S0168-3659(01)00331-5.

Hachim, D., Whittaker, T. E., Kim, H., & Stevens, M. M. (2019). Glycosaminoglycan-based biomaterials for growth factor and cytokine delivery: Making the right choices. *Journal of Controlled Release*, *313*, 131–147. https://doi.org/10.1016/j.jconrel.2019.10.018.

Hardingham, T., & Bayliss, M. (1990). Proteoglycans of articular cartilage: Changes in aging and in joint disease. *Seminars in Arthritis and Rheumatism*, *20*(3 (1)), 12–33. https://doi.org/10.1016/0049-0172(90)90044-G.

Hettiaratchi, M. H., O'Meara, M. J., Teal, C. J., Payne, S. L., Pickering, A. J., & Shoichet, M. S. (2019). Local delivery of stabilized chondroitinase ABC degrades chondroitin sulfate proteoglycans in stroke-injured rat brains. *Journal of Controlled Release*. https://doi.org/10.1016/j.jconrel.2019.01.033.

Huang, W., Lunin, V. V., Li, Y., Suzuki, S., Sugiura, N., Miyazono, H., & Cygler, M. (2003). Crystal structure of Proteus vulgaris chondroitin sulfate ABC lyase I at 1.9 Å resolution. *Journal of Molecular Biology*, *328*(3), 623–634. https://doi.org/10.1016/S0022-2836(03)00345-0.

Imberty, A., Lortat-Jacob, H., & Pérez, S. (2007). Structural view of glycosaminoglycan-protein interactions. *Carbohydrate Research*, *342*(3–4), 430–439. https://doi.org/10.1016/j.carres.2006.12.019.

Iozzo, R. V., & Schaefer, L. (2015). Proteoglycan form and function: A comprehensive nomenclature of proteoglycans. *Matrix Biology*, *42*, 11–55. https://doi.org/10.1016/j.matbio.2015.02.003.

Jackson, R. L., Busch, S. J., & Cardin, A. D. (1991). Glycosaminoglycans: Molecular properties, protein interactions, and role in physiological processes. *Physiological Reviews*, *71*(2), 481–539. https://doi.org/10.1152/physrev.1991.71.2.481.

Jaime-Ramirez, A. C., Dmitrieva, N., Yoo, J. Y., Banasavadi-Siddegowda, Y., Zhang, J., Relation, T., … Kaur, B. (2017). Humanized chondroitinase ABC sensitizes glioblastoma cells to temozolomide. *The Journal of Gene Medicine*, *19*(3), 1–18. https://doi.org/10.1002/jgm.2942.

Jones, L. L., Margolis, R. U., & Tuszynski, M. H. (2003). The chondroitin sulfate proteoglycans neurocan, brevican, phosphacan, and versican are differentially regulated following spinal cord injury. *Experimental Neurology*, *182*(2), 399–411. https://doi.org/10.1016/S0014-4886(03)00087-6.

Karus, M., Ulc, A., Ehrlich, M., Czopka, T., Hennen, E., Fischer, J., … Faissner, A. (2016). Regulation of oligodendrocyte precursor maintenance by chondroitin sulphate glycosaminoglycans. *Glia*, *64*, 270–286. https://doi.org/10.1002/glia.22928.

Kasinathan, N., Volety, S. M., & Josyula, V. R. (2016). Chondroitinase: A promising therapeutic enzyme. *Critical Reviews in Microbiology*, *42*(3), 474–484. https://doi.org/10.3109/1040841X.2014.959893.

Katoh, H., Yokota, K., & Fehlings, M. G. (2019). Regeneration of spinal cord connectivity through stem cell transplantation and biomaterial scaffolds. *Frontiers in Cellular Neuroscience*, *13*(June), 1–22. https://doi.org/10.3389/fncel.2019.00248.

Lander, A. D., & Selleck, S. B. (2000). The elusive functions of proteoglycans: In vivo veritas. *Journal of Cell Biology*, *148*(2), 227–232. https://doi.org/10.1083/jcb.148.2.227.

Lasne, D., Jude, B., & Susen, S. (2006). From normal to pathological hemostasis. *Canadian Journal of Anesthesia*, *53*, 52–511. https://doi.org/10.1007/bf03022247.

Lau, L. W., Keough, M. B., Haylock-Jacobs, S., Cua, R., Döring, A., Sloka, S., … Yong, V. W. (2012). Chondroitin sulfate proteoglycans in demyelinated lesions impair remyelination. *Annals of Neurology*, *72*, 419–432. https://doi.org/10.1002/ana.23599.

Lee, T. Y., Jamieson, A. M., & Schafer, I. A. (1973). Changes in the composition and structure of glycosaminoglycans in the human placenta during development. *Pediatric Research*, *7*(12), 965–977. https://doi.org/10.1203/00006450-197312000-00005.

Lemons, M. L., Howland, D. R., & Anderson, D. K. (1999). Chondroitin sulfate proteoglycan immunoreactivity increases following spinal cord injury and transplantation. *Experimental Neurology*, *160*, 51–65. https://doi.org/10.1006/exnr.1999.7184.

Lin, R., Kwok, J. C. F., Crespo, D., & Fawcett, J. W. (2008). Chondroitinase ABC has a long-lasting effect on chondroitin sulphate glycosaminoglycan content in the injured rat brain. *Journal of Neurochemistry*, *104*(2), 400–408. https://doi.org/10.1111/j.1471-4159.2007.05066.x.

Linhardt, R. J. (2001). Analysis of glycosaminoglycans with polysaccharide lyases. *Current Protocols in Molecular Biology*. https://doi.org/10.1002/0471142727.mb1713bs48 (edited by Frederick M. Ausubel .. [et al.]).

Merle, B., Durussel, L., Delmas, P. D., & Clézardin, P. (1999). Decorin inhibits cell migration through a process requiring its glycosaminoglycan side chain. *Journal of Cellular Biochemistry*, *75*(3), 538–546.

Mohammadyari, H., Shirdel, S. A., Jafarian, V., & Khalifeh, K. (2019). Designing and construction of novel variants of Chondroitinase ABC I to reduce aggregation rate. *Archives of Biochemistry and Biophysics*, *668*, 46–53. https://doi.org/10.1016/j.abb.2019.05.013.

Moon, L. D. F., Asher, R. A., Rhodes, K. E., & Fawcett, J. W. (2001). Regeneration of CNS axons back to their target following treatment of adult rat brain with chondroitinase ABC. *Nature Neuroscience*, *4*, 465–466. https://doi.org/10.1038/87415.

Muir, E., De Winter, F., Verhaagen, J., & Fawcett, J. (2019). Recent advances in the therapeutic uses of chondroitinase ABC. *Experimental Neurology*, *321*, 1–16. https://doi.org/10.1016/j.expneurol.2019.113032.

Prabhakar, V., Raman, R., Capila, I., Bosques, C. J., Pojasek, K., & Sasisekharan, R. (2005). Biochemical characterization of the chondroitinase ABC I active site. *Biochemical Journal*, *390*, 395–405. https://doi.org/10.1042/BJ20050532.

Quraishe, S., Forbes, L. H., & Andrews, M. R. (2018). The extracellular environment of the CNS: Influence on plasticity, sprouting, and axonal regeneration after spinal cord injury. *Neural Plasticity*, 1–18. https://doi.org/10.1155/2018/2952386.

Rolls, A., Shechter, R., & Schwartz, M. (2009). The bright side of the glial scar in CNS repair. *Nature Reviews Neuroscience*, *10*, 235–241. https://doi.org/10.1038/nrn2591.

Rosenzweig, E. S., Salegio, E. A., Liang, J. J., Weber, J. L., Weinholtz, C. A., Brock, J. H., … Tuszynski, M. H. (2019). Chondroitinase improves anatomical and functional outcomes after primate spinal cord injury. *Nature Neuroscience*, *22*(8), 1269–1275. https://doi.org/10.1038/s41593-019-0424-1.

Schwartz, N. B., & Domowicz, M. S. (2018). Proteoglycans in brain development and pathogenesis. *FEBS Letters*, *592*, 3791–3805. https://doi.org/10.1002/1873-3468.13026.

Shi, J., Potash, J. B., Knowles, J. A., Weissman, M. M., Coryell, W., Scheftner, W. A., … Levinson, D. F. (2011). Genome-wide association study of recurrent early-onset major depressive disorder. *Molecular Psychiatry*, *16*, 193–201. https://doi.org/10.1038/mp.2009.124.

Siebert, J. R., Conta Steencken, A., & Osterhout, D. J. (2014). Chondroitin sulfate proteoglycans in the nervous system: Inhibitors to repair. *BioMed Research International*, 1–15. https://doi.org/10.1155/2014/845323.

Silver, D. J., & Silver, J. (2014). Contributions of chondroitin sulfate proteoglycans to neurodevelopment, injury, and cancer. *Current Opinion in Neurobiology*, 171–178. https://doi.org/10.1016/j.conb.2014.03.016.

Tauchi, R., Imagama, S., Natori, T., Ohgomori, T., Muramoto, A., Shinjo, R., … Kadomatsu, K. (2012). The endogenous proteoglycan-degrading enzyme ADAMTS-4 promotes functional recovery after spinal cord injury. *Journal of Neuroinflammation*, *9*(53), 1–10. https://doi.org/10.1186/1742-2094-9-53.

Templeton, D. M. (1992). Proteoglycans in cell regulation. *Critical Reviews in Clinical Laboratory Sciences*, *29*(2), 141–184. https://doi.org/10.3109/10408369209114599.

Tessier-Lavigne, M., & Goodman, C. S. (1996). The molecular biology of axon guidance. *Science*, *274*, 1123–1133. https://doi.org/10.1126/science.274.5290.1123.

Thompson, E. H., Lensjø, K. K., Wigestrand, M. B., Malthe-Sørenssen, A., Hafting, T., & Fyhn, M. (2018). Removal of perineuronal nets disrupts recall of a remote fear memory. *Proceedings of the National Academy of Sciences of the United States of America*, *115*, 607–612. https://doi.org/10.1073/pnas.1713530115.

Tuinstra, H. M., Ducommun, M. M., Briley, W. E., & Shea, L. D. (2013). Gene delivery to overcome astrocyte inhibition of axonal growth: An in vitro model of the glial scar. *Biotechnology and Bioengineering*, *110*(3), 947–957. https://doi.org/10.1002/bit.24750.

Végh, M. J., Heldring, C. M., Kamphuis, W., Hijazi, S., Timmerman, A. J., Li, K. W., … van Kesteren, R. E. (2014). Reducing hippocampal extracellular matrix reverses early memory deficits in a mouse model of Alzheimer's disease. *Acta Neuropathologica Communications*, *2*(76), 1–11. https://doi.org/10.1186/s40478-014-0076-z.

Wade, A., Robinson, A. E., Engler, J. R., Petritsch, C., James, C. D., & Phillips, J. J. (2013). Proteoglycans and their roles in brain cancer. *FEBS Journal*, *280*(10), 2399–2417. https://doi.org/10.1111/febs.12109.

Wang, D., Ichiyama, R. M., Zhao, R., Andrews, M. R., & Fawcett, J. W. (2011). Chondroitinase combined with rehabilitation promotes recovery of forelimb function in rats with chronic spinal cord injury. *Journal of Neuroscience*, *31*(25), 9332–9344. https://doi.org/10.1523/JNEUROSCI.0983-11.2011.

Werz, W., & Schachner, M. (1988). Adhesion of neural cells to extracellular matrix constituents. Involvement of glycosaminoglycans and cell adhesion molecules. *Developmental Brain Research*. https://doi.org/10.1016/0165-3806(88)90101-0.

Xia, T., Ni, S., Li, X., Yao, J., Qi, H., Fan, X., & Wang, J. (2015). Sustained delivery of chondroitinase ABC by poly(propylene carbonate)-chitosan micron fibers promotes axon regeneration and functional recovery after spinal cord hemisection. *Brain Research*, *1624*, 469–478. https://doi.org/10.1016/j.brainres.2015.08.018.

Yanagishita, M. (1993). Function of proteoglycans in the extracellular matrix. *Pathology International*, *43*(6), 283–293. https://doi.org/10.1111/j.1440-1827.1993.tb02569.x.

Zuidema, J. M., Gilbert, R. J., & Osterhout, D. J. (2016). Nanoparticle technologies in the spinal cord. *Cells, Tissues, Organs*, *202*, 102–115. https://doi.org/10.1159/000446647.

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Chapter 26

Phenol neurolysis for spasticity management in people with spinal cord injury

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Abbreviations

BCR	brachioradialis
BUE	bilateral upper extremity
EMG	electromyography
FCR	flexor carpi radialis
FCU	flexor carpi ulnaris
FDP	flexor digitorum profundus
FDS	flexor digitorum superficialis
ITB	intrathecal baclofen
OT	occupational therapists
PT	physical therapists
PWC	power wheelchair
ROM	range of motion
SCI	spinal cord injury

Introduction

Spasticity is one of the most common secondary complications following a complete or incomplete spinal cord injury (SCI). After SCI, the prevalence of spasticity ranges from 65% to 78%, and 35% to 49% have problematic spasticity (Holtz, Lipson, Noonan, Kwon, & Mills, 2017; Maynard, Karunas, & Waring 3rd., 1990). Currently, problematic spasticity is managed through a combination of therapeutic modalities, oral medications, botulinum toxin injections, phenol neurolysis, and surgical procedures (Table 1). Pharmaceutical options include medications delivered orally, via local injections, or through intrathecal baclofen (ITB) pumps. Botulinum toxin injections and chemical neurolysis with phenol or alcohol are the first-line treatment options for problematic focal spasticity. However, after the introduction of botulinum toxins for the treatment of spasticity, the use of phenol/alcohol chemical neurolysis for spasticity management declined over the period. Potential causes of the decline in neurolysis use include laborious techniques that required more precise skill in the pre-ultrasound era. There is a concern for the risk of loss of sensation, dysesthesias, and weakness. However, a review of existing evidence suggests that chemical neurolysis with phenol and alcohol has demonstrated effectiveness in eliminating clonus, decreasing spasticity, improving joint range of motion, decreasing painful spasms, and improving function (Akkaya et al., 2010; Gunduz, Kalyon, Dursun, Mohur, & Bilgic, 1992; Jang et al., 2004; Karri, Mas, Francisco, & Li, 2017; Karri, Zhang, & Li, 2020). In our experience, ultrasound guidance and electrical stimulation improved these procedures' efficiency and quality.

Poorly controlled severe spasticity after SCI can result in multiple complications, including the development of joint contractures (Fig. 1), inability to participate in therapy, skin breakdown, decreased function, poor sleep, and poor quality of

Diagnosis and Treatment of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822498-4.00026-9

TABLE 1 Current treatments approach for management of spasticity in spinal cord injury[a].

Physical Modalities and Therapeutics	Passive or active stretching, Splinting, serial casting, Heat and cold application, Electrical stimulation, Vibration therapy, Orthoses, etc.
Commonly prescribed oral medications	Baclofen, Tizanidine, Diazepam, Dantrolene, Clonidine, etc.
Local interventions	Diagnostic nerve blocks: lidocaine, bupivacaine Neurolysis: phenol, alcohol Chemodenervation (botulinum toxins serotypes A and B)
Surgical interventions	Tendon lengthening procedures, Tendon transfers Intrathecal baclofen pump implantation, Dorsal rhizotomy Peripheral neurectomy

[a]*These are commonly prescribed treatments for spasticity and not an exclusive list of treatment options.*

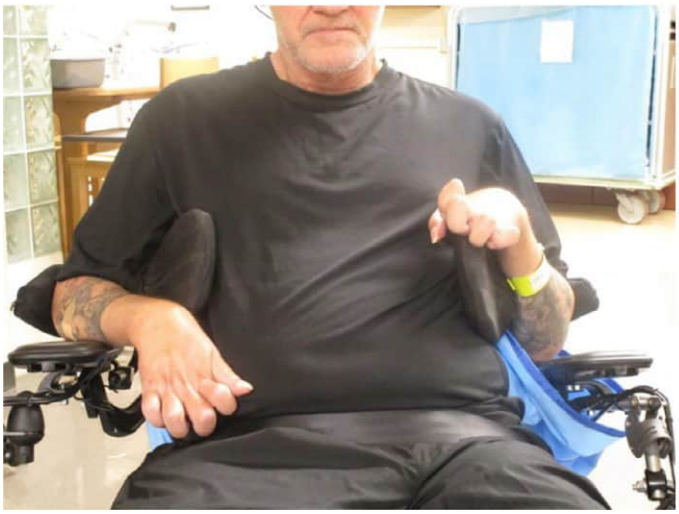

FIG. 1 Joint contracture and deformities due to delayed spasticity management.

life (Holtz et al., 2017; Rekand, Hagen, & Gronning, 2012; Sezer, Akkus, & Ugurlu, 2015). In people with cervical SCI, we are often faced with managing problematic spasticity in all four extremities. In this scenario, a combination of treatment approaches, including phenol or alcohol neurolysis, may help manage spasticity effectively and prevent complications due to poorly controlled spasticity (Escaldi, 2018; Viel, Pellas, Ripart, Pelissier, & Eledjam, 2005). Besides, there are many other case scenarios where neurolysis can be a very useful tool to manage spasticity effectively. Such scenarios include patient refusal of ITB therapy, contraindications to ITB therapy due to ongoing infectious process, hypersensitivity to baclofen, and insufficient resources to pursue botulinum toxin injections or ITB therapy.

Additionally, botulinum toxin and intrathecal baclofen therapies are not available in many parts of the world to date. Untreated spasticity can lead to significant limitations in function and limit recovery (Tibbett, Widerstrom-Noga, Thomas, & Field-Fote, 2019; van Cooten, Snoek, Nene, de Groot, & Post, 2015). Therefore, it is essential to incorporate cost-effective alternative therapies such as phenol neurolysis to treat spasticity. This chapter will describe the following with regard to phenol neurolysis: mechanism, techniques, dosing, risks, and benefits. It will demonstrate the procedure's application in people with SCI with a case study. These procedures are similar to those for alcohol neurolysis.

Phenol or alcohol neurolysis history

The usefulness of chemical neurolysis or nerve block was first recognized in 1863 by Luton to treat pain due to phenol's and alcohol's ability to block nerve conduction (D'Souza & Hooten, 2021). There were many reports of loss of motor function after intrathecal injections of phenol for pain management in the 1950s (Kelly & Gautier-Smith, 1959; Liversedge & Maher, 1960). Between 1964 and 1967, Khalili et al. published their experience of performing peripheral nerve blocks

in patients diagnosed with a stroke, cerebral palsy, and spinal cord injury (Khalili & Betts, 1967). They reported improved spasticity in the muscles following nerve block by a 2%–3% phenol solution to mixed or motor nerves (Khalili & Betts, 1967). They also reported several unanticipated side effects, including loss of sensation in <1% instances following a nerve block. Subsequently, peripheral motor point blocks were performed to minimize sensory side effects under electromyography (EMG) and electrical stimulation guidance (Copp, Harris, & Keenan, 1970; Halpern & Meelhuysen, 1966).

Mechanism of action

Phenol, also known as carbolic acid (C_6H_5OH), is a benzene ring. In a solid state, it exists as a crystal. It is water-soluble at room temperature at ≤6.7% concentration. Phenol is typically used in 3%–6% concentration (Escaldi, 2018). When injected at a concentration of 5% and above, phenol denatures protein, which results in tissue necrosis and axonal degeneration (D'Souza & Hooten, 2021; Escaldi, 2018; Felsenthal, 1974). The effects of neurolysis last longer with 5%–6% concentration. Phenol at <3% concentration causes demyelination and some axonal destruction, resulting in shorter-lasting effects (Horn, Singh, & Dabrowski, 2015). The phenol application to the nerve trunk or motor point results in a short-term anesthetic effect that lasts for few hours. Short-term and immediate local anesthetic effects result in instant spasticity relief (D'Souza & Warner, 2021; Zhang, Darji, Francisco, & Li, 2021). However, long-term and full effects may take 7–9 days after injections due to the time required for axonal degeneration (Zhang et al., 2021). The duration of effects is dependent on the site of injection and concentration of phenol used (Halpern & Meelhuysen, 1967; Sung et al., 2001). Following injection at the proximal portion of a nerve using a higher concentration of phenol, the nerve takes 6–9 months to re-generate, whereas injections at the nerve's distal portion takes 3–4 months to recover. Repeated neurolysis can result in permanent nerve damage and muscle atrophy (Horn et al., 2015).

Phenol neurolysis technique and dose

Extensive knowledge of the anatomy of mixed, motor, and sensory nerve pathways and muscles innervated by individual motor branches is essential to prevent serious side effects and improve outcomes. Phenol neurolysis can be performed with anatomic localization, electrical stimulation guidance, or ultrasound guidance. Often, these techniques are combined to maximize the efficiency of the procedure and minimize errors in localizing targets. In some cases, first performing a temporary nerve block with 1% lidocaine prior to phenol neurolysis may help assess the efficacy and potential loss of function that can be expected with the long-lasting procedure. The injection technique and materials required for performing a motor point block and peripheral neurolysis are similar. Teflon-coated electromyography needles of 25- to 27-gauge, surface electrodes, and a portable electrical stimulator are required for performing injections with electrical stimulation guidance. Anatomical localization along with electrical stimulation allows rapid localization of motor points or peripheral nerves. The use of a lower amount of current (≤1 mA) and stronger contractions suggests closer proximity to motor points or target nerve branches. Ultrasound guidance combined with electrical stimulation can decrease side effects and improve procedure efficiency and efficacy. In a study, injections performed under combined ultrasound and electrical stimulation guidance resulted in a lower phenol dose compared to electrical stimulation guidance alone (Karri et al., 2017; Kaymak, Kara, Gurcay, Aydin, & Ozcakar, 2019; Matsumoto, Berry, Yung, Matsumoto, & Munin, 2018). Motor points typically require multiple injection sites for a reduction in spasticity. Phenol neurolysis of proximal nerve trunk requires injection at one to two sites, and electrical stimulation results in stronger muscle contraction. However, ultrasound guidance requires additional equipment and skill. Typically, at each injection site, 0.2–0.5 mL of 5%–6% phenol is injected. However, the phenol amount per nerve or site may vary based on the practitioner's expertise and guidance used for injections (Karri et al., 2017).

Immediate spasticity relief experienced due to phenol's anesthetic effect during the procedure can be used to titrate the dose when injecting motor points. There are no clear studies about the target recommended dose, but the current literature recommends no more than 1.0–1.2 g in total (e.g., 20 mL of 5%–6% concentration) (D'Souza & Warner, 2021; Gaid, 2012; Horn et al., 2015). However, a study reported safe use of up to 30 mL of 6% phenol (Karri et al., 2017). Systemic doses of 8.5 g and above can result in serious side effects, including cardiovascular and central nervous system dysfunction (Escaldi, 2018; Horn et al., 2015).

The decision to inject the proximal portion of nerve vs distal motor points depends on various factors, including time from injury, complete vs incomplete injury, spasticity management goals, and current functional status. A careful evaluation and discussion of the risks and benefits of various options for spasticity management should be discussed. Before neurolysis, evaluate for any potential for nerve transfers to improve function. It is also essential to remember that while preserving motor points is vital for potential neurorecovery, poorly controlled spasticity can prevent participation in therapies, result in joint contractures, and significantly limit recovery. Current evidence suggests a significant improvement in spasticity in the upper and lower extremity muscles following chemical neurolysis (Awad, 1972;

Chang & Boudier-Reveret, 2020; Chua & Kong, 2001; Copp et al., 1970; Easton, Ozel, & Halpern, 1979; Elovic et al., 2009; Jang et al., 2004; Karri et al., 2017, 2020; Keenan, Tomas, Stone, & Gersten, 1990; Kong & Chua, 2002; Lee, Kim, Kim, Ro, & Lee, 2020).

Upper extremity targets

A list of the phenol neurolysis of upper extremity targets in people with SCI is presented in Table 2. Our center's data suggest that medial and lateral pectoral nerve neurolysis and musculocutaneous motor point block are the most common upper extremity targets for phenol neurolysis in people with SCI. Spasticity of shoulder adductors and shoulder internal rotators muscles can be very severe and challenging in people with spinal cord injury. Stretching is often limited due to pain in the shoulder and inadequate response to botulinum toxin injections. Phenol neurolysis to medial and lateral pectoral and thoracodorsal nerves can successfully decrease spasticity in these muscle groups and improve shoulder range of motion. The pectoral nerves can be easily located with ultrasound guidance between the pectoralis major and pectoralis minor (Fig. 2). Due to the proximity of these nerves to the lungs and pleura, ultrasound guidance is recommended. The musculocutaneous nerve is a mixed nerve and supplies sensation to the lateral forearm by its terminal branch known as the lateral cutaneous nerve of the forearm. The musculocutaneous nerve can be localized near the pectoralis major tendon's distal insertion between the coracobrachialis and the short head of the biceps on the arm's medial side (Keenan et al., 1990). In people with incomplete injury, a motor point block to target muscle is recommended to prevent weakness of the elbow flexors and loss of sensation over the forearm (Sirico, Zappia, Di Meglio, Castaldo, & Nurzynska, 2020). The motor point block to distal muscle groups (finger flexors and wrist flexors) of the upper extremity or mixed nerves can be targeted with ultrasound or electrical stimulation guidance. However, we must isolate the target motor branches or perform motor point blocks to prevent unintended sensory loss and weakness in other muscle groups supplied by the target nerve (Karri et al., 2020; Sirico et al., 2020).

Lower extremity targets

A list of the phenol neurolysis of lower extremity targets in people with SCI is presented in Table 3. The obturator nerve and tibial motor points are the lower extremities' most frequent targets of phenol (Ghai et al., 2013). Though the obturator nerve is a mixed nerve, its sensory branch supplies only a small area over the knee's medial aspect. The obturator nerve can be localized 1–2 cm below and lateral to the pubic tubercle and medial to femoral vessels in the thigh's upper part. Sciatic motor branches to the hamstrings can be localized at two locations; one is located at 20% and the other at 33% of the distance from the ischial tuberosity on a line drawn from the ischial tuberosity to lateral femoral condyle (Seidel, Seidel, Gans, & Dijkers, 1996). The tibial motor points can be located 1–2 cm medial and lateral of a point located 1–2 cm below the popliteal crease's midpoint (Chua & Kong, 2001). The quadriceps are richly innervated with multiple motor points located over the muscles' mid-belly. The practitioner should be cautious while injecting motor branches of the sciatic nerve, femoral nerve, and tibial nerve as these are mixed nerves. A diagnostic lidocaine motor point can help identify cases in which people rely on their spasticity for ambulation prior to phenol motor point blocks. Accessing the motor point to

TABLE 2 Upper extremity targets for phenol neurolysis.

Spasticity pattern	Main target muscles	Nerve block or motor point block
Shoulder adduction and internal rotation	Pectoralis major, Latissimus dorsi	Medial and lateral pectoral nerves, thoracodorsal nerves
Elbow flexors	Brachialis, Biceps brachii, BCR	Musculocutaneous motor points to brachialis and biceps Radial motor branches to BCR
Elbow extensors	Triceps lateral head, long head, and medial head	Radial motor branches to triceps
Pronation	Pronator teres	Median motor points to pronator teres
Wrist flexors	FCR and FCU	Median nerve motor branches to FCR and ulnar motor branches to FCU
Finger flexors	FDS and FDP	Respective median and ulnar motor branches to FDS and FDP

FIG. 2 Lateral pectoral neurolysis under ultrasound and electrical stimulation guidance.

TABLE 3 Lower extremity targets for phenol neurolysis.

Spasticity pattern	Main target muscles	Nerve block or *Motor* point block
Hip adductors	Adductor Magnus, Adductor Longus, Adductor Brevis	Obturator nerve
Hip Flexors	Iliacus, Sartorius, Rectus femoris	Femoral motor branches to iliacus, sartorius, rectus femoris
Knee flexors	Hamstrings	Sciatic motor branches to biceps femoris, semimembranosus, semitendinosus
Knee extensors	Quadriceps	Femoral motor branches to quadriceps
Ankle plantar flexors	Gastrocnemius, soleus	Tibial motor branches to gastrocnemius and soleus

the psoas major can be challenging due to the abdominal viscera and blood vessels in the vicinity. However, there are case reports in people with stroke and SCI describing successful phenol lumbar nerve block and psoas motor point block to treat hip flexor spasticity (Awad, 1972; Koyama, Murakami, Suzuki, & Suzaki, 1992).

Adverse effects

Risks associated with any injection include infection at the site of injection, pain, bleeding, and bruising. Incomplete nerve (mixed or sensory) destruction may cause dysesthesias. A complete nerve block is required to get relief from dysesthesias. A retrospective study evaluating 293 phenol neurolysis procedures reported the following incidence of adverse events; 4% pain. 2.7% inflammation, 0.7% dysesthesias, and 0.7% hypotension (Karri et al., 2017). Other complications include swelling and loss of sensation. Swelling, pain at the injection site, hypotension, and inflammation all resolve within a few days. Accidental intravascular injection of phenol can cause systemic side effects, including flushing, nausea, vomiting, cardiovascular and central nervous system depression, resulting in cardiac arrest and coma (Lee et al., 2020). Systematic side effects are uncommon in doses less than 100 mg (D'Souza & Warner, 2021).

Case study

A 49-year-old African American male patient sustained a pedestrian motor vehicle accident, resulting in incomplete quadriplegia (C4 neurological level), pictured in Fig. 3. After his injury, he had a 2-month stay in an intensive care unit. He was discharged to a skilled nursing facility. He presented to our SCI center 8 months post-injury with several SCI-associated complications, including a stage 4 sacral pressure injury, multiple joint contractures, and severe generalized spasticity. He was bed-bound since the time of injury. After admission to our inpatient rehabilitation facility, oral medications for spasticity control were optimized with minimal benefits. Given significant spasticity in all four extremities, he needed multiple interventions to manage his spasticity to improve his function. Phenol motor point blocks to the bilateral shoulder abductors, elbow flexors, and hip adductors were performed. We also recommended intrathecal baclofen therapy. However, he needed immediate relief from his severe spasticity as it interfered with his positioning in bed and his wheelchair. It also negatively affected his hygiene surrounding the sacral pressure injury, impeding its healing. He also benefitted from botulinum toxin injections to the bilateral pronators, wrist flexors, and finger flexors. These interventions decreased spasticity and improved active and passive ROM.

Figure 3A. Baseline

Figure 3B. After hip adductors, shoulder adductor and elbow flexor motor point blocks with phenol

Figure 3C. Improved spasticity allowed the patient to sit and operate a power chair

Figure 3D. Improved spasticity allowed him to participate in a standing activity

FIG. 3 Effects of phenol neurolysis and spasticity management in a person with SCI.

Physical therapists (PT) and occupational therapists (OT) worked with this patient to manage his spasticity to gain range of motion and prevent further contractures through stretching, joint mobilization, splinting, positioning, and weight-bearing. OT and PT collaborated to create a bed positioning program to facilitate prolonged stretch of spastic muscles and relieve pressure over the sacral wound. His therapy program was updated and modified as the patient gained range of motion in joints through spasticity management efforts. The patient's mobility improved, allowing us to order a power wheelchair (PWC) to improve his access to his environment. Switch access enabled the patient to perform his weight shifts independently and communicate with his friends and family through a Bluetooth joystick connection to a tablet. During physical therapy, the patient worked on prolonged stretching in various positions, including supine, prone, and standing in a standing frame. PT also worked with the patient on safety and endurance with PWC mobility and independence with instruction of all assistance needed for functional mobility and positioning. Improvements in posture allowed for better positioning in bed, and sitting in a PWC resulted in a healed sacral pressure injury without surgical intervention. Improved function achieved was translated into being able to operate a PWC, perform independent pressure reliefs via power tilt, access a tablet with assistive devices, and feeding himself with set up. Caregiver burden for transfers and positioning decreased from 2 people to 1 person.

Conclusion/summary

Severe spasticity can be debilitating and often challenging to manage if appropriate interventions are delayed. A comprehensive team approach to spasticity management can prevent complications and improve quality of life after SCI. In complex situations, a combination of multiple treatment options is required to improve function and independence. Phenol neurolysis can be a very useful tool in these tricky situations. Currently, limited evidence and our experience suggest that chemical neurolysis is a safe, useful tool for spasticity management in people with SCI. Besides, phenol neurolysis utilization has been shown to be associated with no procedure-related severe complications and only a small incidence of observed adverse effects. Ultrasound guidance along with electrical stimulation can reduce the total required dose and minimize procedure-related side effects.

Applications to other areas of neuroscience

Phenol or alcohol neurolysis has been used to manage spasticity in various upper motor neuron disorders. Other than spinal cord injury, the most common diagnoses for which this technique is used are stroke, brain injury, and multiple sclerosis (Karri et al., 2017; Kong & Chua, 1999, 2002; Mas, DiTommaso, & Li, 2019). It is often used in concert with botulinum toxin injections, especially when multiple areas require treatment to avoid using more than the recommended amount of either medication (Karri et al., 2020). Phenol neurolysis can also be used to treat spasticity in children. It is frequently performed to treat hip adductor and elbow flexor spasticity in children with cerebral palsy. Children may not tolerate this procedure, especially if multiple nerves are injected. For these reasons, phenol neurolysis is often performed under general anesthesia in children (Gormley, Krach, & Piccini, 2001). Few case reports of successful use of phenol neurolysis manage dystonia have been reported in the literature (Garcia Ruiz & Sanchez Bernardos, 2000; Kim, Lee, Ko, Ko, & Chung, 2003; Takeuchi, Chuma, & Mano, 2004). Phenol neurolysis has been used for decades in the management of persistent and intractable pain in various conditions. Phenol neurolysis or nerve blocks are frequently used to manage pain in cancer and other diagnoses resulting in chronic pain (Filippiadis et al., 2019; Koyyalagunta & Burton, 2010). It has been reportedly used to manage severe chronic nonmalignant pain to target pain generators, including the lumbar sympathetic chain, medial branches to the facet joints of the spine, the sacroiliac joint, the intercostal nerves, the occipital nerves, and the paracoccygeal area (Welksler et al., 2007).

Mini-dictionary of terms

Neurolysis: Targeted mechanical or chemical injury to the nerve.

Dysesthesia: Abnormal, painful sensation due to damage to the peripheral or central nervous system.

Motor point: Location where motor branches of the nerve enter the muscle.

Nerve block: Injection of a chemical agent to cause temporarily or permanently block the nerve conduction to treat pain, spasticity, etc.

Demyelination: Damage to the myelin sheath, a protective outer layer of the nerve, which helps in nerve conduction.

Spasticity: Muscle tightness or spasms due to upper motor neuron injury such as spinal cord injury, stroke.

Motor nerve: Peripheral nerve fibers that transmit signals from the brain and spinal cord to the muscles.

Sensory nerve: Peripheral nerve fibers that carry sensory information to the spinal cord and brain.
Mixed nerve: A peripheral nerve that carries both sensory and motor fibers.
Intrathecal baclofen pump: A system that delivers baclofen into intrathecal space.

Key facts of phenol

- Phenol is a chemical, also known as carbolic acid (C_6H_5OH), a benzene ring.
- At room temperature, phenol dissolves in water.
- Phenol is used at low concentrations in household cleaners as a disinfectant and antiseptic.
- Phenol is also used as a spray in a concentration of 1.4% for pain relief from sore throat.
- The usefulness of chemical neurolysis or nerve block was first recognized in 1863 for treating pain.
- Accidental exposure of large quantities of phenol can be lethal to humans.

Summary points

- Poorly controlled severe spasticity after spinal cord injury can result in multiple complications, including the development of joint contractures, inability to participate in therapy, skin breakdown, decreased function, poor sleep, and poor quality of life.
- Phenol neurolysis is a cost-effective tool to manage spasticity, which requires skill to localize to the target nerve or motor points.
- Phenol neurolysis can be performed with anatomic localization, electrical stimulation guidance, or ultrasound guidance. Often these techniques are combined to maximize the efficiency of the procedure and minimize errors in localizing targets.
- 5%–6% phenol is typically used for spasticity management with effects lasting from 3 to 9 months.
- Medial pectoral nerves, lateral pectoral nerves, and musculocutaneous motor branches are common targets of the upper extremity for treating shoulder adductor and elbow flexor spasticity.
- Obturator nerve and tibial motor nerves are frequently injected targets of the lower extremity to address hip adductor and ankle plantar flexor spasticity.
- Local adverse effects include pain, dysesthesias, loss of sensation, and swelling.
- Systemic severe side effects can result from the intravascular injection of phenol, resulting in cardiac arrest and coma.

References

Akkaya, T., Unlu, E., Alptekin, A., Gumus, H. I., Umay, E., & Cakci, A. (2010). Neurolytic phenol blockade of the obturator nerve for severe adductor spasticity. *Acta Anaesthesiologica Scandinavica*, *54*(1), 79–85. https://doi.org/10.1111/j.1399-6576.2009.02130.x.

Awad, E. A. (1972). Phenol block for control of hip flexor and adductor spasticity. *Archives of Physical Medicine and Rehabilitation*, *53*(12), 554–557.

Chang, M. C., & Boudier-Reveret, M. (2020). Management of elbow flexor spasticity with ultrasound-guided alcohol neurolysis of the musculocutaneous nerve. *Acta Neurologica Belgica*, *120*(4), 983–984. https://doi.org/10.1007/s13760-020-01300-x.

Chua, K. S., & Kong, K. H. (2001). Clinical and functional outcome after alcohol neurolysis of the tibial nerve for ankle-foot spasticity. *Brain Injury*, *15*(8), 733–739. https://doi.org/10.1080/02699050010009775.

Copp, E. P., Harris, R., & Keenan, J. (1970). Peripheral nerve block and motor point block with phenol in the management of spasticity. *Proceedings of the Royal Society of Medicine*, *63*(9), 937–938.

D'Souza, R. S., & Hooten, W. M. (2021). *Neurolytic blocks*. Treasure Island, FL: StatPearls.

D'Souza, R. S., & Warner, N. S. (2021). *Phenol nerve block*. Treasure Island, FL: StatPearls.

Easton, J. K., Ozel, T., & Halpern, D. (1979). Intramuscular neurolysis for spasticity in children. *Archives of Physical Medicine and Rehabilitation*, *60*(4), 155–158.

Elovic, E. P., Esquenazi, A., Alter, K. E., Lin, J. L., Alfaro, A., & Kaelin, D. L. (2009). Chemodenervation and nerve blocks in the diagnosis and management of spasticity and muscle overactivity. *PM & R: The Journal of Injury, Function, and Rehabilitation*, *1*(9), 842–851. https://doi.org/10.1016/j.pmrj.2009.08.001.

Escaldi, S. (2018). Neurolysis: A brief review for a fading art. *Physical Medicine and Rehabilitation Clinics of North America*, *29*(3), 519–527. https://doi.org/10.1016/j.pmr.2018.03.005.

Felsenthal, G. (1974). Pharmacology of phenol in peripheral nerve blocks: A review. *Archives of Physical Medicine and Rehabilitation*, *55*(1), 13–16.

Filippiadis, D. K., Tselikas, L., Tsitskari, M., Kelekis, A., de Baere, T., & Ryan, A. G. (2019). Percutaneous neurolysis for pain management in oncological patients. *Cardiovascular and Interventional Radiology*, *42*(6), 791–799. https://doi.org/10.1007/s00270-019-02185-x.

Gaid, M. (2012). Phenol nerve block for the management of lower limb spasticity. *Advances in Clinical Neuroscience & Rehabilitation*, *12*(3), 23–25.

Garcia Ruiz, P. J., & Sanchez Bernardos, V. (2000). Intramuscular phenol injection for severe cervical dystonia. *Journal of Neurology*, *247*(2), 146–147. https://doi.org/10.1007/pl00007799.

Ghai, A., Sangwan, S. S., Hooda, S., Garg, N., Kundu, Z. S., & Gupta, T. (2013). Evaluation of interadductor approach in neurolytic blockade of obturator nerve in spastic patients. *Saudi Journal of Anaesthesia*, *7*(4), 420–426. https://doi.org/10.4103/1658-354X.121074.

Gormley, M. E., Jr., Krach, L. E., & Piccini, L. (2001). Spasticity management in the child with spastic quadriplegia. *European Journal of Neurology*, *8* (Suppl. 5), 127–135. https://doi.org/10.1046/j.1468-1331.2001.00045.x.

Gunduz, S., Kalyon, T. A., Dursun, H., Mohur, H., & Bilgic, F. (1992). Peripheral nerve block with phenol to treat spasticity in spinal cord injured patients. *Paraplegia*, *30*(11), 808–811. https://doi.org/10.1038/sc.1992.156.

Halpern, D., & Meelhuysen, F. E. (1966). Phenol motor point block in the management of muscular hypertonia. *Archives of Physical Medicine and Rehabilitation*, *47*(10), 659–664.

Halpern, D., & Meelhuysen, F. E. (1967). Duration of relaxation after intramuscular neurolysis with phenol. *JAMA*, *200*(13), 1152–1154.

Holtz, K. A., Lipson, R., Noonan, V. K., Kwon, B. K., & Mills, P. B. (2017). Prevalence and effect of problematic spasticity after traumatic spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *98*(6), 1132–1138. https://doi.org/10.1016/j.apmr.2016.09.124.

Horn, L. J., Singh, G., & Dabrowski, E. R. (2015). In A. Brashear, & E. Elovic (Eds.), *Chemoneurolysis with phenol and alcohol: A "dying art" that merits revival* (pp. 109–128). New York: Springer Publishing Company.

Jang, S. H., Ahn, S. H., Park, S. M., Kim, S. H., Lee, K. H., & Lee, Z. I. (2004). Alcohol neurolysis of tibial nerve motor branches to the gastrocnemius muscle to treat ankle spasticity in patients with hemiplegic stroke. *Archives of Physical Medicine and Rehabilitation*, *85*(3), 506–508. https://doi.org/10.1016/s0003-9993(03)00468-4.

Karri, J., Mas, M. F., Francisco, G. E., & Li, S. (2017). Practice patterns for spasticity management with phenol neurolysis. *Journal of Rehabilitation Medicine*, *49*(6), 482–488. https://doi.org/10.2340/16501977-2239.

Karri, J., Zhang, B., & Li, S. (2020). Phenol neurolysis for management of focal spasticity in the distal upper extremity. *PM & R: The Journal of Injury, Function, and Rehabilitation*, *12*(3), 246–250. https://doi.org/10.1002/pmrj.12217.

Kaymak, B., Kara, M., Gurcay, E., Aydin, G., & Ozcakar, L. (2019). Selective peripheral neurolysis using high frequency ultrasound imaging: A novel approach in the treatment of spasticity. *European Journal of Physical and Rehabilitation Medicine*, *55*(4), 522–525. https://doi.org/10.23736/S1973-9087.18.05295-4.

Keenan, M. A., Tomas, E. S., Stone, L., & Gersten, L. M. (1990). Percutaneous phenol block of the musculocutaneous nerve to control elbow flexor spasticity. *The Journal of Hand Surgery*, *15*(2), 340–346. https://doi.org/10.1016/0363-5023(90)90120-g.

Kelly, R. E., & Gautier-Smith, P. C. (1959). Intrathecal phenol in the treatment of reflex spasms and spasticity. *Lancet*, *2*(7112), 1102–1105. https://doi.org/10.1016/s0140-6736(59)90095-9.

Khalili, A. A., & Betts, H. B. (1967). Peripheral nerve block with phenol in the management of spasticity. Indications and complications. *JAMA*, *200*(13), 1155–1157.

Kim, J. S., Lee, K. S., Ko, Y. J., Ko, S. B., & Chung, S. W. (2003). Idiopathic foot dystonia treated with intramuscular phenol injection. *Parkinsonism & Related Disorders*, *9*(6), 355–359. https://doi.org/10.1016/s1353-8020(02)00118-9.

Kong, K. H., & Chua, K. S. (1999). Neurolysis of the musculocutaneous nerve with alcohol to treat poststroke elbow flexor spasticity. *Archives of Physical Medicine and Rehabilitation*, *80*(10), 1234–1236. https://doi.org/10.1016/s0003-9993(99)90021-7.

Kong, K. H., & Chua, K. S. (2002). Intramuscular neurolysis with alcohol to treat post-stroke finger flexor spasticity. *Clinical Rehabilitation*, *16*(4), 378–381. https://doi.org/10.1191/0269215502cr508oa.

Koyama, H., Murakami, K., Suzuki, T., & Suzaki, K. (1992). Phenol block for hip flexor muscle spasticity under ultrasonic monitoring. *Archives of Physical Medicine and Rehabilitation*, *73*(11), 1040–1043.

Koyyalagunta, D., & Burton, A. W. (2010). The role of chemical neurolysis in cancer pain. *Current Pain and Headache Reports*, *14*(4), 261–267. https://doi.org/10.1007/s11916-010-0123-9.

Lee, K. H., Kim, D. H., Kim, Y. H., Ro, S. H., & Lee, J. (2020). Neurolytic abdominal wall blocks with alcohol for intractable gastrostomy site pain in a cancer patient—A case report. *Korean Journal of Anesthesiology*, *73*(3), 247–251. https://doi.org/10.4097/kja.19041.

Liversedge, L. A., & Maher, R. M. (1960). Use of phenol in relief of spasticity. *British Medical Journal*, *2*(5191), 31–33. https://doi.org/10.1136/bmj.2.5191.31.

Mas, M. F., DiTommaso, C., & Li, S. (2019). Phenol neurolysis for the management of shoulder spasticity in early recovery from traumatic brain injury: A case report. *PM & R: The Journal of Injury, Function, and Rehabilitation*, *11*(1), 90–93. https://doi.org/10.1016/j.pmrj.2018.06.002.

Matsumoto, M. E., Berry, J., Yung, H., Matsumoto, M., & Munin, M. C. (2018). Comparing electrical stimulation with and without ultrasound guidance for phenol neurolysis to the musculocutaneous nerve. *PM & R: The Journal of Injury, Function, and Rehabilitation*, *10*(4), 357–364. https://doi.org/10.1016/j.pmrj.2017.09.006.

Maynard, F. M., Karunas, R. S., & Waring, W. P., 3rd. (1990). Epidemiology of spasticity following traumatic spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *71*(8), 566–569.

Rekand, T., Hagen, E. M., & Gronning, M. (2012). Spasticity following spinal cord injury. *Tidsskrift for den Norske Lægeforening*, *132*(8), 970–973. https://doi.org/10.4045/tidsskr.10.0872.

Seidel, P. M., Seidel, G. K., Gans, B. M., & Dijkers, M. (1996). Precise localization of the motor nerve branches to the hamstring muscles: An aid to the conduct of neurolytic procedures. *Archives of Physical Medicine and Rehabilitation*, *77*(11), 1157–1160. https://doi.org/10.1016/s0003-9993(96)90140-9.

Sezer, N., Akkus, S., & Ugurlu, F. G. (2015). Chronic complications of spinal cord injury. *World Journal of Orthopedics*, *6*(1), 24–33. https://doi.org/10.5312/wjo.v6.i1.24.

Sirico, F., Zappia, M., Di Meglio, F., Castaldo, C., & Nurzynska, D. (2020). Can we reduce the risk of adverse effects in selective neurolysis of the motor branches of musculocutaneous nerve? Evidence-based anatomy approach to the rescue of patients with muscle spasticity. *European Journal of Physical and Rehabilitation Medicine*, *56*(1), 126–127. https://doi.org/10.23736/S1973-9087.19.05875-1.

Sung, D. H., Han, T. R., Park, W. H., Je Bang, H., Kim, J. M., Chung, S. H., et al. (2001). Phenol block of peripheral nerve conduction: Titrating for optimum effect. *Archives of Physical Medicine and Rehabilitation*, *82*(5), 671–676. https://doi.org/10.1053/apmr.2001.21975.

Takeuchi, N., Chuma, T., & Mano, Y. (2004). Phenol block for cervical dystonia: Effects and side effects. *Archives of Physical Medicine and Rehabilitation*, *85*(7), 1117–1120. https://doi.org/10.1016/j.apmr.2003.10.012.

Tibbett, J., Widerstrom-Noga, E. G., Thomas, C. K., & Field-Fote, E. C. (2019). Impact of spasticity on transfers and activities of daily living in individuals with spinal cord injury. *The Journal of Spinal Cord Medicine*, *42*(3), 318–327. https://doi.org/10.1080/10790268.2017.1400727.

van Cooten, I. P., Snoek, G. J., Nene, A. V., de Groot, S., & Post, M. W. (2015). Functional hindrance due to spasticity in individuals with spinal cord injury during inpatient rehabilitation and 1 year thereafter. *Spinal Cord*, *53*(9), 663–667. https://doi.org/10.1038/sc.2015.41.

Viel, E., Pellas, F., Ripart, J., Pelissier, J., & Eledjam, J. J. (2005). Peripheral neurolytic blocks and spasticity. *Annales Françaises d'Anesthèsie et de Rèanimation*, *24*(6), 667–672. https://doi.org/10.1016/j.annfar.2005.03.015.

Welksler, N., Klein, M., Gurevitch, B., Rozentsveig, V., Rudich, Z., Brill, S., et al. (2007). Phenol neurolysis for sever chronic nonmalignant pain: Is the old also obsolete? *Pain Medicine*, *8*(4), 332–337. https://doi.org/10.1111/j.1526-4637.2006.00228.x.

Zhang, B., Darji, N., Francisco, G. E., & Li, S. (2021). The time course of onset and peak effects of phenol neurolysis. *American Journal of Physical Medicine & Rehabilitation*, *100*(3), 266–270. https://doi.org/10.1097/PHM.0000000000001563.

Chapter 27

Anti-repulsive guidance molecule: An antibody treatment in spinal cord injury

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Abbreviations

BBB	blood brain barrier
BMP	bone morphogenetic protein
CNS	central nervous system
CST	corticospinal tract
DCC	deleted in colorectal cancer
GPI	glycosylphosphatidylinositol
MCAO	middle cerebral artery occlusion
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MS	multiple sclerosis
NMO	neuromyelitis optica
PD	Parkinson's disease
RGC	retinal ganglion cell
RGM	repulsive guidance molecule
Rho GEF	Rho guanine nucleotide exchange factor
SCI	spinal cord injury
SN	substantia nigra
TBI	traumatic brain injury
UEMS	upper extremity motor score

Introduction

The repulsive guidance molecule (RGM) is a membrane-associated glycosylphosphatidylinositol (GPI)-anchored glycoprotein, which was identified as an axon guidance molecule in the retinotectal system (Monnier et al., 2002). By analyzing the development of the retinotectal projection system in chicks—a method frequently used to study the molecular basis of topographic projections, including axon guidance cues—Monnier et al. found that RGM is expressed in a spatial gradient manner along the anterior–posterior axis in the tectum (Fig. 1A). Importantly, in growth cone collapse assays, temporal, but not nasal, retinal growth cones collapsed when confronted with RGM-decorated membranes (Fig. 1B). Similarly, in the stripe assay (Walter, Kern-Veits, Huf, Stolze, & Bonhoeffer, 1987), RGM guides axonal elongation only for temporal retinal axons (Fig. 1C). These findings strongly suggest that RGM can act as an axon-specific repulsive guidance molecule (Monnier et al., 2002).

However, the receptor mechanism for RGM function was not defined at that time. In 2004, Rajagopalan et al. and Matsunaga et al. reported that neogenin mediates the biological effects of RGM as its cognate receptor (Matsunaga et al., 2004; Rajagopalan et al., 2004). Strikingly, neogenin was revealed to be expressed in a temporal–nasal gradient in the retina (Rajagopalan et al., 2004); thus, the repulsiveness of temporal, not nasal, retinal axons by RGM is well explained by RGM–neogenin interactions (Fig. 1A). RGM is also found to act as a co-receptor for bone morphogenetic proteins (BMPs) and modulates BMP signaling (Babitt et al., 2005).

Since then, RGM signaling in the central nervous system (CNS) has been extensively studied and a wide range of functions has been reported; RGM plays multiple roles in neuronal development [e.g., neural tube closure (Matsunaga

Diagnosis and Treatment of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822498-4.00027-0

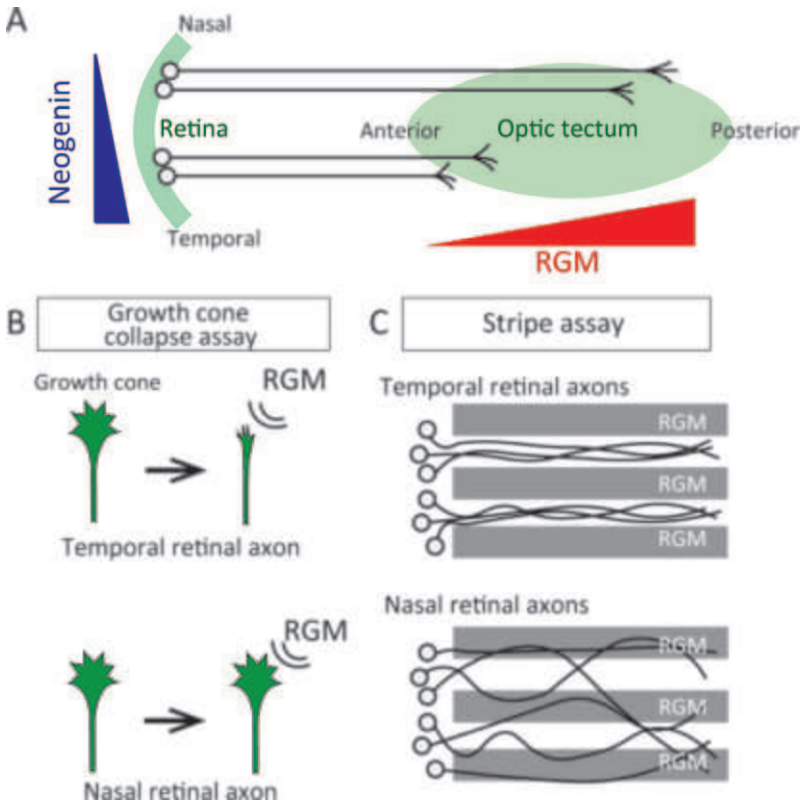

FIG. 1 RGM is an inhibitory axon guidance molecule. (A) Schematic illustration of retinotectal projections and expression patterns of RGMa and neogenin. Nasal retinal ganglion cell (RGC) axons project to the posterior part of the optic tectum, whereas temporal RGC axons project to the anterior part of the tectum. RGM is expressed in an increasing anterior–posterior gradient manner in the tectum, and neogenin is expressed along an elevating nasal–temporal gradient in the retina. (B) Representation of growth cone collapse assay. RGM exerts growth cone collapse effects only for temporal retinal axons. (C) Representation of stripe assay. The gray colored stripe indicates membrane fractions from RGM-transfected cells, whereas the white colored stripe represents membrane fractions from mock-transfected cells.

et al., 2004)], and is also involved in the pathophysiology of various CNS diseases, as discussed below. Moreover, external to the CNS, RGM has been shown to regulate endochondral bone formation (Zhou et al., 2010), iron homeostasis (Babitt et al., 2006), and inflammation (Körner et al., 2019). In mammals, at least three homologues of RGM, RGMa, RGMb (also known as DRAGON), and RGMc (also known as hemojuvelin, HFE2), have been identified. Among them, RGMa is most closely related to chicken RGM (80% homology), and most of the critical findings in CNS development/disease are obtained from RGMa research. Thus, in this review, we mainly focus on the functions of RGMa.

Characteristics of RGMa

Ligand–receptor interactions and downstream signaling of RGMa

As mentioned above, RGM binds to neogenin, a transmembrane protein originally isolated from chick cerebellum as a homolog of deleted in colorectal cancer (DCC: a receptor for the axon guidance molecule netrin-1). RGM also binds to BMP morphogens as a co-receptor and modulates BMP signaling. On the other hand, neogenin is also known as a netrin-1 receptor. How these proteins interact with each other and how downstream signaling is regulated are not fully understood. However, recent studies, including crystal structure analysis (Bell et al., 2013; Healey et al., 2015; Malinauskas, Peer, Bishop, Mueller, & Siebold, 2020), provide direct insight into their interactions.

The major binding site of RGM for neogenin is the carboxyl-terminal domain of RGM (C-RGM) (Bell et al., 2013; Itokazu, Fujita, Takahashi, & Yamashita, 2012). Interestingly, two C-RGMs act as a molecular staple bringing two neogenin receptors together, and this unique architecture is proposed to be important for the subsequent activation of downstream signaling (Bell et al., 2013; Siebold, Yamashita, Monnier, Mueller, & Pasterkamp, 2017). On the other hand, the amino-terminal domain of RGM (N-RGM) has been shown to interact with BMP, and this binding is suggested to link BMP and neogenin signaling by comprising a BMP–RGM–neogenin complex (Healey et al., 2015). RGM–BMP interactions

have been thought to potentiate BMP signaling via the canonical SMAD pathway. However, a recent report revealed that RGM can compete with growth differentiation factor 5 (GDF5), a member of the BMP family, and thus act as an inhibitor of BMP signaling (Malinauskas et al., 2020). Therefore, how intracellular signaling is regulated through interactions involving N-RGM and BMPs is presumed to be context-dependent. Further studies are warranted to determine the physiological roles of RGM–BMP interactions in each developmental/pathological condition.

RGM is thought to transduce signals in both *cis* and *trans* manner. Its distinctive functions, such as inducing growth cone collapse or axon repulsion, are induced in *trans*, that is via cell-to-cell interactions. As the RGM extracellular domain is thought to be cleaved at, and secreted from, cell membranes, *trans*-signaling can be achieved by a gradient of soluble RGM (Fig. 2). However, it is unknown whether long-range signal transduction is possible.

Although a detailed picture of RGM signaling has not yet been obtained, several key aspects have been uncovered. One of the most important downstream signaling pathways involves RhoA activation by RGM, because it is widely accepted that Rho-GTPases play key roles in axon guidance and neurite growth. Indeed, the inhibition of Rho kinase, a downstream effector of RhoA, abolishes the inhibitory effects of RGMa on neurite outgrowth (Hata et al., 2006). These authors also revealed that Unc5B, a member of the netrin receptor family, interacts with neogenin as a co-receptor for RGMa and activates RhoA through LARG, a member of the Rho guanine nucleotide exchange factor (RhoGEF) subfamily (Hata, Kaibuchi, Inagaki, & Yamashita, 2009). In addition, the involvement of Ras activity was also evaluated because of its well-known functions as a mediator of growth cone collapse and neurite retraction (Elowe, Holland, Kulkarni, & Pawson, 2001). As expected, RGMa–neogenin binding has been revealed to inactivate Ras activity, leading to growth cone collapse (Endo & Yamashita, 2009).

More recently, detailed investigations unveiled more complex mechanisms surrounding RGM–neogenin signaling regulation, including the proteolytic processing of RGMa (Tassew, Charish, Seidah, & Monnier, 2012, well summarized in Siebold et al., 2017), ectodomain shedding of neogenin (van Erp et al., 2015), and ϒ-secretase cleavage of the neogenin intracellular domain (Banerjee et al., 2016). Further research is needed to elucidate how these multiple signaling pathways are regulated and integrated in vivo.

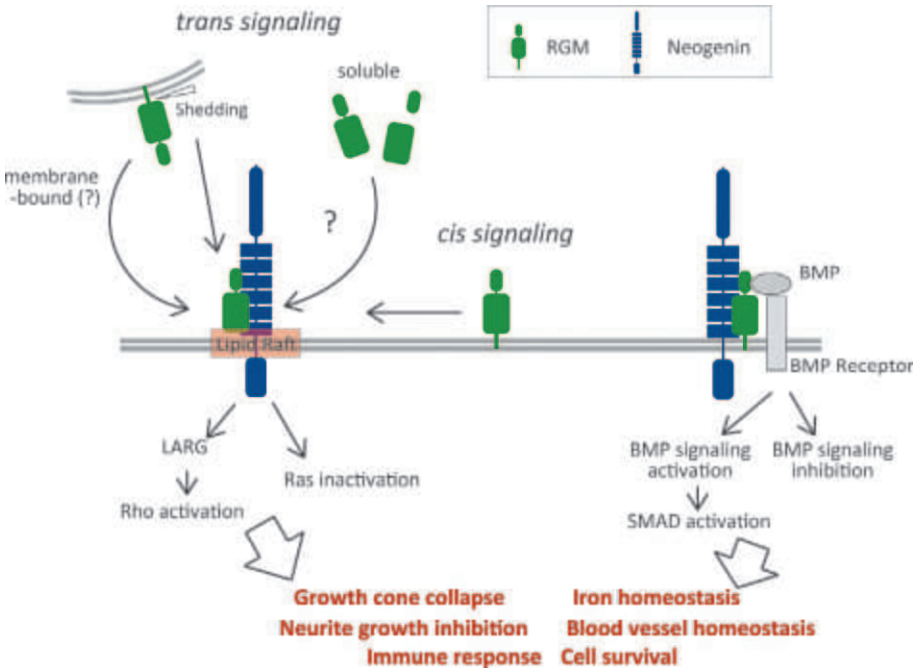

FIG. 2 RGM–neogenin interactions and downstream signaling. Schematic illustration of possible ligand-receptor interactions involving RGMa. The inhibitory effect for neurite outgrowth is brought about by *trans*-signaling; that is, neurogenin-expressing axons are repelled by cell-bound RGMa or via an RGMa gradient established by extracellular shedding. Neogenin localization to lipid rafts—membrane domains enriched in cholesterol, sphingolipids, and protein receptors, present a platform for cellular signaling events, including ligand:receptor interactions—has been proposed to be indispensable for signal transduction.

RGMa in spinal cord injury (SCI)

RGMa expression after SCI

Given that RGMa, as an inhibitory protein, is involved in neural circuit formation during development by modulating the pathfinding activity of growing axons, it is possible that RGMa exerts negative effects on axonal regeneration. To test this concept in vivo, RGMa expression in the spinal cord of adult animals under normal and SCI conditions has been addressed.

Immunohistochemical analysis of rat spinal cord using anti-C-RGMa antibody revealed its localization to neurons and oligodendrocytes under normal conditions (Hata et al., 2006; Schwab, Conrad, et al., 2005). After SCI, RGMa expression around the lesion site is upregulated; with expression by neurons, oligodendrocytes, certain reactive astrocytes, activated microglia, and infiltrating leukocytes (Hata et al., 2006; Schwab, Conrad, et al., 2005). These observations support the possibility that RGMa is an inhibitory protein against axonal regeneration after SCI; therefore, RGMa neutralization is considered to be a potential therapeutic strategy to attenuate neural deficits induced by SCI. An increase in RGMa around the SCI lesion site is also observed in primates (Nakagawa et al., 2019). In that study, RGMa was reported to be mainly expressed by Iba-1-positive microglia/macrophages.

Importantly, RGMa expression patterns in the human spinal cord have also been reported. In the uninjured spinal cord, RGMa is expressed at low levels by neurons and glial cells. However, immunoreactivity for RGMa in the spinal cord is significantly increased following SCI, and the localization of RGMa in neurons, axons, and glial cells has been confirmed (Mothe et al., 2017). On the other hand, the RGMa receptor neogenin is expressed by neurons in the spinal cord in both rats and humans (Mothe et al., 2017).

Taken together, RGMa upregulation induced by SCI is common across divergent species, suggesting the significance of RGMa in the pathophysiology of CNS injury.

RGMa inhibition promotes recovery after SCI in rodents

The first direct evidence of the therapeutic effects of RGMa inhibition on SCI was reported in 2006 (Hata et al., 2006). To test the hypothesis that upregulated RGMa plays a negative role in axonal regeneration in vivo, Hata et al. generated an RGMa-neutralizing antibody (directed against RGM residues 309–322). After receiving Th9/10 dorsal transection, which resulted in both dorsal (main) and lateral corticospinal tract (CST) injury, rats were treated with the RGMa-neutralizing antibody via an osmotic mini-pump with catheters placed near the lesion site, and locomotor functions were monitored. As expected, the Basso–Beattie–Bresnahan (BBB) locomotion score (Basso, Beattie, & Bresnahan, 1995) was significantly improved by RGMa inhibition. The authors also performed anatomical tracing studies and observed a lesser degree of CST retraction, a greater number of collateral formations, and a significant amount of axon extension through the lesion site (Fig. 3A). This enhanced anatomical regeneration temporally correlated with functional recovery.

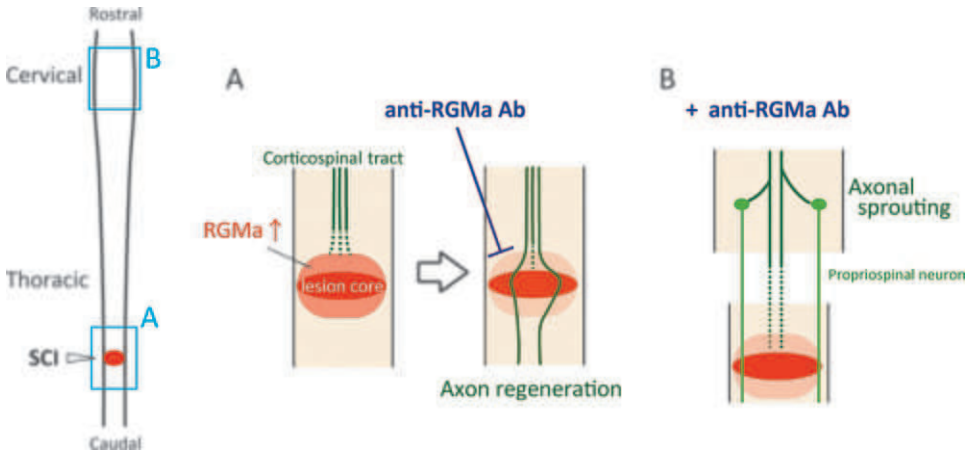

FIG. 3 RGMa neutralization enhances axonal regeneration and neural circuit reorganization after spinal cord injury in rodents. RGMa neutralization promotes several types of neuroplasticity after spinal cord injury. (A) RGMa is upregulated around the lesion site and limits axonal regeneration. Anti-RGMa treatment results in axonal growth of the corticospinal tract (CST). (B) Anti-RGMa treatment is suggested to enhance neural synaptic rearrangement in the cervical spinal cord, distant from the lesion site. Collaterals from hind-limb axons possibly make connections to descending long propriospinal neurons to compensate for the damaged circuit (Bareyre et al., 2004).

Using the same experimental setting, Kyoto et al. tested the possibility that neural circuit plasticity might be enhanced by anti-RGMa antibody treatment—even in lesions distant from the injury site (Kyoto et al., 2007). The results showed that antibody treatment facilitated synapse formation at the level of the cervical spinal cord (Fig. 3B), which may contribute to the rerouting of hind-limb CST connections through propriospinal neurons (Bareyre et al., 2004; Fink & Cafferty, 2016; Oudega & Perez, 2012). This observation may be explained by the notion that the adult CNS offers an inhibitory environment for adoptive reorganization (i.e., neural circuit remodeling) and RGMa is one of its major components; therefore, RGMa inhibition can contribute to the establishment of reorganization-permissive environments.

On the other hand, Tassew et al. explored strategies to inhibit neogenin (Tassew et al., 2014). During developmental stages, neogenin is known to act as a dependence receptor that induces cell death in the absence of RGM (Matsunaga et al., 2004). Therefore, targeting neogenin instead of RGMa may be beneficial, not only for neural circuit reorganization, but also for neuronal survival after SCI. Based on the observation that the receptor functions of neogenin require its localization in lipid rafts, the authors addressed whether blocking neogenin raft association improves SCI outcomes. They found that interactions involving the neogenin 4Ig domain and the N-terminal regions of RGMa (N-RGMa) are critical for the attraction of neogenin to lipid rafts, and recombinant 4Ig treatment effectively abolishes their interactions. Thus, they treated SCI rats with 4Ig (intravenous injection or local intrathecal infusion). As expected, axonal regeneration and functional recovery (as assessed by BBB scores and ladder walk tests) were significantly enhanced. Furthermore, this treatment attenuated neuronal loss in perilesional neurons.

Based on this evidence, humanized monoclonal antibodies specific for N-RGMa were generated (Demicheva et al., 2015), and their therapeutic potential in impact-compression SCI was tested (Mothe et al., 2017). To provide a clinically applicable strategy, the authors examined the efficacy of RGMa inhibition by systemic administration of humanized anti-RGMa antibody and revealed that this treatment effectively enhanced functional recovery (as assessed by BBB scores, ladder walk tests, and footprint analysis). Moreover, by histological and anatomical analysis, it was also confirmed that anti-RGMa antibody treatment enhances neuronal survival and axonal regeneration. Interestingly, anti-RGMa antibody treatment also attenuated neuropathic pain after SCI. Although effects on microglia/macrophage were suggested, the precise mechanisms involved remain unknown. In a recent paper, Mothe et al. also reported that delayed administration (~3 h after SCI) of anti-N-RGMa antibody could still effectively enhance recovery of motor functions, with increased neuronal sparing and axonal plasticity (Mothe et al., 2020). Interestingly, the recovery of bladder function was also enhanced, indicating that anti-RGMa treatment exerts broad beneficial effects in terms of SCI convalescence.

Taken together, the effectiveness of the strategy for RGMa/neogenin signaling inhibition has been repeatedly confirmed in rodent SCI models (Table 1). In the next chapter, evidence from primates is discussed.

TABLE 1 Summary of pre-clinical studies.

Author (Year)	Species	Method of SCI	Intervention	Route of Administration	Functional Outcome	Suggested Mechanism
Hata et al. (2006)	Rat	Dorsal hemisection	anti RGMa-C antibody	intrathecal administration via osmotic minipump	Locomotor recovery ↑ (BBB score)	CST regeneration/sprouting ↑
Kyoto et al. (2007)	Rat	Dorsal hemisection	anti RGMa-C antibody	intrathecal administration via osmotic minipump	*not tested*	Synapse formation of CST in the cervical SC ↑
Tassew et al. (2014)	Rat	Impact compression	4Ig peptide (prevent RGMa-Neogenin interaction)	Intraspinal injection and continuous intrathecal derivery	Motor function ↑ (BBB score, Motor subscore, Ladder walk test)	Axonal regeneration ↑ Neuronal loss ↓
Mothe et al. (2017)	Rat	Impact compression	anti-RGMa-N human antibody	Intravenous administration	Locomotor recovery ↑ (BBB score, Motor subscore, gait analysis) Neuropathic pain ↓	Perilesional neuronal survival ↑ CST axonal growth ↑ Neuronal survival ↑
Chen et al. (2019)	Lamprey	Transection	Neogenin antisense morpholino oligo	Retrograde transport from lesion site	Restoration of locomotor activity	Survival of reticulospinal neurons ↑
Mothe et al. (2020)	Rat	Impact compression	elezanumab (human monoclonal RGMa antibody)	Intravenous delayed administration	3h post-SCI administration: Locomotor recovery ↑ (BBB score, Motor subscore) Bladder function ↑	CST axonal plasticity ↑ Serotonergic axonal plasticity ↑ Perilesional neuronal sparing ↑
Yang et al. (2020)	Rat	Compression	sh-RGMa (lentiviral vector)	Direct injection to the spinal cord	Locomotor recovery ↑ (BBB score)	Nerve regeneration ↑
Nakagawa et al. (2019)	Macaque monkey	Unilateral lesion at C6/C7	anti-human RGMa-C antibody	intrathecal administration via osmotic minipump	Manual dexterity ↑	Axonal sprouting of CST fiber ↑ CST fiber - motoneuron connection ↑

Inhibition of RGMa/neogenin signaling promotes functional recovery after SCI (Chen & Shifman, 2019; Kyoto, Hata, & Yamashita, 2007; Mothe et al., 2017, 2020; Nakagawa, Ninomiya, Yamashita, & Takada, 2019; Tassew et al., 2014; Yang & Sun, 2020).

RGMa inhibition promotes recovery after SCI in primates

Considering the clinical application of potential therapies to SCI patients, differences in possible mechanisms underlying neural circuit remodeling between higher primates and rodents should be taken into account. For example, the CST in rodents mainly descends to the dorsal funiculus, whereas in primates, the CST passes through the lateral and ventral portions of the spinal cord. More importantly, direct corticomotoneuronal connections, which are thought to be critically involved in manual dexterity in primates, are lacking in rodents (Lemon, 1993). Restoring hand dexterity remains a key clinical challenge and addressing whether potential treatments have beneficial effects in terms of skilled motor behavior in primates is of enormous importance.

Therefore, to test the effects of anti-RGMa antibody treatment in higher primates, Nakagawa et al. conducted SCI experiments in rhesus monkeys (Nakagawa et al., 2019). Unilateral spinal cord lesions were performed by transection at C6/C7 (Fig. 4A), which led to the complete loss of lateral CST fibers below the lesion. Then, a neutralizing antibody against C-RGMa was continuously delivered to the lesion site via an osmotic pump. Manual dexterity was assessed by a reaching/grasping task (Nakagawa, Ninomiya, Yamashita, & Takada, 2015) and the modified Brinkman Board Test (Freund et al., 2009). In both tests, monkeys were required to grasp food pellets placed in small horizontal or vertical slots (Fig. 4B). The results of these tests conformed a drastic improvement in the motor performance of the animals in the anti-RGMa antibody-treated group.

Further, the anatomical basis for this improvement was investigated. As summarized in Fig. 4C, anti-RGMa antibody treatment enhanced axonal sprouting of CST fibers arising from the motor cortex in the spinal cord at C7-Th1. Moreover, numbers of biotinylated dextran amine (BDA)-labeled direct contacts of CST fibers with wheat germ agglutinin (WGA)-labeled motor neurons (i.e., corticomotoneuronal direct connections) at the levels of C7, C8, and Th1 were significantly increased. These findings suggest that sprouting CST fibers can find appropriate target motoneurons to promote the efficient recovery of motor functions. Furthermore, inactivation of the contralesional motor cortex by muscimol injection in the anti-RGMa antibody-treated animals was performed. The otherwise recovered manual dexterity was then completely abolished.

Taken together, it is reasonable to assume that improved functional recovery of manual dexterity can be achieved by enhancement of axonal reorganization induced by anti-RGMa antibody treatment.

Clinical studies

Based on preclinical findings, two clinical trials using anti-RGMa antibody are, as at October 2020, underway. One of these, MT-3921, involves a monoclonal antibody against the C fragment of RGMa and is under investigation for the

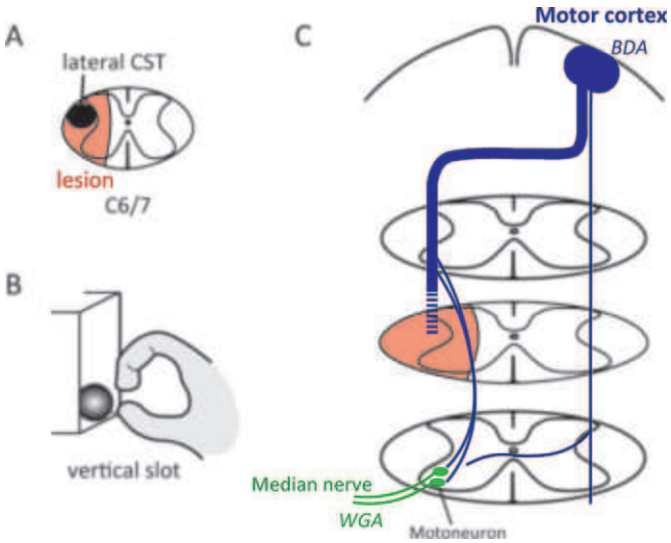

FIG. 4 RGMa neutralization enhances neural circuit reorganization after SCI in primates. (A) Schematic representation of spinal cord lesions in a study by Nakagawa et al. (2019). (B) Behavioral analysis of manual dexterity. Motor performance was greatly recovered by anti-RGMa antibody treatment. This treatment also advanced the commencement of recovery following SCI. (C) RGMa neutralization enhances axonal sprouting of corticospinal tract (CST) fibers. CST axons are labeled by anterograde injection of anterograde tracer (BDA; biotinylated dextran amine). For motoneuron labeling through median nerves, wheat germ agglutinin (WGA) was directly injected into the median nerve.

treatment of acute SCI (NCT04096950, www.clinicaltrials.gov, sponsored by Mitsubishi Tanabe Pharma Development America, Inc.). Another is elezanumab (ABT-555), a monoclonal antibody against the N fragment of RGMa. This antibody is also planned for patients with acute traumatic SCI with C4, C5, C6, or C7 (neurological level) injury (NCT04295538, www.clinicaltrials.gov, sponsored by AbbVie). These trials will determine whether the beneficial effects of RGMa neutralization are also observed in patients suffering from CNS injury.

RGMa in other CNS disorders

Increasing evidence suggests that RGMa is also involved in various CNS disorders, including multiple sclerosis (MS), stroke, traumatic brain injury (TBI), neuromyelitis optica (NMO), and Parkinson's disease (PD). Especially in MS, RGMa inhibition is considered one of the most promising therapeutic strategies (Demicheva et al., 2015; Muramatsu et al., 2011; Tanabe, Fujita, Ikuma, & Yamashita, 2018; Tanabe & Yamashita, 2014). Using an experimental autoimmune encephalomyelitis (EAE) model, Muramatsu et al. showed that anti-RGMa antibody treatment attenuates the symptoms of EAE mice by modulating T cell responses. Particularly impressive is the effect of anti-RGMa treatment on peripheral blood mononuclear cells (PBMCs) obtained from MS patients; this treatment leads to a reduction in their proliferative responses and pro-inflammatory cytokine production (Muramatsu et al., 2011). In another study, RGMa was found to be highly expressed by Th17 cells and mediated neurodegeneration through direct interaction with its receptor, neogenin, which is expressed by neurons (Tanabe & Yamashita, 2014). Demicheva et al. performed histological analysis of human autopsied MS brain tissue and revealed that RGMa is expressed in MS lesions and by infiltrating lymphocytes. To test neural regeneration capacity, they employed a rat targeted-EAE model (established by Kerschensteiner et al., 2004) involving the spinal cord and optic nerve and demonstrated that anti-RGMa treatment promotes both functional recovery and regenerative axonal growth, accompanied by enhanced remyelination and decreased activation of microglia/macrophages (Demicheva et al., 2015). Taken together, anti-RGMa antibody is expected to attenuate MS symptoms by modulating immune responses and axonal regeneration.

The effects of anti-RGMa antibody treatment in NMO were also reported. Harada et al. established a localized NMO model by injecting NMO-IgG obtained from AQP4-Ab–positive NMO patients, into the thoracic spinal cord of rats. After NMO-IgG injection, animals developed motor dysfunction in the tail and hind-limbs, accompanied by the loss of astrocytes in lesion areas, and systemic injection of anti-RGMa antibody effectively attenuated motor deficit, microglial activation, and IL-17A+ T-cell infiltration (Harada et al., 2018).

Several lines of evidence also indicate that RGMa/neogenin pathway inhibition is also a promising strategy to treat patients with cerebral infarction. Based on the observation that RGMa is upregulated in the infarct and peri-infarct (penumbral) lesions of the brain in patients suffering from cerebral infarction (Schwab, Monnier, et al., 2005), Shabanzadeh et al. tested the effect of anti-RGMa antibody in a middle cerebral artery occlusion (MCAO) model in rats and confirmed that such treatment effectively attenuated the infarct area and improved the functional outcomes (Shabanzadeh et al., 2015). RGMa is also suggested to be involved in the blood–brain barrier (BBB) dysfunction (Li et al., 2018), angiogenesis (Wang et al., 2018), and glial scar formation (Zhang et al., 2018) after stroke (MCAO). Recently, Yao et al. revealed that astrocytic neogenin is involved in blood vessel homeostasis. Astrocyte-specific neogenin depletion leads to an increase in the number of blood vessels with leaky BBB in the mouse cortex. Moreover, they showed that neogenin knock-out impairs BMP2-induced netrin-1 expression in astrocytes, which causes a dysregulation of blood vessel homeostasis and function (Yao et al., 2020). Though RGMa involvement was not tested in this study, RGMa may play a direct role in BBB maintenance.

RGMa is also suggested to be involved in PD. Based on the observation that RGMa is upregulated in the substantia nigra (SN) of human PD brains (Bossers et al., 2009), Korecka et al. addressed whether RGMa affects the dopaminergic system, and revealed that AAV-mediated overexpression of RGMa in murine SN results in selective degeneration of dopaminergic neurons with strong microglial activation (Korecka et al., 2017). These results indicate that upregulated RGMa in the SN of PD patients negatively affects midbrain dopaminergic neurons, possibly by inducing microglial accumulation and activation. Indeed, by using 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model, Oda et al. showed that the loss of dopaminergic neurons and accumulation of microglia/macrophages in the SN were attenuated by anti-RGMa antibody treatment (Oda et al., 2021).

In summary, RGMa has been shown to regulate a wide range of pathological events, including immune responses, neuronal survival, and BBB maintenance, following CNS damage. Because SCI also shares these pathological conditions, anti-RGMa antibody treatment might exert its therapeutic effects by modulating various pathological processes involved in SCI (Table 2).

TABLE 2 Therapeutic potential of RGMa inhibition in other CNS disorders.

	Author (Year)	Animal model	RGMa inhibition	Outcome / Suggested Mechanism
Multiple Sclerosis	Muramatsu et al. (2011)	EAE (mouse)	anti RGMa-C antibody (i.t.)	Clinical score ↓, Inflammatory-cell infiltration ↓ / T cell response ↓
	Tanabe et al. (2014)	Th17-induced EAE (mouse)	anti RGMa-C antibody (i.p.)	Clinical score ↓ / Th17 cell-mediated neurodegeneration ↓
	Demicheva et al. (2015)	targeted-EAE (rat)	anti human RGMa-N antibody (i.v.)	Clinical score ↓ / Axonal regeneration ↑
	Tanabe et al. (2018)	NOD-EAE (mouse) as SPMS model	anti human RGMa-C antibody (i.v.)	Secondary progression (clinical score) ↓ / Demyelination ↓, Axonal degeneration ↓
Neuromyelitis Optica	Harada et al. (2018)	NMO-IgG injection into the spinal cord (rat)	anti human RGMa-C antibody (i.v.)	Clinical score ↓, Astrocyte loss ↓ / Inflammatory-cell infiltration ↓
Cerebral Infarction	Shabanzadeh et al. (2015)	MCAO (rat)	4Ig peptide (prevent RGMa-Neogenin interaction), anti RGMa antibody (i.v.)	Motor function ↑ / Infarct volume ↓, Neuronal death ↓
	Li et al. (2018)	MCAO (rat)	sh-RGMa (adenovirus)	Motor function ↑ / Infarct volume ↓, BBB integrity ↑
	Zhang et al. (2018)	MCAO (rat)	6FNIII (RGMa function-blocking peptide) sh-RGMa (adenovirus) (i.c.v.)	Motor function ↑ / TGFβ1 dependent reactive astrogliosis & glial scar formation ↓
Parkinson's disease	Korecka et al. (2017)	AAV-mediated RGMa overexpression in SN (mouse)	-	dopaminergic neuron loss, motor impairment
	Oda et al. (2021)	MPTP model (mouse)	anti human RGMa-C antibody (i.v.)	dopaminergic neuron loss ↓, microglia/macrophages activation ↓

EAE, experimental autoimmune encephalomyelitis; NOD-EAE mouse, experimental autoimmune encephalomyelitis in non-obese diabetic mouse; SPMS, secondary progressive multiple sclerosis; MCAO, middle cerebral artery occlusion; SN, substantia nigra; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; i.t., intrathecal administration; i.p., intraperitoneal administration; i.v., intravenous administration; i.c.v., intracerebroventricular administration.

Conclusions

Over the past decade, experimental studies have greatly enhanced our understanding of neural circuit reorganization after SCI, and various neuro-restorative therapies have been proposed. In particular, a great deal of effort has been invested to identify a biological agent that can modulate the inhibitory function in axonal regeneration/reorganization, with anti-RGMa-neutralizing antibody proving to be one of the most promising candidates with great success in pre-clinical studies. Indeed, various forms of neuroplasticity, including axonal regeneration and neural circuit reorganization, have been shown to be promoted by RGMa inhibition. Moreover, anti-RGMa antibody appears to exert multiple mechanisms of action in SCI, in addition to axonal regeneration, improving neuronal viability, modulating inflammatory responses, or regulating BBB dysfunction. Hopefully, successful clinical trials of this unique therapeutic antibody will open a new window for SCI therapeutics.

Applications to other areas of neuroscience

RGMa has been shown to regulate a wide range of pathological events, including axonal plasticity, immune responses, neuronal survival, and the blood–brain barrier (BBB) maintenance, following central nervous system (CNS) damage. Because most neurological disorders share these pathological conditions to some extent, anti-RGMa antibody treatment might be beneficial for many kinds of CNS diseases.

Indeed, in preclinical studies, RGMa is suggested to be critically involved in multiple sclerosis (MS), stroke, traumatic brain injury (TBI), neuromyelitis optica (NMO), and Parkinson's disease.

In particular, in MS, RGMa inhibition is considered one of the most promising therapeutic strategies. In experimental autoimmune encephalomyelitis (EAE) model mice, anti-RGMa antibody treatment attenuates neurological symptoms by modulating T cell responses. RGMa has also been suggested to be involved in Th17-cell–induced neurodegeneration in EAE.

Inhibition of the RGMa/neogenin pathway has also been proposed as a promising strategy to treat patients with cerebral infarction. RGMa is upregulated in the infarct and peri-infarct lesions, and anti-RGMa antibody treatment improves the functional outcomes in middle cerebral artery occlusion (MCAO) model rats. In the MCAO model, involvement of RGMa in BBB dysfunction, angiogenesis, and glial scar formation has been suggested.

In the main text, we discussed the applications of anti-RGMa treatment for other neurological disorders in greater detail.

Mini-dictionary of terms

Retinotectal projection: This projection is organized in a retinotopic manner, and is frequently used to study the molecular mechanisms underlying neural circuit formation based on chemoaffinity theory.

RhoA: A member of the Rho family of GTPases. Rho proteins play a critical role in actin cytoskeletal reorganization and are thus important for cell motility. Rho activity is tightly regulated by local guanine nucleotide exchange factors (GEFs).

Dorsal transection: One of the major SCI models in rodents. The main CST of rodents descends the dorsal funiculus; thus, severe injury to this area leads to complete loss of the main CST on both sides.

Targeted EAE: As the conventional EAE model shows disseminated inflammatory lesions, testing the relationship between functional deficits and structural damage is difficult. To overcome this limitation, a localized EAE model was generated.

BMP: BMPs are a group of morphogens that belong to the transforming growth factor-β (TGF-β) superfamily, and have diverse functions in the processes of embryogenesis, development, and adult tissue homeostasis.

Key facts of axonal sprouting

CST axons have the capacity to spontaneously sprout after SCI.

Axonal sprouting is one of the mechanisms involved in neural circuit reorganization.

Axonal sprouting occurs both rostrally and caudally to the lesion and occurs from both injured and intact CST axons.

Instead of long-range regeneration, CST axons sprout over short distances and establish synaptic connections with descending propriospinal neurons.

Such newly formed connections can serve as bypass circuits and contribute to functional recovery.

Rehabilitative training or neutralization of neurite outgrowth inhibitory proteins such as Nogo-A and RGMa are thought to enhance axonal sprouting.

Summary points

- RGM was identified as an axon guidance molecule of the retinotectal system.
- RGM induces growth cone collapse and neurite growth inhibition.
- RGM exerts its neurite growth inhibitory effect by interacting with its receptor, neogenin.
- RGMa is upregulated in the injured spinal cord after SCI in rodents, monkeys, and humans.
- In rodents, anti-RGMa-neutralizing antibody treatment enhances axonal regeneration/reorganization and functional recovery after SCI.
- In monkeys, RGMa-neutralizing antibody treatment enhances neural circuit reorganization and functional recovery of hand dexterity.
- RGMa is also involved in the regulation of the immune system, gliosis, blood–brain barrier integrity, and angiogenesis.
- Two lines of clinical trials using antibodies against RGMa are currently underway.

References

Babitt, J. L., Huang, F. W., Wrighting, D. M., Xia, Y., Sidis, Y., Samad, T. A., et al. (2006 May). Bone morphogenetic protein signaling by hemojuvelin regulates hepcidin expression. *Nature Genetics*, *38*(5), 531–539.

Babitt, J. L., Zhang, Y., Samad, T. A., Xia, Y., Tang, J., Campagna, J. A., et al. (2005 August 19). Repulsive guidance molecule (RGMa), a DRAGON homologue, is a bone morphogenetic protein co-receptor. *The Journal of Biological Chemistry*, *280*(33), 29820–29827.

Banerjee, P., Harada, H., Tassew, N. G., Charish, J., Goldschneider, D., Wallace, V. A., et al. (2016 March). Ɣ-secretase and LARG mediate distinct RGMa activities to control appropriate layer targeting within the optic tectum. *Cell Death and Differentiation*, *23*(3), 442–453.

Bareyre, F. M., Kerschensteiner, M., Raineteau, O., Mettenleiter, T. C., Weinmann, O., & Schwab, M. E. (2004 March). The injured spinal cord spontaneously forms a new intraspinal circuit in adult rats. *Nature Neuroscience*, *7*(3), 269–277.

Basso, D. M., Beattie, M. S., & Bresnahan, J. C. (1995 February). A sensitive and reliable locomotor rating scale for open field testing in rats. *Journal of Neurotrauma*, *12*(1), 1–21.

Bell, C. H., Healey, E., van Erp, S., Bishop, B., Tang, C., Gilbert, R. J. C., et al. (2013 July 5). Structure of the repulsive guidance molecule (RGM)-neogenin signaling hub. *Science*, *341*(6141), 77–80.

Bossers, K., Meerhoff, G., Balesar, R., van Dongen, J. W., Kruse, C. G., Swaab, D. F., et al. (2009 January). Analysis of gene expression in Parkinson's disease: Possible involvement of neurotrophic support and axon guidance in dopaminergic cell death. *Brain Pathology*, *19*(1), 91–107.

Chen, J., & Shifman, M. I. (2019 June 1). Inhibition of neogenin promotes neuronal survival and improved behavior recovery after spinal cord injury. *Neuroscience*, *408*, 430–447.

Demicheva, E., Cui, Y. F., Bardwell, P., Barghorn, S., Kron, M., Meyer, A. H., et al. (2015 March 24). Targeting repulsive guidance molecule A to promote regeneration and neuroprotection in multiple sclerosis. *Cell Reports*, *10*(11), 1887–1898.

Elowe, S., Holland, S. J., Kulkarni, S., & Pawson, T. (2001 November). Downregulation of the Ras-mitogen-activated protein kinase pathway by the EphB2 receptor tyrosine kinase is required for ephrin-induced neurite retraction. *Molecular and Cellular Biology*, *21*(21), 7429–7441.

Endo, M., & Yamashita, T. (2009 May 20). Inactivation of Ras by p120GAP via focal adhesion kinase dephosphorylation mediates RGMa-induced growth cone collapse. *The Journal of Neuroscience*, *29*(20), 6649–6662.

Fink, K. L., & Cafferty, W. B. (2016 April). Reorganization of intact descending motor circuits to replace lost connections after injury. *Neurotherapeutics*, *13*(2), 370–381.

Freund, P., Schmidlin, E., Wannier, T., Bloch, J., Mir, A., Schwab, M. E., et al. (2009 March). Anti-Nogo-A antibody treatment promotes recovery of manual dexterity after unilateral cervical lesion in adult primates—Re-examination and extension of behavioral data. *The European Journal of Neuroscience*, *29*(5), 983–996.

Harada, K., Fujita, Y., Okuno, T., Tanabe, S., Koyama, Y., Mochizuki, H., et al. (2018 January 8). Inhibition of RGMa alleviates symptoms in a rat model of neuromyelitis optica. *Scientific Reports*, *8*(1), 34.

Hata, K., Fujitani, M., Yasuda, Y., Doya, H., Saito, T., Yamagishi, S., et al. (2006 April 10). RGMa inhibition promotes axonal growth and recovery after spinal cord injury. *The Journal of Cell Biology*, *173*(1), 47–58.

Hata, K., Kaibuchi, K., Inagaki, S., & Yamashita, T. (2009 March 9). Unc5B associates with LARG to mediate the action of repulsive guidance molecule. *The Journal of Cell Biology*, *184*(5), 737–750.

Healey, E. G., Bishop, B., Elegheert, J., Bell, C. H., Padilla-Parra, S., & Siebold, C. (2015 June). Repulsive guidance molecule is a structural bridge between neogenin and bone morphogenetic protein. *Nature Structural & Molecular Biology*, *22*(6), 458–465.

Itokazu, T., Fujita, Y., Takahashi, R., & Yamashita, T. (2012). Identification of the neogenin-binding site on the repulsive guidance molecule A. *PLoS One*, *7*(3), e32791.

Kerschensteiner, M., Stadelmann, C., Buddeberg, B. S., Merkler, D., Bareyre, F. M., Anthony, D. C., et al. (2004 April). Targeting experimental autoimmune encephalomyelitis lesions to a predetermined axonal tract system allows for refined behavioral testing in an animal model of multiple sclerosis. *The American Journal of Pathology*, *164*(4), 1455–1469.

Korecka, J. A., Moloney, E. B., Eggers, R., Hobo, B., Scheffer, S., Ras-Verloop, N., et al. (2017 September 27). Repulsive guidance molecule a (RGMa) induces neuropathological and behavioral changes that closely resemble Parkinson's disease. *The Journal of Neuroscience*, *37*(39), 9361–9379.

Körner, A., Schlegel, M., Kaussen, T., Gudernatsch, V., Hansmann, G., Schumacher, T., et al. (2019 February 7). Sympathetic nervous system controls resolution of inflammation via regulation of repulsive guidance molecule A. *Nature Communications*, *10*(1), 633.

Kyoto, A., Hata, K., & Yamashita, T. (2007 December). Synapse formation of the cortico-spinal axons is enhanced by RGMa inhibition after spinal cord injury. *Brain Research*, *1186*, 74–86.

Lemon, R. N. (1993 May). The G. L. Brown prize lecture. Cortical control of the primate hand. *Experimental Physiology*, *78*(3), 263–301.

Li, M., Wen, Y., Zhang, R., Xie, F., Zhang, G., & Qin, X. (2018 September). Adenoviral vector-induced silencing of RGMa attenuates blood-brain barrier dysfunction in a rat model of MCAO/reperfusion. *Brain Research Bulletin*, *142*, 54–62.

Malinauskas, T., Peer, T. V., Bishop, B., Mueller, T. D., & Siebold, C. (2020 July 7). Repulsive guidance molecules lock growth differentiation factor 5 in an inhibitory complex. *Proceedings of the National Academy of Sciences of the United States of America*, *117*(27), 15620–15631.

Matsunaga, E., Tauszig-Delamasure, S., Monnier, P. P., Mueller, B. K., Strittmatter, S. M., Mehlen, P., et al. (2004 August). RGM and its receptor neogenin regulate neuronal survival. *Nature Cell Biology*, *6*(8), 749–755.

Monnier, P. P., Sierra, A., Macchi, P., Deitinghoff, L., Andersen, J. S., Mann, M., et al. (2002 September 26). RGM is a repulsive guidance molecule for retinal axons. *Nature*, *419*(6905), 392–395.

Mothe, A. J., Coelho, M., Huang, L., Monnier, P. P., Cui, Y. F., Mueller, B. K., et al. (2020 September). Delayed administration of the human anti-RGMa monoclonal antibody elezanumab promotes functional recovery including spontaneous voiding after spinal cord injury in rats. *Neurobiology of Disease*, *143*, 104995.

Mothe, A. J., Tassew, N. G., Shabanzadeh, A. P., Penheiro, R., Vigouroux, R. J., Huang, L., et al. (2017 September 5). RGMa inhibition with human monoclonal antibodies promotes regeneration, plasticity and repair, and attenuates neuropathic pain after spinal cord injury. *Scientific Reports*, *7*(1), 10529.

Muramatsu, R., Kubo, T., Mori, M., Nakamura, Y., Fujita, Y., Akutsu, T., et al. (2011 April). RGMa modulates T cell responses and is involved in autoimmune encephalomyelitis. *Nature Medicine*, *17*(4), 488–494.

Nakagawa, H., Ninomiya, T., Yamashita, T., & Takada, M. (2015 July 1). Reorganization of corticospinal tract fibers after spinal cord injury in adult macaques. *Scientific Reports*, *5*, 11986.

Nakagawa, H., Ninomiya, T., Yamashita, T., & Takada, M. (2019 February 1). Treatment with the neutralizing antibody against repulsive guidance molecule-a promotes recovery from impaired manual dexterity in a primate model of spinal cord injury. *Cerebral Cortex*, *29*(2), 561–572.

Oda, W., Fujita, Y., Baba, K., Mochizuki, H., Niwa, H., & Yamashita, T. (2021 February 15). Inhibition of repulsive guidance molecule-A protects dopaminergic neurons in a mouse model of Parkinson's disease. *Cell Death & Disease*, *12*(2), 181.

Oudega, M., & Perez, M. A. (2012 August 15). Corticospinal reorganization after spinal cord injury. *The Journal of Physiology*, *590*(16), 3647–3663.

Rajagopalan, S., Deitinghoff, L., Davis, D., Conrad, S., Skutella, T., Chedotal, A., et al. (2004 August). Neogenin mediates the action of repulsive guidance molecule. *Nature Cell Biology*, *6*(8), 756–762.

Schwab, J. M., Conrad, S., Monnier, P. P., Julien, S., Mueller, B. K., & Schluesener, H. J. (2005 March). Spinal cord injury-induced lesional expression of the repulsive guidance molecule (RGM). *The European Journal of Neuroscience*, *21*(6), 1569–1576.

Schwab, J. M., Monnier, P. P., Schluesener, H. J., Conrad, S., Beschorner, R., Chen, L., et al. (2005 October). Central nervous system injury-induced repulsive guidance molecule expression in the adult human brain. *Archives of Neurology*, *62*(10), 1561–1568.

Shabanzadeh, A. P., Tassew, N. G., Szydlowska, K., Tymianski, M., Banerjee, P., Vigouroux, R. J., et al. (2015 May 7). Uncoupling neogenin association with lipid rafts promotes neuronal survival and functional recovery after stroke. *Cell Death & Disease*, *6*(5), e1744.

Siebold, C., Yamashita, T., Monnier, P. P., Mueller, B. K., & Pasterkamp, R. J. (2017 May). RGMs: Structural insights, molecular regulation, and downstream signaling. *Trends in Cell Biology*, *27*(5), 365–378.

Tanabe, S., Fujita, Y., Ikuma, K., & Yamashita, T. (2018 October 17). Inhibiting repulsive guidance molecule-A suppresses secondary progression in mouse models of multiple sclerosis. *Cell Death & Disease*, *9*(11), 1061.

Tanabe, S., & Yamashita, T. (2014 November 20). Repulsive guidance molecule-A is involved in Th17-cell-induced neurodegeneration in autoimmune encephalomyelitis. *Cell Reports*, *9*(4), 1459–1470.

Tassew, N. G., Charish, J., Seidah, N. G., & Monnier, P. P. (2012 February 14). SKI-1 and Furin generate multiple RGMa fragments that regulate axonal growth. *Developmental Cell*, *22*(2), 391–402.

Tassew, N. G., Mothe, A. J., Shabanzadeh, A. P., Banerjee, P., Koeberle, P. D., Bremner, R., et al. (2014 August 21). Modifying lipid rafts promotes regeneration and functional recovery. *Cell Reports*, *8*(4), 1146–1159.

van Erp, S., van den Heuvel, D. M. A., Fujita, Y., Robinson, R. A., Hellemons, A. J. C. G. M., Adolfs, Y., et al. (2015 December 7). Lrig2 negatively regulates ectodomain shedding of axon guidance receptors by ADAM proteases. *Developmental Cell*, *35*(5), 537–552.

Walter, J., Kern-Veits, B., Huf, J., Stolze, B., & Bonhoeffer, F. (1987 December). Recognition of position-specific properties of tectal cell membranes by retinal axons in vitro. *Development*, *101*(4), 685–696.

Wang, Y., Zhang, R., Xing, X., Guo, J., Xie, F., Zhang, G., et al. (2018 January 1). Repulsive guidance molecule a suppresses angiogenesis after ischemia/reperfusion injury of middle cerebral artery occlusion in rats. *Neuroscience Letters*, *662*, 318–323.

Yang, W., & Sun, P. (2020 September 18). Promoting functions of microRNA-29a/199B in neurological recovery in rats with spinal cord injury through inhibition of the RGMA/STAT3 axis. *Journal of Orthopaedic Surgery and Research*, *15*(1), 427.

Yao, L. L., Hu, J. X., Li, Q., Lee, D., Ren, X., Zhang, J. S., et al. (2020 November). Astrocytic neogenin/netrin-1 pathway promotes blood vessel homeostasis and function in mouse cortex. *The Journal of Clinical Investigation*, *3*, 132372.

Zhang, R., Wu, Y., Xie, F., Zhong, Y., Wang, Y., Xu, M., et al. (2018 August). RGMa mediates reactive astrogliosis and glial scar formation through TGFβ1/Smad2/3 signaling after stroke. *Cell Death and Differentiation*, *25*(8), 1503–1516.

Zhou, Z., Xie, J., Lee, D., Liu, Y., Jung, J., Zhou, L., et al. (2010 July 20). Neogenin regulation of BMP-induced canonical Smad signaling and endochondral bone formation. *Developmental Cell*, *19*(1), 90–102.

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Chapter 28

Mitochondrial biogenesis for the treatment of spinal cord injury

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Abbreviations

5-HTR	5-hydroxytryptamine receptor
7,8-DHF	dihydroxyflavone
Ac	acetyl group
AICAR	5-aminoimidazole-4-carboxamide ribonucleotide
Akt	protein kinase B
AMPK	adenosine monophosphate-activated kinase
AP-1	activating protein 1
ATP	adenosine triphosphate
BSCB	blood–spinal cord barrier
cGMP	cyclic guanosine monophosphate
CNS	central nervous system
CO	carbon monoxide
cyt *c*	cytochrome *c*
DEX	dexmedetomidine
DRP1	dynamin-related protein 1
EAAT	excitatory amino acid transporter
eNOS	endothelial nitric oxide synthase
ETC	electron transport chain
FDA	Food and Drug Administration
FIS1	fission 1
Glu-R	glutamate receptor
GPCR	G protein-coupled receptor
HO-1	heme oxygenase 1
IL-6	interleukin 6
MAPK	mitogen-activated protein kinase
MB	mitochondrial biogenesis
Mdivi-1	mitochondrial division inhibitor 1
Mfn	mitofusin
Mn	manganese
mPTP	mitochondrial permeability transition pore
mtDNA	mitochondrial DNA
Nrf	nuclear respiratory factor
NSC	neuronal stem cell
OPA1	optic atrophy 1
OXPHOS	oxidative phosphorylation
P	phosphate group
PDE	phosphodiesterase

Diagnosis and Treatment of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822498-4.00028-2

PGC-1α	peroxisome proliferator-activated receptor-gamma coactivator 1 alpha
PI3K	phosphoinositide-3 kinase
PINK1	PTEN-induced kinase 1
PPAR	peroxisome proliferator-activated receptor
ROS	reactive oxygen species
SCI	spinal cord injury
SIRT1	sirtuin-1
TFAM	mitochondrial transcription factor A
TMP	tetramethylpyrazine
TNFα	tumor necrosis factor alpha
TZDs	thiazolidinediones
U	ubiquitin group
β-AR	β-adrenergic receptor

Introduction

Neuronal integrity is dependent on mitochondrial homeostasis and function, resulting in the central nervous system (CNS) being particularly sensitive to mitochondrial dysfunction (Golpich et al., 2017). Spinal cord injury (SCI) results in an intricate pathology involving heterogeneous cell types with unique roles in injury and recovery. Following SCI, mitochondria are dysfunctional, resulting in an array of consequences including decreased mitochondrial respiration and adenosine triphosphate (ATP) production, depolarization of the mitochondrial membrane, mitochondrial DNA (mtDNA) fragmentation, oxidative stress, compromised calcium homeostasis, altered mitochondrial dynamics, and cell death (Simmons, Scholpa, & Schnellmann, 2020). These cellular dysfunctions contribute to the secondary injury cascade of SCI, exacerbating injury, and hindering recovery.

Mitochondrial biogenesis (MB) is an intricate process involving the generation of new, functional mitochondria (Whitaker, Corum, Beeson, & Schnellmann, 2016). In recent years, there has been an increase in published data documenting that pharmacological induction of MB restores mitochondrial and organ function following various pathological events in vivo, including SCI (Simmons, Scholpa, & Schnellmann, 2020). These findings, in conjunction with the plethora of evidence indicating that restoring mitochondrial homeostasis promotes recovery following SCI, speak to the potential for this treatment strategy. Additionally, in vitro reports have elucidated cell type-specific consequences of mitochondrial dysfunction and MB in SCI-relevant cell types, which could aid in the future development of targeted therapies.

Importantly, there exists an increasing number of U.S. Food and Drug Administration (FDA)-approved pharmaceuticals capable of MB induction, demonstrating the clinical applicability of this approach (Simmons, Scholpa, & Schnellmann, 2020). This perspective will briefly review and explore CNS cell type-specific mitochondrial dysfunction and MB, as well as describe current therapeutic strategies employing inducers of MB post-SCI.

Mitochondrial dysfunction

Mitochondrial dysfunction results from alterations to homeostatic mitochondrial processes, leading to deficient energy metabolism, primarily through decreased oxidative phosphorylation (OXPHOS) and ATP synthesis. Examples of such alterations include inadequate mitochondrial number and/or mass, altered membrane potential, mitochondrial DNA (mtDNA) mutation/fragmentation, defective electron transport chain (ETC) activity, increased production of reactive oxygen species (ROS), intracellular calcium dysregulation, and impaired mitochondrial dynamics and mitophagy (Scholpa & Schnellmann, 2017; Simmons, Scholpa, & Schnellmann, 2020).

Due to high energy demand within the CNS, mitochondrial dysfunction and ensuing loss of ATP can prevent the function of various ATPases (H^+, Ca^{2+}, Na^+/K^+-ATPase) required for effective neurotransmission, thereby deregulating cellular ion gradients. Mitochondrial dysfunction can also disrupt calcium buffering and signaling, which is crucial for neuronal synapses, leading to calcium overload and excitotoxicity (Vos, Lauwers, & Verstreken, 2010). In SCI pathology, activated astrocytes and glial cells release pro-inflammatory cytokines, resulting in mitochondrial dysfunction and ultimately apoptosis (Simmons, Scholpa, & Schnellmann, 2020). Additionally, SCI is characterized by vasculature disruption, leading to loss of blood flow and local ischemia, which contributes to oxidative stress, mitochondrial dysfunction and the propagation of cell death observed during secondary injury (Fig. 1) (Scholpa & Schnellmann, 2017). Therefore, evidence suggests that restoring mitochondrial function could be an effective strategy to mediate multiple facets of injury progression and aid in preventing further cell death.

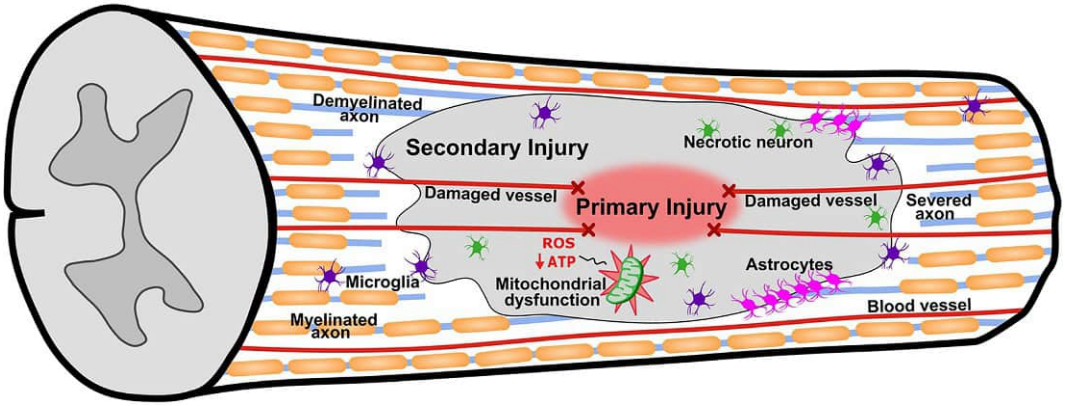

FIG. 1 Spinal cord injury pathology. Damage after spinal cord injury (SCI) is a combination of initial trauma and secondary injury. The primary injury disrupts spinal cord vasculature, reducing local oxygen delivery, decreasing mitochondrial function and adenosine triphosphate (ATP) synthesis, and increasing reactive oxygen species (ROS) production. Additional hallmarks of secondary injury after SCI include neuronal cell death, axon severing and demyelination, microglia activation and glial scar formation. *Duplicated with permission from Scholpa, N. E. & Schnellmann, R. G. (2017). Mitochondrial-based therapeutics for the treatment of spinal cord injury: Mitochondrial biogenesis as a potential pharmacological target*. The Journal of Pharmacology and Experimental Therapeutics, 363, *303–313*.

Mitochondrial biogenesis

Although many studies exist assessing mitochondria-targeted strategies for treatment of SCI, the majority address singular aspects of downstream mitochondrial dysfunction, such as increasing antioxidant defenses or inhibiting opening of the mitochondrial permeability transition pore (mPTP) (Scholpa & Schnellmann, 2017). In contrast, MB is the production of new, functional mitochondria via the growth and division of pre-existing mitochondria, which could therefore address multiple, if not all, facets of mitochondrial dysfunction (Fig. 2). This complex process involves the cooperation of multiple cellular pathways, requiring the synthesis of mtDNA, transcription and translation of mitochondrial- and nuclear-encoded proteins and ultimately assembly of ETC complexes (Whitaker et al., 2016).

Regulation of MB

Coordination of the nuclear and mitochondrial genomes is modulated by transcriptional coactivators, with the most relevant to MB being the "master regulator" peroxisome proliferator-activated receptor-gamma coactivator-1 alpha (PGC-1α) (Liang & Ward, 2006). Activation of PGC-1α can be initiated via multiple post-translational modifications, including deacetylation by sirtuin-1 (SIRT1) and phosphorylation by adenosine monophosphate-activated kinase (AMPK) and p38-mitogen-activated protein kinase (MAPK) (Ventura-Clapier, Garnier, & Veksler, 2008). Additionally, agonism of G-protein-coupled receptors (GPCRs), such as 5-hydroxytryptamine (5-HTRs) and β-adrenergic receptors (β-ARs), can activate the protein kinase B (Akt)/endothelial nitric oxide synthase (eNOS)/cyclic guanosine monophosphate (cGMP) pathway leading to activation of PGC-1α, translocation to the nucleus and, subsequently, induction of MB (Fig. 3) (Garrett, Whitaker, Beeson, & Schnellmann, 2014; Gibbs, Garrett, Beeson, & Schnellmann, 2018; Wills et al., 2012). Importantly, studies have shown that PGC-1α is decreased in the spinal cord after SCI, indicative of disrupted MB (Hu, Lang, Cao, Zhang, & Lu, 2015; Scholpa, Williams, et al., 2019).

PGC-1α regulates MB through interactions with transcription factors such as peroxisome proliferator-activated receptors (PPARs) and nuclear respiratory factors (Nrf1/2), among others (Liang & Ward, 2006; Schreiber et al., 2004). PPARs are involved in the expression of fatty acid oxidation and Krebs cycle enzymes and OXPHOS components (Lin, Handschin, & Spiegelman, 2005; Schreiber et al., 2004). Activation of Nrf1/2 induces transcription of mitochondrial transcription factor A (TFAM) (Gureev, Shaforostova, & Popov, 2019), which translocates to the mitochondria, where it activates mitochondrial gene expression and mtDNA replication (Virbasius & Scarpulla, 1994). Coordination of these transcription factors via PGC-1α culminates in the induction of MB.

Intimately related to MB is mitochondrial dynamics, namely fusion and fission. Fusion is the joining of two mitochondria mediated by mitofusins (Mfn1/2) and optic atrophy 1 (OPA1), whereas fission initiates cleavage and division of mitochondria, and is mediated, in part, by dynamin-related protein 1 (DRP1) and outer membrane receptor fission 1 (FIS1). Dysfunctional mitochondria contain impaired proteins, damaged membranes and fragmented mtDNA, increasing

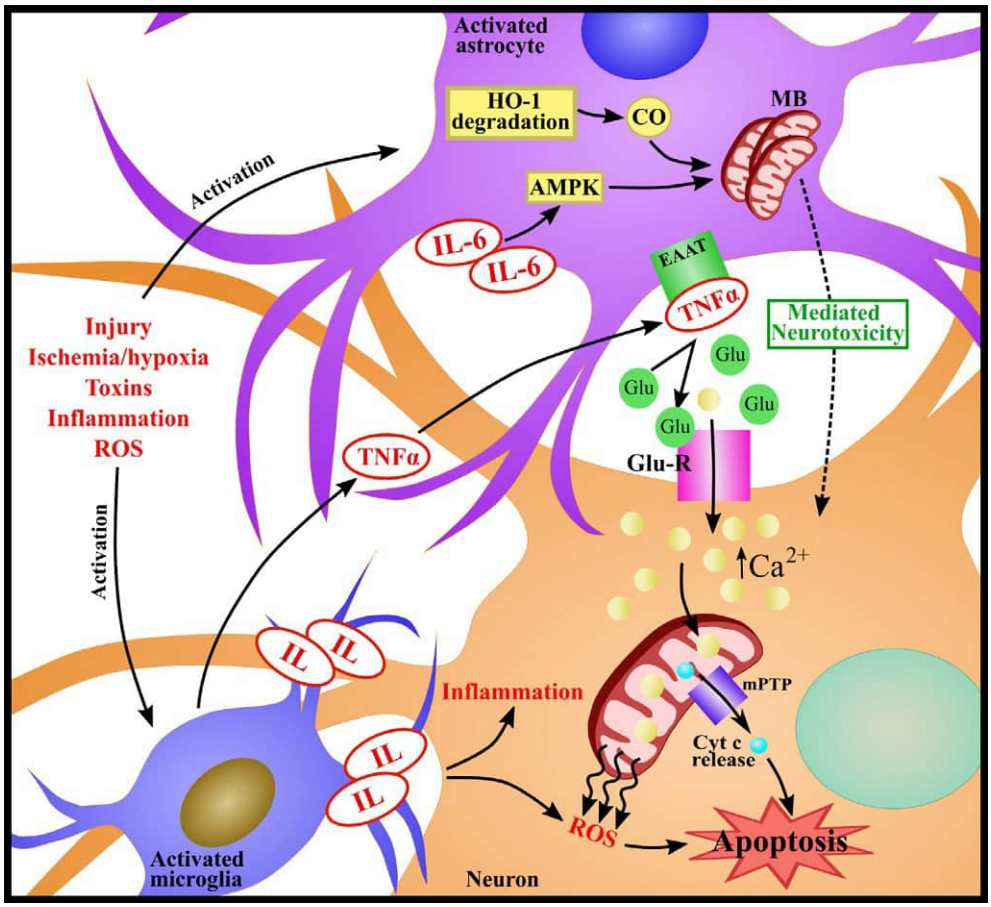

FIG. 2 Role of neuroinflammation on mitochondrial dysfunction. Various stressors can trigger activation of astrocytes and microglia, releasing cytokines and chemokines, promoting calcium overload, apoptosis and neurotoxicity. Conversely, ischemic injury increases astrocyte CO levels via HO-1 degradation. CO as well as IL-6 can promote MB and mediate neurotoxicity. AMPK, adenosine monophosphate-activated kinase; Ca^{+}, calcium; Cyt *c*, cytochrome *c*; EAAT, excitatory amino acid transporter; Glu, glutamate; Glu-R, glutamate receptor; HO-1, heme oxygenase 1; IL, interleukins; IL-6, interleukin-6; mPTP, mitochondrial permeability transition pore; ROS, reactive oxygen species; TNFα, tumor necrosis factor alpha. *Modified with permission from Simmons, E. C., Scholpa, N. E., & Schnellmann, R. G. (2020). Mitochondrial biogenesis as a therapeutic target for traumatic and neurodegenerative CNS diseases.* Experimental Neurology, 329*, 113309.*

fission mechanisms and mitophagy, which is the selective degradation of damaged mitochondria by autophagosomes mediated, in part, by PTEN-induced kinase 1 (PINK1) and E3-ubiquitin ligase (Parkin) interaction (Fig. 4) (Simmons, Scholpa, & Schnellmann, 2020). Conversely, promotion of fusion mechanisms has been implicated in MB and recovery (Scholpa & Schnellmann, 2017). Proper balance of MB, dynamics and mitophagy is critical for mitochondrial function and response to various stressors, including SCI.

Cell type-specific mitochondrial dysfunction and MB

SCI is a complex pathology involving heterogeneous cell types with distinct roles in the progression of injury and recovery. Many in vivo studies exist evaluating the global effects of mitochondrial-based therapies for SCI, while few reports exist detailing cell type-specific effects. Understanding the role of mitochondrial dysfunction and MB in relevant cell types can uncover not only underexplored mechanisms, but also potential therapeutic strategies following SCI.

Neurons

In addition to their primary role in bioenergetics, neuronal mitochondria contribute to regulation of synaptic transmission, calcium homeostasis, neuronal excitability and response to stress (Fanibunda et al., 2019). Neurons are dependent on efficient ATP regulation and have limited capacity to buffer oxidative stress. As such, neurons are particularly vulnerable to

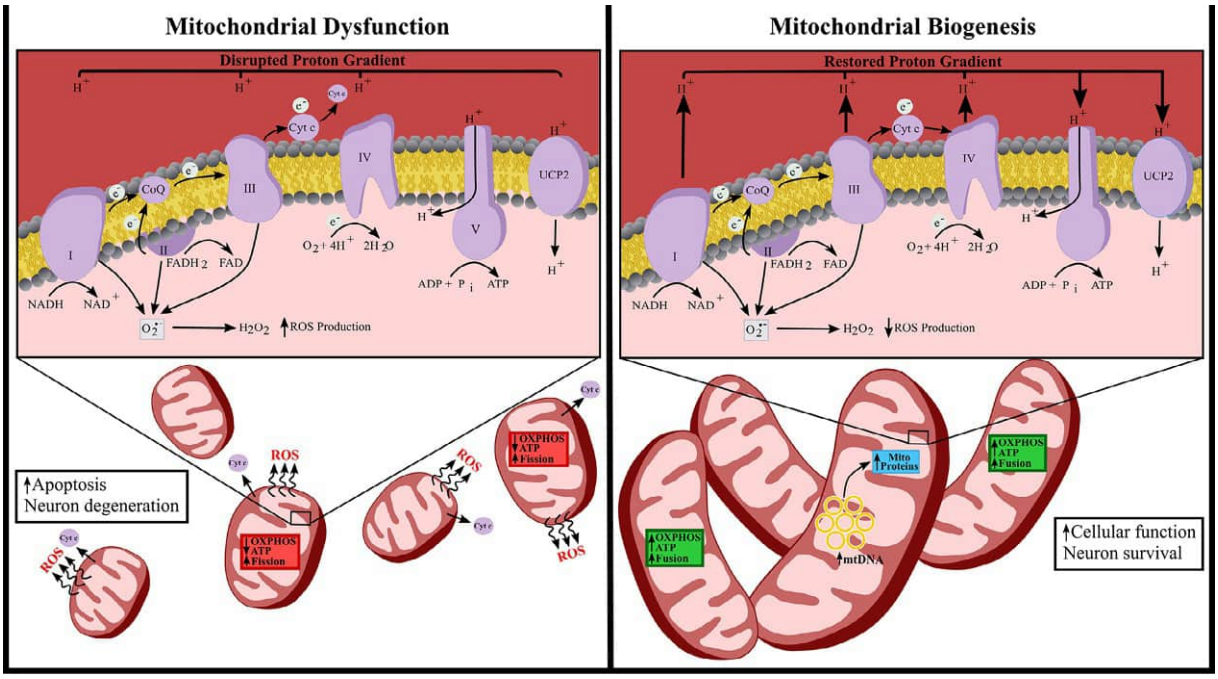

FIG. 3 Mitochondrial dysfunction and biogenesis. Mitochondrial dysfunction is characterized by decreased expression of OXPHOS proteins, impaired mitochondrial membrane potential, reduced ATP production, enhanced mitochondrial fission, ROS production and cyt *c* release. Mitochondrial dysfunction is often paired with increased apoptosis and neural degeneration. Conversely, mitochondrial biogenesis is characterized by mitochondrial fusion, reduced ROS, restoration of membrane potential and increased expression of OXPHOS proteins. CoQ, coenzyme Q; COX1, cytochrome *c* oxidase subunit 1; Cyt *c*, cytochrome *c*; e^-, electron; FAD, Flavin adenine dinucleotide; NAD^+, Nicotinamide adenine dinucleotide; O_2^-, superoxide; OXPHOS, oxidative phosphorylation; P_i, inorganic phosphate; ROS, reactive oxygen species; UCP2, uncoupling protein 2. *Modified with permission from Simmons, E. C., Scholpa, N. E., & Schnellmann, R. G. (2020). Mitochondrial biogenesis as a therapeutic target for traumatic and neurodegenerative CNS diseases.* Experimental Neurology, 329*, 113309*.

mitochondrial dysfunction, resulting in excitotoxicity, calcium overload, axon demyelination and cell death (Scholpa & Schnellmann, 2017).

In the presence of mitochondrial dysfunction in vitro, MB compounds can improve mitochondrial homeostasis and neuronal survival. For example, mitochondrial division inhibitor-1 (Mdivi-1), a DRP1 inhibitor and inducer of MB, improved mitochondrial function and neural conductance in cultured spinal cord neurons following glutamate-induced ischemia-reperfusion. Treatment also reduced oxidative stress markers, neuronal injury and apoptosis in this model (Liu et al., 2015). Serotonin, a neurotransmitter implicated in mitochondrial and functional recovery from SCI, enhanced mtDNA content, mitochondrial concentration and mitochondrial function, while demonstrating neuroprotective effects against oxidative stress in cultured rodent cortical neurons (Fanibunda et al., 2019).

MB is also implicated in stem cell differentiation and neural fate commitment. Treatment with bezafibrate, a PPAR agonist, evoked up-regulation of MB-related genes and improved cell viability, mitochondrial membrane potential and cell number during late-stage differentiation in human-induced pluripotent stem cells (Augustyniak et al., 2019). Furthermore, inherent increases in mtDNA content and MB-related gene and protein expression exist during differentiation of human neuronal stem cells (NSCs) into motor neurons (O'brien, Keeney, & Bennett Jr., 2015). NSC transplantation is being developed to promote recovery of the neural network after SCI (Zhu, Uezono, Yasui, & Nakashima, 2018); the reliance of motor neuron differentiation on MB, however, suggests that differentiating NSCs may be vulnerable to mitochondrial dysfunction after injury (O'brien et al., 2015). Therefore, concurrent treatment employing NSCs and MB compounds may enhance successful motor neuron differentiation, thereby improving NSC-induced neurogenesis and recovery post-SCI.

Astrocytes

Integral within the CNS, astrocytes maintain neuronal energy, metabolism and structural support, modulation of synaptic transmission, regulation of intercellular ion concentration, vasomodulation and promotion of the myelinating activity of

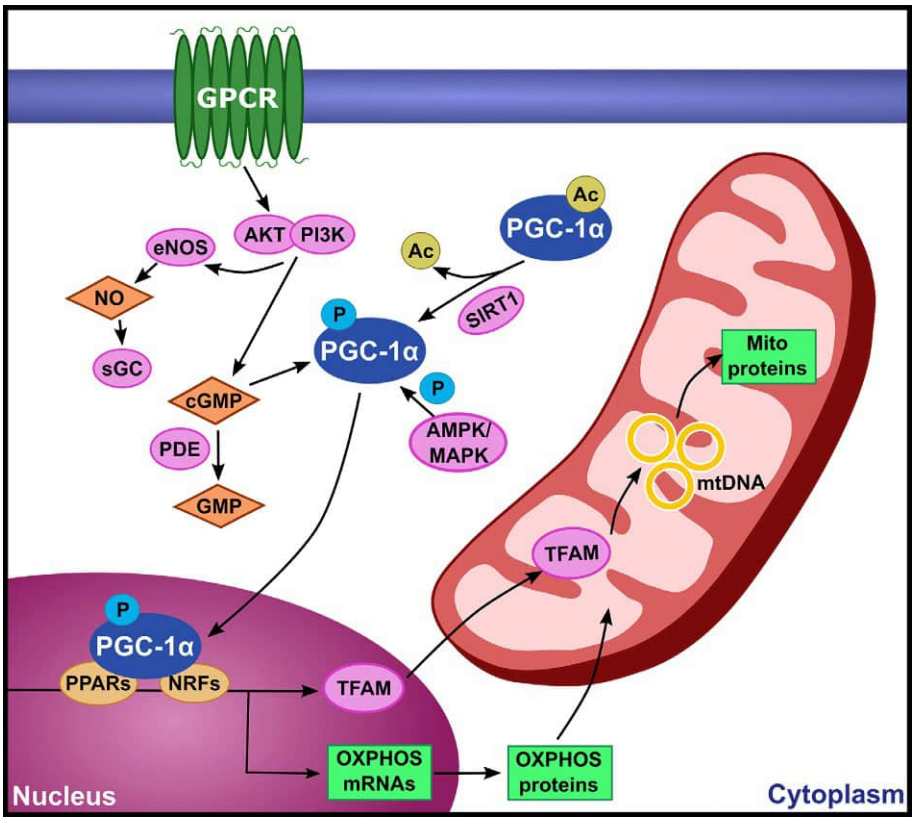

FIG. 4 Regulation of mitochondrial biogenesis. Mitochondrial biogenesis (MB) is a highly regulated process involving diverse pathways. Pharmacological agents can augment MB by targeting different aspects of these pathways, all culminating in increased expression of mitochondrial genes and MB. Ac, acetyl group; AKT, protein kinase B; AMPK, adenosine monophosphate-activated kinase; cGMP, cyclic guanosine monophosphate; eNOS, endothelial nitric oxide synthase; MAPK, mitogen activated protein kinase; mtDNA, mitochondrial DNA; NO, nitric oxide; NRF, nuclear respiratory factor; OXPHOS, oxidative phosphorylation; P, phosphate; PDE, phosphodiesterase; PGC-1α: peroxisome proliferator-activated receptor-gamma coactivator 1 alpha; PI3K, phosphoinositide-3 kinase; PPAR, peroxisome proliferator-activated receptor; sGC, soluble guanylate cyclase; SIRT1, sirtuin 1; TFAM, mitochondrial transcription factor A. *Modified with permission from Scholpa, N. E. & Schnellmann, R. G. (2017). Mitochondrial-based therapeutics for the treatment of spinal cord injury: Mitochondrial biogenesis as a potential pharmacological target*. The Journal of Pharmacology and Experimental Therapeutics, 363*, 303–313*.

oligodendrocytes. Following SCI, astrocytes undergo complex morphological, gene expression and functional changes (Falnikar, Li, & Lepore, 2015). Given that defects in astrocyte activity and metabolism are associated with a variety of neuropathological disorders (Choi et al., 2016), maintaining the metabolic activity of astrocytes is likely crucial for neuronal function post-SCI.

Aβ1–42, a toxic peptide aggregate found in Alzheimer's disease pathology, increases MB in astrocytes, while inducing lipid peroxidation, apoptosis and cell death in neurons. Despite these deleterious neuronal effects, increased neuronal survival, restored mitochondrial homeostasis, improved resistance to oxidative damage and modulation of the neuroinflammatory response were documented when neurons and astrocytes were co-cultured (Aguirre-Rueda et al., 2015). The neuroprotective nature of astrocytic MB reported in this study is compelling, revealing a potential therapeutic target following SCI.

Manganese (Mn) targets astrocytes and promotes the expression of pro-inflammatory cytokine interleukin-6 (IL-6) and tumor necrosis factor alpha (TNFα), leading to mitochondrial dysfunction and neurotoxicity in vitro. In mouse cerebral astrocytes, Mn-induced inflammation led to decreased mitochondrial mass, excessive fission, as well as impaired basal and ATP-linked mitochondrial respiration (Sarkar et al., 2018). Interestingly, the antioxidant mito-apocynin attenuated this inflammatory response and restored mitochondrial mass (Sarkar et al., 2018). While Mn toxicity is often observed following occupational or environmental exposure (Harischandra et al., 2019), this impaired astrocytic mitochondrial profile presents similarly to that following SCI (McAvoy & Kawamata, 2019). As such, future studies should investigate the therapeutic potential of mito-apocynin in mediating astrocytic dysfunction following SCI.

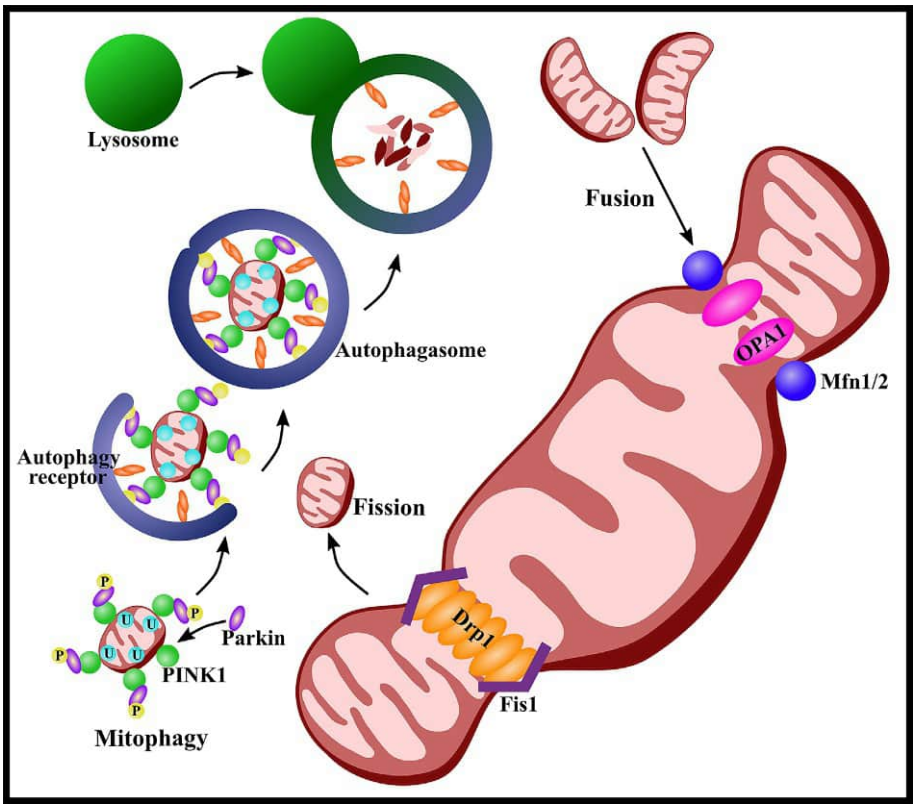

FIG. 5 Mitochondrial dynamics. Mitochondrial fusion is mediated by outer (Mfn1/2) and inner membrane (Opa1) proteins. Fission is initiated by recruitment of DRP1 to the mitochondrial membrane, where it interacts with receptors (Fis1), inducing membrane splitting. Excessive fission may promote mitophagy, which is activated by destabilization of PINK1, which recruits, phosphorylates (P) and activates Parkin, promoting the formation of autophagosomes, which will fuse with a lysosome leading to degradation. Drp1, dynamin-related protein 1; Fis1, fission 1; Mfn1/2, mitofusin 1/2; OPA1, optic atrophy 1; PINK1, PTEN-induced kinase 1. *Duplicated with permission from Simmons, E. C., Scholpa, N. E., & Schnellmann, R. G. (2020). Mitochondrial biogenesis as a therapeutic target for traumatic and neurodegenerative CNS diseases.* Experimental Neurology, 329*, 113309*.

In addition to pharmacological induction, internally driven MB can occur as a programmed response to aid in the recovery of astrocytes following oxidative insults (Fig. 5) (Chen et al., 2018; Choi et al., 2016). Oxidant injuries stimulate the expression of heme oxygenase-1 (HO-1) in astrocytes. Carbon monoxide (CO), a by-product of HO-1-driven heme degradation, regulates energy metabolism and can mitigate tissue injury and inflammation in neurological diseases. In addition, HO-1-derived CO increases MB, as evidenced by increased PGC-1α and ATP synthesis in astrocytes (Choi et al., 2016). Therefore, astrocytic HO-1 induction during ischemic events may be endogenously protective via stimulation of MB, thereby hindering propagation of ischemic damage. Furthermore, reports demonstrate that endogenous and exogenous CO can promote MB in cerebral astrocytes in vitro (Piantadosi, Carraway, Babiker, & Suliman, 2008). As such, CO-mediated MB in astrocytes may be protective following SCI.

In cultures of rat cerebral astrocytes, septic conditions induced neuroinflammation and triggered protective mechanisms to increase MB and ATP at early time points. Additionally, treatment with IL-6, a cytokine mainly produced by astrocytes, enhanced MB through IL-6/AMPK signaling under septic conditions (Chen et al., 2018), suggesting that astrocyte-specific MB in the presence of neuroinflammation may intrinsically combat mitochondrial dysfunction and promote recovery. Although increased IL-6 levels following SCI are considered inherently negative, future studies should explore the potential neuroprotective effects of astrocytic IL-6-induced MB following injury.

Endothelial cells

Endothelial cells are integral components of the blood–spinal cord barrier (BSCB) and are specifically organized to facilitate selective permeability, limiting blood-derived molecules from entering the spinal cord. SCI often results in catastrophic destruction of the BSCB, leading to enhance permeability and allowing neuroinflammation to propagate secondary injury. Conversely, angiogenesis and restoration of BSCB integrity has been associated with improved

pathological and behavioral outcomes. Mitochondrial quality control mechanisms, including mitochondrial dynamics and mitophagy, are needed to maintain angiogenic and vasodilator functions of endothelial cells (Kluge, Fetterman, & Vita, 2013). Though mitochondrial content in endothelial cells is relatively modest, angiogenesis is an energy-demanding process essential for SCI recovery and has been closely linked to MB pathways (Kluge et al., 2013; Kumar, Ropper, Lee, & Han, 2017). A comprehensive review detailing key aspects of mitochondrial function in the endothelium can be found in Kluge et al. (2013) and Eelen et al. (2018).

Therapeutic strategies targeting increased activity of PGC-1α and AMPK consistently demonstrate improved endothelial function. The glycolysis inhibitor 2-deoxyglucose activates AMPK, inducing autophagy and protecting against cell death of endothelial cells in vitro (Kluge et al., 2013). In addition, thiazolidinediones reduce ROS while activating PGC-1α and MB in endothelial cells (Kluge et al., 2013). Metformin, an inhibitor of IL-1β and activator of AMPK, impedes mPTP opening and endothelial apoptosis, thereby preventing endothelial dysfunction (Kluge et al., 2013). Resveratrol also induces MB and reduces hydrogen peroxide levels of endothelial cells in culture (Kluge et al., 2013). These studies suggest that MB strategies may increase recovery following SCI, in part by improving mitochondrial function in the endothelium. In support of this, pharmacological activation of MB following SCI has been shown to improve BSCB integrity, correlating with enhanced recovery in vivo (Simmons, Scholpa, Cleveland, & Schnellmann, 2020).

Mitochondrial biogenesis mediates consequences of SCI

Mitochondrial homeostasis and functional recovery

PGC-1α is decreased in the injured spinal cord in rodent contusion SCI models (Hu et al., 2015; Hu, Lang, Zhang, Ni, & Lu, 2016; Scholpa, Williams, et al., 2019), indicating loss of mitochondrial function and decreased MB. Lentiviral overexpression of PGC-1α in the injured cord has been shown to decrease neuronal cell death and improve recovery (Hu et al., 2015, 2016). Furthermore, treatment with pharmacological agents that induce PGC-1α expression have similar restorative effects (Hu et al., 2015; Scholpa, Williams, et al., 2019; Simmons, Scholpa, Cleveland, et al., 2020).

Tetramethylpyrazine (TMP), a plant extract, is neuroprotective following SCI in rats via induction of PGC-1α and MB, leading to improved locomotor capability and decreased neural apoptosis (Hu et al., 2015). Treatment with the β_2-AR agonist formoterol beginning 8 h post-SCI increased PGC-1α and downstream protein expression in the injured cord, improved locomotor function and decreased lesion volume in a mouse contusion SCI model (Scholpa, Simmons, Tilley, & Schnellmann, 2019; Scholpa, Williams, et al., 2019). Daily administration of the 5-HT_{1F} receptor agonist LY344864 after SCI similarly increased PGC-1α expression, as well as improved markers of functional recovery and decreased BSCB leakage (Simmons, Scholpa, Cleveland, et al., 2020). Of note, formoterol is FDA-approved for the treatment of asthma and the 5-HT_{1F} receptor agonist lasmiditan was recently approved for the treatment of migraines (Lamb, 2019), indicating the potential applicability of this SCI treatment strategy.

Body composition

In addition to local dysfunction in the spinal cord, SCI can decrease peripheral mitochondrial activity, with decreased mitochondrial size, protein expression and function reported in skeletal muscle after injury (Mccully, Mulcahy, Ryan, & Zhao, 2011; Scelsi, Marchetti, Poggi, Lotta, & Lommi, 1982). Paralysis following SCI can lead to disuse atrophy and rapid loss of skeletal muscle function and metabolic activity, which can increase the risk of developing metabolic diseases such as type II diabetes (Gorgey et al., 2019; O'brien & Gorgey, 2016). In fact, while pneumonia and septicemia are the leading causes of death post-SCI, mortality rates for metabolic and musculoskeletal disorders are on the rise (National Spinal Cord Injury Statistical Center, 2020).

Besides its canonical role as an inducer of MB, PGC-1α is also involved in activation of muscle hypertrophy and downregulation of atrophy (Qin, Pan, Wu, Bauman, & Cardozo, 2010; Scholpa, Simmons, et al., 2019). Therefore, induction of PGC-1α and increased MB can address multiple SCI-induced deficits. In support of this, exercise training induces PGC-1α in the skeletal muscle of rodents and humans (Baar et al., 2002; Pilegaard, Saltin, & Neufer, 2003), and increases mitochondrial mass and function in paralyzed muscle (O'brien & Gorgey, 2016). Transgenic overexpression of PGC-1α has also been found to protect against muscle atrophy and promote MB (Dinulovic et al., 2016; Sandri et al., 2006). In addition to improving functional recovery, daily formoterol treatment after SCI increased gastrocnemius muscle mass, corresponding to increased hypertrophy and decreased expression of atrophy markers in mice (Scholpa, Simmons, et al., 2019). Formoterol treatment also restored body weight to that of pre-injury (Scholpa, Simmons, et al., 2019), indicating reestablishment of body composition, which is fundamentally altered following SCI.

Axonal growth

Limited recovery within the spinal cord post-SCI is largely due to lack of axonal growth (Meves & Zheng, 2014). In addition to axons' poor intrinsic growth capabilities, the presence of growth-inhibiting molecules and lack of growth-promoting factors make the CNS environment unconducive to axonal growth after injury. Unfortunately, while multiple attempts have been made to encourage axonal growth, success has been limited (Meves & Zheng, 2014). Neuronal growth requires a substantial amount of energy to not only synthesize the necessary substrates, but also transport these substrates to distal axonal locations. PGC-1α has been demonstrated to regulate mitochondrial density and energy production in both neuronal cell bodies and axons (Wareski et al., 2009). Overexpression of PGC-1α led to a twofold increase in total number of mitochondria in axons, particularly in the distal end furthest from the cell body, corresponding with axonal growth acceleration (Vaarmann et al., 2016). Additionally, suppression of PGC-1α also suppresses neuronal growth, further solidifying the relationship between axonal growth and MB (Vaarmann et al., 2016).

Inflammation

Mitochondria are integral to regulating innate immunity and the inflammatory response (Mohanty, Tiwari-Pandey, & Pandey, 2019) and as such, inflammatory disorders are associated with mitochondrial dysfunction (Missiroli et al., 2020). Within 15 min, SCI initiates inflammation, which plays a central role in the regulation of secondary injury (Zhang, Yin, Xu, Wu, & Chen, 2012). Inflammation can lead to neuron and oligodendrocyte apoptosis, formation of the glial scar and ultimately loss of neuronal function (Zhang et al., 2012). Therefore, it is hypothesized that mitigating inflammation could limit secondary injury progression.

During early inflammation, mitochondrial dysfunction is induced by pro-inflammatory cytokines such as TNFα and interleukins (Cherry & Piantadosi, 2015), with the degree of mitochondrial dysfunction being roughly correlated with clinical outcomes and recovery in humans and rodents (Brealey et al., 2004; Cherry & Piantadosi, 2015). Restoration of mitochondrial function and homeostasis is dependent upon rapid induction of quality control mechanisms, such as MB (Cherry & Piantadosi, 2015). In fact, activation of the inflammatory pathway directly impacts mitochondrial function via up-regulation of MB (Fernandez-Marcos & Auwerx, 2011). Inflammatory receptors activate multiple pathways within a cell, including MAPK and Akt pathways, which in turn lead to the activation of activating protein-1 (AP-1) and p38, ultimately increasing PGC-1α (Cherry & Piantadosi, 2015; Fernandez-Marcos & Auwerx, 2011). Additionally, Akt phosphorylates Nrf1, which induces TFAM activation and the transcription of MB genes (Cherry & Piantadosi, 2015).

While long-term respirometric dysfunction is unsuitable for cell survival, early inflammation-induced mitochondrial dysfunction may be advantageous, attenuating ROS production and decreasing ATP availability, preventing the appropriation of host cell energetics and, ultimately, the spread of infection (Cherry & Piantadosi, 2015). Furthermore, macrophages and microglia have been suggested to be neuroprotective after injury, and complete depletion of neutrophils severely impairs functional recovery after SCI (Okada, 2016; Rust & Kaiser, 2017). Additionally, TNFα signaling appears to be necessary for remyelination (Arnett et al., 2001), and certain parts of the glial scar have been shown to support axon regeneration post-SCI (Anderson et al., 2016). Consequently, therapeutic strategies aimed at mitigating inflammation after SCI via MB induction must take into consideration the potential benefit of the inflammatory response.

Importantly, recent evidence indicates that the SCI-induced inflammatory response is not exclusive to the spinal cord, but is systemic, leading to widespread organ damage (Sun et al., 2016). Treatment with the mitochondrial-targeted peptide SS-31 improved mitochondrial function, controlled the inflammatory response and alleviated lung damage in a mouse model of SCI (Zhu, Li, He, Zhou, & Jiang, 2017). Therefore, systemic pharmacological induction of MB has the potential to mitigate widespread inflammation following SCI.

Limitations of MB

While MB can aid in restoring cellular homeostasis and recovery from injury, limitations do exist. Many disease pathologies, including SCI, present a heterogeneous mix of mitochondrial health, particularly at early stages of disease progression. Although pre-clinical models have consistently demonstrated MB induction can attenuate mitochondrial dysfunction and improve recovery, there exists no way to selectively target healthy mitochondria for replication. As such, MB induction within dysfunctional mitochondria may propagate replication of mutated mtDNA, resulting in increased injury severity and disease progression (Simmons, Scholpa, & Schnellmann, 2020).

Applications to other areas of neuroscience

Considering central nervous system (CNS) function is highly dependent on mitochondrial homeostasis and energetics, it is unsurprising that brain and spinal cord systems are sensitive to mitochondrial dysfunction (Golpich et al., 2017). Both acute and neurodegenerative diseases are characterized by mitochondrial dysfunction and impaired mitochondrial biogenesis (MB). This dysregulation often leads to defective electron transport chain function and reduced adenosine triphosphate production, thereby promoting neuronal death. Remarkably, pharmacological activation of MB has been shown to restore mitochondrial function and homeostasis, and promote recovery across a variety of CNS pathologies (Table 1). MB-related therapies have proven efficacious in restoring mitochondrial homeostasis and cognitive capabilities across pre-clinical models of injury, including stroke and traumatic brain injury (Gibbs, Scholpa, Beeson, & Schnellmann, 2018; Simmons, Scholpa, & Schnellmann, 2020). In addition, mitochondrial dysfunction and MB is well-studied in neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease and multiple sclerosis, with several known MB-inducing pharmaceuticals currently in clinical trials (Gibbs, Scholpa, et al., 2018; Hayashi et al., 2017; Simmons, Scholpa, & Schnellmann, 2020). As such, attenuation of mitochondrial dysfunction through induction of MB is an encouraging therapeutic strategy in several areas of neuroscience. For comprehensive reviews detailing MB in traumatic and neurodegenerative diseases, see Golpich et al. (2017), Sebastian, Palacin, and Zorzano (2017), and Simmons, Scholpa, and Schnellmann (2020).

TABLE 1 Partial list of pharmacological inducers of MB for the treatment of CNS-related diseases.

Disease	Mitochondrial dysfunction	Tested MB treatments
ACUTE/TRAUMATIC		
Spinal Cord Injury	↓mitochondrial homeostasis ↑mtDNA mutations/fragmentation ↓OXPHOS proteins ↓ATP synthesis ↓ATP-dependent cellular processes ↓Ion homeostasis ↑mitophagy ↑Oxidative damage ↓Calcium buffering ↑mPTP opening ↑Cell death	**Formoterol**: ↑PGC-1α: ↓cell death, ↑function **LY344864**: ↑PGC-1α: ↓cell death, ↑function
Traumatic Brain Injury		**Quercetin**: ↑PGC-1α, ↓cell death **DEX**: ↑PGC-1α, ↓cell death, ↑behavior **7,8-DHF**: ↑PGC-1α, ↑function **SS-31**: ↑PGC-1α, ↑function, ↑behavior
Stroke		**Daidzein**: ↓cell death, antioxidant **Metformin**: ↓cell death, ↑behavior **Melatonin**: ↑mitophagy, antioxidant **Resveratrol**: ↑neuron survival
CHRONIC/NEURODEGENERATIVE		
Alzheimer's Disease	↓mitochondrial homeostasis ↑mtDNA mutations/fragmentation ↓OXPHOS proteins ↓ATP synthesis ↓mitophagy ↑Oxidative damage ↑Cell death	**TZDs**: ↑behavior **Resveratrol**: ↑PGC-1α, ↑behavior, ↑pAKT **AICAR**: ↑behavior, ↑pAKT **Melatonin**: ↑PGC-1α, ↑function, ↓Aβ
Parkinson's Disease		**Bezafibrate**: ↑PGC-1α, ↑behavior **Resveratrol**: ↑PGC-1α, ↑function, ↓cell death **LY344864**: ↑PGC-1α, ↑function, ↓cell death **Triterpenoids**: ↑Nrf2, antioxidant
Huntington's Disease		**Resveratrol**: ↑function, ↓cell death
Amyotrophic lateral sclerosis		**Resveratrol**: ↑function, ↓cell death
Huntington's Disease		**Resveratrol**: ↑function, ↓cell death
Multiple Sclerosis		**Dimethyl fumarate**: ↑Nrf2, ↑function **Metformin**: ↑AMPK, ↑function

Arrows indicated increase (↑) and decrease (↓). AMPK, adenosine monophosphate-activated kinase; mPTP: mitochondrial permeability transition pore; mtDNA, mitochondrial DNA; Nrf2, nuclear respiratory factor 2; OXPHOS, oxidative phosphorylation; pAKT, phosphorylated protein kinase B; PGC-1α: peroxisome proliferator-activated receptor-gamma coactivator 1 alpha.
Modified with permission from Simmons, E. C., Scholpa, N. E., & Schnellmann, R. G. (2020). Mitochondrial biogenesis as a therapeutic target for traumatic and neurodegenerative CNS diseases. *Experimental Neurology, 329*, 113309..

Mini-dictionary

- Oxidative Phosphorylation: Metabolic pathway involving mechanisms on the inner mitochondrial membrane including electron transport chain activity to produce adenosine triphosphate.
- Mitochondrial Dysfunction: Disruption of mitochondrial homeostasis, including impairment of oxidative phosphorylation, reduced mitochondrial number and mass, altered membrane potential, intracellular calcium dysregulation and mutated/fragmented mitochondrial DNA.
- PGC-1α: The master regulator of mitochondrial biogenesis, co-activates the transcription of several genes necessary for mitochondrial function.
- Mitophagy: Selective degradation of mitochondria by autophagy.
- Mitochondrial Biogenesis: Complex process by which cells increase mitochondrial mass and function.
- Mitochondrial Dynamics: Morphological cycles of fission and fusion executed by mitochondria, crucial for maintenance of function.
- Neuroinflammation: Inflammation of the nervous system as a response to stressors, such as injury.
- Oxidative Stress: Imbalance between free radicals and antioxidants often present after a traumatic injury such as spinal cord injury.
- Neurotoxicity: Damage caused by endogenous or exogenous neurotoxins resulting in altered activity of the nervous system and neuronal death.
- Ischemia: Local impairment of perfusion often propagating biological dysfunctions including mitochondrial dysfunction and cell death.

Key facts

Activation of mitochondrial biogenesis (MB) restores mitochondrial function in spinal cord injury-related cell types:

- Protects against oxidative stress and improves mitochondrial function in neurons
- Prevents neuronal injury and improves neuronal conductance and cell survival
- Mediates pro-inflammatory assaults and resulting neurotoxicity in astrocytes
- Protects against mitochondrial dysfunction while promoting endothelial cell survival
- Internally driven astrocytic mitochondrial biogenesis can be a programmed response to oxidative stress, hindering propagation of ischemic damage

Pharmacological activation of MB promotes recovery of mitochondrial homeostasis and function after spinal cord injury:

- Improves mitochondrial dynamics and mitophagy
- Restores mitochondrial composition and oxidative buffering capacity
- Recovers mitochondrial respiration and adenosine triphosphate production
- Mediates inflammatory response and neurotoxicity
- Improves blood–spinal cord barrier integrity
- Promotes axonal growth and myelination
- Improves body composition
- Improves locomotor capabilities

Summary points

- Mitochondrial dysfunction is a hallmark of spinal cord injury (SCI), propagating the progression of secondary injury, neuronal cell death and loss of function.
- Mitochondrial biogenesis inducers restore mitochondrial function in cultures of CNS-derived neurons, astrocytes and endothelial cells.
- Pharmacological activation of mitochondrial biogenesis mitigates several consequences of SCI including axonal regeneration, blood–spinal cord barrier integrity, altered body composition and locomotor capabilities in pre-clinical models of SCI.
- Therapies targeting mitochondrial biogenesis induction promote functional recovery across multiple traumatic and neurodegenerative CNS-related diseases.
- Several FDA-approved pharmaceuticals can induce mitochondrial biogenesis; therefore, repurposing these compounds for SCI treatment could be a relatively expeditious process.

References

Aguirre-Rueda, D., Guerra-Ojeda, S., Aldasoro, M., Iradi, A., Obrador, E., Ortega, A., et al. (2015). Astrocytes protect neurons from Aβ1-42 peptide-induced neurotoxicity increasing TFAM and PGC-1 and decreasing PPAR-γ and SIRT-1. *International Journal of Medical Sciences*, *12*, 48–56.

Anderson, M. A., Burda, J. E., Ren, Y., Ao, Y., O'shea, T. M., Kawaguchi, R., et al. (2016). Astrocyte scar formation aids central nervous system axon regeneration. *Nature*, *532*, 195–200.

Arnett, H. A., Mason, J., Marino, M., Suzuki, K., Matsushima, G. K., & Ting, J. P. (2001). TNF alpha promotes proliferation of oligodendrocyte progenitors and remyelination. *Nature Neuroscience*, *4*, 1116–1122.

Augustyniak, J., Lenart, J., Gaj, P., Kolanowska, M., Jazdzewski, K., Stepien, P. P., et al. (2019). Bezafibrate upregulates mitochondrial biogenesis and influence neural differentiation of human-induced pluripotent stem cells. *Molecular Neurobiology*, *56*, 4346–4363.

Baar, K., Wende, A. R., Jones, T. E., Marison, M., Nolte, L. A., Chen, M., et al. (2002). Adaptations of skeletal muscle to exercise: Rapid increase in the transcriptional coactivator PGC-1. *The FASEB Journal*, *16*, 1879–1886.

Brealey, D., Karyampudi, S., Jacques, T. S., Novelli, M., Stidwill, R., Taylor, V., et al. (2004). Mitochondrial dysfunction in a long-term rodent model of sepsis and organ failure. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology*, *286*, R491–R497.

Chen, X. L., Wang, Y., Peng, W. W., Zheng, Y. J., Zhang, T. N., Wang, P. J., et al. (2018). Effects of interleukin-6 and IL-6/AMPK signaling pathway on mitochondrial biogenesis and astrocytes viability under experimental septic condition. *International Immunopharmacology*, *59*, 287–294.

Cherry, A. D., & Piantadosi, C. A. (2015). Regulation of mitochondrial biogenesis and its intersection with inflammatory responses. *Antioxidants & Redox Signaling*, *22*, 965–976.

Choi, Y. K., Park, J. H., Baek, Y. Y., Won, M. H., Jeoung, D., Lee, H., et al. (2016). Carbon monoxide stimulates astrocytic mitochondrial biogenesis via L-type Ca(2+) channel-mediated PGC-1α/ERRα activation. *Biochemical and Biophysical Research Communications*, *479*, 297–304.

Dinulovic, I., Furrer, R., Di Fulvio, S., Ferry, A., Beer, M., & Handschin, C. (2016). PGC-1α modulates necrosis, inflammatory response, and fibrotic tissue formation in injured skeletal muscle. *Skeletal Muscle*, *6*, 38.

Eelen, G., De Zeeuw, P., Treps, L., Harjes, U., Wong, B. W., & Carmeliet, P. (2018). Endothelial cell metabolism. *Physiological Reviews*, *98*, 3–58.

Falnikar, A., Li, K., & Lepore, A. C. (2015). Therapeutically targeting astrocytes with stem and progenitor cell transplantation following traumatic spinal cord injury. *Brain Research*, *1619*, 91–103.

Fanibunda, S. E., Deb, S., Maniyadath, B., Tiwari, P., Ghai, U., Gupta, S., et al. (2019). Serotonin regulates mitochondrial biogenesis and function in rodent cortical neurons via the 5-HT(2A) receptor and SIRT1-PGC-1α axis. *Proceedings of the National Academy of Sciences of the United States of America*, *116*, 11028–11037.

Fernandez-Marcos, P. J., & Auwerx, J. (2011). Regulation of PGC-1α, a nodal regulator of mitochondrial biogenesis. *The American Journal of Clinical Nutrition*, *93*, 884S–890S.

Garrett, S. M., Whitaker, R. M., Beeson, C. C., & Schnellmann, R. G. (2014). Agonism of the 5-hydroxytryptamine 1F receptor promotes mitochondrial biogenesis and recovery from acute kidney injury. *Journal of Pharmacology and Experimental Therapeutics*, *350*, 257.

Gibbs, W. S., Garrett, S. M., Beeson, C. C., & Schnellmann, R. G. (2018). Identification of dual mechanisms mediating 5-hydroxytryptamine receptor 1F-induced mitochondrial biogenesis. *American Journal of Physiology. Renal Physiology*, *314*, F260–F268.

Gibbs, W. S., Scholpa, N. E., Beeson, C. C., & Schnellmann, R. G. (2018). Pharmacological activation of mitochondrial biogenesis for the treatment of various pathologies. In Y. Will, & J. A. Dykens (Eds.), *Mitochondrial dysfunction caused by drugs and environmental toxicants* (pp. 569–592). Wiley Online Books.

Golpich, M., Amini, E., Mohamed, Z., Azman Ali, R., Mohamed Ibrahim, N., & Ahmadiani, A. (2017). Mitochondrial dysfunction and biogenesis in neurodegenerative diseases: Pathogenesis and treatment. *CNS Neuroscience & Therapeutics*, *23*, 5–22.

Gorgey, A. S., Witt, O., O'brien, L., Cardozo, C., Chen, Q., Lesnefsky, E. J., et al. (2019). Mitochondrial health and muscle plasticity after spinal cord injury. *European Journal of Applied Physiology*, *119*, 315–331.

Gureev, A. P., Shaforostova, E. A., & Popov, V. N. (2019). Regulation of mitochondrial biogenesis as a way for active longevity: Interaction between the Nrf2 and PGC-1α signaling pathways. *Frontiers in Genetics*, *10*, 435.

Harischandra, D. S., Ghaisas, S., Zenitsky, G., Jin, H., Kanthasamy, A., Anantharam, V., et al. (2019). Manganese-induced neurotoxicity: New insights into the triad of protein misfolding, mitochondrial impairment, and neuroinflammation. *Frontiers in Neuroscience*, *13*, 654.

Hayashi, G., Jasoliya, M., Sahdeo, S., Saccà, F., Pane, C., Filla, A., et al. (2017). Dimethyl fumarate mediates Nrf2-dependent mitochondrial biogenesis in mice and humans. *Human Molecular Genetics*, *26*, 2864–2873.

Hu, J., Lang, Y., Cao, Y., Zhang, T., & Lu, H. (2015). The neuroprotective effect of tetramethylpyrazine against contusive spinal cord injury by activating PGC-1α in rats. *Neurochemical Research*, *40*, 1393–1401.

Hu, J., Lang, Y., Zhang, T., Ni, S., & Lu, H. (2016). Lentivirus-mediated PGC-1α overexpression protects against traumatic spinal cord injury in rats. *Neuroscience*, *328*, 40–49.

Kluge, M. A., Fetterman, J. L., & Vita, J. A. (2013). Mitochondria and endothelial function. *Circulation Research*, *112*, 1171–1188.

Kumar, H., Ropper, A. E., Lee, S. H., & Han, I. (2017). Propitious therapeutic modulators to prevent blood-spinal cord barrier disruption in spinal cord injury. *Molecular Neurobiology*, *54*, 3578–3590.

Lamb, Y. N. (2019). Lasmiditan: First approval. *Drugs*, *79*, 1989–1996.

Liang, H., & Ward, W. F. (2006). PGC-1α: A key regulator of energy metabolism. *Advances in Physiology Education*, *30*, 145–151.

Lin, J., Handschin, C., & Spiegelman, B. M. (2005). Metabolic control through the PGC-1 family of transcription coactivators. *Cell Metabolism*, *1*, 361–370.

Liu, J. M., Yi, Z., Liu, S. Z., Chang, J. H., Dang, X. B., Li, Q. Y., et al. (2015). The mitochondrial division inhibitor mdivi-1 attenuates spinal cord ischemia-reperfusion injury both in vitro and in vivo: Involvement of BK channels. *Brain Research*, *1619*, 155–165.

McAvoy, K., & Kawamata, H. (2019). Glial mitochondrial function and dysfunction in health and neurodegeneration. *Molecular and Cellular Neurosciences*, *101*, 103417.

Mccully, K. K., Mulcahy, T. K., Ryan, T. E., & Zhao, Q. (2011). Skeletal muscle metabolism in individuals with spinal cord injury. *Journal of Applied Physiology*, *111*, 143–148.

Meves, J. M., & Zheng, B. (2014). Extrinsic inhibitors in axon sprouting and functional recovery after spinal cord injury. *Neural Regeneration Research*, *9*, 460–461.

Missiroli, S., Genovese, I., Perrone, M., Vezzani, B., Vitto, V. A. M., & Giorgi, C. (2020). The role of mitochondria in inflammation: From cancer to neurodegenerative disorders. *Journal of Clinical Medicine*, *9*, 740.

Mohanty, A., Tiwari-Pandey, R., & Pandey, N. R. (2019). Mitochondria: The indispensable players in innate immunity and guardians of the inflammatory response. *Journal of Cell Communication and Signaling*, *13*, 303–318.

National Spinal Cord Injury Statistical Center. (2020). *Facts and figures at a glance*. Birmingham, Alabama: University of Alabama at Birmingham.

O'brien, L. C., & Gorgey, A. S. (2016). Skeletal muscle mitochondrial health and spinal cord injury. *World Journal of Orthopedics*, *7*, 628–637.

O'brien, L. C., Keeney, P. M., & Bennett, J. P., Jr. (2015). Differentiation of human neural stem cells into motor neurons stimulates mitochondrial biogenesis and decreases glycolytic flux. *Stem Cells and Development*, *24*, 1984–1994.

Okada, S. (2016). The pathophysiological role of acute inflammation after spinal cord injury. *Inflammation and Regeneration*, *36*, 20.

Piantadosi, C. A., Carraway, M. S., Babiker, A., & Suliman, H. B. (2008). Heme oxygenase-1 regulates cardiac mitochondrial biogenesis via Nrf2-mediated transcriptional control of nuclear respiratory factor-1. *Circulation Research*, *103*, 1232–1240.

Pilegaard, H., Saltin, B., & Neufer, P. D. (2003). Exercise induces transient transcriptional activation of the PGC-1alpha gene in human skeletal muscle. *The Journal of Physiology*, *546*, 851–858.

Qin, W., Pan, J., Wu, Y., Bauman, W. A., & Cardozo, C. (2010). Protection against dexamethasone-induced muscle atrophy is related to modulation by testosterone of FOXO1 and PGC-1alpha. *Biochemical and Biophysical Research Communications*, *403*, 473–478.

Rust, R., & Kaiser, J. (2017). Insights into the dual role of inflammation after spinal cord injury. *The Journal of Neuroscience*, *37*, 4658–4660.

Sandri, M., Lin, J., Handschin, C., Yang, W., Arany, Z. P., Lecker, S. H., et al. (2006). PGC-1alpha protects skeletal muscle from atrophy by suppressing FoxO3 action and atrophy-specific gene transcription. *Proceedings of the National Academy of Sciences of the United States of America*, *103*, 16260–16265.

Sarkar, S., Malovic, E., Harischandra, D. S., Ngwa, H. A., Ghosh, A., Hogan, C., et al. (2018). Manganese exposure induces neuroinflammation by impairing mitochondrial dynamics in astrocytes. *Neurotoxicology*, *64*, 204–218.

Scelsi, R., Marchetti, C., Poggi, P., Lotta, S., & Lommi, G. (1982). Muscle fiber type morphology and distribution in paraplegic patients with traumatic cord lesion. Histochemical and ultrastructural aspects of rectus femoris muscle. *Acta Neuropathologica*, *57*, 243–248.

Scholpa, N. E., & Schnellmann, R. G. (2017). Mitochondrial-based therapeutics for the treatment of spinal cord injury: Mitochondrial biogenesis as a potential pharmacological target. *The Journal of Pharmacology and Experimental Therapeutics*, *363*, 303–313.

Scholpa, N. E., Simmons, E. C., Tilley, D. G., & Schnellmann, R. G. (2019). Beta2-adrenergic receptor-mediated mitochondrial biogenesis improves skeletal muscle recovery following spinal cord injury. *Experimental Neurology*, *322*, 113064.

Scholpa, N. E., Williams, H., Wang, W., Corum, D., Narang, A., Tomlinson, S., et al. (2019). Pharmacological stimulation of mitochondrial biogenesis using the Food and Drug Administration-approved β(2)-Adrenoreceptor agonist formoterol for the treatment of spinal cord injury. *Journal of Neurotrauma*, *36*, 962–972.

Schreiber, S. N., Emter, R., Hock, M. B., Knutti, D., Cardenas, J., Podvinec, M., et al. (2004). The estrogen-related receptor alpha (ERRalpha) functions in PPARgamma coactivator 1alpha (PGC-1alpha)-induced mitochondrial biogenesis. *Proceedings of the National Academy of Sciences of the United States of America*, *101*, 6472–6477.

Sebastian, D., Palacin, M., & Zorzano, A. (2017). Mitochondrial dynamics: Coupling mitochondrial fitness with healthy aging. *Trends in Molecular Medicine*, *23*, 201–215.

Simmons, E. C., Scholpa, N. E., Cleveland, K. H., & Schnellmann, R. G. (2020). 5-Hydroxytryptamine 1F receptor agonist induces mitochondrial biogenesis and promotes recovery from spinal cord injury. *The Journal of Pharmacology and Experimental Therapeutics*, *372*, 216–223.

Simmons, E. C., Scholpa, N. E., & Schnellmann, R. G. (2020). Mitochondrial biogenesis as a therapeutic target for traumatic and neurodegenerative CNS diseases. *Experimental Neurology*, *329*, 113309.

Sun, X., Jones, Z. B., Chen, X. M., Zhou, L., So, K. F., & Ren, Y. (2016). Multiple organ dysfunction and systemic inflammation after spinal cord injury: A complex relationship. *Journal of Neuroinflammation*, *13*, 260.

Vaarmann, A., Mandel, M., Zeb, A., Wareski, P., Liiv, J., Kuum, M., et al. (2016). Mitochondrial biogenesis is required for axonal growth. *Development*, *143*, 1981–1992.

Ventura-Clapier, R., Garnier, A., & Veksler, V. (2008). Transcriptional control of mitochondrial biogenesis: The central role of PGC-1α. *Cardiovascular Research*, *79*, 208–217.

Virbasius, J. V., & Scarpulla, R. C. (1994). Activation of the human mitochondrial transcription factor A gene by nuclear respiratory factors: A potential regulatory link between nuclear and mitochondrial gene expression in organelle biogenesis. *Proceedings of the National Academy of Sciences of the United States of America*, *91*, 1309–1313.

Vos, M., Lauwers, E., & Verstreken, P. (2010). Synaptic mitochondria in synaptic transmission and organization of vesicle pools in health and disease. *Frontiers in Synaptic Neuroscience*, *2*, 139.

Wareski, P., Vaarmann, A., Choubey, V., Safiulina, D., Liiv, J., Kuum, M., et al. (2009). PGC-1{alpha} and PGC-1{beta} regulate mitochondrial density in neurons. *The Journal of Biological Chemistry*, *284*, 21379–21385.

Whitaker, R. M., Corum, D., Beeson, C. C., & Schnellmann, R. G. (2016). Mitochondrial biogenesis as a pharmacological target: A new approach to acute and chronic diseases. *Annual Review of Pharmacology and Toxicology*, *56*, 229–249.

Wills, L. P., Trager, R. E., Beeson, G. C., Lindsey, C. C., Peterson, Y. K., Beeson, C. C., et al. (2012). The β2-adrenoceptor agonist formoterol stimulates mitochondrial biogenesis. *Journal of Pharmacology and Experimental Therapeutics*, *342*, 106.

Zhang, N., Yin, Y., Xu, S.-J., Wu, Y.-P., & Chen, W.-S. (2012). Inflammation & apoptosis in spinal cord injury. *The Indian Journal of Medical Research*, *135*, 287–296.

Zhu, L. L., Li, M. Q., He, F., Zhou, S. B., & Jiang, W. (2017). Mitochondria targeted peptide attenuates mitochondrial dysfunction, controls inflammation and protects against spinal cord injury-induced lung injury. *Cellular Physiology and Biochemistry*, *44*, 388–400.

Zhu, Y., Uezono, N., Yasui, T., & Nakashima, K. (2018). Neural stem cell therapy aiming at better functional recovery after spinal cord injury. *Developmental Dynamics*, *247*, 75–84.

Chapter 29

Exploring the exogenous and endogenous effects of melatonin on spinal cord injury

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List of abbreviations

COX	cyclooxygenase
GSH	glutathione
IL-1α	interleukin-1α
IL-1β	interleukin-1β
iNOS	inducible nitric oxide synthase
L/D	light/dark
L/L	light/light
LPO	lipid peroxidation
MDA	malondialdehyde
MT	melatonin
NF-κB	nuclear factor-κB
NG-2	neuron/glial antigen 2
SCI	spinal cord injury
SOD	superoxide dismutase
TBI	traumatic brain injury
TNF-α	tumor necrosis factor-α

Introduction

Spinal cord injury (SCI) is a catastrophic incident with a global mortality rate ranging from 4.4% to 16.7%, often leading to neurological disability (Yamazaki, Kawabori, Seki, & Houkin, 2020). Traumatic injury to the spinal cord induces death in a number of local neurons and glia at the lesion site that cannot be recovered or regenerated. The mechanisms of secondary injury begin immediately after the primary insult and continue for weeks or months via a diverse array of pathophysiological processes, including inflammation, excitotoxicity, and oxidative cell damage (Alizadeh, Dyck, & Karimi-Abdolrezaee, 2019). These secondary insults lead to further destruction of neuronal and glial cells and to massive extension of the damage whereby the paralysis can extend to higher segments.

Disruption of circadian rhythm is a common feature in SCI individuals. Circadian misalignment can increase neuronal death, resulting in deterioration of sensorimotor functions and cognitive deficits (Li et al., 2016). In experimental studies, SCI was shown to lead to wide-ranging circadian rhythm disruption, including dysregulated rhythms of body temperature, and inflammatory gene expression (Gaudet et al., 2018). Besides, circulating levels of serum melatonin (MT) has been altered in patients with cervical SCI (Fatima, Sharma, & Verma, 2016), suggesting alteration of diurnal rhythms negatively influencing the SCI recovery process.

As SCI results in permanent or long-term disability and poor quality of life, it imposes an enormous financial burden on society in terms of increased healthcare costs and decreased productivity (Chan, Cadarette, Wodchis, Krahn, & Mittmann, 2019). Although efforts are currently being pursued to develop novel therapeutics to combat the pathogenesis of SCI, the

Diagnosis and Treatment of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822498-4.00029-4

effects of these interventions are generally limited. For example, exercise interventions, which are widely used to improve functional recovery following SCI, have an inadequate ability to improve motor function after SCI (Petrosyan, Alessi, Hunanyan, Sisto, & Arvanian, 2015).

MT is a neurohormone that is synthesized and released from the pineal gland in a 24-h diurnal pattern and exerts its actions in peripheral tissues. This pineal hormone is best known for maintaining the 24-h internal clock and has excellent antioxidant capacity (Sumsuzzman, Choi, Khan, & Hong, 2020). MT exerts beneficial effects by altering the levels of oxidative stress markers, including malondialdehyde (MDA), glutathione (GSH), superoxide dismutase (SOD), and myeloperoxidase, which are generally reported to show abnormalities with progression of SCI (Aghazadeh, Azarnia, Shirazi, Mahdavi, & Zangii, 2007; Erten et al., 2003). MT has other biological functions in SCI, including reduction of pro-inflammatory molecules (Zhang et al., 2019) and regulation of autophagy (Li et al., 2019). Recently, we demonstrated that a significant reduction in endogenous MT levels disrupted neural remodeling, and homeostasis of endogenous MT levels contributed to excitatory synaptic formation and axonal outgrowth in a rodent model of SCI (Hong et al., 2019), indicating MT replacement strategies improve the neuronal repair process following SCI.

In this chapter, we explore the promising molecular mechanisms of MT intervention that may be beneficial in the management of SCI. We discuss MT and exercise combination therapy in SCI. Finally, we also discuss the crucial role of endogenous MT, which may influence the recovery process after SCI.

Effects of exogenous melatonin on secondary injury after spinal cord injury

Neuronal death caused by primary injury from SCI cannot be prevented. Therefore, current research focuses on preventing the secondary injury cascade to mitigate progressive tissue damage, representing a novel strategy for the management of SCI pathology. The timeline of major pathological events of secondary injury and timeline-specific therapeutic strategies are shown in Fig. 1. In this section, we will discuss recent findings on the effects of exogenous MT on SCI, particularly the neuroprotective mechanism of action of MT in secondary injury events.

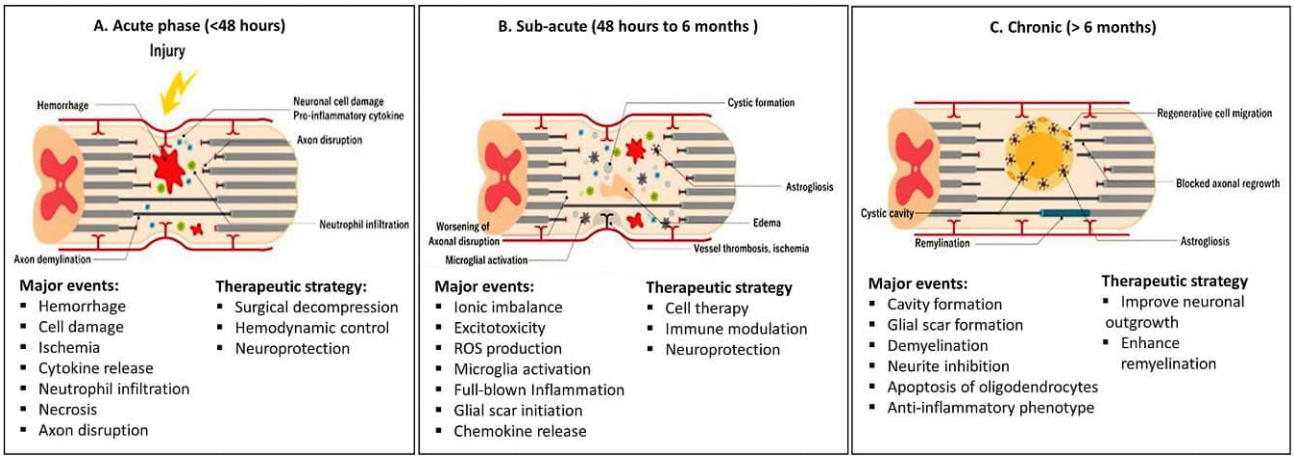

FIG. 1 Timeline of the major pathological events after spinal cord injury (SCI) and the best therapeutic strategies for SCI. The secondary injury mechanisms are initiated after the primary insult and sustained over a long period. The events that occur after primary insults are divided into the acute (<48 h), sub-acute (2 days–6 months), and chronic (>6 months) phases. (A) In the acute phase, hemorrhage, ischemia, and edema cause cell dysfunction and death. In addition, the inflammatory cells infiltrate into the injured spinal cord, resulting in the release of pro-inflammatory cytokines. These excessive inflammatory mediators can disrupt the blood-spinal cord barrier, further exacerbating the injury. (B) In the sub-acute phase, glutamate excitotoxicity, excessive ROS generation, and the full-blown inflammatory response cause further cell death and damage to the spinal cord architecture. Importantly, glial scar formation initiates this phase. (C) In the chronic phases, axons continuously degenerate, and the glial scar matures, inhibiting the neuronal regeneration process. The inflammatory phenotype shifts from pro-inflammatory to anti-inflammatory in this phase. Cavity formation also appears, which suppresses axonal regrowth. During the acute and sub-acute phases of SCI, multiple pathological cascades trigger the cell death process, leading to greater damage than that caused by the primary insult. Therefore, the pathophysiological events associated with the acute and sub-acute phases are the ultimate targets for therapeutic interventions. *ROS*, reactive oxygen species; *SCI*, spinal cord injury. *(Reprinted from Yamazaki, K., Kawabori, M., Seki, T., & Houkin, K. (2020). Clinical trials of stem cell treatment for spinal cord injury.* International Journal of Molecular Sciences, 21, *3994. According to the Creative Commons License (CC-BY-NC-ND).)*

Effects of exogenous melatonin on oxidative stress

Pre-clinical research in animal models has reported that increased production of reactive oxygen species (ROS) and the consequent oxidative stress are crucial pathological events in SCI, which lead to neurological deficits. Oxidative stress is a hallmark of the secondary injury in SCI. Much of the current literature on secondary injury after SCI has focused particularly on oxidative stress because down-regulation of its detrimental effects is considered a key strategy for therapeutic interventions (Cristante, de Barros Filho, Marcon, Letaif, & da Rocha, 2012). After SCI, oxidative stress may increase the level of lipid peroxidation (LPO) (McDonald & Sadowsky, 2002), as determined by quantifying the levels of MDA, GSH, and SOD. Electron resonance spectrometry was used to measure MDA levels and provided the first lines of evidence for ROS production in SCI. Seligman et al. (1977) reported that the level of MDA was significantly increased within the first 5 h following SCI. A recent study showed that the MDA level increased markedly after 1 day and peaked at 7 days after SCI (Song et al., 2013). SOD activity was decreased at 1 day following SCI (Song et al., 2013). Previous studies showed that MT and its derivatives scavenge free radicals and induce the activities of various antioxidant enzymes. Erşahin et al. (2012) investigated the impact of MT in a rat model of standard weight drop-induced moderate SCI and showed that MT significantly restored the MDA and GSH levels. Immediately after laminectomy, treatment of SCI rats with MT once daily for 10 days also resulted in restored GSH levels (Erol et al., 2008). In addition, the pathophysiological mechanism was proposed to involve iron-catalyzed LPO contributing to autodestruction in the injured spinal cord regions (Emerit, Beaumont, & Trivin, 2001). Previous research established that ferrous iron can initiate brain LPO (Behrmann, Bresnahan, Beattie, & Shah, 1992). After SCI, the levels of free iron and MDA were significantly increased but markedly decreased by MT treatment (Liu, Tang, Yang, & Xiao, 2004). Topsakal et al. (2003) investigated the effects of MT, prostaglandin E1, and oxytetracycline on LPO and antioxidant activities in an experimental model of SCI. The results showed that experimentally induced SCI reduced erythrocyte SOD and plasma GSH activities and increased tissue and blood MDA levels (Topsakal et al., 2003). These physiological alterations were inhibited by MT, prostaglandin E1, and oxytetracycline treatments to varying degrees, with MT showing the greatest effect (Topsakal et al., 2003). Taken together, pre-clinical trials suggest that MT may exert neuroprotective effects on SCI by reducing oxidative stress and promoting functional recovery after SCI (Fig. 2).

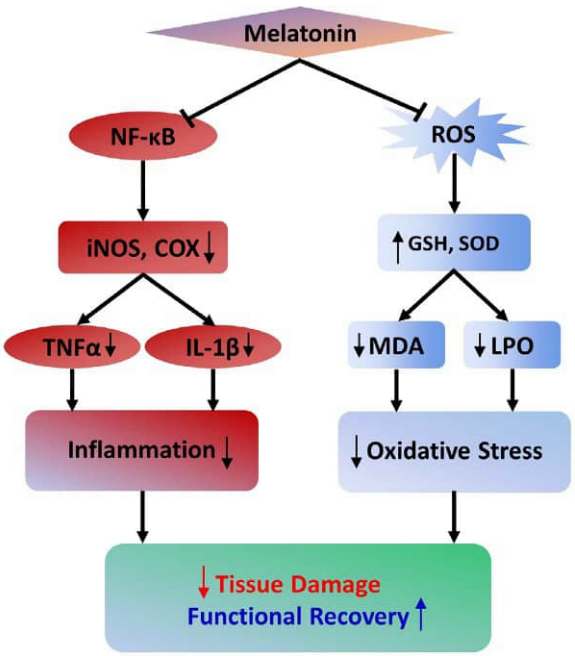

FIG. 2 Schematic representation of the potential mechanisms of action of melatonin in spinal cord injury. Increased production of ROS, MDA, LPO, and consequent oxidative stress is a crucial pathological event in SCI. Melatonin can scavenge free radicals, increase the levels of antioxidant enzymes such as SOD and GSH, and reduce the levels of MDA and LPO following SCI. Moreover, inflammation can directly promote tissue damage and weaken functional recovery after SCI by generating a wide array of inflammatory molecules. However, exogenous melatonin can reduce the levels of inflammatory molecules, such as TNF-α and IL-1β, possibly by inhibiting NF-κB. Melatonin also reduces the expression of iNOS and COX. *COX*, cyclooxygenase; *IL-1β*, interleukin-1β; *iNOS*, nitric oxide synthase; *LPO*, lipid peroxidation; *SOD*, superoxide dismutase; *GSH*, glutathione; *MDA*, malondialdehyde; *NF-κB*, nuclear factor-κ light chain enhancer of activated B cells; *ROS*, reactive oxygen species; *SCI*, spinal cord injury; *TNF-α*, tumor necrosis factor-α.

Effects of exogenous melatonin on inflammation

Within a few hours following SCI, pro-inflammatory cytokines, such as interleukin (IL)-1α, tumor necrosis factor-α (TNF-α), and IL-1β, are activated (Ritz & Hausmann, 2008). After SCI, up-regulation of inducible nitric oxide synthase (iNOS) results in excessive production of nitric oxide (NO), which is abundant in astrocytes and microglial cells (Conti et al., 2007). These excessive levels of NO further stimulate the synthesis of several pro-inflammatory cytokines (Conti et al., 2007). These pro-inflammatory molecules are associated with activation of local microglia and astrocytes, which promote secondary injury after SCI. Several studies have postulated that MT may contribute to reduced inflammation after SCI. Previously, our group reported that iNOS mRNA expression was significantly lower in the MT treatment groups than SCI groups in the region of the injured spinal cord (Park et al., 2010). Moreover, a recent study showed that treatment with MT markedly inhibited the accumulation and proliferation of microglia and astrocytes in the injured spinal cord and suppressed TNF-α, IL-1β, and iNOS expression after SCI (Yang, Bao, Chen, & He, 2020). Those findings may explain the cellular and molecular mechanisms by which MT exerts its neuroprotective effects and contributes to functional recovery after SCI. In a mouse model of severe crush SCI, the inflammatory response appeared to be significantly attenuated at 14 days after MT treatment (10 mg/kg) (Krityakiarana et al., 2016). Immunohistochemical analysis also showed that MT treatment markedly reduced IL-1β and neuron/glial antigen 2 levels (Krityakiarana et al., 2016). The results of that study suggested that MT can decrease the expression and release of pro-inflammatory molecules, thereby inhibiting tissue damage from the secondary inflammatory response. Furthermore, TNF-α may play a pivotal role in the acute phase of SCI. Haddadi and Fardid (2015) conducted a study in radiation-induced SCI rats to assess the efficacy of MT on TNF-α expression and reported that TNF-α expression was markedly increased in the irradiated group compared with the normal group 3 weeks after injury. The most striking result was that the oral MT treatment group (100 mg/kg) showed significantly decreased TNF-α expression compared with the radiation group, suggesting that oral MT impedes the up-regulation of TNF-α expression after radiation-induced SCI (Haddadi & Fardid, 2015). Activation of the nuclear factor-κB (NF-κB) signaling has also been implicated in the induction of inflammation and is considered one of the pathophysiological causes of the spinal cord inflammatory response following SCI (Mao, Wang, Qiao, & Wang, 2010). NF-κB further generates ROS, cyclooxygenase, and iNOS, which synergistically induce inflammation (Mao et al., 2010). Several lines of evidence suggest that MT inhibits the expression of NF-κB and attenuates the production of pro-inflammatory cytokines (Szczepanik, 2007). Recent research on MT suggested that this pineal hormone reduces secondary injury severity and neuronal death after SCI (Schiaveto-de-Souza, da Silva, Defino, & Del Bel, 2013). Another study conclusively showed that MT treatment effectively decreased inflammation and tissue injury in experimental SCI (Genovese et al., 2005). Overall, MT may exert neuroprotective effects on SCI by reducing inflammation and tissue damage after SCI (Fig. 2).

Effects of exogenous melatonin on autophagy

Autophagy plays a significant role in improving the neurological recovery process and enhances neurological function within a short time following acute SCI (Shen et al., 2017). Surprisingly, inhibition of autophagy markedly increased apoptosis in experimental SCI rats (Gao et al., 2016; Wang, Liu, Muharram, Wu, & Lin, 2014). In contrast, enhancing autophagy at the lesion site of the spinal cord significantly inhibited apoptosis (Wang et al., 2016), suggesting that increased levels of autophagy can reduce apoptosis, contribute to the neurological recovery process, and improve neurological function after SCI. A systematic review and network meta-analysis reported that MT improved locomotor recovery by inhibiting neuronal cell apoptosis in a rat model of SCI (Yang et al., 2016). Similarly, Shen et al. (2017) demonstrated that MT impeded neuronal cell apoptosis and encouraged locomotor recovery by activating the Wnt/β-catenin pathway following SCI. Previously, our group examined the endogenous and exogenous effects of MT on autophagic markers (beclin-1, LC3) in a contusion SCI rat model (Park et al., 2012). In that experiment, all groups were exposed to one of the following lighting conditions: 12/12 h light/dark (L/D) or 24/0 h constant light (LL). Western blot analysis showed that the transformation ratio of LC3-I to LC3-II protein was very low or undetectable in the normal control group (Park et al., 2012). Interestingly, the ratio was elevated after injury in a time-dependent manner, particularly in the SCI group under the L/D condition. At the site of the spinal cord lesion, the LC3-II protein level was increased at 3 days and peaked at 28 days post-SCI. In addition, no significant difference in beclin-1 expression was observed under the L/D condition, but its expression was significantly elevated under the LL condition. Surprisingly, exogenous MT treatment markedly decreased these effects under both L/D and LL conditions. Those findings suggest that autophagy-related cell death was increased in the spinal cord, and MT treatment accelerated motor recovery by down-regulation of LC3-II and beclin-1 (Park et al., 2012). These results corroborate with Kanno, Ozawa, Sekiguchi, and Itoi (2009), who also reported that the beclin-1 protein level was significantly increased at the lesion site after SCI. However, as mentioned above, up-regulation of autophagy inhibited apoptosis in the spinal cord, inducing neurological repair following SCI. A recent study

revealed that treatment with MT markedly increased the levels of autophagy-activated proteins, such as beclin-1 and LC3, but decreased the levels of apoptosis-activated proteins, such as caspase-3, caspase-9, and bax, in neurons after SCI (Li et al., 2019). Those findings indicate that MT can improve locomotor function by increasing autophagy as well as decreasing apoptosis after SCI in rats, probably via the PI3K/AKT/mTOR signaling pathway (Li et al., 2019). In summary, MT can increase autophagy, improve neuronal survival, and enhance locomotor function, while decreasing apoptosis in the spinal cord following SCI via the PI3K/AKT/mTOR signaling pathway. Alternatively, MT may improve neuronal survival by down-regulating autophagy-mediated apoptosis after SCI (Fig. 3). Further studies are required to clarify the differential effects of MT on autophagy in several experimental models of SCI.

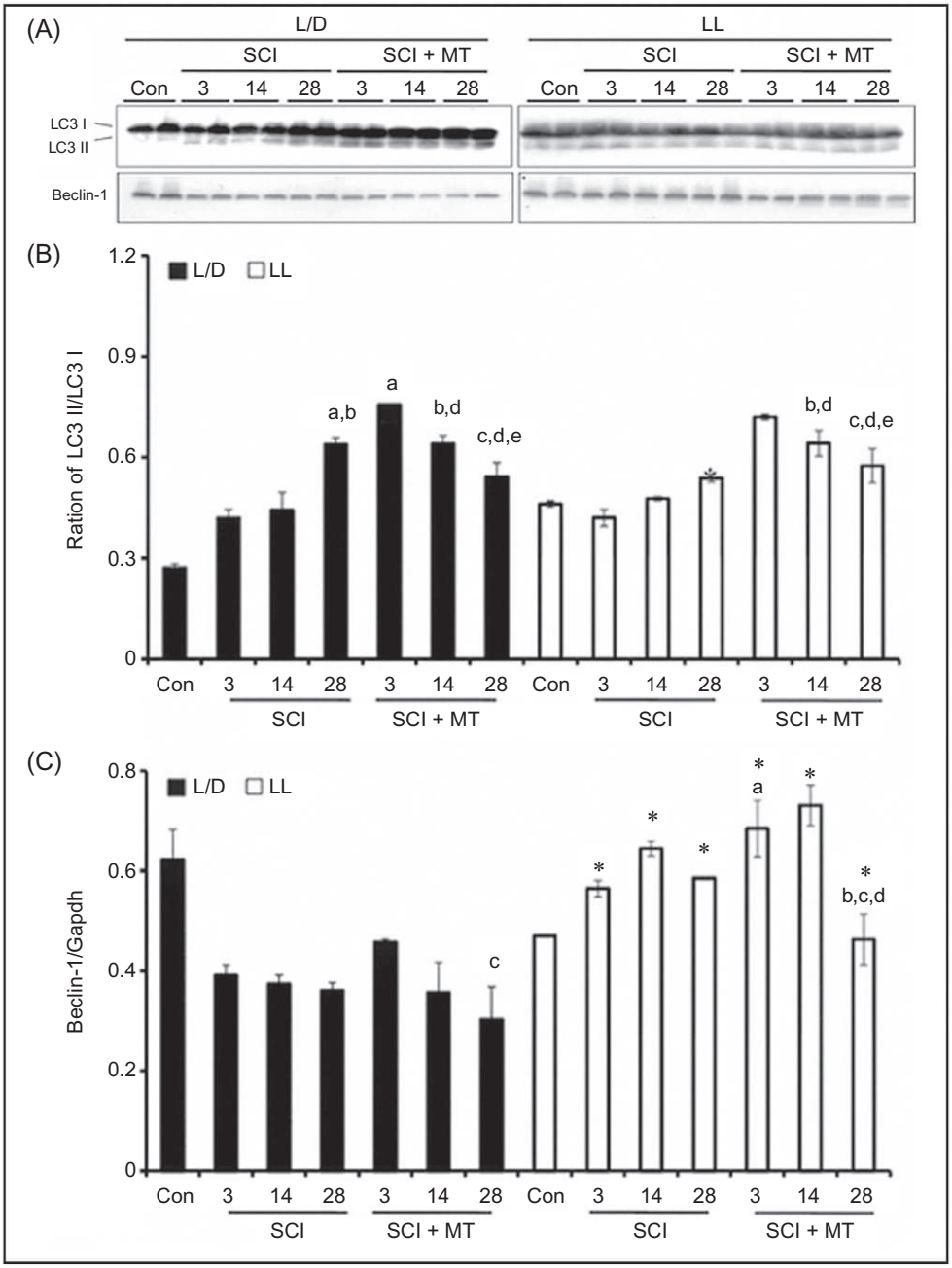

FIG. 3 Effects of exogenous melatonin on autophagy in the injured spinal cord after spinal cord injury. (A–C) Western blot analysis indicated that the autophagy-activating proteins (LC3-II and beclin-1) were decreased by melatonin treatment. *(Republished with permission from Park, S., Lee, S.-K., Park, K., Lee, Y., Hong, Y., Lee, S., Jeon, J.-C., Kim, J.-H., Lee, S.-R., Chang, K.-T., & Hong, Y. (2012). Beneficial effects of endogenous and exogenous melatonin on neural reconstruction and functional recovery in an animal model of spinal cord injury.* Journal of Pineal Research, 52, *107–119. Wiley. Permission conveyed through Copyright Clearance Center, Inc.)*

Combination treatment strategy for spinal cord injury

Although the single-intervention strategy has been effective in pre-clinical trials, the recovery process remains ineffective, and targeting a single barrier has been unsuccessful for improving functional recovery in cases of SCI in clinical trials. In contrast, combination treatment strategies that address diverse aspects of the pathology of SCI have been developed to achieve functional recovery after SCI (Hong et al., 2010; Lee et al., 2015). Most recent pre-clinical and clinical trials on functional recovery after SCI have focused on several combination treatment strategies, including (i) antioxidants plus exercise and (ii) glucocorticoids plus antioxidants (Hong et al., 2010). In this section, we discuss recent studies focusing on the beneficial effects of MT plus exercise on SCI.

Melatonin combined with exercise

Based on recent studies of SCI, the combination of MT and exercise was hypothesized to show synergistic effects, accelerating motor function recovery. As indicated previously, MT reduces LPO and increases the levels of several antioxidant enzymes after SCI (Erol et al., 2008; Erşahin et al., 2012; Liu et al., 2004), indicating that MT itself is a super antioxidant. On the other hand, exercise interventions can influence structural and functional changes in the cerebral cortex, spinal cord, and skeletal muscle, thereby promoting neural and muscular function after SCI. Exercise interventions can accelerate nerve regeneration with functional recovery (Doyle & Roberts, 2006; Park et al., 2015) and sustain the functionality of spinal cord neurons (Fu, Wang, Deng, & Li, 2016). Exercise can enhance neurological function following SCI but inadequate to improve motor function (Petrosyan et al., 2015). These limitations may be due to insufficient neurotrophic factor production by exercise training. In addition to exercise, therefore, several combination strategies have been investigated. Many studies have shown that antioxidants, such as MT, combined with exercise can considerably improve functional recovery following SCI and alleviate spasticity in rats compared with single interventions alone (Fig. 4). The benefit of this combination strategy is that MT can diminish the side-effects related to exercise, such as fatigue and impairment (Park, Park, Lee, Chang, & Hong, 2013). Recently, we reported synergistic effects of MT and exercise on neuronal repair and functional recovery in a contusion-induced SCI animal model (Park et al., 2010), suggesting excessive production of iNOS accelerates secondary damage to spinal tissue, which may be reversed by MT combined with exercise. The results of that study showed that MT combined with exercise markedly elevated hind limb movement, decreased iNOS expression, and increased the proportion of motor neurons in the ventral horn compared with exercise intervention alone (Park et al., 2010). Previously, we also reported synergistic effects of MT and exercise in a rodent SCI model, with notable behavioral enhancement, histological recovery, and elevated numbers of BrdU/nestin double-positive endogenous neural stem/progenitor cells (Lee et al., 2014). This study further demonstrated that MT and exercise intervention had a synergistic effect on nestin expression in the rostral perilesion site, suggesting that nestin may be associated with functional recovery. Using Golgi-Cox analysis, we showed that MT combined with exercise elevated dendritic spine density (Lee et al., 2014). Previously, our group also comprehensively reviewed the therapeutic effects of MT combined with exercise on SCI. In this review, we suggest that MT combined with exercise would not only enhance functional recovery but also alleviate the secondary tissue damage after SCI (Hong et al., 2010). Finally, we propose that future studies should explore the effects of MT and other antioxidants in combination with exercise on SCI recovery, representing a novel strategy for faster recovery after SCI (Hong et al., 2010). Finally, the combination of MT and exercise decreases the secondary injury related to SCI, and thus MT can reduce the side-effects associated with exercise.

Role of endogenous melatonin in spinal cord injury

Poor sleep quality is commonly observed in individuals with SCI, particularly those with tetraplegia, probably due to disruption of circadian rhythmicity (Fatima et al., 2016). SCI also causes circadian rhythm disruption such as dysregulated rhythms of body temperature, and inflammatory gene expression (Gaudet et al., 2018). Misalignment of circadian rhythmicity also alters endogenous MT secretion (Fatima et al., 2016), which further negatively affects the SCI recovery process. In contrast, the levels of endogenous MT were shown to increase under conditions of 24-h darkness, and the elevated endogenous MT levels subsequently showed anti-inflammatory and anti-oxidative effects in lesioned spinal cords, resulting in faster neural remodeling, such as axonal outgrowth, excitatory synapse formation, and oligodendrogenesis (Hong et al., 2019). To better understand, the roles of impaired circadian rhythmicity and its effects on sleep in SCI patients, (Verheggen et al., 2012) analyzed evening onset of MT patterns in patients with cervical (tetraplegia) or thoracic (paraplegia) SCI and revealed a higher prevalence of poor sleep quality in tetraplegia (83%) and paraplegia (75%) compared with able-bodied controls (20%). Additionally, they reported that even though the concentration of endogenous MT started to increase from the evening in both the control and paraplegia groups, this increase was completely absent in the tetraplegia

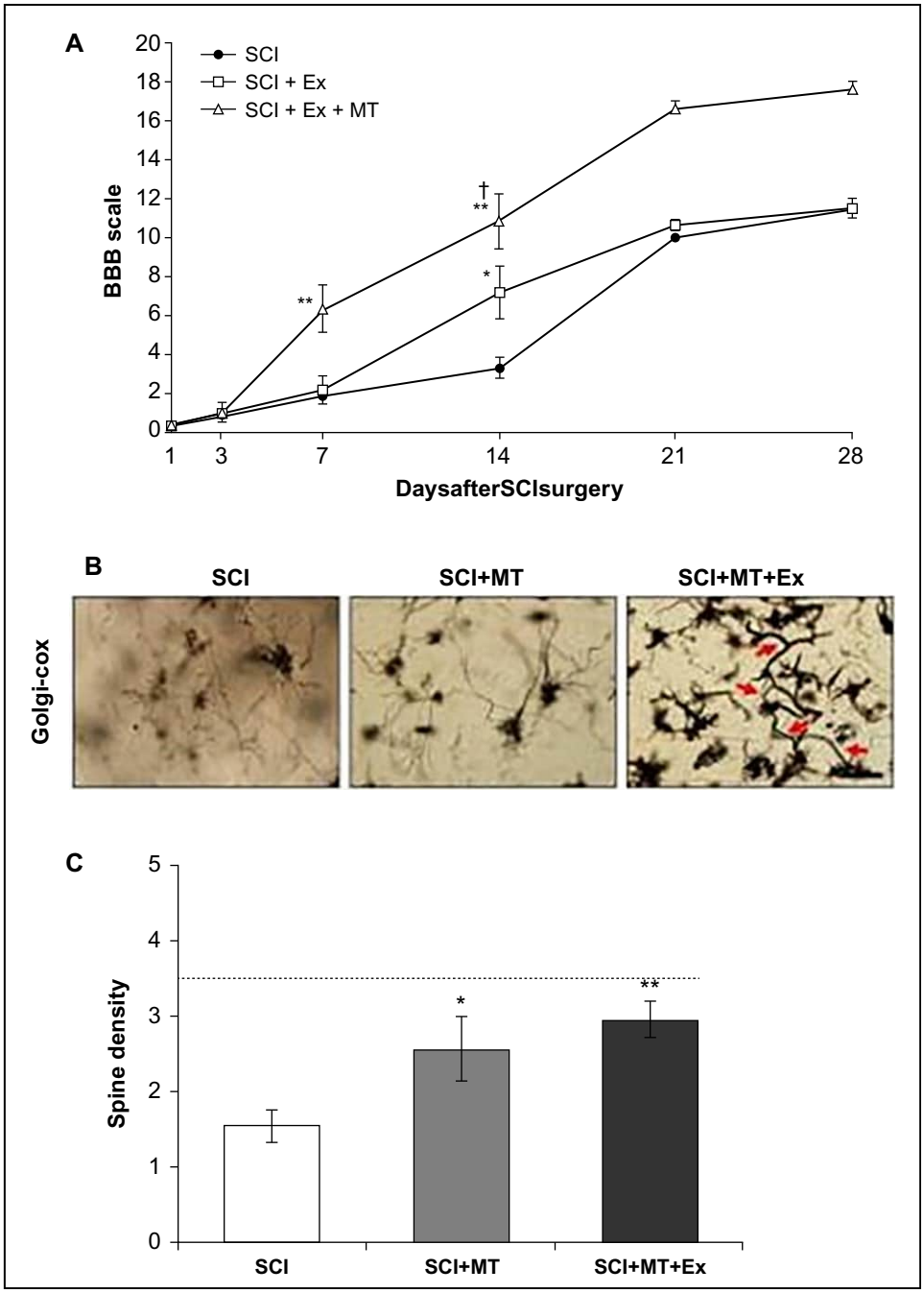

FIG. 4 Combined effects of melatonin and exercise on functional recovery after spinal cord injury. (A) The effects of melatonin combined with exercise on locomotor function in SCI. (B) Golgi-Cox staining indicated that melatonin and exercise promoted neurite outgrowth and production of new vessels *(red arrow)* after SCI. (C) After SCI, the combination of melatonin and exercise greatly increased dendritic spine density compared with melatonin alone. *(Republished with permission from Park, K., Lee, Y., Park, S., Lee, S., Hong, Y., Lee, S.K, & Hong, Y. (2010). Synergistic effect of melatonin on exercise-induced neuronal reconstruction and functional recovery in a spinal cord injury animal model.* Journal of Pineal Research, 48, *270–281. Wiley; and Reprinted from Lee, Y., Lee, S., Lee, S.-R., Park, K., Hong, Y., Lee, M., Park, S., Jin, Y., Chang, K.-T., & Hong, Y. (2014). Beneficial effects of melatonin combined with exercise on endogenous neural stem/progenitor cells proliferation after spinal cord injury.* International Journal of Molecular Sciences, 15, *2207–2222. According to the Creative Commons License (CC-BY-NC-ND).)*

group (Verheggen et al., 2012). Recently, Thøfner Hultén et al. (2018) also demonstrated that MT secretion was decreased to a greater extent in individuals with cervical SCI compared with thoracic SCI (Fig. 5). Patients with SCI were reported to show dysregulated circadian variation in thermoregulatory control (Jones et al., 2014). Elevation of MT during the evening was reported to be inversely correlated with core and skin temperature in able-bodied controls, particularly in paraplegic

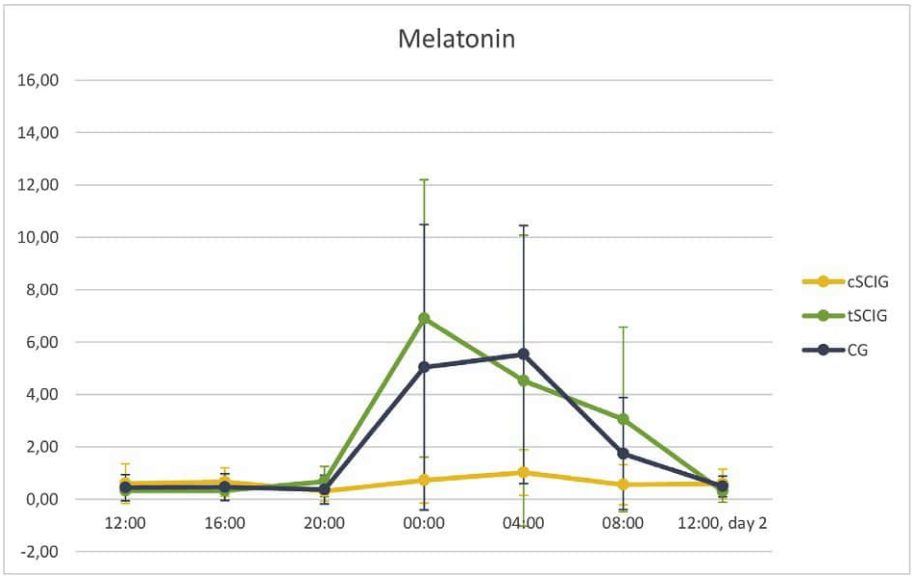

FIG. 5 Saliva melatonin levels in individuals with spinal cord injury. *cSCIG*, cervical spinal cord injury group; *tSCI*, thoracic spinal cord injury group; *CG*, control group. *(Republished with permission from Thøfner Hultén, V. D., Biering-Sørensen, F., Jørgensen, N. R., & Jennum, P. J. (2018). Melatonin and cortisol in individuals with spinal cord injury.* Sleep Medicine, 51, *92–98. Elsevier. Permission conveyed through Copyright Clearance Center, Inc.)*

individuals, while this correlation was absent in tetraplegic individuals during the same period (Jones et al., 2014). In clinical trials, individuals with tetraplegia were more likely to lose their nocturnal production of MT than were those with mild paralysis (Zeitzer, Ayas, Wu, Czeisler, & Brown, 2005), indicating that neurologically complete cervical SCI induces complete loss of nighttime MT production. In a study involving rats with SCI, Gezici, Karakaş, Ergün, and Gündüz (2010) reported that MT secretion began immediately after SCI but slowed substantially 2 to 6 h later. In an animal study, complete lesion of the lower cervical spinal cord was related to insufficient MT secretion; on the other hand, paraplegic rats with complete lesion of the upper thoracic spinal cord showed normal MT secretion (Gezici et al., 2010). The absence of nighttime MT secretion after cervical SCI may partially explain the observed sleep disturbance. These findings raise the possibility that MT replacement therapy may improve sleep in patients with tetraplegia (Scheer et al., 2006). The endogenous MT levels in individuals with complete cervical SCI and healthy controls are illustrated in Table 1.

Clinical application of melatonin in spinal cord injury

Several randomized controlled trials (RCTs) have been conducted to assess the effects of exogenous MT treatment on endogenous MT levels and sleep outcomes in individuals with cervical SCI. Most RCTs showed that endogenous MT levels generally increase with MT supplementation, although there were no impacts on subjective or objective parameters of sleep (Fatima et al., 2016; Kostovski et al., 2015; Spong et al., 2014; Spong, Kennedy, Brown, Armstrong, & Berlowitz, 2013; Zeitzer, Ku, Ota, & Kiratli, 2014). Generally, those trials involved MT supplementation long after the initial injury, with most of the studies conducted at least 16 years after the presenting injury. In this regard, it is hypothesized that MT administration shortly after the initial injury may improve sleep quality. However, Kostovski et al. (2017) reported that the fluctuation of MT concentration alters the expression of several clock genes in individuals with tetraplegia, while exogenous MT treatment may align the expression of these clock genes. Previous studies evaluated the clinical effects of exogenous MT only on sleep in patients with complete cervical SCI. There have been no reports regarding the effects of exogenous MT on neurological recovery or pain scores after complete cervical SCI, and therefore future studies are urgently required. Furthermore, characterization of endogenous MT levels during different phases of SCI is also important to optimize the timing of MT supplementation, as previous trials were performed several years after the initial injury, when the window of beneficial clinical effects may have been missed.

Conclusion

Experimental studies have indicated that exogenous MT may restore neurological function and have neuroprotective effects on SCI. Several cellular and molecular mechanisms, such as reduction of oxidative stress, attenuation of iNOS

TABLE 1 Endogenous melatonin levels in individuals with cervical spinal cord injury.

Author (Year)	Country	Patients characteristic	Detection method (Sample medium)	Day-time MT levels (*P*-value), Time	Night-time MT levels (*P*-value), Time
Li, Jiang, Wang, Jiao, and Pang (1989)	China	1. Sex: 7 M:1F 2. Age: 30.1 3. Location: C3–C7	RIA (Blood)	1. SCI: 11.6 ± 1.9 pg/mL 2. Healthy: 16.3 ± 1.9 pg/mL ($P = .0004$) Time: 14:00 PM	1. SCI: 11.6 ± 3.3 pg/mL 2. Healthy: 67.4 ± 15.6 pg/mL ($P < .0001$) Time: 2:00 AM
Verheggen et al. (2012)	Netherlands	1. Sex: All male 2. Age: 43 3. Location: C4–C7	ELISA (Saliva)	NA	1. SCI: 2.41 ± 1.25 pg/mL 2. Healthy: 10.62 ± 4.59 pg/mL ($P = .0018$) Time: 11:00 PM
Fatima et al. (2016)	India	1. Sex: All male 2. Age: 35.7 3. Location: cervical	ELISA (Blood)	1. SCI: 16.9 pg/mL 2. Healthy: 14.4 pg/mL ($P > .05$) Time: 12:00 PM	1. SCI: 49.3 ± 19.5 pg/mL 2. C: 65.6 ± 10.6 pg/mL ($P < .01$) Time: 12:00 AM
Kostovski et al. (2015)	Norway	1. Sex: All male 2. Age: 46 3. Location: C5–C8	ELISA (Blood)	1. SCI: 5.85 pg/mL 2. Healthy: 36.49 pg/mL (NA) Time: 1:00 PM	1. SCI: 4.62 pg/mL 2. Healthy: 49.78 pg/mL (NA) Time: 1:00 AM
Thøfner Hultén, Biering-Sørensen, Jørgensen, and Jennum (2018)	Denmark	1. Sex: NA 2. Age: 45.9 3. Location: C4–C7	ELISA (Saliva)	1. SCI: 0.59 ± 0.76 pg/mL 2. Healthy: 0.44 ± 0.50 pg/mL ($P = .72$) Time: 12:00 PM	1. SCI: 0.73 ± 0.88 pg/mL 2. Healthy: 5.04 ± 5.45 pg/mL ($P = .01$) Time: 12:00 AM

MT, melatonin; *M*, male; *F*, female; *RIA*, radioimmunoassay; *SCI*, spinal cord injury; *C*, cervical; *NA*, not available.

and pro-inflammatory cytokines, and regulation of autophagy, may be involved in neuroprotection on SCI. The beneficial effects of MT have been shown to be greater when combined with exercise, particularly for neural regeneration and functional recovery after SCI. However, additional studies are needed to determine the proper timing and intensity of MT and exercise for use in clinical practice. Future studies should also explore the effects of MT and other antioxidants and/or traditional anti-inflammatory drugs in combination with exercise on recovery after SCI, which would represent a novel strategy for faster recovery after SCI. Both pre-clinical and clinical trials have shown that endogenous MT production and release are altered and play significant roles in the SCI recovery process. Therefore, further studies are also needed to understand the cellular and molecular mechanisms underlying the pathophysiological effects of altered endogenous MT levels and to identify novel targets for the development of clinical therapies that can be used in SCI patients.

Applications to other areas of neuroscience

The pathophysiological mechanisms of SCI are similar to those of various neuronal disorders, such as ischemic stroke and traumatic brain injury. For example, excessive ROS production is a significant contributor to secondary injury in stroke. Similarly, most pre-clinical research in animal models has also demonstrated that increased production of ROS and consequential development of oxidative stress are crucial pathological events in SCI, which lead to neurological deficits. The considerable level of ROS further stimulates production of abundant pro-inflammatory molecules, including IL-1α, -1β, and TNF-α, which further provoke both SCI and stroke pathology. Moreover, in SCI, the activation of autophagy in the

injured spinal cord may be a double-edged sword for neuronal survival similar to ischemic stroke. As similar pathophysiological mechanisms are involved in both cases, MT, which shows neuroprotective and neuroregenerative effects in SCI, may be helpful for neural regeneration and functional recovery after ischemic stroke. As for SCI, the pathophysiological process of stroke is multifactorial, and therefore combination treatment strategies that address diverse aspects of stroke pathology are required. In this chapter, we highlighted that the combination of MT and exercise exerts synergistic effects to reduce the secondary injury pathologies related to SCI. This combination strategy may also be more effective and promote faster recovery after stroke.

Mini-dictionary of terms

- **Autophagic flux:** A process to quantify the rate of autophagic degradation.
- **Circadian misalignment:** An incorrect arrangement of sleep/wake pattern.
- **Paraplegia:** A state of sensory and motor function loss following injury to the thoracic region of the spinal cord.
- **Secondary injury:** Catastrophic molecular events in cells and tissues, beginning immediately after the primary insult and continuing for hours to weeks, resulting in further damage to cells and tissues.
- **Tetraplegia:** A state of sensory and motor function loss following injury to the cervical region of the spinal cord.

Key facts

Key facts of melatonin and exercise combination strategy for spinal cord injury

- Melatonin and exercise exert synergistic effects on neuronal repair and functional recovery after spinal cord injury.
- Melatonin can diminish the side effects of exercise.
- Melatonin combined with exercise can result in faster motor recovery compared with exercise intervention alone.
- Melatonin combined with exercise intervention triggers nestin expression.
- In spinal cord injury, nestin may be associated with the functional recovery process.

Key facts of endogenous melatonin levels after spinal cord injury

- The secretion of melatonin appears to be decreased to a greater extent in individuals with cervical than thoracic spinal cord lesions.
- The concentration of endogenous melatonin started increasing from the evening in both the able-bodied and paraplegia groups, whereas this increase was completely absent in the tetraplegia group.
- The evening increase in melatonin concentration was inversely correlated with core body temperature in the able-bodied and paraplegia groups, but this correlation was completely absent in tetraplegic individuals.
- The absence of nighttime melatonin secretion after cervical spinal cord injury partially explains the sleep disturbance.
- In clinical trials, endogenous melatonin levels generally increase with exogenous melatonin supplementation.
- Elevated endogenous melatonin causes faster neural remodeling, such as axonal outgrowth and formation of excitatory synapses, after experimental spinal cord injury.

Summary points

- Exogenous melatonin treatment notably decreased LPO and restored the levels of antioxidant enzymes, including GSH and SOD.
- Melatonin treatment effectively decreased the levels of pro-inflammatory molecules, such as TNF-α, IL-1β, and iNOS.
- Melatonin can decrease apoptosis by increase autophagy via the PI3K/AKT/mTOR signaling pathway.
- The combination of melatonin and exercise resulted in faster functional recovery.
- The endogenous melatonin secretion pattern was significantly altered following cervical spinal cord injury.

References

Aghazadeh, S., Azarnia, M., Shirazi, A., Mahdavi, S. R., & Zangii, B. M. (2007). Melatonin as a protective agent in spinal cord damage after gamma irradiation. *Reports of Practical Oncology and Radiotherapy*, *12*, 95–99.

Alizadeh, A., Dyck, S. M., & Karimi-Abdolrezaee, S. (2019). Traumatic spinal cord injury: An overview of pathophysiology, models and acute injury mechanisms. *Frontiers in Neurology*, *10*, 282.

Behrmann, D. L., Bresnahan, J. C., Beattie, M. S., & Shah, B. R. (1992). Spinal cord injury produced by consistent mechanical displacement of the cord in rats: Behavioral and histologic analysis. *Journal of Neurotrauma*, *9*, 197–217.

Chan, B. C.-F., Cadarette, S. M., Wodchis, W. P., Krahn, M. D., & Mittmann, N. (2019). The lifetime cost of spinal cord injury in Ontario, Canada: A population-based study from the perspective of the public health care payer. *The Journal of Spinal Cord Medicine*, *42*, 184–193.

Conti, A., Miscusi, M., Cardali, S., Germanò, A., Suzuki, H., Cuzzocrea, S., & Tomasello, F. (2007). Nitric oxide in the injured spinal cord: Synthases cross-talk, oxidative stress and inflammation. *Brain Research Reviews*, *54*, 205–218.

Cristante, A. F., de Barros Filho, T. E. P., Marcon, R. M., Letaif, O. B., & da Rocha, I. D. (2012). Therapeutic approaches for spinal cord injury. *Clinics (São Paulo, Brazil)*, *67*, 1219–1224.

Doyle, L. M. F., & Roberts, B. L. (2006). Exercise enhances axonal growth and functional recovery in the regenerating spinal cord. *Neuroscience*, *141*, 321–327.

Emerit, J., Beaumont, C., & Trivin, F. (2001). Iron metabolism, free radicals, and oxidative injury. *Biomedicine & Pharmacotherapy*, *55*, 333–339.

Erol, F. S., Kaplan, M., Tiftikci, M., Yakar, H., Ozercan, I., Ilhan, N., & Topsakal, C. (2008). Comparison of the effects of octreotide and melatonin in preventing nerve injury in rats with experimental spinal cord injury. *Journal of Clinical Neuroscience*, *15*, 784–790.

Erşahin, M., Özdemir, Z., Özsavcı, D., Akakın, D., Yeğen, B.Ç., Reiter, R. J., & Sener, G. (2012). Melatonin treatment protects against spinal cord injury induced functional and biochemical changes in rat urinary bladder. *Journal of Pineal Research*, *52*, 340–348.

Erten, S. F., Kocak, A., Ozdemir, I., Aydemir, S., Colak, A., & Reeder, B. S. (2003). Protective effect of melatonin on experimental spinal cord ischemia. *Spinal Cord*, *41*, 533–538.

Fatima, G., Sharma, V. P., & Verma, N. S. (2016). Circadian variations in melatonin and cortisol in patients with cervical spinal cord injury. *Spinal Cord*, *54*, 364–367.

Fu, J., Wang, H., Deng, L., & Li, J. (2016). Exercise training promotes functional recovery after spinal cord injury. *Neural Plasticity*, *2016*, 4039580.

Gao, S., Zhang, Z.-M., Shen, Z.-L., Gao, K., Chang, L., Guo, Y., … Wang, A. M. (2016). Atorvastatin activates autophagy and promotes neurological function recovery after spinal cord injury. *Neural Regeneration Research*, *11*, 977–982.

Gaudet, A. D., Fonken, L. K., Ayala, M. T., Bateman, E. M., Schleicher, W. E., Smith, E. J., … Watkins, L. R. (2018). Spinal cord injury in rats disrupts the circadian system. *eNeuro*, *5*, ENEURO.0328-18.2018.

Genovese, T., Mazzon, E., Muià, C., Bramanti, P., De Sarro, A., & Cuzzocrea, S. (2005). Attenuation in the evolution of experimental spinal cord trauma by treatment with melatonin. *Journal of Pineal Research*, *38*, 198–208.

Gezici, A. R., Karakaş, A., Ergün, R., & Gündüz, B. (2010). Rhythms of serum melatonin in rats with acute spinal cord injury at the cervical and thoracic regions. *Spinal Cord*, *48*, 10–14.

Haddadi, G. H., & Fardid, R. (2015). Oral administration of melatonin modulates the expression of tumor necrosis factor-α (TNF-α) gene in irradiated rat cervical spinal cord. *Reports of Practical Oncology and Radiotherapy*, *20*, 123–127.

Hong, Y., Jin, Y., Park, K., Choi, J., Kang, H., Lee, S.-R., & Hong, Y. (2019). Elevated serum melatonin under constant darkness enhances neural repair in spinal cord injury through regulation of circadian clock proteins expression. *Journal of Clinical Medicine*, *8*, 135.

Hong, Y., Palaksha, K. J., Park, K., Park, S., Kim, H.-D., Reiter, R. J., & Chang, K. T. (2010). Melatonin plus exercise-based neurorehabilitative therapy for spinal cord injury. *Journal of Pineal Research*, *49*, 201–209.

Jones, H., Eijsvogels, T. M. H., Nyakayiru, J., Verheggen, R. J. H. M., Thompson, A., Groothuis, J. T., … Thijssen, D. H. (2014). Within-subject correlations between evening-related changes in body temperature and melatonin in the spinal cord injured. *Chronobiology International*, *31*, 157–165.

Kanno, H., Ozawa, H., Sekiguchi, A., & Itoi, E. (2009). Spinal cord injury induces upregulation of Beclin 1 and promotes autophagic cell death. *Neurobiology of Disease*, *33*, 143–148.

Kostovski, E., Dahm, A. E. A., Mowinckel, M. C., Stranda, A., Skretting, G., Østerud, B., … Iversen, P. O. (2015). Circadian rhythms of hemostatic factors in tetraplegia: A double-blind, randomized, placebo-controlled cross-over study of melatonin. *Spinal Cord*, *53*, 285–290.

Kostovski, E., Frigato, E., Dahm, A., Skretting, G., Mowinkel, M.-C., Sandset, P. M., & Bertolucci, C. (2017). Melatonin modifies peripheral blood cell oscillators in humans. *The FASEB Journal*, *31*(S1), 614.3.

Krityakiarana, W., Sompup, K., Jongkamonwiwat, N., Mukda, S., Pinilla, F. G., Govitrapong, P., & Phansuwan-Pujito, P. (2016). Effects of melatonin on severe crush spinal cord injury-induced reactive astrocyte and scar formation. *Journal of Neuroscience Research*, *94*, 1451–1459.

Lee, S., Park, S., Won, J., Lee, S.-R., Chang, K.-T., & Hong, Y. (2015). The incremental induction of neuroprotective properties by multiple therapeutic strategies for primary and secondary neural injury. *International Journal of Molecular Sciences*, *16*, 19657–19670.

Lee, Y., Lee, S., Lee, S.-R., Park, K., Hong, Y., Lee, M., … Hong, Y. (2014). Beneficial effects of melatonin combined with exercise on endogenous neural stem/progenitor cells proliferation after spinal cord injury. *International Journal of Molecular Sciences*, *15*, 2207–2222.

Li, D., Ma, S., Guo, D., Cheng, T., Li, H., Tian, Y., … Wang, J. (2016). Environmental circadian disruption worsens neurologic impairment and inhibits hippocampal neurogenesis in adult rats after traumatic brain injury. *Cellular and Molecular Neurobiology*, *36*, 1045–1055.

Li, Y., Guo, Y., Fan, Y., Tian, H., Li, K., & Mei, X. (2019). Melatonin enhances autophagy and reduces apoptosis to promote locomotor recovery in spinal cord injury via the PI3K/AKT/mTOR signaling pathway. *Neurochemical Research*, *44*, 2007–2019.

Li, Y., Jiang, D. H., Wang, M. L., Jiao, D. R., & Pang, S. F. (1989). Rhythms of serum melatonin in patients with spinal lesions at the cervical, thoracic or lumbar region. *Clinical Endocrinology*, *30*, 47–56.

Liu, J.-B., Tang, T.-S., Yang, H.-L., & Xiao, D.-S. (2004). Antioxidation of melatonin against spinal cord injury in rats. *Chinese Medical Journal*, *117*, 571–575.

Mao, L., Wang, H., Qiao, L., & Wang, X. (2010). Disruption of Nrf2 enhances the upregulation of nuclear factor-kappaB activity, tumor necrosis factor-α, and matrix metalloproteinase-9 after spinal cord injury in mice. *Mediators of Inflammation*, *2010*, 238321.

McDonald, J. W., & Sadowsky, C. (2002). Spinal-cord injury. *Lancet*, *359*(9304), 417–425.

Park, K., Lee, S., Hong, Y., Park, S., Choi, J., Chang, K.-T., … Hong, Y. (2015). Therapeutic physical exercise in neural injury: Friend or foe? *Journal of Physical Therapy Science*, *27*, 3933–3935.

Park, K., Lee, Y., Park, S., Lee, S., Hong, Y., Lee, S. K., & Hong, Y. (2010). Synergistic effect of melatonin on exercise-induced neuronal reconstruction and functional recovery in a spinal cord injury animal model. *Journal of Pineal Research*, *48*, 270–281.

Park, S., Lee, S.-K., Park, K., Lee, Y., Hong, Y., Lee, S., … Hong, Y. (2012). Beneficial effects of endogenous and exogenous melatonin on neural reconstruction and functional recovery in an animal model of spinal cord injury. *Journal of Pineal Research*, *52*, 107–119.

Park, S., Park, K., Lee, Y., Chang, K.-T., & Hong, Y. (2013). New prophylactic and therapeutic strategies for spinal cord injury. *Journal of Lifestyle Medicine*, *3*, 34–40.

Petrosyan, H. A., Alessi, V., Hunanyan, A. S., Sisto, S. A., & Arvanian, V. L. (2015). Spinal electro-magnetic stimulation combined with transgene delivery of neurotrophin NT-3 and exercise: Novel combination therapy for spinal contusion injury. *Journal of Neurophysiology*, *114*, 2923–2940.

Ritz, M.-F., & Hausmann, O. N. (2008). Effect of 17beta-estradiol on functional outcome, release of cytokines, astrocyte reactivity and inflammatory spreading after spinal cord injury in male rats. *Brain Research*, *1203*, 177–188.

Scheer, F. A. J. L., Zeitzer, J. M., Ayas, N. T., Brown, R., Czeisler, C. A., & Shea, S. A. (2006). Reduced sleep efficiency in cervical spinal cord injury; association with abolished night time melatonin secretion. *Spinal Cord*, *44*, 78–81.

Schiaveto-de-Souza, A., da Silva, C. A., Defino, H. L. A., & Del Bel, E. A. (2013). Effect of melatonin on the functional recovery from experimental traumatic compression of the spinal cord. *Brazilian Journal of Medical and Biological Research*, *46*, 348–358.

Seligman, M. L., Flamm, E. S., Goldstein, B. D., Poser, R. G., Demopoulos, H. B., & Ransohoff, J. (1977). Spectrofluorescent detection of malonaldehyde as a measure of lipid free radical damage in response to ethanol potentiation of spinal cord trauma. *Lipids*, *12*, 945–950.

Shen, Z., Zhou, Z., Gao, S., Guo, Y., Gao, K., Wang, H., & Dang, X. (2017). Melatonin inhibits neural cell apoptosis and promotes locomotor recovery via activation of the Wnt/β-catenin signaling pathway after spinal cord injury. *Neurochemical Research*, *42*, 2336–2343.

Song, Y., Liu, J., Zhang, F., Zhang, J., Shi, T., & Zeng, Z. (2013). Antioxidant effect of quercetin against acute spinal cord injury in rats and its correlation with the p38MAPK/iNOS signaling pathway. *Life Sciences*, *92*, 1215–1221.

Spong, J., Kennedy, G. A., Tseng, J., Brown, D. J., Armstrong, S., & Berlowitz, D. J. (2014). Sleep disruption in tetraplegia: A randomised, double-blind, placebo-controlled crossover trial of 3 mg melatonin. *Spinal Cord*, *52*, 629–634.

Spong, J., Kennedy, G. A., Brown, D. J., Armstrong, S. M., & Berlowitz, D. J. (2013). Melatonin supplementation in patients with complete tetraplegia and poor sleep. *Sleep Disorders*, *2013*, 1–8.

Sumsuzzman, D. M., Choi, J., Khan, Z. A., & Hong, Y. (2020). Protective effects of melatonin against severe burn-induced distant organ injury: A systematic review and meta-analysis of experimental studies. *Antioxidants*, *9*, 1196.

Szczepanik, M. (2007). Melatonin and its influence on immune system. *Journal of Physiology and Pharmacology*, *58*, 115–124.

Thøfner Hultén, V. D., Biering-Sørensen, F., Jørgensen, N. R., & Jennum, P. J. (2018). Melatonin and cortisol in individuals with spinal cord injury. *Sleep Medicine*, *51*, 92–98.

Topsakal, C., Kilic, N., Ozveren, F., Akdemir, I., Kaplan, M., Tiftikci, M., et al. (2003). Effects of prostaglandin E1, melatonin, and oxytetracycline on lipid peroxidation, antioxidant defense system, paraoxonase (PON1) activities, and homocysteine levels in an animal model of spinal cord injury. *Spine*, *28*, 1643–1652.

Verheggen, R. J. H. M., Jones, H., Nyakayiru, J., Thompson, A., Groothuis, J. T., Atkinson, G., et al. (2012). Complete absence of evening melatonin increase in tetraplegics. *The FASEB Journal*, *26*, 3059–3064.

Wang, C., Liu, C., Gao, K., Zhao, H., Zhou, Z., Shen, Z., et al. (2016). Metformin preconditioning provide neuroprotection through enhancement of autophagy and suppression of inflammation and apoptosis after spinal cord injury. *Biochemical and Biophysical Research Communications*, *477*, 534–540.

Wang, Z.-Y., Liu, W.-G., Muharram, A., Wu, Z.-Y., & Lin, J.-H. (2014). Neuroprotective effects of autophagy induced by rapamycin in rat acute spinal cord injury model. *Neuroimmunomodulation*, *21*, 257–267.

Yamazaki, K., Kawabori, M., Seki, T., & Houkin, K. (2020). Clinical trials of stem cell treatment for spinal cord injury. *International Journal of Molecular Sciences*, *21*, 3994.

Yang, L., Yao, M., Lan, Y., Mo, W., Sun, Y., Wang, J., et al. (2016). Melatonin for spinal cord injury in animal models: A systematic review and network meta-analysis. *Journal of Neurotrauma*, *33*, 290–300.

Yang, Z., Bao, Y., Chen, W., & He, Y. (2020). Melatonin exerts neuroprotective effects by attenuating astro- and microgliosis and suppressing inflammatory response following spinal cord injury. *Neuropeptides*, *79*, 102002.

Zeitzer, J. M., Ayas, N. T., Wu, A. D., Czeisler, C. A., & Brown, R. (2005). Bilateral oculosympathetic paresis associated with loss of nocturnal melatonin secretion in patients with spinal cord injury. *The Journal of Spinal Cord Medicine*, *28*, 55–59.

Zeitzer, J. M., Ku, B., Ota, D., & Kiratli, B. J. (2014). Randomized controlled trial of pharmacological replacement of melatonin for sleep disruption in individuals with tetraplegia. *The Journal of Spinal Cord Medicine*, *37*, 46–53.

Zhang, Y., Liu, Z., Zhang, W., Wu, Q., Zhang, Y., Liu, Y., et al. (2019). Melatonin improves functional recovery in female rats after acute spinal cord injury by modulating polarization of spinal microglial/macrophages. *Journal of Neuroscience Research*, *97*, 733–743.

Chapter 30

High-intensity interval training in individuals with spinal cord injury

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Abbreviations

AGREE	Appraisal of Guidelines, Research and Evaluation
HIIT	high-intensity interval training
MIT	moderate-intensity continuous training
NSCISC	National Spinal Cord Injury Statistical Center
SCI	spinal cord injury
SIT	sprint interval training
T2D	type 2 diabetes
VO_2 max	maximal oxygen consumption

Introduction

This chapter summarizes the public health issue of physical inactivity (i.e., lack of participation in health-enhancing exercise behavior) among people with spinal cord injury (SCI). The purpose of this chapter is to provide the reader with an understanding of the importance of exercise and potentially advantageous types of exercise for people with SCI, with a particular focus on high-intensity interval training (HIIT). The chapter is broken into four sections. The first section will present current incidence and prevalence data as well as healthcare burden statistics on individuals with SCI. The second section highlights cardiometabolic comorbidities associated with SCI, low levels of exercise, and difficulties (i.e., barriers) associated with participation. The third section summarizes benefits, guidelines, and strategies to promote exercise participation. The fourth section highlights recent findings on HIIT interventions among people with SCI and developing research in this area.

Section 1: Background and overview

Incidence and prevalence

The National Spinal Cord Injury Statistical Center (NSCISC) estimates 291,000 people are living with an SCI in the United States with 17,730 new cases each year, or 54 per million (National Spinal Cord Injury Statistical Center, 2019). Other studies have found similar incidence rates, ranging from 52 to 56.4 per million (Jain et al., 2015); however, due to varying methodologies, other reports include prevalence estimates of 1.5 million to 2.6 million (GBD 2016 Traumatic Brain Injury and Spinal Cord Injury Collaborators, 2016). For decades, the typical person acquiring SCI was 29; however, that has increased to 43, likely due to an increase in the etiology of falls among an aging population. People with newly acquired SCI are typically male (78%) and white (59.5%) with leading causes of injury vehicle crashes (39.3%) and falls (31.8%). The majority of injuries are incomplete, either tetraplegia (47.6%) or paraplegia (19.9%) followed by complete paraplegia (19.6%) and complete tetraplegia (12.3%).

Diagnosis and Treatment of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822498-4.00030-0

Healthcare and economic burden

Healthcare burden is largely dependent upon the degree of severity of the SCI with hospitalizations in the first year of injury, which includes the bulk of the direct cost estimated at 1.7 billion in the United States (Mahabaleshwarkar & Khanna, 2014). For example, an individual with tetraplegia and vent-dependent has an average healthcare expenditure over 1.2 million dollars in the first year after injury with almost $200,000 in subsequent years, whereas someone with paraplegia cost estimates include $550,381 for the first year and $72,909 in subsequent years (National Spinal Cord Injury Statistical Center, 2019). The first year after following injury is the costliest and the most critical to the life of the person with SCI, as life expectancy increases significantly after living past the first year of injury. For individuals injured at 20 years old, estimated life loss is 7 years among individuals with paraplegia and 48 years of life loss among individuals with higher injury levels and vent dependency. In addition to direct cost and life loss, indirect cost, such as loss of earnings and productivity, is estimated at $76,237 per year.

Depending on the level of injury and personal response, many individuals do not return to full-time work or even part-time work. Data from NSCISC show 66% of individuals working at time of injury with only 17% working 1 year out and 23% working 10 years after injury. Lastly, length of stay for rehabilitation after sustaining an SCI has been reduced from 98 to 34 days over the last 50 years (The 2018 Annual Statistical Report for The Spinal Cord Injury Model Systems, 2018). Post-acute rehabilitation offers people with SCI the benefit of individualized, intensive training before returning home. However, shorter length of stay and lack of intensive programming for the home has been linked to higher incidence of rehospitalization due to secondary health conditions, as well as increased discharge to institutional settings rather than the home, all of which drive healthcare cost (Eastwood, Hagglund, Ragnarsson, Gordon, & Marino, 1999; Rimmer, 2012; Tschoepe, Benfield, Mercer, & Posey, 2019).

Section 2: Cardiometabolic comorbidities associated with SCI

This section will present cardiometabolic comorbidities associated with SCI. There is greater prevalence of these comorbidities due to deconditioning and the myriad of barriers to exercise for this population. Similar to other disability groups, people with SCI encounter three different categories of conditions. This includes the associated conditions, such as paralysis and its impacts motor functioning, sensation, and bodily processes (e.g., bladder functioning); secondary health conditions, such as neuropathic pain, urinary tract infections, pressure ulcers, and social isolation; and chronic conditions (i.e., heart disease, obesity).

Associated risk factors

People with SCI have reduced physical functioning due to loss of motor functioning and loss of muscle mass, which result in deleterious cardiometabolic effects. People with SCI have high rates of secondary health conditions, which are defined by the Institute of Medicine as preventable conditions secondary to the associated condition. These secondary conditions (e.g., pain, pressure ulcer) lead to a downward spiral in health and function for people with SCI and in the aggregate, can impose substantial limitations in rates of participation including employment, social engagement, and performing activities of daily living (Ehde et al., 2003; Ginis et al., 2010; Latimer, Martin Ginis, Craven, & Hicks, 2006; Martin Ginis & Hicks, 2005; Rajan, McNeely, Warms, & Goldstein, 2008; Tian et al., 2013; Turner, Cardenas, Warms, & McClellan, 2001). The NCISC reported in 2018 that within the first year of sustaining an SCI, 36.5% of patients are re-hospitalized due to infections associated with the urinary, respiratory, or integumentary system, with an average length of hospitalization of 19 days (The 2018 Annual Statistical Report for The Spinal Cord Injury Model Systems, 2018). Additionally, Skelton, Hoffman, Reyes, and Burns (2015) reported that within the first year of sustaining an SCI, 57% used emergency room care. Following rehabilitation, health trajectories in people with SCI are impacted by the onset and course of these secondary conditions and their "additive" effect on changes in health and function (Adriaansen et al., 2016). Some of the highest rates of physiological secondary conditions in people with SCI include excess weight gain (i.e., obesity) (Gorgey & Gater, 2007; Laughton, Buchholz, Martin Ginis, & Goy, 2009; Rajan et al., 2008; Tian et al., 2013), extremely low fitness levels (Ginis et al., 2010; Latimer et al., 2006; Martin Ginis & Hicks, 2005), and pain (neuropathic and musculoskeletal) (Ehde et al., 2003; Turner et al., 2001; Fig. 1).

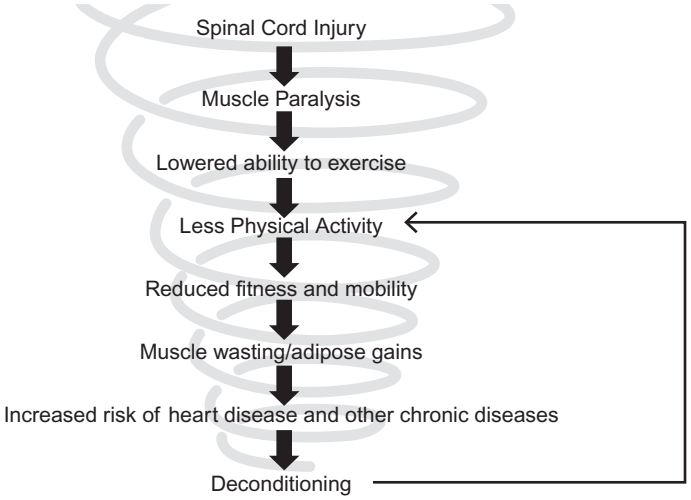

FIG. 1 Downward spiral of deconditioning among people with SCI.

Health disparities, barriers, and SCI

People with SCI have higher rates of health disparities, which includes lower levels of physical activity. Data show that around half of people with SCI obtain little to no aerobic physical activity, which has resulted in people with SCI at three times more likely to have chronic conditions, such as heart disease, obesity, and stroke than the general population (Carroll et al., 2014; Ginis et al., 2010). This is largely due to the reduced physical functioning and sedentary lifestyles acquired by many individuals with SCI due to the issues of deconditioning and secondary conditions discussed in the above section (Galea, 2012; Rimmer, Schiller, & Chen, 2012). This is also related to the low rates of employment previously mentioned, as well as other lower quality of life indicators among people with SCI. There is an extreme challenge faced by people with SCI to lead an active and healthy lifestyle because of muscle loss, reduced motor functioning, and health, environmental, and logistical barriers (Galea, 2012; Martin Ginis, Ma, Latimer-Cheung, & Rimmer, 2016). Deconditioning is only one aspect of a plethora of exercise barriers that span each level of the social ecological model for people with SCI. Many systematic reviews have highlighted the issue of barriers to exercise among people with SCI (Martin Ginis et al., 2016). At the intrapersonal level, people with SCI have low levels of self-efficacy, fear of injuring themselves, and experience an increase in musculoskeletal pain, as well as the addition of neuropathic pain, due to the SCI. On the interpersonal level, there is a lack of social support for individuals with SCI resulting in cases of learned helplessness, which is detrimental to gaining independence. Next, there is a lack of awareness and knowledge about supporting exercise behavior among people with SCI at the organizational level and lack of accessible fitness centers, exercise programs, and equipment at the community level. Lastly, the largest barrier to exercise has been transportation with many dependent upon public transportation.

Section 3: SCI exercise benefits, guidelines, and participation

This section will cover the current state-of-the-science regarding exercise benefits and guidelines for SCI. To date, there are three topic areas in SCI exercise research that are receiving substantial attention: (1) exercise benefits, (2) exercise guidelines, and (3) participation issues. The first subsection, exercise benefits, will summarize the anticipated benefits that people with SCI can obtain from exercise participation. The second subsection will briefly overview issues participation in exercise research. The third subsection will summarize the latest guidelines or recommendations to exercise for people with SCI.

Exercise benefits

Exercise research for SCI is a relatively new area of research inquiry that emerged around the 1980s. Because of this, there is limited high-level evidence that confirms precise physiological benefits of exercise among this population.

Unfortunately, the relatively small prevalence of SCI has made it difficult for researchers to confirm the benefits of exercise in SCI within large high-quality trials, such as randomized controlled trials. This lack of trials has resulted in few systematic reviews for SCI compared with other disability groups (e.g., stroke and multiple sclerosis) and, ultimately, no meta-analyses. Therefore, while the benefits for SCI are likely similar to those observed in the general population, there is a lack of research evidence supporting interventions that can lead to actual benefits in SCI. This makes it difficult for clinicians to prescribe exercise and improve participation. Nevertheless, we hereby present the latest high-quality evidence of benefits in SCI as of the time of this publication.

In 2017, a high-quality systematic review of exercise studies for people SCI reported that exercise could improve fitness cardiometabolic health (Ginis et al., 2018; van der Scheer et al., 2017). The review included a total of 211 studies where exercise interventions were delivered. The review included non-randomized studies (non-randomized trials, case studies, etc.) in addition to randomized studies, which means that we should interpret not only their findings but also the confidence they had in their findings. There were insufficient high-quality studies that included people with acute SCI ($\leq$12 months post-injury). Thus, the findings were presented only for people with chronic SC (189/211 studies). The key findings are presented below:

Benefits summary: (Ginis et al., 2018; van der Scheer et al., 2017)

- Low to moderate confidence evidence demonstrates that exercising 3 to 5 times per week at a moderate to vigorous intensity can improve cardiorespiratory fitness, muscular strength and metabolic health (body composition and cardiovascular risk factors).
- Different doses of exercise result in different health benefits.
- Doses of lower training durations and frequencies can improve fitness (i.e., cardiorespiratory fitness and muscular strength/power).
- Whereas doses with higher training durations and frequencies appear to be necessary to result in cardiometabolic health improvements.

These findings had important implications and informed the development of the latest SCI exercise guidelines.

Of note, the published studies primarily base their evidence off of short-term clinical studies. In other words, the studies are conducted in highly controlled laboratory or clinical settings, as opposed to real-world changes in the lifestyle of the person with SCI after the study. A scoping review examined whether exercise benefits could be sustained after completing the formal intervention of an intervention for adults with disabilities (Lai et al., 2019). The report identified that, from exercise trials published from 2006 to 2016, only one study for SCI found a sustained benefit toward a health outcome that lasted throughout a follow-up period (a period after completing a formal intervention component). Consequently, there is a need to identify programs that not only improve health and function in the short term for SCI, but also demonstrate long-term benefits, which will ultimately require strategies that promote long-term participation.

Exercise guidelines

Given the infancy of the field, exercise guidelines or recommendations designed specifically for SCI are quite new and still evolving. The latest and most widely acknowledged exercise guidelines were created in 2017 by a large international team of highly respected disability-exercise scientists, led by Dr. Kathleen Martin Ginis the University of British Columbia, Canada and Victoria Goosey-Tolfrey at Loughborough University, United Kingdom (Ginis et al., 2018; van der Scheer et al., 2017). The guidelines were split into two different categories, fitness benefits and cardiometabolic health, as stated below:

Guidelines summary: (Ginis et al., 2018; van der Scheer et al., 2017)

- Aerobic exercise should be performed 2 to 3 sessions per week at a moderate to vigorous intensity for 20 to 40 min (at minimum, 20 min).
- Strength exercise should be performed 2 to 3 times per week and each session should include 3 sets of 10 repetitions for large muscle groups (weight should be set at 50% to 80% of the person's maximum weight; at minimum 3 sets should be performed in a week).

When prescribing these guidelines to people with SCI, there are a few important concepts to note. The duration component for aerobic exercise necessary to anticipate health benefits is, at minimum, 20 min. If improving health is the primary goal, people with SCI should aim to exceed the SCI guidelines, particularly since guidelines for SCI are lower than those for the general adult population. The US Department of Health and Human Services recommends the general adult population and adults with disabilities should aim to achieve at least 150 to 300 min of moderate-intensity aerobic exercise per week; or 75

to 150 min of vigorous intensity aerobic exercise (US Department of Health and Human Services Physical Activity Guidelines for Americans, 2018). The collective evidence suggests that the SCI exercise guidelines should be considered as a minimum recommendation or a starting point for exercise promotion. The long-term goal should be to progress toward higher volumes (frequency of exercise sessions per week and session durations) of exercise overtime. As a final note, there will certainly be many people with SCI who will have difficulty achieving or may never achieve the SCI guidelines (barriers discussed in the last subsection). Although achieving the guidelines is an important target for exercise prescription, know that some exercise is always better than none: gains can be made from even low levels of exercise participation, particularly in people who are physically deconditioned or new to exercise.

Exercise participation

Although there is an encouraging amount of literature demonstrating benefits, ultimately, published studies have not demonstrated much success with identifying programs that can increase exercise participation. Specifically, there have been no evidence-based programs successful at maintaining exercise participation over a long term (Lai et al., 2018) and, most importantly, there is substantial difficulty with getting people with SCI enrolled into an exercise intervention. A review study (Lai et al., 2018) found the mean sample size of randomized controlled trials published between the years 2006 to 2016 was 25 people; 14 people per study group when they were randomized to a treatment group and control group. This means exercise interventions may have poor generalizability (i.e., findings may not be able to be projected to the population as a whole), and we must be careful when interpreting study findings. This limitation is currently the largest factor that impedes the growth of exercise research in SCI.

To address this issue, we would urge researchers to use theory-based strategies to enroll people with SCI into exercise interventions or programs. Behavioral change strategies that are framed upon theories (e.g., social cognitive theory) have been found to be successful for promoting physical activity throughout an intervention for people with SCI, albeit for short-to-mid terms (Ma & Martin Ginis, 2018). Conceivably, theory-based strategies should also frame how we enroll people with SCI into exercise interventions. Our team conducted a qualitative investigation that generated a theory for enhancing the likelihood of success with enrollment (Lai et al., 2020). The theory posits that wheelchair users with SCI ($n = 33$) conceive three core concerns with enrolling into an exercise intervention: (1) they first assess their capability to participate in the program due to scheduling, transportation, and secondary health conditions; (2) they mentally balance anticipated benefits versus the difficulty of starting the program; and (3) they assess the desirability of the program characteristics based upon their needs and preferences. Successful recruitment will depend on a recruiters ability to address these three concerns while presenting time-efficient, accessible, and desirable programs (Lai et al., 2020).

Section 4: Health benefits of high-intensity interval training

The primary cited reason for not participating in regular exercise in non-disabled individuals is perceived "lack of time" (Lai et al., 2021; Trost, Owen, Bauman, Sallis, & Brown, 2002). With this in mind, individuals with SCI face even greater challenges as they have few, if any options to participate in physical activity. Three of the most frequently reported barriers to participation, are structural (accessibility to exercise facilities, exercise equipment), time-related (getting dressed/undressed, unreliable transportation services), and lack of knowledgeable exercise personnel (Scelza, Kalpakjian, Zemper, & Tate, 2005). Thus, it is imperative that novel exercise strategies are identified to address these barriers in individuals with SCI.

High-intensity interval training in able-bodied individuals

One mode of training that may overcome some of these barriers and provide similar cardiometabolic health benefits is low-volume high-intensity interval training (HIIT). HIIT can be performed many different ways, but usually consists of brief intervals of higher intensity exercise performed between (~80%–200% of VO_2 max) separated by rest intervals of lower intensity exercise or complete rest (Gillen et al., 2016; MacInnis & Gibala, 2016). Furthermore, interval training can be broken down to HIIT, which consists of repeated bouts of exercise performed at workloads between the ventilatory threshold and VO_2 max, or sprint interval training (SIT), which is performed at workloads greater than VO_2 max (Buchheit & Laursen, 2013; Gibala, Gillen, & Percival, 2014). At this point, there are insufficient data to support the idea that individuals with SCI are able to perform SIT, which requires maximal or supramaximal efforts for the duration of the interval. Thus, for simplicity, we will refer to both of these terms as HIIT when referring to the effects on individuals with SCI throughout this chapter. A growing body of evidence in non-disabled individuals, from our group (Fisher et al., 2015)

and others (Burgomaster et al., 2008; Martins et al., 2015; Richards et al., 2010; Whyte, Gill, & Cathcart, 2010) has demonstrated the potential for low-volume high-intensity interval training (HIIT) to provide comparable or superior improvements in cardiometabolic health outcomes compared to continuous moderate-intensity training (MIT) requiring 60% to 80% greater time commitment. For example, we recently found similar improvements in % fat, blood lipids, and insulin sensitivity in obese males following 6 weeks of training despite HIIT only requiring 20% of the total time commitment as MIT. Importantly, this mode of exercise has been shown to be well tolerated in many different clinical populations, including type 2 diabetes (T2D) (Boudou, Sobngwi, Mauvais-Jarvis, Vexiau, & Gautier, 2003; Little et al., 2011), overweight/obesity (Fisher et al., 2015; Gillen, Percival, Ludzki, Tarnopolsky, & Gibala, 2013; Whyte et al., 2010), cardiovascular disease (Warburton et al., 2005), and metabolic syndrome (Tjønna et al., 2008). Thus, HIIT appears to be a mode of exercise that is well-tolerated, requires minimal time commitment, and provides many of the same cardiometabolic health benefits as MIT in non-disabled individuals.

High-intensity interval training in individuals with spinal cord injury

Exercise guidelines for non-disabled individuals have been developed based on modes of exercise that require weight bearing activities such as running and walking or lower-body exercise such as cycling. This is uniquely different than exercise programs in individuals with SCI, in which upper body exercise training (arm crank cycling, wheelchair movement, and upper body resistance training) is the primary mode used and consists of upper body muscle mass. When SCI occurs, there is a decline in aerobic capacity, onset of skeletal muscle atrophy, increases in body fat, and impaired cardiometabolic health. Thus, this rapid deconditioning greatly enhances risk of cardiovascular and metabolic diseases then able bodied populations (Bauman & Spungen, 2001). Furthermore, while there have been few long-term studies assessing the benefits of exercise on individuals with SCI a recent study showed improvements in VO_2 max and muscular strength compared to no-exercise controls. However, there were no changes in body composition, blood lipids, or blood glucose and insulin following 16 weeks of combined aerobic and resistance training exercise performed twice a week (Totosy de Zepetnek, Pelletier, Hicks, & MacDonald, 2015), suggesting the potential need for greater volume or intensity to modify cardiometabolic risk factors. Thus, HIIT is an attractive form of training to address these potential limitations following lower volume or moderate-intensity exercise. To date, there have been few well-powered studies assessing the potential benefits for improving cardiometabolic health in individuals with SCI. Overall, studies (Brurok, Helgerud, Karlsen, Leivseth, & Hoff, 2011; Harnish, Daniels, & Caruso, 2017; Hasnan, Engkasan, Husain, & Davis, 2013; Tordi et al., 2001) not including a MIT exercise comparison group showed increases in VO_2 peak and peak power output, and have also shown improved stroke volume (Brurok et al., 2011), and decrease % body fat (Harnish et al., 2017). Whereas studies that have compared HIIT to MIT training groups have shown similar improvements in VO_2 peak (de Groot, Hjeltnes, Heijboer, Stal, & Birkeland, 2003; Graham et al., 2019), insulin sensitivity (de Groot et al., 2003; Graham et al., 2019), and peak power output (de Groot et al., 2003; Mcleod, Diana, & Hicks, 2020). Thus, it appears that HIIT can improve some components of cardiometabolic health, similar to that seen following MIT exercise; however, it remains difficult to compare results between studies due to a lack of standardized exercise guidelines when implementing HIIT.

While there is much work needed to draw conclusions of the efficacy of HIIT for improving health in individuals with SCI, several recent studies have shown greater exercise enjoyment (Astorino & Thum, 2018; Gauthier, Brosseau, Hicks, & Gagnon, 2018) following HIIT compared to MIT (15, 20). Furthermore, HIIT studies to date have reported minimal (Astorino & Thum, 2018; Brurok et al., 2011; Gauthier et al., 2018) or no adverse responses (Graham et al., 2019; Mcleod et al., 2020) to HIIT. Therefore, HIIT appears to be a feasible and tolerable form of training in individuals with SCI. Future well powered and long-term studies are needed to determine if HIIT is a more attractive form of training that can address the major barriers (lack of time, enjoyment, and access to facilities) to exercise participation and exercise adherence in individuals with SCI, and lead to long-term improvements in cardiometabolic health.

Telehealth strategies to promote exercise adherence to high-intensity interval training

Participation in exercise remains low in individuals with SCI (50% sedentary) (Ginis et al., 2010). Adherence to exercise treatments in disabled individuals is often reported to be less than 50% (Forkan et al., 2006; Kolt & McEvoy, 2003; McLean, Klaber Moffett, Sharp, & Gardiner, 2013). In addition to low adherence rates, the majority of SCI exercise training studies to date have had small sample sizes (mean = 14) and were often underpowered to determine primary treatment effects (Lai, Young, Bickel, Motl, & Rimmer, 2017). Thus, it is critical to identify novel strategies and tools that can increase exercise participation and improve rates of adherence in SCI. Recent advances in technology, such as smartphones and internet streaming, have been used to deliver health care services to individuals at home. Thus, with emerging

technology it is possible for the implementation of home-based telehealth exercise, which may enable us to overcome many of the reported barriers, such as transportation, accessibility to exercise facilities, and access to knowledgeable exercise personnel (Scelza et al., 2005), in individuals with SCI.

To date, there have been a few pilot studies testing the efficacy of various telehealth exercise interventions (telephone, video, and web-based approaches) in individuals with SCI (Arbour-Nicitopoulos, Tomasone, Latimer-Cheung, & Martin Ginis, 2014; Coulter et al., 2017; Lai, Rimmer, Barstow, Jovanov, & Bickel, 2016; Sweet, Rocchi, Arbour-Nicitopoulos, Kairy, & Fillion, 2017). Telephone-based exercise counseling has been shown to increase exercise participation in adults with SCI from 35% at baseline to 52% after 6 months (Arbour-Nicitopoulos et al., 2014). A recent pilot study by our group assessed an aerobic exercise training program delivered remotely using an upper body ergometer, tablet, physiological monitor, and custom application that delivered video feed to a remote trainer and monitored and recorded exercise data in real time (Lai et al., 2016). This approach resulted in completion of all 24 sessions during the 8 weeks of training and 100% adherence. Another advantage is that technology-based programs might also increase the likelihood that outcomes are maintained after an exercise trial is completed. In a recent review, we observed that technology-driven interventions sustained 56% of all outcomes measured at follow-up, which was higher than all other exercise modalities and the mean of all studies (32%) (Lai et al., 2018). Collectively, these studies demonstrate that home-based telehealth exercise training can be implemented safely and allows individuals and investigators to overcome many of the common barriers to exercise participation and research in SCI. Given the potent health improvements observed following low-volume HIIT and the ability to implement a home-based telehealth exercise approach, HIIT delivered via telehealth may be an optimal exercise training program that improves cardiometabolic health, requires little time, and reduces environmental barriers that typically prevent exercise in SCI. Current research by our group will assess the potential for home-based telehealth HIIT exercise for improving cardiometabolic health in individuals with SCI. We anticipate greater adherence to exercise and significant health improvements as it has been shown that one-on-one training and attention from the trainers are key factors that will make HIIT enjoyable, as it has been shown that working with personal trainers significantly increase adherence to exercise (Tulloch et al., 2013).

Applications to other areas of neuroscience

In this chapter, we have reviewed the impact that spinal cord injury has on the risk and prevalence of developing chronic cardiometabolic diseases. We discuss the benefits that exercise training can have for improving or preventing these adverse health outcomes, and highlight the potential role of high-intensity interval training as a mode of exercise that may lead to greater health benefits and adherence in individuals with spinal cord injury. HIIT has gained traction in recent years as it has shown to provide many similar or superior health benefits as prolonged moderate-intensity exercise training despite requiring a significantly reduction in overall time commitment. It remains to be determined if this mode of exercise will provide similar results in SCI as seen in able-bodied individuals, however a number of studies in other neurological diseases have shown promising results. HIIT was shown to be a feasible form of exercise training that improved cardiovascular fitness, vascular hemodynamics, and cognitive function in individuals with Parkinson's disease (Fernandes et al., 2020; Harvey et al., 2019). HIIT has also been shown to reduce pain, fatigue, stiffness, and inflammation in patients with axial spondyloarthritis (Sveaas et al., 2020). The assessment of HIIT in patients with neurological diseases is relatively new, thus future well controlled and statistically powered studies will better determine the long-term health benefits in individuals with SCI and other neurological conditions.

Mini-dictionary of terms

Spinal cord injury: Traumatic damage to the spinal cord causing a certain degree of paralysis and loss of neurological function.
Paraplegia: Paralysis of the lower limbs.
Tetraplegia: Paralysis of all four limbs.
Healthcare burden: The direct (e.g., hospital stay) and indirect cost (e.g., loss of wages) associated with care for the injury and the lasting effects.
Secondary health conditions: Conditions associated with a disability, either directly or indirectly, and preventable or manageable through healthy behavior, such as exercise.
Psychosocial: The intersection of an individual's psychology and their interaction with their social environment.
Sample size: The number of people enrolled in a research study.

Systematic review: A review that takes a rigorous approach to aggregating and summarizing the effects of published research studies.
Health disparity: Differences in health due to unequal access or resources.
High-intensity interval training: A mode of exercise consisting of brief intervals of higher intensity exercise separated by rest intervals of lower intensity exercise or complete rest.
Moderate-intensity continuous training: A mode of exercise training that involves steady state continuous exercise without rest intervals.
Cardiometabolic health: Risk factors, such as dyslipidemia, elevated blood pressure, impaired glucose intolerance, obesity, reduced cardiovascular fitness, that increase risk of developing diabetes, heart disease, or stroke.

Key facts of SCI and exercise

- Individuals with SCI have reduced physical functioning due to loss of motor function and loss of muscle mass.
- When SCI occurs there is a decline in aerobic capacity, onset of skeletal muscle atrophy, increases in body fat, and impaired cardiometabolic health.
- The primary cited reason for not participating in regular exercise in non-disabled individuals is perceived "lack of time."
- HIIT is a form of training that consists of brief intervals of higher intensity exercise performed between (~80%–200% of VO_2 max) separated by rest intervals of lower intensity exercise or complete rest.
- HIIT appears to be a mode of exercise that is well-tolerated, requires minimal time commitment, and provides many of the same cardiometabolic health benefits as MIT despite requiring significantly less time.

Summary points

- High rates of secondary medical conditions among individuals with SCI include pressure sores, urinary tract infections, and pain.
- Individuals with SCI have reported lower levels of physical activity compared to individuals without a disability.
- Barriers to exercise for people with SCI include unreliable transportation, inaccessible facilities, and lack of knowledge among exercise trainers.
- Exercise guidelines for SCI recommend a minimum of 20 min of aerobic activity 2 to 3 times per week and strength exercise performed 2 to 3 times.
- More needs to be done in creating effective and enjoyable HIIT exercise interventions for individuals with SCI.
- Telehealth could be used to circumvent the majority of barriers to exercise and provide an enjoyable experience with exercise.

References

Adriaansen, J., Post, M. W. M., Brinkhof, M. W. G., deGroot, S., van Asbeck, F. W. A., Stolowijk-Swuste, J. M., et al. (2016). Secondary health conditions in persons with spinal cord injury: A longitudinal study from one to five years post-discharge. *Journal of Rehabilitation Medicine*, *45*, 1016–1022.

Arbour-Nicitopoulos, K. P., Tomasone, J. R., Latimer-Cheung, A. E., & Martin Ginis, K. A. (2014). Get in motion: An evaluation of the reach and effectiveness of a physical activity telephone counseling service for Canadians living with spinal cord injury. *PM & R : The Journal of Injury, Function, and Rehabilitation*, *6*(12), 1088–1096. https://doi.org/10.1016/j.pmrj.2014.05.018.

Astorino, T. A., & Thum, J. S. (2018). Interval training elicits higher enjoyment versus moderate exercise in persons with spinal cord injury. *The Journal of Spinal Cord Medicine*, *41*(1), 77–84. https://doi.org/10.1080/10790268.2016.1235754.

Bauman, W. A., & Spungen, A. M. (2001). Carbohydrate and lipid metabolism in chronic spinal cord injury. *The Journal of Spinal Cord Medicine*, *24*(4), 266–277. https://doi.org/10.1080/10790268.2001.11753584.

Boudou, P., Sobngwi, E., Mauvais-Jarvis, F., Vexiau, P., & Gautier, J. F. (2003). Absence of exercise-induced variations in adiponectin levels despite decreased abdominal adiposity and improved insulin sensitivity in type 2 diabetic men. *European Journal of Endocrinology*, *149*(5), 421–424.

Brurok, B., Helgerud, J., Karlsen, T., Leivseth, G., & Hoff, J. (2011). Effect of aerobic high-intensity hybrid training on stroke volume and peak oxygen consumption in men with spinal cord injury. *American Journal of Physical Medicine & Rehabilitation*, *90*(5), 407–414. https://doi.org/10.1097/PHM.0b013e31820f960f.

Buchheit, M., & Laursen, P. B. (2013). High-intensity interval training, solutions to the programming puzzle: Part I: Cardiopulmonary emphasis. *Sports Medicine*, *43*(5), 313–338. https://doi.org/10.1007/s40279-013-0029-x.

Burgomaster, K. A., Howarth, K. R., Phillips, S. M., Rakobowchuk, M., Macdonald, M. J., McGee, S. L., et al. (2008). Similar metabolic adaptations during exercise after low volume sprint interval and traditional endurance training in humans. *The Journal of Physiology*, *586*(1), 151–160. doi: jphysiol.2007.142109 [pii] https://doi.org/10.1113/jphysiol.2007.142109.

Carroll, D. D., Courtney-Long, E. A., Stevens, A. C., Sloan, M. L., Lullo, C., Visser, S. N., et al. (2014). Vital signs: Disability and physical activity—United States, 2009-2012. *MMWR. Morbidity and Mortality Weekly Report*, *63*(18), 407–413.

Coulter, E. H., McLean, A. N., Hasler, J. P., Allan, D. B., McFadyen, A., & Paul, L. (2017). The effectiveness and satisfaction of web-based physiotherapy in people with spinal cord injury: A pilot randomised controlled trial. *Spinal Cord*, *55*(4), 383–389. https://doi.org/10.1038/sc.2016.125.

de Groot, P. C., Hjeltnes, N., Heijboer, A. C., Stal, W., & Birkeland, K. (2003). Effect of training intensity on physical capacity, lipid profile and insulin sensitivity in early rehabilitation of spinal cord injured individuals. *Spinal Cord*, *41*(12), 673–679. https://doi.org/10.1038/sj.sc.3101534.

Eastwood, E. A., Hagglund, K. J., Ragnarsson, K. T., Gordon, W. A., & Marino, R. J. (1999). Medical rehabilitation length of stay and outcomes for persons with traumatic spinal cord injury—1990–1997. *Archives of Physical Medicine and Rehabilitation*, *80*(11), 1457–1463. https://doi.org/10.1016/S0003-9993(99)90258-7.

Ehde, D. M., Jensen, M. P., Engel, J. M., Turner, J. A., Hoffman, A. J., & Cardenas, D. D. (2003). Chronic pain secondary to disability: A review. *The Clinical Journal of Pain*, *19*(1), 3–17.

Fernandes, B., Barbieri, F. A., Arthuso, F. Z., Silva, F. A., Moretto, G. F., Imaizumi, L. F. I., et al. (2020). High-intensity interval versus moderate-intensity continuous training in individuals with Parkinson's disease: Hemodynamic and functional adaptation. *Journal of Physical Activity & Health*, *17*(1), 85–91. https://doi.org/10.1123/jpah.2018-0588.

Fisher, G., Brown, A. W., Bohan Brown, M. M., Alcorn, A., Noles, C., Winwood, L., et al. (2015). High intensity interval- vs moderate intensity-training for improving cardiometabolic health in overweight or obese males: A randomized controlled trial. *PLoS One*, *10*(10), e0138853. https://doi.org/10.1371/journal.pone.0138853.

Forkan, R., Pumper, B., Smyth, N., Wirkkala, H., Ciol, M. A., & Shumway-Cook, A. (2006). Exercise adherence following physical therapy intervention in older adults with impaired balance. *Physical Therapy*, *86*(3), 401–410.

Galea, M. P. (2012). Spinal cord injury and physical activity: Preservation of the body. *Spinal Cord*, *50*(5), 344–351. https://doi.org/10.1038/sc.2011.149.

Gauthier, C., Brosseau, R., Hicks, A. L., & Gagnon, D. H. (2018). Feasibility, safety, and preliminary effectiveness of a home-based self-managed high-intensity interval training program offered to long-term manual wheelchair users. *Rehabilitation Research and Practice*, *2018*, 8209360. https://doi.org/10.1155/2018/8209360.

GBD 2016 Traumatic Brain Injury and Spinal Cord Injury Collaborators. (2016). Global, regional, and national burden of traumatic brain injury and spinal cord injury, 1990–2016: A systematic analysis for the Global Burden of Disease Study. *The Lancet Neurology*, *18*(1), 56–87.

Gibala, M. J., Gillen, J. B., & Percival, M. E. (2014). Physiological and health-related adaptations to low-volume interval training: Influences of nutrition and sex. *Sports Medicine*, *44*(Suppl. 2), S127–S137. https://doi.org/10.1007/s40279-014-0259-6.

Gillen, J. B., Martin, B. J., MacInnis, M. J., Skelly, L. E., Tarnopolsky, M. A., & Gibala, M. J. (2016). Twelve weeks of sprint interval training improves indices of cardiometabolic health similar to traditional endurance training despite a five-fold lower exercise volume and time commitment. *PLoS One*, *11*(4), e0154075. https://doi.org/10.1371/journal.pone.0154075.

Gillen, J. B., Percival, M. E., Ludzki, A., Tarnopolsky, M. A., & Gibala, M. J. (2013). Interval training in the fed or fasted state improves body composition and muscle oxidative capacity in overweight women. *Obesity (Silver Spring)*, *21*(11), 2249–2255. https://doi.org/10.1002/oby.20379.

Ginis, K. A., Latimer, A. E., Arbour-Nicitopoulos, K. P., Buchholz, A. C., Bray, S. R., Craven, B. C., et al. (2010). Leisure time physical activity in a population-based sample of people with spinal cord injury part I: Demographic and injury-related correlates. *Archives of Physical Medicine and Rehabilitation*, *91*(5), 722–728. https://doi.org/10.1016/j.apmr.2009.12.027.

Ginis, K. A. M., van der Scheer, J. W., Latimer-Cheung, A. E., Barrow, A., Bourne, C., Carruthers, P., et al. (2018). Evidence-based scientific exercise guidelines for adults with spinal cord injury: An update and a new guideline. *Spinal Cord*, *56*(4), 308–321.

Gorgey, A., & Gater, D. R. (2007). Prevalence of obesity after spinal cord injury. *Topics in Spinal Cord Injury Rehabilitation*, *12*, 1–7.

Graham, K., Yarar-Fisher, C., Li, J., McCully, K. M., Rimmer, J. H., Powell, D. C., et al. (2019). Effects of high-intensity interval training versus moderate-intensity training on cardiometabolic health markers in individuals with spinal cord injury: A pilot study. *Vol. 25* (pp. 248–259). Topics in Spinal Cord Injury Rehabilitation.

Harnish, C. R., Daniels, J. A., & Caruso, D. (2017). Training response to high-intensity interval training in a 42-year-old man with chronic spinal cord injury. *The Journal of Spinal Cord Medicine*, *40*(2), 246–249. https://doi.org/10.1080/10790268.2015.1136783.

Harvey, M., Weston, K. L., Gray, W. K., O'Callaghan, A., Oates, L. L., Davidson, R., et al. (2019). High-intensity interval training in people with Parkinson's disease: A randomized, controlled feasibility trial. *Clinical Rehabilitation*, *33*(3), 428–438. https://doi.org/10.1177/0269215518815221.

Hasnan, N., Engkasan, J. P., Husain, R., & Davis, G. M. (2013). High-intensity virtual-reality arm plus FES-leg interval training in individuals with spinal cord injury. *Biomedizinische Technik. Biomedical Engineering*. https://doi.org/10.1515/bmt-2013-4028.

Jain, N. B., Ayers, G. D., Peterson, E. N., Harris, M. B., Morse, L., O'Connor, K. C., et al. (2015). Traumatic spinal cord injury in the United States, 1993-2012. *JAMA*, *313*(22), 2236–2243. https://doi.org/10.1001/jama.2015.6250.

Kolt, G. S., & McEvoy, J. F. (2003). Adherence to rehabilitation in patients with low back pain. *Manual Therapy*, *8*(2), 110–116.

Lai, B., Kim, Y., Wilroy, J., Bickel, C. S., Rimmer, J. H., & Motl, R. W. (2018). Sustainability of exercise intervention outcomes among people with disabilities: A secondary review. *Disability and Rehabilitation*, 1–12. https://doi.org/10.1080/09638288.2018.1432704.

Lai, B., Kim, Y., Wilroy, J., Bickel, C. S., Rimmer, J. H., & Motl, R. W. (2019). Sustainability of exercise intervention outcomes among people with disabilities: A secondary review. *Disability and Rehabilitation*, *41*(13), 1584–1595. https://doi.org/10.1080/09638288.2018.1432704.

Lai, B., Rimmer, J., Barstow, B., Jovanov, E., & Bickel, C. S. (2016). Teleexercise for persons with spinal cord injury: A mixed-methods feasibility case series. *JMIR Rehabilitation and Assistive Technologies*, *3*(2), e8. https://doi.org/10.2196/rehab.5524.

Lai, B. W., Rimmer, J. H., Yates, A., Jeter, A., Young, H.-J., Thirumalai, M., et al. (2020). Critical factors influencing the decision to enroll in a physical activity intervention among a predominant group of adults with spinal cord injury: A grounded theory study. *Spinal Cord*. https://doi.org/10.1038/s41393-020-0530-7.

Lai, B. W., Rimmer, J. H., Yates, A., Jeter, A., Young, H. J., Thirumalai, M., et al. (2021). Critical factors influencing the decision to enroll in a physical activity intervention among a predominant group of adults with spinal cord injury: A grounded theory study. *Spinal Cord*, *59*(1), 17–25. https://doi.org/10.1038/s41393-020-0530-7.

Lai, B., Young, H. J., Bickel, C. S., Motl, R. W., & Rimmer, J. H. (2017). Current trends in exercise intervention research, technology, and behavioral change strategies for people with disabilities: A scoping review. *American Journal of Physical Medicine & Rehabilitation*, *96*(10), 748–761. https://doi.org/10.1097/phm.0000000000000743.

Latimer, A., Martin Ginis, K. A., Craven, B., & Hicks, A. (2006). The physical activity recall assessment for people with spinal cord injury: Validity. *Medicine and Science in Sports and Exercise*, *38*, 208–216.

Laughton, G., Buchholz, A. C., Martin Ginis, K. A., & Goy, R. E. (2009). Lowering body mass index cutoffs better identifies obese persons with spinal cord injury. *Spinal Cord*, *47*, 757–762.

Little, J. P., Gillen, J. B., Percival, M. E., Safdar, A., Tarnopolsky, M. A., Punthakee, Z., et al. (2011). Low-volume high-intensity interval training reduces hyperglycemia and increases muscle mitochondrial capacity in patients with type 2 diabetes. *Journal of Applied Physiology (Bethesda, MD: 1985)*, *111*(6), 1554–1560. https://doi.org/10.1152/japplphysiol.00921.2011.

Ma, J. K., & Martin Ginis, K. A. (2018). A meta-analysis of physical activity interventions in people with physical disabilities: Content, characteristics, and effects on behaviour. *Psychology of Sport and Exercise*, *37*, 262–273. https://doi.org/10.1016/j.psychsport.2018.01.006.

MacInnis, M. J., & Gibala, M. J. (2016). Physiological adaptations to interval training and the role of exercise intensity. *The Journal of Physiology*. https://doi.org/10.1113/JP273196.

Mahabaleshwarkar, R., & Khanna, R. (2014). National hospitalization burden associated with spinal cord injuries in the United States. *Spinal Cord*, *52*(2), 139–144. https://doi.org/10.1038/sc.2013.144.

Martin Ginis, K. A., & Hicks, A. L. (2005). Exercise research issues in the spinal cord injured population. *Exercise and Sport Sciences Reviews*, *33*(1), 49–53.

Martin Ginis, K. A., Ma, J. K., Latimer-Cheung, A. E., & Rimmer, J. H. (2016). A systematic review of review articles addressing factors related to physical activity participation among children and adults with physical disabilities. *Health Psychology Review*, *10*(4), 478–494. https://doi.org/10.1080/17437199.2016.1198240.

Martins, C., Kazakova, I., Ludviksen, M., Mehus, I., Wisloff, U., Kulseng, B., et al. (2015). High-intensity interval training and isocaloric moderate-intensity continuous training result in similar improvements in body composition and fitness in obese individuals. *International Journal of Sport Nutrition and Exercise Metabolism*. https://doi.org/10.1123/ijsnem.2015-0078.

McLean, S. M., Klaber Moffett, J. A., Sharp, D. M., & Gardiner, E. (2013). A randomised controlled trial comparing graded exercise treatment and usual physiotherapy for patients with non-specific neck pain (the GET UP neck pain trial). *Manual Therapy*, *18*(3), 199–205. https://doi.org/10.1016/j.math.2012.09.005.

Mcleod, J. C., Diana, H., & Hicks, A. L. (2020). Sprint interval training versus moderate-intensity continuous training during inpatient rehabilitation after spinal cord injury: A randomized trial. *Spinal Cord*, *58*(1), 106–115. https://doi.org/10.1038/s41393-019-0345-6.

National Spinal Cord Injury Statistical Center. (2019). *Spinal cord injury facts and figures at a glance*. National Spinal Cord Injury Statistical Center.

Rajan, S., McNeely, M. J., Warms, C., & Goldstein, B. (2008). Clinical assessment and management of obesity in individuals with spinal cord injury: A review. *The Journal of Spinal Cord Medicine*, *31*, 361–372.

Richards, J. C., Johnson, T. K., Kuzma, J. N., Lonac, M. C., Schweder, M. M., Voyles, W. F., et al. (2010). Short-term sprint interval training increases insulin sensitivity in healthy adults but does not affect the thermogenic response to beta-adrenergic stimulation. *The Journal of Physiology*, *588*(Pt. 15), 2961–2972. https://doi.org/10.1113/jphysiol.2010.189886.

Rimmer, J. H. (2012). Getting beyond the plateau: Bridging the gap between rehabilitation and community-based exercise. *Physical Medicine and Rehabilitation*, *4*, 857–861.

Rimmer, J. H., Schiller, W., & Chen, M. D. (2012). Effects of disability-associated low energy expenditure deconditioning syndrome. *Exercise and Sport Sciences Reviews*, *40*(1), 22–29. https://doi.org/10.1097/JES.0b013e31823b8b82.

Scelza, W. M., Kalpakjian, C. Z., Zemper, E. D., & Tate, D. G. (2005). Perceived barriers to exercise in people with spinal cord injury. *American Journal of Physical Medicine & Rehabilitation*, *84*(8), 576–583.

Skelton, F., Hoffman, J. M., Reyes, M., & Burns, S. P. (2015). Examining health-care utilization in the first year following spinal cord injury. *The Journal of Spinal Cord Medicine*, *38*(6), 690–695. https://doi.org/10.1179/2045772314y.0000000269.

Sveaas, S. H., Bilberg, A., Berg, I. J., Provan, S. A., Rollefstad, S., Semb, A. G., et al. (2020). High intensity exercise for 3 months reduces disease activity in axial spondyloarthritis (axSpA): A multicentre randomised trial of 100 patients. *British Journal of Sports Medicine*, *54*(5), 292–297. https://doi.org/10.1136/bjsports-2018-099943.

Sweet, S. N., Rocchi, M., Arbour-Nicitopoulos, K., Kairy, D., & Fillion, B. (2017). A telerehabilitation approach to enhance quality of life through exercise among adults with paraplegia: Study protocol. *JMIR Research Protocols*, *6*(10), e202. https://doi.org/10.2196/resprot.8047.

The 2018 Annual Statistical Report for The Spinal Cord Injury Model Systems. (2018).

Tian, W., Hsieh, C.-H., DeJong, G., Backus, D., Groah, S., & Ballard, P. H. (2013). Role of body weight in therapy participation and rehabilitation outcomes among individuals with traumatic spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *94*, S125–S136.

Tjønna, A. E., Lee, S. J., Rognmo, Ø., Stølen, T. O., Bye, A., Haram, P. M., et al. (2008). Aerobic interval training versus continuous moderate exercise as a treatment for the metabolic syndrome: A pilot study. *Circulation*, *118*(4), 346–354. https://doi.org/10.1161/CIRCULATIONAHA.108.772822.

Tordi, N., Dugue, B., Klupzinski, D., Rasseneur, L., Rouillon, J. D., & Lonsdorfer, J. (2001). Interval training program on a wheelchair ergometer for paraplegic subjects. *Spinal Cord*, *39*(10), 532–537. https://doi.org/10.1038/sj.sc.3101206.

Totosy de Zepetnek, J. O., Pelletier, C. A., Hicks, A. L., & MacDonald, M. J. (2015). Following the physical activity guidelines for adults with spinal cord injury for 16 weeks does not improve vascular health: A randomized controlled trial. *Archives of Physical Medicine and Rehabilitation*, *96*(9), 1566–1575. https://doi.org/10.1016/j.apmr.2015.05.019.

Trost, S. G., Owen, N., Bauman, A. E., Sallis, J. F., & Brown, W. (2002). Correlates of adults' participation in physical activity: Review and update. *Medicine and Science in Sports and Exercise*, *34*(12), 1996–2001. https://doi.org/10.1249/01.MSS.0000038974.76900.92.

Tschoepe, R., Benfield, A., Mercer, V., & Posey, R. (2019). Systematic review of community transition programs after acute rehabilitation for adults with traumatic spinal cord injury. *American Journal of Occupational Therapy*, *73*(4_Suppl._1). https://doi.org/10.5014/ajot.2019.73S1-RP102A. 7311510245p7311510241-7311510245p7311510241.

Tulloch, H., Sweet, S. N., Fortier, M., Capstick, G., Kenny, G. P., & Sigal, R. J. (2013). Exercise facilitators and barriers from adoption to maintenance in the diabetes aerobic and resistance exercise trial. *Canadian Journal of Diabetes*, *37*(6), 367–374. https://doi.org/10.1016/j.jcjd.2013.09.002.

Turner, J., Cardenas, D. D., Warms, C. A., & McClellan, C. B. (2001). Chronic pain associated with spinal cord injuries: A community survey. *Archives of Physical Medicine and Rehabilitation*, *82*, 501–508.

U.S. Department of Health and Human Services. (2018). *Physical activity guidelines for Americans* (2nd ed.). Washington, DC: U.S. Department of Health and Human Services.

van der Scheer, J. W., Martin Ginis, K. A., Ditor, D. S., Goosey-Tolfrey, V. L., Hicks, A. L., West, C. R., et al. (2017). Effects of exercise on fitness and health of adults with spinal cord injury: A systematic review. *Neurology*, *89*(7), 736–745. https://doi.org/10.1212/wnl.0000000000004224.

Warburton, D. E., McKenzie, D. C., Haykowsky, M. J., Taylor, A., Shoemaker, P., Ignaszewski, A. P., et al. (2005). Effectiveness of high-intensity interval training for the rehabilitation of patients with coronary artery disease. *The American Journal of Cardiology*, *95*(9), 1080–1084. https://doi.org/10.1016/j.amjcard.2004.12.063.

Whyte, L. J., Gill, J. M., & Cathcart, A. J. (2010). Effect of 2 weeks of sprint interval training on health-related outcomes in sedentary overweight/obese men. *Metabolism*, *59*(10), 1421–1428. https://doi.org/10.1016/j.metabol.2010.01.002.

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Chapter 31

Stem cells and chronic spinal cord injury: Overview

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Abbreviations

ALS	amyotrophic lateral sclerosis
BDNF	brain-derived neurotrophic factor
CNS	central nervous system
DNA	deoxyribonucleic acid
EMG	electromyography
ESC	embryonic stem cell
GABA	gaba-aminobutyric acid
iPSC	induced-pluripotent stem cell
ISNCSCI	International standards for neurological classification of spinal cord injury
MSC	mesenchymal stem cell
ROS	reactive oxygen species
SCI	spinal cord injury

Introduction

Spinal cord injury (SCI) is a devastating condition that is associated with a poor prognosis and long-lasting disability. Globally, SCI has an incidence of 8 to 246 per million and a prevalence of 236 to 1298 per million (Furlan et al., 2013). The lifetime cost for healthcare and living expenses that are attributable to SCI ranges from $1 to $4 million (*The Journal of Spinal Cord Medicine*, 2014). The destruction and demyelination of neurons that occurs in SCI leads acutely to quadriplegia, paraplegia, quadriparesis, and paraparesis, depending on the degree and location of injury. Furthermore, damage to neurons, glia, and vasculature also triggers a downstream sequence of events mediated primarily by inflammatory cells and cytokines. These events can lead to spreading of injury to adjacent segments. SCI can also lead to chronic complications, including bladder and bowel dysfunction, sexual dysfunction, neurogenic pain, and muscle spasticity. The current available treatments for SCI are limited to those that aim to ameliorate these chronic symptoms and complications (Gwak et al., 2016; Koulousakis & Kuchta, 2007). There are currently no therapies available that produce neurological improvement for SCI patients. Thus, the development of therapies seeking to restore sensory and motor function has been an active area of investigation. One approach, stem cell transplantation, aims to replace the cells and signaling factors that are lost in SCI. In the following chapter, we will discuss stem cells, with a particular emphasis on their potential role as a therapy in SCI.

Pathophysiology of SCI

The pathophysiology underlying SCI is thought to begin with an initial insult followed by a secondary injury cascade that is characterized by three overlapping phases: acute, sub-acute, and chronic phases (Table 1). The acute phase refers to the period immediately following mechanical insult that leads to compression or transection of the spinal cord. This initial event damages neurons and glial cells, disrupts membrane integrity and electrical conductance, and destroys local vasculature. These processes disturb the blood–spinal cord barrier, leading to ionic imbalance and excitotoxicity (Alizadeh, Dyck, & Karimi-Abdolrezaee, 2019). The sub-acute phase encompasses the inflammatory cascade and resultant cell death by apoptosis, ischemic necrosis, ferroptosis, and demyelination through Wallerian degeneration (Ahuja et al., 2017).

Diagnosis and Treatment of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822498-4.00031-2

TABLE 1 Summary of events in the pathophysiology of spinal cord injury.

Stage	Key events	Consequences
Acute	Mechanical compression or transection of spinal cord	–Neuronal and glial injury –Disruption of membrane integrity –Destruction of local vasculature –Excitotoxicity
Sub-acute	Triggering of inflammatory and immune responses	–Necrosis –Apoptosis –Demyelination
Chronic	Remodeling and healing	–Glial scar –Cystic cavity

Of note, the key events and consequences can overlap between stages to some degree. However, the above framework is useful for the conceptualization of the cascade of events that follow the initial insult to the spinal cord.

The chronic phase is defined by remodeling and healing which usually produces a glial scar and cystic cavity at the lesion focus (Alizadeh et al., 2019; Pineau & Lacroix, 2007).

This influx of immune cells (such as macrophages, microglia, and neutrophils) is critical for clearing of debris and healing of the initial trauma, but they can also induce further inflammation by cytokine release and spreading of injury to adjacent segments (Kubota et al., 2012; Kumar et al., 2018). In addition to perpetuating further inflammation, immune cells also generate reactive oxygen species (ROS) that can cause oxidative damage to lipids, proteins, and DNA (Su et al., 2019). These oxidative reactions can incite further necrosis and apoptosis (Dizdaroglu et al., 2002; Hausmann, 2003). After the inflammatory process abates, a glial scar is formed from astrocytes. This glial scar serves as a physical and chemical barrier that impedes axonal regeneration and neurite growth (Ahuja, Martin, & Fehlings, 2016).

Ultimately, these processes result in the loss of three components that are critical for sub-serving sensory and motor networks of the spinal cord: neurons, myelin, and neurotrophic factors. Thus, if stem cells could be directed to differentiate into neurons, oligodendrocytes that promote myelination, or neurotrophic factor-producing cells, meaningful functional and clinical recovery may be possible.

Stem cells: A brief overview

Stem cells are characterized by their capability to undergo both differentiation and self-renewal (Tajbakhsh, Rocheteau, & Le Roux, 2009). Classification of stem cells can be based on their potential differentiation into distinct cell types. Totipotent stem cells can become any cell type in the developing embryo, as well as extra-embryonic cells like the placenta. Pluripotent stem cells have a more restricted differentiation potential and are only able to make cells of the developing embryo. In other words, pluripotent cells can become any cell in the adult body. Multi-potent cells are further restricted and are only able to mature into cell types within a particular germ layer (e.g., any cell type derived from embryonic ectoderm).

Embryonic stem cells—An overview of pre-clinical findings

During development, embryonic cells can differentiate into a multitude of different cell types that compose the different organs and organ systems of an adult animal. Thus, embryonic stem cells (ESCs) were among the first reservoirs of pluripotent stem cells to be tapped for use in SCI cell-based therapy research (Table 2).

Animal-derived ESCs

The use of rodent ESCs in animal models of SCI has produced encouraging results at the molecular and functional level. Transplanted ESCs can survive and differentiate into neurons, oligodendrocytes, and astrocytes (Lin et al., 2017; Pajer et al., 2019). Furthermore, these transplanted cells can also form new synaptic connections (Deshpande et al., 2006; Lin et al., 2017). It has been shown that introduction of rodent ESCs with biomaterial scaffolding, may improve survival of transplanted cells, greater retention of cells at the locale of injury, and facilitation of formation of new circuitry (Kourgiantaki et al., 2020; Wang et al., 2018). In addition to scaffolding, survival and maintenance of stem cells may also

TABLE 2 Summary of different stem cell types that have been investigated in pre-clinical studies or human clinical trials.

Stem Cell Type	Source	Pros	Cons
Embryonic stem cells	–Pre-implantation blastocyst	–Very broad potency	–Ethical concerns including destruction of embryo –Potential teratoma formation –Allogeneic transplantation –Potential immune reaction
Mesenchymal stem cells	–Bone Marrow –Umbilical Cord –Adipose Tissue	–Large supply of cells –Potential for autologous transplantation	–Limited potency compared to embryonic stem cells –Potential teratoma formation –Potential immune reaction
Induced pluripotent stem cells	–Adult somatic (e.g., skin or blood)	–Large supply of cells –Potential for autologous transplantation	–Requires genetic manipulation –Potential teratoma formation –Potential immune reaction

be promoted with co-transplantation with factors, such as brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (Lu et al., 2014a; Robinson & Lu, 2017). Functionally, ESC transplanted cells have been demonstrated to improve locomotion in SCI models (Ramadan et al., 2018; Zhang et al., 2015). Lastly, there is also mounting data from SCI rodent model studies suggesting that transplanted ESCs may be able to reduce some of the long-term complications such as chronic pain and cardiovascular dysfunction (Hou et al., 2020; Jergova et al., 2016).

Human-derived ESCs

The advent of molecular protocols capable of directing human ESCs, taken from human blastocysts, to neuronal or glial fates facilitated SCI transplantation studies (Lukovic et al., 2012). Demyelination is one of the hallmarks of SCI and, thus, several investigators have pursued transplanting oligodendrocyte progenitor cells to remyelinate descending spinal cord axons. In one study, Keirstead and colleagues transplanted human ESC derived-oligodendrocyte progenitors into the spinal cord of adult rats that were either 7 days or 10 months after thoracic contusion SCI (Keirstead et al., 2005). Among rats that received the transplant 7 days after injury, the investigators observed differentiation of progenitors into mature oligodendrocytes, remyelination of axons, and improved motor functioning. Differentiation into oligodendrocytes was also seen in rats that were transplanted 10 months after injury. However, these rats failed to demonstrate signs of remyelination or locomotor improvement. These data indicate that the value of transplanting stem cells in SCI patients may depend somewhat on the time since injury. In another study, transplanted human ESCs were shown to further express neurotrophic factors such as BDNF and transforming growth factor-B2 (Zhang, Denham, & Thies, 2006). These factors are, among other things, important for axonal regeneration and neurite growth and could further contribute to the utility of human ESCs as a therapeutic agent.

ESC limitations

Taken together, there is evidence suggesting that transplanted ESCs can survive, mature, reintegrate into existing networks, and promote at least modest motor restoration in vivo. ESC studies, however, have also been accompanied by several limitations. For example, in studying ESCs, they must be collected from the inner cell mass of the blastocyst. This procedure ultimately leads to the demise of the blastocyst (Vazin & Freed, 2010) and has raised ethical concerns (Volarevic et al., 2018). Furthermore, ESC transplantation depends critically on the ability of the stem cell to differentiate specifically into a particular target cell type. When this fails to occur, one of the consequences is the generation of a teratoma, a tumor made up of somatic cells of diverse types (Nussbaum et al., 2007). The final limitation, as is the case for all forms of allogeneic transplantation, is that there always remains a definite concern for inciting an immunologic response against the transplanted cells (Swijnenburg et al., 2008).

Thus, despite the encouraging findings from ESC studies that established stem cells as a promising potential SCI therapy, ESC approaches have suffered from several drawbacks that make clinical translation difficult. For these reasons, alternative sources of stem cells have been investigated.

Toward autologous transplantation: Mesenchymal stem cells

Among these alternative sources are mesenchymal stem cells (MSC), named for their ability to mature into mesoderm derived tissues, such as bone and cartilage (Table 2). MSCs possess their own benefits and challenges distinct from ESCs. Because they can be derived from adult tissues, MSCs are not shrouded in the same ethical controversies as ESCs. MSCs, like other forms of stem cells, can be transplanted intravenously as they are attracted by inflammatory factors to the site of injury. Lastly, because transplantation can be autologous, MSC interventions would be less likely to elicit a significant immune response. With regards to drawbacks, one of the most critical is the limited potency relative to ESCs. Nevertheless, animal studies suggest that they can differentiate into cell types that have sufficient specificity to integrate into the spinal cord and induce functional gains.

Bone marrow–derived MSCs

Adult bone marrow harbors MSCs whose usual physiological role is replacing the cellular components of blood. The migratory ability of bone marrow–derived MSCs was demonstrated when murine bone marrow MSCs were injected into the lateral ventricles of neonatal mice and were found to migrate throughout different regions of the brain, such as the hippocampus, cerebellum, and brain stem (Kopen, Prockop, & Phinney, 1999). This was followed by a study in which bone marrow MSCs were retrieved from the lower extremities of rats and centrally injected into rats up to 7 days after thoracic contusion SCI (Hofstetter et al., 2002). Implanted cells differentiated toward astrocytes near the site of injury and, furthermore, gait improvements were found. Notably, more favorable effects were observed when transplantation of MSCs occurred a week after, rather than immediately after injury. Finally, in a step toward assessing the utility of human adult bone marrow MSCs, another study evaluated the effect of intravenous injection of human bone marrow MSC in SCI rat models 7 days after compression injury. The authors demonstrated with immunohistochemical analysis that the intravenously introduced bone marrow MSCs migrated to the site of injury. More specifically, the MSCs integrated within the ventrolateral white matter tracts. With respect to their role within their new home, MSCs were found to differentiate into oligodendrocytes, and increased axonal growth was observed in areas adjacent to injury. Functionally, locomotor improvement was seen at weeks 3 and 4 (Cízková et al., 2006).

Adipose tissue–derived MSCs

Adipose tissue represents another tissue source with readily available MSCs. Adipose MSCs are unique in that their effect in spinal cord recovery may be mediated by changes in vasculature. One study implanted masses of adipose MSCs from humans into a rat SCI model and found that transplanted cells released angiogenic factors that ultimately led to vascular remodeling (Oh et al., 2012). This was confirmed with another study that intravenously injected adipose MSCs from dorsal fat pads into thoracic contusion SCI model rats 8 days after injury and demonstrated angiogenesis, as well as motor recovery (Ohta et al., 2017). Another interesting feature of adipose tissue is that MSCs isolated from cryopreserved adipose tissue have been shown to exhibit similar biochemical characteristics as adipose MSCs from fresh tissue (Ohta et al., 2018). The implication here is that large stores of adipose can be collected for a tissue bank that can potentially serve as a stem cell reservoir.

Umbilical cord-derived MSCs

Lastly, MSCs derived from umbilical cord blood may also hold therapeutic potential for SCI. The utility of umbilical cell therapy for CNS injury was first introduced in the context of stroke (Chen et al., 2001) and traumatic brain injury (Lu et al., 2002). Given the promising results in these two contexts, their utility in SCI began to be investigated shortly thereafter. Umbilical MSCs have now been shown to promote improved motor function in thoracic compression and contusion SCI rat models (Saporta et al., 2003). Moreover, the specificity of the umbilical cord MSC's targeting of injured cord, if introduced intravenously, has also been well demonstrated. In the study by Saporta and colleagues, umbilical MSCs were only found in the spinal cord of SCI rats at the level of injury. The introduced cells were absent from non-injured areas of the spinal cord and, moreover, were not found in the spinal cord of non-injured rats. Importantly, similar in spirit to what has been shown for bone marrow, injection of umbilical MSCs 5 days after injury yielded superior results over injection 1 day after injury (Saporta et al., 2003). It is posited that the presence of inflammatory cytokines in the hours immediately after traumatic injury restricts the engraftment of transplanted stem cells into native tissue.

Numerous animal model and basic science studies have illustrated the potential utility of MSCs. From a bench-to-bedside translation standpoint, MSCs offer significant advantages such as mobility that allows for intravenous introduction, autologous transplantation, and relatively large available stores. Although there remains some interest in MSCs for SCI therapy, a few years after the first MSC–SCI studies were reported, advances in molecular techniques ushered in an arguably more promising source for stem cells.

Cellular reprogramming: Induced pluripotent stem cells

One of the great feats of molecular biology was the discovery of factors that could be applied to adult somatic cells and cause them to dedifferentiate (Takahashi & Yamanaka, 2006). After application of these factors (e.g., SOX2), somatic cells are transformed into pluripotent cells. These cells, termed induced-pluripotent stem cells (iPSCs), evaded two major limitations that had hindered the progress of the development of ESC therapies. First, production of induced-pluripotent stem cells does not necessitate the destruction of a blastocyst, overcoming some of the ethical concerns tied to ESC. Second, because iPSCs can be derived from the adult tissue of an SCI patient, the subsequent transplant would be autologous and would pose lower risk for an immune-mediated transplant reaction. At the outset, iPSCs looked to be a prime candidate for SCI transplant therapy (Table 2). Results from animal model studies have garnered even further advancement.

One of the first steps in attempting to design iPSC-based transplant therapies was the development of protocols that promote iPSC differentiation specifically into neurons, glia, or their precursors. Several studies have now demonstrated this capability with both murine and human iPSCs (Lu et al., 2014b; Tsuji et al., 2010). In addition to showing that neural and glial precursors could be produced from iPSC, there are mounting data that these cells can be integrated into motor networks after transplantation. In one study, murine iPSCs were transplanted into thoracic contusion SCI mice and differentiated into neurons, astrocytes, and oligodendrocytes. The transplanted cells also promoted axonal growth and remyelination, resulting in improvement of motor function (Tsuji et al., 2010). Studies of human iPSCs have likewise produced promising results. In these studies, human iPSCs derived primarily from adult fibroblasts (Lu et al., 2014b) were transformed into neurospheres or neural stem cells and transplanted into animal models of SCI. The transplanted cells were shown to survive in the recipient animal, differentiate into neurons and glia, grow elongated axons, form synapses with the host cells, produce neurotrophic factors, and engage in remyelination. In summary, human iPSCs transplanted into animal models of SCI can replace neurons, myelination, and neurotrophic factors that are lost to injury, adding to the litany of evidence that advocates for the translation of stem cell therapies to human SCI patients.

As discussed above, the use of iPSCs avoids the ethical challenges of ESCs, but iPSCs are not devoid of limitations. As is the case for ESCs, teratoma formation is also a concern in iPSCs (Gutierrez-Aranda et al., 2010). In fact, in one of the studies discussed above, by Tsuji and colleagues, the investigators categorized their iPSC-derived precursors as either safe or unsafe, prior to engraftment (Tsuji et al., 2010). In contrast to the overall positive results observed in mice that received the safe cells, teratoma formation was found in mice that received the unsafe cells. Teratoma formation would serve as a major hurdle to translating iPSCs to clinical use. Thus, alternative protocols for producing iPSC suitable for clinical use that are less likely to produce teratomas are under investigation (Deng et al., 2018). Finally, although the transplant of iPSCs can potentially be autologous rather than allogeneic, they still carry a risk for transplant reaction (Zhao et al., 2011).

Translation to the bedside

Development of a more accurate model

Since most animal SCI studies conducted to date have been limited to the setting of acute SCI, there is a paucity of evidence indicating whether stem cell transplantation can be successful in chronic SCI patients. Furthermore, most studies have utilized rodent models, where the pathophysiology and long-term functional deficits do not necessarily recapitulate what is found in humans. For example, even after severe injury, rodents are capable of some level of spontaneous recovery (Fischer & Peduzzi, 2007). These points raise the question of how well findings from such models will translate to human patients with chronic SCI and have motivated the development of animal models that more faithfully reflect the cellular and functional changes found in human patients. In one study, investigators developed a chronic SCI model with Gottingen-Minnesota minipigs (Navarro et al., 2012). Using a compression approach, investigators were able to produce stable long-term neurological deficits as well as histopathological changes like those seen in humans. This model has been recently used in a study where iPSC-derived NPCs were grafted 2.5 months after compression. Grafts were found to be capable of surviving in both autologous and syngeneic settings, and capable of differentiating into neurons several months after transplantation (Strnadel et al., 2018). Further studies like these in large animals that more accurately model human SCI will be critical for identifying the cell-based therapies that have the most potential for success in human trials.

Human studies and clinical trials

A few clinical trials examining stem cell transplantation in human SCI patients have been completed, with many others ongoing or planned (Table 3). Many of the completed trials have been early stage and were conducted with small sample sizes, and important lessons are to be gleaned. One early report described case studies on eight SCI patients that received bone marrow–derived stem cells (Geffner et al., 2008). The investigators employed multiple routes of administration: spinal cord, spinal canal, and intravenous injections. The procedure was overall safe and well tolerated. At follow-up, patients reported improved quality of life, based on the Barthel Index previously devised for use in patients in the context of stroke. In another study, Mendonca and colleagues conducted a phase I, non-randomized, uncontrolled clinical trial with 14 subjects that had complete thoracic or lumbar level SCI (Mendonça et al., 2014). The study participants received bone marrow–derived stem cell transplants and were evaluated for sensory and motor changes 6 months after the procedure.

TABLE 3 Examples of human clinical trials for chronic spinal cord injury.

NCT number	Trial title	Phase(s)	Injury inclusion criteria	Stem cell type studied	Primary outcomes	Location(s)
NCT02352077	NeuroRegen scaffold with stem cells for chronic spinal cord injury repair	Phase 1	Complete spinal cord injury at C5-T12	Bone marrow mononuclear cells or mesenchymal stem cells	Number of patients with adverse effects after transplantation	–Beijing, China –Suzhou, China –Affiliated Hospital of Logistics University of CAPF, Tianjin, China
NCT02152657	Evaluation of autologous mesenchymal stem cell transplantation in chronic spinal cord injury: a pilot study	Phase 1	Spinal cord injury below T8	Mesenchymal stem cells	MRI and clinical evaluation for complications	–Salvador, Bahia, Brazil
NCT01772810	Safety study of human spinal cord-derived neural stem cell transplantation for the treatment of chronic SCI	Phase 1	Spinal cord injury in T2-T12 or C5-C7	Human spinal cord derived neural stem cells	Adverse events and lab abnormalities	–San Diego, California, United States
NCT01325103	Autologous bone marrow stem cell transplantation in patients with spinal cord injury	Phase 1	Traumatic spinal cord injury at thoracic or lumbar level	Bone marrow mesenchymal cells	Safety and feasibility of procedure	–Salvador, Bahia, Brazil
NCT02688049	NeuroRegen Scaffold combined with stem cells for chronic spinal cord injury repair	Phase 1 and Phase 2	Complete spinal cord injury at C5-T12	Mesenchymal (Phase 1) and neural (Phase 2) stem cells	Improvements in ASIA, SSEP, and MEP	–Tianjin, China

TABLE 3 Examples of human clinical trials for chronic spinal cord injury—cont'd

NCT number	Trial title	Phase(s)	Injury inclusion criteria	Stem cell type studied	Primary outcomes	Location(s)
NCT00816803	Cell transplant in spinal cord injury patients	Phase 1 and Phase 2	Traumatic spinal cord injury	Bone marrow mesenchymal cells	Changes in motor, sensory, and impairment scores on ASIA scale; acupuncture score	—Cairo, Egypt
NCT01186679	Safety and efficacy of autologous bone marrow stem cells in treating spinal cord injury	Phase 1 and Phase 2	Spinal cord injury in C4-T12	Bone marrow mesenchymal cells	Number of patient with adverse effects; Changes in ASIA impairment scale	—Bangalore, Karnataka, India
NCT03505034	Intrathecal transplantation of UC-MSC in patients with late stage of chronic spinal cord injury	Phase 2	Traumatic spinal cord injury	Umbilical cord mesenchymal stem cells	Changes in motor and sensory scores on ASIA scale	—Guangzhou, Guangdong, China
NCT03521323	Intrathecal transplantation of UC-MSC in patients with early stage of chronic spinal cord injury	Phase 2	Traumatic spinal cord injury	Umbilical cord mesenchymal stem cells	Changes in motor and sensory scores on ASIA scale	—Guangzhou, Guangdong, China
NCT01393977	Difference between rehabilitation therapy and stem cells transplantation in patients with spinal cord injury in China	Phase 2	Traumatic spinal cord injury	Umbilical cord mesenchymal stem cells	Electromyography and brain stem auditory evoked potential	—Beijing, China
NCT02163876	Study of human central nervous system (CNS) stem cell transplantation in cervical spinal cord Injury	Phase 2	Traumatic spinal cord injury in C5-C7	Human spinal cord derived neural stem cells	Changes in ISNCSCI motor score	—Various throughout US and Canada
NCT01676441	Safety and efficacy of autologous mesenchymal stem cells in chronic spinal cord injury	Phase 2 and Phase 3	Cervical spinal cord injury	Mesenchymal stem cells	Changes in motor score on ASIA scale	—Seoul, Korea, Republic of

Continued

TABLE 3 Examples of human clinical trials for chronic spinal cord injury—cont'd

NCT number	Trial title	Phase(s)	Injury inclusion criteria	Stem cell type studied	Primary outcomes	Location(s)
NCT01873547	Different efficacy between rehabilitation therapy and stem cells transplantation in patients with SCI in China	Phase 3	Traumatic spinal cord injury	Umbilical cord mesenchymal stem cells	Changes in ISNCSCI/ASIA scores	—Beijing, China
NCT04213131	Efficacy and safety of hUC-MSCs and hUCB-MSCs in the treatment of chronic spinal cord injury	Not applicable	Traumatic spinal cord injury	Umbilical cord mesenchymal stem cells	Changes in motor, sensory, and impairment scores on ASIA scale; acupuncture score	—Dalian, Liaoning, China

Clinical trials were identified from https://www.clinicaltrials.gov/. Information for human clinical trials discussed in the chapter text, but not captured by our search were also included in the table if they are registered on https://www.clinicaltrials.gov/. Abbreviations: *ASIA*: American Spinal Cord Injury Association; *ISNCSCSI*: International Standards for Neurological Classification of Spinal Cord Injury; *MEP*: motor evoked potentials; *MRI*: magnetic resonance imaging; *NCT*: National Clinical Trial; *SSEP*: somatosensory evoked potentials; *UC-MSC*: umbilical cord mesenchymal stem cell.

Apart from one post-operative complication (cerebrospinal fluid leak), no patients experienced adverse events, deeming the transplantation safe. Additionally, several of the study patients demonstrated modest improvements in sensory, motor, and urologic function.

A pair of recent clinical trials made use of human central nervous system derived stem cells rather than autologous bone marrow cells. Curtis and colleagues recruited four patients with thoracic SCI for a phase 1 clinical trial of NSI-566, a neural stem cell line derived from human spinal cord (Curtis et al., 2018). The transplant procedure was well-tolerated by the study participants and, moreover, no serious adverse events were observed during the follow-up period of 18 to 27 months. Two of the four patients demonstrated motor and sensory improvements as measured by ISNCSCI scores. In one additional patient, although ISNCSCI was unchanged during follow-up, new muscle activity was detected via EMG. In another study, Levi and colleagues conducted a phase II trial of HuCNS-SC, a fetal brain-derived human CNS stem cell line, in SCI patients with cervical injury (Levi et al., 2019). The study was completed in two separate steps. First, six patients were transplanted with varying cell doses to define an optimal dose. In the second step, this derived optimal dose was applied to a treatment group of six new patients that was compared to a control group. Again, the procedure was found to be safe and feasible. Hints at motor recovery were shown in an interim analysis.

Although only a few SCI clinical trials of stem cell transplantation have been conducted, the studies carried out to date have documented safety, tolerability, and feasibility. The studies are low-powered and most did not involve a control group. Nevertheless, glimpses of motor, sensory, and urinary improvements were reported across trials that used different stem cell types for engraftment and recruited patients with varying segmental levels and time-delays since injury. These studies suggest that larger, more rigorous clinical trials with long-term follow-up are needed to determine the utility of stem cell transplantation.

The role of immunity

It is now evident that cells of the immune system become key players in the CNS in the period after SCI. Damage to the spinal cord triggers a cascade of events that recruit several immune and other intrinsic CNS cells to the site of injury. Some macrophage subtypes, for example, communicate with astrocytes to induce reactive astrogliosis (Haan et al., 2015). Macrophages that migrate to the site of injury also can produce nitric oxide that may cause damaged neurons to undergo apoptosis (Satake et al., 2000). Although the activity of immune cells is thought to limit the damage to the spinal cord, the immune response can produce unfavorable consequences and cause detrimental effects on non-damaged cells, such as nitric

TABLE 4 Areas of neuroscience in which stem cells are being investigated for therapy.

Neurological disorder	Pathophysiology	Clinical phenotype
Spinal cord injury	Mechanical, inflammatory, and ischemic insult to neurons, glia, and local vasculature	–Paraplegia, quadriplegia, paraparesis, quadriparesis –Autonomic dysfunction
Parkinson's disease	Degeneration of dopaminergic neurons in substantia nigra pars compacta	–Resting tremor –Rigidity –Bradykinesia
Huntington's disease	Loss of medium spiny neurons in the striatum	–Chorea –Loss of saccadic eye movements –Neuropsychiatric symptoms
Amyotrophic lateral sclerosis	Loss of motor neurons in the spinal cord and brain stem	–Progressive motor dysfunction

As can be appreciated from the pathophysiology column, all four disorders are characterized by loss of one or more types of cells. Stem cell therapy aims to replace or generate these lost components.

oxide induced apoptosis of healthy cells. Further, myeloperoxidase expressed by neutrophils may exacerbate injury by the generation or upregulation of hypochlorous acid, inflammatory cytokines, and apoptotic-genes (Kubota et al., 2012).

The role of the immune system has always been of interest to stem cell transplant therapeutics due to well-known issues such as allograft rejection. However, with these more contemporary observations that suggest that after SCI, there is a pro-inflammatory and pro-immune milieu that makes conditions potentially sub-optimal for stem cell growth and development, the role of immunity has become of even greater salience. The use of classic immuno-suppressive drugs, such as tacrolimus and cyclosporine, as adjuvants with stem cell transplantation have been evaluated in pre-clinical studies (Nutt et al., 2013). In select human clinical trials of stem cell transplantation, immunosuppressive regimens have also been employed (Curtis et al., 2018; Levi et al., 2019).

Applications to other areas of neuroscience

Beyond SCI, stem cells have also been explored to regenerate cells in other neurological disorders (Table 4). In the context of Parkinson's disease, which is characterized by loss of cells in the substantia nigra pars compacta, dopaminergic neurons derived from human embryonic stem cells have been transplanted into rat and mouse models of Parkinson's disease, leading to engraftment and improved motor function (Ganat et al., 2012). Clinically, there have been several reports describing outcomes for Parkinson's disease patients that underwent transplantation of stem cell-derived dopaminergic cells (Kefalopoulou et al., 2014; Schweitzer et al., 2020). These small studies have described clinical improvement in the short-term (2 years) (Schweitzer et al., 2020) and long-term (greater than a decade) (Kefalopoulou et al., 2014), but the utility of stem cells in Parkinson's disease remains uncertain without replication of these findings in controlled trials. In Huntington's disease, the underlying pathophysiology involves degeneration of GABA neurons in the basal ganglia. It has been shown in the pre-clinical setting that GABA neurons derived from ESCs can be transplanted into a mouse model of Huntington's and that transplanted cells can form dopaminergic and glutamatergic synapses, leading to motor improvement (Ma et al., 2012). In the clinical setting, however, investigations involving transplantation into human patients have had less success. Multiple studies have reported that long-term survival of grafts is limited, potentially because grafts may begin to assume a degenerative Huntington phenotype after transplant (Barker et al., 2013). Lastly, in amyotrophic lateral sclerosis (ALS), stem cells have also been used to attempt to rescue motor function or delay the widespread degeneration of motor neurons. Neural stem cells, for example, derived from human spinal cords have been used in rat models of familial ALS to delay disease progression and improve survival (Xu et al., 2006). In human patients, early-stage clinical trials involving transplantation of cells from various sources, including neural stem cells and mesenchymal stem cells, have been completed (Mazzini et al., 2015). Studies have consistently demonstrated safety and feasibility. While some transient motor improvements have been described, larger controlled trials are necessary to further assess therapeutic potential in the context of ALS.

Conclusion

The pathophysiology that underlies SCI can be curtly characterized as loss of neurons, loss of myelination, and loss of neural growth factors. Given stem cells' ability to mature into cells that can restore these lost components, they are an ideal candidate for therapy. The SCI animal model literature is rife with evidence suggesting that transplanted stem cells can survive and integrate into recipient neural networks to promote recovery. Translation of this approach to human patients represents an open frontier that should be further explored, given the encouraging results from early efforts. It is hoped that this foray yields an effective SCI therapy for patients that desperately need one.

Mini-dictionary of terms

Allogeneic: Cell, tissue, or organ that is of different genetic makeup from a particular recipient.
Angiogenesis: Generation of new blood vessels.
Apoptosis: Genetically programmed cell death.
Astrocyte: Nervous system cell responsible for maintenance of blood–brain barrier and scarring.
Autologous: Cell, tissue, or organ that is from the same recipient.
Blastocyst: Multi-cell structure that forms in the first week after fertilization.
Cytokine: Signaling molecule that allows cell to cell communication.
Excitotoxicity: Pathological overactivation of neurons.
Microglia: Cells in the nervous system that scavenge for debris.
Myelin: Sheaths that surround axons to promote action potential propagation.
Necrosis: Process of cellular death that leads to inflammation.
Neutrophil: Immune system cell responsible for defending against infection.
Neurotrophic factor: Proteins that support growth and reproduction of nervous system cells.
Oligodendrocyte: Nervous system cell responsible for generation of myelin.

Key facts for stem cells

- Stem cells can self-renew and differentiate into neurons and glia.
- Stem cell reservoirs include embryonic cells, bone marrow, adipose tissue, and umbilical cells.
- Stem cells transplanted into animal models of spinal cord injury can survive and differentiate into neurons and glia.
- Early clinical trials of stem cell transplantation have demonstrated safety and feasibility.

Key facts for spinal cord injury

- Spinal cord injury is a devastating neurological condition with limited therapeutic options.
- Spinal cord injury is characterized clinically by paraplegia, quadriplegia, paraparesis, quadriparesis, and autonomic dysfunction.
- The pathophysiology of spinal cord injury includes acute, sub-acute, and chronic stages.
- The immune system plays a critical role in the pathophysiology of spinal cord injury.

Summary points

- Transplanted ESCs can survive, mature, reintegrate into existing networks, and promote at least modest motor restoration in vivo, but there is a concern for inciting an allogeneic immunologic response against the transplanted cells.
- Despite the encouraging findings from ESC studies that established stem cells as a promising potential SCI therapy, ESC approaches have suffered from several drawbacks that make clinical translation difficult. For these reasons, alternative sources of stem cells have been investigated.
- MSCs offer significant advantages such as mobility that allows for intravenous introduction, autologous transplantation, and relatively large available stores.
- Induced-pluripotent stem cells are an attractive candidate for SCI since they do not necessitate the destruction of a blastocyst, and transplant could be autologous posing lower risk for an immune-mediated transplant reaction.
- Only a few SCI clinical trials of stem cell transplantation have been conducted, but have documented safety, tolerability, and feasibility.

- Immunomodulation can ameliorate the unfavorable consequences and cause detrimental effects on non-damaged cells after SCI, such as nitric oxide induced apoptosis of healthy cells.
- In addition to spinal cord injury, the therapeutic utility of stem cells is being explored in other neurological disorders, such as Parkinson's disease and amyotrophic lateral sclerosis.

Acknowledgements

None.

Funding

This work was unfunded.

Disclosure statement

The authors report no conflict of interest.

References

Ahuja, C. S., Martin, A. R., & Fehlings, M. (2016). Recent advances in managing a spinal cord injury secondary to trauma. *F1000Research*, *5*.

Ahuja, C. S., et al. (2017). Traumatic spinal cord injury. *Nature Reviews. Disease Primers*, *3*, 17018.

Alizadeh, A., Dyck, S. M., & Karimi-Abdolrezaee, S. (2019). Traumatic spinal cord injury: An overview of pathophysiology, models and acute injury mechanisms. *Front. Neurol.*, *10*, 282.

Barker, R. A., et al. (2013). The long-term safety and efficacy of bilateral transplantation of human fetal striatal tissue in patients with mild to moderate Huntington's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, *84*(6), 657–665.

Chen, J., et al. (2001). Intravenous administration of human umbilical cord blood reduces behavioral deficits after stroke in rats. *Stroke*, *32*(11), 2682–2688.

Cízková, D., et al. (2006). Transplants of human mesenchymal stem cells improve functional recovery after spinal cord injury in the rat. *Cellular and Molecular Neurobiology*, *26*(7-8), 1167–1180.

Curtis, E., et al. (2018). A first-in-human, phase i study of neural stem cell transplantation for chronic spinal cord injury. *Cell Stem Cell*, *22*(6), 941–950.e6.

Deng, J., et al. (2018). Cell transplantation for spinal cord injury: Tumorigenicity of induced pluripotent stem cell-derived neural stem/progenitor cells. *Stem Cells International*, *2018*, 5653787.

Deshpande, D. M., et al. (2006). Recovery from paralysis in adult rats using embryonic stem cells. *Annals of Neurology*, *60*(1), 32–44.

Dizdaroglu, M., et al. (2002). Free radical-induced damage to DNA: Mechanisms and measurement. *Free Radical Biology & Medicine*, *32*(11), 1102–1115.

Fischer, F. R., & Peduzzi, J. D. (2007). Functional recovery in rats with chronic spinal cord injuries after exposure to an enriched environment. *The Journal of Spinal Cord Medicine*, *30*(2), 147–155.

Furlan, J. C., et al. (2013). Global incidence and prevalence of traumatic spinal cord injury. *The Canadian Journal of Neurological Sciences*, *40*(4), 456–464.

Ganat, Y. M., et al. (2012). Identification of embryonic stem cell-derived midbrain dopaminergic neurons for engraftment. *The Journal of Clinical Investigation*, *122*(8), 2928–2939.

Geffner, L. F., et al. (2008). Administration of autologous bone marrow stem cells into spinal cord injury patients via multiple routes is safe and improves their quality of life: Comprehensive case studies. *Cell Transplantation*, *17*(12), 1277–1293.

Gutierrez-Aranda, I., et al. (2010). Human induced pluripotent stem cells develop teratoma more efficiently and faster than human embryonic stem cells regardless the site of injection. *Stem Cells*, *28*(9), 1568–1570.

Gwak, Y. S., et al. (2016). Combined approaches for the relief of spinal cord injury-induced neuropathic pain. *Complementary Therapies in Medicine*, *25*, 27–33.

Haan, N., et al. (2015). Crosstalk between macrophages and astrocytes affects proliferation, reactive phenotype and inflammatory response, suggesting a role during reactive gliosis following spinal cord injury. *Journal of Neuroinflammation*, *12*, 109.

Hausmann, O. N. (2003). Post-traumatic inflammation following spinal cord injury. *Spinal Cord*, *41*(7), 369–378.

Hofstetter, C. P., et al. (2002). Marrow stromal cells form guiding strands in the injured spinal cord and promote recovery. *Proceedings of the National Academy of Sciences of the United States of America*, *99*(4), 2199–2204.

Hou, S., et al. (2020). Grafting embryonic raphe neurons reestablishes serotonergic regulation of sympathetic activity to improve cardiovascular function after spinal cord injury. *The Journal of Neuroscience*, *40*(6), 1248–1264.

Jergova, S., et al. (2016). Recombinant neural progenitor transplants in the spinal dorsal horn alleviate chronic central neuropathic pain. *Pain*, *157*(4), 977–989.

Kefalopoulou, Z., et al. (2014). Long-term clinical outcome of fetal cell transplantation for Parkinson disease: Two case reports. *JAMA Neurology*, *71*(1), 83–87.

Keirstead, H. S., et al. (2005). Human embryonic stem cell-derived oligodendrocyte progenitor cell transplants remyelinate and restore locomotion after spinal cord injury. *The Journal of Neuroscience*, *25*(19), 4694–4705.

Kopen, G. C., Prockop, D. J., & Phinney, D. G. (1999). Marrow stromal cells migrate throughout forebrain and cerebellum, and they differentiate into astrocytes after injection into neonatal mouse brains. *Proceedings of the National Academy of Sciences of the United States of America*, *96*(19), 10711–10716.

Koulousakis, A., & Kuchta, J. (2007). Intrathecal antispastic drug application with implantable pumps: Results of a 10 year follow-up study. *Acta Neurochirurgica. Supplement*, *97*(Pt. 1), 181–184.

Kourgiantaki, A., et al. (2020). Neural stem cell delivery via porous collagen scaffolds promotes neuronal differentiation and locomotion recovery in spinal cord injury. *npj Regenerative Medicine*, *5*, 12.

Kubota, K., et al. (2012). Myeloperoxidase exacerbates secondary injury by generating highly reactive oxygen species and mediating neutrophil recruitment in experimental spinal cord injury. *Spine*, *37*(16), 1363–1369.

Kumar, H., et al. (2018). Neutrophil elastase inhibition effectively rescued angiopoietin-1 decrease and inhibits glial scar after spinal cord injury. *Acta Neuropathologica Communications*, *6*(1), 73.

Levi, A. D., et al. (2019). Clinical outcomes from a multi-center study of human neural stem cell transplantation in chronic cervical spinal cord injury. *Journal of Neurotrauma*, *36*(6), 891–902.

Lin, C.-C., et al. (2017). The therapeutic effectiveness of delayed fetal spinal cord tissue transplantation on respiratory function following mid-cervical spinal cord injury. *Neurotherapeutics*, *14*(3), 792–809.

Lu, D., et al. (2002). Intravenous administration of human umbilical cord blood reduces neurological deficit in the rat after traumatic brain injury. *Cell Transplantation*, *11*(3), 275–281.

Lu, P., et al. (2014a). Promotion of survival and differentiation of neural stem cells with fibrin and growth factor cocktails after severe spinal cord injury. *Journal of Visualized Experiments*, *89*, e50641.

Lu, P., et al. (2014b). Long-distance axonal growth from human induced pluripotent stem cells after spinal cord injury. *Neuron*, *83*(4), 789–796.

Lukovic, D., et al. (2012). Concise review: Human pluripotent stem cells in the treatment of spinal cord injury. *Stem Cells*, *30*(9), 1787–1792.

Ma, L., et al. (2012). Human embryonic stem cell-derived GABA neurons correct locomotion deficits in quinolinic acid-lesioned mice. *Cell Stem Cell*, *10*(4), 455–464.

Mazzini, L., et al. (2015). Human neural stem cell transplantation in ALS: Initial results from a phase I trial. *Journal of Translational Medicine*, *13*, 17.

Mendonça, M. V. P., et al. (2014). Safety and neurological assessments after autologous transplantation of bone marrow mesenchymal stem cells in subjects with chronic spinal cord injury. *Stem Cell Research & Therapy*, *5*(6), 126.

Navarro, R., et al. (2012). Chronic spinal compression model in minipigs: A systematic behavioral, qualitative, and quantitative neuropathological study. *Journal of Neurotrauma*, *29*(3), 499–513.

Nussbaum, J., et al. (2007). Transplantation of undifferentiated murine embryonic stem cells in the heart: Teratoma formation and immune response. *The FASEB Journal*, *21*(7), 1345–1357.

Nutt, S. E., et al. (2013). Caudalized human iPSC-derived neural progenitor cells produce neurons and glia but fail to restore function in an early chronic spinal cord injury model. *Experimental Neurology*, *248*, 491–503.

Oh, J. S., et al. (2012). Transplantation of an adipose stem cell cluster in a spinal cord injury. *Neuroreport*, *23*(5), 277–282.

Ohta, Y., et al. (2017). Intravenous infusion of adipose-derived stem/stromal cells improves functional recovery of rats with spinal cord injury. *Cytotherapy*, *19*(7), 839–848.

Ohta, Y., et al. (2018). Isolation of adipose-derived stem/stromal cells from cryopreserved fat tissue and transplantation into rats with spinal cord injury. *International Journal of Molecular Sciences*, *19*(7).

Pajer, K., et al. (2019). Neuroectodermal stem cells grafted into the injured spinal cord induce both axonal regeneration and morphological restoration via multiple mechanisms. *Journal of Neurotrauma*, *36*(21), 2977–2990.

Pineau, I., & Lacroix, S. (2007). Proinflammatory cytokine synthesis in the injured mouse spinal cord: Multiphasic expression pattern and identification of the cell types involved. *The Journal of Comparative Neurology*, *500*(2), 267–285.

Ramadan, W. S., et al. (2018). Neuroectodermal stem cells: A remyelinating potential in acute compressed spinal cord injury in rat model. *Journal of Biosciences*, *43*(5), 897–909.

Robinson, J., & Lu, P. (2017). Optimization of trophic support for neural stem cell grafts in sites of spinal cord injury. *Experimental Neurology*, *291*, 87–97.

Saporta, S., et al. (2003). Human umbilical cord blood stem cells infusion in spinal cord injury: Engraftment and beneficial influence on behavior. *Journal of Hematotherapy & Stem Cell Research*, *12*(3), 271–278.

Satake, K., et al. (2000). Nitric oxide via macrophage iNOS induces apoptosis following traumatic spinal cord injury. *Brain Research. Molecular Brain Research*, *85*(1–2), 114–122.

Schweitzer, J. S., et al. (2020). Personalized iPSC-derived dopamine progenitor cells for Parkinson's disease. *The New England Journal of Medicine*, *382*(20), 1926–1932.

Strnadel, J., et al. (2018). Survival of syngeneic and allogeneic iPSC-derived neural precursors after spinal grafting in minipigs. *Science Translational Medicine*, *10*(440).

Su, L.-J., et al. (2019). Reactive oxygen species-induced lipid peroxidation in apoptosis, autophagy, and ferroptosis. *Oxidative Medicine and Cellular Longevity*, *2019*, 5080843.

Swijnenburg, R.-J., et al. (2008). Immunosuppressive therapy mitigates immunological rejection of human embryonic stem cell xenografts. *Proceedings of the National Academy of Sciences of the United States of America*, *105*(35), 12991–12996.

Tajbakhsh, S., Rocheteau, P., & Le Roux, I. (2009). Asymmetric cell divisions and asymmetric cell fates. *Annual Review of Cell and Developmental Biology*, *25*, 671–699.

Takahashi, K., & Yamanaka, S. (2006). Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell*, *126*(4), 663–676.

(2014). Spinal cord injury facts and figures at a glance. *The Journal of Spinal Cord Medicine*, *37*(1), 117–118.

Tsuji, O., et al. (2010). Therapeutic potential of appropriately evaluated safe-induced pluripotent stem cells for spinal cord injury. *Proceedings of the National Academy of Sciences of the United States of America*, *107*(28), 12704–12709.

Vazin, T., & Freed, W. J. (2010). Human embryonic stem cells: Derivation, culture, and differentiation: a review. *Restorative Neurology and Neuroscience*, *28*(4), 589–603.

Volarevic, V., et al. (2018). Ethical and safety issues of stem cell-based therapy. *International Journal of Medical Sciences*, *15*(1), 36–45.

Wang, C., et al. (2018). Injectable nanoreinforced shape-memory hydrogel system for regenerating spinal cord tissue from traumatic injury. *ACS Applied Materials & Interfaces*, *10*(35), 29299–29307.

Xu, L., et al. (2006). Human neural stem cell grafts ameliorate motor neuron disease in SOD-1 transgenic rats. *Transplantation*, *82*(7), 865–875.

Zhang, Y. W., Denham, J., & Thies, R. S. (2006). Oligodendrocyte progenitor cells derived from human embryonic stem cells express neurotrophic factors. *Stem Cells and Development*, *15*(6), 943–952.

Zhang, K., et al. (2015). Polarized macrophages have distinct roles in the differentiation and migration of embryonic spinal-cord-derived neural stem cells after grafting to injured sites of spinal cord. *Molecular Therapy*, *23*(6), 1077–1091.

Zhao, T., et al. (2011). Immunogenicity of induced pluripotent stem cells. *Nature*, *474*(7350), 212–215.

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Chapter 32

Viral vector gene therapy approaches for regeneration and repair in spinal cord injury

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List of abbreviations

SCI	spinal cord injury
CNS	central nervous system
AdV	adenovirus
HSV	herpes simplex virus
LV	lentivirus
AAV	adeno-associated virus
IM	intramuscular
IN	intraneural
IV	intravenous
IT	intrathecal
NGF	nerve growth factor
BDNF	brain-derived neurotrophic factor
NT	neurotrophin
BBB	blood-brain barrier
CSPG	chondroitin sulfate proteoglycan
ChABC	chondroitinase ABC
ADAMTS4	a disintegrin and metalloproteinase with thrombospondin motifs 4

Introduction

Traumatic spinal cord injury (SCI) results from a physical insult to the spinal cord. This leads to disruption of the blood supply and loss of tissue near the site of impact. Following this, there is ongoing detrimental change to the tissue, including inflammation, formation of an inhibitory scar, and inhibition of axonal regeneration and remyelination (Fig. 1). A number of approaches have been tested in pre-clinical models including increasing the intrinsic regenerative ability of neurons or removing the inhibitory molecules present after injury. Approaches include the delivery of neurotrophic factors (Keefe, Sheikh, & Smith, 2017), strategies to block inhibitory receptor signaling (Lang et al., 2015) or using enzymes to degrade inhibitory molecules (Bradbury et al., 2002). However, conventional methods of delivery of such factors have limitations, such as poor stability in vivo, poor tissue penetration, and the potential for off-target effects (Bo, Wu, Yeh, & Zhang, 2011). Viral vector gene therapy can be applied to a number of these approaches to help address these issues. This chapter describes different viral vectors that have been used to target the spinal cord, different delivery methods, and examples of how viral gene therapy has been used to effectively target therapeutic agents to the spinal cord.

Viral vector approaches

Viral vectors allow for long-term, stable, and targeted gene expression. A number of viral vectors have been trialed as a gene therapy approach to SCI repair. Each of these approaches has advantages and shortcomings (Fig. 2).

Diagnosis and Treatment of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822498-4.00032-4

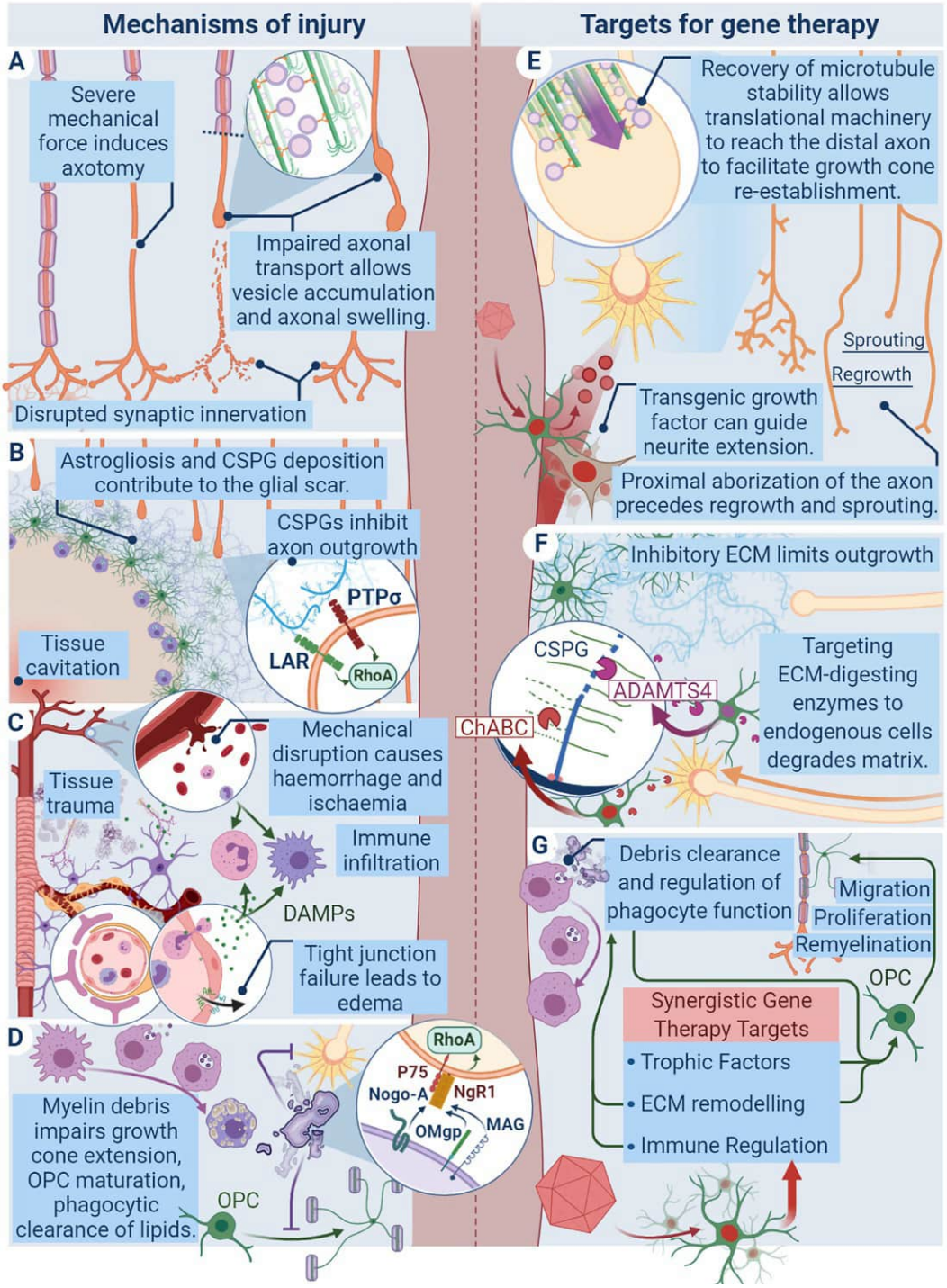

FIG. 1 Overview of traumatic spinal cord injury mechanisms and potential targets for gene-based therapies. **Mechanism**: (A) Mechanical trauma impairs axonal function leading to synaptic dysfunction. (B) ECM deposition by reactive astrocytes at the lesion border and tissue cavitation significantly impairs axonal regrowth through the injury site. (C) Vascular hemorrhage and leakage disrupts nervous tissue homeostasis whilst a large infiltrating immune cell population responds aggressively to inflammatory signals resulting from tissue trauma. (D) Myelin debris resulting from oligodendrocyte death inhibits remyelination and axon regrowth. Overwhelming of lipid metabolism within phagocytes leads to prolonged inflammatory activation. **Treatment targets**: (E) Growth cone reformation is achieved by the re-establishment of anterograde axonal transport. Neurite extension can be stimulated by the presence of transgenic growth factor cues. (F) The digestion of extracellular matrix (ECM) molecules such as chondroitin sulfate proteoglycans (CSPGs) reduces the inhibition of axonal regrowth exerted by the astroglial scar. (G) The mechanisms of many gene therapy approaches have beneficial effects upon multiple injury processes. For example, stimulation of remyelination using current treatment approaches likely results from the direct effects of transgene products upon endogenous oligodendrocyte precursors (OPCs), i.e., neurotropic factors or removal of CSPGs. However, removal of CSPGs can also regulate phagocytic phenotype and function, which in turn promotes myelin repair. Further work should take consideration the interactions of these factors and how combinational viral gene therapy could be used to optimize this beneficial synergy. *(Created with BioRender.com.)*

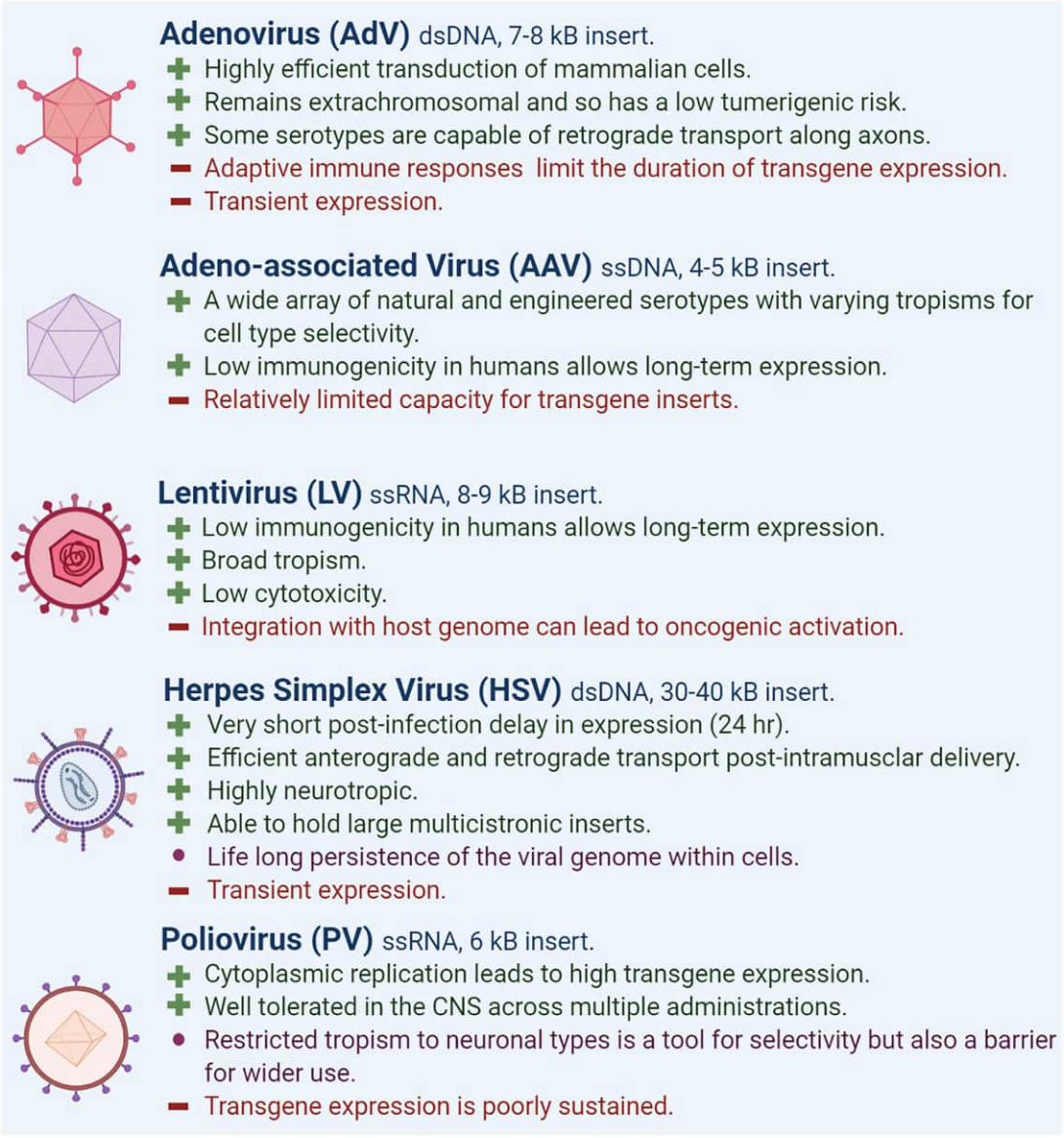

FIG. 2 Overview of viral vector systems commonly used in the treatment and study of spinal cord injury. A number of viral vectors can be used for gene delivery to the spinal cord, each of which has advantages (+) and disadvantages (−). *(Created with BioRender.com.)*

Adenovirus

Adenoviruses (AdVs) are encapsulated double-stranded DNA viruses with a 36 kb genome and therefore have the capability of holding large transgenes. They can transduce both dividing and non-dividing cells and exhibit high transduction efficiency in a wide variety of cell types. The genome remains extra chromosomal in the nucleus, thereby the transgene is not integrated into the host cell's genome, avoiding risk of tumorigenesis. However, transgene expression is only transient and expression is lost during division as the non-integrated genome is received by only one daughter cell. Also, an immune response is elicited against AdV viral antigens leading to inflammation and limiting the period of transgene expression (Byrnes, MacLaren, & Charlton, 1996).

Poliovirus

Polioviruses are small, non-enveloped RNA viruses and recombinant poliovirus replicons can be used for gene therapy (Khromykh, 2000). As infection is restricted to motor neurons in the hind brain and spinal cord these have been suggested as a potential vector for use in the spinal cord (Jackson, Cobbs, Peduzzi, Novak, & Morrow, 2001). Advantages of poliovirus include that its RNA genome is replicated in the cytoplasm, leading to very high levels of gene expression (Khromykh, 2000). Multiple inoculations of poliovirus replicons in the spinal cord has been shown to be safe, give good levels of gene expression with no functional deficits or inflammatory response. However, studies show that gene expression is not sustained (Jackson et al., 2001), although this could be of benefit if transient gene expression is required.

Herpes simplex virus

Herpes simplex virus (HSV) is an enveloped virus that contains a large (150 kb) double-stranded genome, allowing for an almost unlimited packaging capacity for transgenes. They demonstrate an exceptional capability to provide long-lived infections, with the genome being maintained extra-chromosomally in the nucleus of host cells (Glorioso & Fink, 2004). Advantages of HSV are it is neurotrophic and has a tendency to remain latent while permanently transducing target cells. The large size of the vector allows for expression of multiple genes which has been suggested as advantageous in development of effective treatments (Uchida et al., 2014). However, following transduction a number of viral proteins are expressed, leading to cytotoxicity and immune responses against targeted cells (Poulsen, Harrop, & During, 2002).

Lentivirus

Lentiviral vectors (LV) are a sub-class of retroviruses derived from human immunodeficiency viruses. Due to their ability to transduce dividing and non-dividing cells, LV vectors can transduce post-mitotic neurons, making them a powerful tool for targeting the CNS (Naldini et al., 1996) and as such have been used extensively for gene therapy targeting of the spinal cord (Uchida et al., 2014). Because LV genomes are integrated into the host genome they can provide long-term stable gene expression. While integration poses a risk of oncogenic transformation it has been suggested that this is reduced by the virus integrating into gene ends rather than promoter regions (Baum, Kustikova, Modlich, Li, & Fehse, 2006).

Adeno-associated virus

One of the most well-characterized vectors for gene therapy is derived from adeno-associated virus (AAV). Wild type AAVs are small, 4.7 kb, linear, single-stranded DNA (ssDNA) viruses in the Parvovirus family. For therapeutic use, the *rep* and *cap* genes, involved in viral replication and capsid production, respectively, are removed and replaced by an expression cassette containing therapeutic transgenes under the control of a promoter and flanked by the AAV ITRs, required for directing genome replication and packaging, forming what is termed a recombinant AAV (rAAV) (During, Young, Baer, Lawlor, & Klugmann, 2003). AAVs are considered ideal for gene therapy approaches as they are small and non-replicative, can transduce dividing and non-dividing cells, are non-pathogenic to humans and can provide long-lasting changes in gene expression. A disadvantage of AAV vectors is their small genome, impacting on the size of transgenes that can be used. A large number of clinical trials using AAV have demonstrated the relative safety of AAV gene therapy (Penaud-Budloo, François, Clément, & Ayuso, 2018).

Routes of administration

A number of different routes of administration are available for gene therapy delivery to the spinal cord (Fig. 3) and are classified as either remote or direct delivery (Hardcastle, Boulis, & Federici, 2018). Remote delivery involves non-invasive or minimally invasive routes of administration such as intramuscular (IM), intraneural (IN), intravenous (IV), and intrathecal (IT). These are dependent on the capability of specific gene therapy serotypes to travel to the spinal cord following peripheral delivery. Direct delivery involves an invasive surgical approach that directly targets a specific area of the spinal cord tissue via injection of the gene therapy and is referred to as intraparenchymal delivery.

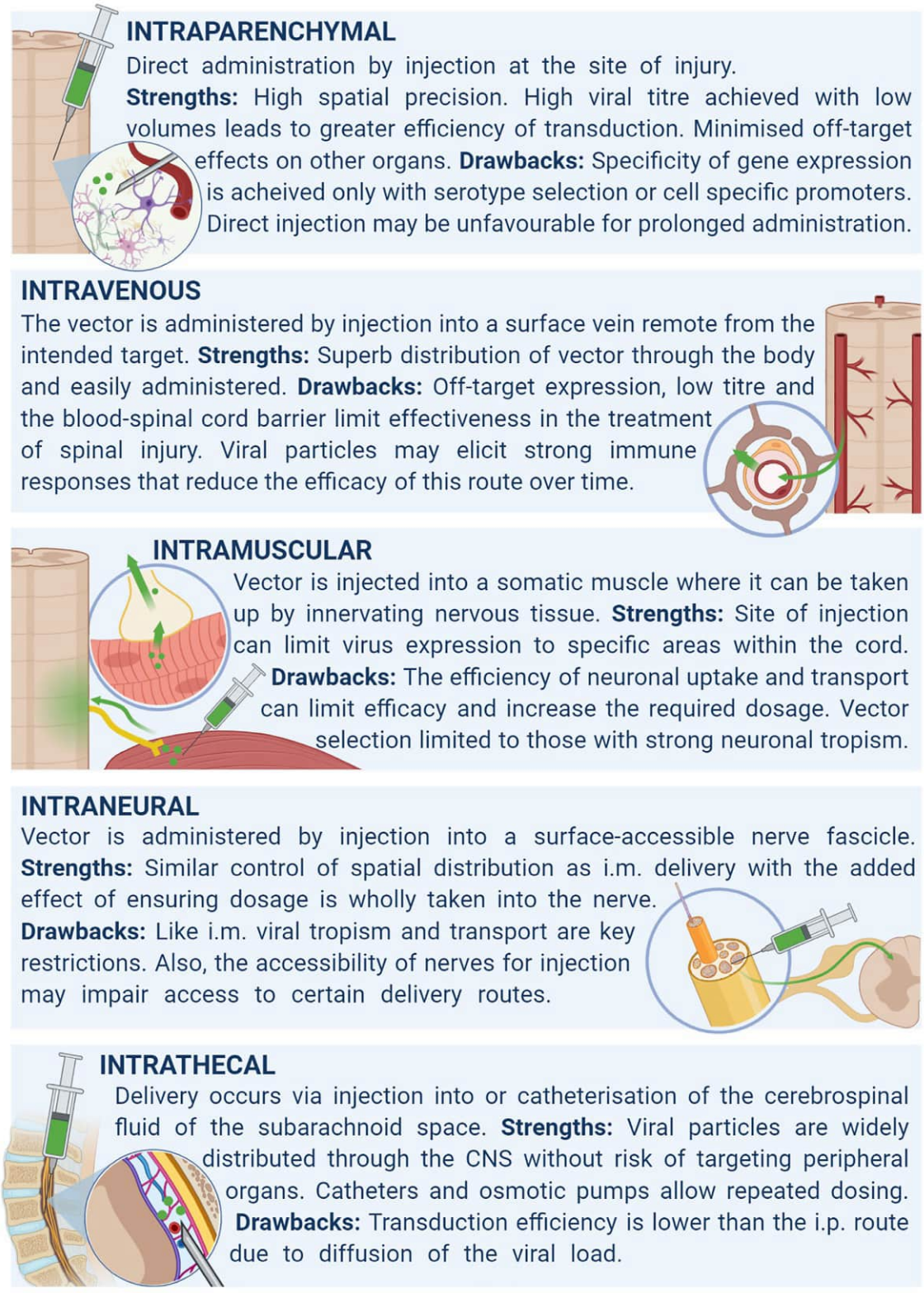

FIG. 3 Overview of common and potential gene therapy delivery routes for the treatment of spinal cord injury. Viral vectors can be delivered to spinal cord via a number of routes allowing for ease of delivery or targeted delivery depending on the desired approach. *(Created with BioRender.com.)*

Intramuscular and intraneural delivery

Retrograde transport is the transport of viral vector particles to neuronal cell bodies via axonal transport following IM or IN (e.g., sciatic nerve) injection. A number of viral gene therapies can be transported to the spinal cord from peripheral injection sites such as skin, muscle, or peripheral nerves (Franz, Weidner, & Blesch, 2012). Following injection of an HSV gene therapy into the gastrocnemius muscle of the rat, gene expression in neurons of the anterior horn spreads widely through the spinal cord and has been shown to be maintained for up to 182 days post-injection (Keir, Mitchell, Feldman, & Martin, 1995; Yamamura et al., 2000). Adenovirus has been used successfully in a number of studies to target the spinal cord via IM injection and delivery of neuroprotective compounds has been achieved (Nakajima et al., 2007; Nakajima et al., 2010). A number of AAV vector serotypes have been demonstrated to transduce neurons of the spinal cord following both IM and IN injection [reviewed in (Hardcastle et al., 2018) (Boulis et al., 2003; Towne, Schneider, Kieran, Redmond Jr., & Aebischer, 2010)]. However, retrograde transport of AAV vectors can have low efficiency. To overcome this, targeted evolution can be used to improve transport (Sun & Schaffer, 2018; Tervo et al., 2016). When Tet1, a peptide with high affinity for the tetanus toxin GT1b receptor that undergoes retrograde transport in the spinal cord, was grafted onto AAV1, enhanced axonal terminal binding and uptake was seen, with this vector showing a four-fold enhancement in retrograde transport in DRG explants (Davis et al., 2015). While IM injection is relatively easy and non-invasive, this largely restricts transduction to motor neurons or other populations in the anterior horn and so is not able to provide a more diffuse treatment. Also, the large amount of vector that would be required to transduce larger human muscles and the relatively long axons compared to rodents has been raised as challenges to this approach for vector delivery.

Intravenous delivery

A number of AAV vectors, especially AAV9 and similar serotypes have been found capable of crossing the blood-brain barrier and shown promise for delivering therapeutic agents to the whole spinal cord (Duque et al., 2009). However, systemic delivery using AAV leads to transduction of peripheral organs and there can be reduced levels of transduction due to the presence of antibodies against the virus. Questions also remain as to whether results seen in animal models will translate to humans. A vector, AAV-PHP, was found to have better transduction of the CNS after IV injection than its parent AAV9 but its ability to cross the BBB has been found to be species and even mouse strain dependent due to lack of its receptor (Ly6A) (Batista et al., 2020). No known analogue for this receptor is found in humans and such species differences may impact on the usefulness of such novel BBB-crossing AAV capsids. Also, while whole spinal cord transduction may be useful for developmental disorders, targeted transduction is likely to be of more use to treat SCI.

Intrathecal delivery

This approach allows for widespread transduction, while avoiding off-target effects (Federici et al., 2012). The vector is delivered into CSF, via the sub-arachnoid space, allowing perfusion into the spinal cord tissue. Gene therapy vectors including AAV (Zhang & Yang, 2020), adenovirus (Mannes, Caudle, O'Connell, & Iadarola, 1998), lentivirus (Thomas, Palma, & Shea, 2015), herpesvirus (Kitamura et al., 2007) and poliovirus (Jackson et al., 2001) have all been used successfully to target the injured spinal cord and delivery therapeutic agents. While intrathecal injections result in greater spatial distribution, the trade-off is a comparatively lower level of expression compared to delivery into the tissue (Mannes et al., 1998).

Intraparenchymal delivery

Intraparenchymal injection of viral vectors into the spinal cord of animal models has been widely explored and used successfully by a number of groups (Blits & Bunge, 2006). This allows for focal targeting of a vector but bio-distribution can be increased by multi-level injections to the cord. Intraparenchymal injection allows for much lower volumes of virus to be used compared to remote delivery techniques. However, a major barrier toward clinical translation is the validation of a safe surgical approach for delivery to the spinal cord in large animal models and humans. Pre-clinical studies have shown the safety of delivering AAV to the cervical spinal cord of pigs (Federici, Riley, Park, Bain, & Boulis, 2009), so this does appear to be a feasible approach.

Viral vector approaches for therapeutic delivery

Neurotrophins

Following SCI, axons fail to regenerate, at least in part due to low intrinsic regenerative capacity. This has led to a large field of study testing the use of neurotrophic factors, including nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and the neurotrophin family (NT-3, NT-4/5), to create a growth permissive environment after an injury (Keefe et al., 2017). However, delivery of neurotrophic factors to the spinal cord has major limitations. Their short half-life and issues with crossing the BBB makes it difficult to deliver biologically relevant amounts to the spinal cord for prolonged periods of time. Also, widespread delivery of neurotrophins can lead to adverse effects (Blesch, Fischer, & Tuszynski, 2012). Viral vector delivery has been used to target neurotrophins to specific neuronal and axonal populations, either directly to the cord for expression from endogenous cells or via viral transduction of cells that are then transplanted into the cord. This has been used successfully to promote axonal regeneration and is extensively reviewed elsewhere (Blesch et al., 2012; Blits & Bunge, 2006; Bo et al., 2011; Franz et al., 2012; Uchida et al., 2014).

While axonal regrowth can be promoted by the presence of neurotrophic factors, growth beyond the spinal cord lesion site is often limited due to continual presence of growth factors and the absence of a gradient of these factors across the injury site (Franz et al., 2012). The use of gene therapy approaches has helped overcome some of these issues through allowing for spatial and temporal regulation of neurotrophin delivery. Viral gene transfer has been used successfully to establish neurotrophin gradients. Viral delivery of NT3 leads to growth of axons through a spinal cord lesion (Alto et al., 2009; Bradbury, Khemani, King, Priestley, & McMahon, 1999) and a gradient established by lentiviral BDNF delivery promoted axonal sprouting toward the highest concentration of BDNF (Bonner, Blesch, Neuhuber, & Fischer, 2010). A study by (Blesch & Tuszynski, 2007) using a tetracycline-regulatable retroviral system to control BDNF expression in transplanted fibroblasts, showed that only transient expression was required to induce axonal growth into the injury site. Viral vectors allow for the targeting of specific cell populations. Targeted evolution of AAV vectors has been successful in promoting specific cell tropism (Deverman, Ravina, Bankiewicz, Paul, & Sah, 2018). As different neurotrophins stimulate different neuronal and axonal populations, the use of engineered AAV viral vectors in conjunction with cell specific promoters would allow for specific targeting of the correct cell type and would help prevent adverse effects caused by widespread neurotrophin delivery.

CSPG

Another major hurdle preventing axon regeneration and repair after SCI is the release of growth inhibitory molecules; myelin-associated growth inhibitors, chemo-repulsive guidance molecules, and highly sulfated proteoglycans, especially chondroitin sulfate proteoglycans (CSPGs) (Bradbury & McMahon, 2006; He & Koprivica, 2004; Park, Liu, Hu, Kanter, & He, 2010). Following CNS injury, CSPGs are rapidly upregulated at the lesion site by reactive astrocytes within the glial scar (Ohtake & Li, 2015) and form a chemical barrier for axon regeneration via interaction of the sugar GAG side chains with a number of receptor proteins (reviewed in (Sharma, Selzer, & Li, 2012).

Degradation of CSPGs to overcome this inhibition is being trialed as a therapeutic intervention for SCI. Chondroitinase ABC (ChABC) is a bacterial enzyme that degrades the GAG side-chains of CSPGs. In vivo delivery of this enzyme leads to beneficial effects in a number of experimental SCI models (Bradbury & Carter, 2011) although results have been mixed, depending on the type of injury (Bartus et al., 2014). This is thought to be at least in part due to issues with enzyme stability (Bartus et al., 2014). Therefore, gene therapy approaches where cells are transduced with a ChABC viral vector have been tested as a promising tool for achieving stable delivery of the enzyme. Early attempts using gene therapy had limited success in digesting CSPGs (Cafferty, Yang, Duffy, Li, & Strittmatter, 2007; Curinga et al., 2007; Jin, Ketschek, Jiang, Smith, & Fischer, 2011). However, modification of ChABC through mutagenesis of key *N*-glycosylation sites allowed the expression and efficient secretion of active ChABC enzyme by mammalian cells (Muir et al., 2010) and a number of studies have successfully shown that lentiviral delivery of mammalianized ChABC leads to improvement in both cervical and thoracic models of SCI, reduced lesion size, improved sensorimotor function (sensory axon conduction, hindlimb function, forelimb reaching, and grasping), increased axonal conduction, and increased serotonergic and vGlut1innervation (Bartus et al., 2014; Burnside et al., 2018; Didangelos, Iberl, Vinsland, Bartus, & Bradbury, 2014; James et al., 2015; Zhao et al., 2011). While to date gene therapy approaches to deliver ChABC have not been trialed in non-rodent species, promising results in large animal models following delivery of ChABC enzyme to the injured cord have been seen. Injection of ChABC into the primate spinal cord following a C7 transection led to improved hand function (Rosenzweig et al., 2019) and a recent clinical trial using ChABC injection in canines with chronic, naturally occurring spinal cord injuries showed

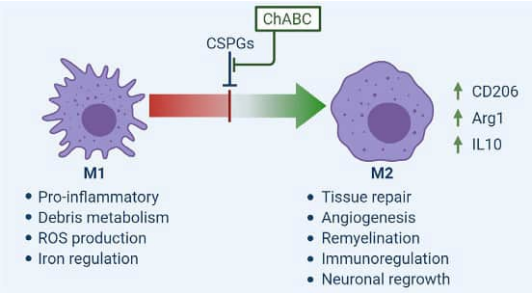

FIG. 4 CSPG digestion by ChABC causes switch to pro-regenerative inflammatory phenotype. Viral vector delivery of chondroitinase ABC modulates the inflammatory response to a pro-regenerative response, promoting tissue repair. *(Created with BioRender.com.)*

improved forelimb-hindlimb coordination (Hu, Granger, Pai, Bellamkonda, & Jeffery, 2018). This suggests that the use of gene delivery of ChABC has potential as a clinical therapy.

It is now well-understood that ECM components, including CSPGs, impact on the inflammatory response following SCI (Gaudet & Popovich, 2014). A number of studies have shown that a lentiviral approach to delivering ChABC, as well as causing extensive remodeling of the extracellular matrix and axonal regeneration, is able to modulate the post-injury immune response (Fig. 4). A study by (Didangelos et al., 2014) using lentiviral delivery of ChABC in a rat thoracic contusion model examined the expression profile of M1/M2 macrophage polarization markers. This study found that ChABC treatment had a distinct effect on the immune signature in the injured tissue, increasing expression of the pro-regenerative cytokine IL-10, with a corresponding reduction in the pro-inflammatory cytokine IL-12B. This demonstrates a distinct, ChABC-mediated anti-inflammatory response following SCI associated with large-scale removal of CSPGs. Lentiviral ChABC delivery leads to an increase in the levels of CD68 and CD206 (Bartus et al., 2014). These are markers of the M2 macrophage phenotype, which promote resolution of inflammation, enhance phagocytosis, angiogenesis, and tissue remodeling following injury (Mantovani, Sozzani, Locati, Allavena, & Sica, 2002).

While there is currently no evidence that long-term expression of ChABC using viral vectors has any detrimental effects, it is known that uncontrolled gene expression can reverse beneficial effects (Fouad, Bennett, Vavrek, & Blesch, 2013) and it has been suggested that long-term, large-scale CSPG digestion and subsequent unintended remodeling could lead to neuropathic pain (Bartus et al., 2014). Therefore, the ability to control the timing and/or duration of treatment administration afforded by the use of viral vector gene therapy would be useful in development of clinically feasible strategies. A study by (Burnside et al., 2018) used a lentivirus to deliver ChABC under the control of the tetracycline-controlled activator. This study included another development by including a glycine-alanine repeat (Hoyng et al., 2014) fused to the transactivator (GARrtTA) to avoid the immune response that can be generated against the system transactivator and which results in cytotoxic T cell-mediated removal of transgene-expressing cells (Latta-Mahieu et al., 2002). This study found short-term ChABC treatment (2.5 weeks) was sufficient to promote improvement in sensory axon conduction and ladder walking performance, however improvement in neuroplasticity of descending motor pathways required for the more complex task of forepaw reaching and grasping required 8 weeks of treatment (Burnside et al., 2018). As well as having clinical potential and allowing for the control of gene expression to avoid detrimental effects, such an approach will be useful in helping determine the most appropriate timing for an intervention, which is also crucial for clinical translation. As lentiviruses integrate into the host genome and so pose a risk of oncogenic transformation, the use of AAV vectors have been trialed for delivery of CSPG-removing enzymes. Our recent study (Griffin et al., 2020) used an AAV5 vector under the control of a GFAP promoter to deliver the human A disintegrin and metalloproteinase with thrombospondin motifs-4 (ADAMTS4) gene, which cause proteolysis of CSPG core proteins, in a rodent model of thoracic contusion SCI. This resulted in significantly decreased lesion size, increased sprouting of hindlimb corticospinal tract axons and serotonergic fiber density and improved hindlimb function when combined with hindlimb exercise rehabilitation. This study used a GFAP promoter to target expression to astrocytes is an example of how viral vector gene therapy can be used to target a specific cell types in the spinal cord to provide therapeutic effect.

Other approaches

A number of other approaches have been trialed via viral vector delivery, including modulating inhibitory receptors and signaling pathways and cell adhesion and delivery of protective molecules such as calcium sensors and anti-apoptotic proteins that have been successful in improving injury outcomes in animal models (Bo et al., 2011). Delivery of pro-

regenerative molecules such as cytokine IL-10 leads to neuronal survival and functional recovery (Zhou, Peng, Insolera, Fink, & Mata, 2009). Using lentivirus to deliver the microRNA miR-133b to the injured mouse spinal cord promotes functional recovery and down regulation of inhibitory pathways and inflammation (Theis et al., 2017). Other recent examples have targeted Hedgehog (Hh) pathway signaling via silencing of the PTC1 and PTC 2 genes (Zhang et al., 2017), apoptotic pathways via overexpression of the peroxisome proliferator activated receptor coactivator 1 alpha which leads to neuronal survival (Hu, Lang, Zhang, Ni, & Lu, 2016) and expression of the mitochondrial protein Prohibitin-1, to protect against mitochondrial dysfunction-induced damage (Li et al., 2015). Viral gene therapy has been used to deliver multiple factors. A study by Wang et al. (Wang, Lu, Chen, Shu, & Qiu, 2015), using lentivirus to deliver the pro-regenerative transcription factor KLF7 and ChABC, enhanced growth of sensory neurons to the injury site following spinal cord transection. Combinational gene therapy approaches have the potential to enhance recovery through targeting of multiple processes. For example, removal of CSPGs using ChABC improves NPC survival, oligodendrocyte differentiation, and remyelination in the presence of growth factors (Karimi-Abdolrezaee, Eftekharpour, Wang, Schut, & Fehlings, 2010; Siebert & Osterhout, 2011). ChABC also regulates macrophage phenotype (Bartus et al., 2014), which in turn promotes myelin repair (Miron & Franklin, 2014). As viral vectors have been used successfully to deliver these therapies, combinational gene therapy to optimize timing of CSPG breakdown and neurotrophic factor delivery could be used to augment the additive beneficial effects of such approaches (Fig. 1G).

In conclusion, viral gene therapy has the ability to deliver a wide-variety of treatments to the cord and with its potential to control the spatiotemporal expression of molecules, has the potential to be a powerful tool in developing effective clinical treatments for SCI.

Applications to other areas of neuroscience

This chapter provides an overview on the use of viral vectors to target gene therapies for SCI. We describe the different viral vector therapies available, methods of delivery and give an overview of how these have been used to trial potential treatments. Further, we outline how viral vector gene therapy can be used to control the spatiotemporal delivery of therapeutic agents, such as neurotrophic factors and enzymes to remove the glial scar, as a means to improve the efficacy of potential treatments. As is the case with SCI, effective delivery of treatments to the central nervous system to ensure delivery to the correct location or cell type and over the most effective timeframe has potential to improve the efficacy of treatments being developed for a number of neurotraumatic and neurodegenerative conditions. Therefore, the therapeutic potential for viral vector gene delivery is applicable to a number of other conditions including stroke (Craig & Housley, 2016), retinal disease (Campa, Gallenga, Bolletta, & Perri, 2017), Alzheimer's Disease (Sudhakar & Richardson, 2019), Parkinson's Disease (Kabra, Sharma, Kabra, & Baghel, 2018), and Huntington's disease (Estevez-Fraga, Flower, & Tabrizi, 2020).

Mini-dictionary of terms

Gene therapy: Delivery of DNA into cells to produce a therapeutic agent.

Viral vector: Tools used to deliver genetic material to cells utilizing mechanisms to efficiently transport their genomes into cells.

Remote delivery: Non-invasive or minimally invasive routes of viral vector administration.

Direct delivery: Involves an invasive surgical approach that directly targets a specific area of the spinal cord tissue via injection of the gene therapy and is referred to as intraparenchymal delivery.

Spatio-temporal delivery: An approach that allows for targeted delivery of a therapeutic agent to a specific region and for a specific period of time.

Key facts of viral vectors and spinal cord injury

- Viral vectors allow for effective delivery of a number of therapeutic agents to the spinal cord.
- Viral vectors can overcome limitations of drug delivery, such as poor stability in vivo, poor tissue penetration, and the potential for off target effects.
- A number of different viral vectors can be used to target genes to the spinal cord.
- A number of different delivery methods can be used that allow either direct or indirect delivery to spinal cord tissue.
- Viral vectors allow for spatiotemporal regulation of gene expression.

Summary points

- This chapter focuses on the use of viral vector gene therapy for delivery of therapeutic agents to treat SCI.
- A number of different viral vector gene therapies have been used to deliver therapeutic agents to the spinal cord to overcome a number of issues related to drug delivery to the spinal cord.
- Viral vectors have been used to deliver neurotrophic factors to the spinal cord and have allowed for generation of concentration gradients, which are required for growth of axons through a spinal cord lesion.
- Viral vectors have been used to deliver enzymes to breakdown the glial scar, which overcomes issues of long-term delivery and enzyme stability.
- The use of inducible systems and cell specific promoters allows for spatiotemporal control of gene delivery
- Viral vector gene therapy could be used to optimize deliver of therapeutic agents as part of a combinational approach to treatment.

References

Alto, L. T., Havton, L. A., Conner, J. M., Hollis, E. R., 2nd, Blesch, A., & Tuszynski, M. H. (2009). Chemotropic guidance facilitates axonal regeneration and synapse formation after spinal cord injury. *Nature Neuroscience*, *12*(9), 1106–1113. https://doi.org/10.1038/nn.2365.

Bartus, K., James, N. D., Didangelos, A., Bosch, K. D., Verhaagen, J., Yanez-Munoz, R. J., … Bradbury, E. J. (2014). Large-scale chondroitin sulfate proteoglycan digestion with chondroitinase gene therapy leads to reduced pathology and modulates macrophage phenotype following spinal cord contusion injury. *The Journal of Neuroscience*, *34*(14), 4822–4836. https://doi.org/10.1523/JNEUROSCI.4369-13.2014.

Batista, A. R., King, O. D., Reardon, C. P., Davis, C., Shankaracharya, P., & V., … Sena-Esteves, M. (2020). Ly6a differential expression in blood-brain barrier is responsible for strain specific central nervous system transduction profile of AAV-PHP.B. *Human Gene Therapy*, *31*(1–2), 90–102. https://doi.org/10.1089/hum.2019.186.

Baum, C., Kustikova, O., Modlich, U., Li, Z., & Fehse, B. (2006). Mutagenesis and oncogenesis by chromosomal insertion of gene transfer vectors. *Human Gene Therapy*, *17*(3), 253–263. https://doi.org/10.1089/hum.2006.17.253.

Blesch, A., Fischer, I., & Tuszynski, M. H. (2012). Gene therapy, neurotrophic factors and spinal cord regeneration. *Handbook of Clinical Neurology*, *109*, 563–574. https://doi.org/10.1016/B978-0-444-52137-8.00035-8.

Blesch, A., & Tuszynski, M. H. (2007). Transient growth factor delivery sustains regenerated axons after spinal cord injury. *The Journal of Neuroscience*, *27*(39), 10535–10545. https://doi.org/10.1523/JNEUROSCI.1903-07.2007.

Blits, B., & Bunge, M. B. (2006). Direct gene therapy for repair of the spinal cord. *Journal of Neurotrauma*, *23*(3–4), 508–520. https://doi.org/10.1089/neu.2006.23.508.

Bo, X., Wu, D., Yeh, J., & Zhang, Y. (2011). Gene therapy approaches for neuroprotection and axonal regeneration after spinal cord and spinal root injury. *Current Gene Therapy*, *11*(2), 101–115. https://doi.org/10.2174/156652311794940773.

Bonner, J. F., Blesch, A., Neuhuber, B., & Fischer, I. (2010). Promoting directional axon growth from neural progenitors grafted into the injured spinal cord. *Journal of Neuroscience Research*, *88*(6), 1182–1192. https://doi.org/10.1002/jnr.22288.

Boulis, N. M., Noordmans, A. J., Song, D. K., Imperiale, M. J., Rubin, A., Leone, P., … Feldman, E. L. (2003). Adeno-associated viral vector gene expression in the adult rat spinal cord following remote vector delivery. *Neurobiology of Disease*, *14*(3), 535–541. https://doi.org/10.1016/j.nbd.2003.08.025.

Bradbury, E. J., & Carter, L. M. (2011). Manipulating the glial scar: Chondroitinase ABC as a therapy for spinal cord injury. *Brain Research Bulletin*, *84*(4–5), 306–316. https://doi.org/10.1016/j.brainresbull.2010.06.015.

Bradbury, E. J., Khemani, S., King, V. R., Priestley, J. V., & McMahon, S. B. (1999). NT-3 promotes growth of lesioned adult rat sensory axons ascending in the dorsal columns of the spinal cord. *The European Journal of Neuroscience*, *11*(11), 3873–3883. https://doi.org/10.1046/j.1460-9568.1999.00809.x.

Bradbury, E. J., & McMahon, S. B. (2006). Spinal cord repair strategies: Why do they work? *Nature Reviews. Neuroscience*, *7*(8), 644–653. https://doi.org/10.1038/nrn1964.

Bradbury, E. J., Moon, L. D., Popat, R. J., King, V. R., Bennett, G. S., Patel, P. N., … McMahon, S. B. (2002). Chondroitinase ABC promotes functional recovery after spinal cord injury. *Nature*, *416*(6881), 636–640. https://doi.org/10.1038/416636a.

Burnside, E. R., De Winter, F., Didangelos, A., James, N. D., Andreica, E. C., Layard-Horsfall, H., … Bradbury, E. J. (2018). Immune-evasive gene switch enables regulated delivery of chondroitinase after spinal cord injury. *Brain*, *141*(8), 2362–2381. https://doi.org/10.1093/brain/awy158.

Byrnes, A. P., MacLaren, R. E., & Charlton, H. M. (1996). Immunological instability of persistent adenovirus vectors in the brain: Peripheral exposure to vector leads to renewed inflammation, reduced gene expression, and demyelination. *The Journal of Neuroscience*, *16*(9), 3045–3055.

Cafferty, W. B., Yang, S. H., Duffy, P. J., Li, S., & Strittmatter, S. M. (2007). Functional axonal regeneration through astrocytic scar genetically modified to digest chondroitin sulfate proteoglycans. *The Journal of Neuroscience*, *27*(9), 2176–2185. https://doi.org/10.1523/JNEUROSCI.5176-06.2007.

Campa, C., Gallenga, C. E., Bolletta, E., & Perri, P. (2017). The role of gene therapy in the treatment of retinal diseases: A review. *Current Gene Therapy*, *17*(3), 194–213. https://doi.org/10.2174/1566523217666171116170040.

Craig, A. J., & Housley, G. D. (2016). Evaluation of gene therapy as an intervention strategy to treat brain injury from stroke. *Frontiers in Molecular Neuroscience*, *9*, 34. https://doi.org/10.3389/fnmol.2016.00034.

Curinga, G. M., Snow, D. M., Mashburn, C., Kohler, K., Thobaben, R., Caggiano, A. O., & Smith, G. M. (2007). Mammalian-produced chondroitinase AC mitigates axon inhibition by chondroitin sulfate proteoglycans. *Journal of Neurochemistry*, *102*(1), 275–288. https://doi.org/10.1111/j.1471-4159.2007.04530.x.

Davis, A. S., Federici, T., Ray, W. C., Boulis, N. M., O'Connor, D., Clark, K. R., & Bartlett, J. S. (2015). Rational design and engineering of a modified adeno-associated virus (AAV1)-based vector system for enhanced retrograde gene delivery. *Neurosurgery*, *76*(2), 216–225. discussion 225 https://doi.org/10.1227/NEU.0000000000000589.

Deverman, B. E., Ravina, B. M., Bankiewicz, K. S., Paul, S. M., & Sah, D. W. Y. (2018). Gene therapy for neurological disorders: Progress and prospects. *Nature Reviews. Drug Discovery*, *17*(10), 767. https://doi.org/10.1038/nrd.2018.158.

Didangelos, A., Iberl, M., Vinsland, E., Bartus, K., & Bradbury, E. J. (2014). Regulation of IL-10 by chondroitinase ABC promotes a distinct immune response following spinal cord injury. *The Journal of Neuroscience*, *34*(49), 16424–16432. https://doi.org/10.1523/JNEUROSCI.2927-14.2014.

Duque, S., Joussemet, B., Riviere, C., Marais, T., Dubreil, L., Douar, A. M., … Barkats, M. (2009). Intravenous administration of self-complementary AAV9 enables transgene delivery to adult motor neurons. *Molecular Therapy*, *17*(7), 1187–1196. https://doi.org/10.1038/mt.2009.71.

During, M. J., Young, D., Baer, K., Lawlor, P., & Klugmann, M. (2003). Development and optimization of adeno-associated virus vector transfer in the central nervous system. *Methods in Molecular Medicine*, *76*, 221–236.

Estevez-Fraga, C., Flower, M. D., & Tabrizi, S. J. (2020). Therapeutic strategies for Huntington's disease. *Current Opinion in Neurology*, *33*(4), 508–518. https://doi.org/10.1097/WCO.0000000000000835.

Federici, T., Riley, J., Park, J., Bain, M., & Boulis, N. (2009). Preclinical safety validation of a stabilized viral vector direct injection approach to the cervical spinal cord. *Clinical and Translational Science*, *2*(2), 165–167. https://doi.org/10.1111/j.1752-8062.2008.00084.x.

Federici, T., Taub, J. S., Baum, G. R., Gray, S. J., Grieger, J. C., Matthews, K. A., … Boulis, N. M. (2012). Robust spinal motor neuron transduction following intrathecal delivery of AAV9 in pigs. *Gene Therapy*, *19*(8), 852–859. https://doi.org/10.1038/gt.2011.130.

Fouad, K., Bennett, D. J., Vavrek, R., & Blesch, A. (2013). Long-term viral brain-derived neurotrophic factor delivery promotes spasticity in rats with a cervical spinal cord hemisection. *Frontiers in Neurology*, *4*, 187. https://doi.org/10.3389/fneur.2013.00187.

Franz, S., Weidner, N., & Blesch, A. (2012). Gene therapy approaches to enhancing plasticity and regeneration after spinal cord injury. *Experimental Neurology*, *235*(1), 62–69. https://doi.org/10.1016/j.expneurol.2011.01.015.

Gaudet, A. D., & Popovich, P. G. (2014). Extracellular matrix regulation of inflammation in the healthy and injured spinal cord. *Experimental Neurology*, *258*, 24–34. https://doi.org/10.1016/j.expneurol.2013.11.020.

Glorioso, J. C., & Fink, D. J. (2004). Herpes vector-mediated gene transfer in treatment of diseases of the nervous system. *Annual Review of Microbiology*, *58*, 253–271. https://doi.org/10.1146/annurev.micro.58.030603.123709.

Griffin, J. M., Fackelmeier, B., Clemett, C. A., Fong, D. M., Mouravlev, A., Young, D., & O'Carroll, S. J. (2020). Astrocyte-selective AAV-ADAMTS4 gene therapy combined with hindlimb rehabilitation promotes functional recovery after spinal cord injury. *Experimental Neurology*, *327*, 113232. https://doi.org/10.1016/j.expneurol.2020.113232.

Hardcastle, N., Boulis, N. M., & Federici, T. (2018). AAV gene delivery to the spinal cord: Serotypes, methods, candidate diseases, and clinical trials. *Expert Opinion on Biological Therapy*, *18*(3), 293–307. https://doi.org/10.1080/14712598.2018.1416089.

He, Z., & Koprivica, V. (2004). The Nogo signaling pathway for regeneration block. *Annual Review of Neuroscience*, *27*, 341–368. https://doi.org/10.1146/annurev.neuro.27.070203.144340.

Hoyng, S. A., Gnavi, S., de Winter, F., Eggers, R., Ozawa, T., Zaldumbide, A., … Verhaagen, J. (2014). Developing a potentially immunologically inert tetracycline-regulatable viral vector for gene therapy in the peripheral nerve. *Gene Therapy*, *21*(6), 549–557. https://doi.org/10.1038/gt.2014.22.

Hu, H. Z., Granger, N., Pai, S. B., Bellamkonda, R. V., & Jeffery, N. D. (2018). Therapeutic efficacy of microtube-embedded chondroitinase ABC in a canine clinical model of spinal cord injury. *Brain*, *141*(4), 1017–1027. https://doi.org/10.1093/brain/awy007.

Hu, J., Lang, Y., Zhang, T., Ni, S., & Lu, H. (2016). Lentivirus-mediated PGC-1alpha overexpression protects against traumatic spinal cord injury in rats. *Neuroscience*, *328*, 40–49. https://doi.org/10.1016/j.neuroscience.2016.04.031.

Jackson, C. A., Cobbs, C., Peduzzi, J. D., Novak, M., & Morrow, C. D. (2001). Repetitive intrathecal injections of poliovirus replicons result in gene expression in neurons of the central nervous system without pathogenesis. *Human Gene Therapy*, *12*(15), 1827–1841. https://doi.org/10.1089/104303401753153893.

James, N. D., Shea, J., Muir, E. M., Verhaagen, J., Schneider, B. L., & Bradbury, E. J. (2015). Chondroitinase gene therapy improves upper limb function following cervical contusion injury. *Experimental Neurology*, *271*, 131–135. https://doi.org/10.1016/j.expneurol.2015.05.022.

Jin, Y., Ketschek, A., Jiang, Z., Smith, G., & Fischer, I. (2011). Chondroitinase activity can be transduced by a lentiviral vector in vitro and in vivo. *Journal of Neuroscience Methods*, *199*(2), 208–213. https://doi.org/10.1016/j.jneumeth.2011.05.007.

Kabra, A., Sharma, R., Kabra, R., & Baghel, U. S. (2018). Emerging and alternative therapies for Parkinson disease: An updated review. *Current Pharmaceutical Design*, *24*(22), 2573–2582. https://doi.org/10.2174/1381612824666180820150150.

Karimi-Abdolrezaee, S., Eftekharpour, E., Wang, J., Schut, D., & Fehlings, M. G. (2010). Synergistic effects of transplanted adult neural stem/progenitor cells, chondroitinase, and growth factors promote functional repair and plasticity of the chronically injured spinal cord. *The Journal of Neuroscience*, *30*(5), 1657–1676. https://doi.org/10.1523/JNEUROSCI.3111-09.2010.

Keefe, K. M., Sheikh, I. S., & Smith, G. M. (2017). Targeting Neurotrophins to specific populations of neurons: NGF, BDNF, and NT-3 and their relevance for treatment of spinal cord injury. *International Journal of Molecular Sciences*, *18*(3). https://doi.org/10.3390/ijms18030548.

Keir, S. D., Mitchell, W. J., Feldman, L. T., & Martin, J. R. (1995). Targeting and gene expression in spinal cord motor neurons following intramuscular inoculation of an HSV-1 vector. *Journal of Neurovirology*, *1*(3–4), 259–267. https://doi.org/10.3109/13550289509114022.

Khromykh, A. A. (2000). Replicon-based vectors of positive strand RNA viruses. *Current Opinion in Molecular Therapeutics*, *2*(5), 555–569.

Kitamura, K., Iwanami, A., Nakamura, M., Yamane, J., Watanabe, K., Suzuki, Y., … Okano, H. (2007). Hepatocyte growth factor promotes endogenous repair and functional recovery after spinal cord injury. *Journal of Neuroscience Research*, *85*(11), 2332–2342. https://doi.org/10.1002/jnr.21372.

Lang, B. T., Cregg, J. M., DePaul, M. A., Tran, A. P., Xu, K., Dyck, S. M., … Silver, J. (2015). Modulation of the proteoglycan receptor PTP sigma promotes recovery after spinal cord injury. *Nature*, *518*(7539), 404–408. https://doi.org/10.1038/nature13974.

Latta-Mahieu, M., Rolland, M., Caillet, C., Wang, M., Kennel, P., Mahfouz, I., … Thuillier, V. (2002). Gene transfer of a chimeric trans-activator is immunogenic and results in short-lived transgene expression. *Human Gene Therapy*, *13*(13), 1611–1620. https://doi.org/10.1089/10430340260201707.

Li, L., Guo, J. D., Wang, H. D., Shi, Y. M., Yuan, Y. L., & Hou, S. X. (2015). Prohibitin 1 gene delivery promotes functional recovery in rats with spinal cord injury. *Neuroscience*, *286*, 27–36. https://doi.org/10.1016/j.neuroscience.2014.11.037.

Mannes, A. J., Caudle, R. M., O'Connell, B. C., & Iadarola, M. J. (1998). Adenoviral gene transfer to spinal-cord neurons: Intrathecal vs. intraparenchymal administration. *Brain Research*, *793*(1–2), 1–6. https://doi.org/10.1016/s0006-8993(97)01422-4.

Mantovani, A., Sozzani, S., Locati, M., Allavena, P., & Sica, A. (2002). Macrophage polarization: Tumor-associated macrophages as a paradigm for polarized M2 mononuclear phagocytes. *Trends in Immunology*, *23*(11), 549–555. https://doi.org/10.1016/s1471-4906(02)02302-5.

Miron, V. E., & Franklin, R. J. (2014). Macrophages and CNS remyelination. *Journal of Neurochemistry*, *130*(2), 165–171. https://doi.org/10.1111/jnc.12705.

Muir, E. M., Fyfe, I., Gardiner, S., Li, L., Warren, P., Fawcett, J. W., … Rogers, J. H. (2010). Modification of N-glycosylation sites allows secretion of bacterial chondroitinase ABC from mammalian cells. *Journal of Biotechnology*, *145*(2), 103–110. https://doi.org/10.1016/j.jbiotec.2009.11.002.

Nakajima, H., Uchida, K., Kobayashi, S., Inukai, T., Horiuchi, Y., Yayama, T., … Baba, H. (2007). Rescue of rat anterior horn neurons after spinal cord injury by retrograde transfection of adenovirus vector carrying brain-derived neurotrophic factor gene. *Journal of Neurotrauma*, *24*(4), 703–712. https://doi.org/10.1089/neu.2006.0004.

Nakajima, H., Uchida, K., Yayama, T., Kobayashi, S., Guerrero, A. R., Furukawa, S., & Baba, H. (2010). Targeted retrograde gene delivery of brain-derived neurotrophic factor suppresses apoptosis of neurons and oligodendroglia after spinal cord injury in rats. *Spine (Phila Pa 1976)*, *35*(5), 497–504. https://doi.org/10.1097/BRS.0b013e3181b8e89b.

Naldini, L., Blomer, U., Gallay, P., Ory, D., Mulligan, R., Gage, F. H., … Trono, D. (1996). In vivo gene delivery and stable transduction of nondividing cells by a lentiviral vector. *Science*, *272*(5259), 263–267. https://doi.org/10.1126/science.272.5259.263.

Ohtake, Y., & Li, S. (2015). Molecular mechanisms of scar-sourced axon growth inhibitors. *Brain Research*, *1619*, 22–35. https://doi.org/10.1016/j.brainres.2014.08.064.

Park, K. K., Liu, K., Hu, Y., Kanter, J. L., & He, Z. (2010). PTEN/mTOR and axon regeneration. *Experimental Neurology*, *223*(1), 45–50. https://doi.org/10.1016/j.expneurol.2009.12.032.

Penaud-Budloo, M., François, A., Clément, N., & Ayuso, E. (2018). Pharmacology of recombinant adeno-associated virus production. *Molecular Therapy - Methods & Clinical Development*, *8*(March), 166–180. https://doi.org/10.1016/j.omtm.2018.01.002.

Poulsen, D. J., Harrop, J. S., & During, M. J. (2002). Gene therapy for spinal cord injury and disease. *The Journal of Spinal Cord Medicine*, *25*(1), 2–9. https://doi.org/10.1080/10790268.2002.11753594.

Rosenzweig, E. S., Salegio, E. A., Liang, J. J., Weber, J. L., Weinholtz, C. A., Brock, J. H., … Tuszynski, M. H. (2019). Chondroitinase improves anatomical and functional outcomes after primate spinal cord injury. *Nature Neuroscience*, *22*(8), 1269–1275. https://doi.org/10.1038/s41593-019-0424-1.

Sharma, K., Selzer, M. E., & Li, S. (2012). Scar-mediated inhibition and CSPG receptors in the CNS. *Experimental Neurology*, *237*(2), 370–378. https://doi.org/10.1016/j.expneurol.2012.07.009.

Siebert, J. R., & Osterhout, D. J. (2011). The inhibitory effects of chondroitin sulfate proteoglycans on oligodendrocytes. *Journal of Neurochemistry*, *119*(1), 176–188. https://doi.org/10.1111/j.1471-4159.2011.07370.x.

Sudhakar, V., & Richardson, R. M. (2019). Gene therapy for neurodegenerative diseases. *Neurotherapeutics*, *16*(1), 166–175. https://doi.org/10.1007/s13311-018-00694-0.

Sun, S., & Schaffer, D. V. (2018). Engineered viral vectors for functional interrogation, deconvolution, and manipulation of neural circuits. *Current Opinion in Neurobiology*, *50*, 163–170. https://doi.org/10.1016/j.conb.2017.12.011.

Tervo, D. G., Hwang, B. Y., Viswanathan, S., Gaj, T., Lavzin, M., Ritola, K. D., … Karpova, A. Y. (2016). A designer AAV variant permits efficient retrograde access to projection neurons. *Neuron*, *92*(2), 372–382. https://doi.org/10.1016/j.neuron.2016.09.021.

Theis, T., Yoo, M., Park, C. S., Chen, J., Kugler, S., Gibbs, K. M., & Schachner, M. (2017). Lentiviral delivery of miR-133b improves functional recovery after spinal cord injury in mice. *Molecular Neurobiology*, *54*(6), 4659–4671. https://doi.org/10.1007/s12035-016-0007-z.

Thomas, A. M., Palma, J. L., & Shea, L. D. (2015). Sponge-mediated lentivirus delivery to acute and chronic spinal cord injuries. *Journal of Controlled Release*, *204*, 1–10. https://doi.org/10.1016/j.jconrel.2015.02.032.

Towne, C., Schneider, B. L., Kieran, D., Redmond, D. E., Jr., & Aebischer, P. (2010). Efficient transduction of non-human primate motor neurons after intramuscular delivery of recombinant AAV serotype 6. *Gene Therapy*, *17*(1), 141–146. https://doi.org/10.1038/gt.2009.119.

Uchida, K., Nakajima, H., Guerrero, A. R., Johnson, W. E., Masri, W. E., & Baba, H. (2014). Gene therapy strategies for the treatment of spinal cord injury. *Therapeutic Delivery*, *5*(5), 591–607. https://doi.org/10.4155/tde.14.20.

Wang, Y. T., Lu, X. M., Chen, K. T., Shu, Y. H., & Qiu, C. H. (2015). Immunotherapy strategies for spinal cord injury. *Current Pharmaceutical Biotechnology*, *16*(6), 492–505. https://doi.org/10.2174/1389201016061504071126 46.

Yamamura, J., Kageyama, S., Uwano, T., Kurokawa, M., Imakita, M., & Shiraki, K. (2000). Long-term gene expression in the anterior horn motor neurons after intramuscular inoculation of a live herpes simplex virus vector. *Gene Therapy*, *7*(11), 934–941. https://doi.org/10.1038/sj.gt.3301185.

Zhang, H., & Yang, T. (2020). FBXW7alpha promotes the recovery of traumatic spinal cord. *Current Molecular Medicine*, *20*(6), 494–504. https://doi.org/10.2174/1566524020666191223164916.

Zhang, Y. D., Zhu, Z. S., Zhang, D., Zhang, Z., Ma, B., Zhao, S. C., & Xue, F. (2017). Lentivirus-mediated silencing of the PTC1 and PTC2 genes promotes recovery from spinal cord injury by activating the hedgehog signaling pathway in a rat model. *Experimental & Molecular Medicine*, *49*(12). https://doi.org/10.1038/emm.2017.220, e412.

Zhao, R. R., Muir, E. M., Alves, J. N., Rickman, H., Allan, A. Y., Kwok, J. C., … Rogers, J. H. (2011). Lentiviral vectors express chondroitinase ABC in cortical projections and promote sprouting of injured corticospinal axons. *Journal of Neuroscience Methods*, *201*(1), 228–238. https://doi.org/10.1016/j.jneumeth.2011.08.003.

Zhou, Z., Peng, X., Insolera, R., Fink, D. J., & Mata, M. (2009). IL-10 promotes neuronal survival following spinal cord injury. *Experimental Neurology*, *220*(1), 183–190. https://doi.org/10.1016/j.expneurol.2009.08.018.

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Chapter 33

Curcumin usage for inflammation and spinal cord injury

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List of abbreviations

AGP	α1-acid glycoprotein
AMPK	adenosine monophosphate-activated protein kinase
AQP4	aquaporin 4
BBB	Basso, Beattie, Bresnahan
ERKs	extracellular signal-regulated kinases
GFAP	glial fibrillary acidic protein
GSK-3β	glycogen synthase kinase 3 beta
HO-1	hemeoxygenase 1
ICE	interleukin 1β converting enzyme
IL	interleukin
IP	intraperitoneal
JAK-STAT	Janus kinase—signal transducer and activator of transcription
MAPK	p38 mitogen-activated protein kinase
MDA	malondialdehyde
MD-2	myeloid differentiation protein 2
NF-H	neurofilament-H
NF-κB	nuclear factor kappa B
NPC	neural progenitor cell
Nrf2/ARE	nuclear erythroid 2-related factor 2/anti-oxidant response element
NSC	neural stem cells
ROS	reactive oxygen species
SCI	spinal cord injury
SC-NPCs	spinal cord neural progenitor cell
SOD	serum superoxide dismutase
SOX-9	sex-determining region Y-box transcription factor 9
STAT	signal transducer and activator of transcriptions
TGF-β	transforming growth factor beta
TNF-α	tumor necrosis factor alpha

Introduction

Traumatic spinal cord injury (SCI) causes necrosis of the central nervous system and subsequent permanent neurological deficit. The mechanism of SCI broadly comprises two stages. First, a primary injury, attributable to the mechanical insult itself and structural damage. A secondary injury is a series of systemic and local neurochemical and physiological changes following the primary injury. The secondary injury occurs via subsequent edema, ischemia, inflammation, cytokine production, free radical damage, glial scar formation, apoptosis, and necrosis (Ormond et al., 2014). Primary injury is immediate and irreversible; in contrast, a secondary injury worsens with time and necessitates therapeutic intervention (Jo et al., 2018; Kim et al., 2014; Lee et al., 2019). The secondary injury develops within hours or days after SCI, causing neurochemical alterations that lead to neurologic functional impairments. Therapeutic modalities that promote recovery could

Diagnosis and Treatment of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822498-4.00033-6

FIG. 1 Curcumin powder and *Curcuma longa* plant. Curcumin is a bright yellow chemical produced by the *C. longa* plants. Curcumin is the principal curcuminoid of turmeric (*C. longa*), a member of the ginger family, Zingiberaceae. It is sold as an herbal supplement, cosmetic ingredient, food-flavoring agent, and food-coloring agent.

be better understood with detailed knowledge of SCI pathophysiology (Ormond et al., 2014). Neurochemical alterations in SCI include increases in the excitatory amino acids, elevation in the calcium influx, stimulation of the calcium-dependent enzymes, generation of reactive oxygen species (ROS), and release of cytokines leading to neuroinflammation (Pouliquen, 2014). These neurochemical alterations affect the neuron and astrocyte activity, induce demyelination, modulate leukocyte infiltration, and activate macrophages (Bramlett & Dietrich, 2004; Jiang et al., 2007). In addition, secreted inflammatory cytokines and growth factors generally up-regulate the pro-survival molecules, such as nuclear factor kappa B (NF-κB) (Ghosh & Hayden, 2008). Thus, the key obstacle in the treatment and recovery process from catastrophic SCI is gliosis caused by the up-regulation of inflammation. Moreover, several studies have demonstrated the potential therapeutic role of curcumin in alleviating the second injury process.

Curcumin [1,7-bis (4-hydroxy-3-methoxyphenyl)-1,6- heptadiene-3, 5-dione] is a yellow extract obtained from *Curcuma longa* and is commonly used in India as a seasoning and food-coloring agent (Fig. 1). It is a polyphenol compound that possesses non-steroidal anti-inflammatory properties. Recent studies indicate that it may have anti-oxidant (Das & Vinayak, 2015), anti-inflammatory (Kim et al., 2014; Lee et al., 2019; Li et al., 2016), neuroprotective (Szczepanowicz et al., 2016) and anti-apoptotic effects (Liu et al., 2015) for SCI. Curcumin has emerged as a promising therapeutic drug in SCI treatment with a tendency to reduce the formation of glial scar and suppress the expression of glial fibrillary acidic protein (GFAP), thus contributing to a more favorable recovery environment (Urdzikova et al., 2016). In a recent study, curcumin inhibited the hypoxia-induced up-regulation of GFAP and neurofilament-H (NF-H) following hypoxia and down-regulated the expression of pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α) and interleukin 1 (IL-1) (Daverey & Agrawal, 2020).

Structure, pharmacology, and biological targets

Curcumin is a polyphenol substance that has been widely used for medicinal purposes, religious rituals, and local cuisines in the Indian subcontinent. The molecule is symmetric in structure. The keto-enol tautomer in the center, the flexible α,β-unsaturated β-diketo linker, and the terminal o-methoxyphenolic groups comprise the three main components of curcumin molecule (Fig. 2).

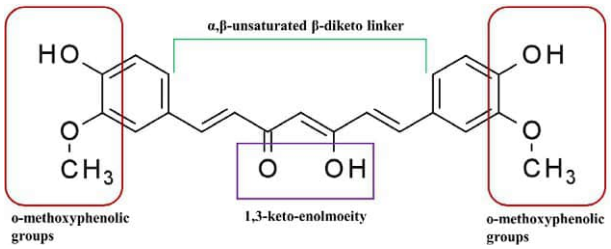

FIG. 2 Structure of curcumin. The curcumin molecule has a symmetric structure and consists of the following three main components: the keto-enol tautomer in the center; the flexible α,β-unsaturated β-diketo linker; and the terminal o-methoxyphenolic groups.

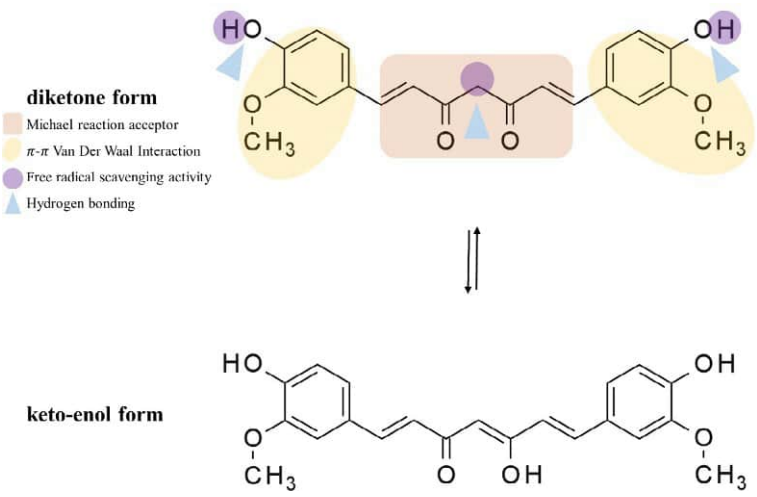

FIG. 3 The diversity of interactions that curcumin offers. Curcumin has a complex pharmacophore that serves as an anti-oxidant, can chelate metals, and can undergo Michael reaction, hydrogen bonding interactions, π-π van der Waals interactions, and free radical scavenging activity.

Curcumin has a complex pharmacophore that could act as an anti-oxidant, chelate metals, and Michael reaction (Minassi, Sánchez-Duffhues, Collado, Muñoz, & Appendino, 2013). Further, curcumin is a hydrophobic molecule comprising two ferulic acid residues linked by a methylene bridge and has high affinity for cellular membranes (Pérez-Lara, Corbalán-García, & Gómez-Fernández, 2011). Curcumin can participate in hydrogen bonding interactions with its β-diketone moiety and the substituents on the aromatic rings. The aromatic rings can also form π-π Van der Waals interactions (Gupta et al., 2011). Structure-activity relationships demonstrate that the β-diketone (keto-enol) moiety serves as a chelator for cationic metals present in the protein-binding sites and as a Michael reaction acceptor for nucleophilic groups, such as reduced selenocysteine and sulfhydryl, that form covalent bonds with curcumin (Gupta et al., 2011). The phenolic hydroxyl group is essential for the anti-oxidant action of curcumin (Priyadarsini et al., 2003; Selvam, Jachak, Thilagavathi, & Chakraborti, 2005). This group and the methylene hydrogen are crucial for free radical scavenging activity, wherein ROS and nitrogen species are subjected to electron transfer or H-atom abstraction (Priyadarsini et al., 2003). The diversity of the interactions that curcumin offers may explain its binding to multiple proteins (Fig. 3).

Molecular docking studies suggest that curcumin adopts different conformations for the maximization of these interactions, primarily via the α,β-unsaturated β-diketone moiety, and generally favors hydrophilic pockets near the cysteine residues (Ali, Haque, Saleem, & Hsieh, 2013; Gupta et al., 2011). Curcumin shares two important characteristics with the phorbol ester pharmacophore owing to the presence of the hydroxyl and carbonyl groups (Majhi, Rahman, Panchal, & Das, 2010). Removing the methylene group and carbonyl group and cutting off the pharmacophore produces a more potent molecule 1,5-bis (4-hydroxy-3-methoxiphenyl)-1,4-pentadiene-3-1 that maintains all curcumin activity (Appiah-Opong, de Esch, Commandeur, Andarini, & Vermeulen, 2008; Minassi et al., 2013).

Curcumin regulates about 100 biological targets (Das, Pany, Panchal, Majhi, & Rahman, 2011) via various mechanisms, including changing of the activity of cellular proteins via changes in the phosphorylation status (Bill et al., 2012). Generally, curcumin demonstrates its effects at concentrations above the micromolar range. This weak binding affinity has facilitated several attempts to optimize the activity of curcumin using a structural-based drug design.

Anti-inflammatory effects

After primary SCI, therapeutic strategies and outcomes depend on how we achieve reduction of inflammation and glial scar. Curcumin is a well-known anti-inflammatory molecule that evokes global inhibition of the inflammation network by suppressing transcription factors, such as NF-κB and signal transducer, as well as the activator of transcriptions (STAT) in the upstream signaling pathways of inflammatory mediators, such as prostaglandins, cytokines, and chemokines (Chandran & Goel, 2012). Curcumin may also bind directly to inflammatory mediators and enzymes in downstream inflammation pathways, such as interleukin 1β converting enzyme (ICE), TNF-α, TNF-α converting enzyme (TACE), p38 mitogen-activated protein kinase (MAPK), myeloid differentiation protein 2 (MD-2), α1-acid glycoprotein (AGP), and glycogen synthase kinase 3 beta (GSK-3β) (Elumalai, Muthaiah, & Alf, 2012; Gupta et al., 2011). Curcumin inhibited the expression of pro-inflammatory cytokines and suppressed reactive gliosis. Moreover, curcumin inhibited the generation of

transforming growth factor beta (TGF-β)1, TGF-β2, and sex-determining region Y-box transcription factor 9 (SOX-9); decreased the deposition of chondroitin sulfate proteoglycan by inhibiting the transforming growth factors and transcription factor; and improved the microenvironment that enabled nerve growth (Yuan et al., 2015). Occurring concurrently with acute inflammation and preceding fibrosis, spinal cord edema plays a crucial role in neurologic damage and patient symptoms; this is a primary reason behind the clinical usefulness of corticosteroids in SCI patients (Sanivarapu, Vallabhaneni, & Verma, 2016). An experimental rat model that was administered 40 mg/kg curcumin intraperitoneally (IP) showed reduced hemorrhage, edema, and neutrophil infiltration of the traumatic spinal cord. Curcumin also inhibited the SCI-associated aquaporin 4 (AQP4) overexpression and GFAP as well as repressed the unusual activation of the Janus kinase-signal transducer and activator of transcription (JAK-STAT) signaling pathway (Zu et al., 2014). Studies on the effect of curcumin on inflammation, fibrosis, and edema after SCI have been summarized in Table 1.

TABLE 1 Evidentiary table: anti-inflammatory properties of curcumin.

Study	Animals/ SCI	Curcumin administration	Description of study	Results
(Lee et al., 2019)	SD rats, $N = 128$ or clipping	200 mg/kg IP daily For 8 weeks	Sham ($n = 32$) SCI only ($n = 32$) SCI & Hyperglycemia ($n = 32$) SCI & Hyperglycemia & Curcumin ($n = 32$)	Curcumin regulate SOD activity increased, MDA level decreased ED-1 macrophage marker level decreased in the SCI-hyperglycemia-curcumin group Reduction in IL-6, IL-8, and TNF-a levels, the phosphorylated-ERKs Lower lesion volume, Higher spared tissue
(Ruzicka et al., 2018)	Wistar rats, $N = 131$ or balloon compression	Curcumin, 6 mg/kg; EGCG 17 mg/kg IP daily & Curcumin, 60 mg/kg; EGCG 17 mg/kg) IM weekly For 28 days	Behavioral examinations: saline ($n = 10$), curcumin ($n = 13$), EGCG ($n = 19$), curcumin + EGCG ($n = 9$) Cytokine group studies: Saline ($n = 20$), curcumin (n = 20), EGCG ($n = 20$), curcumin + EGCG ($n = 20$)	Curcumin and EGCG alone or in combination increased axonal sprouting, decreased glial scar formation, and altered the levels of macrophage inflammatory protein 1-alpha, IL-1β, IL-4, and IL-6
(Ruzicka et al., 2018)	Wistar rats, $N = 135$ or balloon compression	60 mg/kg IT weekly & 6 mg/kg IP daily For 28 days	Saline ($n = 34$), Curcumin ($n = 27$), MSC ($n = 28$), Curcumin + MSC ($n = 26$)	Curcumin + MSC facilitated axonal sprouting, and modulated expression of pro-regenerative factors and inflammatory responses
(Yuan et al., 2017)	SD rats, $N = 280$ or blunt dissection and clipping	100 mg/kg IP daily For 7 days	Sham group ($n = 70$), SCI group ($n = 70$), SCI + curcumin group ($n = 70$), SCI + DMSO group ($n = 70$)	Curcumin regulate both the NF-κb and SOX9 signaling pathways and reduce the expression of intracellular and extracellular glial scar components through dual-target regulating both inflammation and fibrosis after SCI in the rat
(Ni et al., 2015)	SD rats, $N = 48$ or clipping	100 mg/kg IP at 15 min after SCI	Sham group ($n = 16$), SCI group ($n = 16$), SCI + curcumin group ($n = 16$). $N = 16$ per group	Curcumin markedly down regulated the levels of TLR4/NF-κB inflammatory signaling pathway. Significantly ameliorated SCI induced spinal cord edema, and apoptosis
(Lin et al., 2015)	Wild-type C57BL/ 6JNarl mice, $N = 18$ or weight drop	40 mg/kg IP at 30 min after SCI	Sham control ($n = 6$), SCI ($n = 6$), SCI + curcumin ($n = 6$)	Curcumin can attenuate the down-regulation of CISD2 (CISD2 exerts anti-apoptotic and anti-inflammatory effects in neural cells) in SCI and LPS-treated astrocytes

Abbreviations: DMSO, dimethyl sulfoxide; EGCG, epigallocatechin gallate; IM, intramuscular; IP, intraperitoneal; IT, intrathecal; MDA, malondialdehyde; MSC, mesenchymal stem cells; SD, Sprague-Dawley; SOD, superoxide dismutase.

Anti-oxidant effects

Several trials have assessed the anti-oxidant properties of curcumin for SCI. There is a close association between SCI and free radical production, owing to inflammation (Hausmann, 2003). In an experimental study on the anti-oxidant effect of curcumin on SCI in rats, serum superoxide dismutase (SOD) level in the curcumin group (dose: 200 mg/kg/d orally) was higher than that in the control group and methylprednisolone group (dose: 30 mg/kg intraperitoneally). The malondialdehyde (MDA) level in the curcumin group was lower than in that the control group. Further, curcumin effectively protects the spinal cord tissues against oxidative damage (Sahin Kavaklı, Koca, & Alıcı, 2011). Curcumin acts as a free radical scavenger by donating protons to ROS and nitrogen species and quenches them via electron transfer and H-atom abstraction (Priyadarsini et al., 2003). Consequently, oxidative damage, such as lipid peroxidation is inhibited in the brain and the tissues (Priyadarsini et al., 2003; Scapagnini et al., 2011). Curcumin stimulates the intracellular anti-oxidant defense response via the indication of expression of several anti-oxidants, detoxification, and cytoprotective proteins via the unsilencing of relevant genes on the activation of the nuclear erythroid 2-related factor 2 or anti-oxidant response element (Nrf2/ARE) pathway (Scapagnini et al., 2011). Curcumin can boost the activities of anti-oxidant enzymes, such as plasma catalase, erythrocyte SOD, and plasma glutathione peroxidase (DiSilvestro, Joseph, Zhao, & Bomser, 2012). We have presented the anti-oxidant properties of curcumin as found in SCI studies in Table 2.

TABLE 2 Evidentiary table: anti-oxidant properties of curcumin.

Study	Animals or cells/SCI	Curcumin administration	Description of study	Results
(Akar et al., 2017)	Wistar rats, $N = 40$ or ischemia by clamping the aorta	100 mg/kg IP at 30 min before ischemia	Sham ($n = 10$), Ischemia-reperfusion ($n = 10$), Curcumin ($n = 10$), Solvent ($n = 10$)	Curcumin regulates MDA levels in the spinal cord decreased SOD and GPx levels increased
(Daverey & Agrawal, 2016)	HA-sp astrocytes	Cells were treated with curcumin for 24 h	H_2O_2 was used to induce oxidative stress in astrocytes 50 μM of H_2O_2 or 1 μM of curcumin or 50 μM of H_2O_2 + 1 μM of curcumin	Curcumin inhibits oxidative stress-induced cytoskeleton disarrangement, and impedes the activation of astrocytes by inhibiting up-regulation of GFAP, vimentin and Prdx6 Inhibition of oxidative stress-induced inflammation, apoptosis and mitochondria fragmentation after curcumin treatment
(Sanli et al., 2012)	Wistar rats, $N = 40$ or weight drop	300 mg/kg Single IP injection Directly after SCI	Control ($n = 8$), SCI alone ($n = 8$), Methylprednisolone sodium succinate (30 mg/kg) ($n = 8$), Curcumin + DMSO (300 mg/kg) ($n = 8$), DMSO alone (0.1 mg/kg) ($n = 8$)	Decreased lipid peroxidation and MDA levels in curcumin group
(Sahin Kavaklı et al., 2011)	Wistar rats, $N = 24$ or weight drop	200 mg/kg/d orally	SCI + no medication ($n = 8$), SCI + curcumin (200 mg/kg/d orally) ($n = 8$), SCI + methylprednisolone (30 mg/kg, IP) ($n = 8$)	SOD level in the curcumin group was higher than in the control group and methylprednisolone group MDA level in the curcumin group was lower than in the control group

Abbreviations: DMSO, dimethyl sulfoxide, HA-sp, human astrocytes cell line derived from the spinal cord; IP, intraperitoneal; Prdx6, peroxiredoxin.

Stem cell and progenitor cell proliferation

Although studies using stem cells for SCI are being actively conducted, there are still obstacles in the achievement of remarkable therapeutic results. In particular, it is essential to promote the proliferation of neural stem cells (NSC), and some studies have demonstrated the contribution of curcumin in this subject. As per a recent study, curcumin affects the proliferation of spinal cord neural progenitor cells (SC-NPCs) (Son et al., 2014). This study advocated that the anti-inflammatory effects might promote the proliferation of NPCs and showed that a lower dosage (0.1, 0.5, and 1 μM) of curcumin in the culture medium increased SC-NPC proliferation. However, a higher dosage decreased SC-NPC proliferation. They showed that SC-NPCs are more relevant to extracellular signal-regulated kinases (ERKs) and MAPK. The ERKs protein is reported to be related to cell proliferation, survival, and apoptosis (Gangwal, Bhadauriya, Damre, Dhoke, & Sangamwar, 2013), and the p38 protein played a vital role in cellular responses to external stress signals, such as anti-inflammatory reactions (Dent, 2014). Another trial on the proliferation of fetal rat NSC demonstrated the stem-cell proliferative properties of curcumin. In the cell culture (in vitro) study, curcumin increased the proliferation of fetal rat NSC at low doses (1–6 μM). Consecutive in vivo experiments, curcumin induced NPC proliferation, with the majority of subsequent differentiation into neurons/neuroblasts (Hucklenbroich et al., 2014). Ormond et al. published a study on NSC isolated from the sub-ventricular zone wherein curcumin stimulated NSC proliferation in vitro. In combination with stem-cell therapy, it induced profound recovery from severe SCI as evidenced by improved functional locomotor recovery, increased body weight, and soleus muscle mass. The findings showed that curcumin in conjunction with stem-cell therapy, synergistically improved recovery from severe SCI. Furthermore, their results indicate that the effect of curcumin extends beyond its known anti-inflammatory properties to the regulation of stem-cell proliferation (Ormond et al., 2014).

Facilitation of neurologic function recovery

In a systematic meta-analysis review, curcumin appeared to significantly improve the neurological function, as assessed using the Basso, Beattie, Bresnahan (BBB) locomotor rating scale in a random-effects model and decreased MDA using a fixed-effects model. Effect size, assessed using the BBB scale, gradually increased as the curcumin dosage was elevated (Yao et al., 2015). The meta-analysis showed that curcumin significantly improved the neurological function, as assessed using the BBB locomotor rating scale (four studies, rats $n = 132$; pooled mean difference = 3.09; 95% confidence interval, 3.40–4.45; $p = 0.04$) (Yao et al., 2015). A strength of many studies that examined the functional recovery is that a uniform scale (BBB score) was used for making inter-study comparisons, thus making extrapolations at least somewhat more reliable than those in studies using different scales (Sanivarapu et al., 2016). In an animal study involving Wistar rats, the rats were randomized into 2 groups, with 30 rats in the curcumin-treatment group and 30 in the control group. Curcumin (applied locally on the surface of the injured spinal cord immediately after an injury and then administered every day intraperitoneally) treatment improved behavioral recovery within the first week after SCI, as indicated by the improved BBB scores and plantar scores sensory performance) (Machova Urdzikova et al., 2015). This functional improvement is attributable to the anti-inflammatory effect described in the previous paragraph. In another animal study on anti-oxidative properties and function recovery, the curcumin-treatment group showed higher neuromotor scores (BBB), increased SOD, decreased MDA, and macrophage markers during seven consecutive days of intraperitoneal injections after SCI (Kim et al., 2014). One study that compared curcumin to methylprednisolone, which is often used to alleviate the secondary injury of SCI in real clinical practice, showed that curcumin was more effective than methylprednisolone after 2 weeks of the SCI, as indicated by the BBB scores. The author group concluded that curcumin has superior therapeutic potential than methylprednisolone with a prolonged treatment time in SCI (Liu et al., 2018). Thus, rat experiments and the use of BBB scores have provided considerable evidence in favor of the effectiveness of curcumin in terms of functional recover following SCI; the data have been summarized in Table 3.

Conclusion and future direction

Curcumin is a polyphenol compound that is extracted from turmeric rhizomes and is well known for its anti-oxidant and anti-inflammatory properties. These properties are helpful in the protection of neuronal tissue from secondary injury of the spinal cord, such as inflammation, cytokine production, free radical damage, and glial scar formation as well as for superior functional outcomes. Several animal experiments have shown that curcumin enhances active recovery after SCI. There are still several challenges in SCI treatment, and curcumin has several reasonable basic mechanisms as a study subject

TABLE 3 Evidentiary table: functional recovery outcomes (BBB scores) after curcumin administration.

Study	Animals/SCI	Curcumin administration	Description of study	Results
(Liu et al., 2018)	SD rats $N = 60$/weight drop	200 mg/kg IP daily For 56 days	SCI-Curcumin ($n = 27$) SCI-MP ($n = 27$) Sham group ($n = 6$)	Paralleled BBB scores between the two treatment groups (MP vs. Curcumin) on Day 56 after SCI
(Machova Urdzikova et al., 2015)	Wistar rats $N = 60$ or balloon compression	60 mg/kg Epidural locally Immediately after injury & 6 mg/kg IP daily	Curcumin treatment ($n = 30$) Controls ($n = 30$)	Curcumin treatment improved behavioral recovery within the first week following SCI (BBB scores & plantar- sensory performance scores)
(Ormond et al., 2012)	SD rats, $N = 14$ or weight drop	60 mg/kg Epidural locally Within 30 min after SCI & Weekly for 6 weeks	Curcumin treatment (n = 7), DMSO treatment ($n = 7$)	In curcumin group, improved functional scores (BBB) after 3 weeks and greater soleus weight
(Kim et al., 2014)	SD rats, $N = 36$ or clipping	200 mg/kg IP daily For 7 days	Sham ($n = 12$), SCI/vehicle ($n = 12$), SCI/curcumin ($n = 12$)	Curcumin group shows higher Neuromotor (BBB) scores 7–14 days after surgery
(Cemil et al., 2010)	Wistar rats, $N = 40$ or clipping	Curcumin: 200 mg/kg IP Immediately after injury or MP: 30 mg/kg IP Immediately after injury	Only laminectomy ($n = 8$), Laminectomy + SCI ($n = 8$), Laminectomy + SCI + MP ($n = 8$), Laminectomy + SCI + Curcumin ($n = 8$), Laminectomy + SCI + Vehicle (1 mL of rice bran oil) ($n = 8$)	Curcumin treatment improved neurologic outcome (BBB) Decreased level of tissue MDA and Increased levels of SOD, tissue structure preservation
(Lin, Lee, Chiu, & Hung, 2011)	SD rats, $N = 39$ or cord hemisection	40 mg/kg IP daily (1 day before surgery and continuing for 6 days)	Sham ($n = 5$), Vehicle (DMSO) ($n = 17$), Curcumin ($n = 17$)	The BBB scores after hemisection were improved in the curcumin group compared with the vehicle group (on 3–7 days after surgery)

Abbreviations: DMSO, dimethyl sulfoxide; IP, intraperitoneal; MP, methylprednisolone, SD, Sprague-Dawley.

compared to another experimental treatment methods such as stem-cell therapy, electrical nerve stimulation, therapeutic hypothermia that have been attempted.

Future translational research on curcumin is required to enable its clinical application. For the penetration of the blood-brain barrier, oral intake is insufficient, and there is a need to perform a study to establish an effective administration method that would allow the action of curcumin on injured neuronal tissue. Further, safety studies on high-dose

administration of curcumin are warranted. In order to improve the bioavailability of curcumin, a method, such as a megadose delivery, may be required, and dosages of previously commercialized curcumin products should be suggested. In most animal studies, continuous or intermittent curcumin administration was administered at the acute stage within 24 h of the primary injury and the chronic stage after the primary injury. Thus, we recommend future studies focus not only the dosage, but also the effective timing and duration of administration.

Applications to other areas of neuroscience

In this chapter, we have reviewed the effects of curcumin in brain ischemia and brain trauma. These two diseases are active areas in the field of neuroscience for the application of curcumin. First, in an experimental study to evaluate effect of curcumin on focal cerebral ischemic rats, a single intravenous administration of curcumin (1 and 2 mg/kg) alleviated cerebral ischemia and reperfusion injury by preventing nitric oxide-mediated blood-brain barrier disruption. Curcumin reduced the infarct volume, lowered the neurological deficit, and decreased mortality (Jiang et al., 2007). Curcumin inhibits inducible nitric oxide synthase expression and nitric oxide formation mediated by lipopolysaccharide (LPS)/TNF-α in cultured astrocytes. Based on in vitro and in vivo studies, curcumin prevents peroxynitrite-mediated blood-brain barrier damage, lowers lipid peroxidation-mediated damage, retards apoptotic cell death, and inhibits glial cell activation (Jiang et al., 2007). Curcumin potently induces the hemeoxygenase 1 (HO-1) expression and activity in rat astrocytes (Scapagnini et al., 2004). HO-1 system is well established as a defensive mechanism for neurons exposed to oxidative stress. The biochemical changes induced by curcumin treatment correlate with its ability to ameliorate changes in the locomotor activity (Wang et al., 2005). Astrocytes that are exposed to curcumin show increased expression of the phase-II detoxification enzymes, quinone reductase and glutathione S-transferase (Scapagnini et al., 2006). Thus, the inhibition of oxidative stress and neuroinflammation with curcumin improves outcomes after brain ischemia. This neuroprotective effect may be attributable to anti-apoptotic mechanisms (Zhao et al., 2010). Collectively, these studies suggest that the neuroprotective activity of curcumin in cerebral ischemia is mediated via its anti-oxidant activity (Thiyagarajan & Sharma, 2004; Zhao et al., 2010).

Studies on the effect of curcumin in traumatic brain injury indicate that this polyphenol substantially lowers oxidative damage; alters the levels of cyclic adenosine monophosphate-response element binding protein; normalizes the levels of brain-derived neurotrophic factor, and reduces the levels of adenosine monophosphate-activated protein kinase (AMPK), ubiquitous mitochondrial creatine kinase, and cytochrome C oxidase II (Sharma, Zhuang, Ying, Wu, & Gomez-Pinilla, 2009; Wu, Ying, & Gomez-Pinilla, 2006). In addition, curcumin and pyrazole curcumin derivatives suppress the increases in calcium-independent phospholipase A2 activity and decreases in the 4-hydroxynonenal levels and increase the fatty acid transport protein. Furthermore, curcumin supplementation counteracts cognitive impairments induced by traumatic brain injury and effectively restores parameters of membrane homeostasis. These results show that oxidative stress acts via the BDNF system to modulate synaptic plasticity membrane homeostasis in the injured brain and that cognition and curcumin can promote neuroprotective mechanisms (Sharma et al., 2009; Sharma, Ying, & Gomez-Pinilla, 2010; Wu et al., 2006) by facilitating endogenous up-regulation of molecules that are important for neural repair and plasticity.

Mini-dictionary of terms

Basso, Beattie, and Bresnahan scale: It is a semi-quantitative scale based on rats' locomotor response that can take on values ranging from 0 to 21. BBB scale is widely used to test behavioral consequences of SCI to the rat.

Blood-brain barrier: It is a system that has selective permeability between the blood vessels and the brain, allowing only some substances to pass through and others only through particular pathways such as transport proteins.

Curcumin: A major yellow pigment in turmeric, the ground rhizome of *C. longa*. It is a polyphenol compound that pos sesses anti-inflammatory and anti-oxidant properties and has been used for various purposes in Indian medicine for thousands of years.

Free radical scavenger: A substance that exhibits anti-oxidant effects by removing free radicals by giving hydrogen atoms to free radicals. Curcumin acts as a free radical scavenger by donating protons to ROS.

Gliosis: When the central nervous system is damaged by trauma or ischemia, it refers to the proliferation of glial cells (glia) around it occurs.

Inflammation: As one of the defense reactions of injured tissues, it refers to a complex lesion that co-occurs three things: tissue deterioration, circulatory disorders and effusion, and tissue proliferation. It is a critical process in the secondary injury of spinal cord, and curcumin has an anti-inflammatory effect.

Polyphenol: It is a substance that has more than two hydroxyls. Anti-oxidant functions are well known and are being applied to food and medical care. The catechins in green tea are typical polyphenol compounds.

Reactive oxygen species: A type of unstable molecule that contains oxygen and reacts easily with other molecules in the cell. It accumulates through the secondary injury to the spinal cord, causing DNA, RNA, and proteins damage and causing apoptosis.

Secondary injury of spinal cord: A series of systemic and local neurochemical and physiological changes (edema, ischemia, inflammation, cytokine production, free radical damage, glial scar formation, apoptosis, and necrosis) following the primary injury.

Turmeric: Ginger family perennial plant. It is about 1 m high. Several trumpet-shaped pink flowers bloom in late spring.

Key facts of curcumin

Curcumin is a neuroprotective polyphenol compound with pluripotency, oral safety, a long history of use, and reasonable cost.

Many animal experimental studies have showed that curcumin can reduce secondary damage resulting from SCI via anti-inflammatory and anti-oxidant properties as well as stem-cell mobilization.

It decreases the expression of several inflammatory and fibrotic cytokines, viable axonal fibers, GFAP, and MDA after SCI.

Further, curcumin significantly improves the neurological function, as assessed using the Basso, Beattie, and Bresnahan (BBB) locomotor rating scale in a SCI rat model.

Future translational research on curcumin is required to enable its clinical application.

Summary points

- Curcumin is a key active ingredient extracted from turmeric. Turmeric is a rhizomatous plant of the ginger family.
- Curcumin is well known for its extensive pharmacological activity, such as inflammation relief and anti-oxidant effect.
- The neuroprotective effect has been reported in several experimental studies on the animal brain and neuronal tissue.
- Curcumin is a valid and effective therapeutic agent that could alleviate the catastrophic secondary injury process of the spinal cord, namely inflammation, edema, free radical injury, fibrosis, and glial scar formation.
- This potential is supported by immune pathological results proven in several animal experiments; significantly better outcomes were produced with the evaluation using the Basso, Beattie, and Bresnahan locomotor rating scale for recovery of neurologic function.
- However, the evidence-based effectiveness of curcumin for SCI remains in the experimental stage.

References

Akar, İ., İnce, İ., Arici, A., Benli, İ., Aslan, C., Şenol, S., … Akbas, A. (2017). The protective effect of curcumin on a spinal cord ischemia-reperfusion injury model. *Annals of Vascular Surgery*, *42*, 285–292. https://doi.org/10.1016/j.avsg.2016.12.016.

Ali, I., Haque, A., Saleem, K., & Hsieh, M. F. (2013). Curcumin-I Knoevenagel's condensates and their Schiff's bases as anticancer agents: Synthesis, pharmacological and simulation studies. *Bioorganic & Medicinal Chemistry*, *21*(13), 3808–3820. https://doi.org/10.1016/j.bmc.2013.04.018.

Appiah-Opong, R., de Esch, I., Commandeur, J. N., Andarini, M., & Vermeulen, N. P. (2008). Structure-activity relationships for the inhibition of recombinant human cytochromes P450 by curcumin analogues. *European Journal of Medicinal Chemistry*, *43*(8), 1621–1631. https://doi.org/10.1016/j.ejmech.2007.10.034.

Bill, M. A., Nicholas, C., Mace, T. A., Etter, J. P., Li, C., Schwartz, E. B., … Lesinski, G. B. (2012). Structurally modified curcumin analogs inhibit STAT3 phosphorylation and promote apoptosis of human renal cell carcinoma and melanoma cell lines. *PLoS One*, *7*(8). https://doi.org/10.1371/journal.pone.0040724, e40724.

Bramlett, H. M., & Dietrich, W. D. (2004). Pathophysiology of cerebral ischemia and brain trauma: Similarities and differences. *Journal of Cerebral Blood Flow and Metabolism*, *24*(2), 133–150. https://doi.org/10.1097/01.Wcb.0000111614.19196.04.

Cemil, B., Topuz, K., Demircan, M. N., Kurt, G., Tun, K., Kutlay, M., … Kucukodaci, Z. (2010). Curcumin improves early functional results after experimental spinal cord injury. *Acta Neurochirurgica*, *152*(9), 1583–1590. discussion 1590 https://doi.org/10.1007/s00701-010-0702-x.

Chandran, B., & Goel, A. (2012). A randomized, pilot study to assess the efficacy and safety of curcumin in patients with active rheumatoid arthritis. *Phytotherapy Research*, *26*(11), 1719–1725. https://doi.org/10.1002/ptr.4639.

Das, J., Pany, S., Panchal, S., Majhi, A., & Rahman, G. M. (2011). Binding of isoxazole and pyrazole derivatives of curcumin with the activator binding domain of novel protein kinase C. *Bioorganic & Medicinal Chemistry*, *19*(21), 6196–6202. https://doi.org/10.1016/j.bmc.2011.09.011.

Das, L., & Vinayak, M. (2015). Long term effect of curcumin in restoration of tumour suppressor p53 and phase-II antioxidant enzymes via activation of Nrf2 signalling and modulation of inflammation in prevention of cancer. *PLoS One*, *10*(4). https://doi.org/10.1371/journal.pone.0124000, e0124000.

Daverey, A., & Agrawal, S. K. (2016). Curcumin alleviates oxidative stress and mitochondrial dysfunction in astrocytes. *Neuroscience*, *333*, 92–103. https://doi.org/10.1016/j.neuroscience.2016.07.012.

Daverey, A., & Agrawal, S. K. (2020). Curcumin protects against white matter injury through NF-κB and Nrf2 cross talk. *Journal of Neurotrauma*, *37*(10), 1255–1265. https://doi.org/10.1089/neu.2019.6749.

Dent, P. (2014). Crosstalk between ERK, AKT, and cell survival. *Cancer Biology & Therapy*, *15*(3), 245–246. https://doi.org/10.4161/cbt.27541.

DiSilvestro, R. A., Joseph, E., Zhao, S., & Bomser, J. (2012). Diverse effects of a low dose supplement of lipidated curcumin in healthy middle aged people. *Nutrition Journal*, *11*, 79. https://doi.org/10.1186/1475-2891-11-79.

Elumalai, M., Muthaiah, R., & Alf, M. A. (2012). Identification of curcumin targets in neuroinflammatory pathways: Molecular docking scores with GSK-3β, p38 MAPK, COX, ICE and TACE enzymes. *Acta Poloniae Pharmaceutica*, *69*(2), 237–245.

Gangwal, R. P., Bhadauriya, A., Damre, M. V., Dhoke, G. V., & Sangamwar, A. T. (2013). p38 mitogen-activated protein kinase inhibitors: A review on pharmacophore mapping and QSAR studies. *Current Topics in Medicinal Chemistry*, *13*(9), 1015–1035. https://doi.org/10.2174/1568026611313090005.

Ghosh, S., & Hayden, M. S. (2008). New regulators of NF-kappaB in inflammation. *Nature Reviews. Immunology*, *8*(11), 837–848. https://doi.org/10.1038/nri2423.

Gupta, S. C., Prasad, S., Kim, J. H., Patchva, S., Webb, L. J., Priyadarsini, I. K., & Aggarwal, B. B. (2011). Multitargeting by curcumin as revealed by molecular interaction studies. *Natural Product Reports*, *28*(12), 1937–1955. https://doi.org/10.1039/c1np00051a.

Hausmann, O. N. (2003). Post-traumatic inflammation following spinal cord injury. *Spinal Cord*, *41*(7), 369–378. https://doi.org/10.1038/sj.sc.3101483.

Hucklenbroich, J., Klein, R., Neumaier, B., Graf, R., Fink, G. R., Schroeter, M., & Rueger, M. A. (2014). Aromatic-turmerone induces neural stem cell proliferation in vitro and in vivo. *Stem Cell Research & Therapy*, *5*(4), 100. https://doi.org/10.1186/scrt500.

Jiang, J., Wang, W., Sun, Y. J., Hu, M., Li, F., & Zhu, D. Y. (2007). Neuroprotective effect of curcumin on focal cerebral ischemic rats by preventing blood-brain barrier damage. *European Journal of Pharmacology*, *561*(1–3), 54–62. https://doi.org/10.1016/j.ejphar.2006.12.028.

Jo, M. J., Kumar, H., Joshi, H. P., Choi, H., Ko, W. K., Kim, J. M., … Han, I. (2018). Oral administration of α-Asarone promotes functional recovery in rats with spinal cord injury. *Frontiers in Pharmacology*, *9*, 445. https://doi.org/10.3389/fphar.2018.00445.

Kim, K. T., Kim, M. J., Cho, D. C., Park, S. H., Hwang, J. H., Sung, J. K., … Jeon, Y. (2014). The neuroprotective effect of treatment with curcumin in acute spinal cord injury: Laboratory investigation. *Neurologia Medico-Chirurgica (Tokyo)*, *54*(5), 387–394. https://doi.org/10.2176/nmc.oa.2013-0251.

Lee, Y. S., Cho, D. C., Kim, C. H., Han, I., Gil, E. Y., & Kim, K. T. (2019). Effect of curcumin on the inflammatory reaction and functional recovery after spinal cord injury in a hyperglycemic rat model. *The Spine Journal*, *19*(12), 2025–2039. https://doi.org/10.1016/j.spinee.2019.07.013.

Li, G., Cao, Y., Shen, F., Wang, Y., Bai, L., Guo, W., … Fan, Z. (2016). Mdivi-1 inhibits astrocyte activation and Astroglial scar formation and enhances axonal regeneration after spinal cord injury in rats. *Frontiers in Cellular Neuroscience*, *10*, 241. https://doi.org/10.3389/fncel.2016.00241.

Lin, C. C., Chiang, T. H., Chen, W. J., Sun, Y. Y., Lee, Y. H., & Lin, M. S. (2015). CISD2 serves a novel role as a suppressor of nitric oxide signalling and curcumin increases CISD2 expression in spinal cord injuries. *Injury*, *46*(12), 2341–2350. https://doi.org/10.1016/j.injury.2015.07.040.

Lin, M. S., Lee, Y. H., Chiu, W. T., & Hung, K. S. (2011). Curcumin provides neuroprotection after spinal cord injury. *The Journal of Surgical Research*, *166*(2), 280–289. https://doi.org/10.1016/j.jss.2009.07.001.

Liu, J., Zhu, P., Song, P., Xiong, W., Chen, H., Peng, W., … Wang, H. (2015). Pretreatment of adipose derived stem cells with curcumin facilitates myocardial recovery via antiapoptosis and angiogenesis. *Stem Cells International*, *2015*, 638153. https://doi.org/10.1155/2015/638153.

Liu, X., Zhang, Y., Yang, Y., Lin, J., Huo, X., Du, X., … Fang, M. (2018). Therapeutic effect of curcumin and methylprednisolone in the rat spinal cord injury. *The Anatomical Record*, *301*(4), 686–696. https://doi.org/10.1002/ar.23729.

Machova Urdzikova, L., Karova, K., Ruzicka, J., Kloudova, A., Shannon, C., Dubisova, J., … Jendelova, P. (2015). The anti-inflammatory compound curcumin enhances locomotor and sensory recovery after spinal cord injury in rats by immunomodulation. *International Journal of Molecular Sciences*, *17*(1). https://doi.org/10.3390/ijms17010049.

Majhi, A., Rahman, G. M., Panchal, S., & Das, J. (2010). Binding of curcumin and its long chain derivatives to the activator binding domain of novel protein kinase C. *Bioorganic & Medicinal Chemistry*, *18*(4), 1591–1598. https://doi.org/10.1016/j.bmc.2009.12.075.

Minassi, A., Sánchez-Duffhues, G., Collado, J. A., Muñoz, E., & Appendino, G. (2013). Dissecting the pharmacophore of curcumin. Which structural element is critical for which action? *Journal of Natural Products*, *76*(6), 1105–1112. https://doi.org/10.1021/np400148e.

Ni, H., Jin, W., Zhu, T., Wang, J., Yuan, B., Jiang, J., … Ma, Z. (2015). Curcumin modulates TLR4/NF-κB inflammatory signaling pathway following traumatic spinal cord injury in rats. *The Journal of Spinal Cord Medicine*, *38*(2), 199–206. https://doi.org/10.1179/2045772313y.0000000179.

Ormond, D. R., Peng, H., Zeman, R., Das, K., Murali, R., & Jhanwar-Uniyal, M. (2012). Recovery from spinal cord injury using naturally occurring antiinflammatory compound curcumin: Laboratory investigation. *Journal of Neurosurgery. Spine*, *16*(5), 497–503. https://doi.org/10.3171/2012.1.Spine11769.

Ormond, D. R., Shannon, C., Oppenheim, J., Zeman, R., Das, K., Murali, R., & Jhanwar-Uniyal, M. (2014). Stem cell therapy and curcumin synergistically enhance recovery from spinal cord injury. *PLoS One*, *9*(2). https://doi.org/10.1371/journal.pone.0088916, e88916.

Pérez-Lara, A., Corbalán-García, S., & Gómez-Fernández, J. C. (2011). Curcumin modulates PKCα activity by a membrane-dependent effect. *Archives of Biochemistry and Biophysics*, *513*(1), 36–41. https://doi.org/10.1016/j.abb.2011.06.010.

Pouliquen, D. L. C. (2014). *Curcumin: Synthesis, emerging role in pain management and health implications*. New York: Nova Science Publishers, Inc.

Priyadarsini, K. I., Maity, D. K., Naik, G. H., Kumar, M. S., Unnikrishnan, M. K., Satav, J. G., & Mohan, H. (2003). Role of phenolic O-H and methylene hydrogen on the free radical reactions and antioxidant activity of curcumin. *Free Radical Biology & Medicine*, *35*(5), 475–484. https://doi.org/10.1016/s0891-5849(03)00325-3.

Ruzicka, J., Urdzikova, L. M., Kloudova, A., Amin, A. G., Vallova, J., Kubinova, S., … Jendelova, P. (2018). Anti-inflammatory compound curcumin and mesenchymal stem cells in the treatment of spinal cord injury in rats. *Acta Neurobiologiae Experimentalis (Wars)*, *78*(4), 358–374.

Ruzicka, J., Urdzikova, L. M., Svobodova, B., Amin, A. G., Karova, K., Dubisova, J., … Jendelova, P. (2018). Does combined therapy of curcumin and epigallocatechin gallate have a synergistic neuroprotective effect against spinal cord injury? *Neural Regeneration Research*, *13*(1), 119–127. https://doi.org/10.4103/1673-5374.224379.

Sahin Kavaklı, H., Koca, C., & Alıcı, O. (2011). Antioxidant effects of curcumin in spinal cord injury in rats. *Ulusal Travma ve Acil Cerrahi Dergisi*, *17*(1), 14–18.

Sanivarapu, R., Vallabhaneni, V., & Verma, V. (2016). The potential of curcumin in treatment of spinal cord injury. *Neurology Research International*, *2016*, 9468193. https://doi.org/10.1155/2016/9468193.

Sanli, A. M., Turkoglu, E., Serbes, G., Sargon, M. F., Besalti, O., Kilinc, K., … Sekerci, Z. (2012). Effect of curcumin on lipid peroxidation, early ultrastructural findings and neurological recovery after experimental spinal cord contusion injury in rats. *Turkish Neurosurgery*, *22*(2), 189–195. https://doi.org/10.5137/1019-5149.Jtn.5193-11.1.

Scapagnini, G., Butterfield, D. A., Colombrita, C., Sultana, R., Pascale, A., & Calabrese, V. (2004). Ethyl ferulate, a lipophilic polyphenol, induces HO-1 and protects rat neurons against oxidative stress. *Antioxidants & Redox Signaling*, *6*(5), 811–818. https://doi.org/10.1089/ars.2004.6.811.

Scapagnini, G., Colombrita, C., Amadio, M., D'Agata, V., Arcelli, E., Sapienza, M., … Calabrese, V. (2006). Curcumin activates defensive genes and protects neurons against oxidative stress. *Antioxidants & Redox Signaling*, *8*(3–4), 395–403. https://doi.org/10.1089/ars.2006.8.395.

Scapagnini, G., Vasto, S., Abraham, N. G., Caruso, C., Zella, D., & Fabio, G. (2011). Modulation of Nrf2/ARE pathway by food polyphenols: A nutritional neuroprotective strategy for cognitive and neurodegenerative disorders. *Molecular Neurobiology*, *44*(2), 192–201. https://doi.org/10.1007/s12035-011-8181-5.

Selvam, C., Jachak, S. M., Thilagavathi, R., & Chakraborti, A. K. (2005). Design, synthesis, biological evaluation and molecular docking of curcumin analogues as antioxidant, cyclooxygenase inhibitory and anti-inflammatory agents. *Bioorganic & Medicinal Chemistry Letters*, *15*(7), 1793–1797. https://doi.org/10.1016/j.bmcl.2005.02.039.

Sharma, S., Ying, Z., & Gomez-Pinilla, F. (2010). A pyrazole curcumin derivative restores membrane homeostasis disrupted after brain trauma. *Experimental Neurology*, *226*(1), 191–199. https://doi.org/10.1016/j.expneurol.2010.08.027.

Sharma, S., Zhuang, Y., Ying, Z., Wu, A., & Gomez-Pinilla, F. (2009). Dietary curcumin supplementation counteracts reduction in levels of molecules involved in energy homeostasis after brain trauma. *Neuroscience*, *161*(4), 1037–1044. https://doi.org/10.1016/j.neuroscience.2009.04.042.

Son, S., Kim, K.-T., Cho, D.-C., Kim, H.-J., Sung, J.-K., & Bae, J.-S. (2014). Curcumin stimulates proliferation of spinal cord neural progenitor cells via a mitogen-activated protein kinase signaling pathway. *Journal of Korean Neurosurgical Society*, *56*(1), 1–4. https://doi.org/10.3340/jkns.2014.56.1.1.

Szczepanowicz, K., Jantas, D., Piotrowski, M., Staroń, J., Leśkiewicz, M., Regulska, M., … Warszyński, P. (2016). Encapsulation of curcumin in polyelectrolyte nanocapsules and their neuroprotective activity. *Nanotechnology*, *27*(35), 355101. https://doi.org/10.1088/0957-4484/27/35/355101.

Thiyagarajan, M., & Sharma, S. S. (2004). Neuroprotective effect of curcumin in middle cerebral artery occlusion induced focal cerebral ischemia in rats. *Life Sciences*, *74*(8), 969–985. https://doi.org/10.1016/j.lfs.2003.06.042.

Urdzikova, L. M., Karova, K., Ruzicka, J., Kloudova, A., Shannon, C., Dubisova, J., … Jendelova, P. (2016). The anti-inflammatory compound curcumin enhances locomotor and sensory recovery after spinal cord injury in rats by immunomodulation. *International Journal of Molecular Sciences*, *17*(1), 15. https://doi.org/10.3390/ijms17010049.

Wang, Q., Sun, A. Y., Simonyi, A., Jensen, M. D., Shelat, P. B., Rottinghaus, G. E., … Sun, G. Y. (2005). Neuroprotective mechanisms of curcumin against cerebral ischemia-induced neuronal apoptosis and behavioral deficits. *Journal of Neuroscience Research*, *82*(1), 138–148. https://doi.org/10.1002/jnr.20610.

Wu, A., Ying, Z., & Gomez-Pinilla, F. (2006). Dietary curcumin counteracts the outcome of traumatic brain injury on oxidative stress, synaptic plasticity, and cognition. *Experimental Neurology*, *197*(2), 309–317. https://doi.org/10.1016/j.expneurol.2005.09.004.

Yao, M., Yang, L., Wang, J., Sun, Y. L., Dun, R. L., Wang, Y. J., & Cui, X. J. (2015). Neurological recovery and antioxidant effects of curcumin for spinal cord injury in the rat: A network meta-analysis and systematic review. *Journal of Neurotrauma*, *32*(6), 381–391. https://doi.org/10.1089/neu.2014.3520.

Yuan, J., Liu, W., Zhu, H., Chen, Y., Zhang, X., Li, L., … Lin, J. (2017). Curcumin inhibits glial scar formation by suppressing astrocyte-induced inflammation and fibrosis in vitro and in vivo. *Brain Research*, *1655*, 90–103. https://doi.org/10.1016/j.brainres.2016.11.002.

Yuan, J., Zou, M., Xiang, X., Zhu, H., Chu, W., Liu, W., … Lin, J. (2015). Curcumin improves neural function after spinal cord injury by the joint inhibition of the intracellular and extracellular components of glial scar. *The Journal of Surgical Research*, *195*(1), 235–245. https://doi.org/10.1016/j.jss.2014.12.055.

Zhao, J., Yu, S., Zheng, W., Feng, G., Luo, G., Wang, L., & Zhao, Y. (2010). Curcumin improves outcomes and attenuates focal cerebral ischemic injury via antiapoptotic mechanisms in rats. *Neurochemical Research*, *35*(3), 374–379. https://doi.org/10.1007/s11064-009-0065-y.

Zu, J., Wang, Y., Xu, G., Zhuang, J., Gong, H., & Yan, J. (2014). Curcumin improves the recovery of motor function and reduces spinal cord edema in a rat acute spinal cord injury model by inhibiting the JAK/STAT signaling pathway. *Acta Histochemica*, *116*(8), 1331–1336. https://doi.org/10.1016/j.acthis.2014.08.004.

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Chapter 34

Use of (−)-epigallocatechin-3-gallate on spinal cord injury

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List of abbreviations

AGEs	advanced glycation end products
AD	Alzheimer's disease
ACR	acrylamide
AKT	protein kinase B
APP	amyloid precursor protein
AQP4	astrocyte expressing aquaporin-4
ARE	antioxidant response element
α7nAChR	alpha-7 nicotinic acetylcholine receptor
BBB	blood-brain barrier
Bax	Bcl-2-associated X protein
Bcl-2	B-cell lymphoma 2
BDNF	brain-derived neurotrophic factor
CAT	catalase
COX-2	cyclooxygenase-2
EGCG	(−)-epigallocatechin-3-gallate
eNOS	endothelial nitric oxide synthase
FASN	fatty acid synthase
FGF2	fibroblast growth factor 2
GFAP	glial fibrillary acidic protein
GDNF	glial cell line-derived neurotrophic factor
GSH-Px	glutathione peroxidase
GSK-3	glycogen synthase kinase-3
HMGB1	high-mobility group box 1 protein
IRI	ischemia-reperfusion injury
iNOS	inducible nitric oxide synthase
IL-1β	interleukin-1 beta
IL-4	interleukin-4
IL-6	interleukin-6
67LR	67 kDa laminin receptor
LPS	lipopolysaccharide
MDA	malodialdehyde
MDI	motor deficit index
MMP-9	matrix metalloproinase-9
MIP-1α	macrophage inflammatory protein 1-alpha
MPO	myeloperoxidase
NF-κB	nuclear factor Kappa B
NGF	nerve growth factor
Nrf2	nuclear erythroid 2-related factor 2
NF-L	neurofilament triplet L
NADPH-d	nicotinamide adenine dinucleotide phosphate-diaphorase
NO	nitric oxide

Diagnosis and Treatment of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822498-4.00034-8

NOS	neuronal nitric oxide synthase
nNOS	neuronal nitric oxide synthase
NT3	neurotrophin-3
NGFR-p75	nerve growth factor receptor p75
PARP	poly(ADP-ribose) polymerase
PD	Parkinson's disease
PKC	protein kinase C
PI3K	phosphatidylinositol 3-kinase
ROS	reactive oxygen species
RhoA	ras homologue gene family member A
SCI	spinal cord injury
SOD	superoxide dismutase
TNFα	tumor necrosis factor alpha
TUNEL	terminal deoxynucleotidyl transferase dUTP nick end labeling
TLR4	Toll-like receptor 4
Trk-B	tropomyosin receptor kinase B
Trk-C	tropomyosin receptor kinase C
VEGF	vascular endothelial growth factor

Introduction

Over the past decades, a large number of polyphenolic compounds with neuroprotective effects have been described. One of the main sources of these molecules is green tea, the most widely consumed beverage next to water. The chemical composition of green tea contains a number of bioactive components, mainly including polyphenols, caffeine, and amino acids (Dulloo et al., 1999). Green tea polyphenols, generally known as catechins which make up 30% of the dry weight of green tea leaves, are the main bioactive constituents of green tea with a wide variety of beneficial health effects (Graham, 1992). The main catechins in green tea include (+)-catechin, (−)-epicatechin, (+)-gallocatechin, (−)-epigallocatechin, (+)-catechin gallate, (−)-epicatechin gallate, (+)-gallocatechin gallate, and (−)-epigallocatechin-3-gallate (EGCG) (Sutherland, Rahman, & Appleton, 2006). EGCG, chemically (2*R*,3*R*)-5,7-dihydroxy-2-(3,4,5trihydroxyphenyl) chroman-3-yl 3,4,5-trihydroxybenzoate (Fig. 1), is the most abundant composition of the tea catechins, account for 65% of the total catechin content and is thought to be responsible for the majority of biological activity of green tea extracts (Zaveri, 2006). In terms of bioavailability, EGCG is predominantly absorbed in the intestine and presented more than 77% in a free form in plasma as well as its metabolites excreted in urine after oral administration (Lee et al., 2002; Meng et al., 2002;

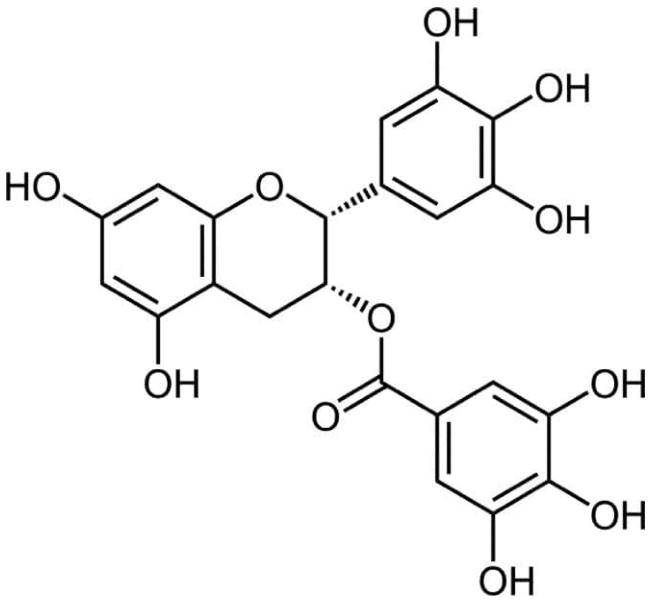

FIG. 1 Chemical structure of epigallocatechin-3-gallate. Chemical structure of epigallocatechin-3-gallate with the molar mass of 458.372 g/mol obtained from Sigma-Aldrich website. The hydroxyl groups on the B- and D-rings can bind to the free radicals and neutralized those.

Moore, Jackson, & Minihane, 2009). The half-life of EGCG in a purified form is around 3 h (Williamson, Dionisi, & Renouf, 2011). Meanwhile, it is well documented that EGCG is able to cross the blood-brain barrier (BBB) and can reach to nervous tissue even at a very low concentration, the first requirement of a dietary compound to apply neuroprotective effects (Lin, Wang, Tseng, Sung, & Tsai, 2007; Pervin et al., 2017). Several experimental studies have shown that EGCG can afford neuroprotection against brain (Itoh et al., 2011) and spinal cord (Urdzikova et al., 2017) injuries, neurodegenerative diseases (Xu, Langley, Kanthasamy, & Reddy, 2017), and peripheral nerve injuries (Renno, Benov, & Khan, 2017). These beneficial effects have been mainly attributed to free radical scavenging or anti-oxidant, anti-inflammatory, and anti-apoptotic properties of EGCG (Ohishi, Goto, Monira, Isemura, & Nakamura, 2016; Oliveira, Nabavi, Daglia, Rastrelli, & Nabavi, 2016; Weinreb, Amit, Mandel, & Youdim, 2009). In this regard, it is well known that green tea catechins due to the hydroxyl groups on the B- and D-rings of the galloylated catechins can bind to the free radicals and neutralized those (Salah et al., 1995). On the other hand, scavenging effects of EGCG lead to attenuation of nuclear factor kappa B (NF-κB) activity (Ohishi et al., 2016), which regulates genes involved in inflammatory processes such as tumor necrosis factor alpha (TNFα), cyclooxygenase-2 (COX-2), and interleukin-1 beta (IL-1β), beside modulation of nitric oxide synthase isoforms (Lawrence & Fong, 2010). Also, catechins have proven to modulate apoptosis at various points in the sequence and messengers, and so regulate the mitochondrial membrane permeabilization (Kalfon, Youdim, & Mandel, 2007; Mandel, Maor, & Youdim, 2004).

In this chapter, we have reviewed the neuroprotective effects of EGCG and its molecular mechanisms responsible for the neuroprotection following spinal cord injury (SCI). Meanwhile, we also compared the neuroprotective effects of EGCG in SCI to other neurological disorders.

In vivo studies

SCI is a complex multifactorial process caused first by ischemia or mechanical trauma and then by various mechanisms of secondary injury (Amar & Levy, 1999). The neurological outcome of SCI depends on the extent of secondary cellular, molecular, and biochemical cascades such as oxygen free radical-induced lipid peroxidation, inflammatory reaction, and apoptosis (Hall, 1993; Liu et al., 1997; Popovich, Wei, & Stokes, 1997). In recent years, much attention has been paid to secondary injuries, as they appear to be prone to therapeutic interventions that may include the use of natural antioxidants, anti-inflammatory, and anti-apoptotic agents (Khalatbary, 2014) such as EGCG (Table 1). In this regard, our previous studies have shown that intraperitoneal injection of EGCG (50 mg/kg, i.p., immediately and 1 h after SCI)

TABLE 1 Neuroprotective effects of epigallocatechin-3-gallate on spinal cord injury.

Model of injury	Treatment schedule	Finding	Possible mechanism	Author	Year
Weight-drop method	50 mg/kg, intraperitoneal, immediately and 1 h after spinal cord injury	Decreased bcl-2-associated X protein and increased b-cell lymphoma 2 expression	Anti-apoptotic activity	Khalatbary et al.	2010
Weight-drop method	50 mg/kg, intraperitoneal, immediately and 1 h after spinal cord injury	Decreased tissue lipid peroxide level	Anti-oxidant activity	Khalatbary and Ahmadvand	2010
Weight-drop method	50 mg/kg, intraperitoneal, immediately and 1 h after spinal cord injury	Attenuated tumor necrosis factor alpha, interleukin-1 beta, Nitrotyrosine, inducible nitric oxide synthase, cyclooxygenase-2 and poly (ADP-ribose) polymerase expression, and decreased myeloperoxidase activity	Anti-inflammatory activity	Khalatbary and Ahmadvand	2011
Vascular clip method	100 mg/kg, between 24 and 72 h after spinal cord injury	Down-regulated astrocyte expressing aquaporin-4 and glial fibrillary acidic protein	Anti-edema effect	Ge et al.	2013

Continued

TABLE 1 Neuroprotective effects of epigallocatechin-3-gallate on spinal cord injury—cont'd

Model of injury	Treatment schedule	Finding	Possible mechanism	Author	Year
Vascular clip method	100 mg/kg, intraperitoneal, immediately after spinal cord injury	Reduced the releasing of tumor necrosis factor alpha and interleukin-1 beta, decreased the water content	Regulating p38MAPK\NF -κB \AQP4 signaling pathway	Tao and Zhu	2013
Weight-drop method	Intrathecal administration of 10 or 20 mg/kg, immediately after spinal cord injury	Improved locomotor function	Up-regulation of brain-derived neurotrophic factor and glial cell line-derived neurotrophic factor	Tian et al.	2013
Weight-drop method	20 mg/kg/hour for continuous 36 h, intravenous, in acutely (initiated within 4 h post-trauma 0 time) and chronically (initiated after 12 months of spinal cord injury onset	Improved motor and sensory functions	Reduced lesion size area	Renno et al.	2014
Weight-drop method	30 mg/kg, intraperitoneal, 30 min after and daily during the first week post-spinal cord injury	Reduced thermal hyperalgesia and gliosis	Via RhoA and FASN pathway	Álvarez-Pérez et al.	2016
Balloon compression method	Intra-spinal injection of 50 mg/kg, immediately and then weekly for up to 28 days	Attenuated nuclear Factor Kappa B pathway and increased gene expression of fibroblast growth factor 2 and vascular endothelial growth factor	Enhanced neuroregeneration	Urdzikova et al.	2017
Weight-drop method	50-mg/kg, intraperitoneal, before and after ischemia-reperfusion injury	Decreased malodialdehyde, attenuated caspase-3, tumor necrosis factor alpha, and inducible nitric oxide synthase, reduction of motor deficit index	Anti-inflammatory and anti-apoptotic activity	Ahadi et al.	2019

A summary of in vivo studies on the neuroprotective effects of epigallocatechin-3-gallate against spinal cord injury, along with treatment schedules, findings, and related molecular mechanisms, is presented in this table.

can protect spinal cord tissue and improve behavioral function after traumatic and ischemia-reperfusion injury (IRI) in rats (Ahadi, Zargari, & Khalatbary, 2019; Khalatbary & Ahmadvand, 2010; Khalatbary et al., 2010). In regard to mechanisms of neuroprotective effects of EGCG, our results revealed that malodialdehyde (MDA) levels as an index of tissue lipid peroxidation, an important pathologic event in post-traumatic neuronal degeneration, were significantly decreased in traumatized spinal cord tissue after EGCG treatment (Khalatbary & Ahmadvand, 2010). It is well documented that EGCG due to hydroxyl groups can bind to the free radicals and neutralize those, while can indirectly increase the body's endogenous antioxidants (Salah et al., 1995). We detected immunohistochemically anti-apoptotic properties of EGCG with decreasing pro-apoptotic protein Bax and increasing anti-apoptotic protein Bcl-2 staining in EGCG-treated rats, which was correlated with terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) staining method (Khalatbary et al., 2010). Also, our other study showed that EGCG treatment (50 mg/kg, i.p., immediately and 1 h after SCI) attenuated pro-inflammatory cytokines such as TNFα and IL-1β in traumatized spinal cord tissue (Khalatbary & Ahmadvand, 2011). In line with the anti-inflammatory properties of EGCG, Ge et al., 2013 documented that EGCG treatment (100 mg/kg, between 24 and 72 h after SCI) decreased spinal tissue edema through down-regulation of astrocyte expressing

aquaporin-4 (AQP4), which plays a critical role in the transport of water from blood/CSF to spinal cord parenchyma, and through down-regulation of glial fibrillary acidic protein (GFAP) as a specific marker of astrocytes. Also, another study found that attenuated NF-κB pathway is a pivotal anti-inflammatory affect of EGCG (intra-spinal injection of 50 mg/kg EGCG immediately and then weekly for up to 28 days) after SCI (Urdzikova et al., 2017). Meanwhile, this study showed a significant increase in the gene expression of fibroblast growth factor 2 (FGF2) and vascular endothelial growth factor (VEGF) after SCI. Tao and Zhu (2013) documented that EGCG (100 mg/kg, i.p., immediately after SCI) can protect secondary SCI by potential mechanism of regulating p38MAPK\NF -κB\AQP4 signaling pathway and thus reduce edema after SCI in rats. Also, another study documented that intrathecal administration of EGCG (10 or 20 mg/kg immediately after SCI) can significantly improve locomotors recovery, which may be related to the inhibition of Bcl-2-associated X protein (Bax) and to the up-regulation of brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF) (Tian et al., 2013). Studies have shown that EGCG has beneficial effects not only on the tissue destruction but also on behavioral and functional outcome, so that intravenous infusion of EGCG (20 mg/kg/hour for continuous 36 h) in acutely (initiated within 4 h post-trauma 0 time) and chronically (initiated after 12 months of SCI onset) spinal cord injured rats improved significantly motor and sensory functions measured using Basso-Beattie-Bresnehan behavioral score test, Louisville forced swim test, and pain behavior assessment tests (Renno et al., 2014). One of the common complications of SCI is neuropathic pain. About the effect of EGCG on neuropathic pain, Álvarez-Pérez et al. (2016) documented that short time EGCG treatment (30 mg/kg i.p., 30 min after and daily during the first week post-SCI) reduced thermal hyperalgesia and gliosis via ras homologue gene family member A (RhoA) and fatty acid synthase (FASN) pathway. In this regard, it is mentioned that some biological properties of EGCG are attributed to its inhibitory action on FASN (Singh, Shankar, & Srivastava, 2011). In another study, the synergistic effects of curcumin and EGCG in an animal model of acute SCI were investigated (Ruzicka et al., 2018). Results of this study revealed that combination of curcumin and EGCG reduced glial scar formation, increased axonal sprouting, and changed the amount of macrophage inflammatory protein 1-alpha (MIP-1α), IL-1β, interleukin-4 (IL-4), and interleukin-6 (IL-6). Recently, our laboratory assessed the neuroprotective effects of EGCG on spinal cord IRI in rats (Ahadi et al., 2019). The level of MDA was significantly reduced in EGCG-treated rats. Attenuated caspase-3 (Fig. 2), TNFα (Fig. 3), and inducible nitric oxide synthase (iNOS) expression could be significantly detected in the EGCG-treated rats. Also, EGCG reduced the extent of degeneration of the spinal cord neurons, in addition to a significant reduction of motor deficit index (MDI). Overall, the behavioral, biochemical, and histopathological evidences demonstrated that pre- (50 mg/kg, i.p., before IRI) and post-ischemic (50 mg/kg, i.p., after IRI) treatment with EGCG had protective effects against spinal cord IRI in rats.

In vitro studies

A number of in vitro studies regarding EGCG's neuroprotection and its underlying molecular mechanisms in neural cells are starting to accumulate which summarized in Table 2.

In regard to anti-apoptotic effects of EGCG, some studies indicated that EGCG led to significant inhibition of apoptosis in PC12 cells by scavenging reactive oxygen species (ROS), modulating cytochrome *c* and caspases, activation of phosphoinositide 3-kinase (PI3K), activation of survival-promoting pathways, and inhibition of glycogen synthase kinase-3 (GSK-3) (Hou et al., 2008; Jung, Han, et al., 2007; Jung, Mo, et al., 2007; Koh et al., 2003; Mandel, Reznichenko, Amit, & Youdim, 2003; Nie, Cao, & Zhao, 2002; Nie, Jin, Cao, Shen, & Zhao, 2002; Srividhya & Kalaiselvi, 2013). Also, studies showed that EGCG has a protective effect on cell death in SH-SY5Y (or SHSY-5Y) cell line through inhibiting ROS production and caspase activity along with activation of protein kinase C (PKC) (Avramovich-Tirosh et al., 2007; Jeong et al., 2004; Levites, Amit, Youdim, & Mandel, 2002; Tai & Truong, 2010). EGCG protects N18D3 neural cells from quinolinic acid-induced apoptosis by regulation of phosphatidyl inositol 3-kinase (PI3K) and modulation of pro- and anti-apoptotic genes due to decreased intra-cellular calcium levels and nitric oxide (NO) production (Zhang et al., 2014). Results of a study showed that EGCG protects the neuronal cells against human prion protein-induced damage through inhibiting Bax and cytochrome *c* translocation and autophagic pathways in primary neuron cells (Lee et al., 2015). Recently, it was documented that EGCG reduced amyloid beta-induced neurotoxicity via inhibiting endoplasmic reticulum stress-mediated apoptosis in SH-SY5Y cells in a dose-dependent manner which is contributed to the down-regulation of cleaved-caspase-3 and -12 (Du et al., 2018).

In regard to microglial activation, a study indicated that EGCG exerts significant protection against microglial activation-induced neuronal injury through the down-regulation of iNOS and TNFα expression (Li, Huang, Fang, & Le, 2004).

In regard to antioxidant properties of EGCG, in vitro study revealed that EGCG treatment decreased MDA level, up-regulated superoxide dismutase (SOD) and catalase (CAT) levels against advanced glycation end products (AGEs)-induced

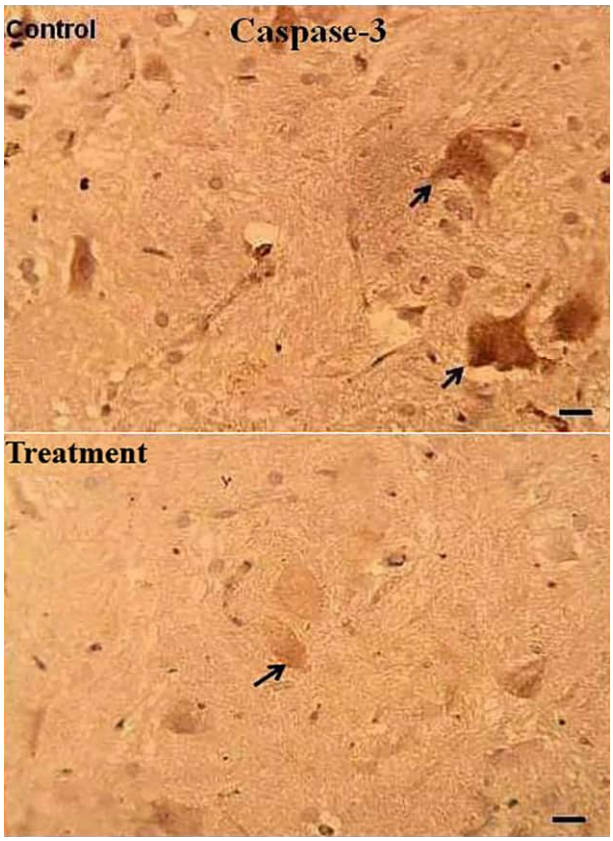

FIG. 2 Immunohistochemical staining of casepase-3. Light photomicrographs show immunohistochemical expression of caspase-3 as an index of apoptosis in control and epigallocatechin-3-gallate treatment groups after spinal cord injury (magnification, ×200). The positive staining of caspase-3 is presented by a brown color of cytoplasm (arrows). This figure prepared in our laboratory.

injury in neuronal cell culture (Lee & Lee, 2007). Also, it was documented that EGCG decreased markedly ROS production via the SIRT1/PGC-1α signaling pathway in 1methyl4-phenyl-pyridine (MMP+)-induced PC12 cells damage (Ye et al., 2012). Evaluation of EGCG's effects on acrylamide-induced cytotoxicity in PC12 cells showed that EGCG inhibited the cytotoxicity of acrylamide and increased the cell viability (Esmaeelpanah, Razavi, Vahdati Hasani, & Hosseinzadeh, 2018).

In regard to anti-inflammatory properties of EGCG, in vitro studies also revealed that EGCG treatment potently inhibited lipopolysaccharide (LPS)-activated microglial secretion of TNFα and significantly exerted anti-inflammatory effects partly as a suppressor of TNFα signaling via the NF-κB pathway in SH-SY5Y (Li et al., 2004) and RPE cells (Fu & Koo, 2006).

It is well known that anti-oxidants can also affect the stem cells differentiation and potency. In this regard, using the PC12 cell model showed for the first time that low concentration of EGCG and unfractionated green tea polyphenols potentiate nerve growth factor (NGF)-induced and BDNF-induced neuritogenesis likely through induction sub-lethal levels of ROS or dependent on 67 kDa laminin receptor (67LR) and H_2O_2 (Gundimeda et al., 2014; Gundimeda, McNeill, Schiffman, Hinton, & Gopalakrishna, 2010).

Applications to other areas of neuroscience

It is well known that EGCG has neuroprotective effects in another neurological disorder such as brain injury, nerve injury, and neurodegenerative diseases (Table 3).

In regard to brain ischemia, it was documented that EGCG through deoxidizing peroxynitrate/peroxynitrite attenuates NO-3/NO-2 concentration without affecting blood flow (Nagai et al., 2002). Another study demonstrated that EGCG due to attenuation of the malondialdehyde level and oxidized/total glutathione ratio protects brain tissue against transient middle cerebral artery occlusion (Choi, Kim, Lee, Kim, & Kim, 2004). A possible mechanism involved in the neuroprotective

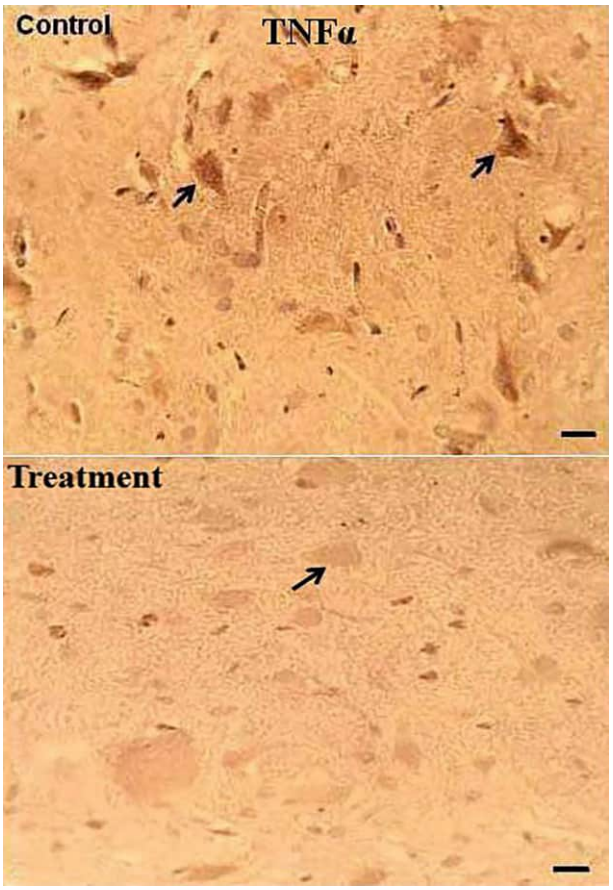

FIG. 3 Immunohistochemical staining of tumor necrosis factor alpha. Light photomicrographs show immunohistochemical expression of tumor necrosis factor alpha (TNFα) as an index of inflammation in control and epigallocatechin-3-gallate treatment groups after spinal cord injury (magnification, ×200). The positive staining of TNFα is presented by a brown color of cytoplasm (arrows). This figure prepared in our laboratory.

effect of EGCG is inhibition of matrix metalloproinase-9 (MMP-9) activity which plays an important role in the pathophysiology of brain ischemia (Park et al., 2010). Also, EGCG exerts protective effect via the activation of the nuclear erythroid 2-related factor 2 (Nrf2) against cerebral ischemia (Han et al., 2014). A further study showed that EGCG promotes angiogenesis via up-regulation of the Nrf2 signaling pathway in the early stage of ischemic stroke (Bai et al., 2017). Modulation of the inflammation-related molecules such as TNFα, IL-1β, IL-6, NF-κB /p65, COX-2, and iNOS is another possible mechanism of action of EGCG following focal cerebral ischemia/reperfusion injury (Zhang, Li, Jiang, Chen, & Huang, 2015). It was found that EGCG also preserves mitochondrial energetics (complex I—V) and citrate synthase activity after brain ischemia (Sutherland et al., 2005). While, it was documented that EGCG through eliminating free radical generation, inhibiting apoptosis, and increasing neural stem cells protects brain against traumatic injury in rats (Itoh et al., 2011, 2012, 2013).

In regard to nerve injury, results of a study showed significantly higher neurofilament triplet L (NF-L) protein expression in EGCG-treated rats compared to non-treated rats following optic nerve crush injury (Xie et al., 2010). Also, EGCG through attenuation of nicotinamide adenine dinucleotide phosphate-diaphorase (NADPH-d)/neuronal nitric oxide synthase (nNOS) increased motor neuron survival time following peripheral nerve crush injury in rats (Wei et al., 2011). Intrathecal injection of EGCG improved pain-like behaviors through decreasing NF-κB, Toll-like receptor 4 (TLR4), TNFα, high-mobility group box 1 protein (HMGB1), and IL-1β following chronic constriction injury (Kuang et al., 2012). EGCG due to the down-regulation of apoptosis related genes, up-regulation of glutathione reductase, and up-regulation of survivin gene accelerates nerve regeneration and improves functional recovery following rat sciatic nerve crush injury (Renno et al., 2017; Renno, Al-Maghrebi, Rao, & Khraishah, 2015). Also, Renno et al. documented that the EGCG neuroprotective effects are mediated through the modulation of BDNF, GDNF and neurotrophin-3 (NT3) neurotrophic factor and their receptors tropomyosin receptor kinase B (Trk-B), tropomyosin receptor kinase C (Trk-C), and nerve growth factor receptor p75 (NGFR-p75) following sciatic nerve crush injury (Renno, Khan, & Benov, 2016).

TABLE 2 In vitro neuroprotective effects of epigallocatechin-3-gallate.

Model of induction	Cell type	Finding	Possible mechanism	Author	Year
Apoptosis	PC12	Inhibited apoptosis	Modulation of cytochrome *c* and caspases, activation of phosphatidylinositol 3-kinase and survival-promoting pathways, inhibition of glycogen synthase kinase-3	Nie et al., Koh et al., Mandel et al., Jung et al., Hou et al., Strividhya and Kalaisali	2002a, 2002b, 2003, 2003, 2007a, 2007b, 2008, 2013
Apoptosis	SH-SY5Y	Inhibited apoptosis	Inhibition of reactive oxygen species production and caspase activity, activation of protein kinase C	Levites et al., Jeong et al., Avramovich-Tirosh et al., Tia and Truong	2002, 2004, 2007, 2010
Apoptosis	N18D3	Attenuated apoptosis	Regulation of phosphatidylinositol 3-kinase and modulation of pro- and anti-apoptotic genes	Zhang et al.	2014
Apoptosis	Primary neuron cells	Attenuated apoptosis	Inhibition of Bcl-2-associated X protein and cytochrome *c* translocation and autophagic pathways	Lee et al.	2015
Apoptosis	SH-SY5Y	Reduced apoptosis	Inhibiting endoplasmic reticulum stress-mediated apoptosis	Du et al.	2018
Microglial activation	SH-SY5Y	Inhibited LPS-activated microglial secretion of nitric oxide and tumor necrosis factor alpha	Down-regulation of inducible nitric oxide synthase and tumor necrosis factor alpha expression	Lee et al.	2004
Oxidative stress	Neuronal cells culture	Up-regulated superoxide dismutase and catalase levels, decreased malodialdehyde and carbonyl levels, and advanced glycation end products formation	Antioxidative properties and interfering with AGEs-RAGE interaction mediated pathways	Lee and Lee	2007
Oxidative stress	PC12	Decreased reactive oxygen species production	via the SIRT1/PGC-1α signaling pathway	Ye et al.	2012
Oxidative stress	PC12	Inhibited the cytotoxicity of acrylamide and increased the cell viability	Without providing possible mechanisms	Esmaeelpanah et al.	2018
Inflammation	SH-SY5Y and ARPE-19	Anti-inflammatory effects	Suppression of tumor necrosis factor alpha signaling via the nuclear Factor Kappa B pathway	Li et al., Fu and Koo	2004, 2006
Neurogenesis	PC12	Potentiated nerve growth factor- and brain derived neurotrophic factor-induced neuritogenesis	Involvement of sub-lethal levels of reactive oxygen species or dependent on 67 LR and H2O2	Gundimeda et al.	2010, 2014

A summary of in vitro studies on the neuroprotective effects of epigallocatechin-3-gallate with related molecular mechanisms is presented in this table.

TABLE 3 Neuroprotective effects of epigallocatechin-3-gallate against other neurological disorders.

Model of injury	Treatment schedule	Finding	Possible mechanism	Author	Year
Brain injury	50 mg/kg, intraperitoneal, immediately after ischemia	Deoxidizing peroxynitrate/ peroxynitrite without affecting blood flow	Attenuation of NO_3^-/ NO_2^-	Nagai et al.	2002
Brain injury	25 mg and 50 mg/kg, intraperitoneal, immediately after ischemia	Attenuated malodialdehyde level and oxidized/total glutathione ratio	Antioxidant effects	Choi et al.	2004
Brain injury	50 mg/kg, intraperitoneal, immediately after ischemia	Reduced neuronal damage	Reduction of matrix metalloproinase-9 activity	Park et al.	2010
Brain injury	40 mg/kg, intraperitoneal, once daily for three consecutive days prior to surgery	Reduced neuronal damage	Activation of nuclear erythroid 2-related factor 2 /antioxidant response element signaling	Han et al.	2014
Brain injury	50 mg/kg, intraperitoneal, immediately after surgery and once daily till day 7	Promoted angiogenesis	Up-regulation of the nuclear erythroid 2-related factor 2 signaling pathway	Bai et al.	2017
Brain injury	50 mg/kg, intraperitoneal, immediately after ischemia	Modulated inflammatory responses	Amelioration of tumor necrosis factor alpha, interleukin-1 beta, interleukin-6, nuclear factor kappa B /p65, cyclooxygenase-2, inducible nitric oxide synthase	Zhang et al.	2015
Brain injury	50 mg/kg, daily for 1 day and 1 h before ischemia	Reduced nitric oxide synthase and inducible nitric oxide synthase, increased endothelial nitric oxide synthase, preserved complex I–V	Complex signal transduction mechanisms	Sutherland et al.	2005
Brain injury	Consuming 0.1% (*w*/*v*) epigallocatechin-3-gallate drinking water ad libitum before and after traumatic injury	Increased neural stem cells number around the damaged area	Antioxidant and antiapoptotic activities	Itoh et al.	2011, 2013, 2012
Brain injury	100 mg/kg, intraperitoneal, after traumatic injury	Reduced interleukin-1 beta and tumor necrosis factor alpha mRNA expression, inhibited astrocyte expressing aquaporin-4 and glial fibrillary acidic protein, elevated superoxide dismutase and glutathione peroxidase activities, decreased nicotinamide adenine dinucleotide phosphate oxidase activation	Inhibition of inflammation and oxidative stress	Zhang et al.	2015

Continued

TABLE 3 Neuroprotective effects of epigallocatechin-3-gallate against other neurological disorders—cont'd

Model of injury	Treatment schedule	Finding	Possible mechanism	Author	Year
Nerve injury	25 mg/kg, injected daily for 5 days and 2 mg/kg orally daily afterwards	Increased density of retinal ganglion cells	Up-regulation of neurofilament triplet L protein expression	Ahadi et al.	Xie 2010
Nerve injury	25 mg/kg, intraperitoneal or orally, daily for 5 days and 2 mg/kg orally daily afterwards	Enhanced motor neuron survival time	Attenuation of nicotinamide adenine dinucleotide phosphate-diaphorase-d/neuronal nitric oxide synthase	Wei et al.	2011
Nerve injury	1 mg/kg, intrathecal, once daily from 1 day before to 3 days after chronic constriction injury	Decreased chronic neuropathic pain	Down-regulation of Toll-like receptor 4, nuclear factor kappa B, high-mobility group box 1 protein, tumor necrosis factor alpha and interleukin-1 beta protein expression	Kuang et al.	2012
Nerve injury	50 mg/kg, intraperitoneal, following rat sciatic nerve crush injury	Enhanced functional recovery and accelerated nerve regeneration	Down-regulation of apoptosis related genes, up-regulation of survivin gene, and up-regulation of glutathione reductase	Renno et al.	2017, 2015
Nerve injury	50 mg/kg, intraperitoneal, starting 1 h after sciatic nerve crush injury	Modulated brain-derived neurotrophic factor, glial cell line-derived neurotrophic factor and neurotrophin-3 and their receptors tropomyosin receptor kinase B, tropomyosin receptor kinase C, and nerve growth factor receptor p75	Up-regulation of neurotrophic factors and their receptors	Renno et al.	2016
Nerve injury	50 mg/kg, intraperitoneal, 1 h after nerve transaction and followed for 3 days	Reduced neural apoptosis	Modulation of malodialdehyde levels, catalase and superoxide dismutase activities, and Caspase3 and cyclooxygenase-2 expression	Kian et al.	2019
Alzheimer's disease	20 mg/kg, intraperitoneal, daily for 60 days	Effective prophylaxis for Alzheimer's disease	Modulation of amyloid precursor protein cleavage and cerebral amyloidosis	Rezai-Zadeh et al.	2005
Neurodegenerative disease	2 or 6 mg/day for 4 weeks, intragastrically	Improved degenerative changes of the brain	Modulation of beta-amyloid and amyloid precursor protein	He et al.	2012

TABLE 3 Neuroprotective effects of epigallocatechin-3-gallate against other neurological disorders—cont'd

Model of injury	Treatment schedule	Finding	Possible mechanism	Author	Year
Neurodegenerative disease	2 mg/kg/day for 4 weeks, intragastrically	Ameliorated learning and memory deficits	Modulation of TrkA/$p75^{NTR}$ signaling and apoptosis	Liu et al.	2014
Parkinson's disease	No available	Alleviated dopaminergic neuronal injury in Parkinson's disease	Inhibition of nitric oxide and tumor necrosis factor alpha	Li et al.	2004
Parkinson's disease	25 mg/kg, oral administration for 7 days	Neurorescue effects in Parkinson's disease	Regulation of the iron-export protein ferroportin and reduction of oxidative stress	Xu et al.	2017
Neurodegenerative disease	300 μg, oral gavage twice daily	Delayed disease onset, induced regeneration of hippocampal axons	Reduction of the inflammatory infiltrates	Herges et al.	2011

A summary of in vivo studies on the neuroprotective effects of epigallocatechin-3-gallate against other neurological disorders, along with treatment schedules, findings, and related molecular mechanisms, is presented in this table.

Recently, we found that EGCG protects sensory and motor neurons through attenuation of COX-2 and caspase-3, and elevation of SOD and CAT activities in rat sciatic nerve transaction model (Kian, Khalatbary, Ahmadvand, Karimpour Malekshah, & Shams, 2019).

In regard to neurodegenerative diseases, research on Alzheimer's disease (AD) revealed that EGCG treatment in Alzheimer transgenic mice reduces cerebral amyloidosis and modulates amyloid precursor protein (APP) cleavage (Rezai-Zadeh et al., 2005). Some existing evidence suggests that the EGCG's neuroprotection against Aβ-induced cell death is somewhat due to phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) transduction signaling and alpha-7 nicotinic acetylcholine receptor (α7nAChR) activity (Zhang et al., 2014). Liu et al. (2014) documented that EGCG through modulating the balance of TrkA/p75NTR signaling in APP/PSI transgenic mice ameliorated memory and learning deficits. Results of a study supported that EGCG in Parkinson's disease (PD) can be a therapeutic approach to alleviate microglia-mediated dopaminergic neuronal injury (Li et al., 2004). Recently the neurorescue effects of EGCG have been proven in a mouse model of PD assessed with behavioral and neurotransmitter analysis (Xu et al., 2017). Also, results of another study indicated that combination therapy of glatiramer acetate and EGCG can be a safe and promising approach for multiple sclerosis (Herges et al., 2011).

Conclusion

In recent years, dietary polyphenols have attracted a lot of attention due to their interesting biological activities. An expanding body of results obtained by pre-clinical in vitro and in vivo studies on the use of EGCG as a therapeutic option for SCI confirmed its neuroprotective properties. These beneficial effects have been mainly attributed to free radical scavenging or anti-oxidant, anti-inflammatory, and anti-apoptotic properties of EGCG. The evidence presented in this review suggests the potential of EGCG in both preventive and therapeutic usages for a variety of SCI models. At the same time, there is a lot of evidence that this natural polyphenol has proper absorption and crosses the BBB with minimal side effects. Of course, considering that no study has been conducted on the neuroprotective effects of EGCG following SCI in human, the design of clinical trials are required regarding EGCG's neuroprotection and its possible mechanisms as well as determining the dose and course of treatment remain to be explored following SCI.

Mini-dictionary of terms

- Catechins: They are natural polyphenol compounds with potent anti-oxidant activity harvested from a variety of sources.
- Free radical scavenging: Inactivation of free radicals in a biological system.

- Endogenous anti-oxidants: They are products of the body's metabolism which act as free radical scavengers.
- Synergistic effects: An effect arising between two or more substances that create a greater effect than the sum of their individual effects.
- Motor deficit index: Evaluation of neurological function with scoring of the placing/stepping reflex and ambulation.
- Intrathecal administration: Injection of therapeutic agents into the spinal sub-arachnoid space.
- Neuritogenesis: A complex phenomenon involving multiple interactions between the extracellular matrix and growing neurite.

Key facts of EGCG

- EGCG has anti-oxidant, anti-inflammatory, and anti-apoptotic properties.
- EGCG is able to cross the BBB and can reach to injured nervous tissue even at a very low concentration.
- Several experimental studies have shown that EGCG can afford neuroprotection against brain and SCIs, neurodegenerative diseases, and peripheral nerve injuries.
- The behavioral, biochemical, and histopathological evidences demonstrated EGCG treatment has protective effects against experimental model of SCI.
- The neuroprotective effects of EGCG are dose-dependent and therefore it is necessary to determine the appropriate dose.

Summary points

- Epigallocatechin-3-gallate is thought to be responsible for the most biological activities of green tea catechins, including anti-oxidant, anti-inflammatory, and anti-apoptotic properties.
- Epigallocatechin-3-gallate has been shown to be some of the neuroprotective effects against injury to the peripheral and central nervous system.
- Treatment of SCI with epigallocatechin-3-gallate improves neurological function and decreases spinal tissue loss.
- Neuroprotective effects of epigallocatechin-3-gallate against SCI are largely due to its anti-inflammatory, anti-apoptotic, and anti-oxidant properties.
- This paper summarizes current knowledge on neuroprotective effects of epigallocatechin-3-gallate and their molecular mechanisms responsible for the neuroprotection following SCI.

References

Ahadi, S., Zargari, M., & Khalatbary, A. R. (2019). Assessment of the neuroprotective effects of (−)epigallocatechin-3-gallate on spinal cord ischemiareperfusion injury in rats. *The Journal of Spinal Cord Medicine*, 1–8.

Álvarez-Pérez, B., Homs, J., Bosch-Mola, M., Puig, T., Reina, F., Verdú, E., et al. (2016). Epigallocatechin-3-gallate treatment reduces thermal hyperalgesia after spinal cord injury by down-regulating RhoA expression in mice. *European Journal of Pain*, *20*, 341–352.

Amar, A. P., & Levy, M. L. (1999). Pathogenesis and pharmacological strategies for mitigating secondary damage in acute spinal cord injury. *Neurosurgery*, *44*, 1027–1039.

Avramovich-Tirosh, Y., Reznichenko, L., Mit, T., Zheng, H., Fridkin, M., Weinreb, O., et al. (2007). Neurorescue activity, APP regulation and amyloid-beta peptide reduction by novel multi-functional brain permeable iron-chelating-antioxidants, M-30 and green tea polyphenol, EGCG. *Current Alzheimer Research*, *4*, 403–411.

Bai, Q., Lyu, Z., Yang, X., Pan, Z., Lou, J., & Dong, T. (2017). Epigallocatechin-3-gallate promotes angiogenesis via up-regulation of Nfr2 signaling pathway in a mouse model of ischemic stroke. *Behavioral Brain Research*, *321*, 79–86.

Choi, Y. B., Kim, Y. I., Lee, K. S., Kim, B. S., & Kim, D. J. (2004). Protective effect of epigallocatechin gallate on brain damage after transient middle cerebral artery occlusion in rats. *Brain Research*, *1019*, 47–54.

Du, K., Liu, M., Zhong, X., Yao, W., Xiao, Q., Wen, Q., et al. (2018). Epigallocatechin gallate reduces amyloid β-induced neurotoxicity via inhibiting endoplasmic reticulum stress-mediated apoptosis. *Molecular Nutrition & Food Research*, *62*, e1700890.

Dulloo, A. G., Duret, C., Rohrer, D., Girardier, L., Mensi, N., Fathi, M., et al. (1999). Efficacy of a green tea extract rich in catechin polyphenols and caffeine in increasing 24-h energy expenditure and fat oxidation in humans. *The American Journal of Clinical Nutrition*, *70*, 1040–1045.

Esmaeelpanah, E., Razavi, B. M., Vahdati Hasani, F., & Hosseinzadeh, H. (2018). Evaluation of epigallocatechin Gallate and epicatechin gallate effects on acrylamide-induced neurotoxicity in rats and cytotoxicity in PC 12 cells. *Drug and Chemical Toxicology*, *41*, 441–448.

Fu, Y., & Koo, M. W. (2006). EGCG protects HT-22 cells against glutamateinduced oxidative stress. *Neurotoxicity Research*, *10*, 23–30.

Ge, R., Zhu, Y., Diao, Y., Tao, L., Yuan, W., & Xiong, X. C. (2013). Anti-edema effect of epigallocatechin gallate on spinal cord injury in rats. *Brain Research*, *1527*, 40–46.

Graham, H. N. (1992). Green tea composition, consumption, and polyphenol chemistry. *Preventive Medicine*, *21*, 334–350.

Gundimeda, U., McNeill, T. H., Fan, T. K., Deng, R., Rayudu, D., Chen, Z., et al. (2014). Green tea catechins potentiate the neuritogenic action of brain-derived neurotrophic factor: Role of 67-kDa laminin receptor and hydrogen peroxide. *Biochemical and Biophysical Research Communications*, *445*, 218–224.

Gundimeda, U., McNeill, T. H., Schiffman, J. E., Hinton, D. R., & Gopalakrishna, R. (2010). Green tea polyphenols potentiate the action of nerve growth factor to induce neuritogenesis: Possible role of reactive oxygen species. *Journal of Neuroscience Research*, *88*, 3644–3655.

Hall, E. D. (1993). Lipid antioxidants in acute central nervous system injury. *Annals of Emergency Medicine*, *22*, 1022–1027.

Han, J., Wang, M., Jing, X., Shi, H., Ren, M., & Lou, H. (2014). (−)-epigallocatechin gallate protects against cerebral ischemiainduced oxidative stress via Nrf2/ARE signaling. *Neurochemical Research*, *39*, 1292–1299.

Herges, K., Millward, J. M., Hentschel, N., Infante-Duarte, C., Aktas, O., & Zipp, F. (2011). Neuroprotective effect of combination therapy of glatiramer acetate and epigallocatechin-3-gallate in neuroinflammation. *PLoS One*, *6*, e25456.

Hou, R. R., Chen, J. Z., Chen, H., Kang, X. G., Li, M. G., & Wang, B. R. (2008). Neuroprotective effects of (−)-epigallocatechin-3-gallate (EGCG) on paraquat-induced apoptosis in PC12 cells. *Cell Biology International*, *32*, 22–30.

Itoh, T., Imano, M., Nishida, S., Tsubaki, M., Hashimoto, S., Ito, A., et al. (2011). (−)-Epigallocatechin-3-gallate protects against neuronal cell death and improves cerebral function after traumatic brain injury in rats. *Neuromolecular Medicine*, *13*, 300–309.

Itoh, T., Imano, M., Nishida, S., Tsubaki, M., Mizuguchi, N., Hashimoto, S., et al. (2012). (−)-Epigallocatechin-3-gallate increases the number of neural stem cells around the damaged area after rat traumatic brain injury. *Journal of Neural Transmission (Vienna)*, *119*, 877–890.

Itoh, T., Tabuchi, M., Mizuguchi, N., Imano, M., Tsubaki, M., Nishida, S., et al. (2013). Neuroprotective effect of (−)-epigallocatechin3-gallate in rats when administered pre- or post-traumatic brain injury. *Journal of Neural Transmission (Vienna)*, *120*, 767–783.

Jeong, J. H., Kim, H. J., Lee, T. J., Kim, M. K., Park, E. S., & Choi, B. S. (2004). Epigallocatechin 3-gallate attenuates neuronal damage induced by 3-hydroxykynurenine. *Toxicology*, *195*, 53–60.

Jung, J. Y., Han, C. R., Jeong, Y. J., Kim, H. J., Lim, H. S., Lee, K. H., et al. (2007). Epigallocatechin gallate inhibits nitric oxide-induced apoptosis in rat PC12 cells. *Neuroscience Letters*, *411*, 222–227.

Jung, J. Y., Mo, H. C., Yang, K. H., Jeong, Y. J., Yoo, H. G., Choi, N. K., et al. (2007). Inhibition by epigallocatechin gallate of CoCl2-induced apoptosis in rat PC12 cells. *Life Sciences*, *80*, 1355–1363.

Kalfon, L., Youdim, M. B., & Mandel, S. A. (2007). Green tea polyphenol (−)-epigallocatechin-3-gallate promotes the rapid protein kinase C- and proteasome-mediated degradation of bad: Implications for neuroprotection. *Journal of Neurochemistry*, *100*, 992–1002.

Khalatbary, A. R. (2014). Natural polyphenols and spinal cord injury. *Iranian Biomedical Journal*, *18*, 120–129.

Khalatbary, A. R., & Ahmadvand, H. (2010). Effects of epigallocatechin gallate on tissue lipid peroxide levels in traumatized spinal cord of rat. *Iranian Journal of Basic Medical Sciences*, *13*, 139–142.

Khalatbary, A. R., & Ahmadvand, H. (2011). Anti-inflammatory effect of the epigallocatechin gallate following spinal cord trauma in rat. *Iranian Biomedical Journal*, *15*, 31–37.

Khalatbary, A. R., Tiraihi, T., Boroujeni, M. B., Ahmadvand, H., Tavafi, M., & Tamjidipoor, A. (2010). Effects of epigallocatechin gallate on tissue protection and functional recovery after contusive spinal cord injury in rats. *Brain Research*, *1306*, 168–175.

Kian, K., Khalatbary, A. R., Ahmadvand, H., Karimpour Malekshah, A., & Shams, Z. (2019). Neuroprotective effects of (−)-epigallocatechin-3-gallate (EGCG) against peripheral nerve transection-induced apoptosis. *Nutritional Neuroscience*, *22*, 578–586.

Koh, S. H., Kim, S. H., Kwon, H., Park, Y., Kim, K. S., Song, C. W., et al. (2003). Epigallocatechin gallate protects nerve growth factor differentiated PC12 cells from oxidative-radical-stress-induced apoptosis through its effect on phosphoinositide 3-kinase/Akt and glycogen synthase kinase-3. *Molecular Brain Research*, *118*, 72–81.

Kuang, X., Huang, Y., Gu, H. F., Zu, X. Y., Zou, W. Y., Song, Z. B., et al. (2012). Effects of intrathecal epigallocatechin gallate, an inhibitor of toll-like receptor 4, on chronic neuropathic pain in rats. *European Journal of Pharmacology*, *676*, 51–56.

Lawrence, T., & Fong, C. (2010). The resolution of inflammation: Antiinflammatory roles for NF-kappaB. *The International Journal of Biochemistry & Cell Biology*, *42*, 519–523.

Lee, S. J., & Lee, K. W. (2007). Protective effect of (−)-epigallocatechin gallate against advanced glycation end products-induced injury in neuronal cells. *Biological and Pharmaceutical Bulletin*, *30*, 1369–1373.

Lee, M. J., Maliakal, P., Chen, L., Meng, X., Bondoc, F. Y., Prabhu, S., et al. (2002). Pharmacokinetics of tea catechins after ingestion of green tea and (−)-epigallocatechin-3-gallate by humans: Formation of different metabolites and individual variability. *Cancer Epidemiology, Biomarkers & Prevention*, *11*, 1025–1032.

Lee, J. H., Moon, J. H., Kim, S. W., Jeong, J. K., Nazim, U. M., Lee, Y. J., et al. (2015). EGCG-mediated autophagy flux has a neuroprotection effect via a class III histone deacetylase in primary neuron cells. *Oncotarget*, *6*, 9701–9717.

Levites, Y., Amit, T., Youdim, M. B., & Mandel, S. (2002). Involvement of protein kinase C activation and cell survival/ cell cycle genes in green tea polyphenol (−)-epigallocatechin 3-gallate neuroprotective action. *Journal of Biological Chemistry*, *277*, 30574–30580.

Li, R., Huang, Y. G., Fang, D., & Le, W. D. (2004). (−)-epigallocatechin gallate inhibits lipopolysaccharide-induced microglial activation and protects against inflammation-mediated dopaminergic neuronal injury. *Journal of Neuroscience Research*, *78*, 723–731.

Lin, L. C., Wang, M. N., Tseng, T. Y., Sung, J. S., & Tsai, T. H. (2007). Pharmacokinetics of (−)-epigallocatechin-3-gallate in conscious and freely moving rats and its brain regional distribution. *Journal of Agricultural and Food Chemistry*, *55*, 1517–1524.

Liu, M., Chen, F., Sha, L., Wang, S., Tao, L., Yao, L., et al. (2014). (−)-Epigallocatechin-3-gallate ameliorates learning and memory deficits by adjusting the balance of TrkA/p75NTR signaling in APP/PS1 transgenic mice. *Molecular Neurobiology*, *49*, 1350–1363.

Liu, X. Z., Xu, X. M., Hu, R., Du, C., Zhang, S. X., McDonald, J. W., et al. (1997). Neuronal and glial apoptosis after traumatic spinal cord injury. *The Journal of Neuroscience*, *17*, 5395–5406.

Mandel, S., Maor, G., & Youdim, M. B. (2004). Iron and alpha-synuclein in the substantia nigra of MPTP-treated mice: Effect of neuroprotective drugs R-apomorphine and green tea polyphenol (−)-epigallocatechin-3-gallate. *Journal of Molecular Neuroscience*, *24*, 401–416.

Mandel, S., Reznichenko, L., Amit, T., & Youdim, M. B. (2003). Green tea polyphenol (−)-epigallocatechin-3-gallate protects rat PC12 cells from apoptosis induced by serum withdrawal independent of P13-Akt pathway. *Neurotoxicity Research*, *5*, 419–424.

Meng, X., Sang, S., Zhu, N., Lu, H., Sheng, S., Lee, M. J., et al. (2002). Identification and characterization of methylated and ringfission metabolites of tea catechins formed in humans, mice, and rats. *Chemical Research in Toxicology*, *15*, 1042–1050.

Moore, R. J., Jackson, K. G., & Minihane, A. M. (2009). Green tea (*Camellia sinensis*) catechins and vascular function. *British Journal of Nutrition*, *102*, 1790–1802.

Nagai, K., Jiang, M. H., Hada, J., Nagata, T., Yajima, Y., Yamamoto, S., et al. (2002). (−)-epigallocatechin gallate protects against NO stressinduced neuronal damage after ischemia by acting as an antioxidant. *Brain Research*, *956*, 319–322.

Nie, G., Cao, Y., & Zhao, B. (2002). Protective effects of green tea polyphenols and their major component. (−)-epigallocatechin-3-gallate (EGCG), on 6-hydroxydopamine-induced apoptosis in PC12 cells. *Redox Report*, *7*, 171–177.

Nie, G., Jin, C., Cao, Y., Shen, S., & Zhao, B. (2002). Distinct effects of tea catechins on 6-hydroxydopamine-induced apoptosis in PC12 cells. *Archives of Biochemistry and Biophysics*, *397*, 84–90.

Ohishi, T., Goto, S., Monira, P., Isemura, M., & Nakamura, Y. (2016). Anti-inflammatory action of green tea. *Anti-Inflammatory & Anti-Allergy Agents in Medicinal Chemistry*, *15*, 74–90.

Oliveira, M. R., Nabavi, S. F., Daglia, M., Rastrelli, L., & Nabavi, S. M. (2016). Epigallocatechin gallate and mitochondria—A story of life and death. *Pharmacological Research*, *104*, 70–85.

Park, J. W., Hong, J. S., Lee, K. S., Kim, H. Y., Lee, J. J., & Lee, S. R. (2010). Green tea polyphenol (−)-epigallocatechin gallate reduces matrix metalloproteinase-9 activity following transient focal cerebral ischemia. *The Journal of Nutritional Biochemistry*, *21*, 1038–1044.

Pervin, M., Unno, K., Nakagawa, A., Takahashi, Y., Iguchi, K., Yamamoto, H., et al. (2017). Blood brain barrier permeability of (−)-epigallocatechin gallate, its proliferation-enhancing activity of human neuroblastoma SH-SY5Y cells, and its preventive effect on age-related cognitive dysfunction in mice. *Biochemistry and Biophysics Reports*, *9*, 180–186.

Popovich, P. G., Wei, P., & Stokes, B. T. (1997). Cellular inflammatory response after spinal cord injury in Sprague-Dawley and Lewis rats. *Journal of Comparative Neurology*, *377*, 443–464.

Renno, W. M., Al-Khaledi, G., Mousa, A., Karam, S. M., Abul, H., & Asfar, S. (2014). (−)-Epigallocatechin-3-gallate (EGCG) modulates neurological function when intravenously infused in acute and, chronically injured spinal cord of adult rats. *Neuropharmacology*, *77*, 100–119.

Renno, W. M., Al-Maghrebi, M., Rao, M. S., & Khraishah, H. (2015). (−)-Epigallocatechin-3-gallate modulates spinal cord neuronal degeneration by enhancing growth-associated protein 43. Bcell lymphoma; 2, and decreasing B-cell lymphoma 2-associated x protein expression after sciatic nerve crush injury. *Journal of Neurotrauma*, *32*, 170–184.

Renno, W. M., Benov, L., & Khan, K. M. (2017). Possible role of antioxidative capacity of (−)-epigallocatechin-3-gallate treatment in morphological and neurobehavioral recovery after sciatic nerve crush injury. *Journal of Neurosurgery. Spine*, *27*, 593–613.

Renno, W. M., Khan, K. M., & Benov, L. (2016). Is there a role for neurotrophic factors and their receptors in augmenting the neuroprotective effect of (−)-epigallocatechin-3-gallate treatment of sciatic nerve crush injury? *Neuropharmacology*, *102*, 1–20.

Rezai-Zadeh, K., Shytle, D., Sun, N., Mori, T., Hou, H., Jeanniton, D., et al. (2005). Green tea epigallocatechin-3-gallate (EGCG) modulates amyloid precursor protein cleavage and reduces cerebral amyloidosis in Alzheimer transgenic mice. *The Journal of Neuroscience*, *25*, 8807–8814.

Ruzicka, J., Urdzikova, L. M., Svobodova, B., Amin, A. G., Karova, K., Dubisova, J., et al. (2018). Does combined therapy of curcumin and epigallocatechin Gallate have a synergistic neuroprotective effect against spinal cord injury? *Neural Regeneration Research*, *13*, 119–127.

Salah, N., Miller, N. J., Paganga, G., Tijburg, L., Bolwell, G. P., & Rice-Evans, C. (1995). Polyphenolic flavanols as scavengers of aqueous phase radicals and as chain-breaking antioxidants. *Archives of Biochemistry and Biophysics*, *322*, 339–346.

Singh, B. N., Shankar, S., & Srivastava, R. K. (2011). Green tea catechin, epigallocatechin-3-gallate (EGCG): Mechanisms, perspectives and clinical applications. *Biochemical Pharmacology*, *82*, 1807–1821.

Srividhya, R., & Kalaiselvi, P. (2013). Neuroprotective potential of epigallo catechin-3-gallate in PC-12 cells. *Neurochemical Research*, *38*, 486–493.

Sutherland, B. A., Rahman, R. M., & Appleton, I. (2006). Mechanisms of action of green tea catechins, with a focus on ischemia-induced neurodegeneration. *The Journal of Nutritional Biochemistry*, *17*, 291–306.

Sutherland, B. A., Shaw, O. M., Clarkson, A. N., Jackson, D. N., Sammut, I. A., & Appleton, I. (2005). Neuroprotective effects of (−)-epigallocatechin gallate following hypoxia-ischemia-induced brain damage: Novel mechanisms of action. *FASEB Journal*, *19*, 258–260.

Tai, K. K., & Truong, D. D. (2010). (−)-Epigallocatechin-3-gallate (EGCG), a green tea polyphenol, reduces dichlorodiphenyl-trichloroethane (DDT)-induced cell death in dopaminergic SHSY-5Y cells. *Neuroscience Letters*, *482*, 183–187.

Tao, L., & Zhu, Y. (2013). Anti-edema effect of epigallocatechin against acute spinal cord injury in rats and its correlation with the P38MAPK/NF-κb signaling pathway. *Journal of Spine*, *S4*.

Tian, W., Han, X. G., Liu, Y. J., Tang, G. Q., Liu, B., Wang, Y. Q., et al. (2013). Intrathecal epigallocatechin gallate treatment improves functional recovery after spinal cord injury by upregulating the expression of BDNF and GDNF. *Neurochemical Research*, *38*, 772–779.

Urdzikova, L. M., Ruzicka, J., Karova, K., Kloudova, A., Svobodova, B., Amin, A., et al. (2017). A green tea polyphenol epigallocatechin-3-gallate enhances neuroregeneration after spinal cord injury by altering levels of inflammatory cytokines. *Neuropharmacology*, *126*, 213–223.

Wei, I. H., Tu, H. C., Huang, C. C., Tsai, M. H., Tseng, C. Y., & Shieh, J. Y. (2011). (−)-Epigallocatechin gallate attenuates NADPH-d/nNOS expression in motor neurons of rats following peripheral nerve injury. *BMC Neuroscience*, *12*, 52.

Weinreb, O., Amit, T., Mandel, S., & Youdim, M. B. (2009). Neuroprotective molecular mechanisms of (−)-epigallocatechin-3-gallate: A reflective outcome of its antioxidant, iron chelating and neuritogenic properties. *Genes & Nutrition*, *4*, 283–296.

Williamson, G., Dionisi, F., & Renouf, M. (2011). Flavanols from green tea and phenolic acids from coffee: Critical quantitative evaluation of the pharmacokinetic data in humans after consumption of single doses of beverages. *Molecular Nutrition & Food Research*, *55*, 864–873.

Xie, J., Jiang, L., Zhang, T., Jin, Y., Yang, D., & Chen, F. (2010). Neuroprotective effects of epigallocatechin-3-gallate (EGCG) in optic nerve crush model in rats. *Neuroscience Letters*, *479*, 26–30.

Xu, Q., Langley, M., Kanthasamy, A. G., & Reddy, M. B. (2017). Epigallocatechin gallate has a neurorescue effect in a mouse model of Parkinson disease. *The Journal of Nutrition*, *147*, 1926–1931.

Ye, Q., Ye, L., Xu, X., Huang, B., Zhang, X., Zhu, Y., et al. (2012). Epigallocatechin-3-gallate suppresses 1-methyl-4-phenyl-pyridine-induced oxidative stress in PC12 cells via the SIRT1/ PGC-1α signaling pathway. *BMC Complementary and Alternative Medicine*, *12*, 82.

Zaveri, N. T. (2006). Green tea and its polyphenolic catechins: Medicinal uses in cancer and noncancer applications. *Life Sciences*, *78*, 2073–2080.

Zhang, F., Li, N., Jiang, L., Chen, L., & Huang, M. (2015). Neuroprotective effects of (−)-epigallocatechin-3-gallate against focal cerebral ischemia/reperfusion injury in rats through attenuation of inflammation. *Neurochemical Research*, *40*, 1691–1698.

Zhang, X., Wu, M., Lu, F., Luo, N., He, Z. P., & Yang, H. (2014). Involvement of α7 nAChR signaling cascade in epigallocatechin gallate suppression of β-amyloid-induced apoptotic cortical neuronal insults. *Molecular Neurobiology*, *49*, 66–77.

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Chapter 35

Vitamin D and spinal cord injury

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Abbreviations

25(OH)D	25-hydroxyvitamin D, also known as calcidiol
1,25(OH)$_2$D	1,25-dihydroxyvitamin D, also known as calcitriol
IOM	Institute of Medicine
UVB	ultraviolet B
SCI	spinal cord injury
VDR	vitamin D receptor

Introduction

Based on data collected from the National Health and Nutrition Examination Survey (NHANES), the prevalence of vitamin D deficiency (<50 nmol/L) in the United States is estimated to be 39.9% (Parva et al., 2018). Historically, vitamin D is known for its role in supporting bone health and preventing osteoporosis (Jin, 2018; Laird, Ward, McSorley, Strain, & Wallace, 2010). However, vitamin D is also important for various functions in the body including immunity, cell growth, and neuromuscular function (Flueck, Hartmann, Strupler, & Perret, 2016). The discovery of vitamin D receptors in skeletal muscle tissue has led to an increase in research examining vitamin D and its potential effects on exercise performance. Active individuals with spinal cord injury (SCI) have been suggested to be at an increased risk for vitamin D insufficiency and deficiency due to low dietary intake of foods high in vitamin D (Gerrish et al., 2017), anticonvulsant medications which interfere with vitamin D metabolism (Gröber & Kisters, 2012), and lifestyle factors such as reduced exposure to sunlight (Flueck & Perret, 2017; Pritchett, Pritchett, Stark, Broad, & LaCroix, 2019). Thus, a sufficient vitamin D (>75 nmol/L) status is dependent on diet, location of residence, skin pigmentation, time spent outdoors and whether an individual wears sunscreen or sun protective clothing (Flueck & Perret, 2017; Pritchett et al., 2016). Research has suggested that dietary intake for both micronutrients and macronutrients are insufficient in the para-athlete population (Scaramella, Kirihennedige, & Broad, 2018).

Vitamin D recommendations: Intake, sources, and status

Vitamin D, also referred to as calciferol, is a fat-soluble vitamin that acts like a prohormone. Vitamin D can be obtained from sun exposure, supplements, and foods like fatty fish, beef liver, eggs, mushrooms, and fortified foods (see Table 1), which are the main source of dietary vitamin D in American diets (National Institutes of Health [NIH], 2020).

While there are several forms (vitamers) of vitamin D, two major forms include cholecalciferol (D_3) and ergosterol (D_2). Ergosterol is added to foods to fortification purposes (i.e., cereal), and it naturally present in fungi like mushrooms. Vitamin D_3 is synthesized in the skin as well as consumed in the diet through animal sources (Ross, Taylor, Yaktine, & Valle, 2011). When exposed to ultraviolet B (UVB) radiation, 7-dehydrocholesterol (7-DHC) is converted into previtamin D_3, and later converted vitamin D (Hossein-nezhad & Holick, 2013) (Fig. 1).

This type of synthesis is influenced by variables like skin exposure, season, and location of residence. There are seasonal variations in vitamin D synthesis for individuals greater than 35 to 37 degrees N latitude during the winter due to the unavailability of UVB radiation during winter months in these locations. Excessive pollution and cloud cover are also variables that can impact the ability to synthesize vitamin D through UVB radiation (Cannell, Hollis, Sorenson, Taft, & Anderson, 2009). Other variables that affect the ability to synthesize vitamin D via sunlight are sunscreen and clothing choice. Recent research suggests that sunscreen use may not play a large role in low 25(OH)D status when using moderate sun protection

Diagnosis and Treatment of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822498-4.00035-X

TABLE 1 Dietary sources of vitamin.

Food	Standard Portion	Approximate Vitamin D Content (IU)
Fortified foods		
Milk, low fat	1 cup	117
Soy beverage (soy milk)	1 cup	119
Yogurt, low fat	8 oz	116
Cheese, American	1.5 oz	85
Orange juice	1 cup	100
Nonfortified foods		
Salmon (various)	3 oz	383–570
Rainbow trout, freshwater	3 oz	645
Light tuna, canned	3 oz	231
Mushrooms (various	1 cup	114–110
Eggs	1 egg	37
Beef liver	3 oz	42

Source: U.S. Department of Agriculture, Agricultural Research service. Food Data Central, 2019. fdc.nal.usda.gov

factor (SPF). Currently, research has not examined the use of high SPF sunscreens and the effect they may have on 25(OH)D concentrations (Neale et al., 2019). Protective clothing as well as increased indoor activity does decrease skin exposure to the sun which may negatively impact 25(OH)D status. Individuals that have dark pigmented skin are at higher risk for vitamin D deficiency as well since darker skin pigmentation requires more sun exposure to absorb the same amount of UVB radiation as someone with lighter skin pigmentation (Holick & Chen, 2008). Fig. 2 displays risk factors for low 25(OH)D status.

Whether synthesized in the skin or ingested through foods and supplements, vitamin D is hydroxylated by the liver into the major circulating form of vitamin D, 25(OH)D, which is the form of vitamin D measured to assess vitamin D status (Hossein-nezhad & Holick, 2013). 25(OH)D is further hydroxylated in the kidneys to form $1,25(OH)_2D$ Vitamin D, which is the biologically active form of vitamin D, performing many functions in the body related to its interactions with vitamin D receptors (VDR) (Hossein-nezhad & Holick, 2013). Vitamin D that has been synthesized by the sun stays in circulation two to three times longer than vitamin D that is taken in supplement form. This is because vitamin D taken in supplement form is partially bound to lipoproteins which is cleared from the system before being absorbed (Wacker & Holick, 2013). Since vitamin D is a fat-soluble vitamin, there is research showing an inverse relationship between adiposity and low vitamin D status, which puts those who are obese at greater risk for vitamin D deficiency (Larson-Meyer & Willis, 2010; Ogan & Pritchett, 2013).

The recommended intakes of vitamin D from the Institutes of Medicine (IOM) and Endocrine Society are noted in Table 2. The IOM guidelines are created from a population model aiming to prevent vitamin D deficiency in most of the population (Hossein-nezhad & Holick, 2013). IOM notes that most of the population intakes enough vitamin D to reach "sufficient" serum 25(OH)D levels (20 ng/mL) (Hossein-nezhad & Holick, 2013). Guidelines from the Endocrine Society recommend higher intakes of vitamin D, as it is based from a medical model that incorporates the wide array of vitamin D functions, and suggests 30 ng/mL 25(OH)D levels are beneficial, and that there is a higher upper limit than IOM suggests (Hossein-nezhad & Holick, 2013).

25(OH)D status can be measured in either nanograms (ng/mL) or in nanomoles (nmol/L). The World Health Organization and Endocrine Society considers a vitamin D deficiency as <50 nmol/L (<20 ng/ml), insufficiency as 50 to 75 nmol/L (25–30 ng/mL) and a sufficient status would be >75 nmol/L (>30 ng/mL) (Holick et al., 2011). The best indicator of vitamin D status is a serum concentration of 25(OH)D according to the National Institute of Health due to its 15-day half-life (National Institutes of Health, 2020). $1,25(OH)_2D$ concentration, on the other hand, is not a good indicator of vitamin D status since concentrations are constantly changing related to metabolic processes (National Institutes of Health, 2020).

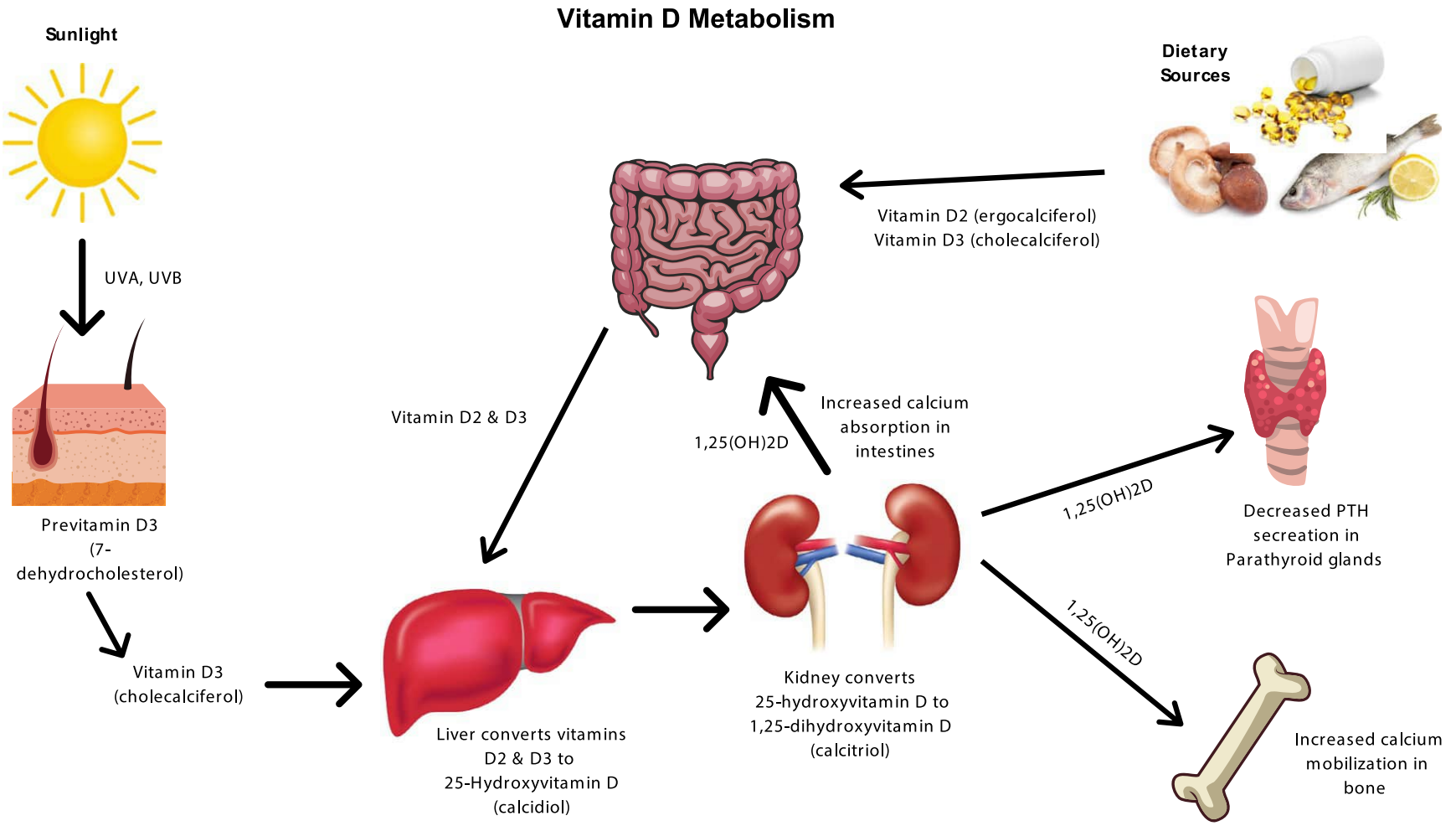

FIG. 1 Vitamin D metabolism.

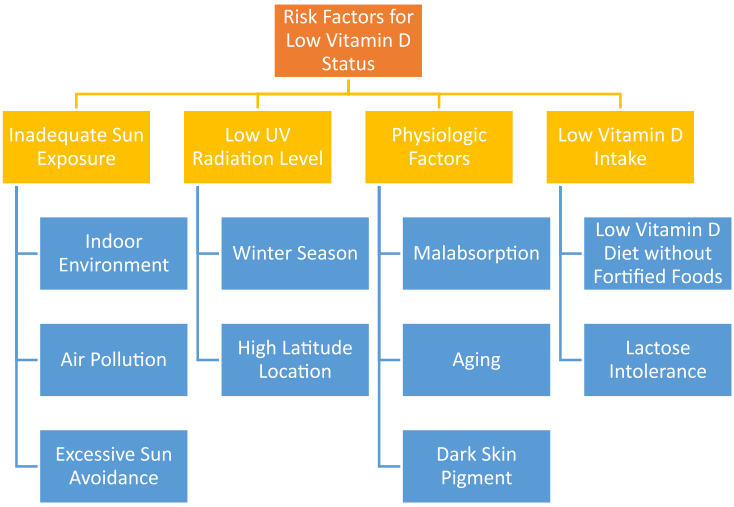

FIG. 2 Risk factors for insufficient/deficient 25(OH)D status.

TABLE 2 Recommended Intake and Upper Limit for Vitamin D.

Age	Recommended Intake (IU/day)	Upper Limit (IU/day)
National Institute of Medicine		
Children (0–18 years)	400–600	2500 (1–3 years) 3000 (4–8 years) 4000 (13–18 years)
Adults (19–70 years)	600	4000
Older Adults (>70 years)	800	4000
Pregnancy/Lactation	600	4000

Table from Ogan, D., & Pritchett, K. (2013). Vitamin D and the athlete: Risks, recommendations, and benefits. *Nutrients, 5* (6), 1856–1868. doi:10.3390/nu5061856.

Function and physiology

Vitamin D plays an important role in many different functions of the body, including immunity, bone health, muscle and neuromuscular function, hormone synthesis, cell development, and gene expression. Vitamin D has also been linked to a reduction in cancer risk, autoimmune disorders, and chronic disease (Ross et al., 2011).

Bone health

Vitamin D is known for its role in bone health and prevention of osteoporosis. Vitamin D is vital to the transcription of calbindin, a carrier protein present in enterocytes which aids in the absorption of calcium, the most abundant mineral in bones. Vitamin D is also involved in the regulation of serum calcium and phosphorus, which is important to the processes of bone mineralization and contraction of muscles (National Institutes of Health, 2020). In athletes, vitamin D status is important to consider for bone health and preventing fractures (Ogan & Pritchett, 2013). Lappe et al. (2008) provided 2000 mg of calcium and 800 IU of vitamin D to a group of female Navy recruits while the other group received a placebo for 8 weeks. The supplement group had a 20% lower prevalence of stress fractures than the placebo group (Lappe et al., 2008).

Muscle function

Vitamin D receptors (VDR) have been identified in nearly every type of cell in the body, including muscle cells (Ogan & Pritchett, 2013). The VDR has either a positive or negative response after being bound with vitamin D which targets gene expression, and therefore may play a large role in regulating skeletal muscle tissue (Ogan & Pritchett, 2013; Tanner & Harwell, 2015). Vitamin D may also affect muscle contractions by influencing calcium levels in the sarcoplasmic reticulum of muscles through alteration in the quantity and/or efficiency of calcium binding sites (Ogan & Pritchett, 2013). In addition to associations found between vitamin D status and muscle weakness, pain, and balance, research has also suggested that vitamin D plays a role in fast twitch muscle fiber morphology. It has been suggested that with an increase in vitamin D status from deficient to sufficient, fast twitch muscle fiber size and number will increase (Cannell et al., 2009; Girgis, Clifton-Bligh, Hamrick, Holick, & Gunton, 2013). However, further research is needed to determine the role of vitamin D in muscle fiber morphology.

Extraskeletal functions

Adequate vitamin D status has been associated with decreased risk of certain cancers, autoimmune disorders, infectious disease, mental disorders, cardiovascular disease, and Type 2 diabetes (Hossein-nezhad & Holick, 2013). Vitamin D can work as an immune modulator, mainly through interactions with receptors and affecting T-cell differentiation (Hossein-nezhad & Holick, 2013). Vitamin D may decrease risk of cardiovascular disease through action in the regulation of the renin-angiotensin-aldosterone system and inflammatory pathways, although clinical trials in this area have not been conclusive (National Institutes of Health, 2020). Vitamin D is involved in neurological function, as VDRs are present on neurons and glia (National Institutes of Health, 2020). VDRs are also present on pancreatic beta cells, and may be involved in insulin signaling, glucose control, and reducing inflammation, thereby possibly decreasing risk of Type 2 diabetes, although more research is needed in this area (National Institutes of Health, 2020).

Vitamin D status of active individuals with SCI

The vitamin D status of active individuals has become a popular area of study over the past decade. Athletes are potentially at an increased risk for vitamin D deficiency due to the increased enzymatic activity that occurs during exercise (Dahlquist, Dieter, & Koehle, 2015). Many studies have found that athletes are at an increased risk for 25(OH)D deficiency during the winter months and that athletes participating in an indoor sport have a higher rate of than those that play an outdoor sport (Cannell et al., 2009; Close et al., 2013; Fields, Payne, Gallo, Busteed, & Jones, 2019; Halliday et al., 2011; Krzywanski et al., 2016; Larson-Meyer & Willis, 2010; Ogan & Pritchett, 2013; Owens, Allison, & Close, 2018; Wiciński et al., 2019).

Recently, research has examined the vitamin D status of athletes with a physical impairment. This includes athletes with SCI, amputations, cerebral palsy, and other impairments as well. Athletes with SCI may be at higher risk for vitamin D deficiency due to a lack of mobility and thermoregulatory dysfunction. Athletes with SCI may also have additional malabsorption concerns due to taking anticonvulsant medications (Flueck, Schlaepfer, & Perret, 2016; Krempien & Barr, 2011; Oleson, Patel, & Wuermser, 2010; Pritchett et al., 2016). These aspects decrease the amount of time that individuals with SCI spend outside, thus decreasing the ability to synthesize vitamin D by sunlight (Flueck & Perret, 2017). It is important for active individuals with SCI to get adequate vitamin D as it is important for bone health.

Krempien and Barr (2011) examined the nutrient intake of elite Canadian athletes with SCI (Krempien & Barr, 2011). This study used self-reported food diaries to assess diet and found energy and micronutrient intake, including vitamin D, to be lower than recommended. Scaramella and colleagues further highlighted that para-athletes are at an increased for carbohydrate, iron, protein, and vitamin D deficiencies (Scaramella et al., 2018).

Studies have also focused on 25(OH)D status related to lifestyle factors in athletes with SCI. These lifestyle factors include diet, place of residence, and skin color. Other factors that are important for determining 25(OH)D status in athletes with SCI are whether they play an indoor or outdoor sport, medication use that may inhibit vitamin D absorption and limited time outdoors due to impaired thermoregulation (Pritchett et al., 2016).

Multiple studies have found that athletes with SCI are at greater risk for vitamin D status. Oleson et al. (2010) found that 96.4% of participants with chronic SCI had an insufficient 25(OH)D status during the winter months, and 81% were insufficient during the summer months (Oleson et al., 2010). This was further supported by another study in Swiss wheelchair athletes that compared 25(OH)D status between winter and summer months, and as indoor versus outdoor athletes. Flueck et al. found that vitamin D insufficiency was more prevalent in athletes during winter months and in athletes that played indoor sports (Flueck, Hartmann, et al., 2016; Flueck, Schlaepfer, & Perret, 2016).

An observational study in athletes from the Canadian Wheelchair Sports Association and the US Olympic Committee Paralympic program was conducted to examine the effects of lifestyle factors on 25(OH)D status during the autumn and winter months (Pritchett et al., 2016). There was no significant difference found in vitamin D status between autumn and winter, with 41% to 51% of athletes having an insufficient and 15.4% having a deficient vitamin D status. Time spent outside was significantly correlated with vitamin D status in the autumn, but not during the winter. Furthermore, a seasonal decline in vitamin D status was not observed regardless that athlete sun exposure decreased from autumn to winter. In this study, a greater percentage of athletes that competed in indoor sports were deficient compared to those that played outdoor sports (Pritchett et al., 2016). Thus, research is needed to identify the optimal 25(OH)D levels for active individuals with SCI.

Vitamin D and athletic performance in athletes with SCI

There have been conflicting results in the literature as to whether vitamin D provides an ergogenic benefit for exercise performance and recovery in active individuals. Flueck et al. examined the effects of vitamin D supplementation in athletes with a chronic SCI on 25(OH)D status and whether it would subsequently impact performance (Flueck, Schlaepfer, & Perret, 2016). Twenty indoor elite wheelchair athletes received 6000 IU of vitamin D_3 over a 12-week period. After 6 weeks of supplementation, vitamin D status increased significantly and reached an optimal level in all athletes. However, there was no significant difference found for any performance measurements except for isokinetic strength in the nondominant hand, although this result may have been influenced by training. In order to truly test whether the neuromuscular changes were due to vitamin D supplementation or a change in 25(OH)D status, a placebo group is needed (Flueck, Schlaepfer, & Perret, 2016).

Another study examined the efficacy of a 12- to 16-week sliding scale vitamin D supplementation protocol on 25(OH)D status and performance measures (handgrip strength, and 20-m wheelchair spring) in elite Paralympic athletes (Pritchett et Al., 2019). Participants with sufficient 25(OH)D status received a maintenance dose (15,000 IU/week of vitamin D), insufficient participants received 35,000 IU/week for 4 weeks and then received the maintenance dose, and participants that were deficient received 50,000 IU/week of vitamin D for 8 weeks and then received the maintenance dose. Mean 25(OH)D status significantly increased after supplementation (66.3 ± 24.3 nmol/mL presupplementation; 111.3 ± 30.8 nmol/mL postsupplementation). There were no significant differences in 20 m wheelchair sprints or handgrip strength; however, 62% of participants did improve handgrip strength.

Conclusion

Further research is warranted in a number of areas surrounding athletic populations, especially athletes with SCI. Recommendations for optimal vitamin D status for the para-populations need to be addressed as this population can be more susceptible to deficiency. Based on previous findings, athletes with SCI should be screened biannually for 25(OH)D status to determine whether supplementation is needed. A 12- to 16-week sliding scale supplementation protocol based on the individual's vitamin D status can be applied for individuals with an insufficient or deficient status. Furthermore, the relationship between athletic performance and vitamin D status remains unclear and there is a need for more research in this area.

Application to other areas of neuroscience (200–750 words)

This chapter reviewed vitamin D status, functions, and physiology. Vitamin D is important for various functions in the body including immunity, cell growth, and neuromuscular function. The discovery of vitamin D receptors in skeletal muscle tissue has led to an increase in research examining vitamin D and its potential effects on exercise performance. Current research suggests that active individuals with SCI are vulnerable populations with an increased risk for vitamin D deficiency. Active individuals with SCI present unique challenges in terms of nutritional needs, including vitamin D status. Thus, it is important that active individuals with SCI to obtain adequate vitamin D as it is important for bone health. It is suggested that active individuals with SCI may be a at higher risk for vitamin D deficiency due to a lack of mobility, thermoregulatory challenges, and malabsorption concerns due to taking anticonvulsant medications. These aspects decrease the amount of time that individuals with SCI spend outside, thus decreasing the ability to synthesize vitamin D by sunlight. Given that the diet does not supply enough vitamin D, active individuals with SCI may need vitamin D supplementation to obtain optimal vitamin D levels. Active individuals with SCI should receive specific and appropriate nutrition assessments and interventions, according to their needs.

Mini-dictionary of terms

Vitamin D—the fat-soluble vitamin available in food and from the sun.

Cholecalciferol—or vitamin D_3, the form of vitamin D found in the skin when exposed to sunlight, and the preferred form found in supplements.

Ergocalciferol—or vitamin D_2 found in supplements and in mushrooms and fungi in the diet.

Vitamers—various forms of vitamins that have a similar physiological activity in the body (i.e., cholecalciferol, and ergocalciferol).

Calcitriol—(1,25 hydroxyvitamin D_3) the active from of vitamin by made by the kidney but used to treat low calcium in individuals with chronic kidney disease or decreased function of the parathyroid glands.

Key facts of vitamin D and spinal cord injury

- Vitamin D is known for its role in bone health and prevention of osteoporosis.
- Vitamin D deficiency (<50 nmol/L) prevalence in the United States is estimated to be 39.9%
- Vitamin D status is assessed by serum 25(OH)D concentration
- Vitamin D can be obtained from sun exposure, foods, and supplements.
- Rickets was one of the first discovered conditions associated with a vitamin D deficiency.

Summary points

- Vitamin D is important for skeletal, muscle, immune, and neurological health.
- Athletes are at higher risk for vitamin D deficiency, related to increased enzymatic activity during exercise and indoor sports.
- Athletes with SCI may be a at higher risk for vitamin D deficiency due to a lack of mobility, thermoregulatory dysfunction, and malabsorption concerns due to taking anticonvulsant medications.
- Active individuals with SCI should be screened biannually for 25(OH)D status to determine whether supplementation is needed.

References

Cannell, J. J., Hollis, B. W., Sorenson, M. B., Taft, T. N., & Anderson, J. J. B. (2009). Athletic performance and vitamin D. *Medicine & Science in Sports & Exercise*, *41*(5), 1102–1110. https://doi.org/10.1249/MSS.0b013e3181930c2b.

Close, G. L., Russell, J., Cobley, J. N., Owens, D. J., Wilson, G., Gregson, W., et al. (2013). Assessment of vitamin D concentration in non-supplemented professional athletes and healthy adults during the winter months in the UK: Implications for skeletal muscle function. *Journal of Sports Sciences*, *31*(4), 344–353. https://doi.org/10.1080/02640414.2012.733822.

Dahlquist, D. T., Dieter, B. P., & Koehle, M. S. (2015). Plausible ergogenic effects of vitamin D on athletic performance and recovery. *Journal of the International Society of Sports Nutrition*, *12*(1), 33. https://doi.org/10.1186/s12970-015-0093-8.

Fields, J. B., Payne, D. C., Gallo, S., Busteed, D. R., & Jones, M. T. (2019). Vitamin D status differs by sex, sport-season, and skin pigmentation among elite collegiate basketball players. *Sports*, *7*(11). https://doi.org/10.3390/sports7110239.

Flueck, J. L., Hartmann, K., Strupler, M., & Perret, C. (2016). Vitamin D deficiency in Swiss elite wheelchair athletes. *Spinal Cord*, 1–5. https://doi.org/10.1038/sc.2016.33.

Flueck, J. L., & Perret, C. (2017). Vitamin D deficiency in individuals with a spinal cord injury: A literature review. *Spinal Cord*, *55*(5), 428–434. https://doi.org/10.1038/sc.2016.155.

Flueck, J. L., Schlaepfer, M. W., & Perret, C. (2016). Effect of 12-week vitamin D supplementation on 25[OH]D status and performance in athletes with a spinal cord injury. *Nutrients*, *8*(10). https://doi.org/10.3390/nu8100586.

Gerrish, H., Pritchett, R., Broad, E., Ogan, D., LaCroix, M., & Pritchett, K. (2017). Nutrient intake of elite athletes with spinal cord injury. *International Journal of Exercise Science*, *10*(7), 1018–1028.

Girgis, C. M., Clifton-Bligh, R. J., Hamrick, M. W., Holick, M. F., & Gunton, J. E. (2013). The roles of vitamin D in skeletal muscle: Form, function, and metabolism. *Endocrine Reviews*, *34*(1), 33–83. https://doi.org/10.1210/er.2012-1012.

Gröber, U., & Kisters, K. (2012). Influence of drugs on vitamin D and calcium metabolism. *Dermato-Endocrinology*, *4*(2), 158–166. PubMed https://doi.org/10.4161/derm.20731.

Halliday, T. M., Peterson, N. J., Thomas, J. J., Kleppinger, K., Hollis, B. W., & Larson-Meyer, D. E. (2011). Vitamin D status relative to diet, lifestyle, injury, and illness in college athletes. *Medicine and Science in Sports and Exercise*, *43*(2), 335–343. https://doi.org/10.1249/MSS.0b013e3181eb9d4d.

Holick, M., & Chen, T. (2008). Vitamin D deficiency: A worldwide problem with health consequences. *The American Journal of Clinical Nutrition*, *87*(4), 1080S–1086S.

Holick, M. F., Binkley, N. C., Bischoff-Ferrari, H. A., Gordon, C. M., Hanley, D. A., Heaney, R. P., et al. (2011). Evaluation, treatment, and prevention of vitamin D deficiency: An Endocrine Society clinical practice guideline. *The Journal of Clinical Endocrinology & Metabolism*, *96*(7), 1911–1930. https://doi.org/10.1210/jc.2011-0385.

Hossein-nezhad, A., & Holick, M. F. (2013). Vitamin D for health: A global perspective. *Mayo Clinic Proceedings*, *88*(7), 720–755. https://doi.org/10.1016/j.mayocp.2013.05.011.

Jin, J. (2018). Vitamin D and calcium supplements for preventing fractures. *JAMA*, *319*(15), 1630. https://doi.org/10.1001/jama.2018.3892.

Krempien, J. L., & Barr, S. I. (2011). Risk of nutrient inadequacies in elite Canadian athletes with spinal cord injury. *International Journal of Sport Nutrition and Exercise Metabolism*, *21*(5), 417–425. https://doi.org/10.1123/ijsnem.21.5.417.

Krzywanski, J., Mikulski, T., Krysztofiak, H., Mlynczak, M., Gaczynska, E., & Ziemba, A. (2016). Seasonal vitamin D status in polish elite athletes in relation to sun exposure and Oral supplementation. *PLoS One*, *11*(10). https://doi.org/10.1371/journal.pone.0164395.

Laird, E., Ward, M., McSorley, E., Strain, J. J., & Wallace, J. (2010). Vitamin D and bone health; potential mechanisms. *Nutrients*, *2*(7), 693–724. https://doi.org/10.3390/nu2070693.

Lappe, J., Cullen, D., Haynatzki, G., Recker, R., Ahlf, R., & Thompson, K. (2008). Calcium and vitamin D supplementation decreases incidence of stress fractures in female navy recruits. *Journal of Bone and Mineral Research*, *23*(5), 741–749. https://doi.org/10.1359/jbmr.080102.

Larson-Meyer, D. E., & Willis, K. S. (2010). Vitamin D and athletes. *Current Sports Medicine Reports*, *9*(4), 220. https://doi.org/10.1249/JSR.0b013e3181e7dd45.

National Institutes of Health. (2020, October 9). *Vitamin D—Health Professional Fact Sheet*. Office of Dietary Supplements. https://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/#en29.

Neale, R. E., Khan, S. R., Lucas, R. M., Waterhouse, M., Whiteman, D. C., & Olsen, C. M. (2019). The effect of sunscreen on vitamin D: A review. *The British Journal of Dermatology*, *181*(5), 907–915. https://doi.org/10.1111/bjd.17980.

Ogan, D., & Pritchett, K. (2013). Vitamin D and the athlete: Risks, recommendations, and benefits. *Nutrients*, *5*(6), 1856–1868. https://doi.org/10.3390/nu5061856.

Oleson, C. V., Patel, P. H., & Wuermser, L.-A. (2010). Influence of season, ethnicity, and chronicity on vitamin D deficiency in traumatic spinal cord injury. *The Journal of Spinal Cord Medicine*, *33*(3), 202–213.

Owens, D. J., Allison, R., & Close, G. L. (2018). Vitamin D and the athlete: Current perspectives and new challenges. *Sports Medicine (Auckland, N.Z.)*, *48* (Suppl 1), 3–16. PubMed https://doi.org/10.1007/s40279-017-0841-9.

Parva, N. R., Tadepalli, S., Singh, P., Qian, A., Joshi, R., Kandala, H., et al. (2018). Prevalence of vitamin D deficiency and associated risk factors in the US population (2011 – 2012). *Cureus*.. https://doi.org/10.7759/cureus.2741.

Pritchett, K., Pritchett, R., Ogan, D., Bishop, P., Broad, E., & LaCroix, M. (2016). 25(OH)D status of elite athletes with spinal cord injury relative to lifestyle factors. *Nutrients*, *8*(6), 374. https://doi.org/10.3390/nu8060374.

Pritchett, K., Pritchett, R. C., Stark, L., Broad, E., & LaCroix, M. (2019). Effect of vitamin D supplementation on 25(OH)D status in elite athletes with spinal cord injury. *International Journal of Sport Nutrition and Exercise Metabolism*, *29*(1), 18–23. https://doi.org/10.1123/ijsnem.2017-0233.

Ross, A. C., Taylor, C. L., Yaktine, A. L., & Valle, H. B. D. (2011). *Overview of vitamin D*. National Academies Press (US). https://www.ncbi.nlm.nih.gov/books/NBK56061/.

Scaramella, J., Kirihennedige, N., & Broad, E. (2018). Key nutritional strategies to optimize performance in Para athletes. *Physical Medicine and Rehabilitation Clinics of North America*, *29*(2), 283–298. https://doi.org/10.1016/j.pmr.2018.01.005.

Tanner, S. B., & Harwell, S. A. (2015). More than healthy bones: A review of vitamin D in muscle health. *Therapeutic Advances in Musculoskeletal Disease*, *7*(4), 152–159. https://doi.org/10.1177/1759720X15588521.

Wacker, M., & Holick, M. F. (2013). Sunlight and vitamin D. *Dermato-Endocrinology*, *5*(1), 51–108. https://doi.org/10.4161/derm.24494.

Wiciński, M., Adamkiewicz, D., Adamkiewicz, M., Śniegocki, M., Podhorecka, M., Szychta, P., et al. (2019). Impact of vitamin D on physical efficiency and exercise performance—A review. *Nutrients*, *11*(11). https://doi.org/10.3390/nu11112826.

Chapter 36

Corticospinal tract regeneration after spinal cord injury: Implications for treatment and recovery

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Abbreviations

A	adult
C	cervical
ChABC	chondroitinase ABC
CNS	central nervous system
CSPG	chondroitin sulfate proteoglycans
CST	corticospinal tract
E	embryonic
Htt	huntingtin gene
KLF	Krüppel-like factor
MSE	motor synergy encoder
mTOR	mammalian target of rapamycin
NgR	Nogo-A receptor
NPC	neural progenitor cell
NT-3	neurotrophine-3
P	post-natal
PTEN	tumor suppressor phosphatase and tensin homolog
SCI	spinal cord injury
SOCS3	suppressor of cytokine signaling 3
T	thoracic
YA	young adult

Introduction

The corticospinal tract (CST) is an axonal bundle that starts from cortical layer V pyramid neurons and travels through brain and brainstem to terminate in spinal cord. One major characteristics of CST is that the majority of the CST axons cross the midline at the pyramidal decussation, resulting the right side of brain to control the left side of the body and vice versa. The location of CST is different among different species, from ventral dorsal column in rodent to dorsal lateral funiculus in cat, non-human primate, and human (Welniarz, Dusart, & Roze, 2017). In addition, the CST termination is different among different species, from dorsal to ventral gray matter.

The main function of the CST is to control primary motor activity of the body, especially the voluntary movements. Disruption of CST along with other tracts after spinal cord injury (SCI) definitely interferes with communication between brain and the spinal cord below the injury, resulting in loss of motor, sensory, and autonomic function. Although studies show that CST sprouts after SCI from uninjured or injured axons, especially after genetically manipulation and therapeutic treatments (Blackmore et al., 2012; García-Alías, Barkhuysen, Buckle, & Fawcett, 2009; Liu et al., 2010; Rosenzweig et al., 2019), true regeneration from transected CST is rarely reported until recently from our lab (Kadoya et al., 2016).

Diagnosis and Treatment of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822498-4.00036-1

Regeneration of CST, including sprouting and regenerative sprouting of CST, is vitally important to restore motor function, especially the voluntary skilled motor function, after SCI.

In this chapter, we will review development of CST and its innervation of spinal cord neurons. In addition, we will review injury-induced CST sprouting, and genetical manipulation and therapeutic treatment to promote CST sprouting and regenerative sprouting. Finally, we will discuss our own work for promotion of CST regeneration by transplantation of caudalized neural progenitor cells (NPCs) after SCI.

CST development

CST outgrowth

The corticospinal tract (CST) is a motor pathway in central nervous system (CNS) starting from the cerebral cortex, traveling through internal capsule and brainstem, most of them crossing the midline at the pyramidal decussation, and ending at the spinal cord (Welniarz et al., 2017). In the popular rodent model of CNS development, CST axons reach brainstem at embryonic day 17 (E17), caudal medulla at E19, and cross the middle line and enter the spinal cord around post-natal day 0 (P0). CST axons continue to extend into entire spinal cord, including cervical cord around P1–2, thoracic around P3, and lumbar around P5–7 (Fig. 1) (Joosten et al., 1989; Welniarz et al., 2017). The development of CST in primate most occurs before birth. For example, CST reaches the entire spinal cord at birth in non-human primate (Welniarz et al., 2017) and reach the entire cervical spinal cord at 24 weeks post-conceptional age in human (Eyre, 2003). The growth of CST is leaded by a small number of "pioneer" axons followed by other axons that eventually populated the CST tract (Joosten et al., 1989). Following the outgrowth of CST, myelination starts around P10 and finishes in the entire spinal cord around 4 weeks in rodent spinal cord (Fig. 1), indicating readiness for electro impulse transmission (Joosten et al., 1989).

CST location and termination pattern in spinal cord

CST travels in the spinal cord white matter, which just likes other descending systems in the spinal cord. However, the location where CST travels in the spinal cord varies among species (Welniarz et al., 2017). While the crossed main CST locates in the most ventral portion of dorsal column in rodent, it shifts to dorsal lateral funiculus in cat and primates, including human (Fig. 2). The small proportion of uncrossed lateral and ventral CST are in similar location among different species. In addition, the termination pattern of CST into spinal cord gray matter is different among species. In rodent, the CST terminates most in dorsal and intermediate zone, but not directly into motor neurons in the ventral horn (Fig. 2A). However, in primates, both crossed main CST tract and uncrossed CST shift their termination ventrally into intermediate zone and ventral horn (Fig. 2C and D), indicating direct cortico-motoneuronal connections (Welniarz et al., 2017).

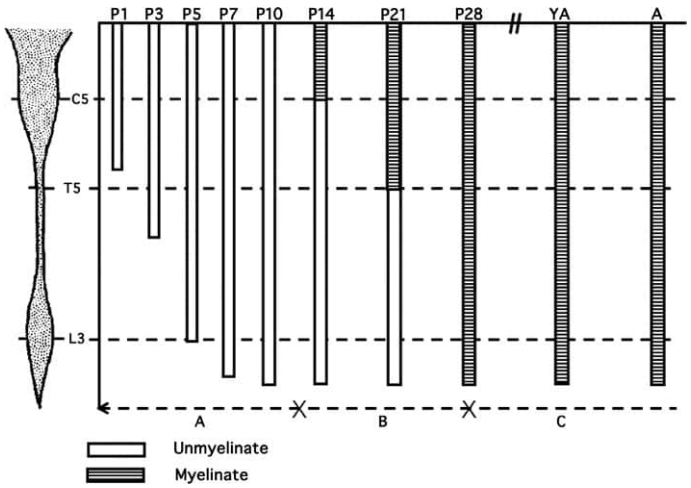

FIG. 1 Corticospinal tract outgrowth, myelination, and maturation. CST outgrowth (A) from post-natal day 1 (P1) to P10, myelination (B) from P10 to P24, and maturation (C) in young adult (YA) and adult (A) spinal cord in rats. *Adopted and redrawn from Joosten, E. A., Gribnau, A. A., & Dederen, P. J. (1989). Postnatal development of the corticospinal tract in the rat. An ultrastructural anterograde HRP study*. Anatomy and Embryology (Berlin), 179, *449–456 with permission*.

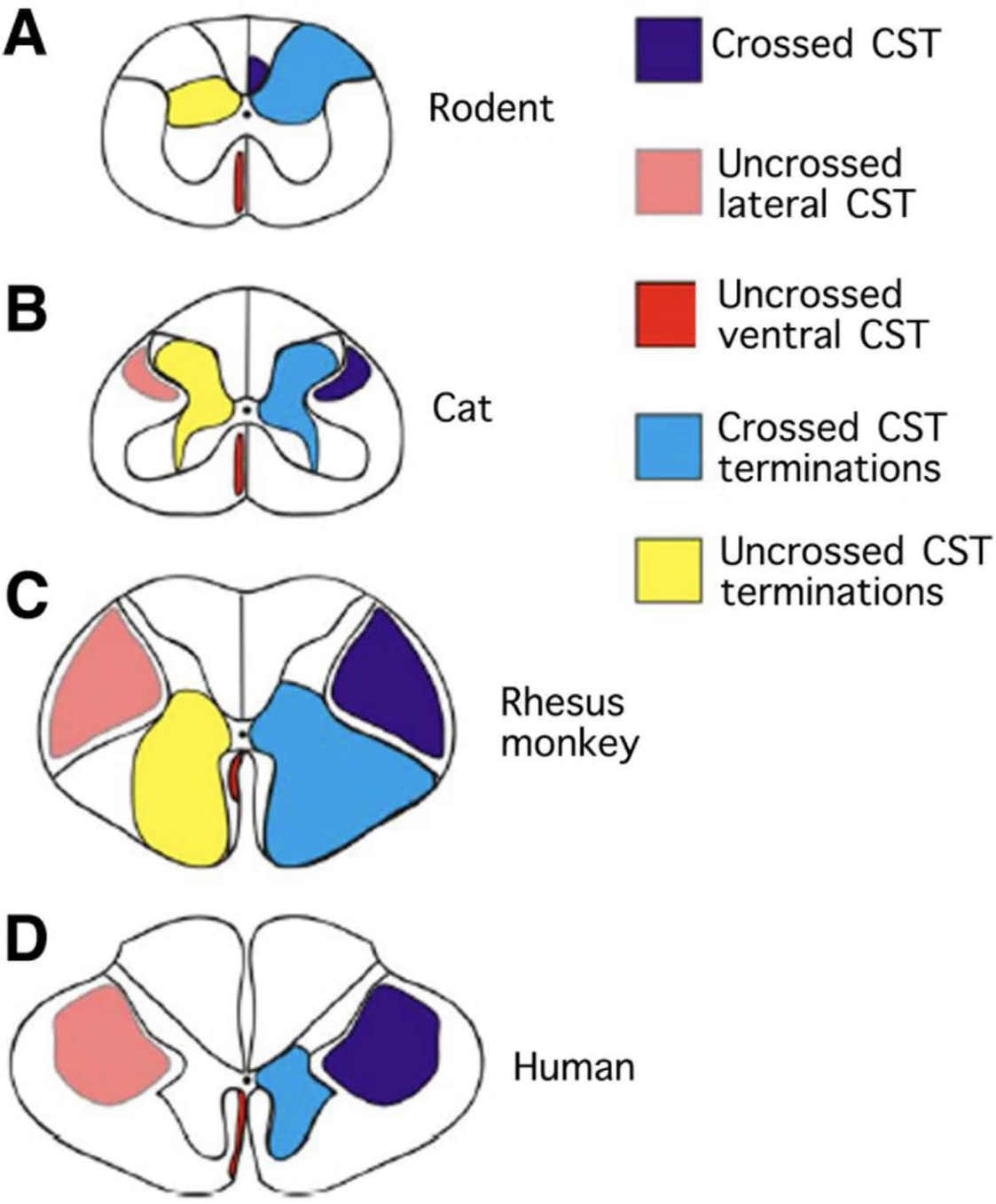

FIG. 2 Location and termination pattern of crossed and uncrossed CST in the spinal cord in mammals. (A) Rodent; (B) cat; (C) monkey; and (D) human. *Reproduced from Welniarz, Q., Dusart, I., & Roze, E. (2017). The corticospinal tract: Evolution, development, and human disorders.* Developmental Neurobiology, 77*, 810–829 with permission.*

Furthermore, our own work demonstrates additional extensive decussation and bilateral termination of CST in cervical region in monkey, nearly twice as many CST axons decussating in the cervical midline (Rosenzweig et al., 2009).

Precise control of skilled motor functions by defined CST populations

A recent study identifies spatially defined CST populations with distinct spinal projections that control different musculature groups and function in skilled forelimb motor function in mice (Wang et al., 2017). They reveal a sequential

activation of topographically organized CST neurons during skilled forelimb performance using in vivo calcium imaging with intersectional approach to specifically label and monitor different regions of CST neurons. Manipulation of region-specific CST neurons by ablation of specific population with diphtheria toxin identifies that caudal forelimb area controls reaching while rostral forelimb area controls grasping. The identification of these spatially defined groups of CST neurons that controls different skilled forelimb movements enables us to understand how CST system precisely works and how to repair it after SCI.

Identification of cellular node for CST control of motor function in mice

Since CST terminate mostly in dorsal and intermediate zone in rodent, it is important to identify those segmental interneurons and propriospinal neurons that relay CST signal into motor neurons. Levine et al. (2014) identify a neuronal population term "motor synergy encoder (MSE)" in the mouse spinal cord that may function as relay neurons from CST to motor neurons for voluntary motor movement. The MSE directly receive CST inputs in addition to sensory pathways, and have monosynaptic connection to spinal motor neurons. Molecular study reveals three candidate genes, *Tfap2b*, *Satb1*, and *Satb2*, that specifically identify MSE. Identification of MSE could direct neural stem cell study to generate these MSE progenitor cells as graft to attract CST regeneration to mimic their relays for CST input into spinal cord motor neurons below SCI.

Spinal cord injury induced spontaneous sprouting of CST

Classical work

Spontaneous sprouting of spared axons may innervate denervated targets and has been regarded as an underlying factor for functional recovery after SCI. In a classical work to investigate anatomical plasticity of CST, Kuang and Kalil (1990) unilaterally lesioned CST tracted at medullary pyramids in young hamster from age 5 to 23 days. They injected vulgaris leucoagglutinin (PHA-L) into intact side to label uninjured CST for 2 weeks. Immunohistochemical study reveals that PHA-L labeled CST sprouts into contralaterally denervated spinal cord side 4 weeks post-injury. CST sprouting is maximal in very young age of 5 days and declines with increased ages. Interestingly, the sprouted CST axons keep the same topographical specificity as normal CST arborization. Their results suggest that sprouting occurs in response to local signals which govern the specificity of denervation and induce sprouting similar to those normal development of corticospinal connections.

Dorsal injury: Ventral CST sprouting

Collateral sprouting after CNS injuries has been proposed as a key mechanism for spontaneous functional recovery. Several studies examined the mechanisms underlying recovery after lesions of motor systems in rodents, including rats and mice. After complete lesions of the main dorsal CST that comprises more than 95% of all CST axons at C3, the uninjured ventral CST spontaneously sprouts into medial motoneuron pools within cervical spinal cord, which correlates with functional recovery (Weidner, Ner, Salimi, & Tuszynski, 2001). When both dorsal and ventral CST axons are lesioned to remove almost all CST axons, functional recovery abolishes. These results indicate that extensive spontaneous structural plasticity of CST is a mechanism underneath the motor functional recovery after SCI.

Dorsal column injury: Dorsolateral CST spouting

The dorsolateral CST is dispersed throughout the dorsolateral columns. The pathways underlying dorsolateral CST spouting remain poorly understood. By performing optogenetic mapping of motor cortex after a mid-cervical dorsal column SCI that interrupts most corticospinal transmission in mice, Hilton et al. (2016) demonstrate that the motor cortex can reestablish output to the limbs longitudinally. Importantly, they dissociated for the first time the role of spared dorsolaterally projecting corticospinal neurons in mediating spontaneous recovery after SCI. They found that silencing of dorsolateral corticospinal neurons projecting caudal to the injury site by inhibitory DREADD (designer receptor exclusively activated by designer drug) was sufficient to result in the reappearance of deficits on the horizontal ladder task early after injury (Hilton et al., 2016). Their results demonstrate that spared dorsolateral CST plays an important role for spontaneous recovery of skilled locomotion in adult mice despite the limited reconstitution of corticospinal density after injury.

Unilateral hemisection: CST cross into denervated side in monkeys

Unilateral hemisection is an important SCI model to assess extensive spontaneous regeneration of adult CST axons that contribute to limited recovery after SCI. This model is especially valid in non-human primates since the main crossed CST locates in dorsolateral funiculus in each spinal cord hemisphere (Fig. 2C). To investigate mechanisms underlying spontaneous recovery after incomplete SCI, Rosenzweig et al. (2010) performed unilateral C7 spinal cord hemisections to adult rhesus monkeys and analyzed behavioral, electrophysiological and anatomical outcomes. They found enhanced spontaneous plasticity of CST axons that cross the midline from intact CST and into denervated injury site below hemisection site with 60% reconstitution of pre-lesion axon density. This extensive CST reconstitution is associated with injured forelimb functional recovery, including coordinated muscle recruitment, hand function and locomotion. This study demonstrates a very extensive CST sprouting to reconstitute injured spinal cord, which highlights the importance of primate model of SCI.

To further dissect the mechanism underlying association of CST sprouting and the forelimb functional recovery, Nakagawa, Ninomiya, Yamashita, and Takada (2015) performed C7–8 unilateral SCI in adult macaque and assessed extent of spontaneous recovery of manual dexterity using a reaching/grasping task. They found gradual recovery of the impaired dexterous manual movements. CST from uninjured hemisphere sprouts into the denervated site below injury. However, they found changes of the laminar distribution of CST axons. The sprouting CST axons preferentially innervate into spinal cord lamia IX containing the spinal motor neuron pool, indicating direct innervation of the motor neurons. On the other hand, sprouting CST axons rarely innervate the dorsal laminae. This study indicates that the reorganization of CST axons below the SCI site is an important mechanism associated with recovery of forelimb movements (Nakagawa et al., 2015).

Rewiring hindlimb CST

Large thoracic spinal cord injuries in adult rats result in disruption of hindlimb function. To assess whether the hindlimb CST can rewire after thoracic spinal cord injury, Bareyre et al. (2004) demonstrate that transected hindlimb CST axons sprout into the cervical gray matter to contact short and long propriospinal neurons (PSNs). Interestingly, long PSNs naturally innervate lumbar motor neurons, which forms a new intraspinal circuit relay that transmits the hindlimb CST input to its original lumbar spinal targets. In a follow-up study, the same group found additional CST plasticity (Ghosh et al., 2010). They found that injured hindlimb CST sprouts into cervical spinal cord after a thoracic SCI, which forms a new forelimb CST projection in the rostral part of the original hindlimb cortex. They confirm this expansion of forelimb CST in sacrifice of injured hindlimb CST by voltage-sensitive dye (VSD) imaging and blood-oxygen-level-dependent functional magnetic resonance imaging (BOLD fMRI). These studies indicate the existence of great CST plasticity and rewiring after SCI.

Promotion of CST regenerative sprouting

Promotion of CST regenerative sprouting by NT-3

Besides above reports about spontaneous sprouting of CST axons after SCI, many researchers attempt to promote further CST sprouting and regenerative sprouting that could support functional recovery using various treatments. In an early prototype study to search whether neurotrophins can enhance SCT sprouting, Schnell, Schneider, Kolbeck, Barde, and Schwab (1994) found that neurotrophine-3 (NT-3) can enhance CST sprouting first in intact post-natal rats (P2–5) just after CST extends into thoracic cord and next in young adult rats (4–7 weeks) that received low thoracic dorsal hemisection injury. Notably, the main CST is completely transected after injury, and there is no regeneration from cut axon tips into lesion site that is an empty cavity. However, CST axons sprout into ventral cord above injury site and continue to grow along the intact ventral portion of cord to reach caudal cord below injury. Combination of NT-3 single injection with an antibody that can block inhibition greatly enhance long distance of CST growth (Schnell et al., 1994).

While Schnell et al. (1994) delivered NT-3 for a single protein injection into spinal cord above injury site, which lasts short period of time, Grill, Murai, Blesch, Gage, and Tuszynski (1997) used an ex vivo gene therapy approach to deliver NT-3 by grafting of genetically modified fibroblasts expressing NT-3 into the same SCI model, low-thoracic dorsal hemisection, for continuous local supply of NT-3 in the rat SCI site. Immunohistochemistry demonstrates significant growth of CST axons at and caudal to the injury site comparing to control rats 3 months post-graft. In addition, a significant partial functional recovery on grid walking is reported, which is associated with CST regenerative sprouting. Similarly, delivery of NT-3 by this ex vivo gene therapy promotes chronically (3 months) injured CST regenerative sprouting up to 15 mm distal to SCI site (Tuszynski et al., 2003). In another study using gene therapy, a long-term NT-3 in vivo delivery to the lumbar

enlargement area through retrograde transport of NT-3 by sciatic injection of adenoviral vector expressing NT-3 promotes CST axonal growth from intact CST into injured side where injury is far rostral at medulla level (Zhou, Baumgartner, Hill-Felberg, McGowen, & Shine, 2003). These studies indicate that NT-3, especially for local and sustained delivery, support CST axonal re-growth after CST injury.

In vivo NT-3 gene delivery may not be easily translated to clinical application. A recent study implants a one-centimeter long biomaterial chitosan scaffold to slowly release NT-3 into a T8 lateral hemisection site in adult rhesus monkey (Rao et al., 2018). Antegrade labeled CST axons regenerate into scaffold and reach the caudal end while there is no regeneration of CST in lesion only control monkey. This is a true regeneration since lateral hemisection completely transects the main CST located in dorsal lateral funiculus and the CST axons grow from their cut ends (Rao et al., 2018). However, there is no empty chitosan scaffold control and no quantification of proportion of CST axon regenerated. In addition, this study shows motor and sensory functional recovery. These studies indicate that NT-3, especially for local and sustained delivery, support CST axonal re-growth after CST injury.

Promotion of CST regenerative sprouting by overcome of myelin inhibitors

While certain neurotrophins can function as chemoattractant to attract CST axon to grow, overcoming of inhibitory environment in the injured adult spinal cord could promote further growth of CST. One of the major inhibitions is myelin-associated inhibitors, such as a 35- and a 250-kd membrane proteins named NI-35 and NI-250, initially discovered by Martin Schwab's group (Sartori, Hofer, & Schwab, 2020). Afterwards they raised a monoclonal antibody, IN-1, against these two inhibitory proteins (Schnell & Schwab, 1990). CST sprouts into caudal cord through spared ventral tissue after mid-thoracic dorsal hemisection in young rats (2–6 weeks) after administration of IN-1 produced by tumors intracerebrally. Following this seminar study, various studies were conducted to demonstrate growth of CST axons after similar incomplete SCI model in adult rodent and monkey using IN-1 or its related antibodies termed anti-Nogo-A with or without other treatments, although the number of sprouting axons is very modest and most injury models are hemisection that is rare in human (Chen et al., 2017; Sartori et al., 2020; Wang et al., 2020). Nevertheless, clinical trial using Nogo-A antibody intrathecally infused continuously for 1 month for acute and severe SCI patients started as early in 2006 and finished in 2011 with certain safety data (Sartori et al., 2020). A phase II trial started 8 years later in 2019 and arrowed down to acute cervical SCI.

In addition to various IN-1 or Nogo-A antibody studies, the cloning of Nogo gene opens a new door to study its receptors for inhibitory signal transduction mechanism as well as CST regeneration in Nogo and its receptor deficient mice (Sartori et al., 2020). Although early studies report variable amount of CST regeneration in incomplete low-thoracic dorsal hemisection in Nogo mutant mice, a later study re-assessed the early findings and found no enhancement of CST regeneration (Lee et al., 2009). Similarly, no enhanced CST regeneration in mice that are deficient of Nogo-A receptor (NgR) that is supposed to mediate inhibition of all three myelin-associated proteins, Nogo, myelin-associated glycoprotein, and oligodendrocyte myelin glycoprotein (Zheng et al., 2005). Inhibition of NgR with their antagonist peptide NEP1–40 also yields controversy results of CST regeneration (Steward, Sharp, Yee, & Hofstadter, 2008). Nevertheless, a soluble function-blocking NgR termed NgR1(310)ecto-Fc, or AXER-204 is tested in rodent, monkey and is in clinical trial at present (Wang et al., 2020).

Promotion of CST regenerative sprouting by overcome of CSPG

Besides myelin-associated inhibitors, another major inhibitor is extracellular matrix molecules associated with glia scar around SCI site, such as chondroitin sulfate proteoglycans (CSPGs) (Tran, Warren, & Silver, 2018). Digestion of CSPG by chondroitinase ABC (ChABC) around C4 dorsal column injury site in rats promotes CST regeneration beyond the injury site, which is associated with functional recovery (Bradbury et al., 2002). Later, the same group delivers ChABC specifically into CST neurons by gene therapy using lentiviral vectors, which reduces CST axon die-back and promotes CST sprouting, but only in short range (Zhao et al., 2011). Following these exciting results in rodents, Rosenzweig et al. (2019) delivered ChABC below C7 lateral hemisection by multiple intraparenchymal injections in rhesus monkeys and found that ChABC delivery promotes significant amount of spared CST axonal sprouting from intact side into gray matter below the injury site where it controls hand function. Delivery of ChABC significantly improves hand function comparing with vehicle-injected controls using non-linear principal component analysis. This large animal primate study may pave a path for clinical translation of this strategy to promote CST regenerative sprouting after SCI.

Promotion of CST regenerative sprouting by genetic manipulation of certain genes

The extrinsic inhibitory environment after SCI is not the only factor to prevent CST axonal regeneration. The down-regulation of intrinsic regeneration-associated gene program in the adult neurons after SCI is another important factor for the failure of CST regeneration (Fagoe, Heest, & Verhaagen, 2014). A seminal study from Zhigang He's group shows that the tumor suppressor phosphatase and tensin homolog (PTEN) is one these genes that are responsible to down-regulate growth-associated genes, such as mammalian target of rapamycin (mTOR) (Liu et al., 2010). Genetic deletion of PTEN in mice reactivates mTOR expression and promotes substantial amount CST axon growth after SCI. Subsequently, the same group finds another cortical suppressor of cytokine signaling 3 (SOCS3) and deletion of SOCS3 can promote CST sprouting from uninjured CST axons to the denervated spinal cord in a unilateral pyramidotomy model (Jin et al., 2015). Co-deletion of SOCS3 and PTEN significantly enhances CST axon sprouting, which results in significant recovery of forelimb skilled locomotion. The deletion of PTEN and SOCS3, however, is at development stage, post-natal day 1, in these studies. A later study demonstrates that diminishing effect of PTEN deletion on CST regeneration in a low-thoracic dorsal hemisection model as the age of mice increases (Geoffroy, Hilton, Tetzlaff, & Zheng, 2016).

Besides deletion of PTEN and SOCS3, directly over-expression of developmentally regulated transcription factors, such as Krüppel-like factor (KLF) family and Sox11, in adult CST neurons by gene therapy improves their regenerative ability after incomplete C4–5 dorsal quadrant injury (Blackmore et al., 2012; Wang, Reynolds, Kirry, Nienhaus, & Blackmore, 2015). In addition, a recent study finds that a subunit of voltage-gated calcium channels alpha2delta2 involving synapse assembly negatively regulates CST axon growth and regeneration (Sun et al., 2019). Pharmacological suppression of alpha2delta2 with gabapentin promotes CST regenerative sprouting from the injury site into the intact side in a C5 lateral hemisection model in mice. The CST reorganization is associated with forelimb motor functional recovery (Sun et al., 2019). Notably, the up-regulation of alpha2delta2 parallels the maturation of CST in the development and the start of synaptogenesis. This indicates that synaptic activity may suppress axonal regeneration (Meve & Zheng, 2016). If this new mechanism for failure of axonal regeneration is proved to be true, it opens a new door to enhance axon regeneration by suppressing synaptic activity.

Robust CST regeneration into caudalized NPC graft after SCI

Transplantation of non-neural cells or fetal neural tissue

Although various above studies show sprouting and regenerative sprouting of CST axons after SCI, very few shows that transected CST can regenerate into a large clinically relevant injury site. A large injury site usually contains cavities where no axons can grow without a cellular substrate. Thus, various tissues or cell types are transplanted into SCI sites in combination with neurotrophin or other therapeutic interventions. However, transplantation of non-neural cells, such as fibroblasts, bone marrow stromal cells into the spinal cord lesion site, does not elicit any CST regeneration (Grill et al., 1997; Kadoya et al., 2016; Tuszynski et al., 2003). Transplantation of fetal (embryonic day 14) spinal cord tissues in a cervical over-hemisection site, however, does elicit very moderate regeneration of CST axons into lesion/transplant sites (Bregman et al., 2002). Sparse regenerated CST axons are usually restricted to the rostral a few hundred micrometers. Delivery of BDNF and NT-3 increases regeneration of CST axons, but the effect is very moderate (Bregman et al., 2002). This study indicates that early stage neural cells could serve as permissive cellular substrates for CST regeneration.

Transplantation of caudalized neural progenitor cells

Based on these previous studies, our group recently modified a transplantation protocol and demonstrated the robust regeneration of CST axons into the caudalized neural progenitor cell (NPC) graft (Kadoya et al., 2016) (Fig. 3). We transplanted freshly dissociated NPCs in single cell suspensions rather than embryonic spinal cord tissues, supported by growth factor cocktail embedding in fibrin matrixes. Transplanted NPCs survive, completely fill in the lesion site, and integrate very well with host tissue, resulting seamless and continuous connections from the transplant to the host tissue (Lu et al., 2012). The good integration of NPC transplant with host is critical since regeneration of CST requires direct contact of transected axon stumps with graft (Kadoya et al., 2016). In addition, CST regeneration requires caudalized and homotypic NPC grafts since CST fail to regenerate into telencephalic grafts, less into hindbrain grafts, and mostly into spinal cord grafts (Kadoya et al., 2016).

Injured CST axons not only robustly regenerate into the NPC graft, they also form synaptic connections with graft-derived neurons (Fig. 4) (Kadoya et al., 2016). Furthermore, our recent studies show that regenerated CST axons make appropriate connections with graft-derived spinal cord neurons (Dulin et al., 2018; Kumamaru, Lu, Rosenzweig,

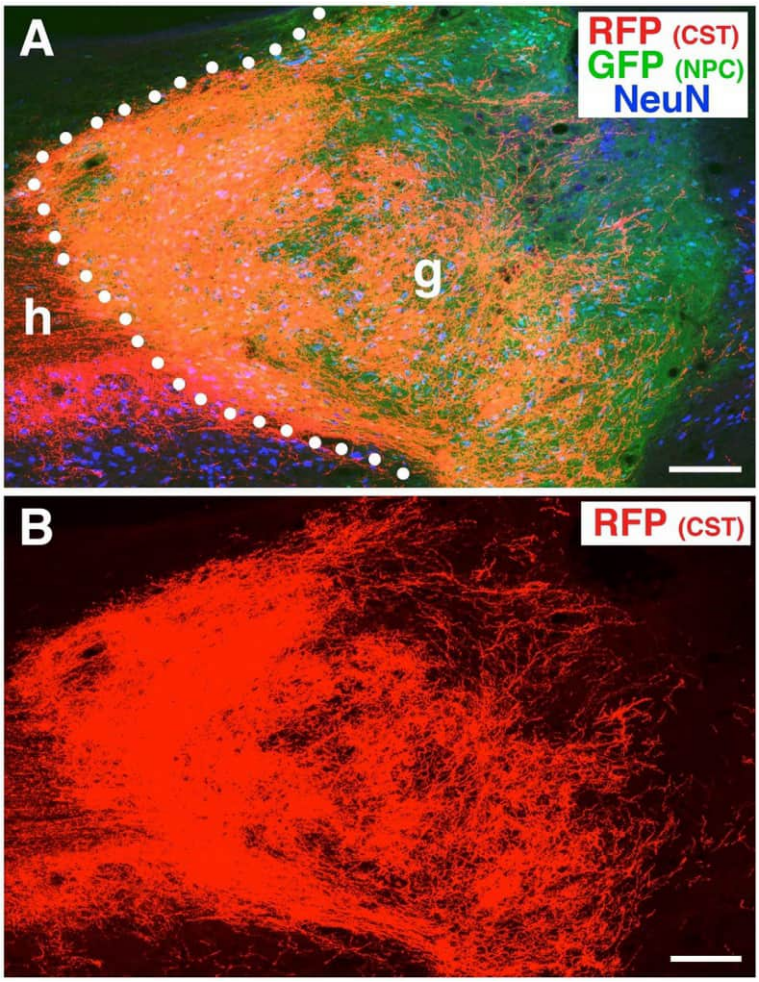

FIG. 3 Robust CST regeneration into NPC graft. (A and B) Triple immunolabeling demonstrates robust regeneration of RFP-labeled CST axons into GFP-labeled NPC graft with differentiation of NeuN-labeled neurons in a C3 dorsal column lesion site that completely transects the main CST. Dashed lines indicate host (h) and graft (g) in the rostral interface in a sagittal section view. Scale bar = 200 μm.

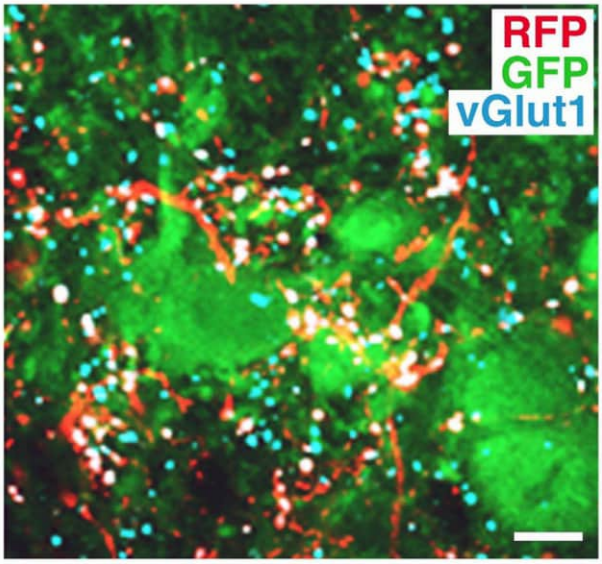

FIG. 4 Connectivity of regenerated CST axons with graft-derived neurons. Triple labeling for RFP, vGlut1, and GFP demonstrates that RFP labeled regenerated CST axons within GFP-labeled NPC graft exhibit bouton-like structures that co-localized with pre-synaptic marker vGlut1, indicating synaptic connections with grafted neurons. Scale bar = 4 μm.

Kadoya, & Tuszynski, 2019). *trans*-Synaptic tracing with herpes simplex virus reveals innervation of CST axons with pre-motor interneurons, such as V2a and Chx10+ excitatory interneurons and motor synergy encoder neurons positive for Satb1 and Ap2b immunolabeling (Levine et al., 2014), which are appropriate target of CST axons. On the other hand, CST axons avoid inappropriate targets of sensory cluster neurons derived from the spinal cord NPC graft. These results indicate that injured CST retains their intrinsic ability to recognize appropriate targets, which is important to achieve functional recovery after SCI.

For translational purpose, our group tests whether CST can regenerate into human NPC graft placed into a low-cervical hemisection site in non-human primate (Rosenzweig et al., 2018). As described above, the main CST in primate is located in the dorso-lateral funiculus that can be completely transected after lateral hemisection. CST axons regenerate by penetration into human fetal spinal cord-derived NPC grafts. Similarly, regenerated CST axons project toward Prdm8 positive pre-motor interneurons and avoid those Tlx3 positive sensory neuron clusters, indicating an appropriate connection with grafted human neurons (Kumamaru et al., 2019). However, it appears qualitatively that the density and distance of primate CST regeneration are less than rodent CST. This could be due to sub-optimal conditions of prolong cultured human neural progenitor cells in vitro.

Mechanisms of CST regeneration

In a follow-up mechanism study, our group discovers that transplanted NPCs are enable CST neurons to reverse to an embryonic transcriptional state for regeneration by transcriptome analysis (Poplawski et al., 2020). We find that the huntingtin gene (Htt) is a central hub in our analysis since conditional deletion of Htt in mice significantly reduces CST regeneration. The discovery of plasticity of injured adult CST neurons that can be reversed back to embryonic transcriptional state is significant since CST neurons and other injured adult neurons can be further manipulated to enhance their regeneration after SCI.

Reconnect injured spinal cord through neuronal relays

Although CST axons can regenerate into NPC graft, regenerated CST axons can only reach certain distance within the graft, usually about 2 mm (Kadoya et al., 2016). In a large severe and clinically relevant cervical contusive injury, regenerated CST can only reach the first half rostral NPC graft and leave the caudal half graft un-occupied. Unlike long-distance growth along the white matter in development, adult CST regeneration is similar to CST termination into gray matter neurons since NPC graft virtually re-constitutes spinal cord gray matter that contains large number of neurons (Lu et al., 2012), some of which are innervated by regenerated CST axons (Kadoya et al., 2016; Kumamaru et al., 2019). The limited distance of CST regeneration within the NPC graft is a challenge since CST signals rarely reach directly into spinal cord neurons caudal (below) to the injury to restore their motor functions.

On the other hand, graft-derived neurons can extend large number of axons into host, up to 29,000 axons counted at 0.5 mm caudal from graft in a rat upper-thoracic transection model (Lu et al., 2012). Graft-derived axons, just like developing neurons, travel along host white matter for long distance crossing several segments in both rostral and caudal directions (Lu et al., 2012). Indeed, our recent study demonstrates that host white matter myelin actually supports growth of NPC graft-derived axons (Poplawski et al., 2018). Grafted human NPCs extend their axons almost into the entire rat CNS axis (Fig. 5) (Lu et al., 2014, 2017). The large number and long-distance growth of graft-derived axons in the host are confirmed in a primate model of SCI where up to 150,000 graft-derived human axons are counted at 2 mm caudal to the lesion and reach up to 50 mm from the graft in caudal direction (Rosenzweig et al., 2018).

The ingrowth of regenerated CST axons and other supraspinal descending axons into the graft and the outgrowth of graft-derived axons into caudal host could constitute neuronal relays to re-connect injured CST neurons with their target spinal cord neurons below the injury (Fig. 6). Indeed, our electrophysiological study demonstrates partial recovery of evoked responses below a T3 complete transection site at T6 when stimulation is above the transection at C7 (Lu et al., 2012). This evoke response recovery depends on the presence of synapses in the graft since the application of kynurenic acid, the *N*-methyl-D-aspartic acid (NMDA) receptor blocker, abolishes this recovery. These results indicate excitatory synaptic transmission across the graft functions as neuronal relays. In addition, a recent study from our lab shows that stimulation of host CST by optogenetic method produces distinct and segregated neuronal network responses in the entire NPC graft in mouse SCI models. Furthermore, stimulation of graft-derived axons also elicits spinal cord neuronal responses below injury, indicating potential neuronal relay formation by grafted neurons (Ceto, Sekiguchi, Takashima, Nimmerjahn, & Tuszynski, 2020). These neuronal relays, in theory, could re-connect injured CSTs with spinal cord

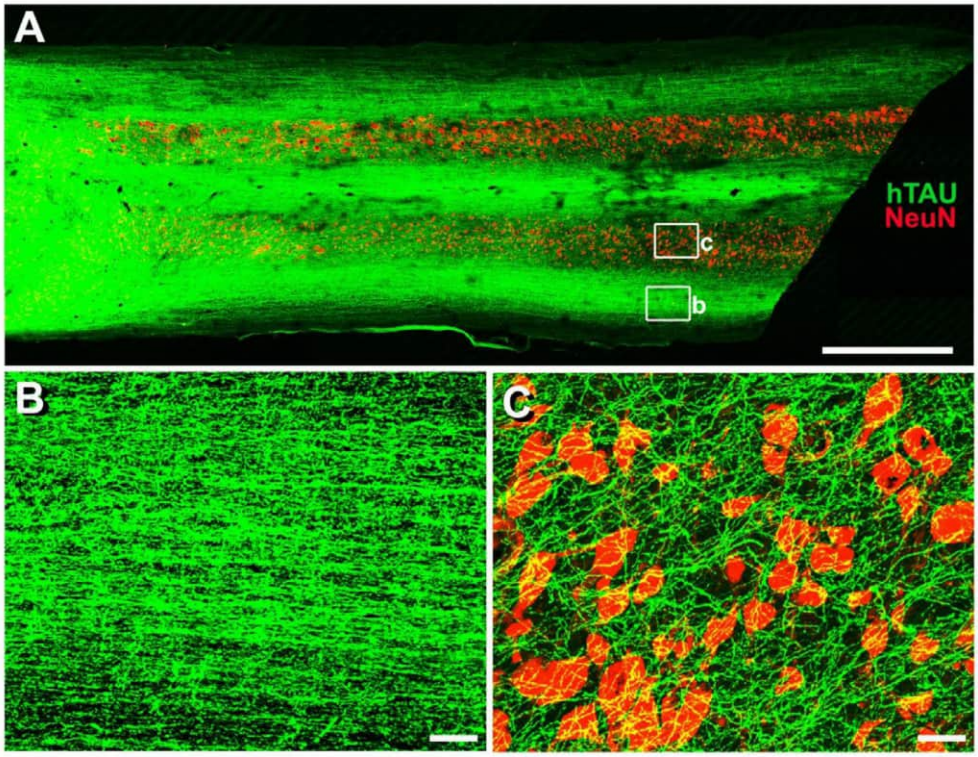

FIG. 5 NPC graft-derived axonal extension. (A) A low magnification horizontal image showing that human Tau labeled human neural progenitor cells (NPCs) extend their axons caudally into host rat spinal cord after NPC graft into the T10 bilateral contusion site for 3 months. NeuN labels both host and graft-derived neurons. Rostral, left, and caudal, right. (B and C) Higher magnification confocal *z*-stack images from the boxed area in panel (A) showing robust and extensive human graft-derived axonal growth in both host (B) white matter and (C) gray matter. Scale bar = 1 mm (A); 32 μm (B and C).

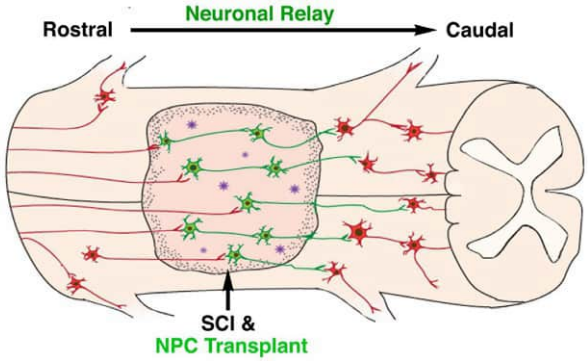

FIG. 6 A cartoon diagram of a neuronal relay formation by transplanted NPCs after SCI. Descending motor axons, including CST (*red*), regenerate into neural progenitor cell (NPC) transplant in spinal cord injury (SCI) site and make synaptic connections with graft-derived neurons (*green*). Graft-derived neurons extend their axons (*green*) into caudal host spinal cord and make synaptic connection with host spinal cord neurons (*red*). The reciprocal connection of host neurons with grafted neurons constitutes a neuronal relay formation. *Drawn by Audelia Arasheben.*

neurons below the injury by either mono-synaptic or poly-synaptic connections between grafted neurons that directly receive regenerated CST inputs and those grafted neurons that directly project into caudal spinal cord (Lu et al., 2019).

Future prospective

Since the major function of CST is cortical control of spinal cord activity, regeneration of CST is vitally important to restore motor function after SCI. Fortunately, studies demonstrate plasticity of CST system that is enable CST axon to sprout from uninjured axons, regenerative sprouting and regeneration either spontaneously or with therapeutic manipulations.

However, the major challenges remain, such as how to enhance CST sprouting in an incomplete SCI since there are always some spared axons where sprouting originates. For a large severe and complete SCI, promotion of CST regeneration crossing the injury site or through the neuronal relay is the only option. Although regenerated CST form functional synapses (Ceto et al., 2020; Jayaprakash et al., 2016; Kadoya et al., 2016), this does not spontaneously translate to motor behavioral recovery. The new circuit from regenerated CST and relay neurons need to be trained to be functional, especially for skilled and fine motor activity. In addition, whether regenerated CST axons are from the appropriate or inappropriate cortical area (forelimb vs hindlimb cortical area) in a defined cervical SCI is unknown. Promotion of CST regeneration from the appropriate cortical area is another potential challenge in the future.

Applications to other areas of neuroscience

Injury to the CST occurs not only in SCI, but also in stroke and brain injuries. The mechanism of spontaneous CST sprouting or therapeutic treatments to enhance CST sprouting and regeneration in SCI can be used for promotion of CST regeneration after stroke and brain injuries. However, the injury mechanism and the location of SCI are different from stroke and brain injuries. For example, a stroke results interruption of the blood supply to certain part of the brain, such as cortical area that contains CST neurons, and affects neuronal survival immediately. Restoration of blood supply at early stage of stroke along with therapeutic strategies discussed in this chapter could save CST neurons and restore their functional connectivity. Once a severe stroke occurs in the cortex and damages a large number of CST soma, a neuronal replacement strategy can be applied by transplantation of cortical NPCs. Our studies demonstrate early stage NPCs have great potential to extend their axons for long-distance growth (Lu et al., 2012). A recent study demonstrates that transplanted human embryonic stem cell-derived cerebral organoids into mouse cerebral cortices extend human axons along the corticospinal tract (Kitahara et al., 2020). These results indicate a great feasibility of a neuronal replacement therapy to restore CST connectivity for stroke and brain injuries.

Mini-dictionary of terms

Corticospinal tract: An axonal bundle that starts from cortical layer V pyramid neurons and travels through brain and brainstem to terminate in spinal cord for control of voluntary motor function of the body.

Spinal cord injury: A traumatic damage to the spinal cord that disrupts the connection between brain and the spinal cord below injury and results paralysis below injury.

Neural progenitor cells: Are cells that are capable of dividing a limited number of times and have the capacity to differentiate into a restricted repertoire of neuronal and glial cell types.

Central nervous system: Consists of the brain and spinal cord. It integrates the received information and coordinates and influences the activity of all parts of the bodies of bilaterally symmetric animals.

Motor synergy encoder: Represent a central node in neural pathways for voluntary and reflexive movement.

CSPG, chondroitin sulfate proteoglycans: Are proteoglycans consisting of a protein core and a chondroitin sulfate side chain.

PTEN, tumor suppressor phosphatase and tensin homolog: Is encoded by the PTEN gene and possesses lipid and protein phosphatase-dependent as well as phosphatase-independent activities.

Axon regeneration: A new growth occurs from tip of a transected axon, which may lead to reinnervation of its normal target.

Regenerative sprouting: Wherein new growth arises not from tip of transected axon, but from region of an axon close to injury sites.

Axonal sprouting: Injury disrupts a pathway that induces compensatory growth of new connections from nearby undamaged axons.

Key facts of corticospinal tract regeneration after spinal cord injury

Spinal cord injury irreversibly damages CST and leads to loss of voluntary motor function below injury.

Uninjured corticospinal tract can spontaneously sprout into denervated injury sites.

Injury can induce regenerative sprouting from injured corticospinal tract axons.

Therapeutic manipulation of inhibitory environment or enhancement of intrinsic growth capacity can promote CST sprouting and regenerative sprouting.

Transplanted neural progenitor cells can enhance robust regeneration of CST.

Summary points

- The corticospinal tract (CST) is the most important voluntary motor control system in humans.
- The regeneration of CST is vitally important for the restoration of the voluntary motor function after spinal cord injury.
- The CST has plasticity since they can spontaneously sprout from uninjured axons into denervated injury sites.
- The CST, however, cannot spontaneously regenerate after injury.
- Therapeutic manipulation is necessary in order to enhance CST regeneration or regenerative sprouting.

References

Bareyre, F. M., Kerschensteine, M., Raineteau, O., Mettenleiter, T. C., Weinmann, O., & Schwab, M. E. (2004). The injured spinal cord spontaneously forms a new intraspinal circuit in adult rats. *Nature Neuroscience*, *7*, 269–277.

Blackmore, M. G., Wang, Z., Lerch, J. K., Motti, D., Zhang, Y. P., Shields, C. B., et al. (2012). Krüppel-like factor 7 engineered for transcriptional activation promotes axon regeneration in the adult corticospinal tract. *Proceedings of the National Academy of Sciences of the United States of America*, *109*, 7517–7522.

Bradbury, E. J., Moon, L. D., Popat, R. J., King, V. R., Bennett, G. S., Patel, P. N., et al. (2002). Chondroitinase ABC promotes functional recovery after spinal cord injury. *Nature*, *416*, 636–640.

Bregman, B. S., Coumans, J. V., Dai, H. N., Kuhn, P. L., Lynskey, J., McAtee, M., et al. (2002). Transplants and neurotrophic factors increase regeneration and recovery of function after spinal cord injury. *Progress in Brain Research*, *137*, 257–273.

Ceto, S., Sekiguchi, K. J., Takashima, Y., Nimmerjahn, A., & Tuszynski, M. H. (2020). Neural stem cell grafts form extensive synaptic networks that integrate with host circuits after spinal cord injury. *Cell Stem Cell*, *27*, 430–440.

Chen, K., Marsh, B. C., Cowan, M., Al'Joboori, Y. D., Gigout, S., Smith, C. C., et al. (2017). Sequential therapy of anti-Nogo-A antibody treatment and treadmill training leads to cumulative improvements after spinal cord injury in rats. *Experimental Neurology*, *292*, 135–144.

Dulin, J. N., Adler, A. F., Kumamaru, H., Poplawsik, G. H. D., Lee-kubli, C., Strobl, H., et al. (2018). Injured adult motor and sensory axons regenerate into appropriate organotypic domains of neural progenitor grafts. *Nature Communications*, *9*, 1–13.

Eyre, J. A. (2003). Development and plasticity of the corticospinal system in man. *Neural Plasticity*, *10*, 93–106.

Fagoe, N. D., Heest, J. V., & Verhaagen, J. (2014). Spinal cord injury and the neuron-intrinsic regeneration-associated gene program. *Neuromolecular Medicine*, *16*, 799–813.

García-Alías, G., Barkhuysen, S., Buckle, M., & Fawcett, J. W. (2009). Chondroitinase ABC treatment opens a window of opportunity for task-specific rehabilitation. *Nature Neuroscience*, *12*, 1145–1151.

Geoffroy, C. G., Hilton, B. J., Tetzlaff, W., & Zheng, B. (2016). Evidence for an age-dependent decline in axon regeneration in the adult mammalian central nervous system. *Cell Reports*, *15*, 238–246.

Ghosh, A., Haiss, F., Sydekum, E., Schneider, R., Gullo, M., Wyss, M. T., et al. (2010). Rewiring of hindlimb corticospinal neurons after spinal cord injury. *Nature Neuroscience*, *13*, 97–104.

Grill, R., Murai, K., Blesch, A., Gage, F. H., & Tuszynski, M. H. (1997). Cellular delivery of neurotrophin-3 promotes corticospinal axonal growth and partial functional recovery after spinal cord injury. *Journal of Neuroscience*, *17*, 5560–5572.

Hilton, B. J., Anenberg, E., Harrison, T. C., Boyd, J. D., Murphy, T. H., & Tetzlaff, W. (2016). Re-establishment of cortical motor output maps and spontaneous functional recovery via spared dorsolaterally projecting corticospinal neurons after dorsal column spinal cord injury in adult mice. *Journal of Neuroscience*, *36*, 4080–4092.

Jayaprakash, N., Wang, Z., Hoeynck, B., Krueger, N., Kramer, A., Balle, E., et al. (2016). Optogenetic interrogation of functional synapse formation by corticospinal tract axons in the injured spinal cord. *Journal of Neuroscience*, *36*, 5877–5890.

Jin, D., Liu, Y., Sun, F., Wang, X., Liu, X., & He, Z. (2015). Restoration of skilled locomotion by sprouting corticospinal axons induced by co-deletion of PTEN and SOCS3. *Nature Communications*, *6*, 8074–8085.

Joosten, E. A., Gribnau, A. A., & Dederen, P. J. (1989). Postnatal development of the corticospinal tract in the rat. An ultrastructural anterograde HRP study. *Anatomy and Embryology (Berlin)*, *179*, 449–456.

Kadoya, K., Lu, P., Nguyen, K., Lee-Kubli, C., Kumamaru, H., Yao, L., et al. (2016). Spinal cord reconstitution with homologous neural grafts enables robust corticospinal regeneration. *Nature Medicine*, *22*, 479–487.

Kitahara, T., Sakaguchi, H., Morizane, A., Kikuchi, T., Miyamoto, S., & Takahashi, J. (2020). Axonal extensions along corticospinal tracts from transplanted human cerebral organoids. *Stem Cell Reports*, *15*, 467–481.

Kuang, R. Z., & Kalil, K. (1990). Specificity of corticospinal axon arbors sprouting into denervated contralateral spinal cord. *Journal of Comparative Neurology*, *302*, 461–472.

Kumamaru, H., Lu, P., Rosenzweig, E. S., Kadoya, K., & Tuszynski, M. H. (2019). Regenerating corticospinal axons innervate phenotypically appropriate neurons within neural stem cell grafts. *Cell Reports*, *26*, 2329–2339.

Lee, J. K., Chan, A. F., Luu, S. M., Zhu, Y., Ho, C., Tessier-Lavigne, M., et al. (2009). Reassessment of corticospinal tract regeneration in Nogo-deficient mice. *Journal of Neuroscience*, *29*, 8649–8654.

Levine, A. J., Hinckley, C. A., Hilde, K. L., Driscoll, S. P., Poon, T. H., Montgomery, J. M., et al. (2014). Identification of a cellular node for motor control pathways. *Nature Neuroscience*, *17*, 586–593.

Liu, K., Lu, Y., Lee, J. K., Samara, R., Willenberg, R., Sears-Kraxberger, I., et al. (2010). PTEN deletion enhances the regenerative ability of adult corticospinal neurons. *Nature Neuroscience*, *13*, 1075–1081.

Lu, P., Ceto, S., Wang, Y., Graham, L., Wu, D., Kumamaru, H., et al. (2017). Prolonged human neural stem cell maturation supports recovery in injured rodent CNS. *Journal of Clinical Investigation*, *127*, 3287–3299.

Lu, P., Gomes-Leal, W., Anil, S., Dobkins, G., Huie, J. R., Ferguson, A. R., et al. (2019). Origins of neural progenitor cell-derived axons projecting caudally after spinal cord injury. *Stem Cell Reports*, *13*, 105–114.

Lu, P., Wang, Y., Graham, L., McHale, A. K., Gao, M., Wu, D., et al. (2012). Long-distance growth and connectivity of neural stem cells after severe spinal cord injury. *Cell*, *150*, 1264–1273.

Lu, P., Woodruff, G., Wang, Y., Graham, L., Wu, D., Poplawski, G., et al. (2014). Long-distance axonal growth of neural stem cells derived from human induced pluripotent stem cells after spinal cord injury. *Neuron*, *83*, 789–796.

Meve, J. M., & Zheng, B. (2016). Synaptic suppression of axon regeneration. *Neuron*, *92*, 267–269.

Nakagawa, H., Ninomiya, T., Yamashita, T., & Takada, M. (2015). Reorganization of corticospinal tract fibers after spinal cord injury in adult macaques. *Scientific Reports*, *5*, 11986–11994.

Poplawski, G. H. D., Kawaguchi, R., Van Niekerk, E., Lu, P., Mehta, N., Canete, P., et al. (2020). Injured adult neurons regress to an embryonic transcriptional growth state. *Nature*, *581*, 77–82.

Poplawski, G. H. D., Lie, R., Hunt, M., Kumamaru, H., Kawaguchi, R., Lu, P., et al. (2018). Adult rat myelin enhances axonal outgrowth from neural stem cells. *Science Translational Medicine*, *10*, 2563–2575.

Rao, J. S., Zhao, C., Zhang, A., Duan, H., Hao, P., Wei, R. H., et al. (2018). NT3-chitosan enables de novo regeneration and functional recovery in monkeys after spinal cord injury. *Proceedings of the National Academy of Sciences of the United States of America*, *115*, 5595–5604.

Rosenzweig, E. S., Brock, J. H., Culbertson, M. D., Lu, P., Moseanko, R., Edgerton, V. R., et al. (2009). Extensive spinal decussation and bilateral termination of cervical corticospinalprojections in rhesus monkeys. *Journal of Comparative Neurology*, *513*, 151–163.

Rosenzweig, E. S., Brock, J. H., Lu, P., Kumamaru, H., Salegio, E. A., Kadoya, K., et al. (2018). Restorative effects of human neural stem cell grafts on the primate spinal cord. *Nature Medicine*, *24*, 484–490.

Rosenzweig, E. S., Courtine, G., Jindrich, D. L., Brock, J. H., Ferguson, A. R., Strand, S. C., et al. (2010). Extensive spontaneous plasticity of corticospinal projections after primate spinal cord injury. *Nature Neuroscience*, *13*, 1505–1510.

Rosenzweig, E. S., Salegio, E. A., Liang, J. J., Weber, J. L., Weinholtz, C. A., Brock, J. H., et al. (2019). Chondroitinase improves anatomical and functional outcomes after primate spinal cord injury. *Nature Neuroscience*, *22*, 1269–1275.

Sartori, A. M., Hofer, A. S., & Schwab, M. E. (2020). Recovery after spinal cord injury is enhanced by anti-Nogo-A antibody therapy from animal models to clinical trials. *Current Opinion in Physiology*, *14*, 1–6.

Schnell, L., Schneider, R., Kolbeck, R., Barde, Y. A., & Schwab, M. E. (1994). Neurotrophin-3 enhances sprouting of corticospinal tract during development and after adult spinal cord lesion. *Nature*, *367*, 170–173.

Schnell, L., & Schwab, M. E. (1990). Axonal regeneration in the rat spinal cord produced by an antibody against myelin-associated neurite growth inhibitors. *Nature*, *343*, 269–272.

Steward, O., Sharp, K., Yee, K. M., & Hofstadter, M. (2008). A re-assessment of the effects of a Nogo-66 receptor antagonist on regenerative growth of axons and locomotor recovery after spinal cord injury in mice. *Experimental Neurology*, *209*, 446–468.

Sun, W., Larson, M. J., Kiyoshi, C. M., Annett, A. J., Stalker, W. A., Peng, J., et al. (2019). Gabapentinoid treatment promotes corticospinal plasticity and regeneration following murine spinal cord injury. *Journal of Clinical Investigation*, *130*, 345–358.

Tran, A. P., Warren, P. M., & Silver, J. (2018). The biology of regeneration failure and success after spinal cord injury. *Physiological Reviews*, *98*, 881–917.

Tuszynski, M., Grill, R., Jones, L., Brant, A., Blesch, A., Low, K., et al. (2003). NT-3 gene delivery elicits growth of chronically injured corticospinal axons and modestly improves functional deficits after chronic scar resection. *Experimental Neurology*, *181*, 47–56.

Wang, X., Liu, Y., Li, X., Zhang, Z., Yang, H., Zhang, Y., et al. (2017). Deconstruction of corticospinal circuits for goal-directed motor skills. *Cell*, *171*, 440–455.

Wang, Z., Reynolds, A., Kirry, A., Nienhaus, C., & Blackmore, M. G. (2015). Overexpression of Sox11 promotes corticospinal tract regeneration after spinal injury while interfering with functional recovery. *Journal of Neuroscience*, *35*, 3139–3145.

Wang, X., Zhou, T., Maynard, G. D., Terse, P. S., Cafferty, W. B., Kocsis, J. D., et al. (2020). Nogo receptor decoy promotes recovery and corticospinal growth in non-human primate spinal cord injury. *Brain*, *143*, 1697–1713.

Weidner, N., Ner, A., Salimi, N., & Tuszynski, M. H. (2001). Spontaneous corticospinal axonal plasticity and functional recovery after adult central nervous system injury. *Proceedings of the National Academy of Sciences of the United States of America*, *98*, 3513–3518.

Welniarz, Q., Dusart, I., & Roze, E. (2017). The corticospinal tract: Evolution, development, and human disorders. *Developmental Neurobiology*, *77*, 810–829.

Zhao, R. R., Muir, E. M., Alves, J. N., Rickman, H., Allan, A. Y., Kwok, J. C., et al. (2011). Lentiviral vectors express chondroitinase ABC in cortical projections and promote sprouting of injured corticospinal axons. *Journal of Neuroscience Methods*, *201*, 228–238.

Zheng, B., Atwal, J., Ho, C., Case, L., He, X. L., Garcia, K. C., et al. (2005). Genetic deletion of the Nogo receptor does not reduce neurite inhibition in vitro or promote corticospinal tract regeneration in vivo. *Proceedings of the National Academy of Sciences of the United States of America*, *102*, 1205–1210.

Zhou, L., Baumgartner, B. J., Hill-Felberg, S. J., McGowen, L. R., & Shine, H. D. (2003). Neurotrophin-3 expressed in situ induces axonal plasticity in the adult injured spinal cord. *Journal of Neuroscience*, *23*, 1424–1431.

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Chapter 37

Trophic factors in patients with spinal cord injury

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Abbreviations

BDNF	brain-derived neurotrophic factor
CNTF	ciliary neurotrophic factor
ES	electrical stimulations
FES	functional electrical stimulation
FGF	fibroblast growth factors
GDNF	glial-derived neurotrophic factor
GH	growth hormone
GnRH	gonadotropin-releasing hormone
IGF-1	insulin-like growth factor-1
iPSCs	induced pluripotent stem cells
MSCs	mesenchymal stem cells
NGF	nerve growth factor
NPCs	neural progenitor cells
NT3	neurotrophin 3
NT4/5	neurotrophin 4/5
OECs	olfactory cells
OPCs	oligodendrocyte progenitor cells
SCI	spinal cord injury
TRH	thyrotropin-releasing hormone

Introduction

Spinal cord injury (SCI) causes temporary or permanent changes in the motor, sensory, and autonomic functions of the spinal cord.

The main symptoms of SCI vary according to where the spinal cord damage occurred. Cervical injuries produce partial or total tetraplegia, shown by paralysis of the four extremities, while injuries in the lower areas induce paraplegia, in which paralysis of the lower body occurs and, in both cases urogenital and digestive alterations.

SCI can directly induce the death of different cell types such as neurons, oligodendrocytes, and astrocytes. Once damage has been generated in the spinal cord, secondary alterations such as demyelination of axons and apoptosis processes in oligodendrocytes occur (see review, Fakhoury, 2015) (Fig. 1).

Thus, in this chapter, we will review the main trophic factors that are released spontaneously in patients when SCI occurs. Likewise, to those trophic factors that are secreted when patients undergo rehabilitation and finally, the perspectives of its use in clinical trials after SCI.

Currently, the concept of trophic factor is applied to substances of a known or unknown nature that have specific effects on cells or tissues through specific receptors called Trk and p75. Particularly when the trophic factor act, on neurons and glia, they are called neurotrophic factors and its actions include support the growth, survival, neurotransmitters release, and differentiation in different stages of development, in maturity or in regenerative processes.

Diagnosis and Treatment of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822498-4.00037-3

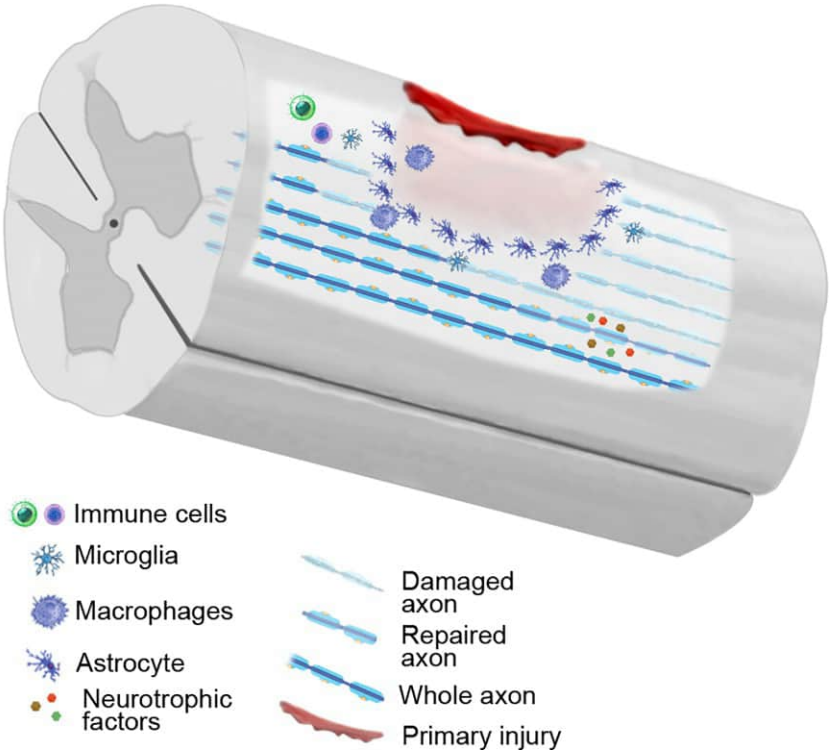

FIG. 1 Spinal cord injury. The image represents the main factors involved in the mechanisms of spinal cord injury. Initially, the primary lesion can produce a hemorrhagic site and edema, as well as cell death due to necrosis and apoptosis. On the other hand, the arrival of immune response cells to the site of injury occurs. At a later stage, a glial scar is formed that incorporates astrocytes and microglia. Therefore, many ascending and descending axons are disrupted and do not regenerate over long distances. Despite this, due to intrinsic neuronal plasticity and the presence of neurotrophic factors, it is possible that some axons grow to form new neuronal circuits.

Although there is evidence of spontaneous recovery, they will largely depend on the magnitude of the injury, spinal level, age of the injury, patient's condition, among others. However, spontaneous repair processes are initiated simultaneously in motor, sensory, and autonomous functions. Thus, the ability of intact corticospinal axons to sprout after SCI could present, as well as remyelination of injured axons.

Another approach to restoring the SCI and perhaps the most common strategy is rehabilitation and that produces environmental conditions that favor neurological recovery. Physical rehabilitation (exercise), electrical stimulation both directly to the muscle and to the spinal cord, produces motor and sensory improvements after SCI.

Cell therapies are used in order to create a suitable environment for restoration after SCI. The therapies include transplantation of stem cells, glial cells, and cells of the olfactory nervous system.

The treatment with trophic factor has been shown to improve conditions in different experimental animal models of SCI. The potential use of trophic factors in patients with SCI is evident, considering the possibility of improving the quality of life. However, a large number of clinical trials for its pharmacological use have to be carried out.

Role of neurotrophic factors in human neural plasticity after SCI

Spontaneous functional recovery in patients with spinal cord injury is limited, it occurs especially in patients in whom at least part of the sensory and motor functions has been preserved. This functional recovery stabilizes between 12 and 18 months and is mainly due to the conservation and sprouting of axons within the conserved medullary tissue adjacent to the injury site (Fawcett, Curt, Steeves, et al., 2006). After SCI, plasticity processes involving axonal regeneration can occur, this reconnection of axons involves the regrowth of transected axons through a site of injury toward their original synaptic targets, while other forms of axonal sprouting result in the reorganization of the circuit; all these processes can lead to restoration of function (Onifer, Smith, & Fouad, 2011). However, many of the axonal sprouts are usually not beneficial, and even cause adverse functional effects such as neuropathic pain, spasticity, and dysreflexia (Kathe, Hutson, McMahon, & Moon, 2016).

Neurotrophic factors can play an important role in structural and functional recovery after spinal cord injury and they are up or down regulation after the damage. These molecules are involved in axonal growth, remyelination, and modulation of the glial response after injury, among others (Afshari, Kappagantula, & Fawcett, 2009). This group of proteins is involved in the processes of natural plasticity after a spinal cord injury, which in patients has been described a relevant functional recovery without any type of treatment (Waters, Adkins, Sie, & Yakura, 1996). Not all neurons or spinal tracts express the same types of receptors, so they may preferentially be sensitive to a particular neurotrophic factor (Blesch, Fischer, & Tuszynski, 2012). The importance of the main trophic factors involved in the intrinsic recovery of neural tissue after the spinal injury is described below.

Nerve growth factor (NGF)

It is known that NGF activity increases after injury and that this factor is partly responsible for the initial regenerative response of the central nervous system, such as the stimulation of axonal sprouting and synaptic plasticity (Mocchetti & Wrathall, 1995). Besides, in the spinal cord, the NGF can influence neural responses to injury on cell types that display specific receptors to this factor, such as nociceptive sensory neurons and α motor neurons (Tuszynski et al., 1996; Verge, Richardson, Benoit, & Riopelle, 1989). The expression of NGF within the spinal cord induces a strong sprouting of nociceptive axons and hyperalgesia (Romero et al., 2000). Because the major trophic effects of NGF following SCI are seen in small-diameter sensory neurons, clinical trials have focused on investigating improvements in sensory components of neurological examinations and in pain assessments (McArthur, Yiannoutsos, Simpson, et al., 2000).

Brain-derived neurotrophic factor (BDNF)

BDNF has been shown to have neuroprotective and growth-promoting effects on different neuronal types after injury. It has particularly been observed in the rubrospinal, reticulospinal, and vestibulospinal tracts, as well as in the proprioceptive neurons of the nucleus of Clarke of the lumbar spinal cord. The neuroprotective effects can be attributed to the signaling cascades activated when BDNF binds to TrkB receptors. There is also evidence showing that BDNF can decrease glutamate-induced apoptosis-mediated cell death in the site of the injury (Almeida, Manadas, et al., 2005; Keefe, Sheikh, & Smith, 2017). However, in addition to the positive effects on the regeneration of motor tracts, the over-secretion of BDNF would only add to an environment that is favorable to not providing adequate plasticity and pain hypersensitivity after SCI (Coull, Beggs, Boudreau, et al., 2005).

Neurotrophin NT3 and NT4/5

These proteins are expressed in low amounts under normal conditions; however, after injury to the nervous system, inflammatory factors stimulate their expression and protect uninjured neurons by promoting the growth and repair of injured nervous tissue (Fang, Liu, et al., 2017). Also, the intrinsic secretion of NT-4/5 attracted Schwann cells to the injury site, causing myelination of affected axons at the injury site. Likewise, neurotrophins induced long-distance axonal growth of propriospinal and supraspinal axons (Engele, Schubert, & Bohn, 1991).

Glial-derived neurotrophic factor (GDNF)

Astrocytes, oligodendrocytes, and Schwann cells produce GDNF (Walker & Xu, 2018). After a spinal cord injury, a dense astrocytic glial scar occurs that surrounds the injury and this astrogliosis process is known to be positive, since it limits both the spread of excitotoxic molecules and the area of injury. In this sense, GDNF has been shown to positively modulate astrogliosis by improving the conditions of the lesion (Ansorena, De Berdt, Ucakar, et al., 2013). On the other hand, one of the mechanisms by which GDNF achieves functional improvement is by reducing secondary damage after SCI. GDNF has been shown to reduce the permeability of the blood–spinal cord barrier (BSCB) and down-regulate nitric oxide synthase (NOS). In this way, edema can be reduced and the survival of different neurons could be favored. In addition, neural apoptosis in the spinal cord after injury is also reduced and this also favors a decrease in secondary damage and greater recovery (Rosich, Hanna, Ibrahim, Hellenbrand, & Hanna, 2017).

Fibroblast growth factors (FGFs)

FGFs are present in the central and peripheral nervous system during development and throughout life, stimulating neuronal differentiation and migration. Its function in the context of spinal cord injuries focuses on the following aspects: stimulating the regeneration and regrowth of axons, guiding and accelerating the regeneration of the axon, carrying out the chemotactic

attraction of the cells of the immune response, as well as the stimulation of the formation of blood vessels; attenuate inflammation, astrocyte activation, and glial scar formation; finally, reducing the death of injured neurons and mediating the gene expression of injured neurons (Zhou, Wang, Li, Li, & Xiao, 2018).

Considering that spinal cord injuries in humans are generally incomplete, any therapeutic strategy that improves the cellular and synaptic function of surviving neurons is potentially useful. In this context, neurotrophic factors become in an important target for the clinical approach, which is discussed in the next sections.

Different environments enhance trophic factors delivery

Microenvironment consequences after primary injury in SCI involves hypoxia, ischemia, cellular swelling, free radical production, immune response, and several other factors that leads an injury tissue. Anti-regenerative profile promoted by damage, glial scar conformation, cellular death, and limited cellular infiltration conform chronic characteristics where axonal regeneration is unable and determinates clinical permanent disability in patients (Yang et al., 2020). Nerve disruptions avoid voluntary muscle contraction control and entails paralyzed muscles. Muscle atrophy determinate fiber lost, diameter decrease and metabolic conversions (Fu, Wang, Deng, & Li, 2016).

Currently, physical exercise is a fundamental therapeutic approach in the management of SCI, due, in part, to the fact that it increases the release of neurotrophic factors. This chapter describes its importance in the next section.

Exercise

Despite great efforts for new SCI treatments so far acute handling is based on high steroid doses and acute rehabilitation. Exercise enhances functional prognosis through neuroprotection actions beyond strength muscle improving.

Experimental studies demonstrate that exercise promotes blood–brain barrier strengthening, this integrity conserves an adequate filtration, and less edema occurs. During exercise, metabolic demand increase linked to further angiogenesis; regular physical practices enhance immune function, anti-inflammatory profile, and neuroprotection (Kohut et al., 2006). Neuroprotective actions also include enhancement of neurotrophins production, these polypeptides induce neuronal preservation, migration, and proliferation (Cobianchi, Arbat-Plana, Lopez-Alvarez, & Navarro, 2017).

Even when in acute injury neurotrophins concentration increase, trophic support decline over the time (Gold, Schulz, Hartmann, et al., 2003). Up-regulation of BDNF due exercise it considers the most important and assessed factor related to neural repair and brain circuit construction in humans. It is primarily produced in central nervous system (75% of circulating BDNF) but also platelets keep a large amount of BDNF protein. There is another neurotrophic factor extensively studied as NGF, NT3 in animal models related to exercise and neuroregeneration. Until now only BDNF has easy access for detection by enzyme-linked immunosorbent assay (ELISA) in humans (Gold et al., 2003; Leech & Hornby, 2017; Rosenfeld et al., 1995; Zeller, Abel, Rojas-Vega, Foitschik, & Strueder, 2015).

Different ways to exercise determinates neurotrophic factors release; variables like intensity, duration, and frequency impact on the expression of these factors, moderate to intermediate intensity are related to a better improve that observed in exhaustive exercise, daily no longer session induces an increase in plasmatic levels of BDNF. Several studies at different circumstances like adult healthy human male and female, SCI athletes, and multiple sclerosis patients, exhibit an elevates concentration of BNDF against control group when exercise develops (Gold et al., 2003; Leech & Hornby, 2017; Zeller et al., 2015).

BDNF is implied at multiple metabolic complex processes like neuroplasticity; up-regulation allows respond to situation as neural network reconstruction; added release is very susceptible to physical activity, and early time after injury exhibits a greater improve.

Furthermore, do not dismiss exercise is a primarily part of the SCI treatment conserving muscle and joins tone and flexibility, reduces contractures, and enhances internal organ functions (Rayegani et al., 2011). Likewise, functional magnetic resonance imaging (fMRI) and electroencephalogram (EEG) records show modifications in cortical sensorimotor area in SCI patients against healthy subjects when exercise perform, functional remodeling and provide functional recovery (Fu et al., 2016).

Injury level determinates the ability to perform physical rehabilitation, below the lesion no voluntary contraction exist. Electrical stimulation supplies neuronal connection, trough electric impulse promoting an action potential in a single muscle or group of muscles.

Electrical stimulation

Electrical stimulations (ES) appear as clinical application in 20th century, since the beginning stimulating electrodes were used to activate motor system and produce muscle contraction, although in some of the patient integrity of peripheral nervous system pathways it is intact, neuronal connection interruption between central nervous system and these tracts impair action potential generation, ES supply as an alternative to conserve muscle contraction, diminish atrophy and delay join alterations.

ES improves axon growth, myelin sheath formation and impact directly in reconstruction pattern independent of voluntary action. Transcutaneous and subcutaneous stimulation system can be applied directly in motor nerve or sensory nerve activation through spinal reflex activation (Yang et al., 2020).

The aim of stimulation determinates electrodes localization; muscle mass stimulation distributes depolarization to fibers around the application site, while nerve trunk stimulation depolarizes entire muscle. Orthodromic and antidromic activation generates a bidirectional stimulus and impacts to cortical brain reorganization (Milosevic et al., 2020).

Currently, complex patterns of stimulations make possible limbs movements control and gait reproduction consequently of transcutaneous implants electrode stimulation, this technique is referred like Functional Electrical Stimulation (FES). Rehabilitation was the first objective of FES, considering some experiments that exhibit TrkB receptor expression and BDNF serum levels enhance after electrical stimulation and brains network reorganization. FES became a treatment strategy (FEST) while patients could stand up and develop gait movements supporting by team assistances moving around short distances (Hogan, Hamilton, & Horner, 2020).

Recently brain–computer interface (BCI) an emerging technology, potency bidirectional stimulation utilizing FES movements control and brain outputs signals that synchronize FES and cortical instructions. Simultaneous activations enhance networks reconstruction (neuroplasticity). Few SCI patients have participant on this technology.

Electrical stimulation similar to physical activities, increase neurotrophic factor release, brain and spinal circuit reorganization, neuroplasticity and improve motor function (Rojas Vega et al., 2008).

Reinforce of neuronal reorganization could be supported by cellular implanted, another way to increase neuroplasticity and neurotrophic factor release.

Cell transplantation

Replace of injury neuronal cells is one of the objectives of cell transplantation; additionally, they promote axon regeneration, neurotrophic factor release and myelination (Griffin & Bradke, 2020).

Clinical application of these cells started since 2010, a relative new strategy, Geron Corporation explored the introduction of oligodendrocyte progenitor cells (OPCs) at injured place, ethical component was very discussed field about origin of the cells, preservation place and growth methods, all these components were determined with a strict limitation (Jin, Medress, Azad, Doulames, & Veeravagu, 2019).

Clinical assays implement different cells for SCI transplantation including neural progenitor cells (NPCs), Schwann cells, olfactory cells (OECs), mesenchymal stem cells (MSCs) and induced pluripotent stem cells (iPSCs) (Jin et al., 2019). Fig. 2 shows the trophic factors released in the different therapeutic approaches.

Additionally, route of administration is a critical point, and determinates potency of treatment most of them are invasive: intramedullary, intrathecal, intravenous, and percutaneous. All administrations represent a certainty risk but also allows introduce cells by infusion or graft containing cells.

Furthermore, after cell transplantation, the rate of cell differentiation and survival is low. This makes it necessary to administer more cells in a second application.

Currently, clinical trial in phase 1 or 2 are a few (<30); they are evaluating safety adverse effects and viability of management (Silvestro, Bramanti, Trubiani, & Mazzon, 2020).

Mesenchymal stem cells obtain from: bone marrow, umbilical cord blood, adipose tissue, is one of the experimental transplanted cells, promotes conditions against apoptosis and substitutes neuronal cell death. Side effects after administration consist in fever, headache, abdominal distention, and backache (Dasari, Veeravalli, & Dinh, 2014). These patients are evaluated through MRI for long periods (more than a year) regarding adverse effects as tumor (ectopic tissue), death or immune reactions. A main risk of stem cell transplantation involves tumors and phenotype conversion in transplanted cells.

Regarding of these treatment options, different techniques exist to over expression and release of neurotrophic factors, exercise and electrical stimulations are safety than cell transplantation although all of them represent an alternative option to improve motor activation in SCI patients.

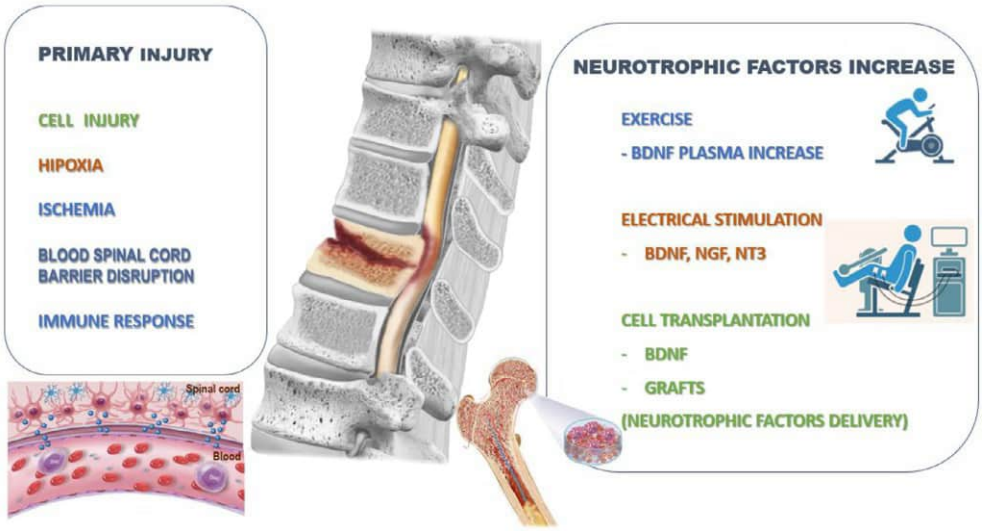

FIG. 2 Representative image of mechanisms presents during primary injury against possible interventions that enhance neurotrophic factor release as a possible management for SCI patient.

Therapeutic potential of trophic factors

Trophic factors mainly participate in the regulation of neuron survival or repair, in the generation of synaptic plasticity, in the secretion of neurotransmitters and in the induction of neuritic changes such as axonal growth, as well as in glial recovery (Harvey et al., 2015; Keefe et al., 2017) (Fig. 3).

Most of them have been tested in animal models with SCI, where their neurotrophic capacity is shown, improving motor conditions, sensitivity, and autonomic functions.

The main neurotrophic factors and their effects and, where appropriate, clinical trials in patients with spinal cord injury are described below.

The first trophic factor to be characterized was the NGF, which regulates nerve regeneration by promoting growth, the formation of new synaptic contacts, inducing differentiation in certain neuronal types, and the recovery of constitutive structures of neural networks. These facts have been described in experimental animals (Xu, Wu, Qin, et al., 2019). However, there is no clinical trial in patients that supports its administration.

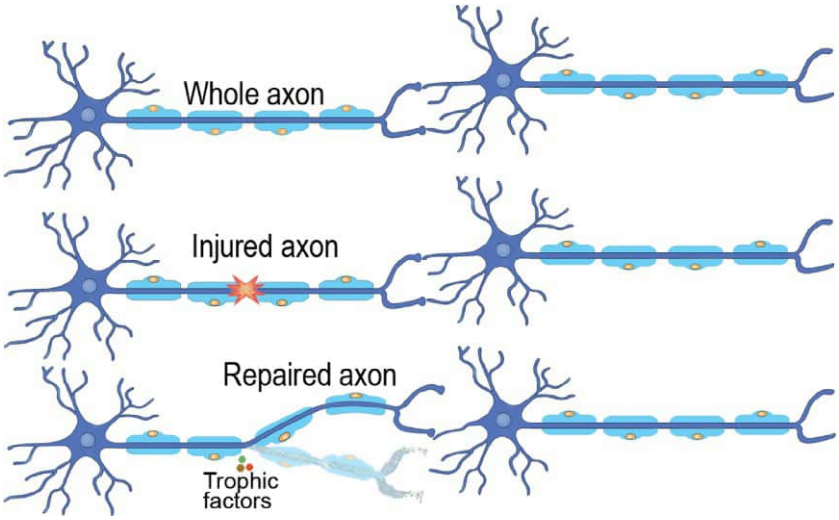

FIG. 3 Schematic representation of trophic factor-induced neuronal plasticity after spinal cord injury. Integral neurons with synaptic contact with the whole axons. After injury, the axon remains incomplete but still viable. Finally, a possible mechanism is shown by which an axon can regenerate induced by trophic factors and return to make synaptic contact with the next neuron.

The BDNF participates in neuroprotective functions in both neurons and glial cells. It induces neuronal growth, particularly of axons and their regeneration in the event of neurological lesions, as well as axonal remyelination (Keefe et al., 2017). One of the most important risks in the management of these neurotrophic factors is their side effects. For this reason, treatment with these factors requires more studies that allow it to be used in patients with SCI.

In the case of neurotrophins, NT-3, NT-4, and NT-5, their role within the nervous system is to repair damaged neurons and promote growth, as well as induce neuronal differentiation (Veneruso et al., 2019). Currently, there is no treatment protocol for patients with SCI, only experimental trials in animal models.

The GDNF promotes axonal recovery and regulates the proliferation of glial cells such as astrocytes. In addition, it has anti-inflammatory effects, which favors the reduction in the size of the lesion, thereby improving the environmental conditions for its recovery (Rosich et al., 2017; Walker & Xu, 2018). Treatment with this neurotrophic factor has been tested in experimental animals, but there are no reports that propose a treatment scheme for patients with SCI.

The ciliary neurotrophic factor (CNTF) plays an important role in the survival of injured nervous tissue, either directly in neurons in regenerating axons or in damaged oligodendrocytes (Ong, Pinese, & Chew, 2019). It is perhaps the trophic factor that could have the greatest impact on a possible treatment for neuronal regeneration in the case of patients with SCI. Its properties are very specific and with few side effects.

Other neurotrophic factor is FGF which induce axonal regeneration and recovery of damaged neurons. Likewise, they induce the activation of astrocytes and the reduction of inflammation (Zhou et al., 2018). A clinical study in patients with SCI, FGF administration after 24 months of treatment, partially improved sensory and motor functions. The most important inconvenient is that an invasive method is required for application of FGF since it is administered at the site of injury (Wu, Huang, Chen, et al., 2011).

Insulin-like growth factor 1 (IGF-1) is involved in axon growth, oligodendrocyte survival, and myelin recovery. In addition, it has antioxidant effects (Allahdadi, de Santana, Santos, et al., 2019). Unfortunately, there are no reports of studies performed in clinical trials with SCI patients treated with IGF-1, only in experimental models in animals with lesion of spinal cord.

Molecules with properties of trophic factor in clinical trials

It has been described that Gonadotropin-releasing hormone (GnRH) presents neurotrophic effects in experimental animal models with traumatic SCI. Recently has been demonstrated the presence of GnRH receptor in the spinal cord of humans (Díaz-Galindo, Calderón-Vallejo, Hernández-Jasso, et al., 2020). The use of synthetic analogues of GnRH such as leuprolide acetate, also improve the conditions of SCI. Leuprolide acetate administered via intramuscular injection, cross the blood-spinal cord barrier (Barrera, Kastin, Fasold, & Banks, 1991). We have reported that in patients with chronic SCI, intra-muscular administration of leuprolide acetate each month during 6 months induces recovery in ASIA (American Spinal Injury Association) scale scores of motors, sensory and functional independence measure (Quintanar, Díaz-Galindo, Calderón-Vallejo, et al., 2018). The main advantage of this treatment is of easy and safe application and that it is a non-invasive method (Fig. 4).

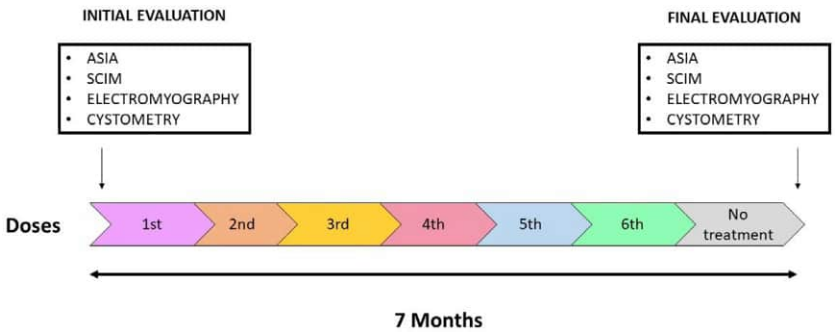

FIG. 4 Scheme of a possible treatment with a GnRH agonist (leuprolide acetate) as a trophic factor administered intramuscularly every month for 6 months in patients with SCI (Quintanar et al., 2018). ASIA score, American Spinal Cord Injury Association; SCIM, Spinal Cord Independence Measure.

Thyrotropin-releasing hormone (TRH) stimulates the release of the thyroid stimulating hormone produced by pituitary gland, which stimulates the thyroid gland for the secretion of thyroid hormones (Fröhlich & Wahl, 2019). Studies have described that patients with SCI treated with TRH, improves of motor or sensitive functions when they were treated within 12 h after trauma. They were evaluated up to 4 months after lesion (Pitts, Ross, Chase, & Faden, 1995). It is possible that the neuroprotective effect of TRH and its analogues is through the stabilization of neuronal membrane, its anti-inflammatory properties and its antioxidant capacity (Faden, Vink, & McIntosh, 1989).

Growth hormone (GH) is a peptide produced by pituitary gland. Has been described its role in neuroregeneration processes, promotion of innervation and neurogenesis (Arámburo, Alba-Betancourt, Luna, & Harvey, 2014; Martínez-Moreno, Calderón-Vallejo, Harvey, Arámburo, & Quintanar, 2018). A clinical case has been published in a patient with incomplete spinal cord development and impaired limb motor activity in which was administered with GH. Treatment induced an improvement in motor function (Devesa, Alonso, López, et al., 2017). This neurotrophic effect could be due to the fact that GH participates in the expression of neurotrophins such as BDNF and IGF-1 (Sharma, 2007).

The hormone melatonin is a peptide produced by the pineal gland (Aygün, Kaplan, Odaci, Onger, & Altunkaynak, 2012). In SCI rats, systemic melatonin administration during 4 weeks induces a reduction of free radical, and therefore oxidative stress, giving its recovery (Erşahin, Özdemir, Özsavcı, et al., 2012).

The estrogens are hormones produced mainly in the ovaries and they have neuroprotective effects. In SCI animal models, treatment of estrogen 48 h after the lesion induces a reduction of calpain and caspase-3 expression which have anti-apoptotic effects (Samantaray, Sribnick, Das, et al., 2010). Likewise, in SCI rats, locomotion was improved and neurons of the spinal cord, the survival was higher after estrogen treatment (Table 1) (Kachadroka, Hall, Niedzielko, Chongthammakun, & Floyd, 2010).

The most important challenges that have to be considered in clinical use of trophic factors in patients are: (a) its half-life is very short, (b) in most cases they do not cross the blood-spinal barrier, (c) the administration would be topical, so they would use invasive techniques (surgical), (d) possible non-specific effects on uninjured tissue, (e) adverse side effects, and (f) the economic costs of a possible treatment.

However, perhaps one of the most important and pending challenges is that there are preclinical trials that have been performed in experimental models using trophic factors and that have not yet been tested in patients with SCI.

It is possible that with the conjunction of several simultaneous therapeutic approaches, such as rehabilitation and the administration of trophic factors, it may give a better result in terms of neurological recovery, thus giving a better quality of life for patients with SCI.

Applications to other areas of neuroscience

Because of the complex nature of the nervous system, when injuries occur to it, possible treatment approaches are also complex. To understand the pathophysiological phenomena that occur with SCI, experimental animal models are initially used. Later the translational consideration would be its applicability in patients with SCI. In the specific case of the application of neurotrophic factors such as nerve growth factor, brain-derived neurotrophic factor, neurotrophin 3 and 4/5, glial-derived neurotrophic factor, fibroblast growth factors, ciliary neurotrophic factor, and insulin-like growth factor-1, have been widely studied. However, not all these factors have been clinical trials, either due to the routes of administration, their chemical characteristics or the adverse effects that they may produce. On the other hand, there are molecules with trophic properties such as gonadotropin-releasing hormone, thyrotropin-releasing hormone, growth hormone, melatonin, and estrogens. These molecules have among their functional properties, neuronal plasticity. Due to these properties, these hormones have been used for the treatment of spinal cord injuries both in experimental models and in some clinical trials. The results observed include improvements in motor, sensory, and autonomic function.

It is possible that these trophic factors can also be used in neurological lesions in other sites of the nervous system such as peripheral nerves and in the brain.

TABLE 1 Summary of trophic factors and their possible therapeutic effects in spinal cord injury patients.

TROPHIC FACTOR	POTENTIAL TERAPHEUTIC EFFECTS IN SCI	REFERENCES
BDNF	✓Stimulate neuroplasticity and neural network reconstruction as well as modifications in cortical sensorimotor area. ✓Conserving muscle and joins tone and flexibility, reduces contractures, and enhance internal organ functions. ✓Develop gait movements supporting by team assistances moving around short distances.	Rayegani et al., 2011; Fu et al., 2016; Hogan et al., 2020.
NT-3, NT-4 and NT-5	✓Repair damaged neurons and promote growth. ✓Attracted Schwann cells to the injury site, causing myelination of affected axons at the injury site. ✓Induced long-distance axonal growth of propriospinal and supraspinal axons.	*Engele et al., 1991; Veneruso et al., 2019.*
GDNF	✓ Promotes axonal recovery. ✓ Regulates the proliferation of glial cells such as astrocytes. ✓It has anti-inflammatory effects, which favors the reduction in the size of the lesion.	Rosich et al., 2017; Walker et al., 2018.
CNTF	✓ Plays an important role in the survival of injured nervous tissue, either directly in neurons in regenerating axons or in damaged oligodendrocytes. ✓ In SCI patients, its properties are very specific and with few side effects.	Ong et al., 2019.
FGF	✓ Induce axonal regeneration and recovery of damaged neurons. ✓ induce the activation of astrocytes and the reduction of inflammation. ✓ In SCI patients, partially improved sensory and motor functions.	Zhou et al., 2018; Wu et al. 2011.
IGF-1	✓ Involved in axon growth, oligodendrocyte survival, and myelin recovery. ✓ It has antioxidant effects.	Allahdadi et al., 2019.
GnRH and analogues	✓ In SCI patients, a partial recovery of motor and sensorial functions. ✓ Increase in functional independence measure in SCI patients.	Quintanar et al, 2018.
TRH and analogues	✓ In SCI patients, a partial recovery of motor and sensory functions. ✓ Anti-inflammatory properties and antioxidant capacity.	Fade et al, 1989.
GH and analogues	✓ In SCI patients, an improvement in motor function. ✓ Stimulate the release of BDNF and IGF-1.	Devesa et al. 2017; Sharma, 2007.
Melatonin	✓ Reduction of oxidative stress, thereby reducing the deterioration of the spinal cord lesion.	Ersahin et al. 2012.
Oestrogens	✓ Reduction of apoptosis. ✓ Improve in locomotion. ✓ The survival of spinal neurons was higher.	Samantaray et al., 2010; Kachadroka et al., 2010.

The column on the left side indicates the name of the different trophic factors. The potential therapeutic effects of each factor are listed in the middle column. The right column contains the information of the references that can be consulted for more details.

Mini-dictionary of terms

Spinal cord injury: An alteration of the spinal cord, caused by trauma or disease. A spinal cord injury often causes permanent loss of strength, sensation, and mobility below the site of injury.

Trophic factors: A group of substances, most of them of a protein nature that, together with hormones and neurotransmitters, induce morphofunctional changes in tissues.

Neural plasticity: Is the ability of the nervous system to change its structure and function as a reaction to the diversity of the environment.

Electrical stimulation: It is the technique that uses electrical current to cause a muscle contraction. Using a device called an electrostimulator, an electrical current is generated to induce muscle contractions or tingling sensations that serve to prevent injuries, train or treat muscles, obtain a therapeutic effect and improve performance.

Physical rehabilitation: A group of methodologies that aims to recover and improve the functional capacity and quality of life of those people who suffer from disability due to illness or injury.

Neurotrophins: A family of proteins which regulate the generation, survival, proliferation, differentiation, and death of neurons in the peripheral and central nervous system. They include NGF, BDNF, NT3, and NT4/5.

Glial-derived neurotrophic factor: A polypeptide factor that binds and activates the TrkB receptor, it has an important role in the physiological processes underlying the plasticity and development of the nervous system.

Ciliary neurotrophic factor: A member of the interleukin-6 family of cytokines. This factor is a differentiating cytokine that drives cells toward a predominantly astrocytic fate.

Fibroblast growth factors: A family of 18-member proteins grouped in 6 subfamilies that have biological activity during early embryo development regulating positive and negative cellular growth, differentiation and survival and during adulthood, mediating metabolic functions, tissue repair and regeneration.

Insulin-like growth factor-1: A polypeptide hormone secreted in multiple tissues by the effect of growth hormone. Most of circulating IGF-I is of hepatic origin and it has been seen to be important in modulating of neurogenesis.

Key facts of spinal cord injury

In the world, more than a million people have affectations caused by SCI. Currently there are no treatment proposals that can give a full recovery of SCI. Depending on the degree, age, level of the injury, and treatment, the degree of neurological recovery and therefore functional improvement of the patient with SCI can be predicted.

Different therapeutic strategies have been developed to improve the conditions of patients with SCI.

Key facts therapeutic approaches

Among the strategies is rehabilitation, which include physical exercise, electrical stimulation, and cell transplantation. These strategies have in common that among their nerve regeneration mechanisms is the induction of trophic factors.

The trophic factor acts on neurons and glia, they are called neurotrophic factors and its actions include support the growth, survival, neurotransmitters release and differentiation in several stages of development, in maturity or in regenerative processes.

Another possible strategy for recovery from spinal cord injury is the administration of neurotrophic factors or molecules that have neurotrophic properties.

Either in preclinical protocols or in clinical trials, different trophic factors have been tested, including nerve growth factor, brain-derived neurotrophic factor, neurotrophin 3 and 4/5, glial-derived neurotrophic factor, fibroblast growth factors, ciliary neurotrophic factor, insulin-like growth factor-1, gonadotropin-releasing hormone, thyrotropin-releasing hormone, growth hormone, melatonin, and estrogens.

The results obtained after carrying out any of the strategies, be it rehabilitation or the administration of trophic factors, have been improvements in motor activity, sensory, and autonomic function with the perspective of giving a possible better quality of life for patients with SCI.

Summary points

- Spinal cord injury in patients causes motor, sensory and autonomic dysfunction.
- There are therapeutic approaches to induce neurological recovery in different experimental models or in clinical trials.
- Rehabilitation induces neurological recovery through the release of neurotrophic factors.

- Therapeutic treatment with directly administered trophic factors induces neurological recovery in SCI.
- There are preclinical trials that have been performed in experimental models using neurotrophic factors and that have not yet been tested in patients with SCI.

References

Afshari, F. T., Kappagantula, S., & Fawcett, J. H. (2009). Extrinsic and intrinsic factors controlling axonal regeneration after spinal cord injury. *Expert Reviews in Molecular Medicine*, *8*(11), e37.

Allahdadi, K. J., de Santana, T. A., Santos, G. C., et al. (2019). IGF-1 overexpression improves mesenchymal stem cell survival and promotes neurological recovery after spinal cord injury. *Stem Cell Research & Therapy*, *10*, 146.

Almeida, R. D., Manadas, B. J., Melo, et al. (2005). Neuroprotection by BDNF against glutamate-induced apoptotic cell death is mediated by ERK and PI3-kinase pathways. *Cell Death and Differentiation*, *12*, 1329–1343.

Ansorena, E., De Berdt, P., Ucakar, B., et al. (2013). Injectable alginate hydrogel loaded with GDNF promotes functional recovery in a hemisection model of spinal cord injury. *International Journal of Pharmaceutics*, *455*(1–2), 148–158.

Arámburo, C., Alba-Betancourt, C., Luna, M., & Harvey, S. (2014). Expression and function of growth hormone in the nervous system: A brief review. *General and Comparative Endocrinology*, *203*, 35–42.

Aygün, D., Kaplan, S., Odaci, E., Onger, M. E., & Altunkaynak, M. E. (2012). Toxicity of non-steroidal anti-inflammatory drugs: A review of melatonin and diclofenac sodium association. *Histology and Histopathology*, *27*, 417–436.

Barrera, C. M., Kastin, A. J., Fasold, M. B., & Banks, W. A. (1991). Bidirectional saturable transport of LHRH across the blood-brain barrier. *American Journal of Physiology. Endocrinology and Metabolism*, *261*(3), E312–E318.

Blesch, A., Fischer, I., & Tuszynski, M. H. (2012). Gene therapy, neurotrophic factors and spinal cord regeneration. *Handbook of Clinical Neurology*, *109*, 563–574.

Cobianchi, S., Arbat-Plana, A., Lopez-Alvarez, V. M., & Navarro, X. (2017). Neuroprotective effects of exercise treatments after injury: The dual role of neurotrophic factors. *Current Neuropharmacology*, *15*(4), 495–518.

Coull, J. A. M., Beggs, S., Boudreau, D., et al. (2005). BDNF from microglia causes the shift in neuronal anion gradient underlying neuropathic pain. *Nature*, *438*(7070), 1017–1021.

Dasari, V. R., Veeravalli, K. K., & Dinh, D. Z. (2014). Mesenchymal stem cells in the treatment of spinal cord injuries: A review. *World Journal of Stem Cells*, *6*(2), 120.

Devesa, J., Alonso, A., López, N., et al. (2017). Growth hormone (GH) and rehabilitation promoted distal innervation in a child affected by caudal regression syndrome. *International Journal of Molecular Sciences*, *18*(1), 230.

Díaz-Galindo, C., Calderón-Vallejo, D., Hernández-Jasso, I., et al. (2020). Gonadotropin-releasing hormone receptor expression in human spinal cord. *Neurochemical Research*. https://doi.org/10.1007/s11064-020-03178-w (Online ahead of print).

Engele, J., Schubert, D., & Bohn, M. C. (1991). Conditioned media derived from glial cell lines promote survival and differentiation of dopaminergic neurons in vitro: Role of mesencephalic glia. *Journal of Neuroscience Research*, *30*(2), 359–371.

Erşahin, M., Özdemir, Z., Özsavcı, D., et al. (2012). Melatonin treatment protects against spinal cord injury induced functional and biochemical changes in rat urinary bladder. *Journal of Pineal Research*, *52*(3), 340–348.

Faden, A. I., Vink, R., & McIntosh, T. K. (1989). Thyrotropin-releasing hormone and central nervous system trauma. *Annals of the New York Academy of Sciences*, *553*, 380–384.

Fakhoury, M. (2015). Spinal cord injury: Overview of experimental approaches used to restore locomotor activity. *Reviews in the Neurosciences*, *26*(4), 397–405.

Fang, H., Liu, C., Yang, et al. (2017). Neurotrophic factor and Trk signaling mechanisms underlying the promotion of motor recovery after acute spinal cord injury in rats. *Experimental and Therapeutic Medicine*, *14*(1), 652–656.

Fawcett, J. W., Curt, A., Steeves, J. D., et al. (2006). Guidelines for the conduct of clinical trials for spinal cord injury as developed by the ICCP panel: Spontaneous recovery after spinal cord injury and statistical power needed for therapeutic clinical trials. *Spinal Cord*, *45*, 190–205.

Fröhlich, E., & Wahl, R. (2019). The forgotten effects of thyrotropin-releasing hormone: Metabolic functions and medical applications. *Frontiers in Neuroendocrinology*, *52*, 29–43.

Fu, J., Wang, H., Deng, L., & Li, J. (2016). Exercise training promotes functional recovery after spinal cord injury. *Neural Plasticity*, *2016*, 1–7.

Gold, S. M., Schulz, K.-H., Hartmann, S., et al. (2003). Basal serum levels and reactivity of nerve growth factor and brain-derived neurotrophic factor to standardized acute exercise in multiple sclerosis and controls. *Journal of Neuroimmunology*, *138*(1–2), 99–105.

Griffin, J. M., & Bradke, F. (2020). Therapeutic repair for spinal cord injury: Combinatory approaches to address a multifaceted problem. *EMBO Molecular Medicine*, *12*(3), e11505.

Harvey, A. R., Lovett, S. J., Majda, B. T., Yoon, J. H., Wheeler, L. P., & Hodgetts, S. I. (2015). Neurotrophic factors for spinal cord repair: Which, where, how and when to apply, and for what period of time? *Brain Research*, *1619*, 36–71.

Hogan, M. K., Hamilton, G. F., & Horner, P. J. (2020). Neural stimulation and molecular mechanisms of plasticity and regeneration: A review. *Frontiers in Cellular Neuroscience*, *14*, 271.

Jin, M. C., Medress, Z. A., Azad, T. D., Doulames, V. M., & Veeravagu, A. (2019). Stem cell therapies for acute spinal cord injury in humans: A review. *Neurosurgical Focus*, *46*(3), E10.

Kachadroka, S., Hall, A. M., Niedzielko, T. L., Chongthammakun, S., & Floyd, C. L. (2010). Effect of endogenous androgens on 17beta-estradiol-mediated protection after spinal cord injury in male rats. *Journal of Neurotrauma*, *27*(3), 611–626.

Kathe, C., Hutson, T. H., McMahon, S. B., & Moon, L. D. F. (2016). Intramuscular neurotrophin-3 normalizes low threshold spinal reflexes, reduces spasms and improves mobility after bilateral corticospinal tract injury in rats. *eLife*, *5*, e18146.

Keefe, K. M., Sheikh, I. S., & Smith, G. M. (2017). Targeting neurotrophins to specific populations of neurons: NGF, BDNF, and NT-3 and their relevance for treatment of spinal cord injury. *International Journal of Molecular Sciences*, *18*(3), 548.

Kohut, M. L., McCann, D. A., Russell, D. W., Konopka, D. N., Cunnick, J. E., Franke, W. D., et al. (2006). Aerobic exercise, but not flexibility/resistance exercise, reduces serum IL-18, CRP, and IL-6 independent of β-blockers, BMI, and psychosocial factors in older adults. *Brain, Behavior, and Immunity*, *20*(3), 201–209.

Leech, K. A., & Hornby, T. G. (2017). High-intensity locomotor exercise increases brain-derived neurotrophic factor in individuals with incomplete spinal cord injury. *Journal of Neurotrauma*, *34*(6), 1240–1248.

Martínez-Moreno, C. G., Calderón-Vallejo, D., Harvey, S., Arámburo, C., & Quintanar, J. L. (2018). Growth hormone (GH) and gonadotropin-releasing hormone (GnRH) in the central nervous system: A potential neurological combinatory therapy? *International Journal of Molecular Sciences*, *19*(2), 375.

McArthur, J. C., Yiannoutsos, C., Simpson, D. M., et al. (2000). A phase II trial of nerve growth factor for sensory neuropathy associated with HIV infection. AIDS Clinical Trials Group team 291. *Neurology*, *54*, 1080–1088.

Milosevic, M., Marquez-Chin, C., Masani, K., Hirata, M., Nomura, T., Popovic, M. R., et al. (2020). Why brain-controlled neuroprosthetics matter: Mechanisms underlying electrical stimulation of muscles and nerves in rehabilitation. *Biomedical Engineering Online*, *19*(1), 81.

Mocchetti, I., & Wrathall, J. R. (1995). Neurotrophic factors in central nervous system trauma. *Journal of Neurotrauma*, *12*, 853–870.

Ong, W., Pinese, C., & Chew, S. Y. (2019). Scaffold-mediated sequential drug/gene delivery to promote nerve regeneration and remyelination following traumatic nerve injuries. *Advanced Drug Delivery Reviews*, *149–150*, 19–48.

Onifer, S. M., Smith, G. M., & Fouad, K. (2011). Plasticity after spinal cord injury: Relevance to recovery and approaches to facilitate it. *Neurotherapeutics*, *8*, 283–293.

Pitts, L. H., Ross, A., Chase, G. A., & Faden, A. I. (1995). Treatment with thyrotropin-releasing hormone (TRH) in patients with traumatic spinal cord injuries. *Journal of Neurotrauma*, *12*(3), 235–243.

Quintanar, J. L., Díaz-Galindo, C., Calderón-Vallejo, D., et al. (2018). Neurological improvement in patients with chronic spinal cord injury treated with leuprolide acetate, an agonist of GnRH. *Acta Neurobiologiae Experimentalis*, *78*(4), 352–357.

Rayegani, S. M., Shojaee, H., Sedighipour, L., Soroush, M. R., Baghbani, M., & Amirani, O. B. (2011). The effect of electrical passive cycling on spasticity in war veterans with spinal cord injury. *Frontiers in Neurology*, *2*, 39.

Rojas Vega, S., Abel, T., Lindschulten, R., Hollmann, W., Bloch, W., & Strüder, H. K. (2008). Impact of exercise on neuroplasticity-related proteins in spinal cord injured humans. *Neuroscience*, *153*(4), 1064–1070.

Romero, M. I., Rangappa, N., Li, L., Lightfoot, E., Garry, M. G., & Smith, G. M. (2000). Extensive sprouting of sensory afferents and hyperalgesia induced by conditional expression of nerve growth factor in the adult spinal cord. *Journal of Neuroscience*, *20*, 4435–4445.

Rosenfeld, R. D., Zeni, L., Haniu, M., Talvenheimo, J., Bennett, L., Miller, J. A., et al. (1995). Purification and identification of brain-derived neurotrophic factor from human serum. *Protein Expression and Purification*, *6*, 465–471.

Rosich, K., Hanna, B. F., Ibrahim, R. K., Hellenbrand, D. J., & Hanna, A. (2017). The effects of glial cell line-derived neurotrophic factor after spinal cord injury. *Journal of Neurotrauma*, *34*, 3311–3325.

Samantaray, S., Sribnick, E. A., Das, A., et al. (2010). Neuroprotective efficacy of estrogen in experimental spinal cord injury in rats. *Annals of the New York Academy of Sciences*, *1199*, 90–94.

Sharma, H. S. (2007). A select combination of neurotrophins enhances neuroprotection and functional recovery following spinal cord injury. *Annals of the New York Academy of Sciences*, *1122*, 95–111.

Silvestro, S., Bramanti, P., Trubiani, O., & Mazzon, E. (2020). Stem cells therapy for spinal cord injury: An overview of clinical trials. *International Journal of Molecular Sciences*, *21*(2), 659.

Tuszynski, M. H., Gabriel, K., Gage, F. H., Suhr, S., Meyer, S., & Rosetti, A. (1996). Nerve growth factor delivery by gene transfer induces differential outgrowth of sensory, motor, and noradrenergic neurites after adult spinal cord injury. *Experimental Neurology*, *137*, 157–713.

Veneruso, V., et al. (2019). Stem cell paracrine effect and delivery strategies for spinal cord injury regeneration. *Journal of Controlled Release*, *300*, 141–153.

Verge, V. M., Richardson, P. M., Benoit, R., & Riopelle, R. J. (1989). Histochemical characterization of sensory neurons with high-affinity receptors for nerve growth factor. *Journal of Neurocytology*, *18*, 583–591.

Walker, M. J., & Xu, X. M. (2018). History of glial cell line-derived neurotrophic factor (GDNF) and its use for spinal cord injury repair. *Brain Sciences*, *8*(6), 109.

Waters, R. L., Adkins, R. H., Sie, I. H., & Yakura, J. S. (1996). Motor recovery following spinal cord injury associated with cervical spondylosis: A collaborative study. *Spinal Cord*, *34*, 711.

Wu, J. C., Huang, W. C., Chen, Y. C., et al. (2011). Acidic fibroblast growth factor for repair of human spinal cord injury: A clinical trial. *Journal of Neurosurgery: Spine*, *15*(3), 216–227.

Xu, D., Wu, D., Qin, M., et al. (2019). Efficient delivery of nerve growth factors to the central nervous system for neural regeneration. *Advanced Materials*, *31*(e), 1900727.

Yang, B., Zhang, F., Cheng, F., Ying, L., Wang, C., Shi, K., et al. (2020). Strategies and prospects of effective neural circuits reconstruction after spinal cord injury. *Cell Death & Disease*, *11*(6), 439.

Zeller, S., Abel, T., Rojas-Vega, S., Foitschik, T., & Strueder, H. K. (2015). Brain-derived neurotrophic factor concentrations in tetraplegic athletes. *Spinal Cord*, *53*(11), 791–794.

Zhou, Y., Wang, Z., Li, J., Li, X., & Xiao, J. (2018). Fibroblast growth factors in the management of spinal cord injury. *Journal of Cellular and Molecular Medicine*, *22*(1), 25–37.

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Section E

Rehabilitation in spinal injury

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Chapter 38

Spinal cord injury: Multiple family group (MFG) education and support

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Introduction

Damage to the spinal cord can be a life-changing event, usually occurring suddenly as a result of an accident, and presenting both acute and long-term medical effects to individuals and their families. Because these events usually happen unexpectedly, suddenly the individual is thrown into the chaos of the health care system. Rarely do people have any idea of the implications on future health, lifestyle, or economic consequences of this kind of event. The impact on the affected individual is profound, producing both paralysis and medical complications to many body systems. Medical prognostication is often uncertain, and many myths surround spinal cord injury (SCI; sciprogress.com, 2020).

Epidemiology of spinal cord injury

Over the past 50 years, the age at time of acute spinal injury has increased by a decade or more, but still, the event affects individuals in the prime of their lives, currently averaging 43 years of age (National Spinal Cord Injury Statistical Center, 2020a). Nearly 80% of all SCI individuals are male. As a result of the age at onset, consequent effects have major socioeconomic impacts on work-lives, family income, and life roles. Despite many improvements in motor vehicles, motor vehicle accidents represent approximately 40% of all SCI cases, with falls accounting for another 30%, gunshots 13.5%, and sports-related causes about 8% (National Spinal Cord Injury Statistical Center, 2020a). Medical issues such as transverse myelitis and intraspinal hemorrhages account for the remainder. Regardless of cause, the effect is hugely traumatizing.

There are approximately 17,700 new cases of SCI each year, representing an annual incidence of 54 cases per 1 million population. Because the pathology is often lasting, it is estimated that around 300,000 persons with SCI are currently living in the United States (National Spinal Cord Injury Statistical Center, 2020b). SCI related disability may affect the cervical, thoracic, lumber and sacral portions of the spinal cord structures, with higher level injuries producing more disability (National Spinal Cord Injury Statistical Center, 2020b). The physical impacts on the spinal cord may produce an incomplete injury with some functions retained or may result in a near-complete loss of function distally. Nearly 60% of all SCIs are at the cervical level producing tetraplegia, and 2/3rds of those are incomplete. Of the 40% remaining injuries producing paraplegia, half are incomplete (National Spinal Cord Injury Statistical Center, 2020b). Less than 1% of affected individuals experience complete recovery by the time of hospital discharge (National Spinal Cord Injury Statistical Center, 2020b).

Life impact and medical support

Everyday activities, from prior independence of basic life activities through vocational function undergo massive change. SCI greatly affects a person's level of independence in mobility, self-care and economic well-being. A little over 30% of affected individuals are married at the time of injury, with 60% single or divorced at injury (National Spinal Cord Injury Statistical Center, 2020b). While nearly 60% are employed at the time of injury, by the end of year one post-injury only about 12% are (National Spinal Cord Injury Statistical Center, 2020b). As a consequence, reliance upon social support systems greatly increases. The level of such support systems varies greatly across the United States, rarely covering all the injured person's needs, especially immediately following injury.

Diagnosis and Treatment of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822498-4.00038-5

Medical care for acute spinal cord injury has changed significantly over the years, with improvements in surgical and medical management resulting in improved survival. But as the physiologic impacts of SCI are usually long-term, this presents a need for comprehensive rehabilitation in order to strengthen the areas affected and instruct the injured person in self-management skills including dressing, hygiene, toileting and skin care, in addition to teaching mobility skills such as wheelchair use and other supported mobility needs. During the 1970s, most SCI-affected individuals spent months (average 142 days) in inpatient rehabilitation facilities learning these skills, gaining competence in self-management, and educating families and immediate caregivers on appropriate ways of providing needed support. By discharge, these skills had been practiced, needs anticipated and support structures provided. During those years, the average length of stay in an inpatient rehabilitation facility for a cervical cord injury was around 5 months and during this period the individual often had opportunities for weekend passes to practice skills in their home environment. Persons with paraplegia stayed for 2 months or longer, with similar opportunities to practice home skills. During those years, the rehabilitation inpatient staff team frequently included physical therapists, occupational therapists, social workers, recreation therapists, vocational counselors and psychologists to teach, guide and support individuals with SCI in the areas affected by their injury. Health care systems have changed dramatically since then, with the overall average length of stay currently just over 1 month (National Spinal Cord Injury Statistical Center, 2020b). Rehabilitation staffs have shrunk as well, with only basic therapy needs provided in many American inpatient rehabilitation facilities. Specialty SCI rehabilitation hospitals may have much larger staffs and longer lengths of stay, but funding for such care is not available for many acute SCI patients. As a consequence of these systematic changes in care provision, there are larger burdens placed upon caregivers and patients.

The dramatic compression of lengths of stay result in a much busier hospital day, especially given that nearly 40% of traumatic SCI patients have other injuries in addition to their spinal cord and 80% will have undergone spinal surgeries (National Spinal Cord Injury Statistical Center, 2020b). There are common co-morbidities including traumatic brain injury and thoracic and abdominal trauma. Focus is on physical recovery, wound healing, pain management and other medical needs, as well as rehabilitation therapies and education. Individuals with significant pain issues have consequent learning difficulties that interfere with the teaching process. The burden of healing, coping, adaptation, and multi-tasking overwhelms even emotionally stable individuals. The cliché of drinking from a firehose is not an exaggeration. The inpatient stay period is intensely stressful for all, patients, spouses, family, and caregivers.

Spinal cord injury after-effects

There are common medical changes resultant from the injury. Bladder management poses issues for about 75% of individuals with SCI, with a variety of urologic adaptations needed, including intermittent catheterization, indwelling catheters, or some form of urinary diversion (National Spinal Cord Injury Statistical Center, 2020b). Medical complications of these alternative solutions may include subsequent urinary tract infections (National Spinal Cord Injury Statistical Center, 2020b). Bowel management may also pose issues, requiring modifications of typical routines, medications and physical techniques which may necessitate caregiver aid. Education regarding skin care is an essential part of the inpatient training process, but follow-through is critical post-discharge and this too may pose caregiver burden, especially if pressure sores occur (National Spinal Cord Injury Statistical Center, 2020b). The need for family and caregiver education is critical to support the person with an acute SCI both medically and with mobility needs.

The preponderance of SCI survivors (87.4%) are discharged to a private home (National Spinal Cord Injury Statistical Center, 2020b). Architectural accessibility of the home to mobility limitations more often than not presents significant problems, especially for those with higher level injuries. Thus, architectural barriers are routinely problematic, as 60% of individuals with SCI rely on a wheelchair for mobility, including both manual and powered chairs (National Spinal Cord Injury Statistical Center, 2020b). In many homes, bedrooms are upstairs, bathrooms are small and inaccessible to wheelchairs and entry and exit present their own challenges. Steps and stairs, narrow doorways, cupboards, and toilet areas cause difficulties for most at discharge. Only rarely is funding for architectural modification available. Transportation poses a common problem, as many vehicles are difficult to enter and exit for someone in a wheelchair and public transportation is often unavailable, especially for rural residents.

The changes in spinal cord injury care over the past decades are many, with some good news in reduction of medical complications, more sophisticated spinal surgery resulting in enhanced neuro recovery and better understanding of medical needs. But there is also less positive news in terms of the reduction in lengths of stay resulting in less opportunity for patient and family education, less medical oversight in the months immediately following the injury and less emphasis on community re-entry education. Community support systems are insufficient. As a consequence of these latter issues, the Multi-family Group Education (MFG) process poses a real opportunity in the long-term approach to the many problems posed by SCI.

Impacts of SCI on family caregivers

There is nearly always a need for caregiver support of people with SCI. For married individuals, this usually falls to the spouse, placing both physical and substantial emotional demands. For unmarried persons, often this role falls to the family and obviously such support varies greatly in time, interest and ability. The caregiving position encompasses more than physical assistance and often includes educating, advising, financially supporting, advocating for and becoming the prevention / management specialist for the injured family member (Guilcher et al., 2012). Family caregivers are thrust into learning much of this on the fly and often don't know how to accomplish all the necessary tasks. As a result, they often become as, or more stressed and overwhelmed as the person with SCI by the added responsibility and adjustments needed to their daily lives. They can experience frustration, isolation and feelings of guilt, as well as resentment toward the injured family member they care for (Kester, Rothblum, Lobato, & Milhous, 1988). Qualitative research on the experience of family caregivers for people with SCI indicates that caregivers experience deterioration in their relationship with the person who has SCI and that they require intentional re-building and maintaining of their relationships (Jeyathevan, Cameron, Craven, Munce, & Jaglal, 2019). Spouses who become caretakers of an SCI injured partner have been found to have significantly more depressive affect than their spouse with SCI and have significantly more physical and emotional stress, burnout, fatigue, anger and resentment, depressive affect and somatic depression than spouses who are not caregivers (Weitzenkamp, Gerhart, Charlifue, Whiteneck, & Savic, 1997). Negative psychological and physical health impacts on caregivers have been indicated across countries and cultures (Ebrahimzadeh et al., 2013).

In an examination of the unique contribution of social support to SCI caregiver burden researchers have found that social support, social interactions, and social integration are significant predictors of caregiver burden, suggesting that interventions such as MFG that promote social support, interaction, and integration hold the potential to decrease caregiver burden (Rodakowski, Skidmore, Rogers, & Schulz, 2012). There is a pressing need for individualized education, support and coaching not only for individuals with SCI, but also for their caregivers, particularly when those caregivers are family members (North, 1999). This need begins immediately and should be in place upon discharge from the hospital.

Impact of multiple family groups (MFG) on psychiatric outcomes

Chronic health conditions require multiple adjustments for both those afflicted and their family caregivers. They are invariably extremely isolating conditions that require coping skills both by patients and their family caregivers. There is now accumulated evidence over a number of decades which supports the idea that, for a number of chronic conditions, a combination of education, support and problem-solving services improves rehabilitative outcomes, community supports and in some cases reduces caregiver burden (Glynn, Dixon, Cohen, & Murray-Swank, 2008; Mueser, 2003; Pilling et al., 2002). Chronic conditions such as severe mental disorders (Dyck, Hendryx, Short, Voss, & McFarlane, 2002; Hazel et al., 2004; McFarlane, 2002), brain injury (Perlick et al., 2013; Rodgers et al., 2007; Straits-Troster et al., 2013), mild cognitive impairment (Schmitter-Edgecombe & Dyck, 2014) and chronic pain (Smith et al., 2017) have all been studied. A pioneering approach which served as a model for our intervention for SCI was developed by McFarlane in the late 70s for the management of schizophrenia (McFarlane, 2002). The intervention called multiple family group (MFG), provides education, support and problem-solving activities to six to eight persons with schizophrenia and their respective family members. The treatment process is a structured interactive format consisting of two mental health clinicians to assist families and patients to improve coping, social support and illness management skills. McFarlane initially enrolled in-patients with schizophrenia and their family caregivers in a 2-year long intervention. The intervention focused initially on preventing relapse and then gradually shifted focus to rehabilitative and occupational goals with community supports. MFG prevented relapse and re-hospitalization and improved rehabilitation outcomes (cf. McFarlane, 2002), relative to single family groups, and MFG became an evidence based best practice in mental health. In the 1990s, psychiatric hospitalization stays became increasingly shorter and more infrequent as treatment services for persons with severe mental illness shifted to the community. We therefore adapted the MFG intervention to a community mental health care setting (Dyck et al., 2000). We enrolled persons with schizophrenia receiving outpatient services and their family members into a two arm randomized clinical trial comparing a 2-year MFG intervention to Standard Care and demonstrated that relative to standard care, relapse, negative symptoms and hospitalization care and costs were all reduced (Dyck et al., 2000; McDonell, Short, Hazel, Berry, & Dyck, 2006). We also found reductions in family caregiver burden and distress (Hazel et al., 2004).

Adapting multiple family group treatment for brain and spinal cord injury

Approximately 15 years ago Becker, Dyck and colleagues sought to adapt MFG for persons with traumatic brain injury (TBI) and SCI. Below we summarize that treatment development process and the quantitative and qualitative outcome evidence supporting these efforts (Rodgers et al., 2007). We reasoned that although the medical conditions and social and behavioral features of schizophrenia are unique, there are also common themes such as chronicity, the need for illness management skills and community supports and extensive impacts on the family support system. It is also the case that these conditions occur most often in younger age groups, resulting in significant functional disability and restriction of vocational options. These conditions also share the increased risk of social isolation and altered family roles to support the affected individuals. We therefore initiated a field development project to adapted MFG for TBI and SCI. The MFG protocol followed the original model (McFarlane, 1994). The stages included (1) joining with patients and the families through several individual sessions, (2) conducting an educational workshop, and (3) teaching management skills for physical and cognitive challenges as well as improving psychosocial functioning and supports through the use of structured problem-solving group sessions. The group sessions lasted approximately 75–90 min and each consisted of: socialization, go-around, problem identification, and problem solving. We retained the structure and format of the original model but modified the content to accommodate the unique issues of TBI and SCI. For example, during the joining sessions we gathered information on the injury event, its impacts on the patient and the family, how and how successfully they were coping with the adjustments and setbacks. The educational workshop covered neuroanatomy basics, aspects of physical rehabilitation and the support and coping responses to the injury needed by patients and family members. In the problem-solving session, the go-arounds often focused on medical complications, equipment concerns and needs, challenges to travel and caregiver issues. The complete intervention lasted between 12 and 18 months and included initially bi-monthly and then monthly meetings. Two clinicians led each group. The clinicians were experienced physical, speech, and occupational therapists and mental health clinicians (social workers and psychologists). Overall, the results were encouraging. For patients, life satisfaction for patients improved over 18 months (Fig. 1). Patients also reported a decrease in depressive symptoms and anger expression. Among family caregivers, burden was reduced (Fig. 2). Focus groups and qualitative analysis further supported the idea that the MFG experience led to a normalization of the caregiving experience, provided important informational and social support and improved the coping and management skills of both injured persons and their caregivers. Several limitations of this initial effort were that, being a treatment development study, the sample was small, there was no control group and the drop-out rate was approximately 20%. In retrospect, the drop-out rate could be the result of a combination of factors: not enrolling participants early enough after the injury, the length of the intervention, and transportation and related logistic issues.

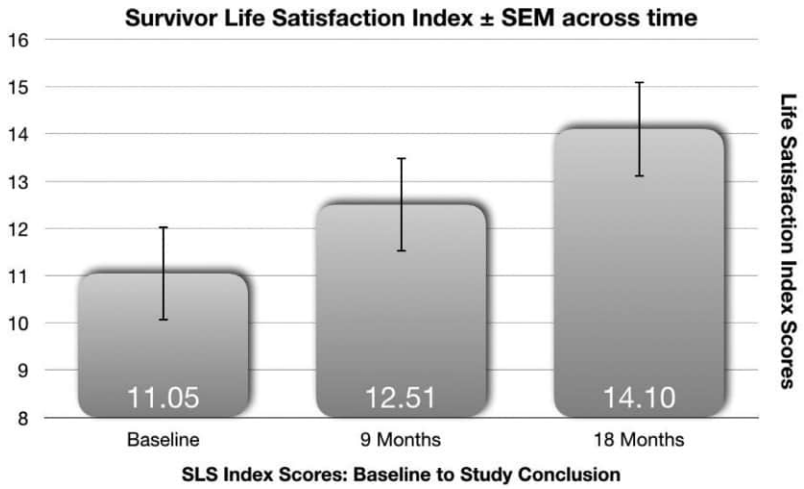

FIG. 1 Mean survivor life satisfaction index scores ± standard error of measure. *Figures adapted from Rodgers, M. L., Strode, A. D., Norell, D. M., Short, R. A., Dyck, D. G., & Becker, B. (2007). Adapting multiple-family group treatment for brain and spinal cord injury intervention development and preliminary outcomes. American Journal of Physical Medicine & Rehabilitation, 86(6), 482–492. https://doi.org/10.1097/Phm.0b013e31805c00a1.*

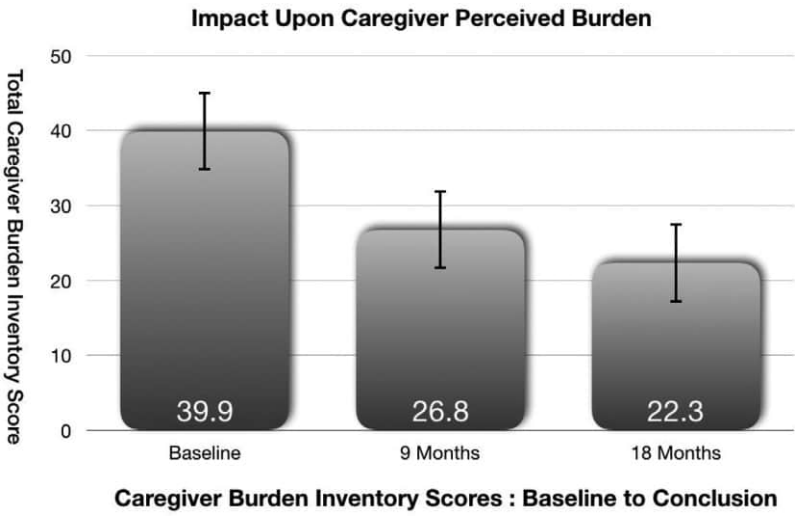

FIG. 2 Mean impact upon caregiver perceived burden ± standard error measurement. *Figures adapted from Rodgers, M. L., Strode, A. D., Norell, D. M., Short, R. A., Dyck, D. G., & Becker, B. (2007). Adapting multiple-family group treatment for brain and spinal cord injury intervention development and preliminary outcomes. American Journal of Physical Medicine & Rehabilitation, 86(6), 482–492. https://doi.org/10.1097/Phm.0b013e31805c00a1.*

Comparison of MFG to educational control (EC)

We have recently completed a small randomized clinical trial comparing MFG to an active Education Control (Dyck, Weeks, Smith, & Shaw, 2020). In an effort to improve treatment retention, we shortened the MFG group to 9 months and recruited participants within 3 years of their injury. All participants were provided a copy of the 4th Edition of the book titled: Yes you can: a guide to self-care for persons with spinal cord injury (Hammond, 2000). We block randomized participants (SCI outpatients and their caregivers), in groups of three or four dyads, to either MFG or EC. Participants with SCI and their caregivers were assessed both with psychometrically validated quantitative measures at baseline, at the conclusion of the 9-month intervention and 6 months following the interventions. Focus groups were conducted with all participants at the end of the intervention to determine participants' perceptions of the value of the overall experience, how helpful it was and recommendations for improvement. SCI participants were eligible if they had a paraplegic or quadriplegic injury with complete or incomplete lesion; were discharged from inpatient rehabilitation within 3 years, were living in the community in a non-group setting, at least 16 years old, had a mobility impairment and planned to remain in the geographic area for at least 12 months. SCI caregivers were eligible if they were the primary instrumental and/or emotional support person for a spouse, partner, relative, or friend with SCI, spent at least 2 h of face to face contact per week with the participant, lived with or near the participant with SCI, were at least 18 years old, and planned to remain in the geographical area for at least 12 months. Exclusion criteria included terminal illness with life expectancy of less than 12 months, being in active cancer treatment and cognitive impairment. An overview and global comparison of MFG and the EC interventions is provided in Table 1. The primary difference was that MFG was an interactive experience that provided education, support, and individualized problem solving to participants, while the EC condition was a typical didactic classroom experience with limited opportunity for interaction or individual problem solving. The EC condition covered the topics in the "Yes, you can" book. While content for the MFG condition was loosely based on the book, participants had considerable voice in selecting what problems were identified for problem solving in the sessions. The content comparison between the MFG and EC interventions is shown in Table 2. Treatment integrity in both conditions was supported by videotaping, weekly supervision, and treatment manuals. The results generally supported what we observed in the earlier treatment development study.

Quantitative analyses indicated that following treatment, MFG participants with SCI more frequently disagreed with passive coping statements from the Family Crisis Personal Evaluation Scales (F-COPES; McCubbin, Larsen, & Olson, 1985) compared to EC participants. Thus, MFG group participants more frequently rejected passive coping strategies such as "believing if we wait long enough the problem will go away" that are counter-productive beliefs for rehabilitation. It is important to note that not only did MFG participants with SCI reject passive coping strategies, so too did MFG caregivers. We also found that MFG participants with SCI also reported higher levels of subjective and overall social support on the Abbreviated Duke Social Support Index (ADSSI; Koenig et al., 1993). A number of other quantitative measures such as

TABLE 1 Global comparison of multiple family group (MFG) and education control interventions (EC).

Treatment component	MFG	EC
Therapeutic strategy	Skills training, problem solving, support	Information only
Contents	SCI effects on the body, maximizing function, coping, living and staying healthy with SCI	SCI effects on the body, maximizing function, coping, living and staying healthy with SCI
Target Group	Persons with SCI and caregivers	All persons with SCI and caregivers
Use of group dynamics/ cohesion	*Social support promoted*: Entire group participates in problem-solving for each dyad and gives support and encouragement	*Social support minimized*: Individual health issues not discussed, education is general, group interaction minimized
Therapeutic stance	Educator stance is collaborative	Educator stance is didactic
Room set-up	Round table	Lecture style (all chairs face forward)
Source of material	Drawn from everyday problems brought in by group members	Supplied by educator
Homework	Assigned and reviewed at the start of the following session	Handouts but not homework provided

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TABLE 2 Content comparison between multiple family group (MFG) and education control (EC) interventions.

Treatment component	MFG-SCI	# sessions	SCIEC	# sessions
Joining	*Dyad-tailored education*[a]: SWOT analysis, SCI problems identified and corrected Formulation of management problems and coping. Recommend one or more strategies and adjustments (individual and dyad)	2(3)[b]	*Standard dyad intake*: History of person with SCI and caregiver focusing on current health, skin care, bladder management, bowel management. No skills training, interventions, or formulation of management problems and needed adjustments	2(3)[b]
Group introductory sessions	*Educational workshop*: ASIA classification, clinical syndromes, rehab therapy, medications, health lifestyle, the family and adjustment, family guidelines. Structure and function of multiple family group, how it can help	2	*Education introduction*: Structure and rationale for intervention. Rules of conduct. Overview of topics to be covered	1
Ongoing group sessions	*Problem-solving and skills training sessions*: Problem-solving designed to address specific problems associated with SCI. Compensatory strategies for SCI problems, planning ahead	12	*SCIEC education*: General information provided to promote healthy living in areas relevant for persons with SCI and caregivers (bladder/bowel management, nutrition, use of alcohol, drugs, safe exercise) Personal health concerns not discussed; however, discuss referral to provider	13
Total		16		16

[a]*The default is two sessions, an optional third session may be used to maintain contact with group members recruited early, or where the dyads are uncertain about continued participation.*
[b]*In addition to basic intake.*

Tables reprinted from Dyck, D. G., Weeks, D. L., Smith, C. L., & Shaw, M. (2020). Multiple family group intervention for spinal cord injury: Quantitative and qualitative comparison with standard education. *The Journal of Spinal Cord Medicine, 44*, 1–11 with publisher permission.

patient activation (Hibbard, Mahoney, Stockard, & Tusler, 2005) and reduced anger expression (Spielberger et al., 1985) approached but did not reach statistical significance, potentially due to a small sample size (Tables 3 and 4).

Qualitative analysis of the focus groups indicated that MFG participants experienced an enhanced sense of belonging and teamwork. They expressed that, the MFG group experience provided them with opportunities to engage with others experiencing similar challenges, which decreased their feelings of isolation. Both participants with SCI and their caregivers requested more and earlier opportunities for this engagement and suggested that the intervention begin while patients with SCI were still inpatients. Participants valued the knowledge and support of the group leaders and spoke at length about their personal ongoing quests for knowledge related to SCI.

Although there were study limitations, such as a small self-selected sample, lack of racial and ethnic diversity and lack of a treatment-as-usual comparison, the results support the earlier treatment development study with a more methodologically rigorous comparison of MFG to an active control intervention.

TABLE 3 Six-step formal problem-solving process utilized in the multiple family group intervention.

Step	Process
1.	Define the problem or goal (MFG members and facilitators)
2.	List all possible solutions (MFG members)
3.	Discuss advantages and disadvantages of each in turn (MFG members and facilitators)
4.	Choose the solution that best fits the situation (MFG members)
5.	Plan how to carry out this solution (facilitators)
6.	Review implementation (facilitators)

Steps are based on brainstorming methods from organizational and business practices.
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TABLE 4 Means (standard deviations) per group for significant group main effects in the outcome measures ($P < 0.05$).

		Group		
	Analysis	Multiple family group	Education control	Effect size
Participants with SCI				
F-COPES passive appraisal scale[a]	Pooled imputed	17.7(2.7)	14.9(3.1)	0.9
	Complete case	18.6(2.1)	15.5(2.2)	1.4
ADSSI subjective social support scale[b]	Pooled imputed	19.3(1.5)	15.8(1.7)	2.1
	Complete case	19.4(1.9)	15.4(2.0)	2.0
ADSSI total score	Pooled imputed	27.1(1.8)	24.0(2.1)	1.5
	Complete case	28.1(2.2)	23.2(2.3)	2.1
Caregivers				
F-COPES passive appraisal scale	Pooled imputed	18.3(2.4)	13.9(2.7)	1.6
	Complete case	18.0(2.5)	14.7(2.6)	1.3

[a]*F-COPES, family crisis oriented personal evaluation scales. Higher scores represent lower passive appraisal.*
[b]*ADSSI, Abbreviated Duke social support index.*

Tables reprinted from Dyck, D. G., Weeks, D. L., Smith, C. L., & Shaw, M. (2020). Multiple family group intervention for spinal cord injury: Quantitative and qualitative comparison with standard education. *The Journal of Spinal Cord Medicine, 44*, 1–11 with publisher permission.

Implementation and dissemination opportunities and barriers

While clinicians and researchers consistently request interventions such as MFG to support individuals with SCI (Ebrahimzadeh et al., 2013; Jeyathevan et al., 2019), and the evidence base for MFG SCI and similar group approaches as an important component of outpatient rehabilitation is growing, it is not yet an evidence based best practice. It is, however, important to consider the barriers and opportunities to bridge the chasm between research and practice. In addition to systemic barriers (e.g., cost, effort and reimbursement issues), one of the biggest challenges to recruitment and retention that we have encountered is the high cost of commitment to an intensive long-term intervention with time and travel demands. The time and travel commitments are especially burdensome in the winter for those who live in rural communities impacted by inclement weather. This not only impacts vehicle travel, but often times sidewalks and other paths are not cleared sufficiently for wheelchair use, which makes it even more difficult during an already challenging time. We believe that in this age of telehealth, MFG could be implemented much more readily and likely as effectively through the use of telehealth technology. Choi et al. (2014) recently reported both improved depression and disability outcomes following telehealth delivered (via Skype video call) problem-solving therapy (PST) for depressed, low income homebound older adults. They compared the efficacy of telehealth PST, to in person PST and telephone care calls to homebound older depressed adults. Both telehealth and in person PST were effective treatment, relative to telephone care; however, the effect of telehealth PST on both depression and disability outcomes were sustained longer than those of in-person PST. Although their study was not a group-based intervention for SCI, it is nevertheless a promising example of improving access to care among low income, underserved, home bound adults by providing them with a laptop and wireless card. A systematic review by Gentry, Lapid, Clark, and Rummans (2019) found that videoconference groups were feasible and resulted in similar outcomes to in-person groups, with high participant satisfaction despite some initial technical learning challenges. Additional research was recommended to identify the optimal method of videoconference group delivery to maximize outcomes and benefit.

Application to other areas of neuroscience

MFG is being adapted to other areas of applied neuroscience. We will summarize two areas that we have had direct involvement in: TBI and mild cognitive impairment (MCI).

TBI: TBI survivors and their families experience many of the same challenges that persons with SCI experience. The injury immediately changes the lives of injured persons and their families, especially relationships with spouses. Our initial field development work (Rodgers et al., 2007) adapted MFG for persons with TBI. Given that in the United States TBI became the signature injury of the Gulf wars, there was a pressing need to provide education and support to Veterans with TBI (often with posttraumatic stress disorder (PTSD) as a co-morbid condition). Taking our initial development work with civilian TBI as a starting point, several investigators (Perlick, Troster, and colleagues) sought our collaboration to adapt MFG for military Veterans with TBI (Straits-Troster et al., 2013). Straits-Troster et al. (2013) evaluated the feasibility, acceptability and helpfulness of MFG for veterans of the wars Iraq and Afghanistan who had sustained a TBI, and their family members. Both veterans and family members reported that MFG helped them explore common struggles, reduced their isolation and helped restore and improve relationships, particularly with their spouses. They also reported a better understanding of the connection between TBI and PTSD. The focus group results were similar to those in our work with SCI and TBI and supported the feasibility, acceptability and need for the MFG support program among veterans with TBI. Perlick et al. (2013) reported that treatment was associated with decreased anger expression and increased social support and occupational activity in veterans, while caregivers reported decreased burden and increased empowerment.

Mild Cognitive Impairment (MCI): Schmitter-Edgecombe and Dyck (2014) integrated the MFG intervention with cognitive rehabilitation (CR) for persons recently diagnosed with MCI and their spousal caregivers. The combined intervention was designed to support the adoption of newly learned cognitive strategies including the use of a memory notebook into everyday life. The combined CR-MFG intervention was associated with improved pre-post group differences on measures of everyday functioning and neuropsychological tests of memory. There was also suggestion that care partners noticed the improvements in the everyday functioning of their spouses with MCI. While preliminary, these results suggest that MFG may produce modest functional benefit for persons with MCI. The study also shows that MFG can be successfully combined with other therapeutic strategies. Thus, MFG would potentially have benefit for other neurological conditions such as stroke and multiple sclerosis.

Conclusion

Although significant surgical and related medical advances have been made in improving clinical and functioning outcomes in persons with SCI, for most individuals SCI is a life-changing injury. This is true not only for the person with SCI but also for their caregivers and family members. We are encouraged that functional outcomes for persons with SCI and caregiver support systems can be strengthened by providing education and support through multiple family groups. However, there remain a number of future opportunities and challenges in implementing and refining our systems of care for persons with SCI and their families. The use of telehealth to conduct education and support should be explored to help overcome logistic and access challenges faced by persons with SCI. In our experience, the biggest challenges to successful implementation of innovative practices are often systemic and financial. In this regard, while it can be argued that MFG has been shown to be cost effective in mental health settings by reducing relapse and re-hospitalization, this has yet to be documented in rehabilitation settings. We recommend this as the next primary goal for future research.

Given the substantial social, quality of life and medical costs of SCI to affected individuals and their families, it is critical to explore methods to reduce these burdens. These costs are unlikely to diminish in the future through existing technology. The multiple family group education process has been shown to reduce the impact of some of these burdens humanely, safely, and with reasonable efficiency. It deserves front-of-mind consideration in the management of spinal cord injury care.

Summary points

a. Spinal cord injury is an unexpected event that immediately and permanently changes the lives of those who experience it and the lives of their loved ones.
b. The majority of persons with spinal cord injury are discharged to home under the care of family members after increasingly abbreviated hospitalization.
c. Family caregivers are often as stressed and overwhelmed as persons with spinal cord injury by the adjustments needed. There is a pressing need for individualized education and support for caregivers.
d. Evidence from research on other chronic medical and psychiatric conditions indicates that individualized education, problem solving, and support provided in a group format improves clinical outcomes.
e. Multiple family group is a group intervention that provides clinical care, support and individualized education to persons with spinal cord injury and their caregivers.
f. In persons with SCI, multiple family group was found to decrease depressive symptoms, anger expression, and passive coping and to increase life satisfaction and levels of subjective and overall social support.
g. Multiple family group participants experience an enhanced sense of belonging and teamwork, reduced isolation, increased knowledge and support.
h. Multiple family group intervention has relevant applications to other areas of Neuroscience such as Traumatic Brain Injury and Mild Cognitive Impairment
i. Implementation and dissemination opportunities and challenges, including telehealth and system and financial barriers should be considered for future dissemination of the multiple family group intervention.

References

Choi, N. G., Hegel, M. T., Marti, C. N., Marinucci, M. L., Sirrianni, L., & Bruce, M. L. (2014). Telehealth problem-solving therapy for depressed low-income homebound older adults. *The American Journal of Geriatric Psychiatry*, *22*(3), 263–271.

Dyck, D. G., Hendryx, M. S., Short, R. A., Voss, W. D., & McFarlane, W. R. (2002). Service use among patients with schizophrenia in nychoeducational multiple-family group treatment. *Psychiatric Services*, *53*(6), 749–754.

Dyck, D. G., Short, R. A., Hendryx, M. S., Norell, D., Myers, M., Patterson, T., et al. (2000). Management of negative symptoms among patients with schizophrenia attending multiple-family groups. *Psychiatric Services*, *51*(4), 513–519.

Dyck, D. G., Weeks, D. L., Smith, C. L., & Shaw, M. (2020). Multiple family group intervention for spinal cord injury: Quantitative and qualitative comparison with standard education. *The Journal of Spinal Cord Medicine*, *44*(4), 572–582.

Ebrahimzadeh, M. H., Shojaei, B.-S., Golhasani-Keshtan, F., Soltani-Moghaddas, S. H., Fattahi, A. S., & Mazloumi, S. M. (2013). Quality of life and the related factors in spouses of veterans with chronic spinal cord injury. *Health and Quality of Life Outcomes*, *11*(1), 48.

Gentry, M. T., Lapid, M. I., Clark, M. M., & Rummans, T. A. (2019). Evidence for telehealth group-based treatment: A systematic review. *Journal of Telemedicine and Telecare*, *25*(6), 327–342.

Glynn, S. M., Dixon, L. B., Cohen, A., & Murray-Swank, A. (2008). *The family member provider outreach program.* Psychiatric Services.

Guilcher, S. J., Casciaro, T., Lemieux-Charles, L., Craven, C., McColl, M. A., & Jaglal, S. B. (2012). Social networks and secondary health conditions: The critical secondary team for individuals with spinal cord injury. *The Journal of Spinal Cord Medicine*, *35*(5), 330–342.

Hammond, M. C. (2000). *Yes, you can!: A guide to self-care for persons with spinal cord injury*. Paralyzed Veterans of America.

Hazel, N., McDonell, M. G., Short, R., Berry, C. M., Voss, W., Rodgers, M., et al. (2004). Impact of multiple-family groups for outpatients with schizophrenia on caregivers distress and resources. *Psychiatric Services*, *55*(1), 35–41.

Hibbard, J. H., Mahoney, E. R., Stockard, J., & Tusler, M. (2005). Development and testing of a short form of the patient activation measure. *Health Services Research*, *40*(6p1), 1918–1930.

Jeyathevan, G., Cameron, J. I., Craven, B. C., Munce, S. E., & Jaglal, S. B. (2019). Re-building relationships after a spinal cord injury: Experiences of family caregivers and care recipients. *BMC Neurology*, *19*(1), 1–13.

Kester, B. L., Rothblum, E. D., Lobato, D., & Milhous, R. L. (1988). Spouse adjustment to spinal cord injury: Long-term medical and psychosocial factors. *Rehabilitation Counseling Bulletin*, *32*, 4–21.

Koenig, H. G., Westlund, R. E., George, L. K., Hughes, D. C., Blazer, D. G., & Hybels, C. (1993). Abbreviating the Duke social support index for use in chronically ill elderly individuals. *Psychosomatics*, *34*(1), 61–69.

McCubbin, H. I., Larsen, A., & Olson, D. (1985). F-COPES: Family crisis oriented personal evaluation scales. In *Family inventories: Inventories used in a national survey of families across the family life cycle* Science Open, Inc (David H. Olson…[et al.]).

McDonell, M. G., Short, R. A., Hazel, N. A., Berry, C. M., & Dyck, D. G. (2006). Multiple-family group treatment of outpatients with schizophrenia: Impact on service utilization. *Family Process*, *45*(3), 359–373.

McFarlane, W. R. (1994). Multiple-family groups and psychoeducation in the treatment of schizophrenia. *New Directions for Mental Health Services*, (62), 13.

McFarlane, W. R. (2002). *Multiple family groups in the treatment of severe psychiatric disorders*. New York, NY: Guilford Press.

Mueser, K. T. (2003). *Integrated treatment for dual disorders: A guide to effective practice*. Guilford Press.

National Spinal Cord Injury Statistical Center. (2020a). *Spinal cord injury facts and figures at a glance*. Retrieved from https://www.nscisc.uab.edu/Public/Facts%20and%20Figures%202020.pdf.

National Spinal Cord Injury Statistical Center. (2020b). *Spinal cord injury model systems 2019 annual report-complete public version*. 2019. Retrieved from https://www.nscisc.uab.edu/public/2019%20Annual%20Report%20-%20Complete%20Public%20Version.pdf.

North, N. (1999). The psychological effects of spinal cord injury: A review. *Spinal Cord*, *37*(10), 671–679.

Perlick, D. A., Straits-Troster, K., Strauss, J. L., Norell, D., Tupler, L. A., Levine, B., et al. (2013). Implementation of multifamily group treatment for veterans with traumatic brain injury. *Psychiatric Services*, *64*(6), 534–540.

Pilling, S., Bebbington, P., Kuipers, E., Garety, P., Geddes, J., Orbach, G., et al. (2002). Psychological treatments in schizophrenia: I. Meta-analysis of family intervention and cognitive behaviour therapy. *Psychological Medicine*, *32*(05), 763–782.

Rodakowski, J., Skidmore, E. R., Rogers, J. C., & Schulz, R. (2012). Role of social support in predicting caregiver burden. *Archives of Physical Medicine and Rehabilitation*, *93*(12), 2229–2236.

Rodgers, M. L., Strode, A. D., Norell, D. M., Short, R. A., Dyck, D. G., & Becker, B. (2007). Adapting multiple-family group treatment for brain and spinal cord injury intervention development and preliminary outcomes. *American Journal of Physical Medicine & Rehabilitation*, *86*(6), 482–492. https://doi.org/10.1097/Phm.0b013e31805c00a1.

Schmitter-Edgecombe, M., & Dyck, D. G. (2014). Cognitive rehabilitation multi-family group intervention for individuals with mild cognitive impairment and their care-partners. *Journal of the International Neuropsychological Society*, *20*(9), 897–908.

sciprogress.com. (2020). *Common myths and misconceptions about spinal cord injury*. Retrieved from https://sciprogress.com/common-myths-misconceptions-spinal-cord-injuries/.

Smith, C. L., Skaer, T. L., Orr, M. F., Barbosa-Leiker, C., Howell, D. N., & Dyck, D. G. (2017). Development of multi-family group and mindfulness treatment for chronic pain: Preliminary outcomes. *Journal of Musculoskeletal Disorders and Treatment*, *3*(4). https://doi.org/10.23937/2572-3243.1510042.

Spielberger, C. D., Johnson, E. H., Russell, S. F., Crane, R. J., Jacobs, G. A., & Worden, T. J. (1985). The experience and expression of anger: Construction and validation of an anger expression scale. In *Anger and hostility in cardiovascular and behavioral disorders* (pp. 5–30). New York: Hemisphere.

Straits-Troster, K., Gierisch, J. M., Strauss, J. L., Dyck, D. G., Dixon, L. B., Norell, D., et al. (2013). Multifamily group treatment for veterans with traumatic brain injury: What is the value to participants? *Psychiatric Services*, *64*(6), 541–546. https://doi.org/10.1176/appi.ps.001632012.

Weitzenkamp, D. A., Gerhart, K. A., Charlifue, S. W., Whiteneck, G. G., & Savic, G. (1997). Spouses of spinal cord injury survivors: The added impact of caregiving. *Archives of Physical Medicine and Rehabilitation*, *78*(8), 822–827.

Chapter 39

Spinal cord injury rehabilitation: Linking service delivery and community integration

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Abbreviations

AR	active rehabilitation
ICF	International Classification of Functioning Disability and Health
SCI	spinal cord injury
TR	transitional rehabilitation
UNCRPD	United Nations Convention on the Rights of Persons with Disabilities
VR	vocational rehabilitation

Introduction

Community integration includes having access to appropriate housing, being able to mobilize in the community, being able to participate in work, leisure or educational activities of choice, and engaging in satisfying social relationships (Barclay, Lalor, Migliorini, & Robins, 2020; Chang, Coster, & Helfrich, 2013). It is synonymous with the term *participation* in the International Classification of Functioning Disability and Health (ICF) (World Health Organization, 2002), which refers to involvement in life situations, and includes active engagement at the community level and social connectedness with other people (Hammel et al., 2008). Participating in meaningful roles and interests in the community, such as leisure and employment, can enable a person to reframe their views on acquired disability (Kratz, Chadd, Jensen, Kehn, & Kroll, 2015), but poor community integration and lack of social participation is one of the biggest challenges for someone following SCI (Craig, Nicholson Perry, Guest, Tran, & Middleton, 2015). Services and models for SCI rehabilitation need to prioritize community integration in order to maximize outcomes and quality of life.

Prioritizing community integration

Following SCI a person will usually spend several months undergoing inpatient rehabilitation in a specialized spinal unit (Dwyer & Mulligan, 2015). Following this, the injured person will be discharged to live in either their own home, or some other form of temporary or alternate accommodation. This period of transition from hospital to home is a very challenging time for people, as they are removed from the safety of the hospital environment with the associated supports, both physical and social, and plunged into environments that may be inaccessible and even hostile toward people with disabilities (Nunnerley, Hay-Smith, & Dean, 2013). This process is made more challenging for people in developing countries, where community infrastructure such as roads, and transport is even less accessible for people with disabilities (Liu et al., 2020). The funding environment, policies and infrastructure in the jurisdiction in which the injured person lives, impacts the availability of the resources they have access to, and may facilitate or hinder this transition process. People with SCI have described feeling unprepared for the difficulties and barriers they are going to face in the real world (Nunnerley et al., 2013). Therefore, in the context of shrinking health budgets, maximizing the efficacy of inpatient rehabilitation to prepare people to reintegrate into their community must be one of the primary goals of rehabilitation (Kratz et al., 2015).

Diagnosis and Treatment of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822498-4.00039-7

Interplay between health condition, person factors, and environmental factors

As depicted in the ICF (Fig. 1), activity and participation are influenced by the health condition and body functions and structures (in this case the injury and associated levels of neurological impairment and secondary health conditions), in addition to person factors such as age, gender, other health conditions, weight, coping style, education and other life experiences, and environmental factors. Environmental factors are frequently not modifiable (e.g., culture, climate, physical environment such as hills). Some environmental factors occur at a societal level and require policy or government involvement (e.g., availability of rehabilitation services, funding for equipment, public transport, discriminatory attitudes, and access to housing) (Carr et al., 2017), while others occur at a family or local community level (for example, social supports, and private transport), and are potentially modifiable (Barclay, McDonald, Lentin, & Bourke-Taylor, 2016). Environmental barriers are often more challenging in developing countries (Sekaran et al., 2010). Personal and environmental factors have a significant role in facilitating or hindering the participation or community integration of people following SCI.

Models and approaches to community integration

Most commonly, service models or programs that aim to support the community integration of people with SCI in the immediate period following inpatient rehabilitation are conducted by specialist SCI units (Kendall, Ungerer, & Dorsett, 2003). Such programs typically include a core multidisciplinary team consisting of physiotherapists, occupational therapists, community nurses and social workers (Momsen, Rasmussen, Nielsen, Iversen, & Lund, 2012). Additional staff may include vocational consultants, psychologists, peer mentors, leisure specialists and exercise physiologists. Community integration programs usually address a large range of issues, including community-based wheelchair skills, physical health education, strategies to increase self-efficacy and self-management skills, goal setting, training or managing carers, and working on improving independence in self-care (Barclay, Lalor, et al., 2020).

There are a range of community integration and/or transitional living models or approaches being used by specialist SCI units internationally, and most can be categorized into one of four models (Barclay, Lalor, et al., 2020). Each of these models is outlined in the next section. It is also important to consider goal setting as an integral outcome tool within these models. In a systematic review of the qualitative literature exploring their experience of, and their perspectives on, goal setting in rehabilitation, people with SCI recognized the importance of being self-directed (Maribo, Jensen, Madsen, & Handberg, 2020). Furthermore, they aspired to take an active role, and had a preference for goal setting oriented around their daily life. This was at times at odds with the health professional, who tended to use the hospital as their point of reference (Maribo et al., 2020). A shared process with goal setting relevant to persons with SCI and their everyday life is needed (Maribo et al., 2020) and formally or informally integrated in community integration models (Fig. 2).

Community integration embedded within inpatient rehabilitation

The first approach to community integration involves preparing people for discharge as part of the inpatient rehabilitation service, that is, there is no separate or specific service for community integration (Fig. 3). This model tends to be in place in countries where length of hospital rehabilitation is longer, and there is less pressure to discharge people quickly. Some services are able to offer patients the opportunity to return home for a short period of time (for example, 1 month) prior

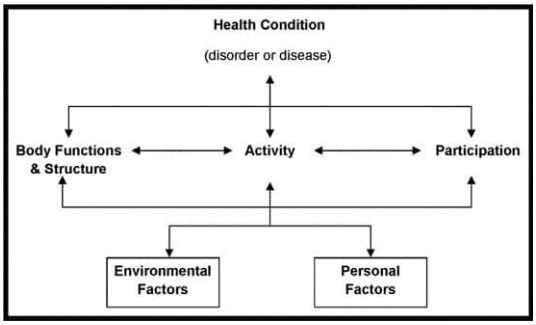

FIG. 1 International classification of functioning disability and health (ICF) (World Health Organization, 2002). Depicts International Classification of Functioning Disability and Health framework. Permission from WHO is not required for the use of WHO materials issued under the Creative Commons Attribution-Non Commercial-ShareAlike 3.0 Intergovernmental Organization (CC BY-NC-SA 3.0 IGO) licence.

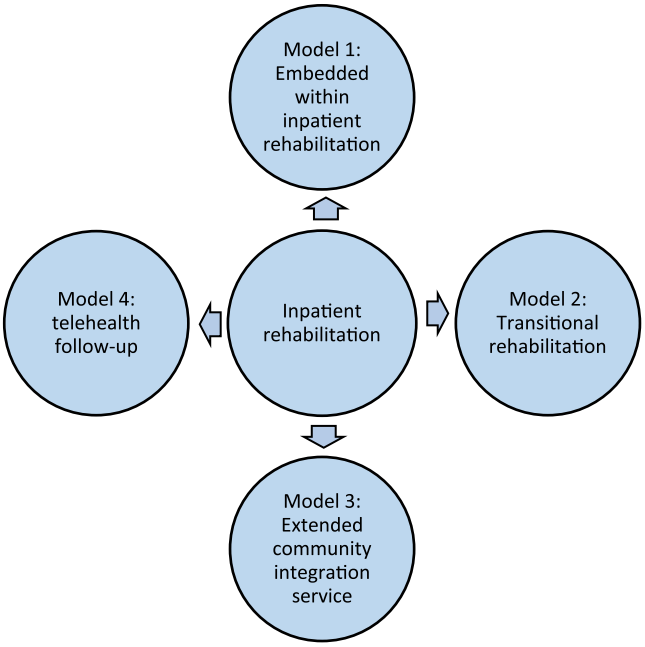

FIG. 2 Models to support community integration. Depicts four models or approaches to community integration.

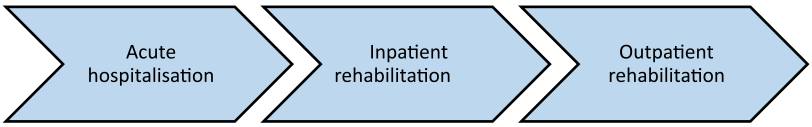

FIG. 3 Community integration embedded in inpatient rehabilitation. Illustrates one model where community integration is embedded within inpatient rehabilitation.

to discharge, and then return to the facility work to on goals that were identified while at home. Other SCI units offer ongoing outpatient therapy on a regular basis for up to 3–4 months, provided the patient lives within driving distance of the SCI unit. Following this, patients are referred onto community-based providers. This approach has advantages and disadvantages. While it allows the injured person and their family time to adjust and prepare for the potential challenges that may be faced when the patient returns home, particularly in relation to organizing assistive technology and an accessible home environment, it is also likely that long periods of hospitalization impact negatively on the patient's self-determination and self-efficacy. The longer the hospital stay, the more likely there are to be entrenched patterns of institutionalization, and the development of greater anxiety when the time comes to return to living in the community (Craig & Nicholson Perry, 2013; Kendall et al., 2003). For example, in hospital, routines are imposed and there are few opportunities to assume responsibility and take an active role in rehabilitation decisions (Craig & Nicholson Perry, 2013). Therefore, the possible benefits of a longer hospital stay need to be weighed against the likely negative impacts.

Transitional rehabilitation program

A transitional rehabilitation (TR) program typically consists of a short "stay" of between 4 and 8 weeks (Fig. 4). In some instances, the patient lives in a self-contained unit during this period, either on or close to the SCI unit or hospital site. In this model, specific goals for community integration are identified collaboratively between the injured person and the

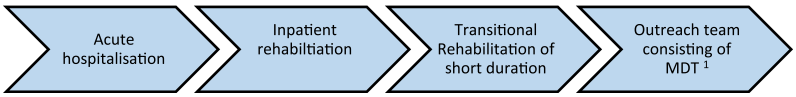

FIG. 4 Transitional Rehabilitation model. [1]MDT = multi-disciplinary team. Depicts the transitional rehabilitation model.

rehabilitation team, using a goal-setting tool. Examples of such tools include Goal Attainment Scaling (GAS) (SRALAB, 2020a), the Needs Assessment Checklist (SRALAB, 2020b), and the Multi-disciplinary Goal Attainment Measure (MGAM) (Kendall & Wallace, 2016). Goals may include, for example, to return to study, to learn to use public transport, or to drive (Kendall & Wallace, 2016). The identified goals are addressed during the 4–8 weeks of the program, are reviewed regularly, and again at the completion of the program. Following completion of the TR program, the patient may either be referred to an SCI outreach service for a short period of time, or referred to community-based services to continue to work on identified goals or set new goals. This approach has the benefit of enabling the patient to address the community integration goals they wish to address, without the negative impacts of institutionalization described above.

Extended community integration service

A third approach provides patient support for a longer period that TR, and can be for up to 12 months. This enables longer term goals to be addressed, allowing the injured person to make use of the expertise of the specialist SCI for longer, and providing more time to address and resolve issues that come up once they have returned home. While this may be helpful for patients that have had a shorter length of inpatient rehabilitation, it is also possible that this approach fosters a greater dependency on the SCI unit (Kendall et al., 2003). It is important when undertaking this approach that patients are actively engaged in decision-making, thereby minimizing dependency and enhancing the patient's confidence and independence skills in preparation for returning home (Craig et al., 2015).

Telehealth follow-up

The final approach involves following up people using telehealth (by either telephone or video conferencing), for a fixed period of time (e.g., up to 60 days). While this approach is becoming more common, it could be more widely utilized to facilitate community integration of people with SCI, particularly for health maintenance or management of secondary health conditions, and to build capacity of community-based therapists (Woo, Guihan, Frick, Gill, & Ho, 2011). While there has been some work done assessing the effectiveness of using telehealth specifically for health self-management following SCI (Houlihan et al., 2017; Phillips, Vesmarovich, Hauber, Wiggers, & Egner, 2001), less information is available regarding using tele-based services for capacity building of community providers such as therapists, general practitioners and community nurses. Utilizing telephone follow-up is particularly useful in countries where people live in rural locations or there is poor infrastructure (Hossain et al., 2017).

Assistive technology, transport, housing

Access to suitably accessible housing, appropriate assistive technology and transport are key in facilitating community integration after SCI (Wright, Colley, & Kendall, 2020).

Assistive technology

In order to facilitate the process of returning home, there is a variety of assistive technologies required for someone to ensure safety and maximize independence (Barclay et al., 2016). Such technologies range from wheelchairs, pressure cushions, and bathing aids (Friesen, Theodoros, & Russell, 2016), through to environmental control systems and Smart Home technology (Hooper, Verdonck, Amsters, Myburg, & Allan, 2018). A detailed discussion of this area is beyond the scope of this chapter; however, it is an important element that needs to be addressed as part of the plan for transitioning the injured person to the community, taking into account funding available and policies within the person's jurisdiction.

Transport

Having access to transport is a key requirement to enable people with SCI to shop, to use the bank, to get to work and education, and to engage in social and leisure activities in the community (Barclay et al., 2016). *The United Nations Convention on the Rights of Persons with Disabilities (UNCRPD) [Article 9]* (n.d.), specifically refers to the importance of the rights of people with disabilities to be able to access transportation on an equal basis with others (United Nations). Yet, transportation issues are consistently identified by people with disabilities as a major challenge and barrier to community participation. This is even more problematic in low and middle income countries (Kett, Cole, & Turner, 2020).

Common issues raised by people with disabilities, such as SCI, regarding using public transport include concerns about accessibility, safety, reliability, affordability, limited services especially in rural areas, and the attitude of the public (Kett et al., 2020). Community integration programs may address these concerns prior to discharge from hospital, by accompanying their patients into the local community where possible to practice using public transport and problem-solve issues that arise (Price, Stephenson, Krantz, & Ward, 2011).

It is common for people in high income countries to prefer the use of private vehicles, with high rates of return to self-driving being associated with high community integration and better life satisfaction (Norweg, Jette, Houlihan, Ni, & Boninger, 2011). However, for someone with an SCI to be able to self-drive a car, or travel as a passenger in a wheelchair, expensive modifications such as hand controls, ramps and modified vehicles are usually needed. Availability of such modifications will depend on the funding and policy environment of the country in which the person lives, but are also influenced by socioeconomic factors as education, income, and employment status (Norweg et al., 2011). Rehabilitation programs need to have a strong focus on working toward driving as a goal, which may require follow-up once the injured person has returned home and for some time after.

Housing

Challenges for people with SCI relate to both housing availability and housing suitability (Wright et al., 2020). An important part of the process of preparing someone with an SCI to transition to live back in the community is ensuring they have somewhere suitable to live. Quality of life and successful community integration after SCI have been associated with discharge residence (Bergmark, Winograd, & Koopman, 2008).

After inpatient rehabilitation, there are a number of possible discharge scenarios for someone with SCI. They may be discharged back to their own or to a previous family home, which will likely require modifications, they may move into physically accessible social housing, or they may need to move into some form of supported accommodation or residential care facility (Wright et al., 2020) (Fig. 5). In addition, access to appropriate formal and informal supports are integral to an individual's experience of optimal social participation (Braaf, Lennox, Nunn, & Gabbe, 2018; Murphy, O'Hare, & Wallis, 2010).

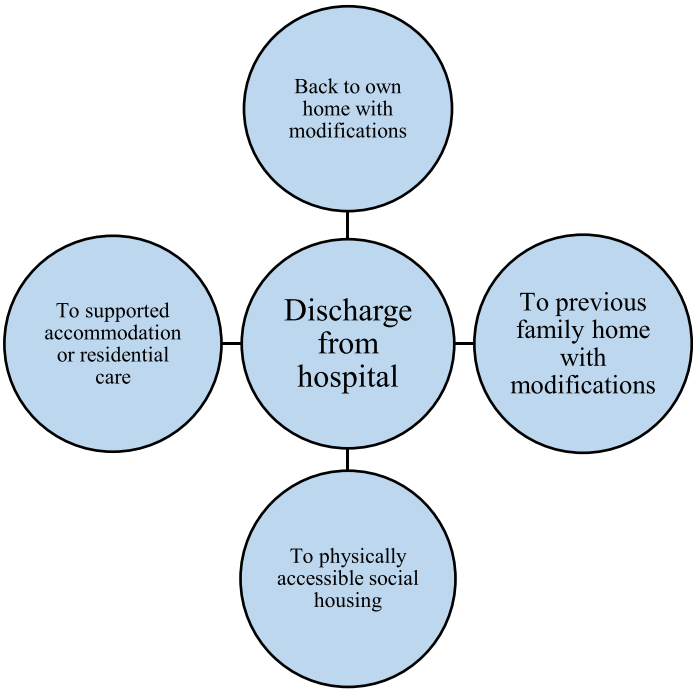

FIG. 5 Discharge destinations. Highlights possible destinations for discharge following inpatient rehabilitation.

Leisure and social participation

Participating in leisure assists adjustment following SCI

Following SCI, people experience a disruption to their leisure identity and a changed leisure repertoire (Lundström, Lilja, Petersson, Lexell, & Isaksson, 2014). How people use their time also changes. A large reduction in time spent in paid employment, potentially makes more time available for avocational pursuits (Barclay et al., 2011). With demonstrated links between engagement in leisure and subjective wellbeing (Kuykendall, Tay, & Ng, 2015; Lloyd & Auld, 2002), exploring leisure identity as part of rehabilitation/community integration can assist people to achieve meaningful adaptation to changed circumstances. Engagement in leisure has a direct influence on the adjustment of individuals following SCI, therefore developing skills in managing leisure becomes critical in the process of community reintegration (Loy, Dattilo, & Kleiber, 2003). In addition, for those unable to reintegrate into paid work, participation in non-vocational activities should also be considered a goal of rehabilitation (Schonherr, Groothoff, Mulder, & Eisma, 2005).

Health benefits of physical leisure participation

Physical leisure activities have an important role in addressing some of the negative health effects associated with lack of physical activity following SCI, including loss of muscle mass, obesity, cardiovascular disease, type-2 diabetes, depression, pain and fatigue (Bombardier et al., 2020). Sports participation has also been associated positively with community integration and quality of life (McVeigh, Hitzig, & Craven, 2009).

The role of peer mentors in community integration

Peer mentors are typically people who have faced similar experiences (such as SCI), and are therefore well positioned to provide practical, emotional and informational support (Barclay & Hilton, 2019). Peer mentors have a vital contribution in assisting people with SCI to have hope and visualize possibilities for the future (Barclay et al., 2016; Veith, Sherman, Pellino, & Yasui, 2006). Peers often use language that can open people's minds. They help create ability in others because of their own critical reflection, and they do this not as a provider of service—but as a role model (Mead & MacNeil, 2006). These reflections can be extrapolated to hospital and community-based settings for people with SCI.

Peer mentors assist in transition from hospital to home

Peer mentors can play an important role in supporting people during the transition from hospital to home, and often fill a service gap between formal hospital-based services and community-based services (Barclay & Hilton, 2019). Peers can promote physical activity (Latimer-Cheung et al., 2013), assist with wheelchair skills training (Best, Miller, Huston, Routhier, & Eng, 2016), and provide effective support in managing ongoing health conditions (Houlihan et al., 2017). Specialist SCI units utilizing emerging best practice approaches to rehabilitation and community integration, include people with lived experience as an employed member of the rehabilitation team (Barclay, Robins, Migliorini, & Lalor, 2020).

Active rehabilitation

Once people with SCI are discharged from inpatient rehabilitation, peer mentors can continue to have a positive influence on development of self-efficacy, through role modelling success and demonstrating how to overcome failures (Divanoglou & Georgiou, 2017). Active Rehabilitation (AR) is a community peer-based approach that typically involves people with SCI attending camps that offer intensive goal-oriented group-based training and peer support activities in a community setting (Divanoglou, Tasiemski, Augutis, & Trok, 2017). Typical activities addressed during AR are wheelchair skills training, activities of daily living, sports and recreational activities, education and setting goals. These are delivered through a combination of SCI peer mentors, and non-disabled assistants. AR offers a unique learning environment through a mixture of resources, activities and a "can-do" attitude, where the peer mentors are viewed as credible role models who have "lived it all" (Divanoglou et al., 2017).

Return to work

Varied meanings of work for a person following SCI have been described as re-developing a sense of self, re-establishing place in the community and regaining economic self-sufficiency, (Ullah, Fossey, & Stuckey, 2018). Since the development

of the first SCI rehabilitation centers, gaining paid employment has been considered an indicator of achieving optimal community integration (Guttmann, 1954) and a measure of rehabilitation success (Britell, 1991; Guttmann, 1954; Post, Reinhardt, & Escorpizo, 2020).

Benefits of employment

Seeking, gaining and maintaining employment after SCI is valued by individuals and the process contributes to people's sense and strength of identity (Krause, Saunders, & Acuna, 2012; Hilton, Unsworth, Stuckey, & Murphy, 2018). Employment has been described as a source of mental stimulation and an opportunity for personal growth and independence (Chan & Man, 2005), and also as part of one's identity and representative of "living a normal life" (Hay-Smith, Dickson, Nunnerley, & Sinnott, 2013). The health and social benefits of employment, including having a place within the community and economic self-sufficiency, are being increasingly recognized (Holmes et al., 2016; Ullah et al., 2018).

Vocational rehabilitation

Vocational rehabilitation (VR) to restore or maintain an individual's vocational participation after major injury may be more effective if actioned sooner (Chan & Man, 2005; Fadyl & McPherson, 2010; Ferdiana et al., 2014), and should be a major focus of community integration (Hilton, Unsworth, & Murphy, 2018). Current evidence supports the practice of intervention as early as when the patient is in the inpatient rehabilitation phase (Hilton, Unsworth, Browne, Murphy, & Olver, 2017; Middleton et al., 2015), and can address modifiable factors associated with barriers to employment (Trenaman, Miller, Querée, & Escorpizo, 2015). In addition to vocational rehabilitation, these modifiable factors include education, functional independence, social support and financial disincentives (Trenaman et al., 2015). The community integration models described earlier in this chapter may also provide appropriate settings for delivery of this early intervention vocational rehabilitation (Hilton et al., 2017; Middleton et al., 2015).

Pre and post injury education consistently appears to facilitate post injury employment, (Ferdiana et al., 2014; Hilton, Unsworth, Stuckey, et al., 2018). Similarly, further education for skill development strengthens opportunities for post injury employment (Hilton, Unsworth, Stuckey, et al., 2018). Vocational rehabilitation within the community integration setting can assist to explore further education and training, facilitating employment trajectories (Hilton, Unsworth, Stuckey, et al., 2018).

Self-management, education and health literacy

Importance of education in maintaining physical and mental health

An important part of being successfully integrated back into the community after SCI is maintaining physical and mental health, and preventing the occurrence of secondary health conditions that may require hospital readmission. People with SCI are at higher risk of hospital readmission (Gassaway et al., 2017), or significant disruption to their social and employment participation due to health problems such as skin injuries, urinary tract infections, chronic pain, spasm and spasticity, and circulatory problems (Callaway, Barclay, McDonald, Farnworth, & Casey, 2015). Rehabilitation has the role of educating people with SCI and their families as to how to stay physically and mentally healthy after discharge. However, people with SCI report that they often leave hospital feeling unprepared to assume responsibility for their health needs (Gassaway et al., 2017). A variety of approaches used by specialist spinal units to educate patients and their families are utilized. Approaches include using hard copy educational handouts, conducting education sessions in hospital, and developing "How To" videos for people to watch at a convenient time (Barclay, Lalor, et al., 2020). After discharge home, ongoing support of patients and their families in relation to maintaining health is vital. Telephone counselling has the potential to reduce medical complications and health care utilization, and improve psychosocial outcomes in the early stages following discharge (Mackelprang & Salsgiver, 2016).

Whatever education is provided should be presented in a form that is suitable for people with low levels of health literacy. It is also recognized that people with SCI often have issues with fatigue and mild cognitive impairment, and therefore may need information repeated frequently and at different time points to maximize impact (Craig, Guest, Tran, & Middleton, 2017). Improvements in knowledge do not necessarily translate into improvements in problem-solving. Therefore, incorporating more active learning strategies, such as role plays within patient education programs may facilitate better transfer of knowledge within life situations (May, Day, & Warren, 2006).

Role of peer educators in facilitating self-management

Facilitating self-management of people with SCI, can help them to take a more active role in managing their health care, and potentially minimize or prevent the development of secondary health conditions listed above. Chronic disease self-management programs focus on increasing perceived self-efficacy to solve problems and make decisions to manage day-to-day health (Hirsche, Williams, Jones, & Manns, 2011). People with SCI report that barriers to self-management include funding and funding policies, and lack of physical access to medical clinics and buildings, while facilitators include peer support (Munce et al., 2014). With appropriate training peers can play an active role in education as they are well placed to form empathic relationships, self-reflect and build understanding through practical life examples (Barclay & Hilton, 2019). One example of integration of lived experience in a peer educator role, which demonstrates benefits in self-management, is the peer-led, telephone based, health self-management intervention called 'My Care My Call' for adults with chronic SCI (Houlihan et al., 2017). Such interventions, however, need to be integrated with, rather than separate to, any other SCI-specific services the patient is receiving. In addition, it is important that specific goals are set with the patient and their family in order for interventions to be targeted and effective (Mackelprang & Salsgiver, 2016).

Summary

This chapter presented an overview of the important process of preparing people with SCI to transition from inpatient rehabilitation to living in the community. The interplay between modifiable and non-modifiable environmental factors, the injury and person factors was highlighted. A range of models and approaches to community integration were presented. Benefits of employment and vocational rehabilitation were described, while for those unable to reintegrate into paid work, the importance of participation in non-vocational activities as a goal of rehabilitation was discussed. The important role of peer mentors in supporting people during the transition from hospital to home, by filling a service gap between formal hospital-based services and community-based services was outlined. Finally, maintenance of physical and mental health, and prevention of secondary health conditions, including ways to facilitate self-management was discussed as a key to maintaining ongoing successful community integration.

Applications to other areas of neuroscience

In this chapter we have discussed the importance of community integration as a major goal of rehabilitation following spinal cord injury. The importance of the link between service delivery during inpatient rehabilitation and the transition to community based services, and the ways in which environmental factors and person based factors influence community integration outcomes is very relevant to other areas of neurological rehabilitation, such as acquired brain injury, or stroke. Rehabilitation services for people following acquired brain injury and stroke function in similar ways to those for spinal cord injury, particularly in high income countries (Cott, Wiles, & Devitt, 2007; Turner et al., 2007). Inpatient rehabilitation usually occurs within a specialist rehabilitation unit, with follow up services occurring in the community (Turner-Stokes, 2008). Similar issues face people with acquired brain injury and stroke as for those with spinal cord injury as they transition to community living. These challenges include low rates of employment (Van Velzen, Van Bennekom, Edelaar, Sluiter, & Frings-Dresen, 2009), challenges with social participation (McLean, Jarus, Hubley, & Jongbloed, 2014), issues with housing and transport (Roessler et al., 2013), and barriers regarding assistive technology (de Joode, van Heugten, Verhey, & van Boxtel, 2010). As with spinal cord injury, there is evidence of the positive influence of peer support for traumatic brain injury survivors and their caregivers in areas of social support, coping, behavioral control and physical quality of life (Wobma, Nijland, Ket, & Kwakkel, 2016). Self-management of ongoing health and secondary conditions is also an issue following stroke, acquired brain injury and multiple sclerosis. Chronic disease health management programs such as those used in spinal cord injury can be equally beneficial in the case of these other conditions (Hirsche et al., 2011).

Mini-dictionary of terms

Community integration: Having access to appropriate housing, being able to mobilize in the community, being able to participate in work, leisure or educational activities of choice, and being able to engage in satisfying social relationships.
Vocational rehabilitation: Aims to restore or maintain an individual's vocational participation after major injury.
Participation: Involvement in life situations.
Secondary health conditions: Common ongoing health concerns experienced after spinal cord injury.
Telehealth: Health care provided remotely by telecommunications technology.

Peer mentors: People with lived experience of spinal cord injury.
Active rehabilitation: A community peer-based approach that usually involves people with SCI attending camps that offer intensive goal-oriented group based training and peer support activities in a community setting.

Key facts of spinal cord injury community integration

- Community integration services and models for spinal cord injury rehabilitation need to prioritize community integration in order to maximize outcomes and quality of life.
- Access to suitably accessible housing, appropriate assistive technology and transport are key facilitators of community integration.
- Participation in leisure activities, and employment after spinal cord injury provides benefits to counter the difficulties of post-injury adjustment.
- People with lived experience working as paid peer mentors support people during the transition home.
- Education to stay physically and mentally healthy after discharge is important.

Summary points

- This chapter focuses on the link between rehabilitation services and community integration following spinal cord injury.
- Community integration is similar in meaning to the term participation in the International Classification of Functioning Disability and Health (ICF).
- There are a range of community integration and/or transitional living models or approaches.
- Access to suitably accessible housing, appropriate assistive technology and transport are key in facilitating community integration.
- Participation in leisure activities provides benefits to counter the difficulties of adjusting to spinal cord injury.
- Peer mentors provide support to people transitioning home from hospital.
- Seeking, gaining, and maintaining employment after spinal cord injury contributes to people's identity.
- Vocational rehabilitation may be more effective if actioned sooner.
- Facilitating self-management of people with spinal cord injury, can help them to take a more active role in managing their health care.

References

Barclay, L., Callaway, L., McDonald, R., Farnworth, L., Brown, T., & Broom, L. (2011). Time use following spinal cord injury: An examination of the literature. *British Journal of Occupational Therapy*, *74*(12), 573–580.

Barclay, L., & Hilton, G. M. (2019). A scoping review of peer-led interventions following spinal cord injury. *Spinal Cord*, *57*(8), 626–635.

Barclay, L., Lalor, A., Migliorini, C., & Robins, L. (2020). A comparative examination of models of service delivery intended to support community integration in the immediate period following inpatient rehabilitation for spinal cord injury. *Spinal Cord*, *58*(5), 528–536.

Barclay, L., McDonald, R., Lentin, P., & Bourke-Taylor, H. (2016). Facilitators and barriers to social and community participation following spinal cord injury. *Australian Occupational Therapy Journal*, *63*, 19–28. https://doi.org/10.1111/1440-1630.12241.

Barclay, L., Robins, L., Migliorini, C., & Lalor, A. (2020). Community integration programs and interventions for people with spinal cord injury: A scoping review. *Disability and Rehabilitation*, *1–11*. https://doi.org/10.1080/09638288.2020.1749889.

Bergmark, B., Winograd, C., & Koopman, C. (2008). Residence and quality of life determinants for adults with tetraplegia of traumatic spinal cord injury etiology. *Spinal Cord*, *46*(10), 684–689.

Best, K. L., Miller, W. C., Huston, G., Routhier, F., & Eng, J. J. (2016). Pilot study of a peer-led wheelchair training program to improve self-efficacy using a manual wheelchair: A randomized controlled trial. *Archives of Physical Medicine and Rehabilitation*, *97*(1), 37–44. https://doi.org/10.1016/j.apmr.2015.08.425.

Bombardier, C. H., Dyer, J. R., Burns, P., Crane, D. A., Takahashi, M. M., Barber, J., et al. (2020). A tele-health intervention to increase physical fitness in people with spinal cord injury and cardiometabolic disease or risk factors: A pilot randomized controlled trial. *Spinal Cord*, *59*, 1–11.

Braaf, S. C., Lennox, A., Nunn, A., & Gabbe, B. J. (2018). Experiences of hospital readmission and receiving formal carer services following spinal cord injury: A qualitative study to identify needs. *Disability and Rehabilitation*, *40*(16), 1893–1899.

Britell, C. W. (1991). Why aren't they working? *The Journal of the American Paraplegia Society*, *14*(1), 1–2.

Callaway, L., Barclay, L., McDonald, R., Farnworth, L., & Casey, J. (2015). Secondary health conditions experienced by people with spinal cord injury within community living: Implications for a National Disability Insurance Scheme. *Australian Occupational Therapy Journal*, *62*(4), 246–254.

Carr, J., Kendall, M., Amsters, D., Pershouse, K., Kuipers, P., Buettner, P., et al. (2017). Community participation for individuals with spinal cord injury living in Queensland, Australia. *Spinal Cord*, *55*(2), 192–197.

Chan, S. K., & Man, D. W. (2005). Barriers to returning to work for people with spinal cord injuries: A focus group study. *Work*, *25*(4), 325–332.

Chang, F. H., Coster, W. J., & Helfrich, C. A. (2013). Community participation measures for people with disabilities: A systematic review of content from an international classification of functioning, disability and health perspective. *Archives of Physical Medicine and Rehabilitation*, *94*(4), 771–781.

Cott, C. A., Wiles, R., & Devitt, R. (2007). Continuity, transition and participation: Preparing clients for life in the community post-stroke. *Disability and Rehabilitation*, *29*(20 – 21), 1566–1574.

Craig, A., Guest, R., Tran, Y., & Middleton, J. W. (2017). Cognitive impairment and mood states after spinal cord injury. *Journal of Neurotrauma*, *34*(6), 1156–1163. https://www.liebertpub.com/doi/10.1089/neu.2016.4632.

Craig, A., & Nicholson Perry, K. (2013). *Guide for health professionals on the psychosocial care of adults with spinal cord injury*. Retrieved from Agency for Clinical Innovation.

Craig, A., Nicholson Perry, K., Guest, R., Tran, Y., & Middleton, J. W. (2015). Adjustment following chronic spinal cord injury: Determining factors that contribute to social participation. *British Journal of Health Psychology*, *20*(4), 807–823. https://doi.org/10.1111/bjhp.12143.

de Joode, E., van Heugten, C., Verhey, F., & van Boxtel, M. (2010). Efficacy and usability of assistive technology for patients with cognitive deficits: A systematic review. *Clinical Rehabilitation*, *24*(8), 701–714.

Divanoglou, A., & Georgiou, M. (2017). Perceived effectiveness and mechanisms of community peer-based programmes for spinal cord injuries—A systematic review of qualitative findings. *Spinal Cord*, *55*(3), 225–234. https://doi.org/10.1038/sc.2016.147.

Divanoglou, A., Tasiemski, T., Augutis, M., & Trok, K. (2017). Active rehabilitation—A community peer-based approach for persons with spinal cord injury: International utilisation of key elements. *Spinal Cord*, *55*(6), 545–552.

Dwyer, K. J., & Mulligan, H. (2015). Community reintegration following spinal cord injury: Insights for health professionals in community rehabilitation services in New Zealand. *New Zealand Journal of Physiotherapy*, *43*(3), 75–85.

Fadyl, J., & McPherson, K. (2010). Understanding decisions about work after spinal cord injury. *Journal of Occupational Rehabilitation*, *20*(1), 69–80. https://doi.org/10.1007/s10926-009-9204-1.

Ferdiana, A., Post, M. W. M., Hoekstra, T., van der Woude, L. H., van der Klink, J. J., & Bultmann, U. (2014). Employment trajectories after spinal cord injury: Results from a 5-year prospective cohort study. *Archives of Physical Medicine and Rehabilitation*, *95*(11), 2040–2046. https://doi.org/10.1016/j.apmr.2014.04.021.

Friesen, E. L., Theodoros, D., & Russell, T. G. (2016). *Assistive technology devices for toileting and showering used in spinal cord injury rehabilitation—A comment on terminology*. Taylor & Francis.

Gassaway, J., Jones, M. L., Sweatman, M., Hong, M., Anziano, P., & DeVault, K. (2017). Effects of peer mentoring on self-efficacy and hospital readmission after inpatient rehabilitation of individuals with spinal cord injury: A randomized controlled trial. *Archives of Physical Medicine and Rehabilitation*, *98*, 1526–1534.

Guttmann, L. (1954). Statistical survey on one thousand paraplegics. *Proceedings of the Royal Society of Medicine*, *47*(12), 1099.

Hammel, J., Magasi, S., Heinemann, A., Whiteneck, G., Bogner, J., & Rodriguez, E. (2008). What does participation mean? An insider perspective from people with disabilities. *Disability and Rehabilitation*, *30*(19), 1445–1460.

Hay-Smith, E. J., Dickson, B., Nunnerley, J., & Sinnott, A. K. (2013). The final piece of the puzzle to fit in: An interpretative phenomenological analysis of the return to employment in New Zealand after spinal cord injury. *Disability and Rehabilitation*, *35*(17), 1436–1446. https://doi.org/10.3109/09638288.2012.737079.

Hilton, G. M., Unsworth, C. A., Browne, M., Murphy, G. C., & Olver, J. (2017). Longitudinal employment outcomes of an early-intervention vocational rehabilitation service for people admitted to rehabilitation with a traumatic spinal cord injury. *Spinal Cord*, *55*, 743–752. https://doi.org/10.1038/sc.2017.24.

Hilton, G. M., Unsworth, C. A., & Murphy, G. (2018). The experience of attempting to return to work following spinal cord injury: A systematic review of the qualitative literature. *Disability and Rehabilitation*, *40*(15), 1745–1753. https://doi.org/10.1080/09638288.2017.1312566.

Hilton, G., Unsworth, C. A., Stuckey, R., & Murphy, G. C. (2018). The experience of seeking, gaining and maintaining employment after traumatic spinal cord injury and the vocational pathways involved. *Work*, *59*(1), 67–84.

Hirsche, R. C., Williams, B., Jones, A., & Manns, P. (2011). Chronic disease self-management for individuals with stroke, multiple sclerosis and spinal cord injury. *Disability and Rehabilitation*, *33*(13–14), 1136–1146.

Holmes, J., Phillips, J., Morris, R., Bedekar, Y., Tyerman, R., & Radford, K. (2016). Development and evaluation of an early specialised traumatic brain injury vocational rehabilitation training package. *British Journal of Occupational Therapy*, *79*(11), 693–702.

Hooper, B., Verdonck, M., Amsters, D., Myburg, M., & Allan, E. (2018). Smart-device environmental control systems: Experiences of people with cervical spinal cord injuries. *Disability and Rehabilitation. Assistive Technology*, *13*(8), 724–730.

Hossain, M., Harvey, L., Rahman, M., Bowden, J., Islam, M., Taylor, V., et al. (2017). A pilot randomised trial of community-based care following discharge from hospital with a recent spinal cord injury in Bangladesh. *Clinical Rehabilitation*, *31*(6), 781–789.

Houlihan, B. V., Brody, M., Everhart-Skeels, S., Pernigotti, D., Burnett, S., Zazula, J., et al. (2017). Randomized trial of a peer-led, telephone-based empowerment intervention for persons with chronic spinal cord injury improves health self-management. *Archives of Physical Medicine and Rehabilitation*, *98*, 1067–1076. https://doi.org/10.1016/j.apmr.2017.02.005.

Kendall, M. B., Ungerer, G., & Dorsett, P. (2003). Bridging the gap: Transitional rehabilitation services for people with spinal cord injury. *Disability and Rehabilitation*, *25*(17), 1008–1015.

Kendall, M. B., & Wallace, M. A. (2016). Measuring goal attainment within a community-based multidisciplinary rehabilitation setting for people with spinal cord injury. *Edorium Journal of Disability and Rehabilitation*, *2*, 43–52.

Kett, M., Cole, E., & Turner, J. (2020). Disability, mobility and transport in low-and middle-income countries: A thematic review. *Sustainability*, *12*(2), 589.

Kratz, A. L., Chadd, E., Jensen, M. P., Kehn, M., & Kroll, T. (2015). An examination of the psychometric properties of the community integration questionnaire (CIQ) in spinal cord injury. *The Journal of Spinal Cord Medicine*, *38*(4), 446–455.

Krause, J. S., Saunders, L. L., & Acuna, J. (2012). Gainful employment and risk of mortality after spinal cord injury: Effects beyond that of demographic, injury and socioeconomic factors. *Spinal Cord*, *50*(10), 784–788. https://doi.org/10.1038/sc.2012.49.

Kuykendall, L., Tay, L., & Ng, V. (2015). Leisure engagement and subjective well-being: A meta-analysis. *Psychological Bulletin*, *141*(2), 364.

Latimer-Cheung, A., Arbour-Nicitopoulos, K., Brawley, L., Gray, C., Wilson, A., Prapavessis, H., et al. (2013). Developing physical activity interventions for adults with spinal cord, injury. Part 2: Motivational counseling and peer-mediated interventions, for people intending to be active. *Rehabilitation Psychology*, *58*(3), 307–315.

Liu, H., Hossain, M. S., Islam, M. S., Rahman, M. A., Costa, P. D., Herbert, R. D., et al. (2020). Understanding how a community-based intervention for people with spinal cord injury in Bangladesh was delivered as part of a randomised controlled trial: A process evaluation. *Spinal Cord*, *58*, 1–10.

Lloyd, K. M., & Auld, C. J. (2002). The role of leisure in determining quality of life: Issues of content and measurement. *Social Indicators Research*, *57*(1), 43–71.

Loy, D. P., Dattilo, J., & Kleiber, D. A. (2003). Exploring the influence of leisure on adjustment: Development of the leisure and spinal cord injury adjustment model. *Leisure Sciences*, *25*(2–3), 231–255.

Lundström, U., Lilja, M., Petersson, I., Lexell, J., & Isaksson, G. (2014). Leisure repertoire among persons with a spinal cord injury: Interests, performance, and well-being. *The Journal of Spinal Cord Medicine*, *37*(2), 186–192.

Mackelprang, R. W., & Salsgiver, R. O. (2016). *Disability: A diversity model approach in human service practice*. Oxford University Press.

Maribo, T., Jensen, C. M., Madsen, L. S., & Handberg, C. (2020). Experiences with and perspectives on goal setting in spinal cord injury rehabilitation: A systematic review of qualitative studies. *Spinal Cord*, *58*, 1–10.

May, L., Day, R., & Warren, S. (2006). Evaluation of patient education in spinal cord injury rehabilitation: Knowledge, problem-solving and perceived importance. *Disability and Rehabilitation*, *28*(7), 405–413.

McLean, A. M., Jarus, T., Hubley, A. M., & Jongbloed, L. (2014). Associations between social participation and subjective quality of life for adults with moderate to severe traumatic brain injury. *Disability and Rehabilitation*, *36*(17), 1409–1418.

McVeigh, S. A., Hitzig, S. L., & Craven, B. C. (2009). Influence of sport participation on community integration and quality of life: A comparison between sport participants and non-sport participants with spinal cord injury. *The Journal of Spinal Cord Medicine*, *32*(2), 115–124.

Mead, S., & MacNeil, C. (2006). Peer support: What makes it unique. *International Journal of Psychosocial Rehabilitation*, *10*(2), 29–37.

Middleton, J. W., Murphy, G. C., Ramakrishnan, K., Savage, N., Harper, R., Compton, J., et al. (2015). Early access to vocational rehabilitation for spinal cord injury inpatients. *Journal of Rehabilitation Medicine*, *47*, 626–631.

Momsen, A.-M., Rasmussen, J. O., Nielsen, C. V., Iversen, M. D., & Lund, H. (2012). Multidisciplinary team care in rehabilitation: An overview of reviews. *Journal of Rehabilitation Medicine*, *44*(11), 901–912.

Munce, S. E., Webster, F., Fehlings, M. G., Straus, S. E., Jang, E., & Jaglal, S. B. (2014). Perceived facilitators and barriers to self-management in individuals with traumatic spinal cord injury: A qualitative descriptive study. *BMC Neurology*, *14*(1), 48.

Murphy, G. C., O'Hare, M. A., & Wallis, L. (2010). The relationships among different types of social support accessed by traumatic spinal cord injury survivors. *International Journal of Disability Management*, *5*(2), 59–66.

Norweg, A., Jette, A. M., Houlihan, B., Ni, P., & Boninger, M. L. (2011). Patterns, predictors, and associated benefits of driving a modified vehicle after spinal cord injury: Findings from the National Spinal Cord Injury Model Systems. *Archives of Physical Medicine and Rehabilitation*, *92*(3), 477–483.

Nunnerley, J. L., Hay-Smith, E., & Dean, S. (2013). Leaving a spinal unit and returning to the wider community: An interpretative phenomenological analysis. *Disability and Rehabilitation*, *35*(14), 1164–1173.

Phillips, V., Vesmarovich, S., Hauber, R., Wiggers, E., & Egner, A. (2001). Telehealth: Reaching out to newly injured spinal cord patients. *Public Health Reports*, *116*(Supp 1), 94–102.

Post, M. W., Reinhardt, J. D., & Escorpizo, R. (2020). Return to work after spinal cord injury. In *Handbook of disability, work and health* (pp. 1–13). Springer.

Price, P., Stephenson, S., Krantz, L., & Ward, K. (2011). Beyond my front door: The occupational and social participation of adults with spinal cord injury. *OTJR: Occupation, Participation and Health*, *31*(2), 81–88.

Roessler, R. T., Bishop, M., Rumrill, P. D., Sheppard-Jones, K., Waletich, B., Umeasiegbu, V., et al. (2013). Specialized housing and transportation needs of adults with multiple sclerosis. *Work*, *45*(2), 223–235.

Schonherr, M., Groothoff, J., Mulder, G., & Eisma, W. (2005). Vocational perspectives after spinal cord injury. *Clinical Rehabilitation*, *19*(2), 200–208. https://doi.org/10.1191/0269215505cr845oa.

Sekaran, P., Vijayakumari, F., Hariharan, R., Zachariah, K., Joseph, S. E., & Kumar, R. S. (2010). Community reintegration of spinal cord-injured patients in rural South India. *Spinal Cord*, *48*(8), 628–632.

SRALAB. (2020a). *Goal attainment scale*. Retrieved from https://www.sralab.org/rehabilitation-measures/goal-attainment-scale.

SRALAB. (2020b). *Needs assessment checklist*. Retrieved from https://www.sralab.org/rehabilitation-measures/needs-assessment-checklist.

Wright, C. J., Colley, J., & Kendall, E. (2020). Exploring the efficacy of housing alternatives for adults with an acquired brain or spinal injury: A systematic review. *Brain Impairment*, *21*(2), 125–153. https://doi.org/10.1017/BrImp.2019.33.

The United Nations Convention on the Rights of Persons with Disabilities (UNCRPD) [Article 9]. Retrieved from: https://www.un.org/development/desa/disabilities/convention-on-the-rights-of-persons-with-disabilities/article-9-accessibility.html.

Trenaman, L. M., Miller, W. C., Querée, M., & Escorpizo, R. (2015). Modifiable and non-modifiable factors associated with employment outcomes following spinal cord injury: A systematic review. *The Journal of Spinal Cord Medicine*, *38*(4), 422–431.

Turner, B., Fleming, J., Cornwell, P., Worrall, L., Ownsworth, T., Haines, T., et al. (2007). A qualitative study of the transition from hospital to home for individuals with acquired brain injury and their family caregivers. *Brain Injury*, *21*(11), 1119–1130.

Turner-Stokes, L. (2008). Evidence for the effectiveness of multi-disciplinary rehabilitation following acquired brain injury: A synthesis of two systematic approaches. *Journal of Rehabilitation Medicine*, *40*(9), 691–701.

Ullah, M. M., Fossey, E., & Stuckey, R. (2018). The meaning of work after spinal cord injury: A scoping review. *Spinal Cord*, *56*(2), 92.

Van Velzen, J., Van Bennekom, C., Edelaar, M., Sluiter, J. K., & Frings-Dresen, M. (2009). How many people return to work after acquired brain injury?: A systematic review. *Brain Injury*, *23*(6), 473–488.

Veith, E. M., Sherman, J. E., Pellino, T. A., & Yasui, N. Y. (2006). Qualitative analysis of the peer-mentoring relationship among individuals with spinal cord injury. *Rehabilitation Psychology*, *51*(4), 289–298.

Wobma, R., Nijland, R. H., Ket, J. C., & Kwakkel, G. (2016). Evidence for peer support in rehabilitation for individuals with acquired brain injury: A systematic review. *Journal of Rehabilitation Medicine*, *48*(10), 837–840.

Woo, C., Guihan, M., Frick, C., Gill, C. M., & Ho, C. H. (2011). What's happening now! Telehealth management of spinal cord injury/disorders. *The Journal of Spinal Cord Medicine*, *34*(3), 322–331.

World Health Organization. (2002). *Toward a common language for functioning, disability and health*. Geneva: World Health Organization.

Chapter 40

Rehabilitation in spinal cord injury: Exercise and testing for cardiorespiratory endurance and musculoskeletal fitness

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Abbreviations

SCI	spinal cord injury
PwSCI	persons with a spinal cord injury
VO_{2peak}	peak volume of oxygen consumption
VO_{2max}	maximal volume of oxygen consumption
ACE	arm crank ergometer
1-RM	one repetition maximum
WMS	WheelMill System
6-MAT	6-minute arm test
6MPT	6-minute push test
RPE	rate of perceived exertion
ASIA	The American Spinal Injury Association Impairment Scale
PO	power output
W	watts
RM	repetition maximum
ROM	range of motion
RER	respiratory exchange ratio

Introduction

Persons with a spinal cord injury (PwSCI) are at increased risk of leading less active lifestyles as compared to the general population. Spinal cord injury (SCI) results in declines in physical capacity and an increased risk of secondary health conditions. Specifically, PwSCI are three times more likely to have one or more chronic diseases such as heart disease, stroke, diabetes, cancer, or obesity compared to persons without disabilities (Jacobs & Beekhuizen, 2005; Keyser, Rasch, Finley, & Rodgers, 2003). SCIs often result in various physiological alterations affecting multiple body systems, including blunted hemodynamics, altered sympathetic innervation, altered glycemic control, reduced active muscle mass, deteriorated circulatory vessels below level of injury, and impaired arterial compliance and function (West, AlYahya, Laher, & Krassioukov, 2013). These pathophysiological alterations amplify the risk and prevalence of cardiovascular and metabolic diseases in PwSCI. PwSCI are also at an increased risk of negative mood states including depression and anxiety (Post & van Leeuwen, 2012). An approach to managing the potential physiological and psychological implications of an SCI is engaging in physical activity or exercise.

Exercise and persons with a spinal cord injury

The typical daily routine of PwSCI does not stress the cardiorespiratory system enough to produce positive health-related changes; therefore, participation in regular exercise is needed to enhance physical capacity and to reduce the likelihood of secondary complications (Hjeltnes & Vokac, 1979; Jacobs & Nash, 2004). Similar to the general population, regular exercise is critical to reducing the risk of developing chronic health conditions and has positive effects on the physiological

Diagnosis and Treatment of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822498-4.00040-3

health and psychological well-being of PwSCI (Carroll et al., 2014; Hicks et al., 2011; Martin Ginis et al., 2010). Participation in exercise is also connected to more established social networks and greater participation in life activities (Crawford, Hollingsworth, Morgan, & Gray, 2008; Rimmer, Chen, McCubbin, Drum, & Peterson, 2010). Increased cardiorespiratory fitness in PwSCI promotes not only improved functional independence, but also improved cardiovascular and metabolic health (van der Scheer et al., 2017).

Exercise and spinal cord injury considerations

PwSCI may experience secondary health conditions that are important to take into consideration when engaging in exercise. Bone loss and osteoporosis are complications that may occur following an SCI and can lead to an increased risk of fractures, which can have further negative consequences on health and functioning (Jiang, Dai, & Jiang, 2006). Upper extremity pain and chronic overuse injuries, particularly in the shoulder joints of PwSCI, are commonly associated with wheelchair self-propulsion and transfers (Lal, 1998). Due to the direct effects of an SCI, PwSCI often lack normal protective sensation below the level of their injury. This lack of sensation combined with the reduced mobility associated with an SCI can result in the development of pressure ulcers (Vidal & Sarrias, 1991). Having an understanding of these possible secondary conditions is important when exercising. Proper biomechanical positioning when exercising, reducing the number of transfers onto exercise equipment, and implementing a regular shoulder strengthening exercise program targeted at the rotator cuff are among the actions that can be taken to prevent or delay these secondary conditions from impacting the exercise routine of a PwSCI.

Exercise recommendations for persons with spinal cord injury

Basic programming guidelines for exercise and physical activity are set forth by organizations including the American College of Sports Medicine's Guidelines for Exercise Testing and Prescription (2020) and the Physical Activity Guidelines for Adults with Chronic Health Conditions and Adults with Disabilities from the U.S. Department of Health and Human Services (2018). The U.S. Department of Health and Human Services recommends at least 150 minutes per week of moderate-intensity aerobic activity or 75 minutes per week of vigorous-intensity aerobic activity for adults with chronic conditions or disabilities, as well as muscle strengthening activities of moderate or greater intensity, 2 or more days a week. Diagnosis-specific guidelines exist for PwSCI and recommend shorter durations of weekly exercise time. For example, to gain cardiometabolic health and fitness and muscle strength benefits, the International Exercise Guidelines for PwSCI recommend that a PwSCI should engage in at least 20 to 30 min of moderate-to-vigorous-intensity aerobic exercise two to three times per week and three sets of strength exercises for each major functioning muscle group, at a moderate-to-vigorous intensity, two times per week (Martin Ginis et al., 2018).

Barriers to exercise

Despite the widely recognized health benefits of regular exercise, PwSCI report lower levels of exercise compared to the general population (Carroll et al., 2014; Martin Ginis et al., 2010; Sullivan, 2009). Because of decreased sympathetic innervation, muscle atrophy, and decreased cardiac reserves, it is difficult for PwSCI to achieve intensity levels necessary to make health-related changes without proper support (Cowell, Squires, & Raven, 1986; Hicks et al., 2011). PwSCI face numerous challenges to participating in exercise, including personal (e.g., lack of motivation and self-efficacy) and environmental (e.g., transportation, access to proper equipment) barriers (Adam & Morgan, 2018). Unlike the surplus of fitness centers and equipment available for the general population, there is a considerable lack of accessible equipment, support, and professional guidance for PwSCI (Cardinal & Spaziani, 2003; Johnson, Stoelzle, Finco, Foss, & Carstens, 2012). In addition, PwSCI do not always have access to the information needed to monitor their progress. Accurate and reliable measures are important so that physical activity levels of PwSCI can be assessed, recommendations can be made to better inform development of exercise programs, and PwSCI can independently track their exercise and take ownership of their health.

Importance of exercise testing

An important aspect of supporting PwSCI to successfully engage, initiate, and maintain exercise is the ability to have reliable information to inform and develop individualized programs and track change. Whether a person is an elite athlete training for the Paralympics or a newly injured PwSCI, having information to guide programs and help people achieve their goals is crucial. The following will discuss different types of testing, testing protocols, considerations for PwSCI, and equipment and adaptations.

Exercise testing for persons with a spinal cord injury

Physical fitness is the ability to perform activities of daily living, leisure activities, and other occupations without excessive fatigue. Physical fitness testing, also known as exercise testing, is important to conduct to determine a baseline fitness level, identify strengths and areas of improvement, and establish realistic goals for individuals. Comprehensive testing best informs exercise professionals to design and implement appropriate, client-centered exercise prescriptions. Follow-up testing results can also be performed and compared to baseline data to evaluate progress during and/or following a prescribed exercise program (Gibson, Wagner, & Heyward, 2019a). Accurate and reliable assessments are important so that exercise and fitness levels can be evaluated, recommendations can be made to better inform development of exercise programs, and PwSCI can independently track their exercise and take ownership of their health.

Exercise testing can include a number of different components; however, the two most common are cardiorespiratory endurance, also known as functional capacity, and musculoskeletal fitness testing. Musculoskeletal fitness is comprised of two components, muscle strength and muscle endurance (Arena et al., 2007; Gibson, Wagner, & Heyward, 2019b).

General considerations for exercise testing for people with spinal cord injury

PwSCI may experience a myriad of multi-system physiological alterations as a result of their injury (West et al., 2013). For these reasons, specific considerations and precautions are recommended when conducting exercise testing with PwSCI. Exercise testing participants should obtain physician approval and signed release prior to initiation of testing. Testers should be well trained in the testing protocol, procedures, and equipment, and also familiar with potentially dangerous conditions associated with SCI, such as autonomic dysreflexia. Testing participants should be supervised and closely monitored throughout the duration of the testing session. Ambient temperature of the testing environment should be comfortable for the participant, keeping in mind persons with a cervical level injury may not be able to control their temperature by sweating and may need a fan blowing on them or cooler room temperatures. Devices such as heart rate monitors and/or other wearable sensors should be worn by testing participants for accurate monitoring of participant status. Vitals and pain level should be taken prior to initiation of testing to ensure that the session can safely proceed. The testing session should be terminated if any of the following distressful issues occur: abnormal heart rate or blood pressure, presence of a bladder infection, presence of a pressure ulcer, unusual spasticity, or autonomic dysreflexia. Testers should also determine a pain threshold at which to terminate testing; recommended thresholds may vary; however, terminating testing if reported pain is $\geq$6 out of 10 has been acceptable (Morgan, Taylor, Tucker, Cade, & Klaesner, 2018).

Cardiorespiratory endurance testing

Cardiorespiratory testing can be categorized into laboratory or field tests. While laboratory tests provide greater accuracy and reliability, they also require advanced technology and training as well as increased cost to perform. The gold standard for assessing cardiorespiratory fitness is the measurement of peak volume of oxygen consumption (VO_{2peak}) during a graded exercise test (Vanhees et al., 2005). Field tests, while less sensitive thanVO_{2peak}, are typically more cost-effective, more readily available to administer in non-laboratory settings, and still provide a submaximal estimation of cardiorespiratory endurance. Examples of cardiorespiratory field tests that will be discussed include the 6-Minute Arm Test (6-MAT) and the 6-Minute Push Test (6MPT).

VO_{2peak} testing in people with spinal cord injury

While the maximal volume of oxygen consumption (VO_{2max}) is widely accepted as the benchmark for measuring cardiorespiratory fitness, the VO_2 plateau and maximal heart rate criteria required to reliably establish VO_{2max} may be difficult for PwSCI to achieve given the various pathophysiological changes with SCI, specifically altered sympathetic innervation and reduced muscle activation. Therefore, VO_{2peak} is considered the gold standard to assess cardiorespiratory fitness and aerobic metabolism for this population. Breath-by-breath cardiometabolic and physiological measures can be obtained during testing using a computer-integrated metabolic measurement system; these measures include respiratory exchange ratio (RER), heart rate, pulmonary ventilation, energy expenditure, and ventilatory threshold (Crouter, Antczak, Hudak, DellaValle, & Haas, 2006; Lovell, Shields, Beck, Cuneo, & McLellan, 2012). VO_{2peak} testing is typically completed in 8 to 12 minutes, depending on the individual's fitness level (Jelleyman et al., 2015). Assessing the participant's rating of perceived exertion (RPE) throughout the graded exercise test is also highly recommended (Lewis, Nash, Hamm, Martins, & Groah, 2007). VO_{2peak} determination typically includes achievement of RER $\geq$ 1.1 and RPE $\geq$ 15–17 as standard indicators for test termination; however, other criteria may be incorporated, including blood lactate and heart rate

(Morgan et al., 2018; Tørhaug, Brurok, Hoff, Helgerud, & Leivseth, 2016). Heart rate is only reliable for people with neurological levels of injury below T7, as autonomic dysfunction and blunted sympathetic innervation occur in individuals with higher injury levels (West et al., 2013). Evidence of norm-reference values for VO_{2peak} in adults with SCI is sparse; however, it is accepted that VO_{2peak} may be impacted by sex and neurological level of injury (Janssen, Dallmeijer, Veeger, & van der Woude, 2002; Simmons, Kressler, & Nash, 2014).

Equipment options for VO_{2peak} fitness testing in people with spinal cord injury

For non-wheelchair users, VO_{2peak} is commonly measured on treadmills or stationary bikes, both common forms of exercise for this population. For individuals with SCI using wheelchairs, the most common method of measuring VO_{2peak} is during a graded exercise test using an arm crank ergometer (Ilias, Xian, Inman, & Martin, 2009), wheelchair ergometer, or a roller-based wheelchair dynamometer (Ilias et al., 2009; Molik et al., 2017).

Arm crank ergometers

An arm crank ergometer (ACE) is a low-impact exercise system for both lower and upper extremity conditioning that has hand cranks and foot pedals and a removable seat for wheelchair access. For PwSCI who use a wheelchair for functional mobility, the hand cranks are used during testing. It is recommended to use an ACE that includes adjustable arm cranks and a removable seat for wheelchair access. Arm cranks should be adjusted where the axes of rotation are positioned just below shoulder level of the participant to ensure proper alignment of the glenohumeral joint to the ACE (Fig. 1A). Proper biomechanics also include ensuring that participants' arms are slightly flexed at the elbows at the moment of furthest reach (Fig. 1B). Participants are able to use their personal wheelchairs (manual or power) during testing; however, if trunk stability safely allows, participants may opt to transfer to the ACE seat.

While ACEs are the most widely used and commercially available devices for cardiorespiratory testing (Ilias et al., 2009; Janssen et al., 2002; Simmons et al., 2014; Tørhaug et al., 2016), have shown to be effective in testing fitness, and provide health-related changes in PwSCI, they present with limitations (Myers, Lee, & Kiratli, 2007). The operation of an ACE requires a movement pattern not typically employed during functional mobility or activities of daily living (Morgan et al., 2018). Functional impairments in hand strength and trunk control can yield further limitations of ACEs. Ace bandage wraps or specialized grip-assist gloves (Fig. 1C) can be used when hand grip impairments are present. Abdominal binders may be used to assist with trunk stabilization during testing.

Wheelchair-based systems

Propulsion is the primary functional movement pattern for PwSCI who use a manual wheelchair. Testing devices such as wheelchair ergometers and roller-based systems provide a simulated over-ground propulsion experience, allowing the individual to remain stationary while engaging in a functional movement pattern during testing. Each of these devices allows manual wheelchair users to use functional propulsion to complete the stepwise VO_{2peak} protocols. Evidence suggests that each device has strengths and weaknesses with no consensus on which type is best for exercise testing (Stephens & Engsberg, 2010).

Wheelchair ergometers, sometimes referred as dynamometers, utilize treadmill and bicycle components to allow participants to propel a manual wheelchair; however, these testing devices have limitations. Wheelchair ergometers often require participants to sit in and propel a designated laboratory wheelchair that has been pre-fit for the device. Participants report that the glide differs from typical wheelchair propulsion, potentially impacting body mechanics and performance

FIG. 1 Setup for VO_{2peak} testing using an arm crank ergometer. (A) Proper alignment of glenohumeral joint in relation to ACE axes of rotation; (B) proper setup for slightly flexed elbows at the moment of furthest reach during cranking motion; (C) example of specialized grip-assist gloves known as Active Hands; VO_{2peak}, peak volume of oxygen consumption. *Photo credit: Michele Berhorst/Washington University.*

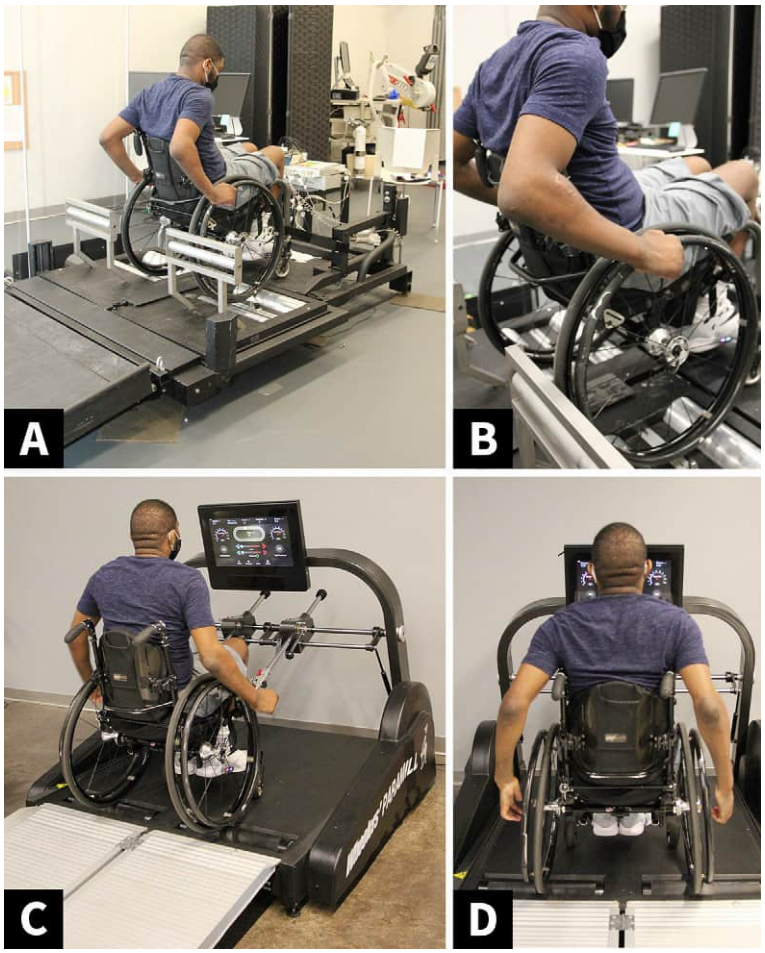

FIG. 2 Examples of roller-based systems allowing for use of personal manual wheelchairs. (A and B) WheelMill System; (C and D) The Paramill. *Photo credit: Michele Berhorst/Washington University.*

during testing. Wheelchair ergometers typically have limited customization or fine tuning that is highly beneficial when working with a diagnosis such as SCI (Rodgers, Keyser, Rasch, Gorman, & Russell, 2001).

Roller-based systems, also referred to as wheelchair dynamometers, consist of one or two parallel rollers and may allow for customizable manipulation of variables such as resistance (Klaesner, Morgan, & Gray, 2014; Morgan, Engsberg, & Klaesner, 2015). Roller-based systems (Fig. 2) further promote the functional movement pattern of propulsion by allowing for participants to use their personal wheelchairs, including sports wheelchairs, optimizing body mechanics, propulsion patterns, and performance during testing. An example of a roller-based system that has been used for VO_{2peak} testing for PwSCI is the WheelMill System (WMS). The WMS is a computer-controlled, motor-driven wheelchair dynamometer that has been used for VO_{2peak} testing (Klaesner et al., 2014; Morgan et al., 2015). Morgan et al. (2018) found that despite similarities in outcomes between ACEs and the WMS during VO_{2peak} testing, participants consistently rated their RPE higher on the ACE compared to the WMS despite the same workload (Morgan et al., 2018). At this time, roller-based systems are not as widely available as ACE, and testers require enhanced training to operate and execute protocols using these devices. Participants should be directly supervised or spotted when transitioning their wheelchair to and from the rollers to prevent falls. Falls and wheelchair tipping should also be prevented during testing using safety straps to secure the wheelchair to the roller-based system.

Submaximal field tests

6-Minute arm test

The 6-MAT is a submaximal cardiorespiratory fitness test performed at a constant power output (PO), which is selected based on the individual's score on the American Spinal Injury Association (ASIA) Scale, sex, mobility device (manual vs

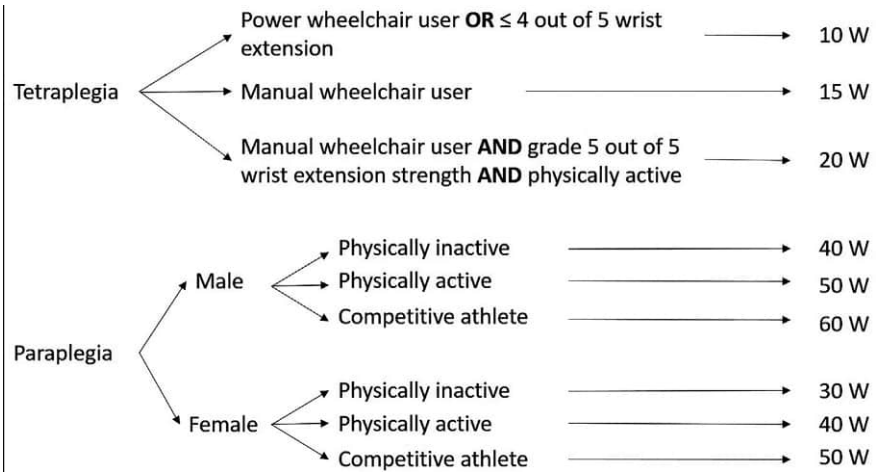

FIG. 3 Power output selection for the 6-minute arm test. The constant power output is based on level of injury, sex, mobility device, manual muscle test, and current physical activity level; W, Watts. *Figure adapted from Hol, A. T., Eng, J. J., Miller, W. C., Sproule, S., & Krassioukov, A. V. (2007). Reliability and validity of the six-minute arm test for the evaluation of cardiovascular fitness in people with spinal cord injury. Archives of Physical Medicine and Rehabilitation, 88(4), 489–495, Table 5.*

power), manual muscle testing, and current physical activity level (inactive, active, or competitive; Fig. 3). A standard, adjustable ACE is used for the 6-MAT. Individuals are instructed to maintain a consistent cadence of 60 rpm at the selected PO for the 6-minute duration of the test. Heart rate should be measured in 1-minute intervals, while RPE may be assessed either at 1-minute intervals and/or immediately following completion of the test (Hol, Eng, Miller, Sproule, & Krassioukov, 2007; Totosy de Zepetnek, Au, Hol, Eng, & MacDonald, 2016). Normative values have not been established for this submaximal field test; however, testers can use wearable sensors to gather data such as heart rate, RPE, total distance cranked, and estimated energy expenditure (Hiremath, Intille, Kelleher, Cooper, & Ding, 2016; Nightingale, Rouse, Thompson, & Bilzon, 2017) to compare pre-post for purposes of determining exercise programming effectiveness. The 6-MAT is appropriate to administer for PwSCI using either a manual or power wheelchair. Considerations for the 6-MAT are related to the aforementioned limitations and considerations of using an ACE.

6-Minute push test

The 6MPT is a physical fitness and functional mobility test involving manual wheelchair users propelling in a designated 30-meter loop. Participants are asked to propel as far as possible on the course for 6 minutes. Total distance propelled is determined by calculating the number of completed 30-meter loops and measuring the partially completed final lap using a tape measure. While the 6MPT employs a familiar, functional movement pattern, the primary limitation of this test is that it is only meaningful for persons able to independently propel a manual wheelchair (Cowan, Callahan, & Nash, 2012).

Musculoskeletal fitness testing

Muscle strength and endurance are key components related to fitness (Liguori & American College of Sports Medicine, 2020). Strength testing for PwSCI may be tested in the same manner as testing done in persons without disability. Consideration should be given to levels of SCI that may require stabilization and/or adaptive equipment to compensate for lack of grip strength and/or trunk control, as well as accessible equipment (Liguori & American College of Sports Medicine, 2020; Martin Ginis et al., 2018). Static strength testing, such as hand dynamometry and other isometric testing methods, are somewhat limited. These testing methods usually test isolated muscle groups at one joint angle, which is not a typical strength demand used for functional activities. The one repetition maximum (1-RM) has been considered the standard to assess dynamic muscular strength for many years (Liguori, & American College of Sports Medicine, 2020; Neto, Guanais, Dornelas, Coutinho, & Costa, 2017), and more recently multiple repetition maximum (RM) tests have been used (Gail, Rodefeld, & Künzell, 2015; Liguori & American College of Sports Medicine, 2020). A 1-RM is the maximal amount of resistance a person can move through their full range of motion (ROM), for a given exercise using proper form, one time. A multiple RM involves using multiple repetitions, usually 5 to 10, having a person move through their full ROM for a given exercise to the point of muscle failure, and then calculating their 1-RM from the multiple RM achieved (Reynolds, Gordon, & Robergs, 2006). 1-RM predictive equations commonly used in people without disability are accurate for use with adults with SCI who complete multiple RM testing of 4 to 12 repetitions (Baechle & Groves, 1998; Brzycki,

1993; Lombardi, 1989; Neto et al., 2017). More recently, some have suggested that, rather than using 1-RM, methods such as determining a number of repetitions completed within a specific time frame, that can be completed with proper form to fatigue, can help determine a baseline level of strength and that level of strength can then be used as a point of comparison for musculoskeletal fitness testing (Carpinelli, 2011; Liguori & American College of Sports Medicine, 2020).

Considerations for strength testing in persons with spinal cord injury

Most PwSCI use a wheelchair for functional mobility. Prior to testing strength with PwSCI, consideration should be given to the accessibility of the equipment used, transfer skills required to use the equipment and the ability of the person to complete the movement required. Consideration should be given to testing the person in their wheelchair vs on equipment that would require a person to transfer. If a transfer is required to use equipment, testers should first determine the individual's level of comfort with transfers as well as their usual method of transfers to determine whether it is safe and reasonable for the PwSCI to transfer to the equipment. Testers should ensure proper positioning of the individual, the test equipment, and spotter(s) prior to beginning the strength testing. Generally, PwSCI above level C8 will have a range of hand and upper extremity weakness from minimal to total paralysis of the muscles of the hand and wrist, and may require grip aids.

Persons with an SCI above L2 may have impairment in the abdominal and core regions ranging from minimal weakness to total paralysis of core musculature, and may require stabilization during strength testing via a human spotter and/or positioning straps at the hip, abdominal, and/or chest area. Additionally, consideration should be given for positioning and stabilization needs related to the wheelchair if the person being tested will remain in their wheelchair. For example, if testing will use a machine similar to the Equalizer (Fig. 4) to perform a vertical bench press, which allows a person to remain in their wheelchair, consideration should be taken to ensure that the back pad is placed at a height and position that will prevent rearward tipping of the wheelchair. Wheelchair locks should be used to assist in keeping the wheelchair stationary during testing, and additional methods such as tie-down straps may be necessary to prevent the wheelchair from sliding on floor surfaces. Persons who perform strength testing out of their wheelchair, such as a standard bench press in the supine position, should be spotted during transfers, may need straps or additional assistance to achieve and maintain the positioning required to complete the test in a safe manner.

FIG. 4 Equalizer bench press equipment. Example of vertical bench press strength testing setup using the Equalizer for manual wheelchair user with a spinal cord injury. *Photo credit: Michele Berhorst/Washington University.*

Strength testing equipment

Dynamic strength testing may be performed on several types of equipment. Equipment used for strength testing with PwSCI should be adjustable to allow for proper positioning, particularly if the person will remain seated in their wheelchair or requires any adaptations to compensate for muscle weakness in order to safely complete the required lift. Standard resistance training equipment, often found in most commercial fitness centers, can be used if the PwSCI being tested is able to transfer to the equipment and remain in a safe and stable position to complete the specific lift. Universally designed resistance training equipment, such as Equalizer and/or Uppertone, allows both wheelchair users and non-wheelchair users to access the equipment. The Uppertone is a wheelchair accessible device that targets upper limb strengthening by using stackable weights for adjusting resistance. The Equalizer is an accessible weight lifting machine that can be used by people who are ambulatory and people who utilize wheelchairs for mobility. For example, the Equalizer 1005VB machines and attachments allow the following exercises to be done: bench press, lat pull down, upright rowing, overhead press, vertical butterfly, biceps curl, triceps extension, leg curl, and leg extension. On the vertical bench press station, each arm works independently so different weights can be used if a participant's upper extremity strength varies between their right and left side. The vertical bench press height, backrest, and hand grips are adjustable to accommodate various users.

Rehabilitation testing equipment such as the BTE™ PrimusRS (Fig. 5) or Biodex dynamometer systems may be used to test isokinetic strength in PwSCI (Ambrosio et al., 2005; Freitas, Serenza, Santana, Manoel, & Riberto, 2017; Shechtman, MacKinnon, & Locklear, 2001; Souza et al., 2005). Typically, strength measures using rehabilitation testing equipment for isokinetic testing gives results in peak torque/weight, work, and power vs a weight resistance value for 1-RM that would be discovered from weight resistance training equipment, and may not readily translate to the standard 1-RM.

FIG. 5 Isokinetic testing equipment set up for a bench press motion using a BTE™ PrimusRS. Example setup of vertical bench press isokinetic strength testing for a manual wheelchair user with a spinal cord injury. *Photo credit: Michele Berhorst/Washington University.*

Testing procedures

The procedures for conducting 1-RM and multiple RM testing have been well established (Gail et al., 2015; Liguori and American College of Sports Medicine, 2020; Neto et al., 2017). Additional steps may need to be taken for PwSCI, particularly those who are wheelchair users. PwSCI should be instructed to complete the motion of each exercise prior to adding weight resistance; those demonstrating sufficient ROM to complete the exercise with proper form can proceed with testing. The process to conduct 1-RM or multiple RM testing with PwSCI is shown in Table 1. As noted previously, it is important to ensure proper positioning of the individual and equipment prior to beginning the strength testing. Also, it is important to ensure that the individual being tested is stabilized to ensure safety and minimize compensatory movement patterns that would make the lift unsafe.

Application to other areas in neuroscience

In this chapter, we have reviewed the importance of exercise, barriers to exercise, recommendations for exercising, and methods for exercise testing for persons with a spinal cord injury. Many of the themes discussed specific to spinal cord injury are seen in persons with other neurological conditions. This includes the impact exercise can have on physical and emotional health and the personal and environmental barriers to exercise experienced. Other medical conditions that also involve impairment of the corticospinal tracts of the central nervous system include multiple sclerosis and cerebral palsy. The benefits and focus of exercise often emphasize walking and balance for persons with multiple sclerosis and balance for persons with cerebral palsy, whereas, for persons with a spinal cord injury, function and aerobic fitness are where improvements were seen in the literature. Persons with a spinal cord injury also experience physiological alterations that impact organ systems that are different than other neurological conditions such as autonomic dysreflexia and temperature control. Many of the methods reviewed for exercise testing could also be adapted to persons with other neurological conditions. The methods were written and adapted for this chapter with the main assumption that persons had the cognitive ability to process instructions. For persons with a stroke or traumatic brain injury, the instructions may need to be modified. Also, for persons with hemiplegia versus paraplegia or tetraplegia, the adaptations may be different.

Mini-dictionary of terms

Cardiorespiratory endurance: integration of the cardiovascular and pulmonary systems to efficiently provide adequate oxygen and nutrients to working skeletal muscles in order to perform tasks and activities requiring sustained aerobic metabolism.

Musculoskeletal fitness: ability of the musculoskeletal system to exert adequate force in order to perform work.

Muscle strength: maximal force producible by a muscle group.

TABLE 1 Strength testing procedures for 1-RM for PwSCI.

1.	Identify any grip aids, core stabilization aids, wheelchair positioning, and wheelchair stabilization needs specific to the equipment being used to complete testing
2.	Complete 1-RM or multiple repetition maximum test after individual has been familiarized/completed practice sessions of the movement to be tested, all necessary adaptations and wheelchair setup and stabilization needs have been trialed, and stabilization and adaptation needs have been established
3.	Warm up with completion of submaximal repetitions of the exercise being tested; following warm-up, adjust any positioning supports and/or stabilizations as needed
4.	Determine 1-RM (or multiple repetition maximum) within four trials; rest for 3–5 min between trials
5.	Select starting weight within perceived capacity
6.	Progressively increase resistance 5–10% from previous attempt for upper body exercise until selected repetitions cannot be completed. Make sure speed of all lift movements is consistent
7.	Record final weight lifted with correct form through full ROM as the 1-RM or multiple repetition maximum

Recommended procedures for conducting upper extremity 1-RM testing for PwSCI. 1-RM, one-repetition maximum; PwSCI, persons with spinal cord injury. Adapted from Liguori, G., & American College of Sports Medicine. (2020). ACSM's guidelines for exercise testing and prescription. Lippincott Williams & Wilkins., p. 99 Box 3.9. Adapted from Ligouri & American College of Sports Medicine, 2020, p. 99, Box 3.9.

Muscle endurance: ability of a muscle group to sustain submaximal force for a prolonged time.
Autonomic dysreflexia: life-threatening condition involving a sudden increase in blood pressure from a reflexive overreaction of the autonomic nervous system in response to noxious stimulation.
Dynamometery: measurement of force produced and used, typically musculoskeletal strength.
1-rep max: maximal amount of resistance that can be moved, one time, through full range of motion for a given exercise using proper technique.
Multiple rep max: maximal amount of resistance that can be moved 5 to 10 repetitions through full range of motion for a given exercise to the point of muscle failure.
Isokinetic: muscle action that maintains a constant velocity.

Key facts of rehabilitation in spinal cord injury: Exercise and testing for cardiorespiratory endurance and musculoskeletal fitness

Key facts of spinal cord injury and exercise

- With less than 25% of adults with disabilities participating in sufficient physical activity to achieve health benefits, persons with spinal cord injury have the lowest engagement in physical activity and exercise
- Persons with spinal cord injury are three times more likely to have one or more chronic diseases such as heart disease, stroke, diabetes, cancer, or obesity compared to persons without disabilities
- Exercise guidelines have been developed specific to persons with a spinal cord injury and recommend at least 90 minutes of moderate-to-vigorous-intensity exercise each week to achieve cardiometabolic health benefits.

Key facts of exercise testing for persons with spinal cord injury

- Peak volume of oxygen consumption testing is the gold standard for assessing cardiorespiratory endurance in persons with a spinal cord injury.
- Exercise test administrators must be well familiar with potentially dangerous conditions associated with spinal cord injury included but not limited to autonomic dysreflexia, temperature dysregulation, abnormal heart rhythms, decubitus ulcers, and bladder infections.
- People with spinal cord injury may require adaptations and/or extra stabilization or use of accessible strength testing equipment to complete dynamic strength testing in a similar manner as persons without disabilities.

Summary points

- Habitual exercise is critical for persons with spinal cord injury (PwSCI) as they are at a greater risk for major health conditions and poorer health outcomes than persons without spinal cord injury.
- Significant barriers exist for PwSCI who desire to participate in exercise, including personal and environmental barriers.
- An important aspect of supporting PwSCI to successfully engage in physical activity is the ability to have reliable information to inform and develop individualized programs and track change.
- Specific considerations and precautions are recommended when conducting exercise testing with PwSCI.
- Cardiorespiratory endurance testing can be conducted in a controlled laboratory setting or during submaximal field tests
- Common equipment used for cardiorespiratory endurance testing for PwSCI include arm crank ergometers, wheelchair ergometers, and roller-based dynamometers.
- PwSCI may participate in strength testing with a variety of resistance equipment when appropriate precautions are taken to ensure safety and proper lifting technique.

References

Adam, S., & Morgan, K. A. (2018). Meaningful components of a community-based exercise program for individuals with disabilities: A qualitative study. *Disability and Health Journal*, *11*(2), 301–305.

Ambrosio, F., Boninger, M. L., Souza, A. L., Fitzgerald, S. G., Koontz, A., & Cooper, R. A. (2005). Biomechanics and strength of manual wheelchair users. *The Journal of Spinal Cord Medicine*, *28*(5), 407–414.

Arena, R., Myers, J., Williams, M. A., Gulati, M., Kligfield, P., Balady, G. J., … Fletcher, G. (2007). Assessment of functional capacity in clinical and research settings. *Circulation*, *116*(3), 329–343.

Baechle, T. R., & Groves, B. R. (1998). *Weight training: Steps to success* (2nd ed.). Champaign, IL: Human Kinetics Publishers.

Brzycki, M. (1993). Strength testing—Predicting a one-rep max from reps-to-fatigue. *Journal of Physical Education, Recreation, & Dance*, *64*, 88–90.
Cardinal, B. J., & Spaziani, M. D. (2003). ADA compliance and the accessibility of physical activity facilities in Western Oregon. *American Journal of Health Promotion*, *17*(3), 197–201.
Carpinelli, R. N. (2011). Assessment of one repetition maximum (1RM) and 1RM prediction equations: Are they really necessary. *Medicina dello Sport*, *15* (2), 91–102.
Carroll, D. D., Courtney-Long, E. A., Stevens, A. C., Sloan, M. L., Lullo, C., Visser, S. N., … Dorn, J. M. (2014). Vital signs: Disability and physical activity—United States, 2009-2012. *Morbidity and Mortality Weekly Report*, *63*(18), 407–413.
Cowan, R. E., Callahan, M. K., & Nash, M. S. (2012). The 6-min push test is reliable and predicts low fitness in spinal cord injury. *Medicine and Science in Sports and Exercise*, *44*(10), 1993–2000.
Cowell, L. L., Squires, W. G., & Raven, P. B. (1986). Benefits of aerobic exercise for the paraplegic: A brief review. *Medicine and Science in Sports and Exercise*, *18*(5), 501–508.
Crawford, A., Hollingsworth, H. H., Morgan, K., & Gray, D. B. (2008). People with mobility impairments: Physical activity and quality of participation. *Disability and Health Journal*, *1*(1), 7–13.
Crouter, S. E., Antczak, A., Hudak, J. R., DellaValle, D. M., & Haas, J. D. (2006). Accuracy and reliability of the ParvoMedics TrueOne 2400 and MedGraphics VO2000 metabolic systems. *European Journal of Applied Physiology*, *98*(2), 139–151.
Freitas, P. S., Serenza, F. D., Santana, T. S., Manoel, L. S., & Riberto, M. (2017). Isokinetic analysis of rotator cuff musculature of sedentary wheelchair users and basketball athletes with spinal cord injury. *Journal of Physical Medicine, Rehabilitation & Disabilities*, *3*(3), 017.
Gail, S., Rodefeld, S., & Künzell, S. (2015). Reproducibility of a 5-repetition maximum strength test in older adults. *Isokinetics and Exercise Science*, *23* (4), 291–295.
Gibson, A. L., Wagner, D. R., & Heyward, V. H. (2019a). Principles of assessment, prescription, and exercise program adherence. In A. L. Gibson, D. R. Wagner, & V. H. Heyward (Eds.), *Advanced fitness assessment and exercise prescription* (pp. 55–78). Champaign IL: Human Kinetics.
Gibson, A. L., Wagner, D. R., & Heyward, V. H. (2019b). Assessing cardiorespiratory fitness. In A. L. Gibson, D. R. Wagner, & V. H. Heyward (Eds.), *Advanced fitness assessment and exercise prescription* (pp. 79–124). Champaign IL: Human Kinetics.
Hicks, A. L., Martin-Ginis, K. A., Pelletier, C. A., Ditor, D. S., Foulon, B., & Wolfe, D. L. (2011). The effects of exercise training on physical capacity, strength, body composition and functional performance among adults with spinal cord injury: A systemic review. *Spinal Cord*, *49*, 1103–1127.
Hiremath, S. V., Intille, S. S., Kelleher, A., Cooper, R. A., & Ding, D. (2016). Estimation of energy expenditure for manual wheelchair users using a physical activity monitoring system. *Archives of Physical Medicine and Rehabilitation*, *97*(7), 1146–1153.
Hjeltnes, N., & Vokac, Z. (1979). Circulatory strain in everyday life of paraplegics. *Scandinavian Journal of Rehabilitation Medicine*, *11*(2), 67–73.
Hol, A. T., Eng, J. J., Miller, W. C., Sproule, S., & Krassioukov, A. V. (2007). Reliability and validity of the six-minute arm test for the evaluation of cardiovascular fitness in people with spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *88*(4), 489–495.
Ilias, N. A., Xian, H., Inman, C., & Martin, W. H. (2009). Arm exercise testing predicts clinical outcome. *American Heart Journal*, *157*, 69–76.
Jacobs, P. L., & Beekhuizen, K. S. (2005). Appraisal of physiological fitness in persons with spinal cord injury. *Topics in Spinal Cord Injury Rehabilitation*, *10*(4), 32–50.
Jacobs, P. L., & Nash, M. S. (2004). Exercise recommendations for individuals with Spinal Cord Injury. *Sports Medicine*, *34*, 727–751.
Janssen, T. W., Dallmeijer, A. J., Veeger, D. J., & van der Woude, L. H. (2002). Normative values and determinants of physical capacity in individuals with spinal cord injury. *Journal of Rehabilitation Research and Development*, *39*(1), 29–39.
Jelleyman, C., Yates, T., O'Donovan, G., Gray, G., King, J. A., Khunti, K., & Davies, M. J. (2015). The effects of high-intensity interval training on glucose regulation and insulin resistance: A meta-analysis. *Obesity Reviews*, *16*, 942–961.
Jiang, S.-D., Dai, L. Y., & Jiang, L. S. (2006). Osteoporosis after spinal cord injury. *Osteoporosis International*, *17*(2), 180–192.
Johnson, M. J., Stoelzle, H. Y., Finco, K. L., Foss, S. E., & Carstens, K. (2012). ADA compliance and accessibility of fitness facilities in western Wisconsin. *Topics in Spinal Cord Injury Rehabilitation*, *18*(4), 340–353.
Keyser, R. E., Rasch, E. K., Finley, M., & Rodgers, M. M. (2003). Improved upper-body endurance following a 12-week home exercise program for manual wheelchair users. *Journal of Rehabilitation Research and Development*, *40*(6), 501.
Klaesner, J., Morgan, K. A., & Gray, D. B. (2014). The development of an instrumented wheelchair propulsion testing and training device. *Assistive Technology: The Official Journal of RESNA*, *26*(1), 24–32.
Lal, S. (1998). Premature degenerative shoulder changes in spinal cord injury patients. *Spinal Cord*, *36*(3), 186–189.
Lewis, J. E., Nash, M. S., Hamm, L. F., Martins, S. C., & Groah, S. L. (2007). The relationship between perceived exertion and physiologic indicators of stress during graded arm exercise in persons with spinal cord injuries. *Archives of Physical Medicine and Rehabilitation*, *88*(9), 1205–1211.
Liguori, G., & American College of Sports Medicine. (2020). *ACSM's guidelines for exercise testing and prescription*. Lippincott Williams & Wilkins.
Lombardi, V. P. (1989). *Beginning weight training: The safe and effective way*. Dubuque, IA: WC Brown.
Lovell, D., Shields, D., Beck, B., Cuneo, R., & McLellan, C. (2012). The aerobic performance of trained and untrained handcyclists with spinal cord injury. *European Journal of Applied Physiology*, *112*(9), 3431–3437.
Martin Ginis, K. A., Arbour-Nicitopoulos, K. P., Latimer, A. E., Buchholz, A. C., Bray, S. R., Craven, C., … Wolfe, D. L. (2010). Leisure time physical activity in a population-based sample of people with spinal cord injury part II: Activity types, intensities, and durations. *Archives of Physical Medicine and Rehabilitation*, *91*, 729–733.
Martin Ginis, K. A., van der Scheer, J. W., Latimer-Cheung, A. E., Barrow, A., Bourne, C., Carruthers, P., … Goosey-Tolfrey, V. L. (2018). Evidence-based scientific exercise guidelines for adults with spinal cord injury: An update and a new guideline. *Spinal Cord*, *56*, 308–321.
Molik, B., Kosmol, A., Morgulec-Adamowicz, N., Lencse-Mucha, J., Mroz, A., Gryko, K., et al. (2017). Comparison of aerobic performance testing protocols in elite male wheelchair basketball players. *Journal of Human Kinetics*, *60*, 243–254. https://doi.org/10.1515/hukin-2017-0140.

Morgan, K. A., Engsberg, J. R., & Klaesner, J. (2015). The testing of an instrumented wheelchair propulsion testing and training device. *Journal of Physical Medicine, Rehabilitation, & Disabilities*, *1*, 003.

Morgan, K. A., Taylor, K. L., Tucker, S. M., Cade, W. T., & Klaesner, J. W. (2018). Exercise testing protocol using a roller system for manual wheelchair users with spinal cord injury. *Journal of Spinal Cord Medicine*, *42*(3), 288–297.

Myers, J., Lee, M., & Kiratli, J. (2007). Cardiovascular disease in spinal cord injury: An overview of prevalence, risk, evaluation, and management. *American Journal of Physical Medicine and Rehabilitation*, *86*(2), 614–625.

Neto, F. R., Guanais, P., Dornelas, E., Coutinho, A. C. B., & Costa, R. R. G. (2017). Validity of one-repetition maximum predictive equations in men with spinal cord injury. *Spinal Cord*, *55*(10), 950–956.

Nightingale, T. E., Rouse, P. C., Thompson, D., & Bilzon, J. L. J. (2017). Measurement of physical activity and energy expenditure in wheelchair users: Methods, considerations, and future directions. *Sports Medicine—Open*, *3*(1), 10.

Post, M. W., & van Leeuwen, C. M. (2012). Psychosocial issues in spinal cord injury: A review. *Spinal Cord*, *50*, 382–389.

Reynolds, J. M., Gordon, T. J., & Robergs, R. A. (2006). Prediction of one repetition maximum strength from multiple repetition maximum testing and anthropometry. *The Journal of Strength & Conditioning Research*, *20*(3), 584–592.

Rimmer, J. H., Chen, M. D., McCubbin, J. A., Drum, C., & Peterson, J. (2010). Exercise intervention research on persons with disabilities: What we know and where we need to go. *American Journal of Physical Medicine and Rehabilitation*, *89*, 249–263.

Rodgers, M. M., Keyser, R. E., Rasch, E. K., Gorman, P. H., & Russell, P. J. (2001). Influence of training on biomechanics of wheelchair propulsion. *Journal of Rehabilitation Research and Development*, *38*(5), 505–511.

Shechtman, O., MacKinnon, L., & Locklear, C. (2001). Using the BTE Primus® to measure grip and wrist flexion strength in physically active wheelchair users: An exploratory study. *American Journal of Occupational Therapy*, *55*(4), 393–400.

Simmons, O. L., Kressler, J., & Nash, M. S. (2014). Reference fitness values in the untrained spinal cord injury population. *Archives of Physical Medicine and Rehabilitation*, *95*, 2272–2278.

Souza, A. L., Boninger, M. L., Fitzgerald, S., Shimada, S. D., Cooper, R. A., & Ambrosio, F. (2005). Upper limb strength in individuals with spinal cord injury who use manual wheelchairs. *The Journal of Spinal Cord Medicine*, *28*(1), 26–32.

Stephens, C. L., & Engsberg, J. R. (2010). Comparison of overground and treadmill propulsion patterns of manual wheelchair users with tetraplegia. *Disability and Rehabilitation. Assistive Technology*, *5*(6), 420–427.

Sullivan, K. J. (2009). Healthcare reform: A call to action for our patients. *Journal of Neurologic Physical Therapy*, *33*(3), 171–172.

Tørhaug, T., Brurok, B., Hoff, J., Helgerud, J., & Leivseth, G. (2016). Arm crank and wheelchair ergometry produce similar peak oxygen uptake but different work economy values in individuals with spinal cord injury. *BioMed Research International*, *2016*, 5481843. https://doi.org/10.1155/2016/5481843.

Totosy de Zepetnek, J. O., Au, J. S., Hol, A. T., Eng, J. J., & MacDonald, M. J. (2016). Predicting peak oxygen uptake from submaximal exercise after spinal cord injury. *Applied Physiology, Nutrition, and Metabolism*, *41*(7), 775–781.

U.S. Department of Health and Human Services. (2018). *2018 physical activity guidelines for Americans*. Washington, DC: U.S. Department of Health and Human Services.

van der Scheer, J. W., Martin Ginis, K. A., Ditor, D. S., Goosey-Tolfrey, V. L., Hicks, A. L., West, C. R., & Wolfe, D. L. (2017). Effects of exercise on fitness and health of adults with spinal cord injury. *Neurology*, *89*(7), 736–745.

Vanhees, L., Lefevre, J., Philippaerts, R., Martens, M., Huygens, W., Troosters, T., & Beunen, G. (2005). How to assess physical activity? How to assess physical fitness? *European Journal of Cardiovascular Prevention & Rehabilitation*, *12*(2), 102–114.

Vidal, J., & Sarrias, M. (1991). An analysis of the diverse factors concerned with the development of pressure sores in spinal cord injured patients. *Paraplegia*, *29*(4), 261–267.

West, C. R., AlYahya, A., Laher, I., & Krassioukov, A. (2013). Peripheral vascular function in spinal cord injury: A systematic review. *Spinal Cord*, *51*, 10–19.

Chapter 41

Community-based activity-based therapy for spinal cord injuries rehabilitation

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Abbreviations

SCI	spinal cord injury
ABT	activity-based therapy
CPGs	central pattern generators
LT	locomotor training
ISNCSCI	International Standards for Neurological Classification of Spinal Cord Injuries
ICF	International Classification of Functioning, Disability and Health
FES	functional electrical stimulation
NMES	neuromuscular electrical stimulation
BWSTT	body weight support treadmill training
WBV	whole body vibration

Introduction

Injuries to the spinal cord result in profound disability and involve many body systems, resulting in severe physiological changes. The most obvious consequence is paralysis, which occurs immediately after injury and may persist throughout life (Harvey, Glinsky, & Bowden, 2016). Paralysis and deconditioning are responsible for reduced mobility and independence and play a significant role in secondary health complications, such as cardiovascular and respiratory dysfunction, metabolic syndrome, bone demineralization, immunosuppression, and musculoskeletal deterioration (Galea, 2012).

Despite all rehabilitation efforts to promote recovery of the injured spinal cord, more than 50% of individuals face long-term disability (Ditunno, 1999). Traditionally, rehabilitation strategies have been successful in improving independence mainly by providing compensatory strategies focused on the use of the preserved muscles above the level of injury and using leverage and momentum to move weak or paralyzed body parts. However, most individuals only have access to physical interventions during the acute and subacute phases of injury through inpatient and outpatient rehabilitation programs (Behrman & Harkema, 2007). After discharge from hospital, most individuals with a spinal cord injury (SCI) face several barriers to continue to exercise and be active in the community, such as lack of specialized professionals, programs, and facilities. Inactivity and sedentary behavior during the chronic phases of injury can lead to decline in mobility and independence and impose a greater risk of developing co-morbidities (Ginis et al., 2011).

The reduction in physical activity levels and the systemic impairments after injury result in a sedentary lifestyle (Wyndaele & Wyndaele, 2006). Sedentary behavior and inactivity are the main risk factors for the development of metabolic and cardiovascular disorders and reduction in muscle strength and aerobic capacity. Therefore, it is necessary to offer specialized physical therapies, exercise programs, sports, and recreation to individuals with SCI to increase their physical activity levels and improve health (Barker et al., 2009).

Over the past years, there has been growing evidence related to the central nervous system plasticity, repair, and regeneration. However, the concept of an irreparable, "hard-wired" nervous system still guides rehabilitation after SCI in most

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Diagnosis and Treatment of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822498-4.00041-5

countries. In general, physical rehabilitation still focuses solely on teaching patients how to achieve day-to-day function by using compensatory strategies and assistive devices, despite significant neurological deficits (Behrman, Bowden, & Nair, 2006).

Activity, defined as both function-specific motor tasks and exercise appears to be a necessity for optimization of functional, metabolic, and neurological status in chronic paralysis (Sadowsky & McDonald, 2009). Exercises that target systems below the level of injury (sensory, musculoskeletal, vascular) are essential to promote recovery after SCI and prevent secondary complications related to paralysis, such as pressure injuries, joint contractures, and pneumonia, promoting a better life (Galea, 2012). And even more important, as the life expectancy after SCI approaches that of the able-bodied population and when the worldwide number of survivors continues to grow to over 2 million people (Fawcett et al., 2007).

The evidence regarding spinal cord plasticity that emerged from animal (Battistuzzo, Callister, Callister, & Galea, 2012) and human studies (Fouad, Krajacic, & Tetzlaff, 2011) and the knowledge that augmented sensory stimulation and repeated active movement can lead to functional improvements (Harkema, Schmidt-Read, Lorenz, Edgerton, & Behrman, 2012) led to the necessity of developing more comprehensive rehabilitative interventions. New interventions focused on functional improvement through neurological recovery aroused. Those interventions were termed Activity-Based Therapies (ABT), and numerous programs emerged globally with the goal of assisting people with SCI at any level or severity to achieve their maximal potential for recovery (Backus, Apple, & Hudson, 2011; Harkema, Behrman, & Barbeau, 2012).

Recovery after spinal cord injuries

The advances in the acute medical management of people with a spinal cord injury (SCI), such as early spinal decompression, pharmacological interventions, and intra-operative temperature management (Kraft, Karpenko, & Rincon, 2016) have been successful in reducing secondary neuronal damage and the extension of the injury, resulting in greater clinical recovery and better outcomes. Neuroprotective strategies have reduced the incidence of complete injuries and have increased the chances for functional recovery.

However, the intrinsic potential for recovery of the spinal cord after injury seems to be limited and not responsive to the conventional treatment strategies. It is well known that during the first weeks, and even months after injury, spontaneous recovery may occur due to the resolution of the swelling and return of the neural activity below the lesion site in response to the acute injury (Marino, Ditunno, Donovan, & Maynard, 1999). Spontaneous motor and sensory recovery have been reported during the first 2 years, with major recovery occurring between 3 and 6 months post-injury (Kirshblum & O'Connor, 1998). Critical factors in determining recovery in the first year after a traumatic SCI include the initial neurological level of injury, initial motor strength and, most importantly, the severity of injury. Kirshblum, Millis, McKinley, and Tulsky (2004) investigated the rate of neurological recovery of 987 individuals with a traumatic SCI during their first 5 years and found small degrees of neurologic recovery between 1 and 5 years, with 5.6% of cases presenting late conversion from a sensorimotor complete to an incomplete lesion status, demonstrating that spinal cord plasticity, similarly to the brain, can persist for many years post-injury.

Substantial functional recovery was seen after SCI in animals in response to training (Fouad & Tse, 2008). The degree of sensorimotor recovery was defined largely by the type and intensity of motor training and sensory stimulation provided following the injury (Edgerton, Tillakaratne, Bigbee, De Leon, & Roy, 2004). Recovery after SCI has been related to the spinal circuits' capacity for automaticity and plasticity. Automaticity is the ability of the spinal cord to perform complex motor tasks without supraspinal inputs and plasticity refers to the ability to recover or change, potentially stimulated by biochemical changes at the cellular level in the spinal cord. There is evidence that plasticity can be induced by physical activity, thus leading to sensorimotor recovery (Lynskey, Belanger, & Jung, 2008). The physiological mechanisms behind spinal cord plasticity are possibly related to changes in the cerebral cortex, growth of new axonal branches, remodeling of synapses, changes in neuronal excitability, and modulation of neurotransmitters in the spinal cord (Edgerton & Roy, 2009).

Training and exercise seem to play an important role in enabling spinal plasticity by inducing changes at the cellular and molecular levels. It is suggested that the spinal cord has the ability to change when the sensory circuits are repeatedly activated (Roy, Harkema, & Edgerton, 2012). This capacity can be due to the activation of complex neuron networks, often termed central pattern generators (CPGs), which are responsible for organizing complex motor movements within the spinal cord.

In humans, similar responses to activity and training have been found, demonstrating the capacity of the human spinal cord to respond to sensory inputs and adapt after injury. Repetitive training is critical for promoting changes to the spinal

networks resulting in functional recovery. Therefore, physical interventions aimed to optimize the neuroplastic mechanisms of the spinal cord are potential tools to promote functional recovery (Edgerton, Kim, Ichiyama, Gerasimenko, & Roy, 2006).

Furthermore, recent studies have shown that approximately 50% of the injuries functionally classified as sensorimotor complete (International Standards for Neurological Classification of Spinal Cord Injury—ISNCSCI A) are actually anatomically incomplete with some degree of preservation of the nervous fibers. This new knowledge unveils the potential for recovery of injuries previously considered immutable, especially in response to interventions aimed at increasing the excitability and activation of the preserved spinal circuitries (Wrigley, Siddall, & Gustin, 2018).

In summary, the scientific findings that support the capacity of the spinal cord to change and recover, even years after injury, warrant that clinicians should employ interventions aimed at the preservation of the function of spinal neuronal circuits under the level of injury as an important condition for regeneration (Dietz & Curt, 2006). The dysfunctional central nervous system (CNS) reorganization and repair are dependent on maintaining an optimal level of neurological activity above and below the site of injury (Sadowsky & McDonald, 2009).

Conventional rehabilitation after spinal cord injuries

Traditionally, management of a person with SCI involves the determination of the person's level of injury and functional capacity, and then the generation of a problem list of activity limitations and prescription for therapies, with the overall goal of having the patient achieve their maximum functional capacity, according to the overall level and severity of neurological injury (Stampas & Tansey, 2014).

Often, clinicians are guided by the World Health Organization International Classification of Functioning, Disability and Health (ICF) framework to assess the rehabilitation needs of people with SCI. The ICF is an integrative and biopsychosocial approach that comprehensively describes the impact of a health condition and health interventions on an individual's functioning. It consists of assessing three domains: (1) Body structure and functioning; (2) Activity limitations; and (3) Participation restrictions (Escorpizo & Bemis-Dougherty, 2015). The ultimate goal of rehabilitation after SCI is to enable the person to return to a productive and satisfying life (Harvey, 2016). Therefore, rehabilitative interventions delivered in the community should focus on strategies to increase activity levels in order to decrease participation restrictions.

Conventional physical rehabilitation aims to restore independence, physical capacity, and community participation, focusing on mobility and self-care (Van Langeveld et al., 2011). Exercise therapy is often employed to the preserved or partially preserved muscles to improve strength, regulate tone and augment muscle length and joint mobility. Moreover, increased fitness, reduced pain and prevention of cardio-metabolic conditions are priorities. Retraining of motor tasks, such as hand and arm function, bed mobility, transfers and wheelchair use, standing, and walking are frequent goals during inpatient rehabilitation (Harvey, Lin, Glinsky, & De Wolf, 2009).

To achieve the rehabilitation goals, therapists rely substantially on providing compensatory strategies focusing on the use of the preserved muscles above the level of injury and using leverage and momentum to teach patients how to move weak or paralyzed body parts. Orthotic devices and modifications to the environment are provided to compensate the loss of function, and the use of the upper limbs is encouraged to substitute for lacking movements of the trunk and lower limbs (Behrman et al., 2006).

While these strategies are effective in increasing mobility, independence and participation (Karimi, Omar, & Fatoye, 2014), they do not target the recovery of the affected areas below the site of injury and do not consider that further functional gains may be possible. They also neglect the need of exercise and activity to the paralyzed areas in order to preserve the body systems below the site of injury and to prevent the deleterious effects of non-use (Galea, 2012). Hence, in the last decades, new physical therapies based on the advances in spinal cord neuroplasticity have emerged, leading to a change in the focus of rehabilitation after SCI from the compensatory model to a recovery-based model (Fig. 1).

Activity-based therapies

Definition

Activity-based therapies (ABTs) are a group of interventions that aim to maximize recovery by focusing on areas above and below the site of injury and this is known as the activity-dependent recovery model (Edgerton & Roy, 2009). ABT employs repetitive task-specific training using weight bearing and external facilitation of neuromuscular activation (Dolbow et al., 2015). In contrast to the traditional approach, ABT interventions aim to drive changes to the nervous and muscular systems

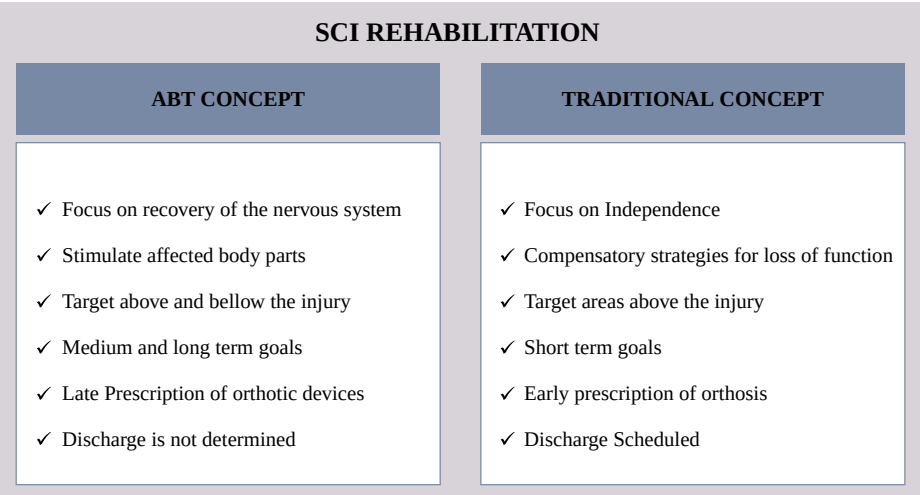

FIG. 1 Differences between the two concepts of rehabilitation in spinal cord injuries.

via repetitive activation of the neuromuscular system above and below the level of injury (Behrman et al., 2006). The key components of ABT interventions that elicit plasticity to the spinal cord are the sensory input, the specificity of the task and the repetitive practice of the task.

Exercise targeted at regions and anatomical structures below the spinal cord injury promoted neuroplastic changes at cellular and biochemical levels in animal models (Roy, Harkema, & Edgerton, 2012) and led to cortical changes in humans with incomplete SCI (Chisholm, Peters, Borich, Boyd, & Lam, 2015). Besides preserving muscle mass and restoring motor and sensory function, exercise can induce synaptic plasticity by increasing the concentration of neurotrophic factors and the number of regenerating neurons (Sandrow-Feinberg & Houle, 2015). This exercise-induced plasticity and the emerging conceptions that the spinal cord has the capacity to undergo plastic changes and control complex movements provide foundation for ABT interventions.

Backus, Apple, and Hudson (2009) defined ABT as "any intervention that specifically uses tools and to improve muscle activation or sensory function below the level of injury in the spinal cord, and does not rely on compensatory mechanisms for improving function after SCI. Such an approach includes interventions that combine intensive active movement with one or more of the following: facilitation techniques (use of tactile or vibratory stimulation; electrical stimulation applied to muscles or nerves (surface or indwelling); body-weight supported locomotor training (manual or robotic); use of upper extremity robotics; or massed-practice training)."

Goals

The general goals of ABT are to optimize the neurological system function to offset the rapid aging, physical deterioration and secondary complications associated with SCI, while promoting functional recovery, increasing autonomy and participation. The ICF framework is used for the decision-making and planning of the rehabilitation program.

Multimodal activity-based therapy

The Reeve Foundation's Neurorecovery Network (NRN) was the pioneer in the research of ABT modalities and its clinical implementation across a network of rehabilitation hospitals and community-based clinics in North America. Other examples of ABT clinics around the world are the NeuroMoves Exercise Programs in Australia, the Acreditando Centre of Neuromotor Recovery in Brazil, and Neurokinex in the United Kingdom.

There is growing evidence on the effects of multimodal ABT delivered in community settings on body structures and function after SCI. Significant improvements in neurological function and walking was reported in chronic individuals with SCI after 6 months of training (Harness, Yozbatiran, & Cramer, 2008). Improvements in sitting balance, general mobility and independence were also found after 3–9 months of ABT delivered in the community to individuals with chronic SCI (Quel de Oliveira, Refshauge, Middleton, de Jong, & Davis, 2017). Furthermore, the various components of ABT (i.e., FES,

activities in load bearing and muscle strengthening above and below the level of injury) reversed negative body composition changes after SCI, resulting in the reduction of risk of cardiovascular and other metabolic diseases (Dolbow et al., 2015).

Community-based ABT clinics and gyms deliver multimodal exercise programs individually tailored to the clients' goals and functional abilities by an exercise physiologist or physiotherapist. Exercises target whole-body strengthening and are performed out of the wheelchair and in positions where load bearing is applied to the paralyzed extremities (e.g., standing, 4-point kneeling). The exercise programs usually involve a combination of (1) activation of motor patterns (locomotor training, and functional electrical stimulation (FES) associated with ergometry); (2) non-standardized motor activation (recruitment, strengthening, and training of specific tasks); and (3) sensory stimulation (sensorimotor training, and body vibration on vibrating platforms) (Sadowsky & McDonald, 2009). Those interventions are discussed in more detail next.

Locomotor and gait training

Locomotor training (LT) aims to improve sensory, motor and autonomic functioning, health and quality of life. The main focus is to promote recovery of postural control and walking after SCI. LT is based on the principles derived from studies using animal models that demonstrated recovery of the ability to weight bear on the hind limbs and walk after exposure to repetitive step training (i.e., by training for the specific motor task) (Harkema, Hillyer, et al., 2012).

The LT protocol developed by the NeuroRecovery Network involves the use of an overhead body-weight support system attached to a harness where the individual is suspended over a treadmill. Trained therapists facilitate control of balance and manually assist trunk and leg movements during stepping and standing to generate sensory information that is consistent with locomotion (Fig. 2A). In conjunction with the body-weight supported treadmill training, LT programs usually include an overground training component, where activity limitations are assessed and task-specific training incorporating sensory feedback is performed outside the body-weight support system with the aim to contribute to functional recovery (Behrman et al., 2005; Harkema, Schmidt-Read, Behrman, et al., 2012).

LT is the most investigated ABT intervention to date and there is mounting evidence of its benefits after acute and chronic SCI. A large number of studies have investigated the effects of LT on walking ability in individuals with incomplete SCI and have demonstrated improvements in walking speed, distance and coordination (Adams & Hicks, 2011; Dobkin et al., 2006; Field-Fote & Roach, 2011). Moreover, neurological recovery has been reported through studies that showed increments in lower extremity motor score and ISNCSCI classification after LT (Anwer et al., 2014). Gains in balance, functional mobility and independence were also reported (Alexeeva et al., 2011).

LT can also be deployed as an exercise modality to improve general health after complete and incomplete SCI. Improvements in cardiorespiratory health (Jeffries et al., 2015), reversal of muscle atrophy (Giangregorio et al., 2006), and enhanced autonomic function related to blood pressure control have been reported after LT (Harkema, Ferreira, Van Den Brand, & Krassioukov, 2008).

FIG. 2 Examples of locomotor and gait training. (A) Body-weight support treadmill locomotor training, (B) body-weight support overground gait training, (C) overground gait training with walker and assistance, (D) overground gait training in parallel bars and assistance, (E) overground gait training with crutches and supervision.

Although LT has demonstrated to be beneficial for individuals with SCI, the training volume required to achieve significant gains is high, ranging from 4 to 5 times per week for 1.5 h per session. Hence, its application in community rehabilitation settings is not always feasible due to the challenges in maintaining adherence and the financial burden to the participants. Therefore, community-based clinics often offer multimodal ABT programs, where LT can be a component of the rehabilitation program. It is worth noting that LT is also employed as a training strategy with the overall aim is to promote neurological recovery and health benefits. The goal may not always be related to walking.

Task-specific gait training strategies are also employed in ABT programs with the aim to promote functional recovery of walking. Similarly to traditional rehabilitation, ABT programs may use external assistance, walking aids and orthotic devices to retrain walking according to the client's abilities and functional goals, as illustrated in Fig. 2B–E. However, in ABT, the prescription of orthotic devices and walking aids is delayed, when compared to traditional rehabilitation, and will occur only when the strategies for recovery are exhausted and the recovery of motor function is not achieved. LT and other modalities of gait training can be used in ABT programs as a form of whole-body exercise with the aim of improving gross motor function (when walking is not a goal), and cardiovascular fitness due to the physiological benefits of moving in the upright position.

Neuromuscular electrical stimulation (NMES) and functional electrical stimulation (FES)

When applied to certain body systems, electrical currents have the property of eliciting an electrical response in different cells, such as muscle and neurons. Over the years, novel currents and devices have been developed to safely elicit a neurological response, such as muscle contraction, in paralyzed or weakened muscles to assist individuals with different medical conditions, including SCI, to gain muscle strength and reverse the deleterious effects of paralysis.

Neuromuscular stimulation (NMES) is the technical name used when electric current is used to reduce deficits resulting from clinical conditions, such as non-use. NMES can increase the individuals' participation in voluntary activities producing contractions of the paralyzed muscles that are still innervated, and as a result can improve muscle trophism, strength, and tone (Marquez-Chin & Popovic, 2020).

Functional electrical stimulation (FES) is a subtype of NMES, in which the stimulation of a nerve or a paralyzed muscle promotes assistance to specific and functional movement such as cycling as illustrated in Fig. 3A, assisted walking (Fig. 3B) or grasping (Fig. 3C and D). FES and other types of neuromuscular electrical stimulation improve blood circulation, range of motion, muscle strength and endurance, and reduce spasticity, atrophy and loss of bone mineral density, while increasing metabolism and cardiorespiratory function (Luo, Xu, Zuo, Liu, & All, 2020; Martin, Sadowsky, Obst, Meyer, & McDonald, 2012).

FIG. 3 Applications of functional electrical stimulation (FES). (A) FES associated with cycling. (B) FES associated with gait training. (C and D) FES associated with grasping.

Due to the evidence on the benefits of the use of electrical stimulation in people with complete and incomplete SCI, this modality is frequently used in ABT programs to increase the activation and strength of the paralyzed or partially paralyzed muscles to promote recovery of function and mobility. Furthermore, when simultaneously applied to multiple large paralyzed muscles, it increases energy consumption and cardiac output and therefore, can be used as a cardiovascular fitness modality in people with severe paralysis.

Developmental postures: Weight-bearing activities

Developmental sequencing is focused on strengthening the primary stabilizing muscles of the trunk and pelvis because of their role in axial stability; this approach involves training in various positions and contributes to better posture, increased trunk control, general mobility (including upright function and walking) and independence. These include activities performed in quadruped (on all fours), kneeling, sitting, and standing (Jones et al., 2014), as illustrated in Fig. 4. Movements and positions are designed to mimic the human developmental process and to allow weight bearing to the paralyzed or partially paralyzed limbs. Weight bearing, especially in standing can improve bowel and bladder function, bone mineral density and joint range of motion; prevent pressure injuries and muscle contractures; enhance autonomic and cardiovascular function (Can, Dosoglu, Karacan, & Karamehmetoglu, 2007); reduce spasticity (Adams & Hicks, 2011); and improve motor function and quality of life.

Vibration

Whole-body vibration (WBV), using vibratory platforms, is commonly used as an exercise or therapeutic tool with numerous benefits for the musculoskeletal system in both able-bodied and clinical populations. In ABT, it is commonly associated with developmental postures and standing (Fig. 5) with the goal to improve spasticity and muscle activation (Ji et al., 2017), proprioception, balance and functional activities such as standing and walking (In, Jung, Lee, & Cho, 2018).

Strength and aerobic training

Strength and aerobic training are essential to prevent clinical complications and promote health in general populations as well as in SCI (Valent, Dallmeijer, Houdijk, Talsma, & van der Woude, 2007). The physical activity guidelines for people with SCI recommends that individuals should engage in aerobic training activities at least 2 days per week (minimum of 20 min continuously) and perform strengthening exercises with every functioning muscle group; both modalities should be exerted at moderate-to-vigorous intensity. In order to exercise safely and effectively, it is important to adapt body positions and equipment according to the individual's level of functionality as demonstrated in Figs. 6 and 7 (Tweedy et al., 2017). Regarding the type of aerobic fitness exercises, arm/leg cycling and wheelchair propulsion training with/without functional electrical stimulation (FES) have been recommended. Also, progressive resistance training, alone or in combination with FES, has shown to increase muscle strength in individuals with SCI (Eitivipart, de Oliveira, Arora, Middleton, & Davis, 2019).

FIG. 4 Developmental Postures. Exercises in load bearing positions. (A) Prone. (B) Quadruped. (C) Kneeling. (D) Standing.

FIG. 5 Examples of whole body vibration (WBV) exercises. (A) WBV for trunk control in sitting. (B) WBV in kneeling. (C) WBV in standing.

FIG. 6 Examples of aerobic exercises. (A) Battle rope in standing. (B) Adapted rowing. (C) Upper limb cycle ergometer.

For this reason, most ABT programs in the community include progressive resistance training and aerobic activities as part of the exercise routine. The exercises are performed mainly out of the wheelchair with engagement of the body parts below the site of injury via load bearing (Fig. 6A), FES (Fig. 3A) or body-weight supported treadmill training (Fig. 2A).

Active and active-assisted exercises

In the body parts where clients have little to no voluntary movement, ABT therapists employ active or active-assisted exercises using facilitation strategies such as: manual guidance, gravity eliminated positions, suspension of the limb, reduction of friction and lever. Therapists help the client through different ranges of motion while assisting or providing resistance

FIG. 7 Examples of strengthening exercise. (A) Exercise using elastic resistance. (B) Exercise using free weights. (C) Exercise using weight training machine.

less than gravity, according to the client's control of the body segment. Clients are instructed to attempt or visualize actively assisting or resisting the movement performed, even when voluntary movement is not possible. Active-assisted exercises attempt to provide sensory stimulus and elicit a motor response, even if minimal, with the goal of generating neural activity, and ultimately, using a high number of repetitions, achieving long-term neural potentiation (Jones et al., 2012).

Dosage

High volumes of training (i.e., frequency and duration) have shown to promote motor learning and skill acquisition for people with neurological conditions (Waddell, Birkenmeier, Moore, Hornby, & Lang, 2014), and therefore facilitate neuroplastic mechanisms. Unlike conventional rehabilitation, ABT interventions require high-volume practice, involving a high number of repetitions and high frequency (Behrman et al., 2006; Edgerton, Kim, Ichiyama, Gerasimenko, & Roy, 2006). ABT performed for 2 to 5 h per day at a frequency of three to five times per week produced benefits in participants with chronic SCI that included improved lower limb muscle strength, balance, mobility, increased gait speed, symmetry, and endurance in participants with chronic SCI (Behrman & Harkema, 2007).

Assessment and outcome measures

SCI has a vast range of clinical features leading to high variability in the classification, which reduces the ability to test the therapeutic efficacy of an intervention accurately (Behrman et al., 2012). There is a critical need to develop valid, reliable, and sensitive scales and assessments to be used in many aspects of rehabilitation of people with SCI, as well as for carrying out patient-centered clinical trials. The lack of more specific scales to assess mobility, functional independence, and quality of life may prevent the detection of changes after an intervention. There is a need to create new tools that are more sensitive to functional gains and changes in movements to assess the effects of programs that are aimed at recovery of function, such as ABT, especially in the chronic phase (Padula et al., 2015; Wilson & Fehlings, 2021).

Community ABT programs often employ multiple tools to assess the individual holistically, using the ICF framework to monitor the effects of the program overtime. Some examples of commonly measures to assess body function and structure in ABT programs are: muscle strength (manual muscle testing, 10 repetition maximum); muscle tone (Modified Ashworth and Tardieu Scales), range of motion, sensation (proprioception, pin prick, light touch). It is essential to also include measures of activity limitations and participation restrictions that are valid to the SCI population (Gaspar, Padula, Freitas, de Oliveira, & Torriani-Pasin, 2019). Some examples of measures of activity limitations are: Spinal Cord Injury Independence Measure (SCIM) and the Walking Index for Spinal Cord Injuries (WISCI). The Community Integration Questionnaire and the Quality of life Index can be used to assess participation outcomes in people with SCI engaging in ABT programs.

The NeuroRecovery Network advises the use of the NeuroRecovery Scale (NRS) to assess recovery and monitor the effects of ABT programs, especially locomotor training. It is an 11-item scale that assesses the quality of movement without compensatory movement patterns by comparing sitting, walking, standing and transfers to typical movement (Harkema, Shogren, Ardolino, & Lorenz, 2016). Development of measures, such as the NRS, is particularly relevant because rehabilitation strategies are encompassing ABT and will soon partner with regenerative medicine to advance neuromuscular recovery post-injury (Behrman et al., 2012; Tester et al., 2016).

Practical aspects of ABT in the community

Most of the ABT training programs are staffed by physiotherapists and exercise specialists. A client entering the program is evaluated by a clinician who designs and implements an ABT program based on their level of injury, strength, skills, personal goals, preferences (Jones et al., 2014), and segments to be stimulated (tetraplegia—exercises for the upper limbs, trunk, and lower limbs and paraplegia—exercises for the trunk and lower limbs) (Padula et al., 2015).

Jones et al. (2014) developed algorithms to guide decision-making and progression of ABT interventions, especially locomotor training. The algorithms include muscle tone, trunk control and gait ability, taking into consideration the client's functional status to prescribe the type, duration and combination of interventions. Thus, individuals with greater deficits receive activities with greater assistance, such as active-assisted exercises, and spend more hours in developmental postures (i.e., standing in a standing frame or with manual guidance from a therapist), while individuals with better functional status, spend most of the time performing activities with less external assistance and less aids.

In conclusion, considering the literature about the needs and objectives of rehabilitation and physical monitoring of people with SCI living in the community, as well as the evidence of the benefits of ABT interventions, a multi-modal ABT program seems to be an appropriate exercise program for this population. Studies that evaluated the effects of a multimodal program within the approach, demonstrated positive results in promoting functional recovery and activity as well as in the prevention and treatment of common comorbidities in this population. Since ABT is a novel approach, with a constantly evolving literature, more studies and protocols are needed to improve assessments, program designs and dosage, while considering the heterogeneity of the population with SCI.

Applications to other areas of neuroscience

In this chapter, we addressed the principles of activity-based therapy and its applicability in the rehabilitation of the people with chronic spinal cord injuries living in the community. However, the same principles apply to in-hospital rehabilitation for individuals in the acute and subacute phases of injury. It's worth noting that activity-based therapy is currently applied to people with other neurological injuries such as traumatic brain injury, stroke, cerebral palsy and multiple sclerosis. Activity-based therapy principles and practices may have similar benefits to conditions such as spina bifida and transverse myelitis, although research in other conditions is still scarce.

Fundamentals of neuroplasticity (intensity, repetition and specificity) form the basis for activity-based therapies. Neuroscientists and neurophysiologists should further investigate the mechanisms of plasticity and adaptability of the spinal cord after injury in order to further develop activity-based therapies, explore its optimal dosage and maximize recovery after spinal cord injuries. Moreover, activity-based therapy seems to be crucial to optimize the effects of upcoming regenerative interventions and treatments, such as stem cells (Belegu, Oudega, Gary, & McDonald, 2007) and epidural stimulation (Rejc, Angeli, Atkinson, & Harkema, 2017) in reversing paralysis and other deleterious consequences from an SCI. It is important to highlight that maintaining a healthy lifestyle and a healthy muscular, nervous and vascular system through exercising below the injury may be a key factor for eligibility and success of those novel regenerative strategies.

Overall, we have gathered information on clinical practice to guide rehabilitation professionals (physicians, physiotherapists, occupational therapists, and exercise physiologists) and academics in their decision-making and understanding of this novel intervention.

Mini dictionary of terms:

Metabolic syndrome: Group of risk factors that raises one's risk for heart disease and other health problems, such as diabetes and stroke.

Compensatory strategies: Environmental modifications or behavioral strategies designed to bypass a persistent impairment. I.e.: use of the arms to transfer in the presence of lower limb paralysis.

Plasticity (neuroplasticity): The ability of the nervous system to form and reorganize synaptic connections, especially in response to learning or experience or following injury.
Orthotic devices: Braces that help support weakened muscles during a functional task such as walking.
Body function and structure: According to the World Health Organization's International Classification of Functioning, Disability and Health, body structure and function refer to impairments related to the physiological functions of body systems and/or to the anatomical parts of the body such as organs, limbs and their components.
Activity limitations: According to the World Health Organization's International Classification of Functioning, Disability and Health, activity limitations refer to difficulties an individual may have in executing activities (task or action).
Participation restrictions: According to the World Health Organization's International Classification of Functioning, Disability and Health, participation restrictions refer to the problems an individual may experience in involvement in life situations.
Transcutaneous electrical stimulation (TENS): Therapy that involves the use of low-voltage electric currents to treat pain.
Task-specific training: Treatment approach focused on function that evolved out of the movement science and motor learning literature. The basic premise is goal-directed practice of functional tasks instead of focusing on impairment reduction exercises.
Neurotrophic factors: Endogenous substances that control cell proliferation and differentiation in the nervous system.

Key facts of activity-based therapy in the community

- Activity-based therapy is a novel concept of rehabilitation of spinal cord injury.
- Activity-based therapy is focused on the recovery of function to the areas affected by the injury.
- Locomotor training, exercises in weight bearing, electrical stimulation and whole-body strengthening exercises, are modalities that compose an activity-based therapy program.
- Activity-based therapies have shown to improve motor and sensory function for acute and chronic spinal cord injury population.
- Activity-based therapies also seem to have a role in reduction of co-morbidities related to paralysis and sedentary behavior.

Summary points

- Spinal cord injury is a condition that results in motor, sensory and systemic dysfunction that reduces mobility, independence, quality of life, and general health status.
- The main objectives of conventional rehabilitation are independence and functionality, targeting areas above the level of injury through compensatory strategies for loss of function.
- In recent years, there has been an increase in scientific evidence on the spinal cord neuroplasticity, showing that interventions that stimulate below the level of injury, such as locomotor training, are effective strategies for functional recovery.
- Activity-based therapy is a novel concept of rehabilitation with a focus on recovery of the damaged nervous system, using activities that stimulate the segments affected by the injury.
- Activity-based therapy employs different modalities in an intensive, holistic, and individualized program.
- It includes multiple interventions for the spinal cord injury population, such as Locomotor Training, Functional Electrical Stimulation, Whole-Body Vibration, developmental postures, strength, and aerobic exercises.
- There is scientific evidence to support the effects of activity-based therapies on functional recovery, participation, quality of life and reduction of secondary complications.
- The activity-based therapy concept can be used in hospital-based or community-based settings and has the potential to optimize the effects of new regenerative interventions such as stem cells and epidural stimulation.

References

Adams, M. M., & Hicks, A. L. (2011). Comparison of the effects of body-weight-supported treadmill training and tilt-table standing on spasticity in individuals with chronic spinal cord injury. *The Journal of Spinal Cord Medicine*, *34*(5), 488–494.

Alexeeva, N., Sames, C., Jacobs, P. L., Hobday, L., di Stasio, M. M., Mitchell, S. A., et al. (2011). Comparison of training methods to improve walking in persons with chronic spinal cord injury: A randomized clinical trial. *The Journal of Spinal Cord Medicine*, *34*(4), 362–379.

Anwer, S., Equebal, A., Palekar, T. J., Nezamuddin, M., Neyaz, O., & Alghadir, A. (2014). Effect of locomotor training on motor recovery and walking ability in patients with incomplete spinal cord injury: A case series. *Journal of Physical Therapy Science*, *26*(6), 951–953.

Backus, D., Apple, D., & Hudson, L. (2009). Systematic review of activity-based interventions to improve neurological outcomes after SCI January 1998—March 2009. In *Disability Research Right to Know*. http://www.bu.edu/drrk/research-syntheses/spinal-cord-injuries/activity-based-interventions.

Backus, D., Apple, D., & Hudson, L. (2011). Neural and functional outcomes after lower extremity and walking activity-based interventions for persons with spinal cord injury: A research synthesis. *Topics in Spinal Cord Injury Rehabilitation*, *16*(65).

Barker, R. N., Kendall, M. D., Amsters, D. I., Pershouse, K. J., Haines, T. P., & Kuipers, P. (2009). The relationship between quality of life and disability across the lifespan for people with spinal cord injury. *Spinal Cord*, *47*(2), 149–155.

Battistuzzo, C. R., Callister, R. J., Callister, R., & Galea, M. P. (2012). A systematic review of exercise training to promote locomotor recovery in animal models of spinal cord injury. *Journal of Neurotrauma*, *29*(8), 1600–1613.

Behrman, A. L., Ardolino, E., Vanhiel, L. R., Kern, M., Atkinson, D., Lorenz, D. J., & Harkema, S. J. (2012). Assessment of functional improvement without compensation reduces variability of outcome measures after human spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *93*(9), 1518–1529.

Behrman, A. L., Bowden, M. G., & Nair, P. M. (2006). Neuroplasticity after spinal cord injury and training: An emerging paradigm shift in rehabilitation and walking recovery. *Physical Therapy*, *86*(10), 1406–1425.

Behrman, A. L., & Harkema, S. J. (2007). Physical rehabilitation as an agent for recovery after spinal cord injury. *Physical Medicine and Rehabilitation Clinics of North America*, *18*(2), 183–202.

Behrman, A. L., Lawless-Dixon, A. R., Davis, S. B., Bowden, M. G., Nair, P., Phadke, C., et al. (2005). Locomotor training progression and outcomes after incomplete spinal cord injury. *Physical Therapy*, *85*(12), 1356–1371.

Belegu, V., Oudega, M., Gary, D. S., & McDonald, J. W. (2007). Restoring function after spinal cord injury: Promoting spontaneous regeneration with stem cells and activity-based therapies. *Neurosurgery Clinics of North America*, *18*(1), 143–168 (xi).

Can, A., Dosoglu, M. S., Karacan, I., & Karamehmetoglu, S. (2007). Effect of axial loading on bone mineral density in patients with traumatic spinal cord injury. *Ulusal Travma ve Acil Cerrahi Dergisi*, *13*(2), 101–105.

Chisholm, A. E., Peters, S., Borich, M. R., Boyd, L. A., & Lam, T. (2015). Short-term cortical plasticity associated with feedback-error learning after locomotor training in a patient with incomplete spinal cord injury. *Physical Therapy*, *95*(2), 257–266.

Dietz, V., & Curt, A. (2006 Aug). Neurological aspects of spinal-cord repair: Promises and challenges. *Lancet Neurology*, *5*(8), 688–694.

Ditunno, J. F., Jr. (1999). Predicting recovery after spinal cord injury: A rehabilitation imperative. *Archives of Physical Medicine and Rehabilitation*, *80*(4), 361–364.

Dobkin, B., Apple, D., Barbeau, H., Basso, M., Behrman, A., Deforge, D., et al. (2006). Weight-supported treadmill vs over-ground training for walking after acute incomplete SCI. *Neurology*, *66*(4), 484–493.

Dolbow, D. R., Gorgey, A. S., Recio, A. C., Stiens, S. A., Curry, A. C., Sadowsky, C. L., et al. (2015). Activity-based restorative therapies after spinal cord injury: Inter-institutional conceptions and perceptions. *Aging and Disease*, *6*(4), 254–261.

Edgerton, V. R., Kim, S. J., Ichiyama, R. M., Gerasimenko, Y. P., & Roy, R. R. (2006). Rehabilitative therapies after spinal cord injury. *Journal of Neurotrauma*, *23*(3–4), 560–570.

Edgerton, V. R., & Roy, R. R. (2009). Activity-dependent plasticity of spinal locomotion: Implications for sensory processing. *Exercise and Sport Sciences Reviews*, *37*(4), 171–178.

Edgerton, V. R., Tillakaratne, N. J. K., Bigbee, A. J., De Leon, R. D., & Roy, R. R. (2004). Plasticity of the spinal neural circuitry after injury. *Annual Review of Neuroscience*, 145–167.

Eitivipart, A. C., de Oliveira, C. Q., Arora, M., Middleton, J., & Davis, G. M. (2019). Overview of systematic reviews of aerobic fitness and muscle strength training after spinal cord injury. *Journal of Neurotrauma*, *36*(21), 2943–2963.

Escorpizo, R., & Bemis-Dougherty, A. (2015). Introduction to special issue: A review of the international classification of functioning, disability and health and physical therapy over the years. *Physiotherapy Research International*, *20*(4), 200–209.

Fawcett, J. W., Curt, A., Steeves, J. D., Coleman, W. P., Tuszynski, M. H., Lammertse, D., … Short, D. (2007). Guidelines for the conduct of clinical trials for spinal cord injury as developed by the ICCP panel: Spontaneous recovery after spinal cord injury and statistical power needed for therapeutic clinical trials. *Spinal Cord*, *45*(3), 190–205.

Field-Fote, E. C., & Roach, K. E. (2011). Influence of a locomotor training approach on walking speed and distance in people with chronic spinal cord injury: A randomized clinical trial. *Physical Therapy*, *91*(1), 48–60.

Fouad, K., Krajacic, A., & Tetzlaff, W. (2011). Spinal cord injury and plasticity: Opportunities and challenges. *Brain Research Bulletin*, *84*(4–5), 337–342.

Fouad, K., & Tse, A. (2008). Adaptive changes in the injured spinal cord and their role in promoting functional recovery. *Neurological Research*, *30*(1), 17–27.

Galea, M. P. (2012). Spinal cord injury and physical activity: Preservation of the body. *Spinal Cord*, *50*(5), 344–351.

Gaspar, R., Padula, N., Freitas, T. B., de Oliveira, J. P. J., & Torriani-Pasin, C. (2019). Physical exercise for individuals with spinal cord injury: Systematic review based on the international classification of functioning, disability, and health. *Journal of Sport Rehabilitation*, *28*(5), 505–516.

Giangregorio, L. M., Webber, C. E., Phillips, S. M., Hicks, A. L., Craven, B. C., Bugaresti, J. M., et al. (2006). Can body weight supported treadmill training increase bone mass and reverse muscle atrophy in individuals with chronic incomplete spinal cord injury? *Applied Physiology, Nutrition, and Metabolism*, *31*(3), 283–291.

Ginis, K. A., Hicks, A. L., Latimer, A. E., Warburton, D. E., Bourne, C., Ditor, D. S., … Wolfe, D. L. (2011). The development of evidence informed physical activity guidelines for adults with spinal cord injury. *Spinal Cord*, *49*, 1088–1096.

Harkema, S., Behrman, A., & Barbeau, H. (2012). Evidence-based therapy for recovery of function after spinal cord injury. *The Hand*, *109*, 259–274.

Harkema, S. J., Ferreira, C. K., Van Den Brand, R. J., & Krassioukov, A. V. (2008). Improvements in orthostatic instability with stand locomotor training in individuals with spinal cord injury. *Journal of Neurotrauma*, *25*(12), 1467–1475.

Harkema, S. J., Hillyer, J., Schmidt-Read, M., Ardolino, E., Sisto, S. A., & Behrman, A. L. (2012). Locomotor training: As a treatment of spinal cord injury and in the progression of neurologic rehabilitation. *Archives of Physical Medicine and Rehabilitation*, *93*(9), 1588–1597.

Harkema, S. J., Schmidt-Read, M., Behrman, A. L., Bratta, A., Sisto, S. A., & Edgerton, V. R. (2012). Establishing the NeuroRecovery network: Multisite rehabilitation centers that provide activity-based therapies and assessments for neurologic disorders. *Archives of Physical Medicine and Rehabilitation*, *93*(9), 1498–1507.

Harkema, S. J., Schmidt-Read, M., Lorenz, D. J., Edgerton, V. R., & Behrman, A. L. (2012). Balance and ambulation improvements in individuals with chronic incomplete spinal cord injury using locomotor training-based rehabilitation. *Archives of Physical Medicine and Rehabilitation*, *93*(9), 1508–1517.

Harkema, S. J., Shogren, C., Ardolino, E., & Lorenz, D. J. (2016). Assessment of functional improvement without compensation for human spinal cord injury: Extending the neuromuscular recovery scale to the upper extremities. *Journal of Neurotrauma*, *33*(24), 2181–2190.

Harness, E. T., Yozbatiran, N., & Cramer, S. C. (2008). Effects of intense exercise in chronic spinal cord injury. *Spinal Cord*, *46*(11), 733–737.

Harvey, L. A. (2016). Physiotherapy rehabilitation for people with spinal cord injuries. *Journal of Physiotherapy*, *62*(1), 4–11.

Harvey, L. A., Glinsky, J. V., & Bowden, J. L. (2016). The effectiveness of 22 commonly administered physiotherapy interventions for people with spinal cord injury: A systematic review. *Spinal Cord*, *54*(11), 914–923.

Harvey, L. A., Lin, C. W. C., Glinsky, J. V., & De Wolf, A. (2009). The effectiveness of physical interventions for people with spinal cord injuries: A systematic review. *Spinal Cord*, *47*(3), 184–195.

In, T., Jung, K., Lee, M. G., & Cho, H. Y. (2018). Whole-body vibration improves ankle spasticity, balance, and walking ability in individuals with incomplete cervical spinal cord injury. *NeuroRehabilitation*, *42*(4), 491–497.

Jeffries, E. C., Hoffman, S. M., de Leon, R., Dominguez, J. F., Semerjian, T. Z., Melgar, I. A., et al. (2015). Energy expenditure and heart rate responses to increased loading in individuals with motor complete spinal cord injury performing body weight-supported exercises. *Archives of Physical Medicine and Rehabilitation*, *96*(8), 1467–1473.

Ji, Q., He, H., Zhang, C., Lu, C., Zheng, Y., Luo, X. T., & He, C. (2017). Effects of whole-body vibration on neuromuscular performance in individuals with spinal cord injury: A systematic review. *Clinical Rehabilitation*, *31*(10), 1279–1291.

Jones, M. L., Evans, N., Tefertiller, C., Backus, D., Sweatman, M., Tansey, K., & Morrison, S. (2014). Activity-based therapy for recovery of walking in individuals with chronic spinal cord injury: Results from a randomized clinical trial. *Archives of Physical Medicine and Rehabilitation*, *95*(12), 2239.

Jones, M. L., Harness, E., Denison, P., Tefertiller, C., Evans, N., & Larson, C. A. (2012). Activity-based therapies in spinal cord injury: Clinical focus and empirical evidence in three independent programs. *Topics in Spinal Cord Injury Rehabilitation*, *18*(1), 34–42.

Karimi, M., Omar, A. H., & Fatoye, F. (2014). Spinal cord injury rehabilitation: Which way forward? *NeuroRehabilitation*, *35*(2), 325–340.

Kirshblum, S., Millis, S., McKinley, W., & Tulsky, D. (2004). Late neurologic recovery after traumatic spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *85*(11), 1811–1817.

Kirshblum, S. C., & O'Connor, K. C. (1998). Predicting neurologic recovery in traumatic cervical spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *79*(11), 1456–1466.

Kraft, J., Karpenko, A., & Rincon, F. (2016). Intraoperative targeted temperature management in acute brain and spinal cord injury. *Current Neurology and Neuroscience Reports*, *16*(2), 18.

Luo, S., Xu, H., Zuo, Y., Liu, X., & All, A. H. (2020). A review of functional electrical stimulation treatment in spinal cord injury. *Neuromolecular Medicine*, *22*(4), 447–463.

Lynskey, J. V., Belanger, A., & Jung, R. (2008). Activity-dependent plasticity in spinal cord injury. *Journal of Rehabilitation Research and Development*, *45*(2), 229–240.

Marino, R. J., Ditunno, J. F., Jr., Donovan, W. H., & Maynard, F., Jr. (1999). Neurologic recovery after traumatic spinal cord injury: Data from the model spinal cord injury systems. *Archives of Physical Medicine and Rehabilitation*, *80*(11), 1391–1396.

Marquez-Chin, C., & Popovic, M. R. (2020). Functional electrical stimulation therapy for restoration of motor function after spinal cord injury and stroke: A review. *Biomedicine Engineering Online*, *19*(1), 34.

Martin, R., Sadowsky, C., Obst, K., Meyer, B., & McDonald, J. (2012). Functional electrical stimulation in spinal cord injury: From theory to practice. *Topics in Spinal Cord Injury Rehabilitation*, *18*(1), 28–33.

Padula, N., Costa, M., Batista, A., Gaspar, R., Motta, C., Palma, G., et al. (2015). Long-term effects of an intensive interventional training program based on activities for individuals with spinal cord injury: A pilot study. *Physiotherapy Theory and Practice*, *31*(8), 568–574.

Quel de Oliveira, C., Refshauge, K., Middleton, J., de Jong, L., & Davis, G. M. (2017). Effects of activity-based therapy interventions on mobility, independence, and quality of life for people with spinal cord injuries: A systematic review and meta-analysis. *Journal of Neurotrauma*, *34*(9), 1726–1743.

Rejc, E., Angeli, C. A., Atkinson, D., & Harkema, S. J. (2017). Motor recovery after activity-based training with spinal cord epidural stimulation in a chronic motor complete paraplegic. *Scientific Reports*, *7*(1), 13476.

Roy, R. R., Harkema, S. J., & Edgerton, R. (2012). Basic concepts of activity-based interventions for improved recovery of motor function after spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *93*(9), 1487–1497.

Sadowsky, C. L., & McDonald, J. W. (2009). Activity-based restorative therapies: Concepts and applications in spinal cord injury-related neurorehabilitation. *Developmental Disabilities Research Reviews*, *15*(2), 112–116.

Sandrow-Feinberg, H. R., & Houle, J. D. (2015). Exercise after spinal cord injury as an agent for neuroprotection, regeneration and rehabilitation. *Brain Research*, *1619*, 12–21.

Stampas, A., & Tansey, K. E. (2014). Spinal cord injury medicine and rehabilitation. *Seminars in Neurology*, *34*(5), 524–533.

Tester, N. J., Lorenz, D. J., Suter, S. P., Buehner, J. J., Falanga, D., Watson, E., … Michele Basso, D. (2016). Responsiveness of the neuromuscular recovery scale during outpatient activity-dependent rehabilitation for spinal cord injury. *Neurorehabilitation and Neural Repair*, *30*(6), 528–538.

Tweedy, S. M., Beckman, E. M., Geraghty, T. J., Theisen, D., Perret, C., Harvey, L. A., & Vanlandewijck, Y. C. (2017). Exercise and sports science Australia (ESSA) position statement on exercise and spinal cord injury. *Journal of Science and Medicine in Sport*, *20*(2), 108–115.

Valent, L., Dallmeijer, A., Houdijk, H., Talsma, E., & van der Woude, L. (2007). The effects of upper body exercise on the physical capacity of people with a spinal cord injury: A systematic review. *Clinical Rehabilitation*, *21*(4), 315–330.

Van Langeveld, S. A., Post, M. W., van Asbeck, F. W., Gregory, M., Halvorsen, A., Rijken, H., et al. (2011). Comparing content of therapy for people with a spinal cord injury in postacute inpatient rehabilitation in Australia, Norway, and the Netherlands. *Physical Therapy*, *91*(2), 210–224.

Waddell, K. J., Birkenmeier, R. L., Moore, J. L., Hornby, T. G., & Lang, C. E. (2014). Feasibility of high-repetition, task-specific training for individuals with upper-extremity paresis. *American Journal of Occupational Therapy*, *68*(4), 444–453.

Wilson, J. R., & Fehlings, M. G. (2021). Management strategies to optimize clinical outcomes after acute traumatic spinal cord injury: Integration of medical and surgical approaches. *Journal of Neurosurgical Sciences*, *56*(1), 1–11.

Wrigley, P. J., Siddall, P. J., & Gustin, S. M. (2018). New evidence for preserved somatosensory pathways in complete spinal cord injury: A fMRI study. *Human Brain Mapping*, *39*(1), 588–598.

Wyndaele, M., & Wyndaele, J. J. (2006). Incidence, prevalence and epidemiology of spinal cord injury: What learns a worldwide literature survey? *Spinal Cord*, *44*(9), 523–529.

Chapter 42

Mobile health apps and self-management for spinal cord injury rehabilitation

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Abbreviations

SCI	spinal cord injury
mHealth	mobile health
eHealth	electronic health
PA	physical activity
SUS	system usability scale

Introduction

For individuals living with spinal cord injury (SCI), inadequate health management can result in adverse psychological and physical health outcomes including autonomic dysreflexia, pressure sores, bowel and bladder dysfunction, depression, and spasticity (Adriaansen et al., 2016). Learning to self-manage health, i.e., symptoms, treatment, and lifestyle changes inherent to living with a chronic condition, has been shown to reduce the severity and prevalence of secondary conditions among those with chronic health condition (Barlow, Wright, Sheasby, Turner, & Hainsworth, 2002; Mortenson et al., 2019). Recent advancements in smartphone technology have resulted in consumers becoming more actively engaged with using mobile health (mHealth) apps to manage their day-to-day health (Gill, Kamath, & Gill, 2012). Because of the widespread adoption of smartphones and tablets, mHealth has the potential to become an accessible, low-cost approach of self-management intervention delivery (Lewis, Boissaud-Cooke, Aungst, & Eysenbach, 2014). This chapter provides insight into the implementation of mHealth apps for the self-management and prevention of secondary conditions related to SCI. Specifically, this chapter will (1) provide background on chronic disease management, (2) describe traditional approaches to SCI-related health self-management, and (3) highlight the latest research and advancements in mHealth apps for individuals living with SCI.

Chronic disease management

Chronic conditions are long lasting and generally incurable conditions that require varying degrees of management (Shiel Jr., 2020). Examples of conditions meeting these criteria include diabetes, arthritis, dementia, and SCI (Government of Canada, 2020). Given the varied nature of the aforementioned conditions, their risk factors, prevalence, and management vary considerably. The presence of one chronic condition or disease is often associated or accompanied by subsequent chronic diseases resulting in multimorbidity (Sakib, Shooshtari, John, & Menec, 2019). Demographic characteristics have also been shown to be related to outcomes associated with chronic conditions. For example, increased age and longer time with injury are both associated with higher rates of secondary conditions among people with SCI (Jensen et al., 2013). Furthermore, the age at which SCI is acquired displays a bimodal distribution in North America (Noonan et al., 2012). SCIs earlier in life occur primarily among males, who tend to be injured from high velocity events such as motor vehicle accidents, while SCIs in later life tend to occur from falls equally for both men and women (Chen, Tang, Vogel, & Devivo, 2013).

Diagnosis and Treatment of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822498-4.00042-7

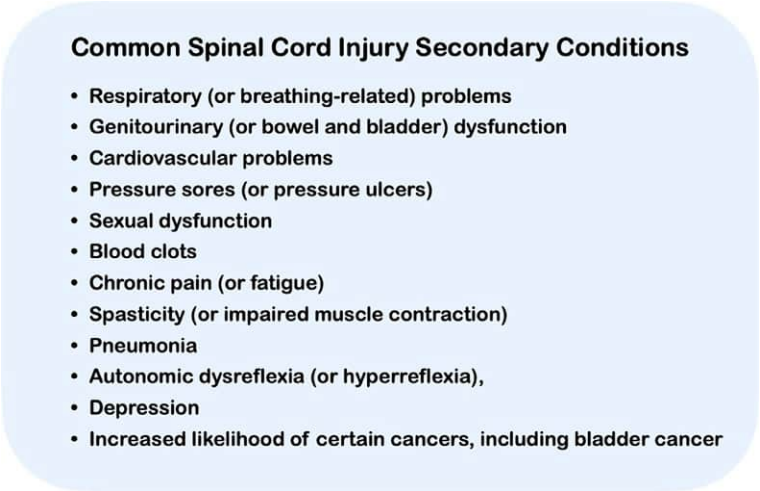

FIG. 1 List of common SCI secondary conditions. A list of common spinal cord injury-related secondary conditions. *This previously unpublished figure was created by the authors of this book chapter.

Given the prevalence of chronic conditions, interventions that improve self-management have a substantial potential impact both personally and societally. Chronic conditions are thought to be responsible for the deaths of 41 million people each year with a disproportionate percentage of deaths occurring in less resourced countries (World Health Organization, 2019). Given the global significance of this problem, the World Health Organization Global Action Plan set targets to reduce the prevalence of chronic conditions by 2025 (World Health Organization, 2013). In Canada age-standardized chronic condition prevalence has been decreasing over time (Hamm et al., 2019). However, chronic conditions still represent a significant burden to the health care system with 44% of Canadian adults having at least 1 of 10 common chronic conditions and direct health care costs to the Canadian economy of $68 billion annually (Chronic Disease Prevention Alliance of Canada, 2017; Government of Canada, 2019). In England, more than 40% of people aged 65 years and over report having at least one chronic condition and 15% reported having at least two (Organization for Economic Cooperation and Development, 2019). Similarly, in the United States, chronic conditions equate for 75% of health care costs with 133 million residents living with at least one chronic condition and almost a third living with multiple chronic conditions (National Health Council, 2014). Improving management of these chronic conditions would result in considerable personal and societal benefits.

Similar to other chronic conditions, SCI requires complex management as a result of a constellation of both physiological and psychological challenges. Common secondary conditions (Fig. 1) include pressure sores, problematic spasticity, genitourinary dysfunction, autonomic dysreflexia, and depression (Adriaansen et al., 2016). Pressure sores occur when an area of skin, often over bony areas, is placed under constant pressure, such as prolonged sitting, resulting in the breakdown of the skin and underlying tissue (Bhattacharya & Mishra, 2015). Spasticity can be characterized by increased muscle tone, increased tendon reflexes, and increased reflex responses from external stimuli (Skold, Levi, & Seiger, 1999). Genitourinary dysfunction relates to disturbance to the urinary tract and sexual function (Beck & Fowler, 1994). Injuries at thoracic level T6 or above may disrupt the autonomic nervous system, which can result in autonomic dysreflexia characterized by high blood pressure along with headaches, sweating, flushing, bradycardia, nasal congestion, feelings of apprehension, and piloerection (Ekland, Krassioukov, McBride, & Elliott, 2008). Poor management of these secondary conditions, among others, can limit social participation, reduce quality of life, and may prove fatal in extreme cases (Adriaansen et al., 2016). Leading causes of death for individuals with SCI include respiratory disease, cardiovascular disease, and sepsis, thus prevention of these through self-management is essential (Savic et al., 2017).

Traditional SCI self-management interventions

Following SCI, self-management is encouraged early in the rehabilitation process. Rehabilitation hospitals often provide client education sessions and resources related to self-management techniques. Key self-management topics identified in the client education sessions may involve pressure sores, urinary tract infections, sexual health, pain management, and others; however, motivation to participate in optional sessions and length of stay in inpatient rehabilitation may minimize opportunities to develop self-management skills. Several interpersonal barriers may relate to engagement in self-

management classes within inpatient rehabilitation including pain, fatigue, emotional status, denial, low self-efficacy (Jerant, von Friederichs-Fitzater, & Moore, 2005).

A study by Munce et al. (2016) revealed the different perspectives patients, caregivers, and managers have about SCI-related self-management interventions. Patients with traumatic SCI emphasized that self-management requires them to take responsibility for their health by incorporating "wellness awareness" and "monitoring for secondary complications" (Munce et al., 2016, p. 7). Furthermore, caregivers and patients with SCI felt that an understanding of self-management required "ownership of one's own care/empowerment in care" (Munce et al., 2016, p. 7). In contrast, managers indicated a belief in shared responsibility between patients and health professionals with implementing self-management interventions (Munce et al., 2016). These multiple perspectives are relevant for the development and administration of self-management programs for individuals with SCI.

Historically, self-management programs for chronic conditions have focused on providing information, drug management, symptom management, management of psychological consequences, lifestyle, social support, communication, and others (e.g., goal setting, problem solving, spirituality) (Barlow et al., 2002). A recent scoping review of self-management interventions following SCI identified that the primary component of programming has been the delivery of general or topic-specific SCI information (McIntyre et al., 2020), which is consistent with the historical focus of self-management programs for chronic conditions.

Although individuals with SCI have identified self-management needs in different areas, programming options are limited. For example, individuals with SCI would like to improve self-management related to exercise nutrition, pain management, aging, communication with healthcare professionals, problem solving, community reintegration, and confidence (Munce et al., 2014). Despite the variety of topics believed to be important for SCI self-management interventions, many of the 102 unique self-management programs related to SCI, identified in the aforementioned scoping review, have focused on pain (McIntyre et al., 2020). This suggests a large unmet need.

The self-management needs of people with SCI are diverse and complex. Stakeholders (i.e., individuals with SCI, and their formal and informal caregivers) involved in the development of a self-management app for people with SCI emphasized that it needed to be "individualized and user friendly" (Mortenson et al., 2019). To address the diverse nature of SCI, 54% of interventions included in the aforementioned scoping review incorporated "self-tailoring" (McIntyre et al., 2020). Self-tailoring has the potential to address the unique needs among individuals with SCI.

Many rehabilitation hospitals and experimental interventions have implemented components of Bandura's social cognitive theory, which "posits that people learn from one another, via observation, imitation, and modeling" (Nabavi, 2012). Strategies congruent with social cognitive theory include the incorporation of a social context in self-management delivery that allows for dynamic and reciprocal interactions (Hirsche, Williams, Jones, & Manns, 2011; Kim & Cho, 2017). Not surprisingly, upwards of 45% of SCI self-management programs have adopted a group or mixed (group and individual) approach (McIntyre et al., 2020). Peer-based inpatient programs have been evaluated in major rehabilitation hospitals and have identified benefits such as improved self-efficacy and reduced unplanned readmissions (Gassaway et al., 2017; Jones, Gassaway, & Sweatman, 2019).

Nearly 63% of individuals with SCI identified that the best mode of delivery for a self-management program would be "internet-based" (Munce et al., 2014). With increasing technology development, the delivery mode of self-management education and resources has been becoming increasingly digital. Digital resources may improve accessibility for individuals with SCI who are based in rural locations, as they are often wide-reaching, cost effective, and accessible for people with SCI using personal computers they have already adapted to using, provided they have access to the internet. In a scoping review of studies published prior to April 2018, McIntyre et al. (2020) identified 17 SCI self-management programs that incorporated online elements, 10 of which exclusively used an online format.

eHealth technology and mHealth apps

First coined by Mitchell and expanded on by Eysenbach, eHealth can be described as information or a health service delivered or enhanced by the internet or related technologies (Eysenbach, 2001; Mitchell, 1999). Instead of being considered simply an adjunctive electronic health technology that supplements traditional face-to-face services, as technology becomes more embedded into healthcare over time, "eHealth" may become an integral part of healthcare (Cunningham, Wake, Waller, & Morris, 2014). Since the turn of the 21st century, there has been a dramatic shift toward the use of eHealth technologies for health-related self-management and information seeking (Gill et al., 2012). Common examples of eHealth technologies include electronic health records, telemedicine, and mHealth apps.

With advancements in smartphones and tablets, mHealth apps have emerged as means to seek health information and better health service delivery and accessibility (Lewis et al., 2014). Furthermore, the introduction of mHealth apps has

made it easier to provide cost-effective, population-based, self-management interventions for individuals living with chronic conditions such as SCI. For example, a study examining the views of individuals with traumatic SCI on the use of mHealth apps for health self-management, found that 63% of participants felt it was the best means of self-management delivery (Munce et al., 2014). Popular examples of mHealth apps that promote mainstream self-management include Apple Health, Google Fit, and Samsung Health. However, for individuals with chronic conditions such as SCI, these "one-size-fits-all" mHealth apps may not meet their specific health management needs. As a result, multiple mHealth apps have been developed to promote health self-management training among individuals with SCI.

mHealth app needs among individuals with SCI

Multiple studies have evaluated the mHealth app-specific needs among individuals with SCI. For example, a consumer led study conducted by The Hopkins Centre (Queensland, Australia) explored the perspectives of 138 participants with SCI on a self-management mobile app. It found that a majority of participants (58%) reported that they would use an app to manage at least one SCI-related secondary condition (Colley, Atresh, Parekh, & Salehi, 2017). Furthermore, participants felt that if an app were developed, it should include three key features: (1) communication with healthcare providers, (2) effective self-management advice, and (3) resources and videos on relevant health topics (Colley et al., 2017). As part of a needs assessment to guide the development of a healthy lifestyle mobile app for wheelchair users with SCI, goal attainment and social support were identified as critical personal and environment determinants that promote physical activity and healthy dietary behaviors (Holla et al., 2020; Van den Akker et al., 2020). To identify preferred potential features for a web-based physical activity self-management app, a participatory study explored key stakeholders' perspectives including individuals with SCI and health care professionals (Pancer et al., 2019). The study identified five key features: (1) guidance management (i.e., exercise tutorials), (2) achievements system (i.e., tool monitoring achievements and milestones), (3) self-regulation strategies (i.e., goal setting and reminders), (4) interactivity (i.e., peers and health professional integration), and (5) format (i.e., appearance and ease of use) (Pancer et al., 2019). These studies speak to the range in health and lifestyle needs across diverse SCI populations.

Development and pilot implementation of mHealth apps for SCI self-management

Over the past decade, several studies have been conducted to develop and pilot test mHealth apps for SCI self-management (Fig. 2). Apps range from those designed to manage specific secondary conditions to those that serve a variety of self-care-related purposes. In terms of secondary condition-specific apps, for individuals experiencing chronic bladder retention, a web-based mobile app was developed to self-monitor and manage intermittent catheterization, fluid intake, urinary output, and symptoms of urinary tract infections (Wilde et al., 2017). A study conducted on the feasibility of this app revealed that in a sample of 30 participants, self-management of bladder dysfunction improved, and participants' self-management scale scores increased significantly ($P = 0.032$) (Wilde et al., 2017). Similarly, to assist with self-managing secondary conditions such as pain, weight gain, and fatigue, a small-scale study was conducted to document the impact of a physical activity (PA) tracking self-management mobile app on overall PA levels among individuals with SCI (Hiremath et al., 2019). By providing real-time feedback on PA levels, in a sample of 20 participants, the majority (69%) demonstrated greater light to

FIG. 2 List of mobile and web apps for SCI self-management and rehabilitation. A list of mobile and web apps for spinal cord injury self-management and rehabilitation. *This previously unpublished figure was created by the authors of this book chapter.

moderate intensity PA compared to baseline (Hiremath et al., 2019). In order to develop a mHealth app for pressure injury prevention among individuals with SCI, a study was conducted to develop a working app prototype and conduct usability testing (Amann et al., 2020). Using a co-design approach, a working prototype was developed with features that included a pressure injury diary, smart camera, expert consultation service, and knowledge repository. Results from usability testing demonstrated above average system usability scale (SUS) score (78.5/100) with a majority of participants being able to fluently navigate the app (Amann et al., 2020; Lewis, 2018).

In order to provide individuals living with SCI with an app that can address both general and SCI-specific health self-management needs, we developed a mHealth app funded by the Craig Nielsen Foundation called *SCI Health Storylines* (Mortenson et al., 2019). *SCI Health Storylines* (Fig. 3) is a mHealth app that includes various general health tools (e.g., medication tracker, health journal), SCI-specific tools (e.g., SCI goal-setting tool, bowel and bladder tracker, pain tracker), and lifestyle tools (e.g., physical activity tracker, recreational resources tool, nutritional planner). Our app was developed using a user-centered design process with input from rehabilitation inpatients, clinicians, and informal caregivers (Mortenson et al., 2019). During the app's development, participants identified three core themes about the functionality of the app which needed to (1) be tailor-made for individuals with SCI, (2) target goals to promote self-management, and (3) increase social participation in the community (Mortenson et al., 2019). Furthermore, small-scale

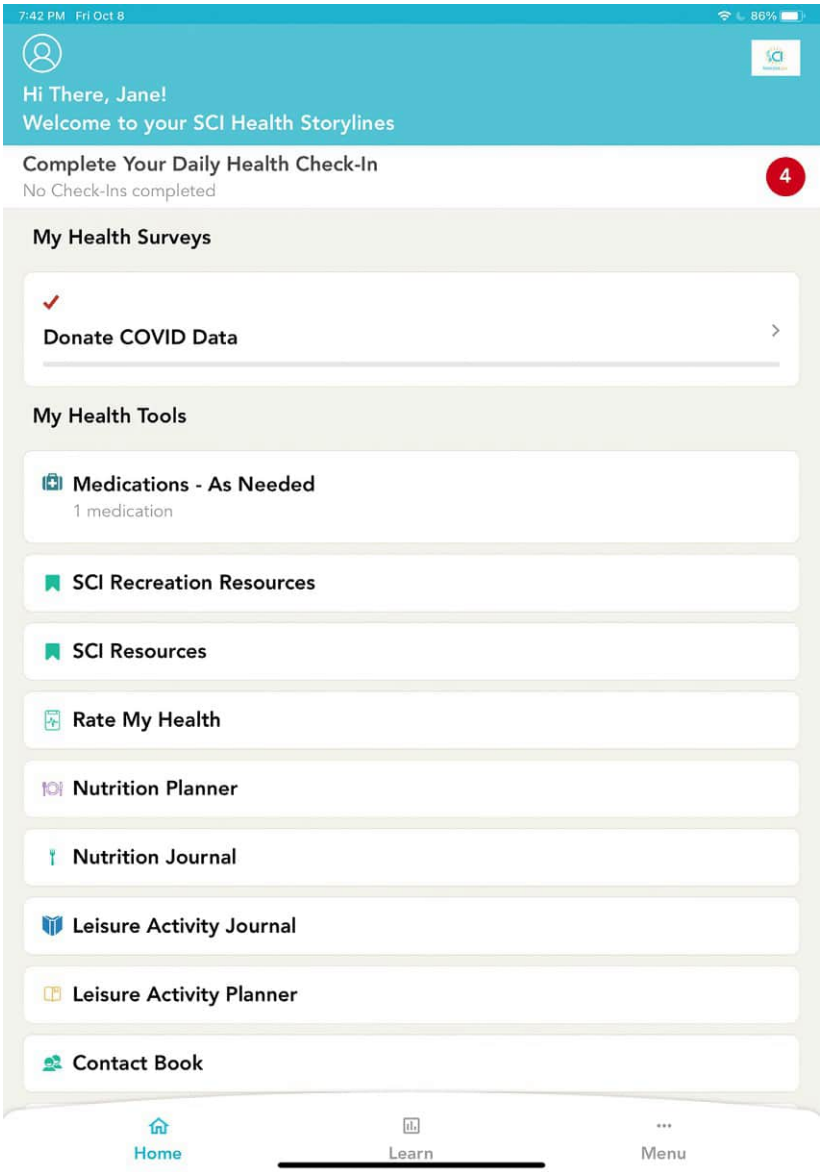

FIG. 3 *SCI Health Storylines* mHealth App. A screenshot of the splash page of the SCI Health Storylines mHealth app. *The source of this previously unpublished figure is the *SCI Storylines App* on the iOS Platform. Copyright permission has been obtained from Self Care Catalysts (Toronto, Canada) to use this figure in this book chapter.

intervention feasibility and app usability studies were also conducted among 20 rehabilitation inpatients on the implementation of our app during inpatient rehabilitation and following community discharge (MacGillivray et al., 2019; Singh et al., 2019). In terms of feasibility, our research revealed retention was 85% at inpatient discharge and 70% 3 months post-discharge, participants' bowel self-management confidence improved between admission and discharge ($P < 0.01$), and indicators of strong overall feasibility to support a larger clinical trial (MacGillivray et al., 2019). Furthermore, our mobile app was found to have above average SUS scores (Lewis, 2018) both at discharge (78.1/100) and 3 months post-discharge (71.6/100).

Clinical interventions on mHealth apps for SCI self-management

With the recent emergence of mHealth apps designed to promote self-management and SCI rehabilitation, only two large-scale clinical interventions have been or are in the process of being conducted at the time of writing this chapter. Kryger and colleagues completed a randomized controlled trial (RCT) to determine if their mHealth app, *iMHere* (Fig. 4), could improve overall health outcomes and promote the self-management of secondary conditions such as urinary tract infection, depression, and pressure sores over a 9-month period (Kryger et al., 2019; Parmanto et al., 2013). Key findings from the RCT included statistically significant reductions in urinary tract infections ($P = .03$), and a non-significant trend toward

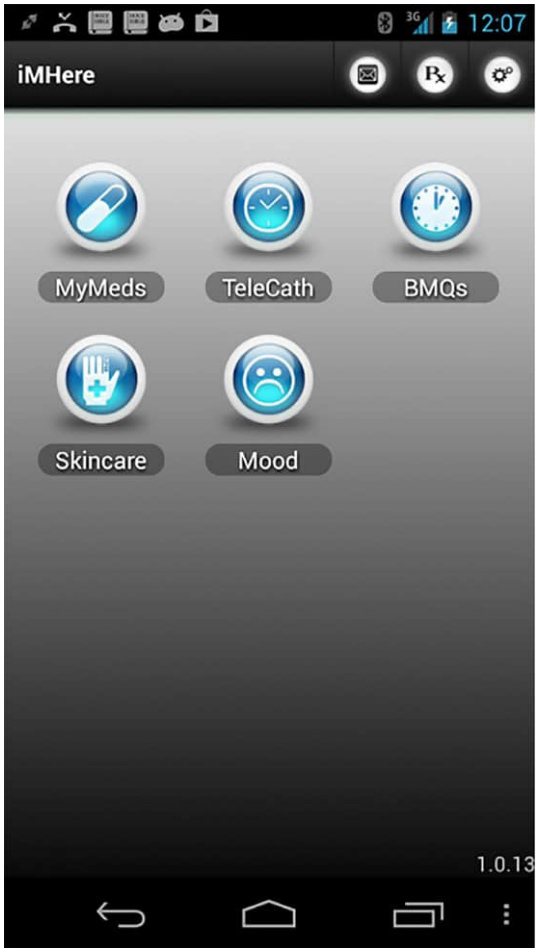

FIG. 4 *iMHere* mHealth App. A screenshot of the splash page of the iMHere mHealth app (Parmanto et al., 2013). *This figure was obtained from an open-access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work, first published in JMIR mHealth and uHealth, is properly cited. The complete bibliographic information, a link to the original publication on http://mhealth.jmir.org/, as well as this copyright and license information must be included. © Bambang Parmanto, Gede Pramana, Daihua Xie Yu, Andrea D Fairman, Brad E Dicianno, Michael P McCue. Originally published in JMIR mHealth and uHealth (http://mhealth.jmir.org), 11.07.2013.

reduced depressive symptoms (Kryger et al., 2019), among 38 participants randomized to two groups (intervention: mHealth app and standard care; control: standard care only). The chapter authors are in the process of completing a mixed-methods rater-blinded RCT, with a stepped wedge design (Hemming, Haines, Chilton, Girling, & Lilford, 2015), evaluating the efficacy of our self-management mHealth app, *SCI Health Storylines*, in the community setting (Mortenson et al., 2018). The principle outcome measures of this RCT include successful attainment of self-selected self-management goals, and reductions in both self-reported SCI-related secondary conditions and adverse health events. With the study nearing completion, findings on our mHealth app's efficacy in promoting self-management delivery are not currently available. However, three key themes emerged from a qualitative study exploring user's expectations of our mHealth app intervention, including participants' desire to improve their overall health outcomes, learn about the mHealth app's potential and functionality, and improve their sense of personal and social autonomy (Mortenson et al., 2019). If the results of our clinical intervention are positive, this study will provide new knowledge on the implementation of mHealth apps for self-management delivery in clinical practice.

Applications to other areas of neuroscience

In this chapter, we reviewed chronic disease management, with a particular emphasis on SCI-related secondary condition management. We also highlighted the traditional approaches to SCI health self-management and the emerging transition toward the use of mHealth apps to provide population-based self-management delivery. The interconnection between mHealth apps and chronic disease self-management can be applied to disability groups more broadly in other areas of neuroscience, including stroke (Kang et al., 2019; Li et al., 2020; Sarfo & Ovbiagele, 2017), multiple sclerosis (Ruzic, Mahajan, & Sanford, 2018), traumatic brain injury (Christopher, Alsaffarini, & Jamjoom, 2019), and Parkinson's disease (Bot et al., 2016). Similar to the various SCI-related apps reviewed in this chapter, many apps designed for other neurological diseases and conditions feature similar core tools to promoting health self-management including medication tracking, symptom tracking, and daily journaling tools. Whereas similar general health tools can be seen in mHealth apps across many areas of neuroscience, studies in other areas of neuroscience also highlight the benefits of app tools relevant to their targeted chronic disease population. For example, an app for SCI may include tools related to monitoring various involuntary physiological processes (e.g., blood pressure, digestion, and respiration) and apps designed for traumatic brain injury self-management often include tools for sports-related concussion monitoring (Christopher et al., 2019; Kryger et al., 2019; Mortenson et al., 2019). As novel mHealth apps continue to be introduced to individuals living with other neurological conditions, it is important they provide individualized tools that meet the needs of those specific populations and they undergo independent evaluation to determine their efficacy.

Mini-dictionary of terms

Traumatic Spinal Cord Injury: An injury to the spinal cord that is a result of physical trauma including during falls, motor vehicle accidents, and sports injuries (Pickett, Campos-Benitez, Keller, & Duggal, 2006).

Non-Traumatic Spinal Cord Injury: An injury to the spinal cord as a result of factors unrelated to an external force, including tumors, infections, post-surgical complications, and neurogenerative diseases (New et al., 2015).

Secondary Condition: An additional physical, physiological or psychological condition resulting from a primary disabling condition (Rowland, 2020).

Spasticity: A common secondary condition characterized with increased muscle tone, sustained involuntary somatic reflexes, and/or muscle spasms (Rabchevsky & Kitzman, 2011).

Pressure Sores: An area of localized soft tissue necrosis resulting from prolonged pressure to skin (Agrawal & Chauhan, 2012).

Autonomic Dysreflexia: An abnormal stimulation of the autonomic nervous stimulation than can result in symptoms including changes in heart rate, high blood pressure, and excessive sweating (Allen & Leslie, 2020).

Self-Management: A person's ability to manage the symptoms, treatment, and lifestyle changes inherent to living with a chronic condition or disease (Barlow et al., 2002).

Mixed-Methods Study: The collection or analysis of quantitative and qualitative data within a single study (Creswell, 2015).

Telemedicine: The delivery of clinical health services remotely (Sood et al., 2007).

eHealth: Information or a health service being delivered or enhanced by the Internet and related technologies (Eysenbach, 2001).

Mobile Health (mHealth): The application of mobile and wireless devices (e.g., cell phones and tablets) to improve health care delivery and health outcomes (Tucker, 2015).
Mobile App: A software program that operates on a mobile or wireless device (Harrison, Flood, & Duce, 2013).
System Usability Scale: A short questionnaire designed to determine the usability of website, software program, or application (Brooke, 1996).

Key facts of spinal cord injury

Spinal cord injury is a neurological disorder.
It occurs from damage to the spinal cord from contusion, rotation, compression, or distraction.
Based on location and severity of damage, the injury can result in a variety of secondary conditions.
It can be classified as traumatic or non-traumatic.
Traumatic spinal cord injury is caused by physical trauma from factors like falls, sports injuries, and motor vehicle accidents.
Non-traumatic spinal cord injury is caused by factors unrelated to an external force such as infections, diseases, tumors, and post-surgical complications.

Key facts of eHealth

eHealth was first coined in 1999 by John Mitchell.
It is described as information or a health service delivered or enhanced by the Internet or related technologies.
Advancements in Internet technologies have resulted in increased popularity of the eHealth field.
Mobile health falls under the eHealth umbrella.
An individual's ability to seek, find, and understand health information using Internet technologies is called eHealth literacy.

Summary points

- Spinal cord injury is a chronic condition that may lead to various physical, and psychological sequelae
- In-person, health self-management training has been found to reduce the prevalence and reoccurrence of spinal cord injury-related secondary conditions
- Recent advancements in smartphone technology and access, mobile health apps have emerged as a cost-effective, population-based means to facilitate behavioral change related to self-management
- Multiple mobile health apps have been developed to promote self-care and assist with secondary condition management among people with spinal cord injury
- Despite their emerging prevalence and success in small-scale implementation studies, further clinical trials and large-scale interventions are needed to determine the effectiveness of mHealth apps for spinal cord injury populations

References

Adriaansen, J., Ruijs, L., van Koppenhagen, C., van Asbeck, F., Snoek, G., van Kuppevelt, D., et al. (2016). Secondary health conditions and quality of life in persons living with spinal cord injury for at least then years. *Journal of Rehabilitation Medicine*, *48*, 853–860.
Agrawal, K., & Chauhan, N. (2012). Pressure ulcers: Back to the basics. *Indian Journal of Plastic Surgery*, *45*(2), 244–254.
Allen, K. J., & Leslie, S. W. (2020). *Autonomic dysreflexia*. Treasure Island, FL: StatsPearls Publishing.
Amann, J., Fiordelli, M., Brach, M., Bertschy, S., Scheel-Sailer, A., & Rubinelli, S. (2020). Co-designing a self-management app prototype to support people with spinal cord injury in the prevention of pressure injuries: Mixed methods study. *JMIR mHealth and uHealth*, *8*(7), e18018.
Barlow, J., Wright, C., Sheasby, J., Turner, A., & Hainsworth, J. (2002). Self-management approaches for people with chronic conditions: A review. *Patient Education and Counselling*, *48*(2), 177–187.
Beck, R., & Fowler, C. (1994). Clinical neurophysiology in the investigation of genitourinary tract dysfunction. In D. N. Rushton (Ed.), *Handbook of neuro-urology* (pp. 151–181). New York: Marcel Dekker Inc.
Bhattacharya, S., & Mishra, R. (2015). Pressure ulcers: Current understanding and newer modalities of treatment. *Indian Journal of Plastic Surgery*, *48*, 4–16.
Bot, B. M., Suver, C., Neto, E. C., Kellen, M., Klein, A., Bare, C., et al. (2016). The mPower study, Parkinson disease mobile data collected using ResearchKit. *Scientific Data*, *6*, 160011.
Brooke, J. (1996). *A "quick and dirty" usability scale*. London: Taylor & Francis.

Chen, Y., Tang, Y., Vogel, L., & Devivo, M. (2013). Causes of spinal cord injury. *Topics in Spinal Cord Injury Rehabilitation*, *19*, 1–8.

Christopher, E., Alsaffarini, K. W., & Jamjoom, A. A. (2019). Mobile health for traumatic brain injury: A systematic review of the literature and mobile application market. *Cureus*, *11*(7), e5120.

Chronic Disease Prevention Alliance of Canada. (2017, August 4). *2018 pre-budget submission to the House of Commons Standing Committee on Finance*. Retrieved from https://www.ourcommons.ca/content/committee/421/fina/brief/br9073636/br-external/chronicdiseasepreventionallianceofcanada-e.pdf.

Colley, J., Atresh, S., Parekh, S., & Salehi, N. (2017). *Potential of smartphone apps to assist people with spinal cord injury*. Retrieved from https://www.hopkinscentre.edu.au/project/potential-of-smartphone-apps-to-assist-people-31.

Creswell, J. W. (2015). *A concise introduction to mixed methods research*. Thousand Oaks, CA: Sage.

Cunningham, S., Wake, D., Waller, A., & Morris, A. (2014). Definitions of eHealth. In *eHealth, care and quality of life*. Milan: Springer.

Ekland, M. B., Krassioukov, A. V., McBride, K. E., & Elliott, S. L. (2008). Incidence of autonomic dysreflexia and silent autonomic dysreflexia in men with spinal cord injury undergoing sperm retrieval: Implications for clinical practice. *Journal of Spinal Cord Medicine*, *31*(1), 33–39.

Eysenbach, G. (2001). What is e-health? *Journal of Medical Internet Research*, *3*(2), e20.

Gassaway, J., Jones, M. L., Sweatman, W. M., Hong, M., Anziano, P., & DeVault, K. (2017). Effects of peer mentoring on self-efficacy and hospital readmission after inpatient rehabilitation of individuals with spinal cord injury: A randomized controlled trial. *Physical Medicine and Rehabilitation*, *98*(8), 1526–1534.

Gill, P. S., Kamath, A., & Gill, T. S. (2012). Distraction: An assessment of smartphone usage in health care work settings. *Risk Management and Healthcare Policy*, *5*, 105–114.

Government of Canada. (2019, February 5). *Prevalence of chronic diseases among Canadian adults*. Retrieved from https://www.canada.ca/en/public-health/services/chronic-diseases/prevalence-canadian-adults-infographic-2019.html.

Government of Canada. (2020, August 31). *Chronic Diseases*. Retrieved from https://www.canada.ca/en/public-health/services/chronic-diseases.html.

Hamm, N., Pelletier, L., Ellison, J., Tennenhouse, L., Reimer, K., Paterson, J., et al. (2019). Original quantitative research—Trends in chronic disease incidence rates from the Canadian Chronic Disease Surveillance System. *Health Promotion and Chronic Disease Prevention in Canada*, *39*, 216–224.

Harrison, R., Flood, D., & Duce, D. (2013). Usability of mobile applications: Literature review and rationale for a new usability model. *Journal of Interaction Science*, 1–16.

Hemming, K., Haines, T. P., Chilton, P. J., Girling, A. J., & Lilford, R. J. (2015). The stepped wedge cluster randomised trial: Rational, design, analysis, and reporting. *BMJ*, *350*, h391.

Hiremath, S. V., Amiri, A. M., Thapa-Chhetry, B., Snethen, G., Schmidt-Read, M., Ramos-Lamboy, M., et al. (2019). Mobile health-based physical activity intervention for individuals with spinal cord injury in the community: A pilot study. *PLoS One*, *14*(10), e0223762.

Hirsche, R. C., Williams, B., Jones, A., & Manns, P. (2011). Chronic disease self-management for individuals with stroke, multiple sclerosis and spinal cord injury. *Disability and Rehabilitation*, *33*(13–14), 1136–1146.

Holla, J. F. M., van den Akker, L. E., Dadema, T., de Groot, S., Tieland, M., Weijs, P. J. M., et al. (2020). Determinants of dietary behaviour in wheelchair users with spinal cord injury or lower limb amputation: Perspectives of rehabilitation professionals and wheelchair users. *PLoS One*, *15*(1), e0228465.

Jensen, M. P., Truitt, A. R., Schomer, K. G., Yorkston, K. M., Baylor, C., & Molton, I. R. (2013). Frequency and age effects of secondary health conditions in individuals with spinal cord injury: A scoping review. *Spinal Cord*, *51*(12), 882–892.

Jerant, A. F., von Friederichs-Fitzater, M. M., & Moore, M. (2005). Patients' perceived barriers to active self-management of chronic conditions. *Patient Education and Counselling*, *57*(3), 300–307.

Jones, M. L., Gassaway, J., & Sweatman, M. W. (2019). Peer mentoring reduces unplanned readmissions and improves self-efficacy following inpatient rehabilitation for individuals with spinal cord injury. *The Journal of Spinal Cord Medicine*, 1–9.

Kang, Y. N., Shen, H. N., Lin, C. Y., Elwyn, G., Huang, S. C., Wu, T. F., et al. (2019). Does a mobile app improve patients' knowledge of stroke risk factors and health-related quality of life in patients with stroke? A randomized controlled trial. *BMC Medical Informatics and Decision Making*, *19*(282), 1–9.

Kim, J. Y., & Cho, E. (2017). Evaluation of a self-efficacy enhancement program to prevent pressure ulcers in patients with a spinal cord injury. *Japan Journal of Nursing Science*, *14*, 76–86.

Kryger, M. A., Crytzer, T. M., Fairman, A., Quinby, E. J., Karavolis, M., Pramana, G., et al. (2019). The effect of the interactive mobile health and rehabilitation system on health and psychosocial outcomes in spinal cord injury: Randomized Controlled Trial. *Journal of Medical Internet Research*, *21*(7), e14305.

Lewis, J. R. (2018). The system usability scale: Past, present, and future. *International Journal of Human Computer Interaction*, *34*(7), 577–590.

Lewis, T. L., Boissaud-Cooke, M. A., Aungst, T. D., & Eysenbach, G. (2014). Consensus on use of the term "app" versus "application" for reporting of mHealth research. *Journal of Medical Internet Research*, *16*(7), e174.

Li, L., Huang, J., Wu, J., Jiang, C., Chen, S., Xie, G., et al. (2020). A mobile health app for the collection of functional outcomes after inpatient stroke rehabilitation: Pilot randomized controlled trial. *JMIR mHealth and uHealth*, *8*(5), e17219.

MacGillivray, M. K., Sadeghi, M., Mills, P. B., Adams, J., Sawatzky, B. J., & Mortenson, W. B. (2019). Implementing a self-management app for spinal cord injury during inpatient rehabilitation and following community discharge: A feasibility study. *The Journal of Spinal Cord Medicine*, *43*(5), 676–684.

McIntyre, A., Marrocco, S. L., McRae, S. A., Sleeth, L., Hitzig, S., Jaglal, S., et al. (2020). A scoping review of self-management interventions following spinal cord injury. *Topics in Spinal Cord Injury Rehabilitation*, *26*(1), 36–63.

Mitchell, J. (1999). *From telehealth to e-health: The unstoppable rise of e-health*. Canberra, Australia: National Office for the Information Technology.

Mortenson, W. B., Mills, P. B., Adams, J., Singh, G., MacGillivray, M., & Sawatzky, B. (2018). Improving self-management skills among people with spinal cord injury: Protocol for a mixed-methods study. *JMIR Research Protocols*, *7*(11), e11069.

Mortenson, W. B., Singh, G., MacGillivray, M., Sadeghi, M., Mills, P., Adams, J., et al. (2019). Development of a self-management app for people with spinal cord injury. *Journal of Medical Systems*, *43*(6), 145.

Munce, S. E., Fehlings, M. G., Straus, S. E., Nugaeva, N., Jang, E., Webster, F., et al. (2014). Views of people with traumatic spinal cord injury about the components of self-management programs and program delivery: A Canadian pilot study. *BMC Neurology*, *14*, 209.

Munce, S. E. P., Webster, F., Fehlings, M. G., Straus, S. E., Jang, E., & Jaglal, S. B. (2016). Meaning of self-management from the perspective of individuals with traumatic spinal cord injury, their caregivers, and acute care and rehabilitation managers: An opportunity for improved care delivery. *BMC Neurology*, *16*(11), 1–9.

Nabavi, R. T. (2012). *Bandura's social learning theory & social cognitive learning theory*. Retrieved from https://www.researchgate.net/publication/267750204_Bandura%27s_Social_Learning_Theory_Social_Cognitive_Learning_Theory.

National Health Council. (2014). *About chronic disease*. Retrieved from https://nationalhealthcouncil.org/wp-content/uploads/2019/12/AboutChronicDisease.pdf.

New, P., Reeves, R., Smith, E., Townson, A., Eriks-Hoogland, I., Gupta, A., et al. (2015). International retrospective comparison of inpatient rehabilitation for patients with spinal cord dysfunction epidemiology and clinical outcomes. *Archives of Physical Medicine and Rehabilitation*, *96*, 1080–1087.

Noonan, V., Fingas, M., Farry, A., Baxter, D., Singh, A., Fehlings, M., et al. (2012). Incidence and prevalence of spinal cord injury in Canada: A national perspective. *Neuroepidemiology*, *38*, 219–226.

Organization for Economic Cooperation and Development. (2019). *State of health in the EU: United Kingdom country health profile 2019*. Retrieved from https://www.oecd-ilibrary.org/docserver/744df2e3-en.pdf?expires=1605149953&id=id&accname=guest&checksum=38BD5378D6BB08537E80336C84B485EC.

Pancer, M., Manganaro, M., Pace, I., Marion, P., Gagnon, D. H., Laramee, M. T., et al. (2019). A web-based physical activity portal for individuals living with a spinal cord injury: Qualitative study. *JMIR Formative Research*, *3*(3), e12507.

Parmanto, B., Pramana, G., Yu, D. X., Fairman, A. D., Dicianno, B. E., & McCue, M. P. (2013). iMHere: A novel mHealth system for supporting self-care in management of complex and chronic conditions. *JMIR mHealth and uHealth*, *1*(2), e10.

Pickett, G. E., Campos-Benitez, M., Keller, J. L., & Duggal, N. (2006). Epidemiology of traumatic spinal cord injury in Canada. *Spine*, *31*(7), 799–805.

Rabchevsky, A. G., & Kitzman, P. H. (2011). Latest approaches for the treatment of spasticity and autonomic dysreflexia in chronic spinal cord injury. *Neurotherapeutics*, *8*(2), 274–282.

Rowland, J. (2020). *Defining secondary conditions for people with disabilities*. Retrieved from https://www.nchpad.org/360/2050/Defining~Secondary~Conditions~for~People~with~Disabilities.

Ruzic, L., Mahajan, H. P., & Sanford, J. A. (2018). Evaluating an evidence-based mHealth application, MS assistant, individuals again with multiple sclerosis. *International Journal on Advances in Life Sciences*, *10*(3), 156–168.

Sakib, M., Shooshtari, S., John, P., & Menec, V. (2019). The prevalence of multimorbidity and associations with lifestyle factors among middle-aged Canadians: an analysis of Canadian Longitudinal Study on Aging data. *BMC Public Health*, *19*.

Sarfo, F. S., & Ovbiagele, B. (2017). Mobile health for stroke: A promising concept for research and practice. *mHealth*, *3*, 4.

Savic, G., DeVivo, M. J., Frankel, H. L., Jamous, M. A., Soni, B. M., & Charlifue, S. (2017). Causes of death after traumatic spinal cord injury—A 70-year British study. *Spinal Cord*, *55*, 891–897.

Shiel, W. C., Jr. (2020). *Medical definition of chronic disease*. Retrieved from https://www.medicinenet.com/script/main/art.asp?articlekey=33490.

Singh, G., MacGillivray, M., Mills, P., Adams, J., Sawatzky, B., & Mortenson, W. B. (2019). Patients' perspectives on the usability of a mobile app for self-management following spinal cord injury. *Journal of Medical Systems*, *44*(1), 26.

Skold, C., Levi, R., & Seiger, A. (1999). Spasticity after traumatic spinal cord injury: Nature, severity and location. *Archives of Physical Medicine and Rehabilitation*, *80*, 1548–1557.

Sood, S., Mbarika, V. W. A., Jugoo, S., Doohky, R., Doarn, C. R., Prakash, N., et al. (2007). What is telemedicine? A collection of 104 peer-reviewed perspectives and theoretical underpinnings. *Telemedicine Journal and eHealth*, *13*(5), 573–590.

Tucker, S. (2015). Welcome to the world of mHealth. *mHealth*, *1*, 1.

Van den Akker, L., Holla, J. F. M., Dadema, T., Visser, B., Valent, L. J., de Groot, S., et al. (2020). Determinants of physical activity in wheelchair users with spinal cord or lower limb amputation: Perspectives of rehabilitation professionals and wheelchair users. *Disability and Rehabilitation*, *42*(14), 1934–1941.

Wilde, M. H., McMohan, J. M., Fairbanks, E., Brasch, J., Parshall, R., Zhang, F., et al. (2017). Feasibility of a web-based self-management intervention for intermittent urinary catheter users with spinal cord injury. *Journal of Wound, Ostomy, and Continence Nursing*, *43*(5), 529–538.

World Health Organization. (2013). *Global action plan for the prevention and control of noncommunicable diseases 2013–2020*. Retrieved from https://apps.who.int/iris/bitstream/handle/10665/94384/9789241506236_eng.pdf;jsessionid=B7659CDABAE694BE369DAD0E42B777B4?sequence=1.

World Health Organization. (2019). *Noncommunicable diseases*. Retrieved from https://www.who.int/en/news-room/fact-sheets/detail/noncommunicable-diseases.

Chapter 43

Biomaterials, spinal cord injury, and rehabilitation: A new narrative

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List of abbreviations

AEMA	2-aminoethyl methacrylate
BBB	Basso, Beattie, Bresnahan score
BDNF	brain-derived neutrophic factor
BSCB	blood–spinal cord barrier
CNS	central nervous system
ECM	extracellular matrix
HA	hyaluronic acid
HP	hydroxyphenyl
MOEAA	[2-(methacryloyloxy)ethoxy]acetic acid
MOETA+	[2-(methacryloyloxy)ethyl]trimethylammonium chloride
MSCs	mesenchymal stem cells
NFs	nanofibers
NPs	nanoparticles
NTs	nanotubes
NT-3	neurotrophin-3
NWs	nanowires
PCL	poly(ε-caprolactone)
PEG	polyethylene glycol
PEI	polyethyleneimine
PHEMA	poly(2-hydroxyethyl methacrylate)
PHPMA	poly(N-(2-hydroxypropyl)-methacrylamide)
PLA	polylactic acid
PLGA	poly(lactic-*co*-glycolic acid)
RGD	Arg-Gly-Asp
SC	spinal cord
SCI	spinal cord injury
SC-ECM	spinal cord extracellular matrix
SEM	scanning electron microscopy
SIKVAV	ser-Ile-Lys-Val-Ala-Val
UB-ECM	urinary bladder extracellular matrix
UC-ECM	umbilical cord extracellular matrix

Introduction

Spinal cord injury (SCI) is a lesion of the spinal cord which leads to the permanent loss of sensory and motor functions below the injury site. The traumatic effect of SCI is due to the low regenerative capability of the tissue, which is in contrast

Diagnosis and Treatment of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822498-4.00043-9

with the fast inflammatory response that occurs in the first minutes after the injury and starts the secondary injury in the following hours. The latter is characterized by demyelinization and the formation of a glial scar tissue which represents a physical barrier to the growth of axons. Nowadays, there are no effective clinical treatments able to regenerate the nervous tissue and restore the motor functions, so new strategies are being developed by researchers in order to overcome these limitations. One strategy is represented by scaffolds able to provide a structure that mimics the extracellular matrix (ECM) and at the same time supports the cellular attachment, growth and differentiation. The scaffolds must be biocompatible, non-toxic and have mechanical and morphological properties suitable for the tissue regeneration. In addition, they can chemically bind or physically entrap one or more drugs and release them in a controlled manner. The materials used for scaffold development can be synthetic or natural. Examples of the most used chemically synthetized materials are aliphatic polyesters such as polylactide, polyglycolide, and polycaprolactone (Pires & Pêgo, 2015). Synthetic materials present the advantage of being able to be controlled and modified from the point of view of chemistry, mechanical and structural properties in order to mimic as much as possible the ECM. In contrast, natural scaffolds are more similar in composition to ECM because some of the molecules are already present in the ECM, such as e.g., collagen, fibronectin, and hyaluronic acid but they have some differences in composition depending on their origin and previous treatments. Other natural materials such as alginate, agarose, and chitosan are widely used too. In addition, also the mechanical properties of the scaffold should be similar to the target biological tissue in order to avoid adverse effects. For the treatment the SCI, a stiff scaffold is not suitable because it is not able to support flexible movements of spinal cord without further lesioning other surrounding tissues. In addition, it was demonstrated that a stiff material promotes astrocyte growth (Georges, Miller, Meaney, Sawyer, & Janmey, 2006) and causes glial cell activation which leads to inflammation response and formation of a fibrotic tissue. Hence, soft scaffold, such as hydrogel, better matches the mechanical properties of the nervous tissue. Hydrogels are suitable for this purpose not only because of their flexibility, but also because of their bioadhesive and swelling properties, which confer the ability to stay localized in situ and to exchange metabolites with the surrounding tissue fluids. Other factors can influence the tissue regeneration, such as the pore sized distribution of the scaffold which has to guarantee the possibility for cells and fluids to enter inside the scaffold. The topography, the charge, the composition of the surface and the orientation of the fibers influence actin cytoskeleton and hence cell adhesion, spreading and differentiation.

In the case of nerve tissue regeneration, fibers arranged in a longitudinal way and pore size of 50 to 100 μm enhance nerve regeneration (Jurga et al., 2011; Yuan et al., 2014). Moreover, scaffold can be made of non-degradable or degradable materials. In the first case, the scaffold remains inside the body so the tissue can partially regenerate occupying the space between the fibers, whereas in the second case, it is necessary that the rate of degradation of the scaffold matches tissue regeneration speed.

Hydrogels and scaffolds

Synthetic-based hydrogels

Among synthetic non-biodegradable hydrogel used for SCI repair poly(N-(2-hydroxypropyl)-methacrylamide) (PHPMA) is very promising. The research group of Woerly et al. developed a hydrogel made of PHPMA, obtained by a radical polymerization of the monomer HPMA with the use of a divinyl cross-linking agent (Woerly et al., 1999), functionalized by a synthetic peptide which includes RGD sequence (Woerly, Pinet, De Robertis, Van Diep, & Bousmina, 2001). The implantation of the hydrogel into the neonatal and adult spinal cord reveals a good infiltration of cells and blood vessels and the following implantation of the hydrogel seeded with rat mesenchymal stem cells (MSCs) in rats results in better Basso, Beattie, Bresnahan (BBB) score than the control group without the implantation (Hejčl et al., 2010). Another investigated polymer in nerve tissue regeneration is the biocompatible and hydrophilic poly(2-hydroxyethyl methacrylate) (PHEMA). As previously said, the charge and the structure of the hydrogel can influence the behavior of cells and the ingrowth of the new tissue. A study by Hejcl et al. (Hejčl et al., 2010) was conducted to compare the different effects of the surface charge and structure of HPMA and HEMA hydrogels on tissue regeneration. Specifically, four different hydrogels were prepared and seeded with rat MSCs: one HPMA-RGD hydrogel by using heterophase separation (HPMA-HS-RGD), which resulted in a structure characterized by microparticles, two HPMA hydrogels by using a solid porogen, one functionalized by RGD peptide (HPMA-SP-RGD), and one without functionalization (HPMA-SP), which resulted in network structures, and the last hydrogel made by positively charged copolymers of HEMA with [2-(methacryloyloxy)ethyl]trimethylammonium chloride (MOETA+). After successful in vitro studies, hydrogels were implanted into rat SCI hemisection model. The best results in terms of in vitro adhesiveness and in vivo survival of MSC was found in the positively charged HEMA-MOETA+ hydrogel, whereas the best results in terms of axonal ingrowth and vascularization was found in the HPMA-SP-RGD

hydrogel demonstrating the higher efficacy of the network architecture respect to the globular ones. With respect to the influence of the RGD peptide, it increases the vascularization but has no effect the growth of axons.

Hydrogel functionalization with cell-adhesive peptides

The presence of cell-adhesive peptides on hydrogels, such as the laminin-derived peptide sequence SIKVAV [Ser-Ile-Lys-Val-Ala-Val] and fibronectin-derived peptide RGD [Arg-Gly-Asp], can enhance cell adhesion, migration on the scaffold, proliferation, and differentiation (Rossi & van Griensven, 2014). The research group of Kubinova et al. functionalized a copolymer-based hydrogel of HEMA and 2-aminoethyl methacrylate (AEMA) with the laminin-derived Ac-CGGASIKVAVS-OH peptide by disulfide bridges (Kubinová et al., 2010). The functionalization with SIKVAV and RGD (Macková et al., 2016) was made on the same type of hydrogel also through the maleimide-thiol coupling reaction. All the functionalized hydrogels guarantee the adhesion and proliferation of rat MSCs maintaining their multi-lineage potential. In addition, in vivo studies results shown a higher connective tissue and vascularization on fibronectin-modified HEMA hydrogel compared to the non-functionalized one (Hejčl et al., 2018). Other molecules such as serotonin can be used as neurotransmitter and can improve neuronal differentiation of implanted or endogenous neuronal progenitor precursors. Despite promising in vitro results, in vivo model studies on implanted PHEMA functionalized with serotonin showed a migration of seeded neural progenitor out from the polymer leading to a fail in proving a long-term effect on nerve tissue reconstruction (Růžička et al., 2013).

Porosity orientation

The orientation of fibers is important for tissue regeneration because it provides preferential lines along with the cells growth and proliferation. In addition, adequate porosity and mechanical properties have to support the movements of the organ and the regeneration of the new tissue. Hence, in the case of scaffolds for nervous tissue regeneration, the best one has to be characterized by parallel guiding channels and pores. The group of Kubinová et al. (2015) developed SIKVAV-modified PHEMA hydrogels with parallel oriented pores prepared by a salt-leaching method with ammonium oxalate needle-like crystals, and added 8%, 4%, and 0% (wt%) of [2-(methacryloyloxy)ethoxy]acetic acid (MOEAA) obtaining three hydrogels with 57%–77% porosity, pore diameter of $\sim$60 mm, and an elastic modulus of 6.7, 27.4, and 45.3 kPa along the pore axis and 2.9, 3.6, and 11 kPa in a perpendicular direction. After 2 months of implantation the results showed that the softest hydrogel collapses because of the thinness of walls causing a sparse axonal growth inside the hydrogel, whereas the stiffest hydrogel supported axonal ingrowth into the pore guides but cyst formed at the tissue-scaffold interface because of difference in mechanical properties between the two components. The best results in terms of axonal ingrowth, presence of blood vessels and Schwann cells are obtained using the hydrogel with the moderate elasticity modulus of 27.4 kPa along the pores. Unfortunately, the use of the moderate scaffold seeded with MSCs was not able to promote a sufficient axonal growth.

Indeed, the rate of axonal growth resulted very slow and after 6 months from the implantation only few axons were be able to cross the hydrogel and infiltrate the caudal stump (Hejčl et al., 2018). Therefore, other factors are necessary in order to promote axonal regeneration. For example, the presence of MSCs overexpressing of an NT-3 receptor (Zeng et al., 2015) or brain-derived neutrophic factor (BDNF) (Gao et al., 2013) on the scaffold can be added in order to enhance axonal growth and recovery of motor functions.

Natural-based hydrogels

This type of hydrogels may be made by ECM derived components such as collagen or hyaluronic acid. Hyaluronic acid (HA) is a natural biocompatible polymer, biodegradable and non-toxic, but it is does not favor the attachment of cells. A possible overcoming solution is represented by the use the hydroxyphenyl derivative of HA which is able to covalently crosslink in situ, forming a hydrogel in presence of horseradish peroxidase enzyme and hydrogen peroxidase (Kučera et al., 2015). Moreover, the RGD peptide can be linked to the HA-PH derivative (Zaviskova et al., 2018) in order to favor the attachment of cells on (HP-HA) hydrogel. Human Wharton's jelly derived mesenchymal stem cells (hWJ-MSCs) were encapsulated in the hydrogel, which then was injected in the sub-acute spinal cord hemisection. In situ crosslinking had no cytotoxic effect or negative effect on cells. HA-PH-RGD hydrogel was able to favor axonal ingrowth and the presence of hWJ-MSCs increases the effect. However, there were no improvements of motor function probably due to the low quantity of cells incapsulated inside the gel.

Extracellular matrix-based hydrogels

Another type of natural-based hydrogel is represented by decellularized ECM: it is suitable for tissue regeneration because of its biocompatibility, biomolecular and complex chemical composition which characterize it and distinguish it from other scaffolds. Decellularization is performed by different chemical, physical or enzymatic method and then the decellularized ECM is transformed in a liquid phase using pepsin solubilization at pH < 2 in order to be injected into the site of injury. The physiological temperature and pH favor its crosslinking in situ, leading to its original structure. The research group of Kubinova tried to use ECM-based hydrogels derived from CNS, such as porcine spinal cord (SC-ECM), and non-CNS derived, such as human umbilical cord tissue (UB-ECM) and porcine urinary bladder (UB-ECM). After implantation into injured spinal cord they stimulated nerve tissue regeneration and no differences on biological response were seen between the use of CNS and non-CNS–derived ECM (Kočí et al., 2017; Medberry et al., 2013). However, a critical problem was represented by the fast degradation rate of the scaffold, which was due to the infiltration of resident cells present in the site of lesion.

Therefore, inadequate structure was provided to the new tissue and a correct regeneration of the tissue was compromise. In order to decrease the rate of degradation it was necessary to increase the number of crosslinks. This can be done using crosslinking agents such as genipin, which is able to bridge free amino groups present in the ECM. Its use on the UC-ECM hydrogel did not increase in vivo inflammatory response (Výborný et al., 2019), moreover the lack of ethical problems and the allogeneic source leads to consider promising the use of umbilical cord in neural tissue regeneration.

Nanomaterials

Nanotechnology and nanomedicine

Nanotechnology is the synthesis and characterization of nanosystems and their application in different fields, from the research to the industrial practice. When nanotechnology is applied in medicine and healthcare, it is called nanomedicine. Nanomedicine covers different medical fields such as prevention, diagnosis and treatment. It uses nanomaterials in the range of 10–1000 nm for interacting with biological systems at the molecular level. In addition, the resulting high surface area per unit volume favors a higher number of interactions with biological systems. Thanks to the binding with specific cellular receptors nanosystems can also deliver drugs and molecules in specific site without damaging the surrounding healthy tissue. Nanomedicine developed a lot of structures such as nanoparticles, nanotubes, nanorods, nanogels, quantum dots, etc., but the most used in SCI field are nanoparticles, nanogels, and nanotubes.

Properties of nanomaterials

The treatment of SCI with drugs administrated by oral, intravenous or intra-arterial ways is not effective due to the filtrating action of the blood–spinal cord barrier (BSCB) which prevents the passage of foreign and immunological substance from bloodstream to the SC parenchyma. Nanomaterials can be developed by top-down, bottom-up or hybrid methods. The first method consists in transforming a bulk material to a nanosized material, the second one consists in forming a nanomaterial starting from molecular arrangements and interactions whereas the last method is based on mixing the previous two. Nanocarriers have to correspond to specific size in order to favor their migration across the biological barrier of spinal cord and the target the desired tissue. Smaller particles are more suitable for this purpose and the possible presence of ligands on their surface can bind to receptor molecule of neural cells favoring the activation of specific cellular response. The drawback of using small particles is the limited control on modification in a batch-to-batch synthesis approach (Saraiva et al., 2016). Furthermore, the shape of the nanovectors influences their behavior inside biological environments and their cellular uptake too.

Specifically, in the case of nervous system, nanorods characterized by targeting peptides are considered more able than nanoparticles in accumulating in specific vascular environment without activating immune clearance (Kolhar et al., 2013) or, for example, biconcave nanoparticles enhance the release of drug respect to spherical or tubular particles (Zuidema, Gilbert, & Osterhout, 2016). Finally, surface charge has a key role with respect to the final aim of particles. In general, positively charged nanoparticles are better internalized by cells (Xiao et al., 2011; Yue et al., 2011) but the modification with chemical groups or peptides can change the surface charge leading to a different aim such as to target a specific area or avoid activation of immune systems. As for the composition of hydrogels, also nanomaterials can be made by synthetic or natural materials. Natural nanomaterials are in general biocompatible, non-toxic and very similar in composition and chemical features with the biological environment allowing a weak immune response, but it is difficult to achieve a good

reproducibility during their development and production. On the other hand, synthetic nanomaterials guarantee a high reproducibility and possibility to modify their chemical, physical and morphological properties adapting them to the final purpose, but their immunogenicity is higher compared to the natural ones. Natural materials used for developing nanoparticles are collagen, lipids, albumin, fibrin, silicone, alginate, agarose, hyaluronic acid, chitosan, cellulose, heparin and chondroitin sulfate, whereas synthetic materials used are polyethylene glycol (PEG), polyethyleneimine (PEI), polylactic acid (PLA), poly(lactic-co-glycolic acid) (PLGA), polyglycolic derivatives, polymethacrylate, polyacrylates, polycyanoacrylates, and poly(ε-caprolactone) (PCL). Fig. 1 represents a summary of natural and synthetic polymers.

Nanoparticles

Nanoparticles are colloidal systems made of polymer chains from which is possible to obtain nanospheres or nanocapsules (Fig. 2). Nanosphere are systems with a size of 100–200 nm composed of a solid matrix with physically or chemically entrapped drug (Liu, Xiao, & Allen, 2004). They can be covered at their surface with surfactants or hydrophilic polymers which avoid opsonization and subsequent internalization from immune cells. Nanocapsules are nanosystems composed by an external polymeric layer which surround a lipophilic core.

These systems are very useful in encapsulating hydrophobic drugs in the core of nanoparticle and releasing them in situ. Generally, they are made of PLA, PLGA or PCL surrounded by hydrophilic PEG in order to avoid the activation of immune system. Finally, polymersomes are nanocapsules made of an aqueous core able to encapsulate hydrophilic drugs. In this case the aqueous core is enclosed by amphiphilic copolymers which expose hydrophilic segments in the core and external surface, whereas hydrophobic segment in the middle.

There are different techniques used to synthetize nanoparticles:

- Emulsion: it consists in emulsifying an oil phase containing hydrophobic monomers with a water phase containing surfactants. The polymerization of hydrophobic monomers starts after the addition of oil-soluble initiators forming polymeric particles inside an aqueous phase. In order to avoid opsonization and aggregation between nanoparticles, surfactants bind to the surface of particles by a polycondensation reaction between the two monomers present in the oil and in the aqueous phase or by the presence of initiators. The drug can be encapsulated during the polymerization process or absorbed at the end of the polymerization.
- Nanoprecipitation: it consists in desolvation of polymers dissolved in the solvent solution after the addition of it to the non-solvent solution.
- Solvent evaporation: emulsifying agents dissolved in water phase are added to an organic phase containing drug and polymer dissolved. The formation of oil/water emulsions is followed by solvent evaporation by using temperature or low pressure obtaining the nanoparticles.
- Salting out: the organic solution containing the polymer is added to an aqueous phase containing an emulsifier and a high concentration of salts. Then, pure water is added to promote the diffusion of organic solvent into water phase forming nanoparticles.
- Controlled gelification: gel nanospheres can be formed by using sodium alginate and calcium chloride.
- Desolvation: this method can be used only on natural polymers which are dissolved in aqueous environment. The following drip of a desolvating agent, such as ethanol or acetone, containing active molecule and the addition of cross-linking molecules in polymeric solution allow to obtain nanoparticles.
- Coacervation: coacervates are formed by electrostatic interactions between cargo aqueous phase and polymer.

As regard to nanocapsules, they are formed by mixing an oil-containing lipophilic surfactants with an aqueous phase miscible with organic solvent containing polymeric chains and therapeutic molecules. Under stirring, oil droplets are forming in the aqueous phase and polymers interact with the two phases exposing the hydrophobic chain toward the oil component and the hydrophilic one toward the aqueous phase. A method recently developed is based on following addition of water to the system favoring the passage of solvent from the center of nanoparticles to the external phase. Finally, polymersomes are formed starting from a copolymers dissolved in an organic solvent. Then the solvent evaporates leading to the formation of a polymeric layer and water is added to rehydrate polymers.

The following sonication and extrusion of solution lead to the formation of polymersomes. In the case the therapeutic molecule is a protein, some steps such as the use of organic solvent or sonication can denature the protein leading to its inactivation. In this case, the addition of natural salts or alcohols can affect its 3D structure favoring aggregates with polymer chains. At last, the use of glutaraldehyde can stabilize the nanoparticles.

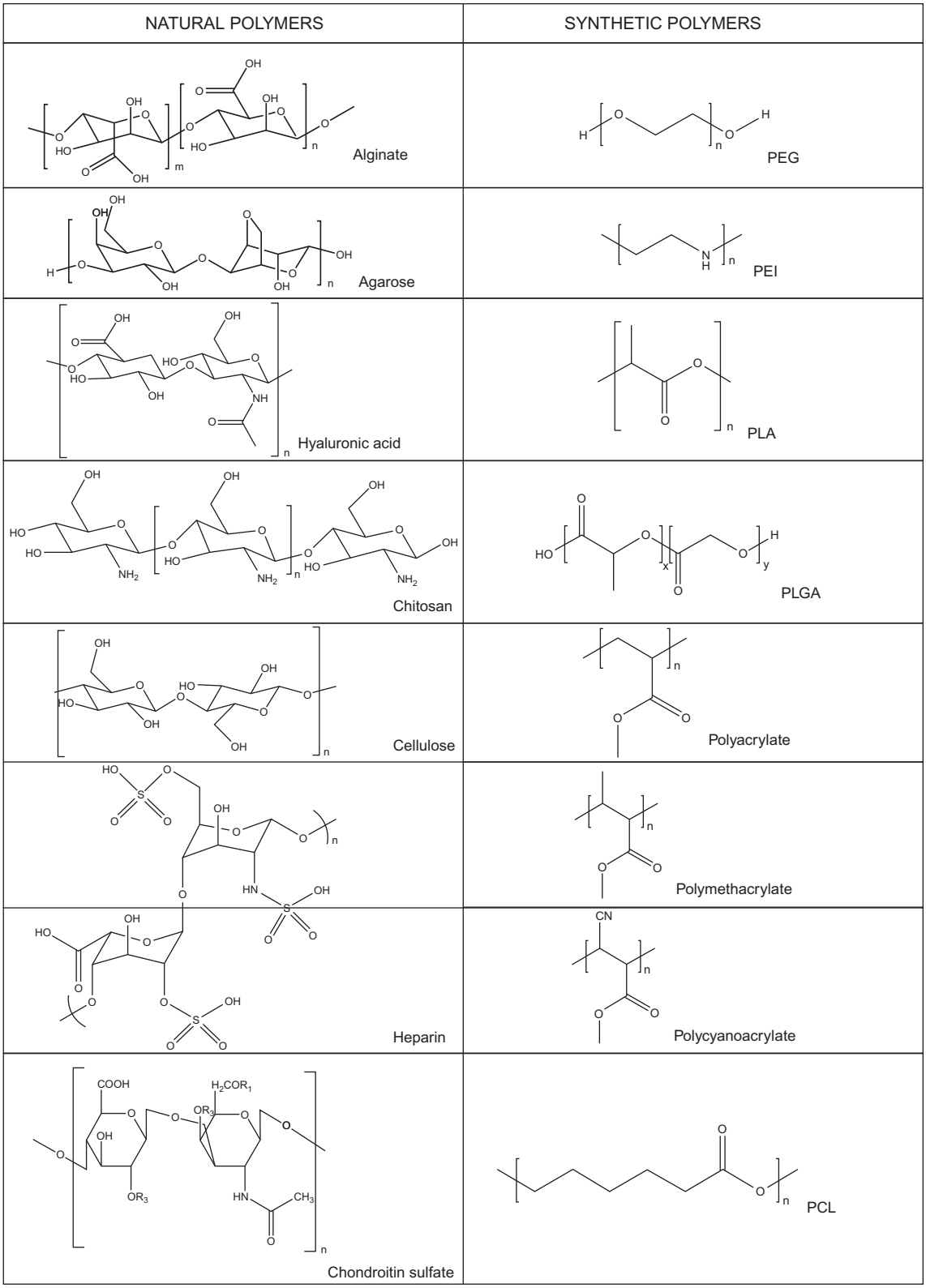

FIG. 1 Polymers for NPs. Chemical structure of natural and synthetic polymers used for developing NPs.

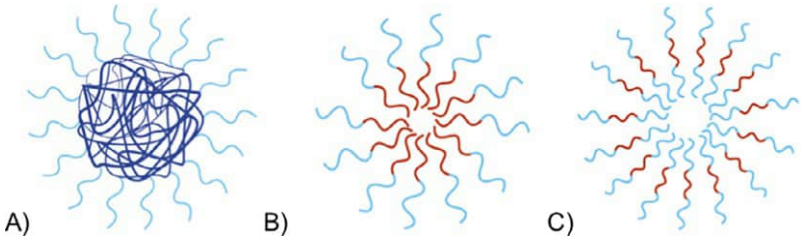

FIG. 2 Different NPs. Structure of (A) nanospheres, (B) nanocapsules, and (C) polymersomes.

Functionalization of nanoparticles

Nanoparticle functionalization is needed in order to increase its half-life and favor its interaction with the targeted cells. In case of SCI it is important that nanoparticles are able to pass across the BSCB and reach the site of injury providing neuroprotective and/or neuro-regenerative effect. The functionalization can consist in addition of surfactants, biomolecule, dyes (for in vitro and in vivo tracking) and peptides by linking them to functional polymer groups such as hydroxyl, amine, carboxylic or alkyl groups. For example the presence of antioxidant enzyme superoxide dismutase on the surface of nanoparticles induces neuroprotective action (Varma et al., 2013) or the release of encapsulated fibroblast growth factor-2 inside PLGA nanoparticles reduces vasoconstriction in SCI during primary injury and favors angiogenesis (Kang, Baumann, Tator, & Shoichet, 2012). Reactions with functional groups such as the carboxyl group can link chitosan to a PEG grafting biotin able to attract monoclonal antibody OX26 leading to a decrement of neuronal cell death in injured spinal cord (Aktaş et al., 2005). The functionalization can be performed also on cation polymers such as PEI or chitosan. The most common methods to functionalize amine groups are making a reaction with thiol or maleimide group forming a disulfide bond.

The effects of encapsulated neurotrophin

Neurotrophin is a protein that induces axonal regeneration and can be used as therapeutic molecule in case of SCI. The research group of Elliot Donaghue et al. was able to encapsulate neurotrophin-3 (NT-3) inside PLGA 220 nm nanoparticles through a double emulsion-solvent evaporation method, and then to entrap nanoparticles inside a hyaluronan/methyl cellulose matrix in order to have a more confined and controlled release of NT-3 (Elliott Donaghue, Tator, & Shoichet, 2015). In particular, the diffusion of NT-3 outside the matrix lasted 50 days in in vitro studies and 28 days in in vivo studies, leading to consider this system as a possible solution in order to limit the number of dosing. In addition, a higher locomotor recovery and axonal growth was seen in mouse model study after the treatment with PLGA NPS loaded with NT-3, compared to the controls.

Nanogels

Nanogels are innovative nanoparticles with hydrophilic properties and high colloidal stability. They are characterized by swelling behavior which gives them the unique ability to exchange ions and biological molecules with the surrounding environment maintaining an equilibrium of metabolites between the internal and external parts. In addition, their deformability allows an easy passage through biological barrier and this characteristic, together with the swelling behavior, allows considering nanogels soft materials because of their similar properties to hydrogels. Nanogels can be developed starting from monomers of low molecular weight or from polymeric precursors. In the first case, monomers polymerize thanks to a controlled living radical polymerization using an initiator molecule from which the polymerization starts and propagates forming the nanoparticle, whereas in the second case the process is characterized by an inter-polymer interactions. Particularly, functional groups of polymer precursors chemically interact each other forming covalent bonding between polymer chains. Another possible technique is based on physical interactions between polymer chains such as hydrogen bonding, electrostatic interactions, Van der Walls forces or hydrophilic/hydrophobic interactions. In this case, the final nanogel has a low stability and its structure can be easily compromised by temperature, pH or external forces. A new strategy that can be used to produce nanogels is represented by the non-wetting templates (PRINT) technology. It is a lithographic technique that uses non-wetting elastomeric templates inside which nanogels are formed allowing a high reproducibility. Another new approach is represented by molecular imprinting, although its use is very difficult in nanogel developing. It consists in a linkage of a chosen protein on a functional monomer in order to form a template molecule. Then the polymerization starts

using cross-linking agent and the protein is detached. The remaining polymer will present a cavity complementary to the protein and it will be used for selective cell targeting during the treatment of SCI.

Functionalization of nanogels

The functionalization of nanogels with drug, peptides, proteins, enzymes, dyes, etc. can be performed using different types of reactions (Fig. 3): formation of amide bond from an ester bond, esterification, ring opening and Schiff base reactions,

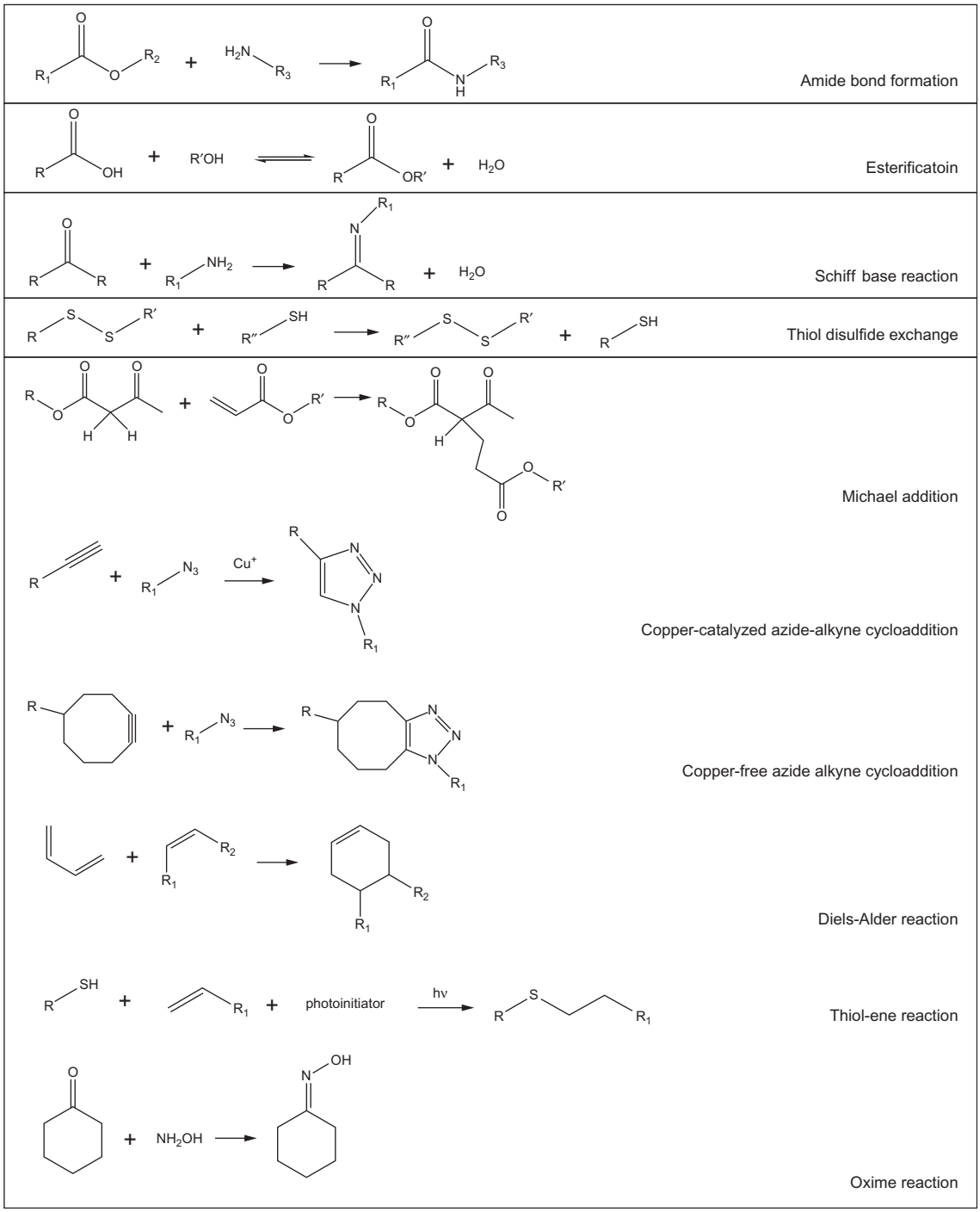

FIG. 3 Polymer functionalization. Different strategies of polymer functionalization.

thiol disulfide exchange and finally click chemistry which includes Michael type addition, copper-catalyzed and copper-free azide-alkyne cycloaddition, Diels–Alder reaction, thiol-ene reaction or oxime reaction. Depending on the type of chemical bond, the *cargo* can be released according to a change of temperature, pH, the presence of enzymes or other external stimuli able to break the bond. For example, redox-responsive NGs are able to accumulate in the target tissue and release the cargo only when redox stimulus is applied (Ghorbani & Hamishehkar, 2019).

In another study, the research group of Mauri et al. (2017) developed nanogels able to be internalized by microglia cells and release the therapeutic *cargo* only in the cytosol. In this case, the fast release in biological fluids that characterizes the hydrophilic drugs and the following rapid clearance from the body is avoided. The drug mimetic, rhodamine, was linked to PEG using the thiol chemistry forming a disulfide bond that can be broken in the cytosol by glutathione or cysteines, whereas the Cy5 dye was linked to the PEI by copper-catalyzed alkyne-azide cycloaddition. Finally, carbamate bonds formed the final nanogel. In vitro studies showed florescent signals inside the cytosol demonstrating the internalization of nanogels from microglia and the release of drug in the cytosol after 4 days. The functionalization can also be non-covalent if other interactions occur. This is the case of PEI functionalization in which electrostatic attraction between genes, peptide or growth factor and protonated amine on polymer chains is used to functionalize the nanogel.

Nanochannels, nanotubes, nanowires, and conduits

It is worth mentioning other nanostructures that are used in SCI repair: tubular particles such as nanotubes (NTs), nanowires (NWs), and nanofibers (NFs) can guide axonal regeneration and limit the local inflammation at the same time.

Nanotubes are cylinders with a diameter in the order of nanometers, made of graphene. These structures are similar to cytoskeletal elements in neurons, signaling proteins and ion channels, so their presence does not activate immune or inflammatory responses. Their flexibility, electrical conductivity, and durability allow their implantation in the spinal cord for a long time. In addition, they can be functionalized with active molecules, such as 4-hydroxynonenal which promotes neurons spatial orientation and interconnections (Mattson, Haddon, & Rao, 2000), neurotrophic factors which provide neuroprotective effect or chemical groups which confers superficial charge to stimulate axonal growth. In vivo studies about the injection of NTs during the secondary injury phase showed a reduction of injured site, an increment of neurofilament-positive fibers and a partial recovery of locomotor functions (Roman, Niedzielko, Haddon, Parpura, & Floyd, 2011).

Nanowires are structures similar in shape with that on nanotubes but in this case the length is much longer than the diameter. In addition, they are generally made with metals, semiconductors, insulators or polymers with electric properties. They can be used for SCI repair in order to provide cell adhesion, proliferation, and electric stimulation as made by Bechara and coworkers (Bechara, Wadman, & Popat, 2011) with PCL NWs linked with polypyrrole, an electroconductive polymer.

Nanofibers (NFs) are the third most common nanosystems used for nerve regeneration. Their spatial orientation and diameter are able to positively influence cell behavior and differentiation. In particular, cell aggregation decreases and cell proliferation increases as the diameter of NFs decreases, whereas aligned NFs results in higher rate of neural stem cell differentiation than NFs oriented in random way (Xie et al., 2009; Yang, Xu, Kotaki, Wang, & Ramakrishna, 2004). Also in this case, NFs can be functionalized at their surface with specific chemical groups or molecules which confers surface charges, such as Rolipram in PLGA NFs (Zhu et al., 2010), able to improve axonal growth and reduce inflammatory response in the site of injury.

Conduits are cylindrical systems used to cover nerve gap and provide a guide for nerve regeneration. Promising conduits are made of PLGA-chitosan or PCL because of their effect in promoting remyelination of axons. Even if their use has positive effects on nerve repair, their implantation is invasive causing infections, inflammation and other permanent damages, making the risk/benefit balance unfavorable.

Case study: Agarose–carbomer-based hydrogels

Even if the polymers used for biomaterials preparation are biocompatible, this does not ensure they promote a correct cell viability; functional compounds are hence needed in order to provide an interaction between the cells and the polymeric scaffold. RGD peptide, for example, can be used for scaffold functionalization because of its ability to bind to the receptors present on the surface of cell membrane and activate a cell adhesion response. The research group of Perale and Rossi (Caron et al., 2016; Papa et al., 2018) proved the extremely promising results obtained with functionalized poly-acrylic acid (PAA) and polyethylene glycol (PEG) with RGD peptide by using a click chemistry strategy. In particular, PAA polymer was previously functionalized with an alkyne group (Fig. 4) (Mauri et al., 2018). Then, CuAAC click reaction between RGD azide and alkyne polymers was conducted at 50°C–60°C forming the triazole. Finally, the hydrogel was synthesized by microwave-assisted polycondensation between mixed RGD-functionalized polymers and agarose.

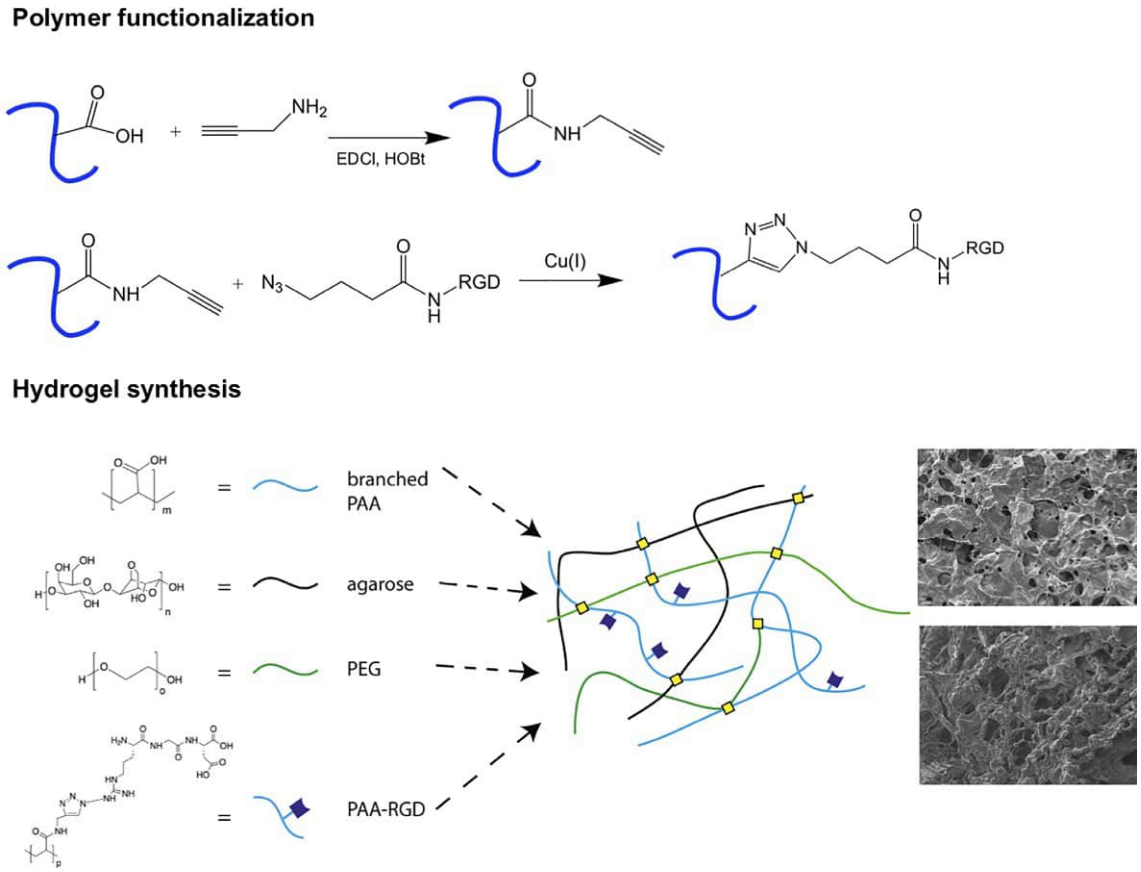

FIG. 4 Agarose–Carbomer-based hydrogels. Schematic representation of RGD-functionalized (HG-RGD) hydrogels. *(Adapted from Mauri, E., Sacchetti, A., Vicario, N., Peruzzotti-Jametti, L., Rossi, F., & Pluchino, S. (2018). Evaluation of RGD functionalization in hybrid hydrogels as 3D neural stem cells culture systems.* Biomaterials Science*, 6(3), 501–510. doi:10.1039/c7bm01056g, with permission from the Royal Society of Chemistry.)*

From SEM analysis of the final hydrogel, there were not differences in polymer network and porous structure compared to the non-functionalized one, and adequate mechanical and morphological properties result from physical and chemical characterization. The system is highly biocompatible, can remain localized in the lesion site, can maintain the stemness of the loaded cells (Fig. 5) in vitro and in vivo improving the locomotor performances of mice (Fig. 6).

Applications to other areas of neuroscience

SCI remains one of the most devastating conditions in neurological diseases. Most of the post traumatic degeneration of the tissue is caused by a multifactorial secondary injury including several interconnected processes. Relevant is the involvement of acute and chronic inflammation, represented mostly by inflammation that contributes to the cascade of harmful events during the secondary injury, in the end leading to spreading and chronicity of SCI. An unresolved inflammation is a pathological hallmark of many neuropathologies and microglial cells can play a relevant role in these scenarios. The current view suggests that under normal physiological condition the acute inflammatory response is a transitory process, aiming at eliminating many potential toxic stimuli, which is followed by resolution of the inflammation and a return to homeostasis. Hence, an acute neuro-inflammatory response is considered generally beneficial to the CNS, since it tends to limits the damages and contributes to the repair of injured tissue. However, in many neuropathologies, an over-activation and an accumulation of microglial cells occurs, due to persistent insults or triggered by factors released in the damaged environment by dead cell. Indeed, a sustained release of pro-inflammatory mediators can propagate the inflammatory reaction, promoting microglia proliferation and further releasing pro-inflammatory factors that fed an uncontrolled response. Therefore, a prolonged and unresolved chronic inflammation due to over-activation of microglial cells can have neurotoxic consequences that could lead to the exacerbation of the pathology.

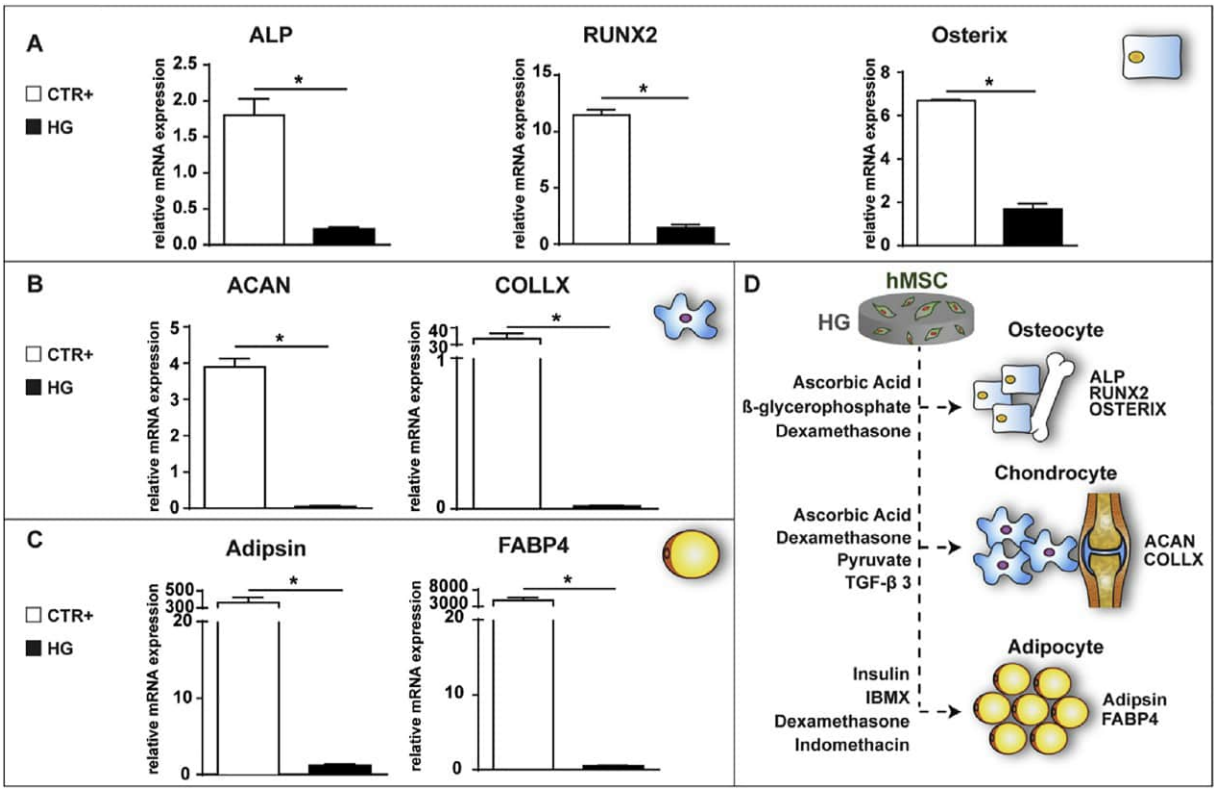

FIG. 5 mRNA analysis of hMSCs encapsulated within biomimetic scaffold. Graphs representing the expression of specific genes related to three differentiation lineages: alkaline phosphatase (ALP), runt-related transcription factor 2 (RUNX2) and osterix for osteogenic differentiation; aggrecan (ACAN) and collagen type X (COLLX) for chondrogenic differentiation and adipsin and fatty acid binding-protein 4 (FABP4) for adipogenic differentiation. hMSCs encapsulated within HG for 21 days are compared to the positive control represented by hMSCs loaded in HG and treated with specific differentiating media for 21 days. *(Reprinted with permission from Caron, I., Rossi, F., Papa S., Aloe, R., Sculco, M., Mauri, E., Sacchetti, A., et al. (2016). A new three dimensional biomimetic hydrogel to deliver factors secreted by human mesenchymal stem cells in spinal cord injury*. Biomaterials, *75(1), 135–147. doi:10.1016/j.biomaterials.2015.10.024, Elsevier.)*

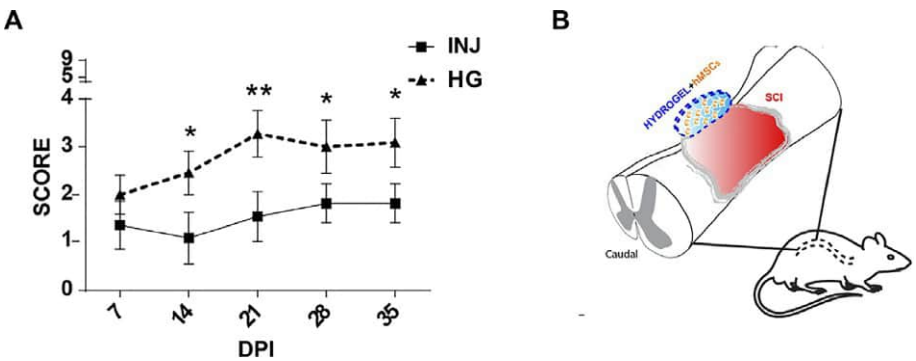

FIG. 6 HG ability to improve locomotor performance in SCI mice. In vitro HG ability to improve locomotor performance in SCI mice: (A) untreated SCI mice (INJ) or treated (HG) 1 DPI examined weekly starting 7 days post treatment, using the Basso Mouse Scale-BMS (score 0, complete paralysis, 9 complete mobility, referred to healthy mice). (C) Positioning of the hydrogel + cells in the SCI mouse model. *(Reprinted with permission from Papa, S., Vismara, I., Mariani, A., Barilani, M., Rimondo, S., De Paola, M., et al. (2018). Mesenchymal stem cells encapsulated into biomimetic hydrogel scaffold gradually release CCL2 chemokine in situ preserving cytoarchitecture and promoting functional recovery in spinal cord injury*. Journal of Controlled Release, 278*(10), 49–56. doi:10.1016/j.jconrel.2018.03.034, Elsevier.)*

Several neurodegenerative CNS disorders, including traumatic brain injury, spinal cord injury, stroke, amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease, epilepsy and multiple sclerosis are associated with chronic neuro-inflammation and high levels of several cytokines. For these reasons, new therapeutic approaches able to modulate activated microglial cells are needed. In recent years, new evidences, from both in vitro and in vivo studies, suggest that nanoparticles can be selectively internalized by a specific phagocytic activity of macrophages, exploiting them as Trojan horses to selectively treat these cells. This delivery approach represents a promising strategy to develop tailored treatment during the inflammatory response.

Mini-dictionary of terms

Colloids: system composed by a disperse phase with a size range between 1 and 1000 nm dissolved in an incompatible continuous phase.

Drug delivery system: engineered materials able to load and deliver drugs with a controlled kinetics, maintaining the pharmacological activity during time.

Emulsion: thermodynamically unstable colloid constituted by two immiscible liquids.

Functionalization: chemical reaction between two reactive sites with consequent formation of covalent chemical bond.

Hydrogel: network of cross-linked hydrophilic polymeric chains able to absorb an extremely large amount of water (dispersion medium).

Nanogels: nanoparticle, usually in the tens to hundreds of nanometers in diameter, composed of a cross-linked hydrophilic polymer network composed of synthetic polymers or biopolymers chemically or physically cross-linked.

Nanomedicine: medical applications of nanomaterials that range from biological devices, to nanoelectronics biosensors, molecular nanotechnology such as biological machines.

Nanoparticles: particles of matter with size range between 1 and 100 nm (nm) in terms of diameter.

Polymer: substance constituted by very large molecules, or macromolecules, composed of many repeating subunits and that can be synthesized by step-growth or chain-growth mechanisms.

Tissue engineering: biomedical engineering discipline that uses a combination of cells, engineering, materials methods, and suitable factors to maintain, restore or replace different types of biological tissues.

Key facts of "Biomaterials, spinal cord injury, and rehabilitation: A new narrative"

- SCI is the most frequent disabling spinal injury, estimated 2.5 million people worldwide live with SCI
- SCI is a multifactorial where most of the medical problems are caused by cascade of events (secondary injury)
- A winning therapeutic strategy is represented by the possibility to work against different pathological mechanisms.
- Hydrogels, three-dimensional polymeric networks thanks to their water affinity to maintain cells viable and able to restore the damaged tissue.
- Nanoparticles, thanks to their ability to be cell selective, can carry and deliver drugs into specific cells working as Trojan horses.

Summary points

- SCI is a debilitating condition caused by damage to the spinal cord.
- More than 130,000 new spinal cord injuries are reported every year.
- Hydrogel can restore the tissue carrying cells within the damage site.
- Scaffold can drive axonal growth across their ordered pores.
- Nanoparticles can selectively deliver drugs within cells reducing secondary injury issues.

References

Aktaş, Y., Yemisci, M., Andrieux, K., Gürsoy, R. N., Alonso, M. J., Fernandez-Megia, E., et al. (2005). Development and brain delivery of chitosan-PEG nanoparticles fnnctionalized with the monoclonal antibody OX26. *Bioconjugate Chemistry*, *16*(6), 1503–1511. https://doi.org/10.1021/bc050217o.

Bechara, S., Wadman, L., & Popat, K. C. (2011). Electroconductive polymeric nanowire templates facilitates in vitro C17.2 neural stem cell line adhesion, proliferation and differentiation. *Acta Biomaterialia*, *7*(7), 2892–2901. https://doi.org/10.1016/j.actbio.2011.04.009.

Caron, I., Rossi, F., Papa, S., Aloe, R., Sculco, M., Mauri, E., et al. (2016). A new three dimensional biomimetic hydrogel to deliver factors secreted by human mesenchymal stem cells in spinal cord injury. *Biomaterials*, *75*(1), 135–147. https://doi.org/10.1016/j.biomaterials.2015.10.024.

Elliott Donaghue, I., Tator, C. H., & Shoichet, M. S. (2015). Sustained delivery of bioactive neurotrophin-3 to the injured spinal cord. *Biomaterials Science*, *3*(1), 65–72. https://doi.org/10.1039/c4bm00311j.

Gao, M., Lu, P., Bednark, B., Lynam, D., Conner, J. M., Sakamoto, J., et al. (2013). Templated agarose scaffolds for the support of motor axon regeneration into sites of complete spinal cord transection. *Biomaterials*, *34*(5), 1529–1536. https://doi.org/10.1016/j.biomaterials.2012.10.070.

Georges, P. C., Miller, W. J., Meaney, D. F., Sawyer, E. S., & Janmey, P. A. (2006). Matrices with compliance comparable to that of brain tissue select neuronal over glial growth in mixed cortical cultures. *Biophysical Journal*, *90*(8), 3012–3018. https://doi.org/10.1529/biophysj.105.073114.

Ghorbani, M., & Hamishehkar, H. (2019). Redox-responsive smart nanogels for intracellular targeting of therapeutic agents: Applications and recent advances. *Journal of Drug Targeting*, *27*(4), 408–422. Taylor and Francis Ltd https://doi.org/10.1080/1061186X.2018.1514041.

Hejčl, A., Kekulová, K., Svobodová, B., Proks, V., Macková, H., Jiránková, K., et al. (2018). Modified methacrylate hydrogels improve tissue repair after spinal cord injury. *International Journal of Molecular Sciences*, *19*, 2481. https://doi.org/10.3390/ijms19092481.

Hejčl, A., Růžička, J., Proks, V., Macková, H., Kubinová, Š., Tukmachev, D., et al. (2018). Dynamics of tissue ingrowth in SIKVAV-modified highly superporous PHEMA scaffolds with oriented pores after bridging a spinal cord transection. *Journal of Materials Science: Materials in Medicine*, *29*(7), 89. https://doi.org/10.1007/s10856-018-6100-2.

Hejčl, A., Šedý, J., Kapcalová, M., Toro, D. A., Amemori, T., Lesný, P., et al. (2010). HPMA-RGD hydrogels seeded with mesenchymal stem cells improve functional outcome in chronic spinal cord injury. *Stem Cells and Development*, *19*(10), 1535–1546. https://doi.org/10.1089/scd.2009.0378.

Jurga, M., Dainiak, M. B., Sarnowska, A., Jablonska, A., Tripathi, A., Plieva, F. M., et al. (2011). The performance of laminin-containing cryogel scaffolds in neural tissue regeneration. *Biomaterials*, *32*(13), 3423–3434. https://doi.org/10.1016/j.biomaterials.2011.01.049.

Kang, C. E., Baumann, M. D., Tator, C. H., & Shoichet, M. S. (2012). Localized and sustained delivery of fibroblast growth factor-2 from a nanoparticle-hydrogel composite for treatment of spinal cord injury. *Cells, Tissues, Organs*, *197*(1), 55–63. https://doi.org/10.1159/000339589.

Kočí, Z., Výborný, K., Dubišová, J., Vacková, I., Jäger, A., Lunov, O., et al. (2017). Extracellular matrix hydrogel derived from human umbilical cord as a scaffold for neural tissue repair and its comparison with extracellular matrix from porcine tissues. *Tissue Engineering—Part C: Methods*, *23*(6), 333–345. https://doi.org/10.1089/ten.tec.2017.0089.

Kolhar, P., Anselmo, A. C., Gupta, V., Pant, K., Prabhakarpandian, B., Ruoslahti, E., et al. (2013). Using shape effects to target antibody-coated nanoparticles to lung and brain endothelium. *Proceedings of the National Academy of Sciences of the United States of America*, *110*(26), 10753–10758. https://doi.org/10.1073/pnas.1308345110.

Kubinová, Š., Horák, D., Hejčl, A., Plichta, Z., Kotek, J., Proks, V., et al. (2015). SIKVAV-modified highly superporous PHEMA scaffolds with oriented pores for spinal cord injury repair. *Journal of Tissue Engineering and Regenerative Medicine*, *9*(11), 1298–1309. https://doi.org/10.1002/term.1694.

Kubinová, Š., Horák, D., Kozubenko, N., Vaněček, V., Proks, V., Price, J., et al. (2010). The use of superporous Ac-CGGASIKVAVS-OH-modified PHEMA scaffolds to promote cell adhesion and the differentiation of human fetal neural precursors. *Biomaterials*, *31*(23), 5966–5975. https://doi.org/10.1016/j.biomaterials.2010.04.040.

Kučera, L., Weinfurterová, R., Dvořákova, J., Kučera, J., Pravda, M., Foglarová, M., et al. (2015). Chondrocyte cultivation in hyaluronan-tyramine cross-linked hydrogel. *International Journal of Polymeric Materials and Polymeric Biomaterials*, *64*(13), 661–674. https://doi.org/10.1080/00914037.2014.996715.

Liu, J., Xiao, Y., & Allen, C. (2004). Polymer-drug compatibility: A guide to the development of delivery systems for the anticancer agent, ellipticine. *Journal of Pharmaceutical Sciences*, *93*(1), 132–143. https://doi.org/10.1002/jps.10533.

Macková, H., Plichta, Z., Proks, V., Kotelnikov, I., Kučka, J., Hlídková, H., et al. (2016). RGDS- and SIKVAVS-modified superporous poly(2-hydroxyethyl methacrylate) scaffolds for tissue engineering applications. *Macromolecular Bioscience*, *16*(11), 1621–1631. https://doi.org/10.1002/mabi.201600159.

Mattson, M. P., Haddon, R. C., & Rao, A. M. (2000). Molecular functionalization of carbon nanotubes and use as substrates for neuronal growth. *Journal of Molecular Neuroscience*, *14*(3), 175–182. https://doi.org/10.1385/JMN:14:3:175.

Mauri, E., Sacchetti, A., Vicario, N., Peruzzotti-Jametti, L., Rossi, F., & Pluchino, S. (2018). Evaluation of RGD functionalization in hybrid hydrogels as 3D neural stem cells culture systems. *Biomaterials Science*, *6*(3), 501–510. https://doi.org/10.1039/c7bm01056g.

Mauri, E., Veglianese, P., Papa, S., Mariani, A., De Paola, M., Rigamonti, R., et al. (2017). Double conjugated nanogels for selective intracellular drug delivery. *RSC Advances*, *7*(48), 30345–30356. https://doi.org/10.1039/c7ra04584k.

Medberry, C. J., Crapo, P. M., Siu, B. F., Carruthers, C. A., Wolf, M. T., Nagarkar, S. P., et al. (2013). Hydrogels derived from central nervous system extracellular matrix. *Biomaterials*, *34*(4), 1033–1040. https://doi.org/10.1016/j.biomaterials.2012.10.062.

Papa, S., Vismara, I., Mariani, A., Barilani, M., Rimondo, S., De Paola, M., et al. (2018). Mesenchymal stem cells encapsulated into biomimetic hydrogel scaffold gradually release CCL2 chemokine in situ preserving cytoarchitecture and promoting functional recovery in spinal cord injury. *Journal of Controlled Release*, *278*(10), 49–56. https://doi.org/10.1016/j.jconrel.2018.03.034.

Pires, L. R., & Pêgo, A. P. (2015). Bridging the lesion-engineering a permissive substrate for nerve regeneration. *Regenerative Biomaterials*, *2*(3), 203–214. https://doi.org/10.1093/rb/rbv012.

Roman, J. A., Niedzielko, T. L., Haddon, R. C., Parpura, V., & Floyd, C. L. (2011). Single-walled carbon nanotubes chemically functionalized with polyethylene glycol promote tissue repair in a rat model of spinal cord injury. *Journal of Neurotrauma*, *28*(11), 2349–2362. https://doi.org/10.1089/neu.2010.1409.

Rossi, F., & van Griensven, M. (2014). Polymer functionalization as a powerful tool to improve scaffold performances. *Tissue Engineering Part A*, *20*(15), 2043–2051. https://doi.org/10.1089/ten.tea.2013.0367.

Růžička, J., Romanyuk, N., Hejčl, A., Vetrík, M., Hrubý, M., Cocks, G., … Jendelova, P. (2013). Treating spinal cord injury in rats with a combination of human fetal neural stem cells and hydrogels modified with serotonin. *Acta Neurobiologiae Experimentalis (Wars)*, *73*, 102–115.

Saraiva, C., Praça, C., Ferreira, R., Santos, T., Ferreira, L., & Bernardino, L. (2016). Nanoparticle-mediated brain drug delivery: Overcoming blood-brain barrier to treat neurodegenerative diseases. *Journal of Controlled Release*, *235*, 34–47. Elsevier B.V https://doi.org/10.1016/j.jconrel.2016.05.044.

Varma, A. K., Das, A., Wallace, G., Barry, J., Vertegel, A. A., Ray, S. K., et al. (2013). Spinal cord injury: A review of current therapy, future treatments, and basic science frontiers. *Neurochemical Research*, *38*(5), 895–905. Springer New York LLC https://doi.org/10.1007/s11064-013-0991-6.

Výborný, K., Vallová, J., Kočí, Z., Kekulová, K., Jiráková, K., Jendelová, P., et al. (2019). Genipin and EDC crosslinking of extracellular matrix hydrogel derived from human umbilical cord for neural tissue repair. *Scientific Reports*, *9*(1). https://doi.org/10.1038/s41598-019-47059-x.

Woerly, S., Petrov, P., Syková, E., Roitbak, T., Simonová, Z., & Harvey, A. R. (1999). Neural tissue formation within porous hydrogels implanted in brain and spinal cord lesions: Ultrastructural, immunohistochemical, and diffusion studies. *Tissue Engineering*, *5*(5), 467–488. https://doi.org/10.1089/ten.1999.5.467.

Woerly, S., Pinet, E., De Robertis, L., Van Diep, D., & Bousmina, M. (2001). Spinal cord repair with PHPMA hydrogel containing RGD peptides (NeuroGel™). *Biomaterials*, *22*(10), 1095–1111. https://doi.org/10.1016/S0142-9612(00)00354-9.

Xiao, K., Li, Y., Luo, J., Lee, J. S., Xiao, W., Gonik, A. M., et al. (2011). The effect of surface charge on in vivo biodistribution of PEG-oligocholic acid based micellar nanoparticles. *Biomaterials*, *32*(13), 3435–3446. https://doi.org/10.1016/j.biomaterials.2011.01.021.

Xie, J., MacEwcm, M. R., Willerth, S. M., Li, X., Moran, D. W., Sakiyama-Elbert, S. E., et al. (2009). Conductive core-sheath nanofibers and their potential application in neural tissue engineering. *Advanced Functional Materials*, *19*(14), 2312–2318. https://doi.org/10.1002/adfm.200801904.

Yang, F., Xu, C. Y., Kotaki, M., Wang, S., & Ramakrishna, S. (2004). Characterization of neural stem cells on electrospun poly(L-lactic acid) nanofibrous scaffold. *Journal of Biomaterials Science, Polymer Edition*, *15*(12), 1483–1497. https://doi.org/10.1163/1568562042459733.

Yuan, N., Tian, W., Sun, L., Yuan, R., Tao, J., & Chen, D. (2014). Neural stem cell transplantation in a double-layer collagen membrane with unequal pore sizes for spinal cord injury repair. *Neural Regeneration Research*, *9*(10), 1014–1019. https://doi.org/10.4103/1673-5374.133160.

Yue, Z. G., Wei, W., Lv, P. P., Yue, H., Wang, L. Y., Su, Z. G., et al. (2011). Surface charge affects cellular uptake and intracellular trafficking of chitosan-based nanoparticles. *Biomacromolecules*, *12*(7), 2440–2446. https://doi.org/10.1021/bm101482r.

Zaviskova, K., Tukmachev, D., Dubisova, J., Vackova, I., Hejcl, A., Bystronova, J., et al. (2018). Injectable hydroxyphenyl derivative of hyaluronic acid hydrogel modified with RGD as scaffold for spinal cord injury repair. *Journal of Biomedical Materials Research Part A*, *106*(4), 1129–1140. https://doi.org/10.1002/jbm.a.36311.

Zeng, X., Qiu, X. C., Ma, Y. H., Duan, J. J., Chen, Y. F., Gu, H. Y., et al. (2015). Integration of donor mesenchymal stem cell-derived neuron-like cells into host neural network after rat spinal cord transection. *Biomaterials*, *53*, 184–201. https://doi.org/10.1016/j.biomaterials.2015.02.073.

Zhu, Y., Wang, A., Shen, W., Patel, S., Zhang, R., Young, W. L., et al. (2010). Nanofibrous patches for spinal cord regeneration. *Advanced Functional Materials*, *20*(9), 1433–1440. https://doi.org/10.1002/adfm.200901889.

Zuidema, J. M., Gilbert, R. J., & Osterhout, D. J. (2016). Nanoparticle technologies in the spinal cord. *Cells, Tissues, Organs*, *202*(1–2), 102–115. S. Karger AG https://doi.org/10.1159/000446647.

Chapter 44

Support in spinal cord injury: A focus on robotics

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List of abbreviations

ADL	activity of daily living
AIS	ASIA impairment scale
ARTIC	advance robotic therapy integrated centers
ASIA	American Spinal Injury Association
CNS	central nervous system
CPG	central pattern generator
FES	functional electrical stimulation
SCI	spinal cord injury

Introduction

The incorporation of robotics in the field of neurorehabilitation is taking place rapidly, both in research and in its clinical applications, and is presented as a very promising tool that is changing therapeutic paradigms. In the late 1980s and early 1990s, basic research findings constituted a major change in therapeutic intervention in neurorehabilitation. One of most relevant was that in experimental models with cats subjected to a spinal cord injury (SCI), the subsequent training of the locomotor function applied to them offered good results. In fact, it was shown that these cats with SCI walked effectively when placed on a treadmill with partial weight support (Barbeau & Rossignol, 1987). The suggested mechanism is the activation of the basic neuronal circuitries sufficient to generate efficient stepping patterns and independent standing. Indeed, the operations underlying the elaboration of motor patterns for walking and standing are essentially achieved by the neuronal networks embedded within the lumbosacral segments of the spinal cord (Grillner & Zangger, 1984). These findings led to the concept of spinal learning via activity-dependent plasticity. Following this concept, it was found that locomotor activity can be activated in patients with severe SCI via passive activation of the legs on a treadmill (Barbeau, Danakas, & Arsenault, 1993). Synchronous reciprocal movements of both legs, simulating normal walking are required to activate the locomotor centers in the spinal cord. The repetitive and simultaneous activation of certain sensory and motor pathways with task-specific training can select and reinforce those spinal circuits improving the ability to perform the practiced movement successfully. Thus, functional rehabilitation (i.e., walking) had to be intensive and task-oriented. Intensive and task-oriented are the two are the pillars of the motor learning neuroplasticity-based neurorehabilitation concepts that also justify the development of robotic therapy (Cai et al., 2006; Edgerton, Courtine, Gerasimenko, et al., 2008).

Although these interventions appear promising, in order to translate them into clinical practice in humans, a great effort is needed to standardize the assessments of the therapies applied (Curt, Schwab, & Dietz, 2004). Gait training using partial weight bearing systems on treadmills in patients who had suffered a stroke or SCI was extended in the early 1990s following motor learning principles. This therapy initially presented high costs in terms of personnel and effort, as it required the participation of at least two physiotherapists to mobilize the paralyzed lower extremities of the patient with the intention of reproducing the treadmill walking cycle (Dietz & Harkema, 2004). The great effort that this activity demanded from the physiotherapists limited the duration of the treatment sessions. This limitation led to the idea that a robotic device could

Diagnosis and Treatment of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822498-4.00044-0

serve as an alternative to manual treatment and that such a device could cover the demands of functional training (Colombo, Joerg, Schreier, & Dietz, 2000). This led to the first robotic systems for walking training with weight suspension on treadmills.

These robotic assistive devices enable to start a functional and task-oriented training as soon as possible after the injury and allow an intensive application of adequate afferent feedback and a high number of repetitions of functional movements (Wirz & Rupp, 2012).

Furthermore, the outcome of rehabilitation is better if the patient is more motivated and involved in the treatment (Weber & Stein, 2018). All these without forgetting one of the most evident shortcomings of conventional systems, which is the need to incorporate sensors that provide objective variables of the patient's condition or of the execution of the task, need to be trained. These issues are satisfactorily addressed by robotic devices. This therapy can be applied alone or in combination with other new technologies such as functional electrical stimulation (FES) or virtual reality.

Robotic therapy has experienced a huge boom in the last 15 years. In fact, different clinical guidelines approved its use as a complementary element to conventional therapy in the rehabilitation of patients with upper limb deficits after suffering a stroke (Department of Veterans Affairs et al., 2010). Robotic devices are appropriately adapted to the need to assist limb movements based on their ability to perform simple, repetitive tasks in a consistent manner that facilitates functional recovery and adaptive plasticity (Edgerton & Roy, 2009). There are two main categories: distal end effector devices and exoskeleton-type devices. Distal end effectors were the first to appear and are characterized by the fact that they use a single distal point of contact to guide the movement of the entire limb. In the upper extremity, it can make contact in the hand or forearm, facilitating the movements of the elbow and shoulder. They produce combined movements being difficult to isolate pure simple movements. The operation of exoskeletons is different. They are structures located in parallel to the different parts of the extremities with more than one point of interaction with the person. They provide direct control over each segment of the limb by incorporating individualized motors, also called actuators, which coincide with the anatomical axis of each joint. Thus, each actuator triggers the movement of each joint on which it is located. The design of exoskeletons seems to be more suitable than that of distal effector systems to achieve large joint paths (Krebs, Conroy, Bever, & Hogan, 2012).

In this chapter, we will focus on upper limb robots, stationary and ambulatory lower limb exoskeletons.

Upper limb robots

Cervical SCI can result in partial or complete tetraplegia. Each small improvement in motor control of the upper extremity can translate to significant ameliorations in function and increases independence for the individual. As mentioned above, this type of therapy offers new possibilities in the rehabilitation not only for the lower limbs but also for the upper limbs. The robotic devices allow the application of high-intensity sessions during longer periods of time, remaining invariable certain physical parameters such as speed, strength, or precision (Page, Hill, & White, 2013; Takahashi, Der-Yeghiaian, Le, Motiwala, & Cramer, 2008). There is evidence that suggests task-based therapy specifically designed to deal with lost abilities produce better results than resistance strengthening exercises (Teasell & Kaira, 2004). This task should be performed by the patient as far as possible. That's why the devices should be equipped with a controller that provides the least assistance needed to accomplish the movement (assist as needed) and reproducible treatment protocols.

Some studies point out that by focusing the improvement of robotic therapy more on the proximal recovery of the upper limb (shoulder and elbow), it does not translate into improvement of the functional ability that depends on hand control. However, the best results seem to be found by adding the application of both types of therapies (Bayona, Bitensky, Salter, & Teasell, 2005). Despite the low number of studies, results from these studies suggest that robotic training protocols are feasible and well tolerated and have a positive impact on improving arm and hand functions in selected patients with cervical SCI, but the results must be interpreted with caution (Mehrholz, Platz, Kugler, & Pohl, 2009). In any case, studies with larger samples are needed, especially those that analyze the distal region of the upper limb, in order to have solid conclusions about the effectiveness of these devices.

Most of the current devices include a virtual reality module with visual or haptic feedback to improve sensory feedback, as well as patient motivation and engagement. They also have the capability to obtain movement kinematics that can provide precise information about movement quality that otherwise is not included in functional assessments (Esquenazi & Talaty, 2019).

Although there is a number of different robotic devices currently used for neurorehabilitation of the upper extremities following SCI (Fig. 1), we will now focus on the most commonly used:

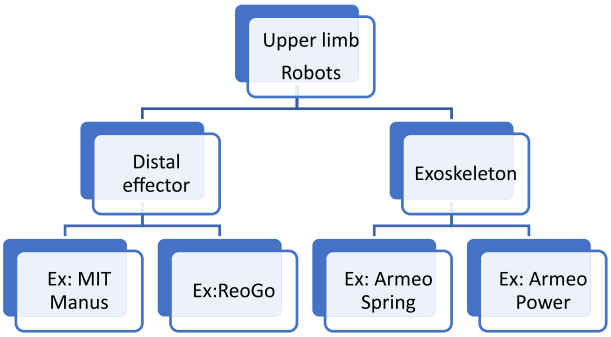

FIG. 1 Types of upper limb robots.

MIT MANUS

It was designed to provide high-intensity and reproducible upper limb rehabilitation in adults and older children. This modular distal effector system consists of a series of proximal and distal components that can be used individually or together for upper extremity training. It comprises two modules and 5 degrees of freedom, two for elbow and forearm motion, and three for wrist motion and allows patients to perform reaching movements in horizontal plane. The robot can move, guide, or perturb the movement of a patient's upper limb and record quantities, such as position, velocity, and force. The operating paradigm is the so-called "assist as needed." Thanks to motion sensors, the mobility of the joint segments can always be monitored. The patient–robot interface consists of video games for elbow, shoulder, and wrist exercises that can be used to increase the quality of therapy sessions as well as keep the user engaged (Krebs, Hogan, Aisen, & Volpe, 1998). It has initially been used in the rehabilitation of the upper limb of stroke patients, proving effective in the sub-acute and chronic phases by reducing motor deficits, improving function and bringing about a lasting change (Bayón-Calatayud et al., 2014; Fasoli et al., 2004). The commercialized version of MIT-MANUS, INMOTION (Bionik Laboratories Corp., Toronto, Canada), has been used in patients with SCI to a limited extent although one study demonstrated that after a training protocol, significant improvements in quality of movement were found with no changes in upper extremity strength, pain, or spasticity (Cortés et al., 2013).

ReoGo

The ReoGo system (Motorika Medical, Caesarea, Israel) is a stationary fixed based end-effector arm rehabilitation robot, which facilitates the mobilization of the upper limb on a support that allows a wide range of movements in the 3 dimensions of space. The Reo-Go allows for movements at the shoulder, elbow, and wrist. It also uses a real-time visual feedback monitor to display games for the subject to perform. Although it has primarily been used for stroke patients, it has also been applied in SCI. Reo-Go was incorporated into an acute incomplete SCI patient therapy protocol. The subject demonstrated remarkable improvements in muscle strength, active range of motion and functional assessment (Siedziewski, Schaaf, & Mount, 2012).

Armeo

Armeo devices (Hocoma AG, Volketswil, Switzerland) were the first unilateral upper extremity exoskeletons marketed for upper limb rehabilitation. This range of devices includes the Armeo Power for the most affected patients, the Armeo Spring, the Armeo Spring for children and the Armeo Senso for those less affected.

The Armeo system is a well-documented device and is the only device shown to offer better functional results after stroke compared to traditional therapy. Two studies showed the utility of this device for upper limbs in SCI subjects focusing on the potential of these devices in performing upper limb assessment (Rudhe, Albisser, Starkey, Curt, & Bolliger, 2012; Zariffa et al., 2012). The Armeo Power is one of the most advanced active exoskeletons for upper extremity rehabilitation. It is based on the ARMin device, which consists of an exoskeleton covering the upper limb and allowing anthropometric adaptations. It provides support for the weight of the patient's upper limb and features different modes of use, such as mobilization mode, 2D and 3D games and functional training of daily life activities. ARMin provides three actuated degrees of freedom for the shoulder and one for the elbow joint. It offers three different therapy modes: the movement therapy, the game therapy and the ADL (activity of daily living) training mode. Like the MIT-MANUS, Armeo

FIG. 2 Armeo Spring. Upper limb device that works through a system of springs that eliminate the weight of the body as an enabler.

Power uses an "assist as needed" mode of operation, allowing the clinician to adapt the difficulty of the task to the degree of recovery. There are studies that demonstrate its usefulness in patients with SCI (Rudhe et al., 2012).An earlier version is the Armeo Spring that manages to cover the shoulder and elbow, and also works the wrist flexo-extension and manual gripping. It is a passive exoskeleton (Fig. 2). It works through a system of springs that eliminate the weight of the body as an enabler instead of using motors to assist movement as the Armeo Power does. Both feature a monitor with motivational games to encourage repetitive movements. The software allows the clinician to select the task and its degree of difficulty by defining the required joint path and the rhythm of the selected game.

Other devices

There are other devices on the market such as the DIEGO (Tyromotion, Graz, Austria) which uses a wiring system to support and mobilize the limb, the Bi-Manu-Track (RehaStim, Germany) which facilitates the treatment of both upper limbs simultaneously. There are devices that focus on the individual mobility of each finger but allow practice in gripping by controlling the performance of each finger. This would be the case of AMADEO (Tyromotion, Graz, Austria), HAND-CARE 2 and RUTGERS-MASTER II (Rutgers University, USA), although the latter excludes the treatment of the fifth finger. It is not common but in some cases two robotic devices have been used in combination, such as the Armeo Power and the Amadeo, using the first for the shoulder, elbow, and carpal and the second for the shoulder, elbow, and carpal.

Stationary lower limb robots

Thoracic and lower SCIs can result in partial to complete paralysis of the lower extremities. Independent mobility for many can only be achieved at a wheelchair level, although walking oftentimes remains a priority (Dittuno, Patrick, Stineman, & Dittuno, 2008). Lower limb robots have emerged as potential upright mobility devices for those with lower limb paralysis. Locomotor training focuses on retraining the motor function via plastic change (Morawietz & Moffat, 2013; Nam et al., 2017), and the neurophysiological mechanism underlying the restoration of human restoration after SCI involve enhancing the afferent input to the spinal cord and activating CPG (central pattern generator) embedded within the lumbosacral spinal cord (Dietz, Wirz, & Curt, 1998). Plastic changes can be induced in both the spinal cord level and sensory motor cortex via intensive locomotor training, mainly in incomplete SCI subjects (Hubli & Dietz, 2013).

As it has been previously referred, to manually replicate a normal walking pattern with the patient in body weight-supported on a treadmill two or three therapists are needed to control and move lower limbs. This is a strenuous and exhausting task for therapist, so sophisticated automated electromechanical devices have been developed (Tefertiller, Pharo, Evans, & Winchester, 2011) that offers several advantages, including the ability to increase the intensity and total duration of training while maintaining a physiological gait pattern.

TABLE 1 Types of lower limb robots.

Lower limb robots		
Stationary robots		**Ambulatory exoskeletons**
Distal effector	Stationary exoskeletons	Ex: Ekso Bionics, Rewalk, Indego, etc.
Ex: Gait Trainer	Ex: Lokomat	

As in the case of the upper limbs, in the lower limb robots we also find, depending on their structure, distal effectors and exoskeletons (Table 1). Among lower limb robotic exoskeletons, we can distinguish the stationary and the ambulatory ones. In this section we will discuss the stationary ones, and the ambulatory will be analyzed in the following section.

End effector devices

End-effector-based systems work like conventional elliptical trainers: the subject's feet are strapped to two footplates moving along a gait-like trajectory, as in an elliptical trainer, moving the entire lower limb. They work based on a constraint at the distal end of the kinetic chain that specifies the trajectory there and the proximal joints can simply move as the body geometry and articulations dictate. The footplates generate the stance and swing phases in most instances with symmetric motion. The main difference compared with exoskeletons with a treadmill is that the feet are always in contact with the moving platform, simulating the gait phases but not necessarily generating true swing and stance phases. The trajectories of the footplates, as well as the vertical and horizontal movements of the center of mass, are programmable. The end-effector design lends itself to gait retraining and star climbing (Hesse, Waldner, & Tomelleri, 2010). Examples of end-effector devices include Gait Trainer GT1 (Reha-Stim, Berlin, Germany), G-EO (Reha Technologies, Switzerland) and Lokohelp. In relation to SCI patients, 3-dimensional data were obtained with Lokomat and G-EO. Their kinematic data were compared when devices were used by SCI or traumatic brain injury patients. The results confirmed a more controlled and repetitive gait pattern when using Lokomat and the G-EO system provided a gait pattern that had more variability of motion for the hips and knees, with slightly reduced knee motion, and the gait pattern differed slightly from that observed during overground walking (Esquenazi & Talaty, 2019).

Stationary exoskeletons

Stationary exoskeletons have a device that surrounds the patient's legs, which may be suspended from an overhead guide rail, supported by a metal frame on wheels, or the exoskeleton can even be directly supported by a mobile robot. They are usually connected directly to the ground through a rigid frame or bolted to a wall, enhancing and ensuring total safety. Stationary exoskeletons can have a large and powerful motors and controllers. They often involve walking on a treadmill. These devices are less complex in their engineering requirements and more stable and safer than ambulatory exoskeletons that allow overground walking due to the elimination of fall risk. They are less accommodating of individual gait variations, such as changes of speed or direction. This group of stationary exoskeletons includes the Lokomat, Walk-Trainer, LOPES or ReoAmbulator.

The Lokomat (Hocoma AG, Volketswil, Switzerland) is the most clinically implanted and studied robot on the market. The Lokomat is a bilaterally driven gait orthosis that is used in conjunction with a body support system (Colombo et al., 2000). It is essentially a robotic implementation of the treadmill walking training system with partial weight support and manual mobilization of the patient by physiotherapists. This system consists of a treadmill, a partial weight support system and a bilateral exoskeleton that provides action on the hips and knees with the ankle being passively supported by a spring to facilitate dorsiflexion of the swing phase of walking (Riener, 2012). The Lokomat moves the patient legs through the gait cycle mainly in the sagittal plane (Fig. 3). The device's hip and knee are actuated by linear drives integrated into an exoskeleton structure. There is no actuator on the ankle and dorsal flexion during the swing phase is achieved passively by means of springs. The lower limb motion can be controlled with highly repeatable predefined hip and knee joint trajectories on the basis of a conventional position control strategy. The exoskeleton is fixed to the rigid frame of the body weight support system and the patient is fixed to the exoskeleton with straps around the waist, thighs and shanks.

The hip and knee joint trajectories can be manually adjusted to the individual patient by changing amplitude and offsets. Signals obtained from force sensors may be used to determine the interactions torques between the patient and the device,

FIG. 3 Lokomat. Lokomat system with a spinal cord-injured patient.

which inform about the voluntary muscle effort produced by the patient (Riener, 2012). The device allows some anthropometrical adaptation to the lower limb segments size via telescopic bars so that the exoskeleton can be used by subjects with different shank and thigh lengths. The width of the hip exoskeleton may also be adjusted by changing the distance between the two lower limbs.

The body weight support system consists of a harness worn by the patient, ropes and pulleys and a counterweight used to partial unload the patient. A patient-cooperative control strategy has been developed that recognize the patient's movement intention and motor ability by monitoring muscular efforts and adapt the robotic assistance to the patient's contribution (Riener et al., 2005). It is recommended that the control and strategies should do the same as a human therapist assisting the patient's movement only as much as needed and informing the patient how to optimize voluntary muscle efforts.

The largest body of scientific is for Lokomat when used by individuals with SCI or stroke. However, there is no consensus of whether and how it affects outcomes in comparison with conventional therapies (Alcobendas-Maestro et al., 2012; Ucar, Parker, & Bugdayci, 2014; Westlake & Patten, 2009) although a recent review provide evidence that acute SCI patients treated with Lokomat showed significantly greater improvement in gait distance and functional level of mobility and independence, and chronic SCI patients a significantly greater improvement in speed and balance were observed than in the group with no intervention (Nam et al., 2017). The Advance Robotic Therapy Integrated Centers (ARTIC) network has recently been set up to collect a large amount of data in order to obtain results with statistical significance. The database includes almost 600 patients not only with SCI but with other neurological conditions with gait deficits who used the Lokomat as part of their rehabilitation (Van Hedel et al., 2018). Other devices, such as the ReoAmbulator (Motorika, New Jersey, USA) have very limited published reports with inconclusive results (Mantone, 2006). A report on LOPES (University of Twente, the Netherlands) showed improved walking ability, as well as gait quality, in subjects with incomplete SCI after an 8 weeks treatment program, with slower walking subjects showing greater benefits (Fleerkotte et al., 2014).

Ambulatory exoskeletons

Ambulatory exoskeletons are used as a powerful tool in the clinical environment and promoting gait training. Both patients with complete and incomplete SCI can use these exoskeletons but with different aim. Patients with incomplete injuries present an improvement prognosis considering the exoskeletons as a rehabilitation tool. In those cases of complete SCI in which recovery is not foreseeable, its use is intended with the aim of permitting the patient to gain a standing up position, walking short distances and replacing the wheelchair as a means of movement in the community in the future.

They adapt to the lower limbs and have electric motors or other kind of powered actuators that mobilize the joints to produce an automatic overground gait. Furthermore, they offer different approaches on the intelligence of the system, from merely healthy normal gait pattern repetition to EMG-based actuation, passing through error augmentation (Marchal-Crespo & Reinkensmeyer, 2009). These robotic systems make it possible for subjects with SCI to perform the action of walking over ground without the need of partial weight support, harnesses, or the treadmill.

Probably the most popular of these robotic exoskeletons for ambulatory walking is the ReWalk (ReWalk Robotics, Inc., Marlborough, MA, USA). It is a lower limb exoskeleton with two active joints (knee and hip), intended to be used with patients with SCI from T4 to L5 and allowing standing up, sitting down, walking, climbing and descending stairs. There are two versions: for personal use and for rehabilitation. Both exoskeletons are composed of a metallic structure that is adjusted by means of tapes or straps, a pelvic support and motors at the hip and knee joints. The difference between both versions is that the exoskeleton for personal use is customized to the dimensions of the user, whereas, in the case of rehabilitation version, the hip and lateral components are replaceable. It offers several levels of assistance and starts ambulation thanks to a sensor that detects the forwards-leaning of the trunk as a signal to start walking.

The different modes of action (walking forward, going from sitting to standing, stopping, going from standing to sitting) are controlled by a control unit located on the patient's wrist. The device has also a "manual" mode (only in sitting position), where the user can control each joint from its local control system (interface at each joint), useful mode for hazards such as spasticity.

Another lower limb exoskeleton is the Vanderbilt exoskeleton, marketed as Indego (Parker Hanninfin Corp., Cleveland, OH, USA), with a modular design that facilitates its adaptation. This product is intended to be used with patients with SCI or stroke. As other commercial exoskeletons, the hip and knee are motorized. On the other hand, the knee joints consist of an electromechanical brake that blocks the motor in the event of a power failure, to avoid the fall of the patient. This exoskeleton allows gaits at a speed of up to 0.8 km/h (with a battery life of up to an hour). The control of this product is based on postural information and is composed of three detachable elements facilitating the donning and doffing of the user. It can be used in patients with level of injury C7 to L5 in rehabilitation facilities.

Like the previous two, the Ekso (Ekso Bionics, Richmond, CA, USA) has actuators on the hips and knees and has a backpack that contains the batteries and controllers. Ekso Bionics mainly commercializes two lower limb exoskeletons: Hulc (Human Universal Load Carrier) and Ekso (eLEGS at the start). The first one is a hydraulic exoskeleton intended to be used for the transport and handling of loads, not a medical device, thus falling outside of the focus of this short review. Ekso, on the other hand, was introduced by the company to allow paraplegics to stand up and walk using crutches or a walker. This exoskeleton is made up of force and movement sensors, which collect information and transfer it to movement. The approximate weight of this product is 20 kg and it can reach a speed of 3.2 km/h with a battery life of up to 6 h. Its software allows the clinician to adjust the amount of assistance provided at each limb and. The control of the device is performed by the therapist accompanying the patient. Patients with level of injury from T4 to L5 can use this exoskeleton or even from C7 if AIS (ASIA Impairment Scale) D (Mekki, Delgado, Fry, Putrino, & Huang, 2018).

HAL (Hybrid Assitive Limb) developed by the Japanese company Cyberdine was initially developed to assist older adults with muscle weakness in walking (Kawamoto & Sankai, 2002) although it is also used for gait rehabilitation in patients with SCI. It consists of a modular design that provides uni-or bilateral actuation at the hip and/or knee joints. The system allows automatic and voluntary control thanks to the activation of certain muscles whose signal is collected by EMG electrodes.

Currently marketed HAL exoskeleton version is intended to be used for different applications, namely rehabilitation, work that requires force, rescue work and even entertainment. There are currently different versions but HAL-5 is full-body exoskeleton for paraplegic users. Both the hip and the knee function actively; however, the ankle is a passive joint.

These four exoskeletons are approved by the FDA, ReWalk and Indego for use in clinical centers and in the community, while Ekso is only for clinical use with medical supervision.

Unlike already described exoskeletons, Hank (Gogoa Mobility Robots, Guipúzcoa, Spain) has six actuated joints including the two ankles to avoid the effect of foot drop during gait (Asín-Prieto, Intxaurburu Sarasua, Fernández Seco, & Fernández Isoird, 2020). It is based on Exo-H2 (Technaid S.L., Madrid, Spain) (Bortole et al., 2015). Hank is intended for patients with incomplete SCI. Its operating system is also based on the "assist as needed" mode and allows a certain deviation from the ideal gait pattern before applying the correcting force (Fig. 4). It presents an open control architecture to be able to make it compatible with other neural interfaces such as brain computer interfaces (BCI) or brain–machine interface systems, or other technologies that facilitate the recovery process such as functional electrical stimulation (FES). The control modes range from rigid trajectory tracking, to transparent mode, passing thru adjustable assistance per joint. The trajectory is tuned depending on the selected speed and can also be adjusted to user constraints. The device can also perform sit to stand and stand to sit actions.

The first exoskeleton marketed that has its own balance system is the REX (REX Bionics, New Zealand), freeing the patient from using crutches for use, as is the case with other devices. In this way, its use is preferably reserved to treat alterations in postural balance although it also allows walking. It is also the first device intended to be used without any help, as a substitute of the wheelchair, in a daily environment.

As is to be expected due to the novelty of its appearance, the experiences registered with exoskeletons that have been carried out so far present small samples that make it difficult to obtain significant results. Several studies on specific

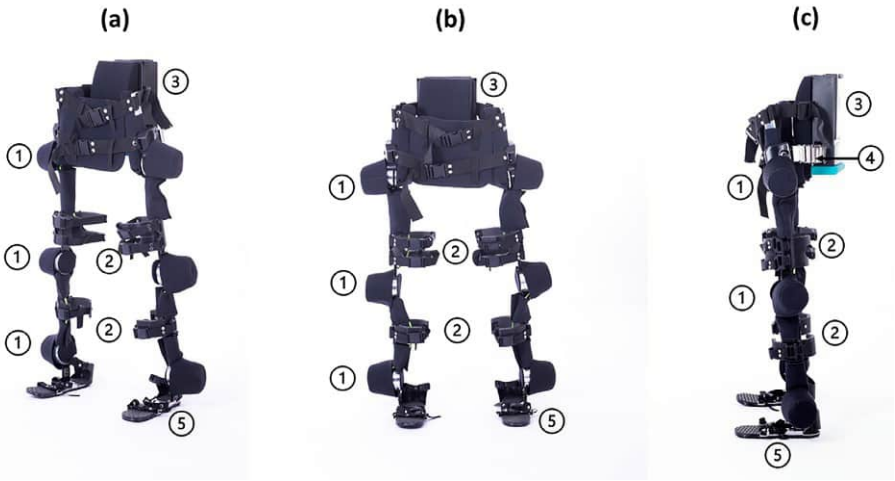

FIG. 4 Hank exoskeleton. HANK exoskeleton; (A) oblique view, (B) frontal view, (C) lateral view; (1) actuators, (2) attachment and fitting, (3) backpack tat containing battery, main microprocessor and the communication electronics connects, (4) flexible arm for adaptation to pelvis, (5) force-sensing-resistors for measuring foot-floor contact.

exoskeletons and feasibility have been conducted and they have found to be practical for use (Bach Baunsgaard et al., 2018; Benson, Hart, Tussler, & van Middentrop, 2016; Esquenazi, Talaty, Packel, & Saulino, 2012; Tefertiller et al., 2018). There are some studies that compare different exoskeletons systems as tools for rehabilitation in the chronic SCI population (Contreras-Vidal et al., 2016). The benefits that have been reported to date include strengthening the muscles, increasing speed and gait efficiency, as well as improvements in aspects of SCI such as spasticity, pain, cardiovascular and metabolism, in the control of intestinal rhythm, in osteoporosis and in quality of life (Winchester et al., 2005) and benefits also in the budget for the recovery (Pinto et al., 2020).

Applications to other areas of neuroscience

In this chapter we have presented the new features of robotic-based treatments from the point of view of neuroplasticity and their application in therapy. There is an increasing evidence to support the concept for reorganization and plasticity of the injured central nervous system (CNS). The potential for reorganization is particularly high after CNS injury but also possible at later stages. Reorganization in a functionally meaningful way seems to depend on motor activity as executed during rehabilitative training and followed by functional improvements. The science behind exercise in CNS disorders is supported by the therapy concept of increased dosage effect. Task oriented, high repetition movements based on the principles of motor learning can improve muscle strength, motor control, and movement coordination in patients with neurological impairments. All these findings are also applied not only after a SCI but also after brain damage (ictus, traumatic brain injury, cerebral palsy). Robots enhance the rehabilitation process and may improve therapeutic outcomes and have the potential to support clinical evaluation by allowing instrumented measurement of physiological and performance parameters, precisely control and measure the therapeutic interventions, implement novel forms of mechanical manipulation impossible for therapists to provide and supply different forms of feedback, thereby increasing patient's motivating and improving outcomes.

Mini-dictionary of terms

Neuroplasticity: Ability of the Central Nervous System to make functional changes after injury and adapt to new situation.
Task-oriented training: Training focused on recovering a specific task such as walking.
Robotic device: Device that use robotic technology in rehabilitation programs.
Functional electrical stimulation (FES): Type of electrotherapy aimed at achieving a functional improvement (such as walking) and not the analytical stimulation of a muscle group without having a functional objective.
Virtual reality: It is an environment of scenes or objects of real appearance. The most common meaning refers to an environment generated by computer technology, which creates in the user the sensation of being immersed in it.

Distal end effector devices: Distal end effectors are characterized by the fact that they use a single distal point of contact to guide the movement of the entire limb.

Exoskeleton-type devices: They are structures located in parallel to the different parts of the extremities with more than one point of interaction with the person. They provide direct control over each segment of the limb by incorporating individualized motors.

Actuators: This term is synonymous with motors.

Haptic: Haptic perception is based on the forces experienced during contact with the robotic device, this has allowed the creation of virtual haptic sensations with different qualities of perception.

Degrees of freedom: It refers to the number of planes in which a joint can be moved.

Assist as needed: This term refers to the robotic control strategy in which the actuators act to complete a certain joint path that the patient cannot perform.

Swing phase: This term refers to the gait cycle phase in which the foot is not in contact with the ground and allows the limb to move forward.

Stance phase: This term refers to the phase of the walking cycle in which the foot is in contact with the ground giving stability to the limb.

Key facts of functional recovery

- It is based on the concept of spinal learning via activity-dependent plasticity.
- The training effects of any motor task depend on the provision of sufficient and appropriate stimuli.
- Locomotor activity can be activated in patients with severe SCI via passive activation of the legs on a treadmill.
- Functional rehabilitation (i.e., walking) had to be intensive and task-oriented.
- Gait training using partial weight support systems on treadmills is based on the principles of functional recovery.
- Robotic therapy allows task-oriented treatments and intensive.

Summary points

- New technologies in neurorehabilitation represents a huge change in treatment protocols for spinal cord injuries
- The training effects depend on the provision of sufficient and appropriate stimuli
- Training must be task-oriented
- Training must be intensive
- Partial body weight support systems on treadmills is based on the principles of functional recovery
- Robotic therapy allows task-oriented and intensive treatment
- Robots offers objective data of patient performance
- There are robots for upper limb and lower limbs
- Robots be classified in distal end effector devices, stationary exoskeletons and ambulatory exoskeletons

References

Alcobendas-Maestro, M., Esclarín-Ruz, Casado-López, R. M., Muñoz-González, A., Pérez-Mateos, G., González-Valdizán, E., et al. (2012). Lokomat robotic-assisted versus overground training within 3 to 6 months of incomplete spinal cord lesion: Randomized controlled trial. *Neurorehabilitation and Neural Repair*, *26*(9), 1058–1063.

Asín-Prieto, G., Intxaurburu Sarasua, A., Fernández Seco, M., & Fernández Isoird, C. (2020). *HANK_case_study.pdf*. https://doi.org/10.6084/m9.figshare.13041983.v1.

Bach Baunsgaard, C., Vig Nissen, U., Katrin Brust, A., Frotzler, A., Ribeill, C., Kalke, Y. B., et al. (2018). Gait training after spinal cord injury: Safety, feasibility and gait function following 8 weeks of training with the exoskeleton form Ekso bionics. *Spinal Cord*, *56*(2), 106–116.

Barbeau, H., Danakas, M., & Arsenault, B. (1993). The effects of locomotor training in spinal cord injured subjects: A preliminary study. *Restorative Neurology and Neuroscience*, *5*, 81–84.

Barbeau, H., & Rossignol, S. (1987). Recovery of locomotion after chronic spinalization in the adult cat. *Brain Research*, *412*, 84–95.

Bayona, N. A., Bitensky, J., Salter, K., & Teasell, R. (2005). The role of task-specific training rehabilitation therapies. *Topics in Stroke Rehabilitation*, *12*(3), 58–65.

Bayón-Calatayud, M., Gil-Agudo, A., Benavente-Valdepeñas, A., Drozdowskyj-Palacios, O., Sánchez-Martín, G., & del Alamo-Rodríguez, M. J. (2014). Efficacy of new therapies in neurorehabilitation of the upper limb in stroke. *Rehabilitación (Madr)*, *48*, 232–240.

Benson, I., Hart, K., Tussler, D., & van Middentrop, J. J. (2016). Lower-limb exoskeletons for indivuduals with chronic spinal cord injury: Findings from a feasibility study. *Clinical Rehabilitation*, *30*(1), 73–84.

Bortole, M., Venkatakrishna, A., Zhu, F., Moreno, J. C., Francisco, G. E., Pons, J. L., et al. (2015). The H2 robotic exoskeleton for gait rehabilitation after stroke: Early findings form a clinical study. *Journal of Neuroengineering and Rehabilitation*, *12*, 54.

Cai, L. L., Courtine, G., Fong, A. J., Burdick, J. W., Roy, R. R., & Edgerton, V. R. (2006). Plasticity of functional connectivity on the adult spinal cord. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *361*(1473), 1635–1646.

Colombo, G., Joerg, M., Schreier, R., & Dietz, V. (2000). Treadmill training of paraplegic patients using a robotic orthosis. *Journal of Rehabilitation Research and Development*, *37*, 693–700.

Contreras-Vidal, J. L., Bhagat, N. A., Brantley, J., Cruz-Garza, J. G., He, Y., Manley, Q., et al. (2016). Powered exoskeletons for bipedal locomotion after spinal cord injury. *Journal of Neural Engineering*, *13*(3), 031001.

Cortés, M., Elder, J., Rykman, A., Murray, L., Avedissian, M., & Stampas, A. (2013). Improved motor performance in chronic spinal cord injury following upper limb robotic training. *NeuroRehabilitation*, *33*(1), 57–65.

Curt, A., Schwab, M. E., & Dietz, V. (2004). Providing the clinical basis for new international therapies: Refined diagnosis and assessment of recovery after spinal cord injury. *Spinal Cord*, *42*, 1–6.

Department of Veterans Affairs. Department of Defense, American Heart Association, American Stroke Association. (2010). *VA/DoD Clinical Practice Guideline for the management of stroke rehabilitation*. The Office of Quality and Performance, VA, Washington, DC and Quality Management Division, United States Army MEDCOM. (Version 3.0). Available form http://www.healthquality.va.gov. or http://www.qmo.amedd.army.mil.

Dietz, V., & Harkema, S. J. (2004). Locomotor activity in spinal cord injured persons. *Journal of Applied Physiology*, *96*, 1954–1960.

Dietz, V., Wirz, M., & Curt, A. (1998). Locomotor pattern in paraplegic patients: Training effects and recovery of spinal cord function. *Spinal Cord*, *36*, 380–390.

Dittuno, P. L., Patrick, M., Stineman, M., & Dittuno, J. F. (2008). Who wants to walk? Preferences for recovery after SCI: A longitudinal and cross-sectional study. *Spinal Cord*, *46*(7), 500–506.

Edgerton, V. R., Courtine, G., Gerasimenko, Y. P., et al. (2008). Training locomotor networks. *Brain Research Reviews*, *57*(1), 241–254.

Edgerton, V. R., & Roy, R. R. (2009). Robotic training and spinal cord injury plasticity. *Brain Research Bulletin*, *78*(1), 4–12.

Esquenazi, A., & Talaty, M. (2019). Robotics for lower limb rehabilitation. *Physical Medicine and Rehabilitation Clinics of North America*, *30*, 385–397.

Esquenazi, A., Talaty, M., Packel, A., & Saulino, M. (2012). The ReWalk powered exoskeleton to restore ambulatory function to individuals with thoracic-level motor-complete spinal cord injury. *American Journal of Physical Medicine & Rehabilitation*, *91*(11), 911–921.

Fasoli, S. E., Krebs, H. I., Stein, J., Frontera, W., Hughes, R., & Hogan, N. (2004). Robotic therapy for chronic motor impairments after stroke: Follow-up results. *Archives of Physical Medicine and Rehabilitation*, *85*(7), 1106–1111.

Fleerkotte, B. M., Koopman, B., Buurke, J. H., van Asseldonk, E. H. F., van der Kooij, H., & Rietman, J. S. (2014). The effect of impedance-controlled robotic gait training on walking ability and quality in individuals with chronic incomplete spinal cord injury: An explorative study. *Journal of Neuroengineering and Rehabilitation*, *11*, 26.

Grillner, S., & Zangger, P. (1984). The effect of dorsal root transection on the efferent motor pattern in the cat's hindlimb during locomotion. *Acta Physiologica Scandinavica*, *120*(3), 393–405.

Hesse, S., Waldner, A., & Tomelleri, C. (2010). Innovative gait robot for the repetitive practice of floor walking and stair climbing up and down in stroke patients. *Journal of Neuroengineering and Rehabilitation*, *7*, 30.

Hubli, M., & Dietz, V. (2013). The physiological basis of neurorehabilitation-locomotor training after spinal cord injury. *Journal of Neuroengineering and Rehabilitation*, *105*.

Kawamoto, H., & Sankai, Y. (2002). Power assist system HAL-3 for gait disorder person. In *International conference on computers for handicapped persons* (pp. 196–203). Berlin, Heidelberg: Springer.

Krebs, H. I., Conroy, S. S., Bever, C. T., & Hogan, N. (2012). Forging Mens et Manus: The MIT experience in upper extremity robotic therapy. In V. Dietz, T. Nef, & W. Zev Rymer (Eds.), *Neurorehabilitation Technology* (pp. 125–140). London: Springer-Verlag.

Krebs, H. I., Hogan, N., Aisen, M. L., & Volpe, B. T. (1998). Robot aided neurorehabilitation. *IEEE Transactions on Rehabilitation Engineering*, *6*(1), 75–87.

Mantone, J. (2006). Getting a leg up? Rehab patients get an assist from devices such as Health South's Auto Ambulator, but the robot's clinical benefits are still in doubt. *Modern Healthcare*, *36*(7), 58–60.

Marchal-Crespo, L., & Reinkensmeyer, D. J. (2009). Review of control strategies for robotic movement training after neurologic injury. *Journal of Neuroengineering and Rehabilitation*, *6*(1), 1–15.

Mehrholz, J., Platz, T., Kugler, J., & Pohl, M. (2009). Electromechanical and robot-assisted arm training for improvement arm function and activities of daily living after stroke. *Stroke*, *40*(5), E392–E393.

Mekki, M., Delgado, A. D., Fry, A., Putrino, D., & Huang, V. (2018). Robotic rehabilitation and spinal cord injury: A narrative review. *Neurotherapeutics*, *15*, 604–617.

Morawietz, C., & Moffat, F. (2013). Effects of locomotor training after incomplete spinal cord injury: A systematic review. *Archives of Physical Medicine and Rehabilitation*, *94*, 2297–2308.

Nam, K. Y., Kim, H. J., Kwon, B. S., Park, J. W., Lee, H. J., & Yoo, A. (2017). Robot-assisted gait training (Lokomat) improves walking function and activity in people with spinal cord injury: A systematic review. *Journal of Neuroengineering and Rehabilitation*, *14*, 24.

Page, S. J., Hill, V., & White, S. (2013). Portable upper extremity robotics is a efficacious as upper extremity rehabilitation therapy: A randomized controlled pilot trial. *Clinical Rehabilitation*, *27*(6), 494–503.

Pinto, D., Garnier, M., Barbas, J., Chang, S. H., Charlifue, S., Field-Fote, E., et al. (2020). Budget impact analysis of robotic exoskeleton use for locomotor training following spinal cord injury in four SCI Model Systems. *Journal of Neuroengineering and Rehabilitation*, *17*(1), 1–13.

Riener, R. (2012). Technology of the robotic gait orthosis Lokomat. In V. Dietz, T. Nef, & W. Zev Rymer (Eds.), *Neurorehabilitation technology* (pp. 221–232). London: Springer-Verlag.

Riener, R., Lunenburger, L., Jezernik, S., Anderschitz, M., Colombo, G., & Dietz, V. (2005). Patient-cooperative strategies for robot-aided treadmill training: First experimental results. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, *13*, 380–394.

Rudhe, C., Albisser, U., Starkey, M. L., Curt, A., & Bolliger, M. (2012). Reliability of movement workspace measurements in a passive arm orthosis used in spinal cord injury rehabilitation. *Journal of Neuroengineering and Rehabilitation*, *9*, 37.

Siedziewski, L., Schaaf, R. C., & Mount, J. (2012). Use of robotics in spinal cord injury: A case report. *The American Journal of Occupational Therapy*, *66* (1), 51–58.

Takahashi, C. D., Der-Yeghiaian, L., Le, V. H., Motiwala, R., & Cramer, S. C. (2008). Robot-based hand motor therapy after stroke. *Brain*, *131*(Pt 2), 425–437.

Teasell, R. W., & Kaira, L. (2004). What's new in stroke rehabilitation. *Stroke*, *35*, 383–385.

Tefertiller, C., Hays, K., Jones, J., Jayaraman, A., Hartigan, C., Bushnik, T., et al. (2018). Initial outcomes from a multicenter study utilizing the Indego powered exoskeleton in spinal cord injury. *Topics in Spinal Cord Injury Rehabilitation*, *24*(1), 78–85.

Tefertiller, C., Pharo, B., Evans, N., & Winchester, P. (2011). Efficacy of rehabilitation robotics for walking training in neurological disorders: A review. *Journal of Rehabilitation Research and Development*, *48*, 387–416.

Ucar, D. E., Parker, N., & Bugdayci, D. (2014). Lokomat: A therapeutic chance for patients with chronic hemiplegia. *NeuroRehabilitation*, *34*(3), 47–453.

Van Hedel, H. J. A., Severini, G., Scarton, A., O'Brien, A., Reed, T., Gaebler-Spira, D., et al. (2018). Advanced robotic therapy integrated centers (ARTIC): An international collaboration facilitating the application of rehabilitation technologies. *Journal of Neuroengineering and Rehabilitation*, *15*, 30.

Weber, L. M., & Stein, J. (2018). The use of robots in stroke rehabilitation. A narrative review. *NeuroRehabilitation*, *43*, 99–110.

Westlake, K. P., & Patten, C. (2009). Pilot study of Lokomat versus manual-assisted treadmill training for locomotor recovery post-stroke. *Journal of Neuroengineering and Rehabilitation*, *6*, 18.

Winchester, P., McColl, R., Querry, R., Foreman, N., Mosby, J., Tansey, K., et al. (2005). Changes in supraspinal activation patterns following robotic locomotor therapy in motor-incomplete spinal cord injury. *Neurorehabilitation and Neural Repair*, *19*(4), 313–324.

Wirz, M., & Rupp, R. (2012). Application issues for robotic. In V. Dietz, T. Nef, & W. Zev Rymer (Eds.), *Neurorehabilitation technology* (pp. 23–38). London: Springer-Verlag.

Zariffa, J., Kapadia, N., Kramer, J. L., Taylor, P., Alizadeh-Meghrazi, M., Zivanovic, V., et al. (2012). Relationship between clinical assessment of function and measurements from an upper-limb robotic rehabilitation device in cervical spinal cord injury. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, *20*(3), 341–350.

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Section F

Resources

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Chapter 45

Recommended resources and sites for the neuroscience of spinal cord injury

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List of Abbreviation

SCI Spinal cord injury

Introduction

Any insult to the spinal cord temporarily or permanently affecting its function can be defined as a spinal cord injury (SCI). Motor vehicle incidents are currently the most common reason for SCI (Chen, Tang, Vogel, & Devivo, 2013). Approximately, a third of all new SCI is attributable to this single preventable cause (Chen et al., 2013). This is particularly upsetting because, depending on the location (i.e., level) and severity of insult, SCI may significantly impair autonomic, sensory, and/or motor function. As such, SCI often afflicts young people and results in permanent, life-changing, and devastating disabilities.

The first documented reports of patients with SCI are contained in the Edwin Smith Papyrus which arises from around 2500 years BC (Hughes, 1988). Indeed, it is important to note that this seminal document states that SCI is "an ailment not to be treated" (Donovan, 2007; Hughes, 1988). Nearly 5000 years ago, most SCI was probably related to injuries sustained in combat (Donovan, 2007). In that setting, it was probably appropriate to triage the scare resources available on the battlefield to those patients with injuries which would not prevent a return to active military service (Donovan, 2007). Yet, regrettably, in the 21st century, besides those few specialists in neurorehabilitation, many clinicians still approach SCI with a significant degree of therapeutic nihilism.

Until relatively recently, the limited clinical literature on SCI focused purely on the feasibility and appropriateness of surgical intervention (Donovan, 2007). This was in part because developments in the field of anesthesia facilitated surgery for SCI. Regardless, technological advances such as advanced orthotic devices (To, Kirsh, Kobetic, & Triolo, 2005) and powered wheelchairs (Algood, Cooper, Fitzgerald, Cooper, & Boninger, 2005) allow those who are managed conservatively (i.e., without surgery) to have a good quality of life.

Perhaps the most internationally renowned clinician for the rehabilitation of patients with SCI was Sir Ludwig Guttmann (Donovan, 2007). He is most widely recognized as the founder of the Stoke-Mandeville Games which subsequently became the Paralympics (Donovan, 2007). Yet his contribution to improving the outcomes of SCI is equally important. A neurosurgeon appointed to lead the SCI unit at Stoke-Mandeville Hospital, Buckinghamshire, England in 1944; he advocated a holistic approach to this cohort and highlighted the importance of their physicians focusing on rehabilitation rather than acting as single organ "ologists" (Donovan, 2007; Guttmann, 1976). The National Spinal Injuries Centre (NSIC) at Stoke-Mandeville Hospital became a role-model for the handful of centers which subsequently blossomed worldwide.

The NSIC continues to advocate for this complex cohort. It is important to prevent insidious neglect from the misconception that the outcomes of patients with SCI are poor. Indeed, a recent series of patients with SCI admitted to the intensive care unit at Stoke-Mandeville Hospital found that survival to hospital discharge is very good (78%; Adam, Rouse, Ali, & Rajendram, 2019). Thus, although, as yet, there is no cure for SCI, therapeutic nihilism is unwarranted.

The inability of victims of SCI to regain neurological function has been thought (for over 100 years) to be due to the failure of the neurons of the central nervous system to regenerate (Cajal, 1928). Thus, considerable resources have focused

Diagnosis and Treatment of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822498-4.00045-2

on attempts to stimulate neuronal regeneration. As a consequence, novel tools for the study of SCI have recently become available. Our understanding of the neuroscience of SCI has advanced, although more slowly than desired. Importantly, the neurons of the central nervous system have been shown to have greater plasticity and greater capacity to regenerate than originally thought (Barnabe-Heider & Frisen, 2008).

Although the promise of being able to initiate neuronal regeneration looms elusively on the horizon, extensive further research is required for SCI to become an ailment that can be cured. Regardless, it even experienced scientists struggle to remain up to date. To assist colleagues who are interested in understanding more about the neuroscience of spinal cord injury, we have therefore produced tables containing up-to-date resources in this chapter. The experts who assisted with the compilation of these tables of resources are acknowledged below.

Resources

Tables 1–5 list the most up-to-date information on the regulatory bodies (Table 1), journals (Table 2), books (Table 3), professional societies (Table 4), research groups, and centers emerging technologies, platforms, and other resources (Table 5) that are relevant to an evidence-based approach to the neuroscience of spinal cord injury. Some organizations are listed in more than one table as they occasional fulfill more than one role.

TABLE 1 Regulatory bodies and relevant organizations.

American Spinal Injury Association (ASIA)	https://asia-spinalinjury.org/
American Society for Surgery of the Hand (ASSH)	https://www.assh.org/hande/s/tetraplegia
Asociación de personas con lesión medular y otras discapacidades física (ASPAYM)	https://www.aspaym.org
Associação Brasileira de Fisioterapia Neurofuncional	https://abrafin.org.br/
Associazione Aspal Paratetraplegici Liguria	www.associazione-paratetraplegici-liguria.it
Associazione Gruppo Animazione Lesionati Midollari (GALM)	www.galm.it
Associazione Il Melograno Organizzazine di Volontariato	http://www.ilmelogranoodv.org/
Associazione Medullolesi Siciliana	http://www.ass-medullolesi.org/
Associazione Paraplegici di Roma e del Lazio	www.apromaelazio.it
Associazione Paraplegici Lombardia - Onlus	www.apl-onlus.it
Associazione Paraplegici Marche	https://www.apmarche.org/
Associazione Paraplegici Toscana	http://www.atponlus.org
Associazione Paratetraplegici Nord Est	http://www.paratetraplegicinordest.it
Associazione Spina Bifida Italia	www.spinabifidaitalia.it;
Associazione Tetra-Paraplegici Friuli Venezia Giulia Onlus	http://www.paraplegicifvg.it/
Associazione Voglia di Vivere	https://www.vdvpistoia.org/
Australian Spinal Injury Alliance	https://spinalinjuryalliance.com.au/
Canadian Spinal Cord Injury Rehabilitation Association	https://cscira.ca/
Canadian Spinal Research Organization	https://www.csro.com/
Centre for the Rehabilitation of the Paralysed (CRP) Bangladesh	https://www.crp-bangladesh.org/
Christopher and Dana Reeve Foundation	https://www.christopherreeve.org/
Comitato Paralimpico Italiano	http://www.comitatoparalimpico.it/
Craig H Neilsen Foundation	https://chnfoundation.org/
elearnSCI	http://www.elearnsci.org/
European Commission	https://ec.europa.eu/info/index_en

TABLE 1 Regulatory bodies and relevant organizations—cont'd

European Network on Independent Living	www.enil.it
European Paralimpic Committee	https://www.europaralympic.org/
European Spinal Cord Injury Federation	http://www.escif.org/
Federation of European Societies for Surgery of the Hand (FESSH)	https://fessh.com/
Federazione Associazioni Italiane Paratetraplegici	http://www.faiponline.it/drupal/
Fundación Lesionado Medular	www.medular.org
International Group for Research into Spinal Cord Injury (SCI-Research Group)	https://sites.hss.univr.it/npsy-labvr/spinal-cord-injury-research-center/
International Spinal Cord Society	https://www.iscos.org.uk/
International Spinal Research Trust	https://spinal-research.org/
Japan Spinal Cord Foundation	http://www.jscf.org/
Life Rolls On	Liferollson.org
Ministério da Saúde Ministry of Health of Brazil	https://www.gov.br/saude/pt-br
National Council on Independent Living (NCIL)	https://ncil.org
National Institute for Health and Care Excellence	https://www.nice.org.uk/guidance/ng41
National Institute of Neurological Disorders and Stroke	https://www.commondataelements.ninds.nih.gov/Spinal%20Cord%20Injury
National Spinal Cord Injury Association of Illinois	https://sci-illinois.org/
Paralyzed Veterans of America	https://www.pva.org/
Reeve Foundation (also known as Christopher & Dana Reeve Foundation)	https://www.christopherreeve.org/
Rick Hansen Foundation	https://www.rickhansen.com/
Sarah Network Rehabilitation Hospitals	www.sarah.br
Sheperd Center. Rehabilitation Hospital	https://www.shepherd.org/
Spinal Cord Injuries Australia	https://scia.org.au/
Spinal Cord Injuries: Clinical Trials	https://stemcellsportal.com/clinical_trials_spinal_cord_injuries
Spinal Cord Injury Alberta	https://sci-ab.ca/
Spinal Cord Injury British Columbia	https://sci-bc.ca/
Spinal Cord Injury Research Program- Mayo Clinic	https://www.mayo.edu/research/centers-programs/spinal-cord-injury-research-program
Spinal injuries association	https://www.spinal.co.uk/
SpinalCord-ItalianLab	https://spinalcord-italianlab.it/
The Community Research and Development Information Service (CORDIS)	https://cordis.europa.eu/article/id/89878-spinal-cord-injury-treatment-and-rehabilitation
The International Spinal Cord Society	https://www.iscos.org.uk/
The National Spinal Cord Injury Foundation	www.spinalcord.org
Unite2fight paralysis	https://u2fp.org
United Spinal Association	https://unitedspinal.org/
United States Food and Drug Administration (FDA)	https://www.fda.gov/home
World Health Organization	https://www.who.int

This table lists the regulatory bodies and organizations involved with the neuroscience of spinal cord injury and associated specialties or interests. The links were accurate at the time of going to press but may move or alter. In these cases, the use of the "Search" tabs should be explored at the parent address or site. See also Table 4.

TABLE 2 Relevant journals publishing original research and review articles related to the neuroscience of spinal cord injury.

Spinal Cord
Journal of Spinal Cord Medicine
World Neurosurgery
Journal of Neurotrauma
Neural Regeneration Research
Archives of Physical Medicine and Rehabilitation
Experimental Neurology
Scientific Reports
Spinal Cord Series and Cases
PLoS One
Topics in Spinal Cord Injury Rehabilitation
Chinese Journal of Tissue Engineering Research
Spine
Neuroscience Letters
International Journal of Molecular Sciences
Journal of Neurosurgery Spine
Disability and Rehabilitation
European Spine Journal
Neurourology and Urodynamics
Journal of Neuroscience
Spine Journal
Molecular Neurobiology
Neuroscience
Frontiers in Neuroscience
Journal of Neuroinflammation
Frontiers in Neurology
Global Spine Journal
Frontiers in Cellular Neuroscience
American Journal of Physical Medicine and Rehabilitation
Medicine United States

Journals publishing original research and review articles related to the neuroscience of spinal cord injury. Included in this list are the top 30 journals which have published the most number of articles on spinal cord injury over the past 5 years. Data derived from Scopus.

Application to other areas of neuroscience

The pathophysiology and management of spinal cord injuries are similar to traumatic injuries to the other components of the nervous system. These include the brain and the peripheral nervous system. Thus, the contents of this chapter are also relevant to the understanding of traumatic brain injuries and peripheral neuropathies.

TABLE 3 Relevant books.

Book title	Authors or editors	Publisher	Year
AACD Reabilitação	Fernandes AC, Ramos ACR, Morais Filho MC, Ares MJJ	Manole	2014
AOSpine Masters Series, Volume 7: Spinal Cord Injury and Regeneration	Vialle LR, Fehlings M, Weidner N	Thieme	2016
CNS Regeneration: Basic Science and Clinical Advances	Tuszynski MH, Kordower J	Elsevier	1999; 2007
Critical Care in Spinal Cord Injury	Fehlings M	Future Medicine LTD	2013
Delisa's Physical Medicine and Rehabilitation: Principles and Practice	Delisa JA	Lippincott Williams & Wilkings	2010
Diagnostic Imaging: Spine	Ross JS, Moore R	Elsevier	2020
Diseases of the Spinal Cord	Hattingen, E	Springer	2015
Diseases of the Spinal Cord: Novel Imaging, Diagnosis and Treatment	Hattingen, EHattingen E, Weidauer S, Setzer M, Klein JC, Vrionis F	Springer	2013
Essentials of Spinal Cord Injury. Basic Research to Clinical Practice	Fehlings MG, Vaccaro AR, Boakye M, Rossignol S, Dituno JF Jr., Burns AS	Thieme Medical Publishers	2012
Essentials of the Adult Neurogenic Bladder	Corcos J, Karsenty G, Kessler T, Ginsberg D,	Taylor & Francis Group	2015
Functional Electrical Stimulation: Standing and Walking After Spinal Cord Injury	Kralj AR, Bajd T	CRC Press	1989
Hand Function A Practical Guide to Assessment	Duruöz MT	Springer	2019
Incontinence 6th edition	Abrams P, Cardozo L, Wagg A, Wein A	International Consultation on Urological Diseases	2017
Ischemic and Traumatic Brain and Spinal Cord Injuries Mechanisms and Potential Therapies	Farooqui A	Academic Press	2018
Lesión medular. Enfoque multidisciplinar	Esclarin de Ruz A	Panamericana	2020
Living with Spinal Cord Injury: A Wellness Approach	Cristian A	Demos Medical Publishing	2010
Management and Rehabilitation of Spinal Cord Injuries	Ko HY	Springer	2019
Management of Spinal Cord Injuries: A Guide for Physiotherapists	Harvey L	Elsevier	2008
Manual de Medicina Fisica y Rehabilitación	Frontera WR, Silver JK, Rizzo T	Elsevier España	2020
Medicina e Reabilitação: Princípios e Práticas	Fernandes AC, Ramos ACR, Casilis MEP, Herbert SK	Artes Médicas	2013
Neurological Aspects of Spinal Cord Injury	Weidner N, Rupp R, Tansey K	Springer	2017
Neurotrauma: A Comprehensive Textbook on Traumatic Brain Injury and Spinal Cord Injury	Wang K	Oxford University Press	2018
Programa de Atualização em Fisioterapia Neurofuncional (PROFISIO)	Faria C, Leite H	Artmed	2021
Recovery of Motor Function Following Spinal Cord Injury	Fuller, H	IntechOpen	2016
Rehabilitation in Spinal Cord Injuries	Reznik J, Simmons J	Elsevier	2020

Continued

TABLE 3 Relevant books—cont'd

Book title	Authors or editors	Publisher	Year
Spinal Cord Injuries Management and Rehabilitation	Sisto SA, Druin E, Sliwinski MM	Elsevier	2008
Spinal cord injury	Holtz A, Levi R	Oxford University Press.	2010
Spinal Cord Injury (SCI) Repair Strategies	Giuseppe P, Filippo R	Elsevier Health Sciences	2019
Spinal Cord Injury: A guide for patient and families (American Academy of Neurology)	Selzer M, Dobkin B	Demos Health	2008
Spinal Cord Injury: Management and Rehabilitation	Sisto SA, Druin E, Sliwinski MM	Mosby-Elsevier	2009
Spinal Cord Medicine	Kirshblum S, Campagnolo DI	Lippincott Williams & Wilkins	2011
Spinal Cord Medicine, 3rd Edition	Kirshblum S, Vernon WL	Springer	2018
Spinal Trauma: Imaging, Diagnosis and Management	Schwaartz ED, Flanders AE	Lippincott Williams & Wilkins	2006
Spine and Spinal Cord Trauma	Vaccaro A, Fehlings M, Dvorak M	Thieme Medical Publishing	2011
Textbook of neurogenic bladder Third edition	Corcos J, Ginsberg D, Karsenty G	Taylor & Francis Group	2015
The art of healthy living with physical impairments	Lagerstrom A-C, Wahman K	Spinalis	2014
The Physiology of Exercise in Spinal Cord Injury	Taylor JA	Springer	2017
Therapeutic Strategies to Spinal Cord Injury	Jendelova P	MDPI	2018
Traumatic Brain and Spinal Cord Injury. Challenges and Developments	Morganti-Kossmann C, Raghupathi R, Maas A	Cambridge	2012
Urologic management of the spinal cord injured patient	Elliott S, Gomez R	SIU Academy	2017
Vascular Anatomy of the Spinal Cord	Thron AK	Springer	2016

This table lists books on the neuroscience of spinal cord injury.

TABLE 4 Professional societies and other organizations.

Society name	Web address
Academy of Spinal Cord Injury Professionals	https://www.academyscipro.org/
Academy of Spinal Cord Injury Professionals (ASCIP)	https://www.academyscipro.org/
American Academy of Physical Medicine and Rehabilitation (AAPM&R)	https://www.aapmr.org/
American Congress of Rehabilitation Medicine (ACRM)	https://acrm.org/
American Spinal Cord Injury Association (ASIA)	https://asia-spinalinjury.org/
AO Spine Knowledge Forum Spinal Cord Injury	https://aospine.aofoundation.org
Asian Spinal Cord Network (ASCoN)	https://ascon.info/
Asociación Española de Enfermería especializada en Lesión Medular	www.aselme.com
ASSH (American Society for Surgery of the Hand)	https://www.assh.org/hande/s/tetraplegia
Association of Academic Physiatrists (AAP)	https://www.physiatry.org/

TABLE 4 Professional societies and other organizations—cont'd

Society name	Web address
Australian and New Zealand Spinal Cord Society	https://anzscos.org/
Canadian Spinal Cord Injury Rehabilitation Association	https://cscira.ca/
Christopher & Dana Reeve Foundation	www.christopherreeve.org
European Spinal Cord Injury Federation (ESCIF)	http://www.escif.org/
Federation of European Societies for Surgery of the Hand (FESSH)	https://fessh.com/
Fehlings Lab Twitter	www.twitter.com/DrFehlings
Fehlings Lab Website	www.drfehlings.ca
International Continence Society	https://www.ics.org
International Neuro-Urology Society	https://www.neuro-uro.org
International Society of Physical Medicine and Rehabilitation (ISPRM)	https://www.isprm.org/
International Spinal Cord Society (ISCoS)	https://www.iscos.org.uk/
Korean Spinal Cord Society	http://www.koscos.kr/
National Organization For Rare Disorders (NORD)	https://rarediseases.org/organizations/national-spinal-cord-injury-association/
North American Spine Society	https://www.spine.org/
Praxis Spinal Cord Institute	www.praxisinstitute.org
Protection Center of Spinal Cord Disables of Iran	www.irannokhaa.ir (not viable at the time of going to press)
Sheperd Center. Rehabilitation Hospital	https://www.shepherd.org/
Shirley Ryan Hability Lab	https://www.sralab.org/conditions/spinal-cord-injury
Sociedad Española de Paraplejia	www.sociedaddeparaplejia.com
Società Italiana Chirurgia della Mano (SICM)	https://www.sicm.it/
Society for neuroscience	https://www.sfn.org
Spinal Cord Injury Associations & Organizations (USA)	https://www.sci-info-pages.com/spinal-cord-injury-organizations/
Spinal Cord Injury Canada	https://sci-can.ca/about-us
Spinal Cord Injury Ontario	https://sciontario.org/
Spinal Cord Injury Research Evidence (SCIRE)	https://scireproject.com/
Spinal Cord Society-Indian Chapter	http://www.scs-isic.com/
Spinal Injuries Association	https://www.spinal.co.uk/
The Academy of Spinal Cord Injury Professionals	https://www.academyscipro.org/
The Asian Spinal Cord Network	https://ascon.info/
The Canadian Spinal Research Organization (CSRO)/American Spinal Research Organization (ASRO)	https://www.csro.com/
The International Spinal Cord Society	https://www.iscos.org.uk/
The Nordic Spinal Cord Society	http://noscos.org/
United Spinal Association	https://unitedspinal.org/

This table lists some societies and organizations devoted to understanding the neuroscience of spinal cord injury. Please note, occasionally the location of the websites or web address changes. Not viable at the time of going to press indicates that the site has changed or is the process of being changed. See also Table 1.

TABLE 5 Emerging techniques, platforms, and other sites of interest relevant to the neuroscience of spinal cord injury.

Organization or company or society name	Web address
Acreditando	https://www.acreditando.com.br/
American Society for Surgery of the Hand (ASSH)	https://www.assh.org/hande/s/tetraplegia
American Spinal Injury Association (ASIA)-e Learning Center	https://asia-spinalinjury.org/learning/
Association for Assistance of Disabled Children (AACD)	https://aacd.org.br/centro-de-reabilitacao
Avery biomedical devices	https://www.averybiomedical.com/spinal-cord-injury-treatments/
California Institute for Regenerative Medicine (CIRM)	https://www.cirm.ca.gov
Christopher & Dana Reeve Foundation	https://www.christopherreeve.org/
Clinical Trials. Gov	https://clinicaltrials.gov
Dalhousie University Faculty of Medicine Wheelchair Skills Program (WSP)	https://wheelchairskillsprogram.ca/en/
Elearning-SCI	http://www.elearnsci.org
European Multicenter Study about Spinal Cord Injury (EMSCI)	https://www.emsci.org
facing disability	https://facingdisability.com/resources/assistive-technology
Federation of European Societies for Surgery of the Hand (FESSH)	https://fessh.com/
Gaylord Speciality Healthcare	https://www.gaylord.org/Patients-Families/Conditions-Services/Spinal-Cord-Injury-Program
inspire neurocare	https://www.inspireneurocare.co.uk/
Instituto de Medicina Física e Reabilitação (Rede Lucy Montoro)	https://www.redelucymontoro.org.br/site/programa-de-reabilitacao.html
Instituto Novo Ser	http://www.novoser.org.br/index.html
International Collaboration on Repair Discoveries (ICORD)	https://icord.org/
International Group for Research into Spinal Cord Injury (SCI-Research Group)	https://sites.hss.univr.it/npsy-labvr/spinal-cord-injury-research-center/
International Society of Spinal Cord Injury	www.iscos.org.uk
Kentucky Spinal Cord Injury Research Center	https://louisville.edu/kscirc
Kessler Foundation	https://kesslerfoundation.org/
Mayo Foundation for Medical Education and Research	https://www.mayo.edu/research/centers-programs/spinal-cord-injury-research-program
Miami Project to Cure Paralysis	https://www.themiamiproject.org/
Model System Knowledge Translation Center (MSKTC)	https://msktc.org/sci
National Institute of Neurological Disorders and Stroke: SCI	https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Hope-Through-Research/Spinal-Cord-Injury-Hope-Through-Research
Ontario Neurotrauma Foundation	https://spauldingrehab.org/
Physiopedia (Assistive Devices for Spinal Cord Injury)	https://www.physio-pedia.com/Assistive_Devices_for_Spinal_Cord_Injury
Praxis Spinal Cord Institute	https://praxisinstitute.org/

TABLE 5 Emerging techniques, platforms, and other sites of interest relevant to the neuroscience of spinal cord injury—cont'd

Organization or company or society name	Web address
ProBed	https://www.pro-bed.com/blog/info/top-10-spinal-cord-research-organizations
PropelPysiotherapy	https://propelphysiotherapy.com/spinal-cord-injury/assistive-devices-sci-rehabilitation
Rede SARAH (Specialized assistance in rehabilitation)	https://www.sarah.br/especialidades/neurorreabilitacao-em-lesao-medular/
ReWalk	https://rewalk.com/
Shepherd Center	https://www.shepherd.org/resources-healthcare-professionals/research/spinal-cord-injury/current
Società Italiana Chirurgia Della Mano (SICM)	https://www.sicm.it/
Spaulding Rehabilitation Network	https://onf.org/knowledge-mobilization/spinal-cord-injury-2/knowledgemobilization-sci-networkssummits/
Spinal Cord Injury Adaptive Equipment And Assistive Technology	https://www.sci-info-pages.com/adaptive-equipment/
Spinal Cord Injury and You (SCI-U)	http://sci-u.ca/
Spinal Cord Injury Research Evidence	https://scireproject.com/
Spinal Cord Injury Trials Finder	https://scitrialsfinder.net
Spinal Cord Outcomes Partnership Endeavor	https://scope-sci.org/
Spinal Cord Research Centre	https://scrc.umanitoba.ca/wp/
Spinal Research	https://spinal-research.org/
Spinal Research Institute	https://www.thesri.org/spinal-cord-research-hub/
SpineUniverse	https://www.spineuniverse.com/
The American Trauma Society	https://www.amtrauma.org/
The Big Idea	https://reevebigidea.org/
Transforming Research and Clinical Knowledge in Spinal Cord Injury (TRACK-SCI)	https://spinalcordinjury.ucsf.edu
Unite 2 Fight Paralysis	https://u2fp.org/
United Spinal Association	https://askus-resource-center.unitedspinal.org/index.php?pg=kb.book&id=32

This table lists some emerging technologies and platforms relevant to the neuroscience of spinal cord injury. Please note, occasionally the location of the websites or web address changes.

Mini-dictionary of terms

Orthotic device: A support/brace for the spine or limbs.
Neuronal plasticity: The ability of neural networks to adapt and/or change by reorganization and/or growth.
Neuronal regeneration: The repair/regrowth of neurons by the formation of new axons, synapses neurons, or glia.
Neurorehabilitation: The process which aims to restore function to patients who have sustained a neurological insult such as stroke or spinal cord injury.
Therapeutic nihilism: The perception that it is impossible to improve the outcome of a patient with a specific condition.

Key facts of spinal cord injury

- Any insult to the spinal cord temporarily or permanently affecting, its function can be defined as a spinal cord injury.
- Spinal cord injury often afflicts young people and results in permanent, life-changing, and devastating disabilities.

- Following spinal cord injury, therapeutic nihilism is unwarranted as survival to discharge home is good and technological advances have greatly improved quality of life.
- Lack of functional recovery post spinal cord injury is thought to be due to failure of central neurons to regenerate.
- Despite great advances, vast amounts must still be learned about the neuroscience of spinal cord injury before this devastating condition can be cured.

Summary points

- Patients with spinal cord injury often survive to be discharged at home, and their quality of life has been improved by technological advances.
- Although there is currently no cure for spinal cord injury, prognostic pessimism is unwarranted.
- There is significant interest in stimulating neuronal regeneration to promote functional recovery after spinal cord injury.
- Recent advances have suggested that central neurons have greater plasticity than previously thought. This seed plants the hope that the ability to control neuronal regeneration is on the horizon.
- The expansion of the knowledge and understanding of the neuroscience of spinal cord injury has been slow but steady. It is becoming increasingly difficult for those interested in this field to remain up to date.

Acknowledgements (in alphabetical order)

We would like to thank the following authors for contributing to the development of this resource. We apologize if some suggested material was not included in this chapter or has been moved to different sections.
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References

Adam, M., Rouse, A., Ali, T., & Rajendram, R. (2019). Intensive care unit resource use by patients with spinal cord injury. *Journal of the Intensive Care Society*, *20*(Suppl. 1 EP.240), 182.

Algood, S. D., Cooper, R. A., Fitzgerald, S. G., Cooper, R., & Boninger, M. L. (2005). Effect of a pushrim-activated power-assist wheelchair on the functional capabilities of persons with tetraplegia. *Archives of Physical Medicine and Rehabilitation*, *86*, 380–386.

Barnabe-Heider, F., & Frisen, J. (2008). Stem cells for spinal cord repair. *Cell Stem Cell*, *3*, 16–24.

Cajal, R. (1928). *Degeneration and regeneration of the nervous system*. London: Oxford University Press.

Chen, Y., Tang, Y., Vogel, L. C., & Devivo, M. J. (2013). Causes of spinal cord injury. *Topics in Spinal Cord Injury Rehabilitation*, *19*, 1–8.

Donovan, W. H. (2007). Donald Munro lecture. Spinal cord injury- -past, present, and future. *The Journal of Spinal Cord Medicine*, *30*, 85–100.

Guttmann, L. (1976). Management of spinal fractions. In L. Guttmann (Ed.), *Spinal cord injuries, comprehensive management and research* (pp. 7–21). London: Blackwell Scientific Publications, Oxford Press.

Hughes, J. T. (1988). The Edwin Smith Papyrus; an analysis of the first case reports of spinal cord injuries. *Paraplegia*, *26*, 71–82.

To, C. S., Kirsh, R. F., Kobetic, R., & Triolo, R. J. (2005). Simulation of a functional neuromuscular stimulation powered mechanical gait orthosis with coordinated joint locking. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, *13*, 227–235.

Index

Note: Page numbers followed by *f* indicate figures and *t* indicate tables.

B

C

D

E

F

G

H

I

J

K

L

M

N

O

P

Q

R

S

T

U

V

W

Z

DIAGNOSIS AND TREATMENT OF SPINAL CORD INJURY

THE NEUROSCIENCE OF SPINAL CORD INJURY

EDITED BY
RAJKUMAR RAJENDRAM, VICTOR R. PREEDY, AND COLIN R. MARTIN

Diagnosis and Treatment of Spinal Cord Injury will enhance readers' understanding of the complexities of the diagnosis and management of spinal cord injuries. Featuring chapters on drug delivery, exercise, and rehabilitation, this volume discusses in detail the impact of the clinical features, diagnosis, management, and long-term prognosis of spinal cord injuries on the lives of those affected. The book has applicability for neuroscientists, neurologists, clinicians, and anyone working to better understand spinal cord injuries.

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An imprint of Elsevier
elsevier.com/books-and-journals

TITLE ISBN
ISBN 978-0-12-822498-4
9 780128 224984

SET ISBN
ISBN 978-0-323-99198-8
9 780323 991988

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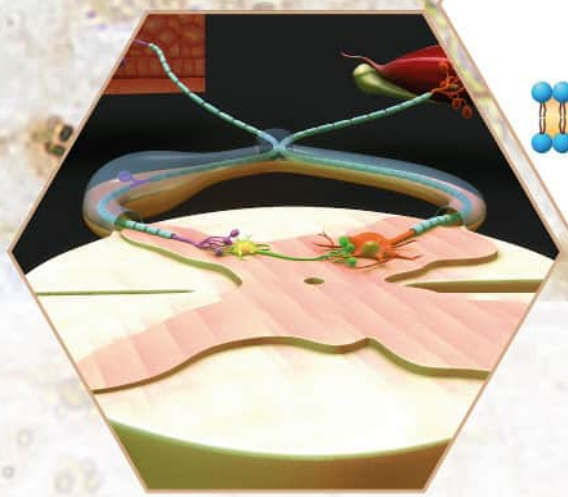
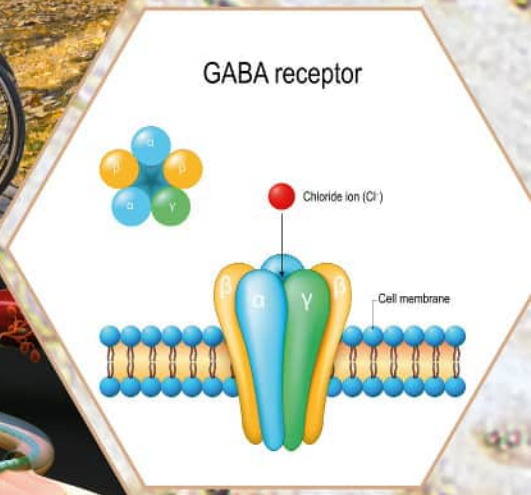
THE NEUROSCIENCE OF SPINAL CORD INJURY





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Cellular, Molecular, Physiological, and Behavioral Aspects of Spinal Cord Injury

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The Neuroscience of Spinal Cord Injury

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525 B Street, Suite 1650, San Diego, CA 92101, United States
50 Hampshire Street, 5th Floor, Cambridge, MA 02139, United States
The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, United Kingdom

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ISBN 978-0-12-822427-4

SET ISBN 978-0-323-99198-8

Publisher: Nikki Levy
Acquisitions Editor: Natalie Farra
Editorial Project Manager: Timothy Bennett
Production Project Manager: Paul Prasad Chandramohan
Cover Designer: Mark Rogers

Typeset by STRAIVE, India

Dedication

**I dedicate this book to my wonderful daughter, Dr. Caragh Brien,
of whom I am so incredibly proud.
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Preface

Spinal injury affects about 10 million people annually worldwide. Many of these injuries are preventable and occur due to falls, violence, and road traffic accidents. However, spinal cord damage may also result from nontraumatic injury, for example, due to toxins, infection, cancer, intervertebral disc damage, and vascular disease.

Spinal injuries may cause significant, lifelong disabilities and thereby impact the family unit. Symptoms are varied and include paresthesia, spasticity, and loss of motor control. In extreme cases, affected individuals are chair- or bedbound for life. These debilitating injuries may also be accompanied by severe pain. Loss of bladder and bowel control increases dependency and further reduces quality of life.

Diagnosis is generally based on symptoms and various imaging techniques in the clinical context of a traumatic injury to the spinal cord. Various syndromes are associated with spinal cord injury (e.g., central, anterior, and posterior cord syndromes). However, various pathological processes are involved in the initiation of primary and secondary damage to the spinal cord.

Physical trauma may be accompanied by multiorgan cellular and biochemical injury. These injuries include neurodegeneration, free radical damage, changes in gene expression, and physiological changes such as loss of the regulation of blood pressure. So the manifestation of symptoms and signs from any given injury may be highly variable.

The patient's functional outcome predominantly depends on the level of spinal column injury (i.e., cervical, thoracic, lumbar, or sacral), the location of the damage within the spinal cord (e.g., central, anterior, and posterior), and the severity. This functional outcome may be modified to some extent by medical therapies and rehabilitation.

To fully comprehend and positively influence the trajectory of patients' outcomes, it is necessary to understand the fundamental principles of the conditions that arise as a result of spinal cord injury. Presently, the availability of much of this information is sporadic, in different scientific domains, and designed for different scientific specialities. Spinal cord injuries are diverse, so a multidisciplinary approach is needed. This is addressed in the two-volume set *The Neuroscience of Spinal Cord Injury* comprising the 2 books:

Diagnosis and Treatment of Spinal Cord Injury
Cellular, Molecular, Physiological, and Behavioral Aspects of Spinal Cord Injury

This book, *Cellular, Molecular, Physiological, and Behavioral Aspects of Spinal Cord Injury,* comprises the following four sections:

- *Setting the scene and introductory chapters*
- *Cellular and molecular aspects of spinal injury*
- *Physiological and metabolic effects*
- *Behavioral and psychological effects*

Each chapter has the following sections:

- *Abstract (published online)*
- *Key facts*
- *Mini-dictionary of terms*
- *Applications to other areas of neuroscience*
- *Summary points*

The sections *Key facts*, *Mini-dictionary of terms*, and *Summary points* enable the reader to cross the transintellectual and transdisciplinary divides. The section *Applications to other areas of neuroscience* pertains to the translational aspects of the chapter and the applicability of the information.

The Neuroscience of Spinal Cord Injury is designed for research and teaching purposes. It is suitable for neurologists, surgeons, trauma specialists, psychologists, health scientists, public health workers, doctors, pharmacologists, and research scientists. It is valuable as a personal reference book and also for academic libraries that cover the domains of trauma and neurology. Contributions are from leading national and international experts including those from world-renowned institutions. It is suitable for undergraduate and postgraduate students as well as lecturers and academic professors.

Rajkumar Rajendram, Victor R. Preedy, and Colin R. Martin
(Editors)

Section A

Setting the scene and introductory chapters

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Chapter 1

Causes of spinal injury: Motor vehicle accidents and beyond

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List of abbreviations

AACN Advanced Automatic Collision Notification
MVA motor vehicle accident

Introduction

As has been known widely, motor vehicle accident (MVA) is one of the most common causes of spinal injury, together with accidental fall and sports injury (Blackmore, Goswami, & Chancey, 2012) (Fig. 1). Take the cervical spine injury for example: it has recently been reported that approximately 869,000 traffic crash-related cervical spine injuries were seen in hospitals in the United States annually, including 841,000 sprain/strain injuries, 2800 disc injuries, 23,500 spine fractures, 2800 spinal cord injuries, and 1500 facet joint dislocations (Freeman & Leith, 2020). There are numerous occupant-specific, vehicle-specific, and environmental factors that may influence the location and severity of MVA-related spinal injuries (Table 1).

While the circumstances of MVAs are quite diverse, the number of subjects with a MVA-associated spinal injury was greatest among automobile drivers, followed by pedestrians hit by cars, car passengers, and motorcycle riders (Wang et al., 2016). As a consequence, male aged 20–60 are the population most likely to sustain MVA-related spinal injury. Historically, spinal injuries sustained by automobile drivers have been studied most extensively because they are relatively easy to simulate or reproduce in laboratory settings, and may be preventable or at least minimizable with the use of protective devices such as seatbelt and airbag. Numerous basic research studies to simulate the spinal injury have been conducted for this purpose (Xu et al., 2018). For example, dummies which are equipped with various sensors and transducers have been used in crash tests for decades (Fig. 2), providing useful information to automobile manufacturers and researchers. More recently, computational models of the human spine (Wang, Feng, and Hu, 2018) have been so developed that they can reliably simulate and estimate quantity of stress sustained by each vertebral column and ligament (Fig. 3).

In a large retrospective study conducted in the Wisconsin State, as many as 12.5% of drivers who were admitted after experiencing a severe MVA had been found to have a spinal injury (Wang, Pintar, Yoganandan, & Maiman, 2009). The seat position within an automobile may not influence the likelihood of spinal injury: there was no statistical difference in the frequency of spinal injury between drivers and passengers in that study. Spinal injury patterns substantially differ between the four-wheeled vehicles and two-wheeled vehicles: in other words, it may reflect differing mechanisms of injury between the automobile occupants who are mostly restrained and motorcycle riders who are mostly unrestrained. While the thoracic spine is most frequently injured in motorcycle riders, the cervical spine is most frequently injured in automobile occupants (Robertson, Branfoot, Barlow, & Giannoudis, 2002). In addition, the motorcycle riders are more likely to sustain multiple spinal injuries compared to automobile drivers. Interestingly, spinal injuries sustained by bicycle riders are most likely to develop at the lower cervical spine (Broe, Kelly, Groarke, Synnott, & Morris, 2018). Unlike automobile occupants, the characteristics of spinal injury in pedestrians have been reported much less often. A study from the California State described that the incidence of cervical spine injury was 2.1% among 8401 pedestrian injuries caused by automobiles, and the incidence increased with age and severity of head trauma (Yanar et al., 2007).

Cellular, Molecular, Physiological, and Behavioral Aspects of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822427-4.00001-0

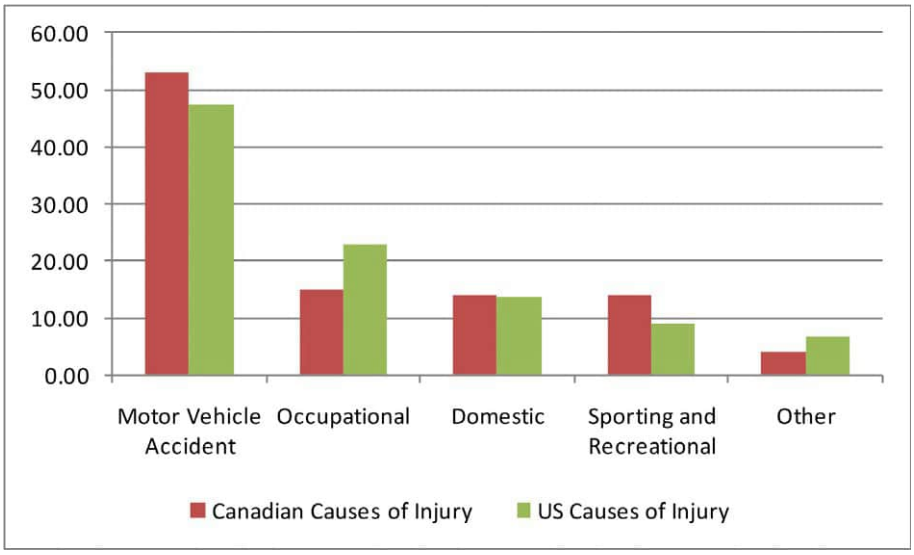

FIG. 1 Activities causing cervical spine injuries. Causes of spine injury in Canada (*brown*) and the United States (*green*) in percentages. *From: Blackmore, M.E., Goswami, T., & Chancey C. (2012). Cervical spinal injuries and risk assessment. In T. Goswani (Ed),* Injury and skeletal biomechanics *(*Chapter 7*). Reprint with permission. ©2012 IntechOpen Ltd.*

TABLE 1 Factors that may influence location and severity of spinal injury in car passengers.

• Type of vehicle (weight, shape, year-model)
• Type of collision (frontal, lateral, rear-end, rollover)
• Speed and degree of deceleration of the vehicle
• Type and condition of road
• Weather
• Use of seatbelt by car passengers
• Use of medication or drugs that may influence the mental status of a driver
• Stature, weight, age, and sex of car passengers
• Position (seat) of car passengers

Difference in the type of four-wheeled vehicle may not substantially influence the frequency or severity of spine injury. There was no significant difference between the frequency of cervical spine injury among drivers of sedan, light truck, and sports utility vehicle (Stein et al., 2011). More recently, a study from Japan found that the frequency of spinal injury did not differ significantly between drivers of sedan and those of K-cars (Inamasu, Kujirai, Izawa, Kase, & Shinozaki, 2019).

Spinal injury in automobile drivers

While spinal column mechanics and stability are typically concerned with compression forces, the cervical column is also exposed to a variety of other loading modes such as flexion/extension, lateral bending, axial rotation, tension, and shear during physiologic and traumatic loading scenarios (Stemper, Pintar, & Rao, 2011). In anatomical perspective, the lower cervical spine and the thoracolumbar junction are the most common locations for spine fractures among automobile drivers who experience a severe MVA. However, the frequency of spinal cord injury is much higher in the former group: while 33% of drivers with cervical spine fractures sustained a spinal cord injury, only 18% of drivers with thoracolumbar spine injury sustained a spinal cord injury (Smith, Siegel, & Siddiqi, 2005).

Automobile crashes may be quadrichotomized into frontal, lateral, rear-end, and rollover crash depending on the direction of the impact to the vehicle. Among them, frontal crash is one of the most frequently encountered automobile

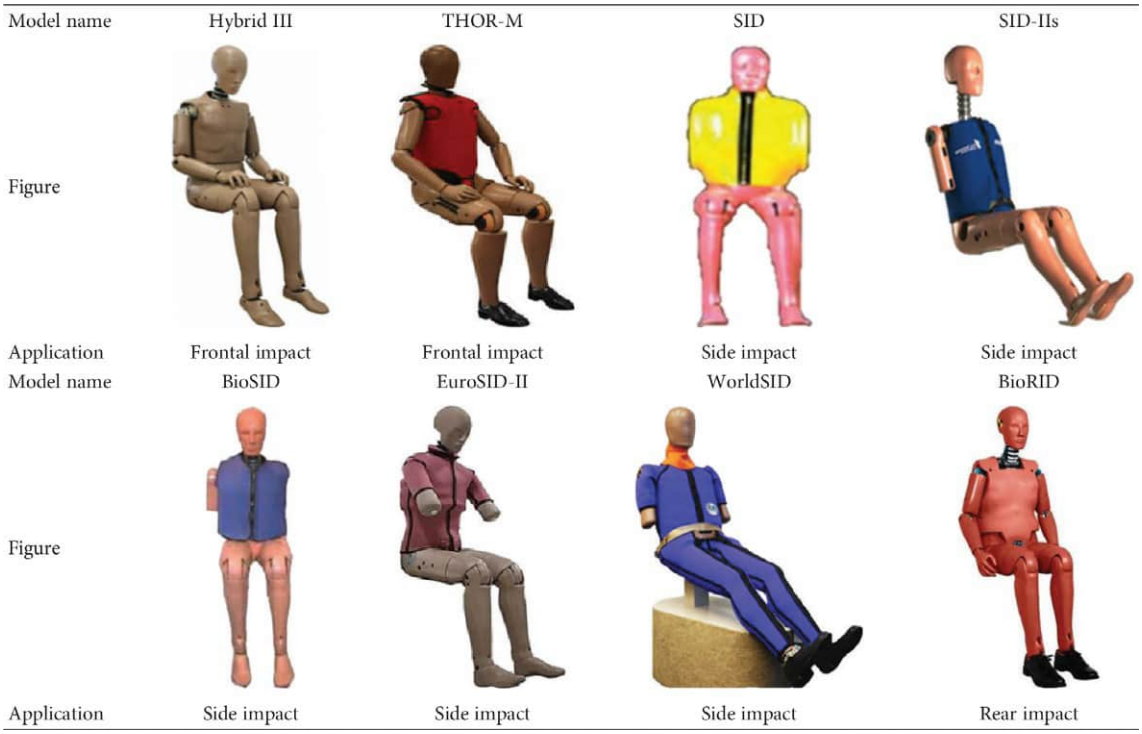

FIG. 2 Various crash test dummies. Various crash test dummies used by automobile manufacturers are presented. *From: Xu, T., Sheng, X., Zhang, T., Liu, H., Liang, X., & Ding, A. (2018). Development and validation of dummies and human models used in crash test.* Applied Bionics and Biomechanics, *3832850, Table 3 Reprint with permission. ©2018 Hindawi Publishing Co.*

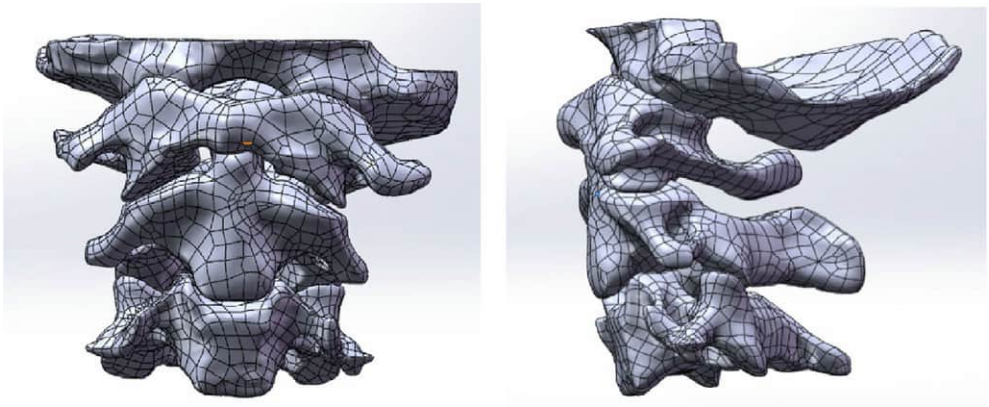

FIG. 3 3-D model of the upper cervical spine. An example of computational 3-D model of the upper cervical spine for evaluation of mechanical stress is presented. *From: Wang, X.D., Feng, M.S., Hu, Y.C. (2018). Establishment and finite element analysis of a three-dimensional dynamic model of upper cervical spine instability.* Orthopaedic Surgery, 11, *500–509, Fig. 4. Reprint with permission ©2019 John Wiley & Sons.*

crashes (Parenteau & Viano, 2014). In the frontal crash, impact transmitted to the spine of a restrained driver is mostly in the sagittal direction. During a frontal crash, the vehicle and its seat bases abruptly decelerate upon impact. Inertia of the torso causes the trunk to accelerate forward (Svensson et al., 2000). Head inertia and cervical spine flexibility cause relative forward acceleration and motion between the head and torso. The relative acceleration and motion may in turn cause the cervical spine injury. In a biomechanical study during simulated frontal crash, the greatest flexion motion beyond the physiologic limit was observed at C7-T1, followed by C5–6 (Ivancic, 2016). The finding was compatible to studies using finite element analysis (Panzer, Fice, & Cronin, 2011). Cervical spine injuries after frontal crashes are more likely

to be of flexion-extension type. The finite element analysis study also found that the annulus fibrosus of the cervical spine was the anatomical component which was primarily injured after the frontal impact (Panzer et al., 2011).

Regarding the thoracolumbar spine injury, it has been reported that compression and/or flexion injuries frequently occurred in frontal crashes due to seat pan and vertical loading (Pintar, Yoganandan, Maiman, Scarboro, & Rudd, 2012). The thoracolumbar spine was most commonly fractured at either the T12 or L1 level. Majorly, burst-type fractures occurred predominantly at T12, L1, or L5; wedge fractures were most common at L1. Most of automobile occupants in that study had been restrained with seatbelt. Interestingly, there was an increasing trend in incidence rate of thoracolumbar fractures in frontal impact crashes as a function of vehicle model year from 1986 to 2008 reason of which remained unknown (Pintar et al., 2012). Our group also made an investigation on thoracolumbar fractures caused during frontal crashes, and found that the incidence of neurological deficit in the unrestrained automobile occupants with a thoracolumbar fracture was approximately six times higher compared with restrained automobile occupants with a thoracolumbar fracture (Inamasu & Guiot, 2007).

During a lateral crash, the struck vehicle and its seat bases accelerate laterally. Inertia of the occupant's torso causes it to displace laterally toward the point of impact. Prior studies have demonstrated that occupants of lateral crashes are at higher risk of more severe injuries than those of frontal crashes because the greater crash-related energy is transferred to the occupant in the former group (Inamasu, Nakaya, Kujirai, Mayanagi, & Nakatsukasa, 2018). Additionally, seatbelt is less effective in preventing injuries due to lateral loading. Cervical spine motions beyond physiologic limits were observed in the lateral bending at C1–2 and C3–4 through C7-T1 (Ivancic, 2016). Multiplanar soft tissue injuries were also observed at C3–4 to C7-T1 due to simulated lateral crashes (Ivancic, 2016).

Most researchers agree that the risk of spinal injury is greatest in rollover collision. It has recently been reported that among the four categories of automobile crash, the rate of spinal cord injury was highest in rollover crash, and was lowest in frontal crash (Parenteau & Viano, 2014). In another study from Baltimore, the risk of cervical spine injury was 5.3 times higher among drivers who experienced a rollover crash compared with those who experienced a frontal crash (Stein et al., 2011). Roof deformation and protrusion has been thought responsible for this disproportionally high rate of cervical spine injury after rollover crashes (Bidez, Cochran Jr., King, & Burke, 2007). Our group investigated the difference in the injury pattern between restrained and unrestrained drivers who sustained a thoracolumbar junction fracture after rollover crash (Inamasu & Guiot, 2009). Neurologic deficits were present exclusively in the unrestrained group, and rotational thoracolumbar spine injury was present exclusively in the unrestrained group.

Rear-end collision is unique that severity of the spinal injury is usually modest and fractures occur less often compared with other types of collision. This is mainly because the speed of the vehicles involved is usually lower in rear-end collisions. However, there are many automobile occupants who suffer from whiplash injury as a sequela of rear-end crash. The whiplash injury mostly consists of damages to the soft tissue such as muscles, ligaments, discs, and joint capsules, which persists for months to years. Occasionally, elderly automobile occupants with pre-existing cervical canal stenosis such as ossification of the posterior longitudinal ligament may sustain a cord injury without fracture after low-speed rear-end collision (Hussain, Abu-Khumra, Alnajjar, & Abdo, 2016).

Role of seatbelt and airbag in protecting spine

There is little doubt about the importance of seatbelt (three-point seatbelt) and airbag in prevention of the spinal injury for automobile occupants. Nevertheless, spine injuries do occur in drivers wearing a seatbelt and for whom an airbag has deployed. In a recent US study, 89 of the 1067 (8%) drivers with MVA-related cervical spine injuries had been restrained and an airbag deployed (Wang et al., 2009). The combination of seatbelt and airbag is considered to be most effective. There have been several studies which evaluated efficacy of seatbelt and/or airbag in the reduction of spinal injury (Claytor, MacLennan, McGwin Jr., Rue 3rd, & Kirkpatrick, 2004; Reed et al., 2006; Wang et al., 2009; Williams et al., 2008). Those results as relative risk reduction of seatbelt and/or airbag are summarized in Table 2. While outcome parameters were somewhat different among studies, the relative risk reduction of cervical spine injury in belted, airbag-deployed drivers compared with non-restrained drivers was unequivocal, which ranged from 0.19 to 0.67. While the incidence of thoracic spine injury was also significantly reduced in belted, airbag-deployed drivers, there was no significant difference in the incidence of lumbosacral spine injury between the two groups (Wang et al., 2009). Ejection of automobile occupants from their vehicle is problematic particularly in rollover crashes. The efficacy of seatbelt is quite obvious in this setting. In restrained automobile occupants, partial ejection and complete ejection occurred in 2.4% and 0.03%. On the other hand, 3.8% and 20% of unrestrained automobile occupants sustained partial and complete ejection, respectively (Funk et al., 2012).

TABLE 2 Relative risk reduction of seatbelt and/or airbag against spine injury.

Author, year	Parameter	Unrestrained (Ref)	Seatbelt only	Airbag only	Seatbelt and airbag
Claytor et al. (2004)	Cervical spine injury	1	0.40	1.02	0.19
Reed et al. (2006)	Spinal cord injury	1	0.57	1.14	0.25
Williams et al. (2008)	Cervical spine injury	1	0.57	0.49	0.41
Wang et al. (2009)	Spine injury	1	1.17	1.05	0.67

It has been known for many years that airbag alone may not afford adequate protection to automobile occupants. A study from Pittsburg demonstrated that airbag-deployed but unrestrained drivers were 6.7 times more likely to suffer from the cervical cord injury compared with those using both protective devices (Donaldson 3rd., Hanks, Nassr, Vogt, & Lee, 2008). The risk of thoracic organ injury may also be increased in that situation (Khouzam, Al-Mawed, Farah, & Mizeracki, 2014). Airbag may potentially be deleterious to children and adult drivers with short stature (Blacksin, 1993). We recently reported that population might particularly be at elevated risk for hyper-extension injury of the upper cervical spine after severe impact, even though they were properly restrained by seatbelt, because their jaws are forcefully lifted upward owing to a rapidly expanding airbag (Inamasu & Kato, 2018). The mechanism of such airbag-induced spine injury and representative case is illustrated in Fig. 4. Many traffic safety guidelines strongly advise that children <12 years of age should not be seated in the front seat for fear of this type of injury. Catastrophic atlanto-occipital dislocations were more common than any other type of dislocation for 8- to 12-year-olds, even though they were seated in rear-seats (Mallory, Stammen, & Zhu, 2019).

Historically, Chance fracture, flexion-extension injuries of the thoracolumbar spine that extend to involve all three (anterior, middle, posterior) spinal columns, have been associated with the use of lap (two-point) seatbelt (Fig. 5). Since use of the two-point lap belt in automobile has been outlawed in many countries, Chance fracture has rarely been encountered in emergency departments nowadays. Interestingly, several cases of Chance fracture have been reported after crash landing of commercial flights, in which two-point seatbelt is equipped with passenger seat (Lee et al., 2015).

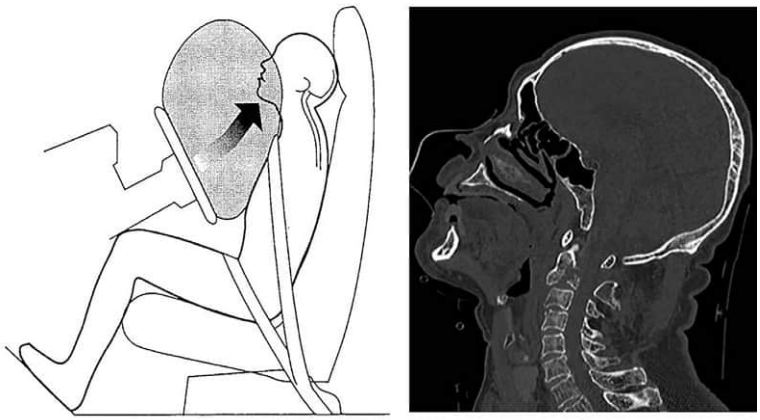

FIG. 4 Airbag-induced cervical spine injury. (A): An illustration showing mechanism of airbag-induced hyperextension injury of the cervical spine. (B): A sagittal CT scan of the spine showing an atlanto-axial dislocation caused by excessive inflation of an airbag. *Panel (A) From: Blacksin MF (1993). Patterns of fracture after air bag deployment.* Journal of Trauma, 35, *840–843, Fig. 4 Reprint with permission ©1993 Wolters Kluver.*

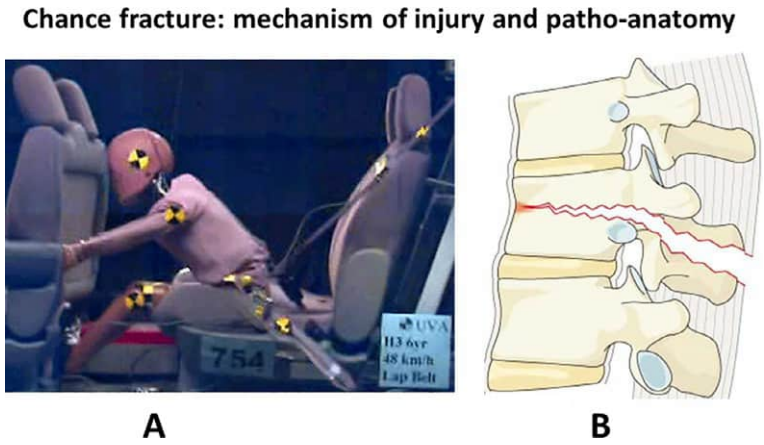

FIG. 5 Chance fracture. (A): A frontal crash test on a dummy wearing a two point seatbelt to simulate Chance fracture. (B): A schema of the Chance fracture of the lumbar spine illustrating extent of bony and soft tissue damage.

Prevention of spinal injury among motorcycle riders

Unlike automobile drivers, there have been no universally accepted protective devices for motorcyclists. Several researchers suggest that hard-shell back protective device may be effective: in a study from Italy, the percentage of spinal injuries among those who used a high-level safety device (hard-shell back protective device and/or airbags) was reduced by approximately 50% compared to those who used only protective clothing (Giustini et al., 2014). Because of lack of studies, however, it remains unclear to what degree those protective devices are effective. Helmets, which are intended to protect the head of the motorcycle rides from impact, may have protective effect against cervical spine injury. According to a recent study from South Korea, the use of helmet was associated with approximately 50% decrease in the frequency of cervical spine injury among motorcyclists (Park et al., 2019).

Application to other areas of neuroscience

In the automobile industry, biomechanical engineers have been working hard to create safer cars which minimize damage inflicted to automobile occupants. Thanks to a recent rapid development in information technology, more and more new vehicles are equipped with Advanced Automatic Collision Notification (AACN), which is a system on a motor vehicle that notifies a public safety answering point, either directly or through a third party, that the vehicle has had a crash. The AACN system enables earlier notification of an MVA and provides an injury prediction that can help dispatchers and first responders make better decisions about how and where to transport the injured passengers, thus getting the patients to definitive care sooner (Lee, Wu, Kang, & Craig, 2017). Considering that the spinal injury is both medical and surgical emergency for which prompt therapeutic intervention is required, we expect that the outcomes of patients with MVA-related spinal injury be improved with further expansion and refinement of the AACN system. Moreover, the concept of active safety is increasingly being introduced to avoid or minimize the impact of a crash. The active safety research today focuses primarily on sensor-based systems, such as advanced driver-assistance systems including adaptive cruise control and collision-warning/avoidance/mitigation systems (Li et al., 2019). It is expected that those sophisticated systems will dramatically reduce the incidence of MVA-related spine injury in the near future.

Mini-dictionary of terms

Spinal injury: in this chapter, the word is used to include spine (vertebral) injury, spinal cord injury, and soft tissue injury.

Frontal crash: it is a crash where the front end of a vehicle is impacted. It can further be classifiable to offset and non-offset collisions.

Lateral (side) crash: it is a crash where the side of one or more vehicles is impacted, and may be classifiable to near-side crash and far-side crash. It frequently occurs at intersections.

Rollover crash: is a crash in which a vehicle tips over onto its side or roof.

Rear-end crash: it is a crash that occurs when a vehicle crashes into the one in front of it.

Seatbelt: it is a vehicle safety device designed to secure the car occupants against harmful movement that may result during a crash. In an automobile setting, it usually refers to three-point seatbelt.

Key facts of spinal injury simulation

- Simulation of spinal injury consists of crash test dummies and computational models.
- Historically, crash test dummies have played an important role in simulation of the cervical spine injury.
- Crash test dummies may be classifiable into three categories depending on the direction of impact (frontal, lateral, and rear-end).
- Crash test dummies are designed based on American and European population, and damage prediction may be limited in other regions.
- The computational models began with finite element models of the body parts in the 1970s, evolving into more sophisticated full human body models.

Summary points

- While the circumstances of motor vehicle accidents (MVAs) are quite diverse, the number of MVA-associated spinal injury was greatest among automobile drivers.
- The frequency and severity of spinal injury is influenced by crash patterns, and rollover crash is associated with highest frequency of spinal injury.
- The combination of seatbelt and airbag is considered to be most efficacious in preventing or minimizing the spinal injury of automobile occupants.
- Various crash test dummies and computational models have been developed to simulate the spinal injury sustained by automobile occupants.
- Advanced Automatic Collision Notification (AACN), which is a system on a motor vehicle that notifies a public safety answering point that the vehicle has had a crash, is expected to improve the outcomes of patients with MVA-related spinal injury.

References

Bidez, M. W., Cochran, J. E., Jr., King, D., & Burke, D. S., 3rd. (2007). Occupant dynamics in rollover crashes: Influence of roof deformation and seat belt performance on probable spinal column injury. *Annals of Biomedical Engineering*, *35*, 1973–1988.

Blackmore, M. E., Goswami, T., & Chancey, C. (2012). Cervical spinal injuries and risk assessment. In T. Goswani (Ed.), *Injury and skeletal biomechanics (chapter 7)*. London: IntechOpen Ltd.

Blacksin, M. F. (1993). Patterns of fracture after air bag deployment. *Journal of Trauma*, *35*, 840–843.

Broe, M. P., Kelly, J. C., Groarke, P. J., Synnott, K., & Morris, S. (2018). Cycling and spinal trauma: A worrying trend in referrals to a national spine Centre. *The Surgeon*, *16*, 202–206.

Claytor, B., MacLennan, P. A., McGwin, G., Jr., Rue, L. W., 3rd, & Kirkpatrick, J. S. (2004). Cervical spine injury and restraint system use in motor vehicle collisions. *Spine*, *29*, 386–389.

Donaldson, W. F., 3rd., Hanks, S. E., Nassr, A., Vogt, M. T., & Lee, J. Y. (2008). Cervical spine injuries associated with the incorrect use of airbags in motor vehicle collisions. *Spine (Phila Pa 1976)*, *15*, 631–634.

Freeman, M. D., & Leith, W. M. (2020). Estimating the number of traffic crash-related cervical spine injuries in the United States; an analysis and comparison of national crash and hospital data. *Accident Analysis & Prevention*, *142*, 105571.

Funk, J. R., Cormier, J. M., Bain, C. E., Wirth, J. L., Bonugli, E. B., & Watson, R. A. (2012). Factors affecting ejection risk in rollover crashes. *Annals of Advances in Automotive Medicine*, *56*, 203–211.

Giustini, M., Cedri, S., Tallon, M., Roazzi, P., Formisano, R., & Pitidis, A. (2014). Use of back protector device on motorcycles and mopeds in Italy. *International Journal of Epidemiology*, *43*, 1921–1928.

Hussain, K., Abu-Khumra, S. K. A., Alnajjar, F. J. K., & Abdo, M. M. (2016). Triple trouble: A case of traumatic cervical spinal cord injury in a patient with ossification of posterior longitudinal ligament and disc prolapse. *Turkish Journal of Emergency Medicine*, *16*, 129–131.

Inamasu, J., & Guiot, B. H. (2007). Thoracolumbar junction injuries after motor vehicle collision: Are there differences in restrained and non-restrained front seat occupants? *Journal of Neurosurgery. Spine*, *7*, 311–314.

Inamasu, J., & Guiot, B. H. (2009). Thoracolumbar junction injuries after rollover crashes: Difference between belted and unbelted front seat occupants. *European Spine Journal*, *18*, 1464–1468.

Inamasu, J., & Kato, M. (2018). Airbag deployment and cervical spine injury in restrained drivers following motor vehicle collisions. *Neuroradiology*, *60*, 1307–1313.

Inamasu, J., Kujirai, D., Izawa, Y., Kase, K., & Shinozaki, H. (2019). Difference in severity and distribution of bodily injuries following collision between drivers of K-cars and standard vehicles. *Injury*, *50*, 205–209.

Inamasu, J., Nakaya, M., Kujirai, D., Mayanagi, K., & Nakatsukasa, M. (2018). Frequency and characteristics of traumatic brain injury in restrained drivers involved in road traffic accidents. *Acta Neurochirurgica (Wien)*, *160*, 1921–1929.

Ivancic, P. C. (2016). Mechanisms and mitigation of head and spinal injuries due to motor vehicle crashes. *The Journal of Orthopaedic and Sports Physical Therapy*, *46*, 826–833.

Khouzam, R. N., Al-Mawed, S., Farah, V., & Mizeracki, A. (2014). Next-generation airbags and the possibility of negative outcomes due to thoracic injury. *Canadian Journal of Cardiology*, *30*, 396–404.

Lee, H. J., Moon, B. J., Pennant, W. A., Shin, D. A., Kim, K. N., Yoon, D. H., et al. (2015). Three cases of spine fractures after an airplane crash. *Korean Journal of Neurotrauma*, *11*, 195–200.

Lee, E., Wu, J., Kang, T., & Craig, M. (2017). Estimate of mortality reduction with implementation of advanced automatic collision notification. *Traffic Injury Prevention*, *29*(Sup. 1), S24–S30.

Li, F., Liu, N., Li, H., Zhang, B., Tian, S., Tan, M., et al. (2019). A review of neck injury and protection in vehicle accidents. *Transportation Safety and Environment*, *1*, 89–105.

Mallory, A., Stammen, J., & Zhu, M. (2019). Cervical and thoracic spine injury in pediatric motor vehicle crash passengers. *Traffic Injury Prevention*, *20*, 84–92.

Panzer, M. B., Fice, J. B., & Cronin, D. S. (2011). Cervical spine response in frontal crash. *Medical Engeneering & Physics*, *33*, 1147–1159.

Parenteau, C. S., & Viano, D. C. (2014). Spinal fracture-dislocations and spinal cord injuries in motor vehicle crashes. *Traffic Injury Prevention*, *15*, 694–700.

Park, G. J., Shin, J., Kim, S. C., Na, D. S., Lee, H. J., Kim, H., et al. (2019). Protective effect of helmet use on cervical injury in motorcycle crashes: A case-control study. *Injury*, *50*, 657–662.

Pintar, F. A., Yoganandan, N., Maiman, D. J., Scarboro, M., & Rudd, R. W. (2012). Thoracolumbar spine fractures in frontal impact crashes. *Annals of Advances in Automotive Medicine*, *56*, 277–283.

Reed, M. A., Naftel, R. P., Carter, S., MacLennan, P. A., McGwin, G., Jr., & Rue, L. W., 3rd. (2006). Motor vehicle restraint system use and risk of spine injury. *Traffic Injury Prevention*, *7*, 256–263.

Robertson, A., Branfoot, T., Barlow, I. F., & Giannoudis, P. V. (2002). Spinal injury patterns resulting from car and motorcycle accidents. *Spine (Phila Pa 1976)*, *27*, 2825–2830.

Smith, J. A., Siegel, J. H., & Siddiqi, S. Q. (2005). Spine and spinal cord injury in motor vehicle crashes: A function of change in velocity and energy dissipation on impact with respect to the direction of crash. *Journal of Trauma*, *59*, 117–131.

Stein, D. M., Kufera, J. A., Ho, S. M., Ryb, G. E., Dischinger, P. C., O'Connor, J. V., et al. (2011). Occupant and crash characteristics for case occupants with cervical spine injuries sustained in motor vehicle collisions. *Journal of Trauma*, *70*, 299–309.

Stemper, B. D., Pintar, F. A., & Rao, R. D. (2011). The influence of morphology on cervical injury characteristics. *Spine (Phila Pa 1976)*, *36*(25 Suppl), S180–S186.

Svensson, M. Y., Boström, O., Davidsson, J., Hansson, H. A., Håland, Y., Lövsund, P., et al. (2000). Neck injuries in car collisions: A review covering a possible injury mechanism and the development of a new rear-impact dummy. *Accident Analysis & Prevention*, *32*, 167–175.

Wang, X. D., Feng, M. S., & Hu, Y. C. (2018). Establishment and finite element analysis of a three-dimensional dynamic model of upper cervical spine instability. *Orthopaedic Surgery*, *11*, 500–509.

Wang, H., Liu, X., Zhao, Y., Ou, L., Zhou, Y., Li, C., et al. (2016). Incidence and pattern of traumatic spinal fractures and associated spinal cord injury resulting from motor vehicle collisions in China over 11 years: An observational study. *Medicine (Baltimore)*, *95*, e5220.

Wang, M. C., Pintar, F., Yoganandan, N., & Maiman, D. J. (2009). The continued burden of spine fractures after motor vehicle crashes. *Journal of Neurosurgery. Spine*, *10*, 86–92.

Williams, R. F., Fabian, T. C., Fischer, P. E., Zarzaur, B. L., Magnotti, L. J., & Croce, M. A. (2008). Impact of airbags on a level I trauma center: Injury patterns, infectious morbidity, and hospital costs. *Journal of the American College of Surgeons*, *206*, 962–968.

Xu, T., Sheng, X., Zhang, T., Liu, H., Liang, X., & Ding, A. (2018). Development and validation of dummies and human models Used in crash test. *Applied Bionics and Biomechanics*, 3832850.

Yanar, H., Demetriades, D., Hadjizacharia, P., Nomoto, S., Salim, A., Inaba, K., et al. (2007). Pedestrians injured by automobiles: Risk factors for cervical spine injuries. *Journal of the American College of Surgeons*, *205*, 794–799.

Chapter 2

Magnetic resonance imaging (MRI) findings in spinal cord injury during acute and chronic phases

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List of abbreviations

DTI	diffusion tensor imaging
DWI	diffusion weighted imaging
FA	fractional anisotropy
fMRI	functional magnetic resonance imaging
GRE	gradient echo images
MPM	multiparametric mapping
SCI	spinal cord injury
SPAM	subacute progressive ascending myelopathy
STIR	short-tau inversion recovery
T1W	T1-weighted
T2W	T2-weighted

Introduction

MRI is considered the gold standard in imaging soft tissue structures in spinal trauma (Bozzo, Marcoux, Radhakrishna, Pelletier, & Goulet, 2011). It plays an especially important role in cases of spinal cord injury without radiological abnormality (SCIWORA) where first-line imaging, i.e., CT and radiography fail to show features of injury despite neurological deficits (Shen et al., 2007) In cases where both MRI and CT are required, it can help as an initial complex imaging in guiding a restricted CT scan for assessment of bony structures, preventing excessive radiation dose in spinal cord injury (SCI) patients who are mostly young (Chandra et al., 2012).

In the acute phase of injury, MRI plays a crucial role in diagnostic workup, surgical planning, and prognostication (Bozzo et al., 2011). It allows better visualization of the cord as well as the discoligamentous complex and guides the clinician in evaluating the site, severity, extent, and mechanism of the injury (Chandra et al., 2012; Freund et al., 2019; Kumar & Hayashi, 2016). Features including cord hematoma, severity of maximal cord compression and length of cord edema on MRI correlate significantly with functional outcomes (Chandra et al., 2012). MRI in the subacute and chronic phases of injury guides in the assessment of recovery and neuro-rehabilitation (Chandra et al., 2012; Freund et al., 2019). In this chapter, we elaborate various MRI sequences applicable to SCI management, findings observed in the acute, subacute and chronic phases of SCI, and their correlation with clinical features.

MRI sequences used in SCI

With the advancements in imaging technology, a multitude of sequences of MRI have been developed which range from conventional to novel and quantitative MRI techniques for the evaluation of varied aspects of SCI (Table 1).

Cellular, Molecular, Physiological, and Behavioral Aspects of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822427-4.00002-2

TABLE 1 Applications of MRI sequences in phases of SCI.

Phase of SCI	MRI sequences	Applications
Acute	Sagittal T1W, sagittal and axial T2W, sagittal and axial T2W GRE (injury site), sagittal STIR sequences (whole spine)	diagnostic workup, surgical planning, prognostication
Subacute	Sagittal T1W, sagittal and axial T2W (injury site)	evaluation of postoperative complications or ascending neurological deficits
Chronic	T1W, T2W, DTI, Magnetization transfer, Multiparametric mapping, task-based fMRI	evaluation of late complications and recovery, clinical trials on neurorehabilitation.

Conventional MRI

Conventional MRI sequences used for evaluating SCI include T1-weighted (T1W) and T2-weighted images (T2W) to observe the primary pathological changes at the injury epicentre (Freund et al., 2019). These sequences elucidate the level of the injury and the length of intramedullary or extramedullary damage seen as edema and hemorrhage, the degree of spinal cord compression, extent of disk herniation, and the ligamentous damage (Freund et al., 2019). Axial T2-weighted is used for classifying acute cord injury in the Brain and Spinal Injury Center (BASIC) score (Freund et al., 2019). Lesions such as disk herniation and spinal cord compression are also evident on axial T2 sequences and guide the decision for surgical decompression (Bozzo et al., 2011; Freund et al., 2019). These sequences also have a role in follow up of SCI patients to see the changes evolving in the subacute phase of injury such as posttraumatic cyst (Freund et al., 2019). Moreover, the sagittal T2-weighted MRI shows midsagittal tissue bridges which predict sensorimotor recovery and can be used to stratify patients in clinical trials (Freund et al., 2019; Vallotton et al., 2019).

Use of MRI may be limited by the high cost incurred by many sequences and issues of logistics in trauma (Bozzo et al., 2011). Besides, image quality may be compromised by susceptibility artefacts due to metallic clips and dental implants, cerebrospinal fluid (CSF) flow artefact, Gibbs artefact, and chemical shift (Chandra et al., 2012; Kumar & Hayashi, 2016).

Novel and quantitative MRI sequences

Recently developed sequences like gradient echo images (GRE) offer better visualization of hemorrhage (Bozzo et al., 2011; Chandra et al., 2012), while short-tau inversion recovery (STIR), a fat suppressed version of T2-weighted, and gradient recall acquisition steady state (GRASS) can be useful for ligamentous injuries (Bozzo et al., 2011). Despite their utility, these sequences are yet to be included in injury classification scales. Functional MRI, based on blood flow, is being used in research to study the affected sensorimotor networks and plasticity occurring in the brain and spinal cord (Freund et al., 2019).

Quantitative MRI techniques have a role in demonstrating secondary microstructural changes reflecting neurodegeneration and neuroplasticity occurring throughout the neuraxis. Latest software-based image processing enables the calculation of various parameters at the voxel level (Freund et al., 2019). Diffusion weighted imaging (DWI), which utilizes information from the Brownian motion of water molecules, is sensitive to changes in axons and myelin. DWI can detect white matter tract changes as hyperintense lesions in acute SCI when conventional MRI fails to detect any abnormality (Shen et al., 2007). Diffusion Tensor Imaging (DTI) uses tensor models to depict these changes quantitatively (Zaninovich et al., 2019). Values of DTI parameters depict microstructural and degenerative changes that correlate with the severity of SCI and prognostic scores (Cheran et al., 2011; Ellingson, Ulmer, Kurpad, & Schmit, 2008). However, DWI is less established in the cord region due to small tissue volume, CSF flow and motion artefacts (Chandra et al., 2012). Moreover, DTI metrics are seen to be inconsistent across different SCI studies (Zaninovich et al., 2019). Machine learning and improved imaging methods are needed to improve DTI results (Zaninovich et al., 2019). Multiparameter mapping is another quantitative technique that combines magnetization transfer and relaxation mapping to indicate demyelination and iron deposition in the cervical cord and the brain (Freund et al., 2019).

Combined with conventional sequences, these techniques enable quantification of the degeneration and repair processes at various endpoints. Thus, they are useful biomarkers to predict the long-term outcomes as well as in clinical trials on spinal cord regeneration (Seif, Wheeler-Kingshott, Cohen-Adad, Flanders, & Freund, 2019).

Protocols for MRI in SCI

It is recommended to perform the imaging within 24–72 h of the trauma (Bozzo et al., 2011; Freund et al., 2019) Specifically, the sagittal T2W MRI should be done in the acute phase of SCI for prognostication of neurological outcome and clinical decision-making (Bozzo et al., 2011). The length of edema on sagittal T2W MRI increases proportionally with the delay in time of imaging in the acute phase (Leypold, Flanders, & Burns, 2008). After the acute phase, MRI sensitivity to detect ligamentous injury is also decreased (Kumar & Hayashi, 2016).

Recommended MRI protocol for acute spinal injury includes sagittal fast spin echo T1W, sagittal and axial T2W, sagittal and axial T2W gradient recalled echo (GRE) sequences of the primary injury site, and sagittal whole spine short tau inversion recovery (STIR) sequences for non-contiguous remote vertebral injuries (Chandra et al., 2012; Kumar & Hayashi, 2016). In the subacute phase, only targeted T1W and T2W images of the injury site are required for evaluation of postoperative complications or ascending neurological deficits (Chandra et al., 2012).

MRI findings in acute SCI

MRI reveals important features of acute SCI such as edema, hematoma, and compression as well as damage to extramedullary structures. These features are important when considering the acute management and deciding between surgical and nonsurgical options (Bozzo et al., 2011; Chandra et al., 2012). In obtundated patients with neurological deficit, MRI may be useful in picking up cervical injuries missed on CT scan and lead to surgical interventions (Bozzo et al., 2011). These findings are also integral to prognostication of SCI (Kulkarni, Bondurant, Rose, & Narayana, 1988).

Extra-medullary findings

Extra-medullary lesions are located within the dural sac but lie outside the spinal cord. MRI is important for evaluating the level and extent of extra-medullary lesions and spinal stability to guide clinical decision-making (Freund et al., 2019).

Ligamentous injury

Although CT displays most imaging findings of instability such as widening of the facet joints, it is unable to detect ligamentous injuries (Kumar & Hayashi, 2016). MRI, specially STIR, proves to be a more sensitive imaging modality for direct visualization and evaluation of soft tissue structures including subtle ligamentous injuries (Izzo et al., 2019; Kumar & Hayashi, 2016). Normal spinal ligaments are visualized as continuous bands of low signal intensity. Tears in ligaments can be either partial or complete; the former appears as hyperintense areas on STIR images due to injury-related edema and hemorrhage with variable intact fibers, while the latter differs in that there is a complete lack of intact fibers and hence appears discontinuous (Kumar & Hayashi, 2016).

Disc damage

Damage to intervertebral discs can be classified as an internal disc injury or disc herniation. Damage to the internal structure of the disc substance leading to edema or hemorrhage appears as an irregular narrowing or widening of a disk space with an abnormal high-intensity signal within the disc on T2W or STIR images (Dundamadappa & Cauley, 2012; Provenzale, 2007). MRIs are well suited for evaluating traumatic disc herniation due to a good signal contrast between the vertebral body, disc material, and cerebrospinal fluid. Additionally, sagittal plane imaging aids in determining if a fragment of the disc has been detached which is useful in surgical planning (Provenzale, 2007).

Other soft tissues

MR imaging also allows for visualization of prevertebral soft tissue injuries, which appears abnormally thickened due to associated edema and hemorrhage and is seen as a high intensity signal on T2-weighted or STIR images (Provenzale, 2007). Muscle strains are accompanied by edema which also appear as hyperintense signals on STIR images, whereas muscle hemorrhages present with a heterogeneous intensity signal due to a combination of hemorrhage and edema (Kumar & Hayashi, 2016).

Vascular injury

Typically, a normal artery demonstrates flow void on long TE sequences on an axial MRI. Hence, most vascular injuries will present as a disruption or loss of normal flow void on T2W images (Dundamadappa & Cauley, 2012; Kumar &

Hayashi, 2016). In the presence of an arterial thrombus or retarded flow, axial T2W images will demonstrate signal hyperintensity. Axial fat-suppressed T1W or T2W imaging along with MR angiography is better suited in cases of intramural hematoma associated with dissection for better luminal narrowing visualization and the hemorrhage is seen as a hyper intense signal on T1W or T2W images (Dundamadappa & Cauley, 2012).

Extramedullary hematoma

Spinal extradural hematomas are considered an emergency when they begin to compress the spinal cord. MRI is the preferred diagnostic tool compared to CT due to superior tissue contrast between the hematoma and adjacent soft tissues and structures (Izzo et al., 2019). Epidural hematomas will typically appear as an isointense to hyperintense signal on T1W images and hyperintense on T2W images (Fig. 1). The hematoma may also demonstrate heterogeneity on T2W imaging depending on its age (Ghasemi, Haddadi, & Shad, 2015; Sklar, Post, & Falcone, 1999). In addition, sagittal MRI allows visualization of the extent of the hematoma along the entire cranio-caudal axis (Izzo et al., 2019). Similarly, subdural hematoma and subarachnoid hemorrhage are also seen as varying signal intensities (Kumar & Hayashi, 2016; Sklar et al., 1999).

Fractures

Although CT is considered the imaging modality for diagnosing fractures, it is challenging to distinguish acute from chronic fractures. MRI can do so due to the presence of accompanying edema and hemorrhage in acute fractures. Bone marrow of acute fractures appears as hypointense signals on T1W images and hyperintense on T2W and STIR images, indicating marrow edema (Provenzale, 2007). In chronic fractures, the fatty marrow will produce an increased signal on both T1W and T2W images (Kumar & Hayashi, 2016). MR imaging can also distinguish various pathological fractures. Osteoporotic fractures show hypointense signal bands on T1W and T2W images and spared normal fatty marrow signal intensity along with a retropulsed posterior bone fragment. Metastatic compression fractures are characterized by an abnormal signal intensity involving the pedicles or posterior elements, convexity of the posterior vertebral wall and presence of epidural and paraspinal masses (Jung, Jee, McCauley, Ha, & Choi, 2003).

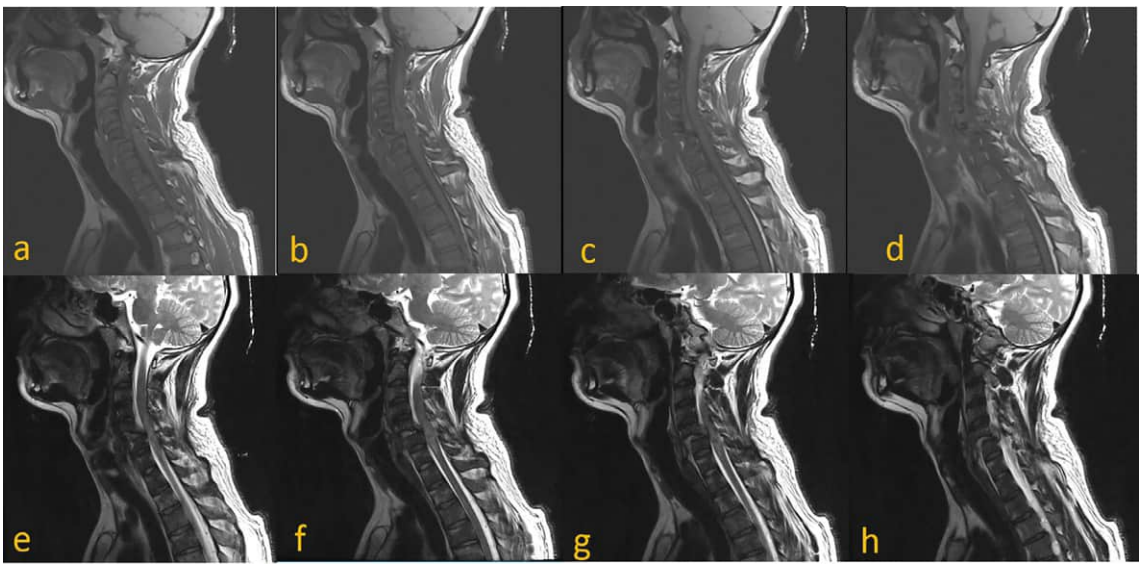

FIG. 1 Epidural hematoma and C5–C6 Spondylolisthesis with cord edema. (A)–(D) Sagittal T1W and (E)–(H) Sagittal T2W cervical spine show swollen C5–C6 intervertebral disc with heterogenous T2 hyperintense signals which is bulging posteriorly resulting in canal narrowing and mild cord compression. On T2W, heterogenous hyperintensity is observed at C5–C7 cord representing acute cord edema. Diffuse abnormal T2 hyperintense signals identified in epidural space from C2 to C4 level represent epidural hematoma.

Intramedullary findings

In the acute phase, cord may be affected with varying severity ranging from mild concussion to edema, hemorrhage, and even complete transection. MRI provides an excellent evidence base to determine the patient's severity level with a good radio–pathological correlation (Chandra et al., 2012).

Cord concussion

Spinal cord concussion is a temporary disturbance of the cord function present with or without vertebral damage, mostly associated with contact sports and whiplash injuries (Nesnídal, Stulík, & Barna, 2012). It often presents along with pre-existing vertebral abnormalities resulting in areas of hypermobility or narrowing of spinal cord with motor weakness and sensory impairment that resolves between two days to two months (Chandra et al., 2012). Cord concussion may show no signal change in either T1W or T2W images throughout the clinical course and has a very favorable outcome (Kumar & Hayashi, 2016; Nesnídal et al., 2012).

Cord compression

Spinal cord compression is an emergency which develops when the vertebral body exerts pressure on the spinal cord following traumatic impact or a pathological fracture. Timely diagnosis of cord compression and surgical decompression is required to resolve the neurological deficit (Alizadeh, Dyck, & Karimi-Abdolrezaee, 2019). The degree of cord compression and maximum canal stenosis at the site of injury are both linked to degree of neurological deficit and functional outcome (Miyanji, Furlan, Aarabi, Arnold, & Fehlings, 2007). On MRI, displaced or fractured vertebral bodies are seen compressing the cord which shows no signal change on T2W. However, a high signal within the soft tissues on sagittal STIR images is seen (Chandra et al., 2012).

Cord edema

Cord edema is the swelling of the spinal cord after spinal cord injury (Cho, Hachem, & Fehlings, 2017). Cord edema is not static; it occurs in the acute phase or often 2–3 days after the injury and may resolve after 14 days of injury (Cho et al., 2017; Leypold et al., 2008). Spinal cord edema spreads from the initial site of injury as one vertebral segment per 30 hours in the first three days post-SCI (Chandra et al., 2012; Cho et al., 2017). This can be detected as a high T2 signal and a normal or a low T1 signal inside the cord on MRI (Fig. 1) (Chandra et al., 2012). STIR images are particularly sensitive in detecting edema because of more uniform fat suppression (Kumar & Hayashi, 2016). The length of swelling is associated with the neurological presentation and outcome of the patient. Patients with transient edema have a favorable neurological outcome whereas worse baseline American Spinal Injury Association (ASIA) motor scores and neurological recovery are seen with persistent edema (Chandra et al., 2012).

Hemorrhagic contusion

Spinal cord injuries that occur as high-energy blunt trauma cause contusion injuries with crushed cord tissue and bleeding (Ju, Wang, Wang, & Zhao, 2014). On MRI, it is seen as a central intramedullary focus of low signal in the cord that is surrounded by a thick rim of hyperintense signals on T2W image (Fig. 2). Hemorrhage is best seen on T2W GRE images. However, T1W images can show subtle increase in signal denoting acute hemorrhage (Kulkarni et al., 1988). Presence of hemorrhage is associated with complete cord injury and worse ASIA motor score, and indicates poor prognosis (Chandra et al., 2012; Kumar & Hayashi, 2016). The extent of hemorrhage correlates with the outcome, a small hemorrhage of less than 4 mm has a better clinical and radiological improvement chances on follow-up imaging (Chandra et al., 2012).

Cord hematoma

Spinal cord hematoma is a severe and rare condition of the cord that often leads to permanent neurological deficit if not treated promptly (Kreppel, Antoniadis, & Seeling, 2003). On MRI, it shows up as a large (>4 mm) focus of intramedullary low signal that is surrounded by a thin rim of high signal, best seen on T2W GRE but also visible on T2W imaging (Chandra et al., 2012).

Cord ischemia

Trauma is one of the reasons for spinal cord ischemia with a poor prognosis. On MRI, axial sequences are useful to differentiate it from other causes (Vargas et al., 2015). Findings on MRI show up as hyperintense signal on T2W with cord

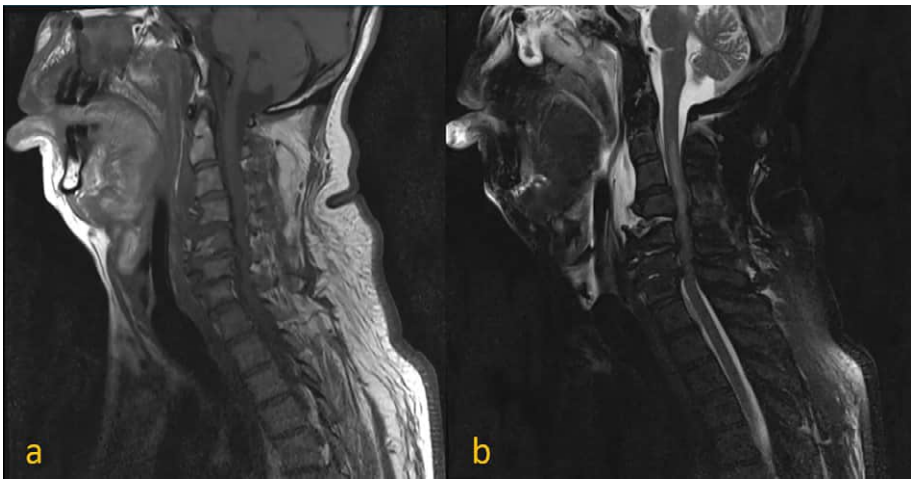

FIG. 2 Cord contusion. (A) Sagittal T1W and (B) Sagittal T2W cervical spine show prevertebral space collection extending from C2 to C6 vertebra. Compression fracture of C5 vertebra is seen with grade I retrolisthesis of C6 over C7 vertebra resulting in moderate spinal canal stenosis and severe bilateral radicular compression. On T2W, hyperintensity in the cord extending from C2–C3 intervertebral disc level to C6–C7 intervertebral disc level represents cord contusion.

enlargement (Chandra et al., 2012). Also, where traditional MRI techniques may fail to show any abnormalities, DWI shows promise in showing reduced apparent diffusion coefficient value in transverse plane specifying restricted diffusion (Chandra et al., 2012; Nogueira et al., 2012). Diffusion restriction correlates with unfavorable outcomes (Nedeltchev et al., 2004).

Cord transection

Spinal cord transection is the most severe and rare SCI, seen with unstable spinal fractures with associated spondylolisthesis or penetration injury with not much apparent bony injury (Baliyan et al., 2016). The former can be due to blast injury like gunshot or due to a direct tear (Chandra et al., 2012). It results in irreversible neurological impairment (Baliyan et al., 2016). On MRI, it appears as a complete disruption of the cord with high-signal CSF seen between the severed ends of the cord on T2W images (Fig. 3) (Mostafa, 2019).

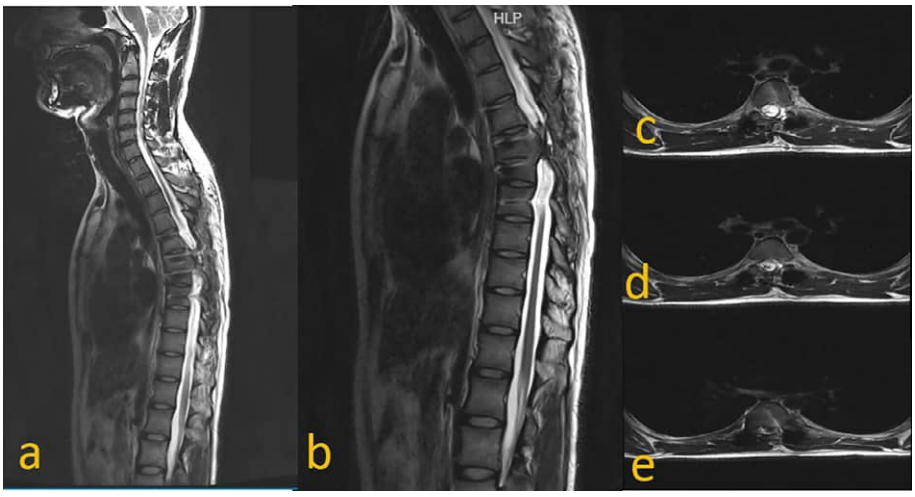

FIG. 3 Complete disruption of the dorsal cord. (A) Sagittal T2W whole spine (B) Sagittal T2W dorsal spine (C)–(E) Axial T2W dorsal spine show long segment of complete disruption of the cord extending from T5 to T9 vertebral levels. Multilevel fixation screws with residual kyphosis can be seen.

MRI findings in subacute SCI

Following the acute phase of injury, spinal cord lesions such as edema and hemorrhage evolve as well as begin to resolve as the cord is infiltrated by macrophages and blood–brain barrier starts to repair (Hausmann, 2003). In the first month post-injury, posttraumatic cyst begins to form, and small tissue bridges develop around the cyst (Huber, Lachappelle, Sutter, Curt, & Freund, 2017).

Subacute progressive ascending myelopathy

Subacute progressive ascending myelopathy (SPAM) is a rare SCI complication with an incidence of 1.8–6% (Planner, Pretorius, Graham, & Meagher, 2008). SPAM presents as delayed ascending neurological deterioration traumatic within 30 days of SCI and is often associated with early surgical interventions and infections (Planner et al., 2008). Although the exact cause is not well understood, it may develop due to mechanical insult, altered CSF flow, vascular injury or immune-mediated mechanisms (Zhang & Wang, 2017). Most patients show some recovery; however, it is associated with a 10% mortality rate (Zhang & Wang, 2017).

MRI shows typical progression of edema more than four segments cephalad the original injury in a tapered fashion, sometimes extending up till medulla oblongata (Zhang & Wang, 2017). Edema often subsides, but some edema remains above the initial level (Chandra et al., 2012). It shows characteristic sparing of the cord periphery while the hyperintense signal abnormality remains central on T2W image. SPAM shows heterogeneous intramedullary signal on T1W image along with an expanded spinal cord (Farooque, Kandwal, & Gupta, 2014; Zhang & Wang, 2017).

Early syrinx

Syrinx is a longitudinal fluid filled structure, as opposed to a small and localized posttraumatic cyst, formed in 3% of patients after a period of months to years post SCI. It may span many segments of the cord leading to progressive myelopathy (Ahuja et al., 2017). Syrinx has tapered cephalad and caudal extents which expand beyond the injured section and gives off isointense signals to CSF on sagittal T2W MRI (Chandra et al., 2012). In patients with Chiari 1 malformation, MRI shows compression of retro-cerebellar CSF spaces differentiating it from early syrinx due to SCI (Klekamp, 2018).

MRI findings in chronic SCI

The chronic phase of SCI spans months to years after onset of injury and it involves neuroplastic and degenerative changes in the spinal cord and brain. Despite conventional MRI's unprecedented importance in acute SCI management, it provides little information about the ongoing microstructural neurodegeneration and neuroplasticity in the chronic phase of injury (Freund et al., 2016). In contrast, quantitative MRI techniques like magnetization transfer, magnetic resonance relaxation mapping, and diffusion imaging have shown to play a vital role in detection of spinal cord atrophy, demyelination and iron deposition, painting a picture of progressive neurodegeneration (Freund et al., 2019). Tensor-based morphometry and multiparametric mapping (MPM) have been used as quantitative methods to measure volumetric changes and microstructural demyelination post SCI. This further aids clinicians in prognosticating the outcome of patients and exploiting the sensitivity and specificity of MRI findings as biomarkers in clinical trials (Freund et al., 2019).

Neurodegeneration and demyelination of the spinal cord post SCI

Features in chronic SCI seen on conventional MRI include myelomalacia, atrophy, and formation of cystic cavities and tethering of cord. Myelomalacia is seen on MRI as a poorly defined area of signal intensity between CSF and normal cord (Fig. 4) (Burks et al., 2019). Burks et al. observed changes in chronic (>1 year) SCI patients on sagittal T2W images and found myelomalacia as the most frequent finding, followed by cysts, septation, and cord tethering. Another study using T2W MRI showed a transition of acute changes (edema and hemorrhage) to subacute intramedullary lesion expansion in the span of a year. After resolution of the acute changes, a posttraumatic cyst appeared after a month of the injury and small tissue bridges were detected around the cyst. The quantification and location of these bridges on T2W MRI scans can serve as a prognostic tool as they provide valuable information on tract-specific electrophysiology and long-term functional recovery (Huber et al., 2017).

In a prospective longitudinal study, signs of remote spinal cord atrophy at the C2/C3 level were observed on T1W images over one year. Compared to controls, patients had a significantly greater rate of change in spinal cord area (decrease

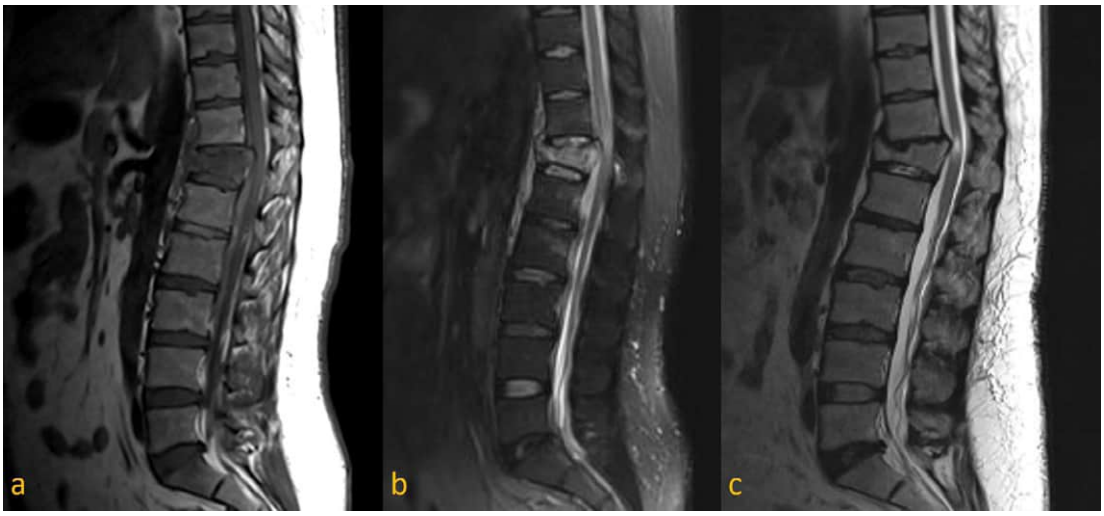

FIG. 4 D12 fracture secondary to road traffic accident. (A) Sagittal T1W Lumber spine and (B) Sagittal T2W Lumber spine show compression fracture of D12 vertebra. This is associated with retropulsed bony fragment, which is causing significant pressure over the anterior theca at this level. T2-hypointense signals at this level indicate cord edema. (C) Sagittal T2W Lumber spine of the same patient after 8 years show hyperintense T2 signals suggesting focal myelomalacia at D12 level.

of 0·46 mm^2 per month) (Freund et al., 2013). Huber et al. showed evidence of remote neurodegeneration in dorsal horns, ventral horns, and white matter at cervical spinal cord in patients with chronic spinal cord injury on T2W images. Atrophy of dorsal and ventral horns correlated clinically with sensory and motor outcomes, respectively (Huber et al., 2018). It is still unclear whether the rate of spinal cord atrophy is linked to level of the lesion or severity of the injury (Freund et al., 2019). MPM studies demonstrated that spinal cord atrophy was also paralleled with an increase in iron content and decreased myelin content (Ziegler et al., 2018). Interestingly, histological analysis also showed that the iron accumulated in phagocytic macrophages 28–35 days after spinal cord injury (Freund et al., 2019).

Altered DTI metrics have been observed at injury level as well as remotely, specifically in the corticospinal tract and dorsal columns corresponding to axonal degeneration in acute and chronic SCI (David, Freund, & Mohammadi, 2017). Similar DTI patterns have been noted in in the lumbar enlargement indicating trans-synaptic degeneration of motor neuron pools deprived of input (Koskinen et al., 2014). Ellingson et al. showed low fractional anisotropy (FA) values at injury level, these values were directly proportional to ASIA classification. While FA values were low throughout the cord compared to controls, a sharp drop in FA at the injury site implies utility of DTI to localize the lesion (Ellingson et al., 2008). A decreased fractional anisotropy and an increased ADC are associated with neuropathological changes like axonal loss, demyelination, gliosis, astrocytic scarring and an increase in extracellular matrix (Pierpaoli et al., 2001). Moreover, fMRI studies of the cord show preservation of task-related spinal activities above and below the site of injury (Freund et al., 2019).

Neurodegeneration of the brain post-SCI

Studies have shown a link between brain atrophy and SCI most likely due to retrograde degeneration and demyelination of tracts (Freund et al., 2019). Brain atrophy after spinal cord injury is particularly prominent across the cranial projections of the corticospinal tracts, primary motor cortex, insula, anterior cingulate gyrus, and thalamus (Fig. 5) (Freund et al., 2013; Grabher et al., 2015; Ziegler et al., 2018). Parallel analysis using MPM related these volume changes to demyelination of axons and their cell bodies (Freund et al., 2013). Volumetric changes in structural T1W MRI have been linked with clinical outcomes and can be used to monitor treatment effects. Significant volume reductions in the brainstem have been associated with poorer prognosis for lower limb motor function recovery; whereas lower limb training in patients with SCI showed increases in the brain volume owing to reorganization processes (Villiger et al., 2015).

DTI studies in chronic SCI patients also show altered metrics in the white matter of the brain reflecting compromised structural connectivity (Zaninovich et al., 2019). Statistically significant differences in DTI parameters are observed between chronic SCI injury patients and healthy controls in areas such as posterior area of the centrum semiovale, corona radiata, cerebral peduncles, and internal capsule (Koskinen et al., 2014; Zaninovich et al., 2019). Functional reorganization of cortical sensorimotor networks in chronic SCI can be investigated using fMRI techniques in order to understand the process of plasticity and recovery in these patients (Freund et al., 2019).

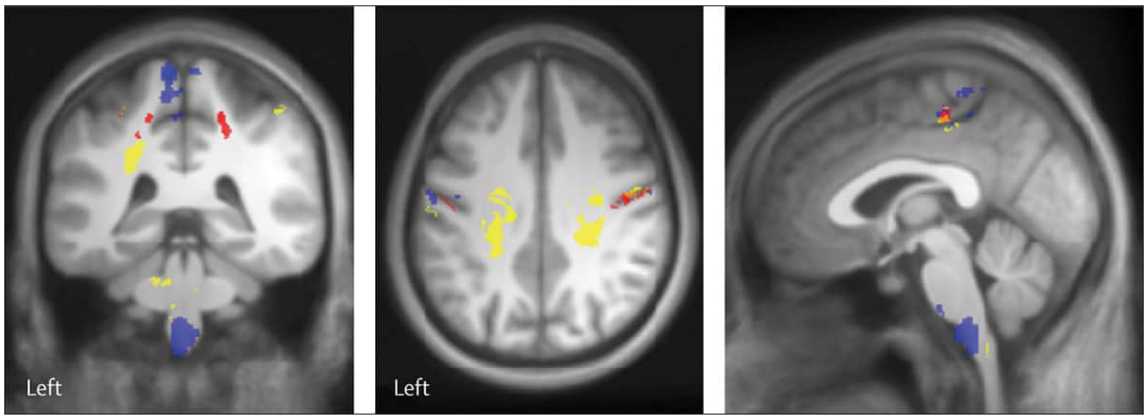

FIG. 5 Changes at 12 months shown by voxel-wise analysis of microstructure and volume. Overlay of statistical parametric maps (uncorrected $P < 0{\cdot}001$, shown for descriptive purposes, masked by the union of the cranial corticospinal tract and the bilateral sensorimotor cortex) showing regions of reduced volume of grey and white matter (*blue*) in patients compared with controls at 12-month follow-up. The reductions in longitudinal relaxation rate R1 (*yellow*) and magnetization transfer MT (*red*) in patients compared with controls at 12-month follow-up suggest changes in myelination. *Courtesy Freund, P., Weiskopf, N., Ashburner, J., Wolf, K., Sutter, R., Altmann, D. R., et al. (2013). MRI investigation of the sensorimotor cortex and the corticospinal tract after acute spinal cord injury: A prospective longitudinal study*. The Lancet Neurology, 12 *(9), 873–881; under Creative Commons.*

Thus, advanced MRI techniques show huge potential in allowing clinicians to plan and monitor treatment protocols by getting valuable microstructural information.

Conclusion

MRI plays a pivotal role in determining the underlying cause and extent of neurological deficits in the acute phase of SCI for a prompt diagnosis and prognostication. Conventional MRI sequences elaborate findings including extramedullary damage, edema, hemorrhage, and compression of the cord that are present at the time of injury as well as syrinx, SPAM, atrophy, and myelomalacia which develop in the subacute and chronic phases of injury. Advanced quantitative MRI techniques show microstructural changes that occur in the long term and reflect degeneration and plasticity, offering potential as biomarkers to monitor treatment and evaluate outcomes in clinical trials. There is a need to develop methods to overcome the high cost associated with MRI. Currently, advanced techniques like DTI, MPM, and fMRI are used in research only. Enhanced signal-to-noise ratio and machine learning approaches for consistent results will enable translation of these techniques from clinical trials to the bedside management of SCI.

Applications to other areas of neuroscience

MRI supersedes all other imaging modalities when it comes to investigating the structure of spinal cord and associated soft structures such as nerve roots and ligaments. Examples of spinal disorders with a central role for MRI include nontraumatic spinal cord emergencies, inflammatory disorders and spinal cord neoplasms. Nontraumatic spinal cord emergencies requiring MRI studies include extramedullary compressive causes such as epidural abscess and intramedullary etiologies such as transverse myelitis and spinal cord infarct. MRI findings can give clues regarding the diagnosis and guide on the level of compression for treatment planning (Flanagan & Pittock, 2017). Inflammatory conditions such as multiple sclerosis and neuromyelitis optica (NMO) show hyperintense signals in the cord on T2W MRI (Ciccarelli et al., 2019). Atrophy and myelomalacia are also seen in NMO (Ciccarelli et al., 2019). Contrary to SCI, gadolinium contrast enhancement is an important feature in these conditions (Bozzo et al., 2011; Ciccarelli et al., 2019). In spinal tumors, MRI findings have accuracy in determining the site, i.e., extradural, intradural, extramedullary, or intramedullary, as well as tissue characterization aided with contrast enhancement (Yadav et al., 2016). In COVID—19-associated acute necrotizing myelitis, T2W MRI shows hyperintense lesion involving medulla and cervical cord with patchy enhancing lesions (Sotoca & Rodríguez-Álvarez, 2020). Quantitative MRI has useful information on degeneration and comprises an important part of work-up and research for other degenerative disorders. For example, MPM of spinal cord in Amyotrophic Lateral Sclerosis enabled quantification of cord atrophy which can predict disease progression (El Mendili et al., 2014). Similarly, in chronic traumatic brain injury (TBI), quantification of grey matter volumes using T1W scans and correlating these with neuropsychological testing helps in understanding the neural correlates of cognitive impairment experienced in chronic TBI (Levine et al., 2013).

Mini-dictionary of terms

Conventional MRI is standard MRI imaging which includes T1W and T2W images.
Quantitative MRI is an imaging technique which obtains maps of meaningful physical or chemical variables that can be measured in physical units and compared between tissue regions and among subjects like magnetic resonance relaxation times, magnetization transfer, and diffusion of water molecules.
Cord concussion is a type of mild spinal cord injury which manifests as transient paraplegia, variable degrees of sensory impairment and motor weakness which typically resolve within 72 h.
Cord compression is a condition that occurs due to external pressure on the spinal cord often due to a malignant growth or disc herniation. This often leads to pain, numbness and weakness symptoms below the level of the compression.
Hemorrhagic contusion of the spinal cord is a discrete focus of hemorrhage within the substance of the spinal cord often secondary to a crush injury. This most commonly is present within the central grey matter of the spinal cord at the point of impact.
Cord transection is a transverse cut within the spinal cord due to significant traumatic injury. This leads to permanent loss of central control of motor, sensory, and autonomic functions below the level of injury.
Sub-acute progressive ascending myelopathy is a sequela of spinal cord injury starting within the first few weeks of the injury. There is ascending neurological deterioration till at least four vertebral levels above the level of injury.
Syrinx is a fluid filled central cavity within the spinal cord.

Key facts of SPAM

- Subacute progressive ascending myelopathy (SPAM) is a rare complication arising within 3 weeks of spinal cord injury, presenting with ascending neurological deficit.
- It was first described by Frankel in 1969 with an incidence of 1% in 808 admissions with SCI.
- It mostly affects young and middle-aged patients with a ~5.1 male to female ratio.
- MRI is the gold standard imaging and shows cord changes at least four vertebral levels above the initial site of insult.
- It has been postulated to arise from venous thrombosis, arterial occlusion, fibrocartilage embolism, CSF flow disruption, mechanical insult, infection, and immune-mediated response.
- Risk factors include complete SCI, initial injury site at thoracolumbar junction, asymptomatic low blood pressure and early postoperative orthostatic mobilization.
- It is associated with a mortality of 9%. Recovery is generally present, but this improvement is up to a vertebral level higher than original site of injury.
- MRI shows resolution of changes in recovered patients with a small focal region of myelomalacia seen at the level of initial insult and vertebral level above it.

Summary points

- MRI is the modality of choice for imaging soft tissue in SCI.
- Conventional T1W and T2W MRI along with newer GRE and STIR sequences reveal important characteristics associated with intramedullary as well as extramedullary spinal cord injuries.
- In the acute phase, these include edema, hemorrhage, hematoma, and compression. While in the subacute phase, edema is seen to resolve with formation of posttraumatic cysts and syrinx.
- Novel quantitative MRI techniques including volumetry, DTI and magnetization transfer demonstrate microstructural changes in the chronic phase of SCI.
- These changes indicate neurodegeneration, providing important information regarding spinal cord atrophy, demyelination, and iron deposition. Thus, these advanced techniques have a potential role in neurorehabilitation and clinical trials.

References

Ahuja, C. S., Wilson, J. R., Nori, S., Kotter, M. R., Druschel, C., Curt, A., et al. (2017). Traumatic spinal cord injury. *Nature Reviews. Disease Primers*, *3*(1), 1–21.

Alizadeh, A., Dyck, S. M., & Karimi-Abdolrezaee, S. (2019). Traumatic spinal cord injury: An overview of pathophysiology, models and acute injury mechanisms. *Frontiers in Neurology*, *10*, 282.

Baliyan, V., Shylendran, S., Ajay, K. Y., Kumar, A., Gamanagatti, S., & Sinha, S. (2016). Unusual cord transection in a patient with traumatic spondylolisthesis. *Asian Journal of Neurosurgery*, *11*(1), 72.

Bozzo, A., Marcoux, J., Radhakrishna, M., Pelletier, J., & Goulet, B. (2011). The role of magnetic resonance imaging in the management of acute spinal cord injury. *Journal of Neurotrauma*, *28*(8), 1401–1411.

Burks, J. D., Gant, K. L., Guest, J. D., Jamshidi, A. G., Cox, E. M., Anderson, K. D., et al. (2019). Imaging characteristics of chronic spinal cord injury identified during screening for a cell transplantation clinical trial. *Neurosurgical Focus*, *46*(3), E8.

Chandra, J., Sheerin, F., De Heredia, L. L., Meagher, T., King, D., Belci, M., et al. (2012). MRI in acute and subacute post-traumatic spinal cord injury: Pictorial review. *Spinal Cord*, *50*(1), 2–7.

Cheran, S., Shanmuganathan, K., Zhuo, J., Mirvis, S. E., Aarabi, B., Alexander, M. T., et al. (2011). Correlation of MR diffusion tensor imaging parameters with ASIA motor scores in hemorrhagic and nonhemorrhagic acute spinal cord injury. *Journal of Neurotrauma*, *28*(9), 1881–1892.

Cho, N., Hachem, L. D., & Fehlings, M. G. (2017). Spinal cord edema after spinal cord injury: From pathogenesis to management. In *Brain edema* (pp. 261–275). Elsevier.

Ciccarelli, O., Cohen, J. A., Reingold, S. C., Weinshenker, B. G., Amato, M. P., Banwell, B., et al. (2019). Spinal cord involvement in multiple sclerosis and neuromyelitis optica spectrum disorders. *The Lancet Neurology*, *18*(2), 185–197.

David, G., Freund, P., & Mohammadi, S. (2017). The efficiency of retrospective artifact correction methods in improving the statistical power of between-group differences in spinal cord DTI. *NeuroImage*, *158*, 296–307.

Dundamadappa, S. K., & Cauley, K. A. (2012). MR imaging of acute cervical spinal ligamentous and soft tissue trauma. *Emergency Radiology*, *19*(4), 277–286.

El Mendili, M.-M., Cohen-Adad, J., Pelegrini-Issac, M., Rossignol, S., Morizot-Koutlidis, R., Marchand-Pauvert, V., et al. (2014). Multi-parametric spinal cord MRI as potential progression marker in amyotrophic lateral sclerosis. *PLoS One*, *9*(4), e95516.

Ellingson, B., Ulmer, J., Kurpad, S., & Schmit, B. (2008). Diffusion tensor MR imaging in chronic spinal cord injury. *American Journal of Neuroradiology*, *29*(10), 1976–1982.

Farooque, K., Kandwal, P., & Gupta, A. (2014). Subacute post-traumatic ascending myelopathy (SPAM): Two cases of SPAM following surgical treatment of thoracolumbar fractures. *Neurology India*, *62*(2), 192.

Flanagan, E., & Pittock, S. J. (2017). Diagnosis and management of spinal cord emergencies. In *Vol. 140. Handbook of clinical neurology* (pp. 319–335). Elsevier.

Freund, P., Friston, K., Thompson, A. J., Stephan, K. E., Ashburner, J., Bach, D. R., et al. (2016). Embodied neurology: An integrative framework for neurological disorders. *Brain*, *139*(6), 1855.

Freund, P., Seif, M., Weiskopf, N., Friston, K., Fehlings, M. G., Thompson, A. J., et al. (2019). MRI in traumatic spinal cord injury: From clinical assessment to neuroimaging biomarkers. *The Lancet Neurology*, *18*(12), 1123–1135.

Freund, P., Weiskopf, N., Ashburner, J., Wolf, K., Sutter, R., Altmann, D. R., et al. (2013). MRI investigation of the sensorimotor cortex and the corticospinal tract after acute spinal cord injury: A prospective longitudinal study. *The Lancet Neurology*, *12*(9), 873–881.

Ghasemi, A., Haddadi, K., & Shad, A. A. (2015). Comparison of diagnostic accuracy of MRI with and without contrast in diagnosis of traumatic spinal cord injuries. *Medicine*, *94*(43), e1942.

Grabher, P., Callaghan, M. F., Ashburner, J., Weiskopf, N., Thompson, A. J., Curt, A., et al. (2015). Tracking sensory system atrophy and outcome prediction in spinal cord injury. *Annals of Neurology*, *78*(5), 751–761.

Hausmann, O. B. (2003). Post-traumatic inflammation following spinal cord injury. *Spinal Cord*, *41*(7), 369–378.

Huber, E., David, G., Thompson, A. J., Weiskopf, N., Mohammadi, S., & Freund, P. (2018). Dorsal and ventral horn atrophy is associated with clinical outcome after spinal cord injury. *Neurology*, *90*(17), e1510–e1522.

Huber, E., Lachappelle, P., Sutter, R., Curt, A., & Freund, P. (2017). Are midsagittal tissue bridges predictive of outcome after cervical spinal cord injury? *Annals of Neurology*, *81*(5), 740–748.

Izzo, R., Popolizio, T., Balzano, R. F., Pennelli, A. M., Simeone, A., & Muto, M. (2019). Imaging of cervical spine traumas. *European Journal of Radiology*, *117*, 75–88.

Ju, G., Wang, J., Wang, Y., & Zhao, X. (2014). Spinal cord contusion. *Neural Regeneration Research*, *9*(8), 789.

Jung, H. S., Jee, W. H., McCauley, T. R., Ha, K. Y., & Choi, K. H. (2003). Discrimination of metastatic from acute osteoporotic compression spinal fractures with MR imaging. *Radiographics*, *23*(1), 179–187.

Klekamp, J. (2018). How should syringomyelia be defined and diagnosed? *World Neurosurgery*, *111*, e729–e745.

Koskinen, E., Hakulinen, U., Brander, A., Luoto, T., Ylinen, A., & Öhman, J. (2014). Clinical correlates of cerebral diffusion tensor imaging findings in chronic traumatic spinal cord injury. *Spinal Cord*, *52*(3), 202–208.

Kreppel, D., Antoniadis, G., & Seeling, W. (2003). Spinal hematoma: A literature survey with meta-analysis of 613 patients. *Neurosurgical Review*, *26*(1), 1–49.

Kulkarni, M. V., Bondurant, F. J., Rose, S., & Narayana, P. A. (1988). 1.5 tesla magnetic resonance imaging of acute spinal trauma. *Radiographics*, *8*(6), 1059–1082.

Kumar, Y., & Hayashi, D. (2016). Role of magnetic resonance imaging in acute spinal trauma: A pictorial review. *BMC Musculoskeletal Disorders*, *17*(1), 310.

Levine, B., Kovacevic, N., Nica, E. I., Schwartz, M. L., Gao, F., & Black, S. E. (2013). Quantified MRI and cognition in TBI with diffuse and focal damage. *NeuroImage: Clinical*, *2*, 534–541.

Leypold, B., Flanders, A., & Burns, A. (2008). The early evolution of spinal cord lesions on MR imaging following traumatic spinal cord injury. *American Journal of Neuroradiology*, *29*(5), 1012–1016.

Miyanji, F., Furlan, J. C., Aarabi, B., Arnold, P. M., & Fehlings, M. G. (2007). Acute cervical traumatic spinal cord injury: MR imaging findings correlated with neurologic outcome—Prospective study with 100 consecutive patients. *Radiology*, *243*(3), 820–827. https://doi.org/10.1148/radiol.2433060583.

Mostafa, M. A. (2019). Traumatic cervical spinal cord transection. *BJR Case Reports*, *5*(1), 20180043.

Nedeltchev, K., Loher, T. J., Stepper, F., Arnold, M., Schroth, G., Mattle, H. P., et al. (2004). Long-term outcome of acute spinal cord ischemia syndrome. *Stroke*, *35*(2), 560–565.

Nesnídal, P., Stulík, J., & Barna, M. (2012). Spinal cord concussion: A retrospective study of twenty-four patients. *Acta Chirurgiae Orthopaedicae et Traumatologiae Cechoslovaca*, *79*(2), 150–155.

Nogueira, R. G., Ferreira, R., Grant, P. E., Maier, S. E., Koroshetz, W. J., Gonzalez, R. G., et al. (2012). Restricted diffusion in spinal cord infarction demonstrated by magnetic resonance line scan diffusion imaging. *Stroke*, *43*(2), 532–535.

Pierpaoli, C., Barnett, A., Pajevic, S., Chen, R., Penix, L., Virta, A., et al. (2001). Water diffusion changes in Wallerian degeneration and their dependence on white matter architecture. *NeuroImage*, *13*(6), 1174–1185.

Planner, A., Pretorius, P., Graham, A., & Meagher, T. (2008). Subacute progressive ascending myelopathy following spinal cord injury: MRI appearances and clinical presentation. *Spinal Cord*, *46*(2), 140–144.

Provenzale, J. (2007). MR imaging of spinal trauma. *Emergency Radiology*, *13*(6), 289–297.

Seif, M., Wheeler-Kingshott, C. A. G., Cohen-Adad, J., Flanders, A. E., & Freund, P. (2019). Guidelines for the conduct of clinical trials in spinal cord injury: Neuroimaging biomarkers. *Spinal Cord*, *57*(9), 717–728.

Shen, H., Tang, Y., Huang, L., Yang, R., Wu, Y., Wang, P., et al. (2007). Applications of diffusion-weighted MRI in thoracic spinal cord injury without radiographic abnormality. *International Orthopaedics*, *31*(3), 375–383.

Sklar, E. M. L., Post, J. M. D., & Falcone, S. (1999). MRI of acute spinal epidural hematomas. *Journal of Computer Assisted Tomography*, *23*(2), 238–243.

Sotoca, J., & Rodríguez-Álvarez, Y. (2020). COVID-19-associated acute necrotizing myelitis. *Neurology® Neuroimmunology & Neuroinflammation*, *7*(5), e803.

Vallotton, K., Huber, E., Sutter, R., Curt, A., Hupp, M., & Freund, P. (2019). Width and neurophysiologic properties of tissue bridges predict recovery after cervical injury. *Neurology*, *92*(24), e2793–e2802.

Vargas, M., Gariani, J., Sztajzel, R., Barnaure-Nachbar, I., Delattre, B., Lovblad, K., et al. (2015). Spinal cord ischemia: Practical imaging tips, pearls, and pitfalls. *American Journal of Neuroradiology*, *36*(5), 825–830.

Villiger, M., Grabher, P., Hepp-Reymond, M.-C., Kiper, D., Curt, A., Bolliger, M., et al. (2015). Relationship between structural brainstem and brain plasticity and lower-limb training in spinal cord injury: A longitudinal pilot study. *Frontiers in Human Neuroscience*, *9*, 254.

Yadav, P., Sharma, A., Sikarwar, J., Goyal, S., Soni, V. K., & Chandravanshi, M. (2016). Magnetic resonance imaging in spinal tumours and its histo-pathological correlation. *Journal of Evolution of Medical and Dental Sciences*, *5*(104), 7616–7622.

Zaninovich, O. A., Avila, M. J., Kay, M., Becker, J. L., Hurlbert, R. J., & Martirosyan, N. L. (2019). The role of diffusion tensor imaging in the diagnosis, prognosis, and assessment of recovery and treatment of spinal cord injury: A systematic review. *Neurosurgical Focus*, *46*(3), E7.

Zhang, J., & Wang, G. (2017). Subacute posttraumatic ascending myelopathy: A literature review. *Spinal Cord*, *55*(7), 644–650.

Ziegler, G., Grabher, P., Thompson, A., Altmann, D., Hupp, M., Ashburner, J., et al. (2018). Progressive neurodegeneration following spinal cord injury: Implications for clinical trials. *Neurology*, *90*(14), e1257–e1266.

Chapter 3

Exercise programs and spinal cord injury (SCI): Linking the clinical, physiological, and psychological consequences of SCI

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List of abbreviations

ANS	autonomic nervous system
CVD	cardiovascular disease
FES	functional electrical stimulation
FM	fat mass
HDL-C	high-density lipoprotein cholesterol
LB	lower body
LDL-C	low-density lipoprotein cholesterol
PA	physical activity
QoL	quality of life
SCI	spinal cord injury
TG	triglycerides
UB	upper body
WB	whole body

Prevalence and consequences of spinal cord injury

A spinal cord injury (SCI) is a major life event leading to serious physical disability and secondary clinical problems (Kang et al., 2017). Worldwide, the incidences of SCI are rising with an annual estimate of 10.4–83 cases per million worldwide (Jazayeri, Beygi, Shokraneh, Hagen, & Rahimi-Movaghar, 2015). SCI management requires significant healthcare and can place a substantial financial burden through rehabilitation services, expensive personal assistance, lost productivity due to disability, and social isolation. Given the effects of SCI, there is a pressing need to identify effective methods to manage these injuries and reduce the extent of future disability.

Clinical, physiological, and psychological consequences of SCI (Fig. 1)

Primary consequences of SCI: Paralysis and ANS

Paralysis of the voluntary musculature is the most obvious consequence of SCI (Maynard, Karunas, & Waring, 1990). Damage to the descending motor tracts, anterior horn cells, or nerve roots leads to an impaired capacity to contract the skeletal muscles at or below the level of the lesion (Assinck, Duncan, Hilton, Plemel, & Tetzlaff, 2017). This paralysis results in a loss of control over the trunk and extremities. Because muscles below injury levels are denervated, these paralyzed muscles undergo rapid changes, including the loss of muscle mass as well as biochemical and morphological changes. These biochemical and morphological changes include the loss of capillarization and changes in the muscle fiber

Cellular, Molecular, Physiological, and Behavioral Aspects of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822427-4.00003-4

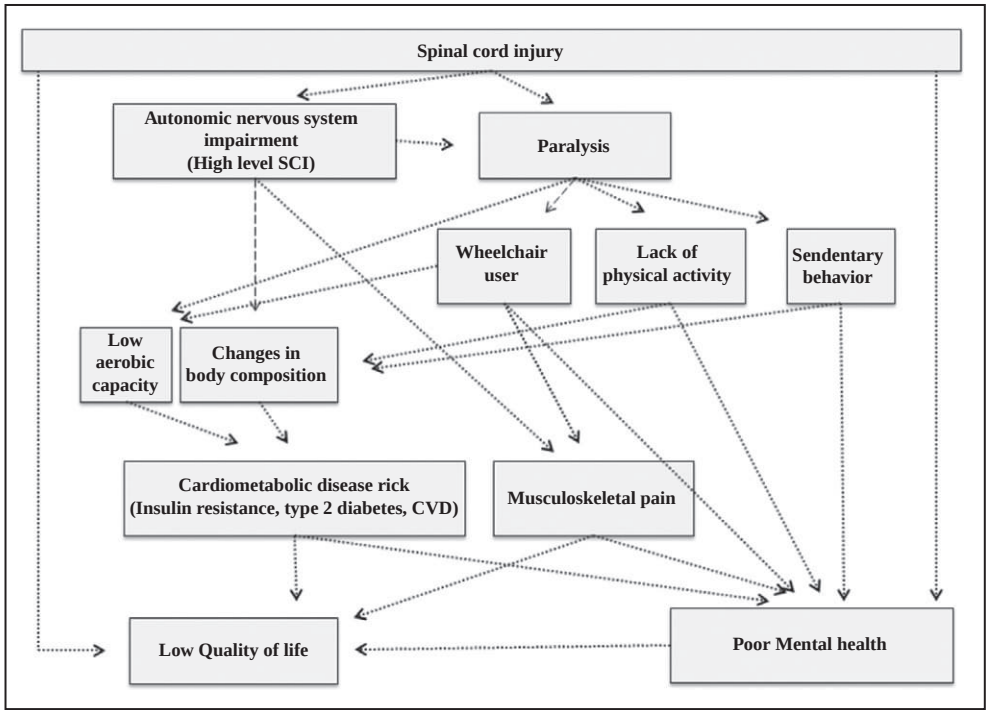

FIG. 1 Overview of the pathophysiology and health consequences after SCI. SCI is an acquired disorder that leads to dramatic changes in a person's lifestyle and requires continuous observation and treatment. Due to paralysis and ANS dysfunction, people with SCI have lower physical activity and higher sedentary behavior as well as increased risk of chronic diseases compared to the able-bodied. Also, people with spinal cord injuries use their shoulders excessively because they use wheelchairs for transportation. For this reason, most experience shoulder joint problems such as rotator cuff tears and subacromial impingement syndrome. Besides an increased risk of developing physical health consequences, people with SCI also have mental health problems such as fatigue, anxiety, and depression.

type from oxidative to glycolytic (i.e., Type 1 to IIb) (Burnham et al., 1997). Interestingly, both reductions in muscle loss and changes in muscle characteristics are associated with poor cardiometabolic profiles, most importantly insulin resistance (Gater, Farkas, & Tiozzo, 2021).

In addition to devastating paralysis, SCI also results in significant dysfunctions of the ANS (Wang et al., 2000). The ANS regulates many functions, in particular cardiovascular functions such as coronary blood flow, cardiac contractility, heart rate, and peripheral vasomotor responses (Garstang & Miller-Smith, 2007). In addition, ANS controls blood flow to the skeletal muscles, kidneys, splanchnic circulation, and skin. Impaired ANS regulation caused by SCI leads to many of the clinical issues seen in people with SCI. SCI above T1 causes a complete disruption of the sympathetic pathways and results in a variety of problems, including bradycardia, neurogenic pulmonary edema, arrhythmias, and hypotension (Sweis & Biller, 2017). SCI above T6 causes an altered splanchnic outflow, which causes hypotension and altered vascular regulation (Garstang & Miller-Smith, 2007). Even people with injuries below T6 have changes in cardiovascular response as a consequence of the altered ANS regulation (Garstang & Miller-Smith, 2007). Thus, the role of autonomic dysfunction in people with SCI is crucially important when designing an exercise program for them because many aspects of the altered physiology seen in these individuals are directly caused by ANS dysregulation.

Secondary consequences of SCI

Physical inactivity and sedentary behavior

Due to the loss of motor, sensory, and ANS below the lesion level, people with SCI are often restricted in their activity of daily living. Most people with SCI are considered to be at high risk for an inactive lifestyle (Fernhall, Heffernan, Jae, & Hedrick, 2008). One prospective study on the course of everyday physical activity (PA) levels with 40 people with SCI reported that the PA levels increased during inpatient rehabilitation, but shortly after discharge from the rehabilitation center, the level decreased significantly (van den Berg-Emons et al., 2008). Furthermore, Van den Berg-Emons et al. reported that the PA levels of people with SCI were only 40% of the PA levels of able-bodied peers and were even lower

than those of people with other chronic diseases (van den Berg-Emons, Bussmann, & Stam, 2010). Besides insufficient PA, sedentary time is much greater, which poses a greater threat to the health of people with SCI. One cross-sectional study with 695 people with SCI (male = 531, female = 164) reported that an estimated 50% of people with SCI live completely sedentary lives (Ginis et al., 2010). These findings may especially apply to people with SCI who are often wheelchair bound and spend large amounts of time sitting compared to the general population.

Body composition and poor metabolic profile

The clinical consequences of SCI, paired with insufficient PA and sedentary behavior, often result in a reduction in muscle mass and an increase in FM. Compared to the general population, people with SCI show increased levels of intramuscular fat at 6 weeks post-injury, and this continues to increase over the next 3 months (Gorgey & Dudley, 2007). A loss of skeletal muscle in people with SCI could be the result of paralysis, but it could also be secondary from a lack of PA and exercise. Because skeletal muscle mass is the most important determinant of the resting metabolic rate, a reduction in muscle mass increases the risk of obesity (Zurlo, Larson, Bogardus, & Ravussin, 1990). Spungen et al. demonstrated that people with SCI have an average of 5 kg more FM and 50% more total body fat while also being 13.1% fatter per unit of body mass index (BMI) compared to able-bodied controls matched by age, height, and ethnicity (Spungen et al., 2003). Knowing that an intact SNS is required for the anti-obesity hormone leptin, people with SCI may have a greater risk of obesity and obesity-associated cardiometabolic diseases (Jeon et al., 2003). Indeed, the deterioration of body composition after SCI such as an increase in FM and a loss of lean mass have been associated with a higher risk of type 2 diabetes (Bauman & Spungen, 2001). Furthermore, many individuals with SCI have increased levels of triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and decreased high-density lipoprotein cholesterol (HDL-C) (Bauman et al., 1992; Bauman & Spungen, 2001). Bauman et al. reported that more than 37% of individuals with SCI have less than 35 mg/dL of HDL-C. Also, 18% of this population has an LDL-C level greater than 160 mg/dL (Bauman et al., 1992). This may explain why people with SCI are at a higher risk of developing type 2 diabetes and cardiovascular disease (CVD) than the general population.

Poor musculoskeletal conditions

As a consequence of lower extremities weakness or paralysis after SCI, the increased use of the upper extremities has been associated with high incidences of musculoskeletal pain in the shoulder, elbow, and wrist with a prevalence ranging from 5% to 78% among people with SCI (Capoor & Stein, 2005). After SCI, they are forced to bear weight on the upper extremity joints for mobility and transferring, pushing up, and hand-propelling the wheelchair (Riek, Ludewig, & Nawoczenski, 2008). Previous studies have reported that musculoskeletal pain causes poorer psychological functioning and has a negative impact on the quality of life (QoL) among people with SCI (Ullrich et al., 2013). Therefore, it is important to set priorities and design effective programs to manage musculoskeletal pain and improve the QoL in people with SCI.

Poor mental health and low QoL

While muscle paralysis may be the most obvious consequence of SCI, people with SCI are susceptible to several functional complications such as sexual dysfunction, spontaneous urine loss, incontinence, and pain, which lead to considerable changes in the QoL (Ahuja et al., 2017). Furthermore, people with SCI have significantly elevated risks of chronic fatigue, anxiety, and depression (Le & Dorstyn, 2016). A recent meta-analysis indicated that the prevalence of depression after SCI is substantially greater than that in the general medical population (Williams & Murray, 2015). Consequently, people with SCI have a higher prevalence of psychological morbidity and suicide (Kennedy & Garmon-Jones, 2017). Therefore, seeking ways to improve the psychological well-being in people with SCI is of importance. In this regard, participation in PA and exercise might be an effective strategy to improve the psychological well-being in people with SCI.

Exercise and SCI (Fig. 2)

As mentioned previously, SCI may result in various health consequences. Some of these health consequences are primary consequences of paralysis (ANS, muscle fiber type, muscle mass loss in the paralyzed muscle) and some are secondary consequences of SCI, such as a lack of PA and exercise (FM increase, cardiometabolic profiles) (Harvey & Graves, 2011). Likewise, some variables related to the psychological well-being change due to physical impairment, but some are related to a lack of PA and exercise. Thus, it is logical to think that exercise and PA participation would reverse some secondary consequences of SCI. Some exercises such as functional electrical stimulation (FES)-assisted exercise, either FES-assisted contraction of the paralyzed muscle alone or combined with voluntary muscle contraction of the unparalyzed

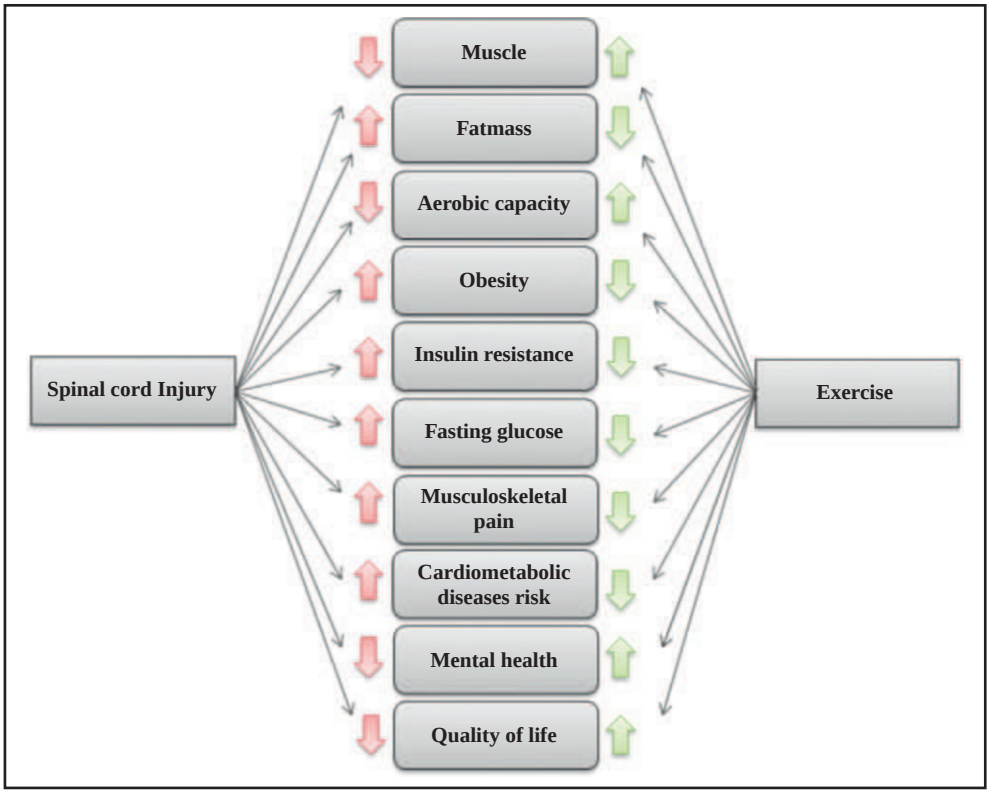

FIG. 2 Mechanism of exercise-associated reduction in spinal cord injury. Increasing PA and regular participation in exercise in people with SCI have a positive physiological effect such as improving insulin resistance. In particular, participation in aerobic and/or resistance exercise in people with SCI is reported to prevent cardiovascular complications and improve cardiovascular function. Moreover, people with SCI have many shoulder joint and muscle problems due to excessive shoulder use. Therefore, these problems can be prevented in advance by doing shoulder strengthening exercises such as shoulder extension and elbow flexion exercises. Additionally, increasing PA and exercise in people with spinal cord injury is critical to improving their psychological well-being and life satisfaction.

muscle, may reverse both the direct and indirect consequences of SCI. Further, other exercises such as wheeling and participation in sport activities generally increase PA levels, which could reverse the secondary consequences of paralysis. In some cases, specialized therapeutic exercises could be applied to reduce pain or improve joint condition, such as the elbow and shoulder joints of people with SCI. There is substantial evidence that increased PA participation is associated with increased aerobic capacity and muscle strength as well as a smaller risk of CVD in people with SCI (Nooijen et al., 2012). Moreover, people with SCI who participate in more PA have lower levels of depression and anxiety as well as higher levels of social support compared to those who don't participate in PA as much (Kim, Lee, Park, & Jeon, 2020). In this next section, types of exercises and their potential health benefits on the primary and secondary consequences of SCI will be discussed. Previous studies that investigated the effect of exercise programs in people with SCI are summarized in Table 1.

Exercise programs for people with SCI

According to the current literature, we can identify four different types of exercises in which people with SCI can participate: (1) upper-body (UB) aerobic exercises (arm ergometer, wheeling), (2) UB resistance exercises (free weights, weight machines, and thera-bands), (3) FES-assisted lower-body (LB) exercises (FES cycling), and (4) whole-body (WB) exercises (hybrid FES cycling and arm ergometer as well as FES rowing). In addition to the exercise type, the exercise intensity is also important when developing an exercise program for optimal health benefits. In that regard, when the lesion level is high (i.e., above C6–7), it is difficult to perform a high-intensity exercise. In this case, FES-assisted cycling or FES rowing may enable people to increase the exercise intensity to improve cardiopulmonary and cardiometabolic health. Likewise, people with shoulder problems such as shoulder impingement syndrome due to scapular abduction may benefit from thera-band and rowing exercises, which may strengthen the scapular adductors and external rotators. Likewise, the exercise program should be designed according to each individual's physical condition.

TABLE 1 Previous studies of effect and types of exercise programs in people with SCI.

No	Author (year)	Subject	Injury level	Exercise type	Duration	Results (significant)
1	Fornusek, Davis, and Russold (2013)	Eight individuals with chronic SCI	C7 ~ T11	Isokinetic FES cycle ergometer	6 weeks, 3 days/ week	– Muscle hypertrophy ↑ – Muscle strength ↑
2	Giangregorio et al. (2012)	34 Individuals with SCI	C2 ~ T12/ASIA: C or D	FES assisted walking	16 weeks, 2 days/ week	– Body fat ↓ – Muscle strength ↑
3	Jeon et al. (2010)	Six male participants with paraplegia	T4–5 and T10	FES rowing	12 weeks, 3–4 days/ week	– Peak oxygen consumption ↑ – Leptin level ↓ – Glucose levels ↓
5	Johnston, Smith, Mulcahey, Betz, and Lauer (2009)	30 Children with SCI	C4 ~ T11/ASIA: A, B, or C	FES cycling	6 months, 3 days/ week	– Oxygen uptake ($\dot{V}O_2$) ↑ – Cholesterol levels ↓
6	Griffin et al. (2009)	18 Subjects with SCI	C4, T3	FES cycling	10 weeks, 2–3 days/ week	– Muscle strength ↑ – Thigh sensory scores ↑ – IL-6, TNF-a, CRP ↓
7	Johnston, Smith, Betz, and Lauer (2008)	Four subjects with SCI	C7 ~ T6/ASIA: A	FES cycling passive motion cycling	6 months, 3 days/ week	– Left femoral neck ↑ – Distal femur ↑ – Resting heart rate ↓
8	Frotzler et al. (2008)	17 Subjects with spinal cord injury	T3 ~ T12	FES cycling	12 months, 5 days/ weekly	– BMD ↑ – Muscle CSA ↑ – CSA fat ↓
9	Zbogar et al. (2008)	Four subjects with SCI	C4, C5, T4, T7	FES leg cycle ergometer	3 days/ weeks Total: 36 times	– Small artery compliance ↑
10	Castello, Louis, Cheng, Armento, and Santos (2012)	Six subjects with SCI	C3, C3, C4, C5, T4	FES cycling	9 months, 3 days/ week	– Pediatric quality of life – Inventory ↑ – Bone mineral density (BMD) ↑
11	Janssen and Pringle (2008)	12 With chronic SCI	C4 ~ T11	Electrical stimulation induced leg cycle ergometer	6 weeks, 3 days/ week	– Cardiorespiratory responses, stroke volume, peak values for power output ↑
12	Latimer, Ginis, Hicks, and McCartney (2004)	21 Individuals with SCI	C3 ~ T7	Stretching, aerobic, arm ergometer exercise, resistance exercise	9 months, 2 days/ week	– Pain ↓ – Stress ↓ – Depression ↓
13	Silva et al. (1998)	12 People with SCI and 12 able-bodied controls	T1 ~ T12	Arm crank ergometer training	6 weeks, 3 days/ week	– Forced vital capacity ↑ – Ventilatory muscle endurance test ↑

Continued

TABLE 1 Previous studies of effect and types of exercise programs in people with SCI—cont'd

No	Author (year)	Subject	Injury level	Exercise type	Duration	Results (significant)
14	Liusuwan, Widman, Abresch, Styne, and McDonald (2007)	20 Adolescents (aged 11–18) with spinal cord dysfunction	Non	Aerobic (arm ergometer), strengthening exercises	16 weeks, 3 days/ week	– Shoulder extension strength ↑ – Maximum power output ↑ – Whole body lean tissue ↑ – Work efficiency ↑ – Resting oxygen uptake ↑
15	Mahoney et al. (2005)	Five men with SCI	C5 ~ T9	Knee extensions by electric stimulation unit	12 weeks, 2 days/ week	– Skeletal muscle cross-sectional area (CSA) in the right and left quadriceps femoris ↑
16	Giangregorio et al. (2005)	Five individuals with traumatic SCI	C3, C5, C6, C6, C8	Body weight supported treadmill	6– 8 months, 2 days/ week Total: 48 sessions	– Muscle CSAs ↑ – Lumbar spine BMD ↑
17	Giangregorio et al. (2006)	14 Patients with SCI	C4 ~ T12	Body weight supported treadmill training	12 months, 3 days/ week	– Whole-body lean mass ↑ – Muscle CSAs ↑ – Whole-body bone density ↑
18	Wirz et al. (2005)	20 Chronic patients with SCI	ASIA: C ($n = 9$) and D ($n = 11$)	Locomotor training (using robotic-assisted, body weight supported treadmill training)	8 weeks, 3–5 days/ week	– Velocity, endurance, and performance of functional tasks ↑
19	Field-Fote and Tepavac (2002)	14 Subjects with incomplete SCI	C4 ~ T7	Combining body weight support, electrical stimulation, and treadmill training	12 weeks, 3 days/ week	– Over ground and treadmill walking speed ↑
20	Ditor et al. (2003)	Seven subjects with SCI	C5 ~ T12/ASIA: A ~ D	Supervised exercise training (arm ergometer, stretching, resistance exercise)	3 months, 2 days/ week	– Exercise adherence ↓ – PQOL ↓ – Pain ↓ – Stress ↓
21	Hicks et al. (2005)	14 Individuals with incomplete SCI	C4 ~ T12	Body-weight-supported treadmill training	12 months, 3 days/ week	– Treadmill walking ability ↑ – Treadmill walking speed ↑ – Treadmill walking distance ↑ – Capacity to walk over ground ↑ – Physical function ↑
22	Hicks et al. (2003)	34 Subjects with traumatic SCI	C4 ~ L/ASIA: A ~ D	Supervised exercise (arm ergometer, stretching, resistance exercise)	2 days/ week	– Submaximal arm ergometer power output ↑ – Upper body muscle strength ↑ – Pain, stress and depression ↓

UB aerobic exercise includes the use of an arm ergometer and a wheelchair, whereas UB resistance exercises include free weights, weight machines, and thera-bands. LB exercise includes cycles that use electrical stimulation, such as FES and WB exercises that include a combination of those exercises and a rowing machine.

UB aerobic and strength exercise

UB exercises have been widely studied as an effective form of aerobic and strength exercise for individuals with SCI. Aerobic exercise programs such as the arm ergometer and hand bike are effective in improving body composition and cardiopulmonary fitness as well as reducing insulin resistance in people with SCI (Kim et al., 2019). In addition to the well-established benefits of UB aerobic exercise as an effective means to improve fitness in people with SCI, arm ergometers also offer an exercise modality that is accessible and does not require overly specialized expertise or infrastructure. Recently, a randomized controlled trial study with an exercise program on indoor hand bikes equipped with an information technology system for people with SCI showed significantly improved cardiopulmonary fitness and UB strength as well as reduced BMI, waist circumference, insulin levels, and HOMA-IR levels (Kim, Lee, Lee, Kim, & Jeon, 2015). Moreover, aerobic exercise using a manual wheelchair, in particular backward wheeling exercises, have been shown to effectively strengthen the scapular retractor muscles (Olenik, Laskin, Burnham, Wheeler, & Steadward, 1995).

In terms of UB resistance exercises, such as free weights, weight machines, and thera-band exercise programs has shown to improve the cardiorespiratory fitness, muscle strength and the tolerance of shoulder pain in people with SCI (Jacobs, Nash, & Rusinowski, 2001). As the upper extremities are used for most daily activities, shoulder problems may lead to difficulties in propelling wheelchairs and transferring the body (i.e., a wheelchair to a bed). Thus, strengthening the shoulder muscles may also reduce shoulder pain (i.e., rotator cuff impingement syndrome and general shoulder pain). Recently, Kim et al. reported that 6 weeks of UB resistance exercise improved UB muscle strength, as measured by shoulder flexion, extension, abduction, and adduction, as well as elbow flexion (Kim et al., 2019). Kim et al. further reported that UB resistance exercise significantly increased the HDL-C levels, UB muscle strength, and VO_2 peaks of the participants (Kim et al., 2019).

Despite this benefit of UB exercises, potential issues related to UB overuse injuries, such as shoulder joint ligament tears, muscle strains, tendon sprains, or stress fractures, may occur (Dyson-Hudson, Sisto, Bond, Emmons, & Kirshblum, 2007). These concerns are based on repetitive upper limb activities such as wheelchair propulsion and other activities of daily living such as transfers and vertical lifts involves pushing actions (shoulder flexion and horizontal adduction) (Van Drongelen et al., 2005). Therefore, backward wheeling, rowing exercises, and thera-band exercises that require shoulder extensions, external rotations, and scapula retractions would be beneficial exercises for people with SCI (Kim et al., 2019).

FES-assisted LB and/or WB exercise

Using FES would reverse some primary consequences of SCI such as changes in muscle mass, skeletal muscle capillarization, and fiber type (Collins, 2007). Currently, FES is the most common technique used to generate muscle contractions to maintain muscle quality and produce purposeful movement after SCI (Ibitoye, Hamzaid, Hasnan, Abdul Wahab, & Davis, 2016). For LB exercises, FES cycling has been shown to be effective in increasing cardiopulmonary fitness and the protein expression of glucose transporters in the paralyzed muscle while decreasing insulin resistance. It is also beneficial to dyslipidemia via muscle fiber type changes, capillarization, and even the protein expression of glucose transporter 1 and 4 in the vastus lateralis muscle (Jeon et al., 2002). Especially, FES-assisted cycling has been tested most extensively on acute and chronic physiological responses (Castello et al., 2012; Frotzler et al., 2008; Griffin et al., 2009; Jeon et al., 2002; Johnston et al., 2008; Johnston et al., 2009; Zbogar et al., 2008).

In terms of WB exercises, a combination of FES cycling and arm ergometer exercises (Verellen et al., 2001; Verellen, Vanlandewijck, Andrews, & Wheeler, 2007) as well as FES rowing exercises (Kim, Park, Lee, & Jeon, 2014) has been reported to be effective for improving the cardiovascular system and imparting positive effects to people with SCI. Hooker et al. previously demonstrated that hybrid exercise, which uses both upper and LB muscles, is a more effective exercise modality to improve cardiovascular fitness than the arm ergometer and FES cycle alone (Hooker et al., 1992). Specifically, rowing exercises require a strong physical condition for fast muscle contraction because the mobilization of anaerobic energy sources is higher than in other exercises (Wagenmakers, Coakley, & Edwards, 1990). The FES rowing exercise has been reported to be effective at improving cardiovascular fitness, UB strength, and body composition of people with SCI (Jeon et al., 2010; Kim et al., 2014). Furthermore, backward wheeling, and isolated and strengthening the scapular retractor muscle during the FES rowing exercise was effective and would improve the scapular stability which is important in prevention and treatment of shoulder problems in people with SCI (Kim et al., 2014; Olenik et al., 1995). Individuals with higher levels of SCI may benefit the most from FES-assisted exercise; however, FES rowing, cycling, and the arm ergometer have limitations due to the high cost of equipment and lack of availability.

Tailored exercise for people with SCI

Although exercise have been shown to confer beneficial physiological and mental effects to people with SCI, the levels of SCI can influence the individual's ability to perform exercise limiting type, intensity, and duration of exercise. Furthermore, to maximize the health benefits of exercise, the type, duration, and intensity should be prescribed according to participant comorbidities (obesity, type 2 diabetes, CVD) as well as shoulder and elbow joint conditions. However, most studies that demonstrated the beneficial effect of exercise on the cardiometabolic profile and joint problems in individuals with SCI applied the same exercise protocols regardless of participants' level of injuries, degree of adiposity, and comorbidities. Therefore, it is important to develop personalized exercise programs for people with SCI by considering the multiple factors of their exercise ability and the potential benefits they could reasonably obtain from such exercise programs. In this regard, Kim et al. attempted to personalize exercise programs for people with SCI. They personalized an exercise program for SCI based on four factors: level of SCI (A1–7), comorbidities (B1–6), purpose of exercise (C1–4), and joint conditions (D1–3). Therefore, there could be 504 different exercise programs based on their levels of injury, comorbidities, purpose of exercise, and joint condition (Table 2). This exercise program consisted of 25 min of warm up, 30 min of exercise, and 5 min of cool down. A total of 17 people with SCI participated in this pilot randomized controlled trial. These participants' fasting insulin levels, surrogate measures of insulin resistance (HOMA-IR), and FM were significantly decreased. Furthermore, UB muscle strength, measured by elbow flexion/extension and shoulder adduction/abduction/flexion/extension, were significantly improved in all measurements. Lastly, the psychological well-being improved significantly among those in the exercise group; however, these results have not been published in a peer-review journal yet (Kim, 2014). Although this study was a pilot randomized controlled trial, studies like this should be expanded further with a larger sample size and the addition of FES (if available).

Conclusion and future perspective

In this chapter, the effects of different exercises on health outcomes in people with SCI were summarized and discussed. In general, exercise and PA are beneficial on their cardiometabolic, musculoskeletal, and psychosocial health. Yet, due to their paralysis, people with SCI have less choices on the mode of exercise. They also have to be more careful not to injure their joints because UB joints are essential for their mobility and daily living. In the future, more personalized exercise program should be applied according to their levels of injury, comorbidities, and purpose of exercise participation.

Applications to other areas of neuroscience

The primary consequences of SCI are paralysis and autonomic nervous system dysfunction while the secondary consequences including physical inactivity, changes in body composition and metabolic profiles, poor musculoskeletal problems, and poor mental health. Various exercise programs such as UB aerobic and resistance exercise and LB and

TABLE 2 Development of tailored exercise programs for people with different levels of SCI.

	Option 1	Option 2	Option 3	Option 4
Screening	Level of injury	Chronic disease	Exercise purpose	Joint stability
Contents	Component of resistance exercise	Exercise frequency and intensity level	Ratio of aerobic, resistance, and circuit training	Rehabilitation exercise
Category	A type A1: C4–6 A2: C7–8 A3: T1–6 A4: T7–L2 A5: L3 A6: L4–5 A7: S1–2	B type B1: Metabolic syndrome B2: Hypertension B3: Diabetes B4: Osteoporosis B5: Obesity B6: None	C type C1: Functional fitness C2: Weight loss C3: Muscle strength C4: Cardiovascular fitness	D type D1: Shoulder D2: Elbow D3: Wrist

To maximize the health benefits of exercise for people with SCI, the exercise should be tailored to the presence of chronic diseases (metabolic syndrome, hypertension, type 2 diabetes, osteoporosis, and obesity) and the existence of joint problems while the level of SCI should also be considered.

WB were discussed. Regular exercise and increased PA in people with SCI seem beneficial for overall fitness and psychological well-being, and can even help those with high spinal cord lesions. Exercise is beneficial in all neurological disorders or conditions whether they are progressive (i.e., Parkinson's disease) or non-progressive (i.e., traumatic brain injury and cerebral palsy). Evidence exists that exercise slows down the progression of neurologic disorders while improving physical function and the QoL of people with different neurological conditions. However, no evidence-based personalized exercise program has yet been developed for people with other neurological disorders. Because the level of injury can influence the patient's ability to perform particular exercises, exercise programs for people with neurological disorders vary according to their types and levels of injury. Furthermore, the level of adiposity, joint problems, and the presence of chronic diseases such as type 2 diabetes, hypertension, and CVD may also influence the type, intensity, duration, and frequency of exercise in which people with SCI can participate. Just as exercise should be personalized for people with SCI, exercise should be personalized for different neurological disorders to maximize benefits while minimizing side effects.

Mini-dictionary of terms

- **Spinal cord injury (SCI):** Damage to the spinal cord resulting from trauma, disease, or degeneration. Symptoms of SCI depend on the severity of injury and its location on the spinal cord. Symptoms may include partial or complete loss of sensory function or motor control of the upper body, lower body, and/or the whole-body.
- **Exercise:** Physical activity that is planned, structured, and repetitive for the purpose of conditioning the body. Exercise consists of aerobic, resistance, and flexibility.
- **Body mass index:** Person's weight in kilograms divided by the square of height in meters. It's an easy screening method for weight category (underweight, healthy weight, overweight, and obese).
- **Type 2 diabetes mellitus:** The most common type of diabetes, which is a disease that occurs when your blood glucose is too high.
- **Cardiovascular disease:** Any disease of the heart and its associated blood vessels, most commonly coronary heart disease, stroke, and peripheral vascular disease.
- **Muscle strength:** Defined as the amount of force you can put out or the amount of weight you can lift.
- **Functional electrical stimulation:** Treatment that involves the application of a mild electrical stimulus to a muscle to produce functional movement after paralysis.

Key facts on exercises and people with SCI

- The clinical consequences of SCI, paired with a reduction in physical activity and increased sedentary time, often result in a deterioration of body composition and metabolic profile.
- Significant changes in both body composition and metabolic profiles after SCI can result in significant health consequences and increased risk of chronic disease.
- Exercise has been shown to improve muscle strength, aerobic capacity, and psychological well-being in people with SCI.
- Wheelchair propulsion as well as transfers cause and increase musculoskeletal problems, such as shoulder, elbow, and wrist pain in people with SCI.
- Musculoskeletal problems in people with SCI may be partially a result of overuse; however, certain exercises and routines can help reduce pain while strengthening and stretching the muscles used for joint function.
- Personalized exercise programs for people with a SCI should be developed by considering multiple factors capable of influencing their exercise ability, and the potential benefits they could reasonably obtain from such exercise programs are important.

Summary points

- This chapter focuses on the effects of exercise and various exercise programs for people with SCI.
- SCI is a catastrophic injury with potential devastating impacts, including far-reaching physical and psychological consequences.
- Lack of exercise and physical inactivity are the primary causes of chronic diseases such as cardiovascular disease, type 2 diabetes, hypertension, and metabolic syndrome in people with SCI.

- Evidence suggests that different types of upper body exercise and lower body and whole body exercise with functional electrical stimulation programs is effective in the physical and psychological well-being of people with SCI.
- However, the levels of SCI can influence the individual's ability in regard to the type, intensity, and duration of exercise.
- Therefore, personalized exercise program should be applied according to their levels of injury, comorbidities, and purpose of exercise participation.

References

Ahuja, C. S., Wilson, J. R., Nori, S., Kotter, M. R., Druschel, C., Curt, A., & Fehlings, M. G. (2017). Traumatic spinal cord injury. *Nature Reviews Disease Primers*, *3*(1), 1–21.

Assinck, P., Duncan, G. J., Hilton, B. J., Plemel, J. R., & Tetzlaff, W. (2017). Cell transplantation therapy for spinal cord injury. *Nature Neuroscience*, *20*(5), 637–647.

Bauman, W., Spungen, A., Zhong, Y.-G., Rothstein, J., Petry, C., & Gordon, S. (1992). Depressed serum high density lipoprotein cholesterol levels in veterans with spinal cord injury. *Spinal Cord*, *30*(10), 697–703.

Bauman, W. A., & Spungen, A. M. (2001). Carbohydrate and lipid metabolism in chronic spinal cord injury. *Journal of Spinal Cord Medicine*, *24*(4), 266–277. https://doi.org/10.1080/10790268.2001.11753584.

Burnham, R., Martin, T., Stein, R., Bell, G., MacLean, I., & Steadward, R. (1997). Skeletal muscle fibre type transformation following spinal cord injury. *Spinal Cord*, *35*(2), 86–91. https://doi.org/10.1038/sj.sc.3100364.

Capoor, J., & Stein, A. B. (2005). Aging with spinal cord injury. *Physical Medicine and Rehabilitation Clinics*, *16*(1), 129–161.

Castello, F., Louis, B., Cheng, J., Armento, M., & Santos, A. M. (2012). The use of functional electrical stimulation cycles in children and adolescents with spinal cord dysfunction: A pilot study. *Journal of Pediatric Rehabilitation Medicine*, *5*(4), 261–273. https://doi.org/10.3233/PRM-2012-00221.

Collins, D. F. (2007). Central contributions to contractions evoked by tetanic neuromuscular electrical stimulation. *Exercise and Sport Sciences Reviews*, *35*(3), 102–109.

Ditor, D. S., Latimer, A. E., Ginis, K. A. M., Arbour, K. P., McCartney, N., & Hicks, A. L. (2003). Maintenance of exercise participation in individuals with spinal cord injury: Effects on quality of life, stress and pain. *Spinal Cord*, *41*(8), 446–450. https://doi.org/10.1038/sj.sc.3101487.

Dyson-Hudson, T. A., Sisto, S. A., Bond, Q., Emmons, R., & Kirshblum, S. C. (2007). Arm crank ergometry and shoulder pain in persons with spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *88*(12), 1727–1729.

Fernhall, B., Heffernan, K., Jae, S. Y., & Hedrick, B. (2008). Health implications of physical activity in individuals with spinal cord injury: A literature review. *Journal of Health and Human Services Administration*, *30*(4), 468–502.

Field-Fote, E. C., & Tepavac, D. (2002). Improved intralimb coordination in people with incomplete spinal cord injury following training with body weight support and electrical stimulation. *Physical Therapy*, *82*(7), 707–715.

Fornusek, C., Davis, G. M., & Russold, M. F. (2013). Pilot study of the effect of low-cadence functional electrical stimulation cycling after spinal cord injury on thigh girth and strength. *Archives of Physical Medicine and Rehabilitation*, *94*(5), 990–993. https://doi.org/10.1016/j.apmr.2012.10.010.

Frotzler, A., Coupaud, S., Perret, C., Kakebeeke, T. H., Hunt, K. J., Donaldson, N. D. N., & Eser, P. (2008). High-volume FES-cycling partially reverses bone loss in people with chronic spinal cord injury. *Bone*, *43*(1), 169–176. https://doi.org/10.1016/j.bone.2008.03.004.

Garstang, S. V., & Miller-Smith, S. A. (2007). Autonomic nervous system dysfunction after spinal cord injury. *Physical Medicine and Rehabilitation Clinics of North America*, *18*(2), 275–296.

Gater, D. R., Jr., Farkas, G. J., & Tiozzo, E. (2021). Pathophysiology of neurogenic obesity after spinal cord injury. *Topics in Spinal Cord Injury Rehabilitation*, *27*(1), 1–10.

Giangregorio, L., Craven, C., Richards, K., Kapadia, N., Hitzig, S. L., Masani, K., & Popovic, M. R. (2012). A randomized trial of functional electrical stimulation for walking in incomplete spinal cord injury: Effects on body composition. *Journal of Spinal Cord Medicine*, *35*(5), 351–360. https://doi.org/10.1179/2045772312Y.0000000041.

Giangregorio, L. M., Hicks, A. L., Webber, C. E., Phillips, S. M., Craven, B. C., Bugaresti, J. M., & McCartney, N. (2005). Body weight supported treadmill training in acute spinal cord injury: Impact on muscle and bone. *Spinal Cord*, *43*(11), 649–657. https://doi.org/10.1038/sj.sc.3101774.

Giangregorio, L. M., Webber, C. E., Phillips, S. M., Hicks, A. L., Craven, B. C., Bugaresti, J. M., & McCartney, N. (2006). Can body weight supported treadmill training increase bone mass and reverse muscle atrophy in individuals with chronic incomplete spinal cord injury? *Applied Physiology, Nutrition, and Metabolism*, *31*(3), 283–291. https://doi.org/10.1139/h05-036.

Ginis, K. A. M., Latimer, A. E., Arbour-Nicitopoulos, K. P., Buchholz, A. C., Bray, S. R., Craven, B. C., … Potter, P. J. (2010). Leisure time physical activity in a population-based sample of people with spinal cord injury part I: Demographic and injury-related correlates. *Archives of Physical Medicine and Rehabilitation*, *91*(5), 722–728.

Gorgey, A., & Dudley, G. (2007). Skeletal muscle atrophy and increased intramuscular fat after incomplete spinal cord injury. *Spinal Cord*, *45*(4), 304–309.

Griffin, L., Decker, M. J., Hwang, J. Y., Wang, B., Kitchen, K., Ding, Z., & Ivy, J. L. (2009). Functional electrical stimulation cycling improves body composition, metabolic and neural factors in persons with spinal cord injury. *Journal of Electromyography and Kinesiology*, *19*(4), 614–622. https://doi.org/10.1016/j.jelekin.2008.03.002.

Harvey, L., & Graves, D. (2011). International standards for the neurological classification of spinal cord injury. *Journal of Physiotherapy*, *57*(2), 129.

Hicks, A., Martin, K., Ditor, D., Latimer, A., Craven, C., Bugaresti, J., & McCartney, N. (2003). Long-term exercise training in persons with spinal cord injury: Effects on strength, arm ergometry performance and psychological well-being. *Spinal Cord*, *41*(1), 34–43.

Hicks, A. L., Adams, M. M., Martin Ginis, K., Giangregorio, L., Latimer, A., Phillips, S. M., & McCartney, N. (2005). Long-term body-weight-supported treadmill training and subsequent follow-up in persons with chronic SCI: Effects on functional walking ability and measures of subjective well-being. *Spinal Cord*, *43*(5), 291–298. https://doi.org/10.1038/sj.sc.3101710.

Hooker, S. P., Figoni, S. F., Rodgers, M. M., Glaser, R. M., Mathews, T., Suryaprasad, A., & Gupta, S. (1992). Metabolic and hemodynamic responses to concurrent voluntary arm crank and electrical stimulation leg cycle exercise in quadriplegics. *Journal of Rehabilitation Research and Development*, *29*(3), 1–11.

Ibitoye, M. O., Hamzaid, N. A., Hasnan, N., Abdul Wahab, A. K., & Davis, G. M. (2016). Strategies for rapid muscle fatigue reduction during FES exercise in individuals with spinal cord injury: A systematic review. *PLoS One*, *11*(2), e0149024.

Jeon, J. Y., Hettinga, D., Steadward, R. D., Wheeler, G. D., Bell, G., & Harber, V. (2010). Reduced plasma glucose and leptin after 12 weeks of functional electrical stimulation–rowing exercise training in spinal cord injury patients. *Archives of Physical Medicine and Rehabilitation*, *91*(12), 1957–1959.

Jeon, J. Y., Steadward, R. D., Wheeler, G. D., Bell, G., McCargar, L., & Harber, V. (2003). Intact sympathetic nervous system is required for leptin effects on resting metabolic rate in people with spinal cord injury. *Journal of Clinical Endocrinology and Metabolism*, *88*(1), 402–407. https://doi.org/10.1210/jc.2002-020939.

Jacobs, P. L., Nash, M. S., & Rusinowski, J. W. (2001). Circuit training provides cardiorespiratory and strength benefits in persons with paraplegia. *Medicine & Science in Sports & Exercise*, *33*(5), 711–717. https://doi.org/10.1097/00005768-200105000-00005.

Janssen, T. W. J., & Pringle, D. D. (2008). Effects of modified electrical stimulation-induced leg cycle ergometer training for individuals with spinal cord injury. *Journal of Rehabilitation Research and Development*, *45*(6), 819–830. https://doi.org/10.1682/jrrd.2007.09.0153.

Jazayeri, S. B., Beygi, S., Shokraneh, F., Hagen, E. M., & Rahimi-Movaghar, V. (2015). Incidence of traumatic spinal cord injury worldwide: A systematic review. *European Spine Journal*, *24*(5), 905–918. https://doi.org/10.1007/s00586-014-3424-6.

Jeon, J., Weiss, C., Steadward, R., Ryan, E., Burnham, R., Bell, G., … Wheeler, G. (2002). Improved glucose tolerance and insulin sensitivity after electrical stimulation-assisted cycling in people with spinal cord injury. *Spinal Cord*, *40*(3), 110–117.

Johnston, T. E., Smith, B. T., Betz, R. R., & Lauer, R. T. (2008). Exercise testing using upper extremity ergometry in pediatric spinal cord injury. *Pediatric Physical Therapy*, *20*(2), 146–151. https://doi.org/10.1097/PEP.0b013e318171faa1.

Johnston, T. E., Smith, B. T., Mulcahey, M. J., Betz, R. R., & Lauer, R. T. (2009). A randomized controlled trial on the effects of cycling with and without electrical stimulation on cardiorespiratory and vascular health in children with spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *90*(8), 1379–1388. https://doi.org/10.1016/j.apmr.2009.02.018.

Kang, Y., Ding, H., Zhou, H., Wei, Z., Liu, L., Pan, D., & Feng, S. (2017). Epidemiology of worldwide spinal cord injury: A literature review. *Journal of Neurorestoratology*, *6*, 1–9.

Kennedy, P., & Garmon-Jones, L. (2017). Self-harm and suicide before and after spinal cord injury: A systematic review. *Spinal Cord*, *55*(1), 2–7.

Kim, D.-I. (2014). *(The) effect of exercise on fasting insulin and fitness levels in people with spinal cord injury*. Doctoral dissertation Seoul: Graduate School, Yonsei University. Retrieved from http://www.riss.kr/link?id=T13599229.

Kim, D.-I., Lee, H., Lee, B.-S., Kim, J., & Jeon, J. Y. (2015). Effects of a 6-week indoor hand-bike exercise program on health and fitness levels in people with spinal cord injury: A randomized controlled trial study. *Archives of Physical Medicine and Rehabilitation*, *96*(11), 2033–2040. e2031.

Kim, D. I., Park, D., Lee, B., & Jeon, J. (2014). A six-week motor-driven functional electronic stimulation rowing program improves muscle strength and body composition in people with spinal cord injury: A pilot study. *Spinal Cord*, *52*(8), 621–624.

Kim, D.-I., Taylor, J. A., Tan, C. O., Park, H., Kim, J. Y., Park, S.-Y., … Jeon, J. Y. (2019). A pilot randomized controlled trial of 6-week combined exercise program on fasting insulin and fitness levels in individuals with spinal cord injury. *European Spine Journal*, *28*(5), 1082–1091.

Kim, D., Il, Lee, J., Park, H., & Jeon, J. Y. (2020). The relationship between physical activity levels and mental health in individuals with spinal cord injury in South Korea. *International Journal of Environmental Research and Public Health*, *17*(12). https://doi.org/10.3390/ijerph17124423.

Latimer, A. E., Ginis, K. A. M., Hicks, A. L., & McCartney, N. (2004). An examination of the mechanisms of exercise-induced change in psychological well-being among people with spinal cord injury. *Journal of Rehabilitation Research and Development*, *41*(5), 643–652. https://doi.org/10.1682/jrrd.2003.04.0043.

Le, J., & Dorstyn, D. (2016). Anxiety prevalence following spinal cord injury: A meta-analysis. *Spinal Cord*, *54*(8), 570–578.

Liusuwan, R. A., Widman, L. M., Abresch, R. Ted., Styne, D. M., & McDonald, C. M. (2007). Body composition and resting energy expenditure in patients aged 11 to 21 years with spinal cord dysfunction compared to controls: Comparisons and relationships among the groups. *Journal of Spinal Cord Medicine*, *30*(Suppl 1), S105–S111. https://doi.org/10.1080/10790268.2007.11754613.

Mahoney, E. T., Bickel, C. S., Elder, C., Black, C., Slade, J. M., Apple, D., Jr., & Dudley, G. A. (2005). Changes in skeletal muscle size and glucose tolerance with electrically stimulated resistance training in subjects with chronic spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *86*(7), 1502–1504. https://doi.org/10.1016/j.apmr.2004.12.021.

Maynard, F., Karunas, R., & Waring, W., 3rd. (1990). Epidemiology of spasticity following traumatic spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *71*(8), 566–569.

Nooijen, C. F., de Groot, S., Postma, K., Bergen, M. P., Stam, H. J., Bussmann, J., & Van den Berg-Emons, R. (2012). A more active lifestyle in persons with a recent spinal cord injury benefits physical fitness and health. *Spinal Cord*, *50*(4), 320–323.

Olenik, L., Laskin, J., Burnham, R., Wheeler, G., & Steadward, R. (1995). Efficacy of rowing, backward wheeling and isolated scapular retractor exercise as remedial strength activities for wheelchair users: Application of electromyography. *Spinal Cord*, *33*(3), 148–152.

Riek, L., Ludewig, P., & Nawoczenski, D. (2008). Comparative shoulder kinematics during free standing, standing depression lifts and daily functional activities in persons with paraplegia: Considerations for shoulder health. *Spinal Cord*, *46*(5), 335–343.

Silva, A. C., Neder, J. A., Chiurciu, M. V., Pasqualin, D. C., da Silva, R. C., Fernandez, A. C., … Tufik, S. (1998). Effect of aerobic training on ventilatory muscle endurance of spinal cord injured men. *Spinal Cord*, *36*(4), 240–245. https://doi.org/10.1038/sj.sc.3100575.

Spungen, A. M., Adkins, R. H., Stewart, C. A., Wang, J., Pierson, R. N., Jr., Waters, R. L., & Bauman, W. A. (2003). Factors influencing body composition in persons with spinal cord injury: A cross-sectional study. *Journal of Applied Physiology (1985)*, *95*(6), 2398–2407. https://doi.org/10.1152/japplphysiol.00729.2002.

Sweis, R., & Biller, J. (2017). Systemic complications of spinal cord injury. *Current Neurology and Neuroscience Reports*, *17*(1), 1–8.

Ullrich, P. M., Lincoln, R. K., Tackett, M. J., Miskevics, S., Smith, B. M., & Weaver, F. M. (2013). Pain, depression, and health care utilization over time after spinal cord injury. *Rehabilitation Psychology*, *58*(2), 158.

van den Berg-Emons, R. J., Bussmann, J. B., Haisma, J. A., Sluis, T. A., van der Woude, L. H., Bergen, M. P., & Stam, H. J. (2008). A prospective study on physical activity levels after spinal cord injury during inpatient rehabilitation and the year after discharge. *Archives of Physical Medicine and Rehabilitation*, *89*(11), 2094–2101.

van den Berg-Emons, R. J., Bussmann, J. B., & Stam, H. J. (2010). Accelerometry-based activity spectrum in persons with chronic physical conditions. *Archives of Physical Medicine and Rehabilitation*, *91*(12), 1856–1861.

Van Drongelen, S., Van der Woude, L. H., Janssen, T. W., Angenot, E. L., Chadwick, E. K., & Veeger, D. H. (2005). Mechanical load on the upper extremity during wheelchair activities. *Archives of Physical Medicine and Rehabilitation*, *86*(6), 1214–1220.

Verellen, J., Kerby, B., Olijnyk, B., Saab, S., Smith, G., Jeon, J., … Wheeler, G. (2001). A comparison of the peak physical work capacity during arm ergometry, Fes cycling and two hybrid exercise conditions in spinal cord injured. In *Paper presented at the 7th Vienna international workshop on functional electrical stimulation*.

Verellen, J., Vanlandewijck, Y., Andrews, B., & Wheeler, G. D. (2007). Cardiorespiratory responses during arm ergometry, functional electrical stimulation cycling, and two hybrid exercise conditions in spinal cord injured. *Disability and Rehabilitation: Assistive Technology*, *2*(2), 127–132.

Wagenmakers, A., Coakley, J., & Edwards, R. (1990). Metabolism of branched-chain amino acids and ammonia during exercise: Clues from McArdle's disease. *International Journal of Sports Medicine*, *11*(S2), S101–S113.

Wang, Y.-H., Huang, T.-S., Lin, J.-L., Hwang, J.-J., Chan, H.-L., Lai, J.-S., & Tseng, Y.-Z. (2000). Decreased autonomic nervous system activity as assessed by heart rate variability in patients with chronic tetraplegia. *Archives of Physical Medicine and Rehabilitation*, *81*(9), 1181–1184.

Williams, R., & Murray, A. (2015). Prevalence of depression after spinal cord injury: A meta-analysis. *Archives of Physical Medicine and Rehabilitation*, *96*(1), 133–140.

Wirz, M., Zemon, D. H., Rupp, R., Scheel, A., Colombo, G., Dietz, V., & Hornby, T. G. (2005). Effectiveness of automated locomotor training in patients with chronic incomplete spinal cord injury: A multicenter trial. *Archives of Physical Medicine and Rehabilitation*, *86*(4), 672–680. https://doi.org/10.1016/j.apmr.2004.08.004.

Zbogar, D., Eng, J. J., Krassioukov, A. V., Scott, J. M., Esch, B. T. A., & Warburton, D. E. R. (2008). The effects of functional electrical stimulation leg cycle ergometry training on arterial compliance in individuals with spinal cord injury. *Spinal Cord*, *46*(11), 722–726. https://doi.org/10.1038/sc.2008.34.

Zurlo, F., Larson, K., Bogardus, C., & Ravussin, E. (1990). Skeletal muscle metabolism is a major determinant of resting energy expenditure. *Journal of Clinical Investigation*, *86*(5), 1423–1427.

Chapter 4

Use of anodal transcranial direct current stimulation: Features, facets, and applications to incomplete spinal cord injury

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List of abbreviations

AEs	adverse effects
ANS	autonomic nervous system
ASIA	American Spinal Injury Association Scale
a-tDCS	anodal transcranial direct current stimulation
BDNF	Brain-derived neurotrophic factor
CE	cortical excitability
cSCI	complete spinal cord injury
DC	direct current
iSCI	incomplete spinal cord injury
M1	primary motor cortex
mA	milliampere
mA/cm^2	milliampere by square squares
MEP	motor evoked potential
MF	motor function
NMDA	*N*-methyl-D-aspartate
NP	neuropathic pain
SCI	spinal cord injury
tDCS	transcranial Direct Current Stimulation

Introduction

Discovery of the direct current therapeutic effect and technological progress

It is estimated that in the first century before Christ the first Direct Current (DC) generator was created, an invention attributed to the ancient Persian civilization probably used for therapeutic purposes. After, in 1800, Alessandro Volta created an electric battery called "voltaic battery" and it is making possible the transcranial application. DC was applied to a farmer who suffered from major depression and the symptoms were reduced after a few weeks (Sarmiento, San-Juan, & Prasath, 2016). Thus, the use of transcranial DC opened the door for experiments on psychiatric and neurological conditions. Fig. 1 shows the progress of the technologies for DC over time.

In 1883, methods and dosages to enhance the benefits of DC application through experimental research were established. Initially, the technological limitation and the protocols variability prevented researchers from understanding the DC effects (Erb, 1883). Only in 1964, experimental researchers about the difference between two types of transcranial

Cellular, Molecular, Physiological, and Behavioral Aspects of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822427-4.00004-6

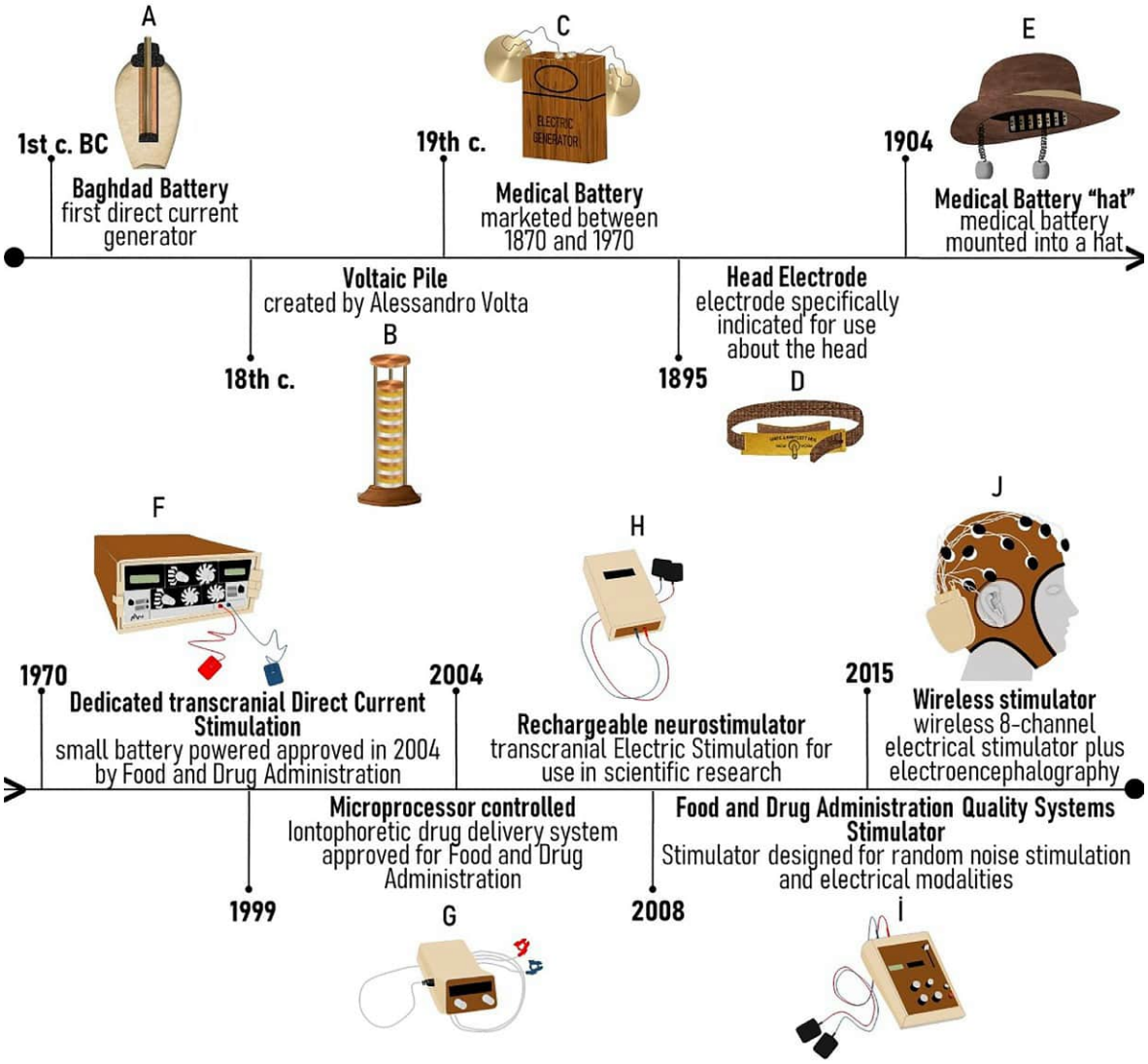

FIG. 1 Timeline of technological progress for direct current over time. Timeline shows the direct current devices in different forms from 1st BC until the year 2015 based on the report of the first studies using each. Unpublished. tDCS, transcranial Direct Current Stimulation.

DC, anodal and cathodal, were started in some clinical outcomes. The initial evidence provided knowledge of the transcranial DC effects on cortical excitability (CE) as a specific modulator of polarity from the neurons (Lippold & Redfearn, 1964). Later, in 2000, the term transcranial Direct Current Stimulation (tDCS) was cited for the first time by Nitsche and Paulus (2000) in an experiment that showed a significant increase in motor CE during anodal stimulation (a-tDCS) and a significant decrease during cathodal stimulation.

Based on the current evidence, tDCS can be considered a noninvasive, painless, and safe neurological stimulation. The tDCS uses a low-intensity DC between 1 and 4 mA distributed to the skull and brain through electrodes on specific cortical areas (Renga, 2020). The current flow depends on the electrode site. In a-tDCS, the anode is on a target brain area, and the cathode on a referential area. Thus, the current flow occurs from the anode to the cathode with a depolarization threshold reduction in the neuronal membrane. Instead, when the cathode is targeted on a brain area the current flow is the inverse, and the stimulation causes hyperpolarization in the neurons (Renga, 2020).

Neurophysiological basis of the a-tDCS

The neurophysiological basis of the a-tDCS can be divided into primary or secondary effects. Primary effects have been related to modulation of sodium and calcium-dependent voltage channel activity in the neuronal membrane and, therefore,

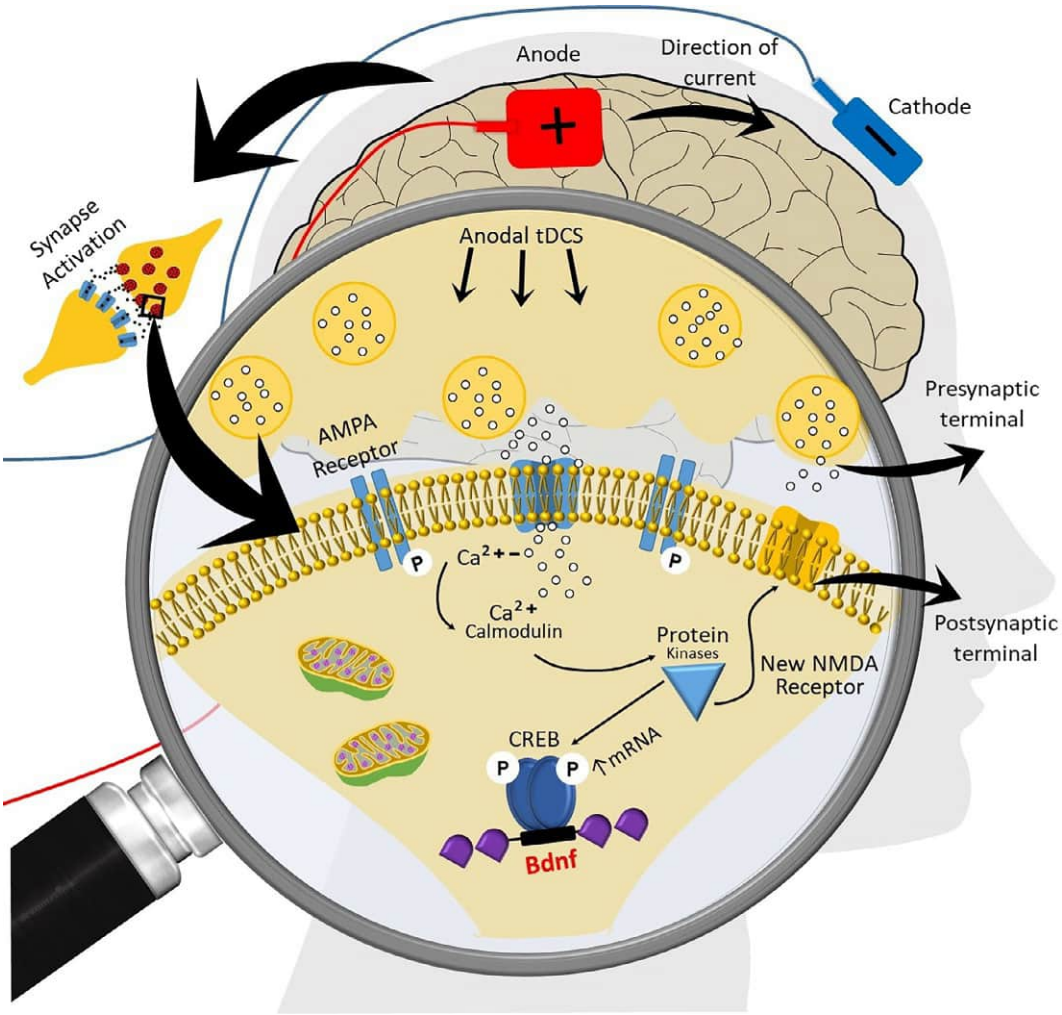

FIG. 2 Neurophysiological basis of a-tDCS primary effects. a-tDCS current flow modulates dependent voltage channel causing depolarization of the presynaptic membrane. The neurotransmitters release activates the NMDA receptors in the postsynaptic membrane and increases the influx of calcium, activating protein kinases signalization to a BDNF gene transcription. New NMDA receptors and, therefore, neuroplasticity like a long-term potentiation occurs. Unpublished. *tDCS*, transcranial Direct Current Stimulation; *NMDA*, *N*-methyl-D-aspartate; *AMPA*, alpha-amino-3-hydroxy-methyl-5-4-isoxazol-propionic; *Ca*, Calcium; *P*, Potassium; *CREB*, cAMP response element-binding protein, an intracellular protein related to expression of genes; *mRNA*, messenger RiboNucleic Acid; *Bndf*, Brain-derived neurotrophic factor.

with an influx of sodium (Horvath, Vogrin, Carter, Cook, & Forte, 2016; Jamil et al., 2020). These effects are closely linked to the potential in reducing the depolarization threshold of neurons because axons demonstrate susceptibility to changes in membrane potential (Jamil et al., 2020; Lefaucheur et al., 2017). When the DC induced by the a-tDCS reaches the neurons a modification in the transmembrane conduction, axonal transport and the structural conformation of plasmalemma may occur. Thus, a-tDCS facilitates neuronal depolarization, the activity of neurons, and, therefore, enhances CE (Horvath et al., 2016; Jamil et al., 2020). Fig. 2 illustrates the primary effects of a-tDCS in the neuronal membrane.

a-tDCS primary effects at the neuronal membrane induce the secondary effects (Lefaucheur et al., 2017) linked to neuroplastic changes in the neuronal circuit. The neuroplasticity induced by a-tDCS appears to be related to a repetitive activation of the *N*-methyl-D-aspartate (NMDA) receptors, which induces an influx of calcium in the postsynaptic neurons. As a consequence, a cascade of neurophysiological changes may be activating a signalization to a Brain-derived neurotrophic factor (BDNF) gene transcription to new NMDA receptors (Jamil et al., 2020; Lefaucheur et al., 2017; Podda et al., 2016). Finally, dependent activity neuroplasticity like a long-term potentiation in the glutamatergic neurons at the postsynaptic membrane may occur. Besides that, a-tDCS has been demonstrated to reduce the gabaergic transmission by a blockage of the receptors of gamma-aminobutyric acid, conducting a reinforcement of the glutamatérgic synapses. Therefore, a-tDCS interferes with the functional connectivity of cortical and subcortical networks.

Previous studies observed a-tDCS effects in the glial, endothelial, and lymphatic cells also. Effects on endothelial cells were related to increased cerebral blood flow. Moreover, glial cells respond to a-tDCS improving the regulation of the neurons. These effects were pointed to as predictors of long-term effects stimulation due to the enhancement of substrates for neuronal functioning (Jamil et al., 2020).

In the iSCI, the a-tDCS potential to neuroplasticity by modulating the CE and motor descending pathways such as the corticospinal tract have an important place in rehabilitation. Previous studies showed the a-tDCS effect on the CE underlying the stimulation site, corticospinal pathways, and medullary neurons (Bunday & Perez, 2012; Lefaucheur et al., 2017). For example, the stimulation on the hand or leg motor area in the primary motor cortex (M1) appears to increase the CE and fire neurons from the descending motor circuit to the medullary neurons, which will generate muscle responses (Bunday & Perez, 2012; Cortes et al., 2017; Lefaucheur et al., 2017; Potter-Baker et al., 2018; Yamaguchi et al., 2016; Yozbatiran et al., 2016). Thus, the knowledge of the a-tDCS neuroplasticity effects is important to formulate an ideal intervention to promote effective rehabilitation. The neuronal circuit activated by a-tDCS on M1 is shown in Fig. 3.

Importance of the a-tDCS after iSCI

Impairments in motor and sensory functions after iSCI generates a significant reduction in the functionality and quality of life. Besides, morbidities, psychological stress, and the changes imposed by the injury impair the reintegration of affected individuals into activities of daily living and work (Khorasanizadeh et al., 2019). Therefore, effective interventions and adequate management should be a priority to the rehabilitation after iSCI.

Epidemiological data help to understand the profile of iSCI affected individuals and appropriate rehabilitation. The International Spinal Cord Society points to a global incidence rate of 23 cases per million, resulting in approximately 179 thousand new cases annually. Overall, men have been more affected than women with odds ratios ranging from 2.4:1 to 4:1. Incomplete injuries were more frequent—ranging between 47.8% and 80.5%. A high number of men over the age of 40 and working-age individuals have been victims in developed and developing countries, respectively. Findings motivate researchers for effective rehabilitation. Thus, the a-tDCS has been pointed out as a potential intervention to reach better functionality and quality of life.

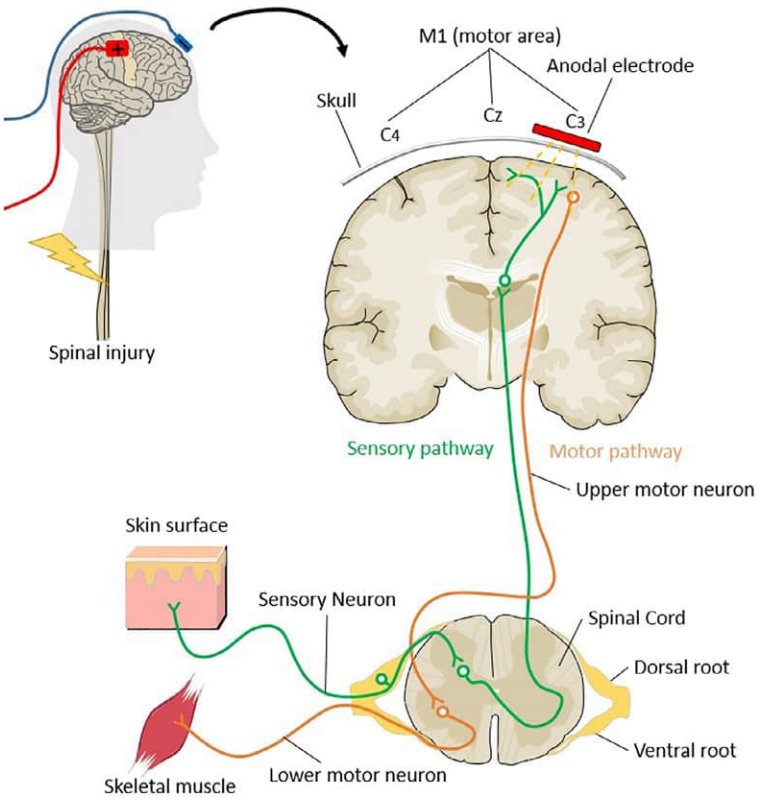

FIG. 3 Neuronal circuit activated by a-tDCS on M1 and electrode site. a-tDCS at M1 increases the CE and fire neurons from the descending motor circuit to the medullary neurons, generating muscle and sensory responses. Unpublished. *iSCI*: incomplete spinal cord injury; *a-tDCS*: anodal transcranial direct current stimulation; *CE*: cortical excitability.

A-tDCS outcomes after iSCI

CE and neuroplasticity-related outcomes

The CE was found as an outcome related to a-tDCS effects in protocols to improve motor function (MF). Two previous studies reported increases in the CE after one or five sessions at 1 or 2 mA during 20/60 min on the M1 (Murray et al., 2015; Potter-Baker et al., 2018) (see Table 1). Murray et al. showed modulation of CE through the motor evoked potential (MEP) measurements in the extensor carpi radialis immediately after a-tDCS on M1, but not maintained as a long-term effect.

TABLE 1 a-tDCS protocols parameters applied to iSCI.

Study (year)	Outcomes	Anodal electrode site	Cathodal electrode site	Electrode size	Intensity	Current density	Session duration	Sessions (n)
Soler et al. (2010)	Neuropathic Pain	C3 or C4	Contralateral supraorbital area	35 cm^2	2 mA	0.0571 mA/cm^2	20 min	10
Kumru et al. (2013)	Neuropathic Pain	C3 or C4	Contralateral supraorbital area	35 cm^2	2 mA	0.0571 mA/cm^2	20 min	10
Yoon et al. (2014)	Neuropathic Pain	C3	Contralateral supraorbital area	–	2 mA	–	20 min	20
Ngernyam et al. (2015)	Neuropathic Pain	C3 or C4	Contralateral shoulder	35 cm^2	2 mA	0.0571 mA/cm^2	20 min	1
Li, Stampas, Frontera, and Davis, (2018); Li, Fan, Yang, He, and Li, (2018)	Neuropathic Pain	C3	Contralateral supraorbital area	35 cm^2	2 mA	0.0571 mA/cm^2	20 min	1
Soler, Moriña, Kumru, Vidal, and Navarro (2020)	Neuropathic Pain	C3 or C4	Contralateral supraorbital area	25 cm^2	2 mA	0.08 mA/cm^2	20 min	10
Thibaut, Carvalho, Morse, Zafonte, and Fregni (2017)	Neuropathic Pain/Quality of life	M1	Contralateral supraorbital area	35 cm^2	2 mA	0.0571 mA/cm^2	20 min	5–10
Salmon et al. (2014)	Motor Function	M1	Contralateral supraorbital area	25 cm^2	2 mA	0.08 mA/cm^2	20 min	12
Murray et al. (2015)	Cortical excitability	C3	Contralateral supraorbital area	3.14 cm^2	1 mA	0.31-or 0.63 mA/cm^2	20 min	1
Kumru, Murillo, Benito-Penalva, Tormos, and Vidal (2016)	Motor Function/ Functionality	M1	Contralateral supraorbital area	35 cm^2	2 mA	0.0571 mA/cm^2	20 min	20

Continued

TABLE 1 a-tDCS protocols parameters applied to iSCI—cont'd

Study (year)	Outcomes	Anodal electrode site	Cathodal electrode site	Electrode size	Intensity	Current density	Session duration	Sessions (n)
Raithatha et al. (2016)	Motor Function/ Functionality	M1	Contralateral supraorbital area	25 cm^2	2 mA	0.08 mA/cm^2	20 min	36
Yamaguchi et al. (2016)	Motor Function/ Functionality	M1	Ipsilateral supraorbital area	35 cm^2	1 mA	0.028 mA/cm^2	20 min	1
Yozbatiran et al. (2016)	Motor Function/ Functionality	C3 or C4	Contralateral supraorbital area	35 cm^2	2 mA	0.0571 mA/cm^2	20 min	10
Yozbatiran et al. (2017)	Motor Function/ Functionality	C3 or C4	Contralateral supraorbital area	35 cm^2	2 mA	0.0571 mA/cm^2	20 min	10
Cortes et al. (2017)	Motor Function/ Functionality	C3 or C4	Contralateral supraorbital area	3 cm^2	1 mA	0.6 or 0.3 mA/cm^2	20 min	1
Potter-Baker et al. (2017)	Motor Function/ Functionality	C3 or C4	Contralateral supraorbital area	35 cm^2	2 mA	0.0571 mA/cm^2	30 min	10
da Silva et al. (2017)	Autonomic modulation	Cz	Occipital protuberance area	35 cm^2	2 mA	0.055 mA/cm^2	12 min	1

Table shows a-tDCS parameters applied in each study based on the main outcomes. Unpublished.
a-tDCS, transcranial direct current stimulation; *iSCI,* incomplete spinal cord injury; *C3 or C4,* hand motor area; *M1,* primary motor cortex; *Cz,* leg motor area; *cm^2,* square centimeters; *mA,* milliampere; – not available; *min,* minutes; *n,* number of sessions.

Increases in the CE has been associated with a boost of the neuroplasticity on the spinal cord, which facilitates the movement of weak muscles below the level of injury (Carmel, Berrol, Brus-Ramer, & Martin, 2010) and contribute to more lasting improvements in motor function after a-tDCS (Potter-Baker et al., 2018). Potter-Baker et al. demonstrated the increased MEPs after stimulation on M1 at a site related to the most affected and weakest muscle below the level of the injury. Improvements in MF on chronic iSCI, which were maintained for 3 months, appears to be related to neuroplasticity in the volume of the motor map related to the weak muscles and CE enhancements. The results were stronger in this study due to the greater number of the sessions as well as the a-tDCS uses paired with massed practice training.

Motor function and functionality outcomes

The crucial role of neuroplasticity of the residual cortical and spinal pathways to reach a recovery of the MF has been reported (Fawcett et al., 2007). Stimuli to neuroplasticity occurs by the modulation of CE and reinforcement of the synapses (Martin, 2016). Thus, a-tDCS have been shown as a potential intervention that might be able to promote neuroplasticity, MF rehabilitation, and functionality in iSCI individuals.

The current evidence shows some studies reporting positive a-tDCS effects on MF or functionality after iSCI. A systematic review and meta-analysis based on the six randomized clinical trials showed a significant improvement in functionality, but not muscle strength (De Araújo et al., 2020) after a-tDCS at 2 mA from 20 to 30 min with the anode on the leg or hand motor area. Overall, studies applied to the a-tDCS paired with conventional therapies, which appears to reinforce the effects (see Table 1).

Some studies showed a significant improvement on the hand and leg MF immediately after isolated a-tDCS at 2 mA or when the stimulation was paired with specific upper or lower extremities training. Improvements in muscle strength and functionality were observed immediately and lasted for up to 3 months after the intervention (Cortes et al., 2017; Raithatha et al., 2016; Yozbatiran et al., 2017). Under these results, the study of Yamaguchi et al. demonstrated a significantly

increased number of ankle movements immediately after the a-tDCS at 1 mA on the leg motor area. On the other hand, Kumru et al. despite reporting a significant improvement in the muscle strength of lower extremities, the results did not significantly differ from the group of participants who received the a-tDCS in the sham mode. Thus, the results of the previous studies suggest a small moderate short-term effect of a-tDCS following iSCI (de Araújo et al., 2020), which needs to be confirmed by future randomized clinical trials.

Studies reported positive effects of the a-tDCS on the MF or functionality based on finds that stimulation could modulate excitability on the cortical motor area and corticospinal pathways, which might cause spinal plasticity and, therefore, improvements in hand or leg functions on iSCI (Cortes et al., 2017; Potter-Baker et al., 2018; Yamaguchi et al., 2016; Yozbatiran et al., 2016). Overall, most studies reported positive results of the a-tDCS in people with chronic iSCI, which needs to reinforce the neuroplasticity to continued gains in the MF (de Araújo et al., 2020).

Chronic neuropathic pain (NP)

Chronic NP has been frequently related to iSCI because of the injuries on the nervous system affecting the somatosensory system (Treede et al., 2008). In the current evidence has been reported a-tDCS effects in iSCI individuals chronic NP. The a-tDCS was paired with breathing-controlled electrical stimulation, and results pointed to a reduction of pain (Li, 2013; Li, Stampas, Frontera, & Davis, 2018). The pain reduction was related to the greater number of sessions, which induced lasting neuroplasticity and synaptic strengthening. Moreover, it appears that the higher the pain levels, the greater the reduction in pain after a-tDCS in iSCI individuals (Thibaut et al., 2017) (see Table 1). Despite the positive effects pointed out in this study, few researchers are aiming to investigate the a-tDCS effects of NP reduction after iSCI. Previous studies were formed by a mixed sample with iSCI and complete SCI (cSCI). For example, Yoon et al. (2014) showed a significant NP reduction, but not clinic reduction in the pain level after 20 sessions at 2 mA a-tDCS for 20 min. Similarly, Ngernyam et al. (2015) reported significant NP reduction in iSCI and cSCI individuals immediately after one a-tDCS session.

A meta-analysis evidenced the positive effects of a-tDCS in the NP in SCI but only 32.5% of the sample had iSCI. Results indicated a reduction of NP and highlighted a trend to greater positive effects in individuals with pain duration less than 5 years. Moreover, some studies pointed out that the a-tDCS effects appear more evident in the long term (Mehta, Mcintyre, Guy, Teasell, & Loh, 2015). Thus, the pain was smaller when measured after 1 week from the stimulation. Curiously, a meta-analysis recently published presented controversial results and reported no positive effect of the a-tDCS in NP after iSCI (Yu, Qiu, Li, Zhong, & Li, 2020).

Some studies have applied the a-tDCS at 2 mA paired with visual illusion in which individuals were in front of a mirror with projected legs simulating walking (Soler et al., 2010). Findings suggested the positive effects to reduce the perception of heat pain in rostral dermatomes at the level of injury (Kumru et al., 2013). However, the a-tDCS results in the NP must be observed with caution because are heterogeneous, based on nonstandardized protocols, and in a mixed sample (i.e., iSCI and cSCI).

Other a-tDCS outcomes

Some additional outcomes have been studied in the current researches with a-tDCS on iSCI individuals. Thibaut et al. (2017) applied five to 10 a-tDCS sessions at 2 mA to evaluate the quality of life, without significant results. Although the quality of life is a clinically relevant outcome impacted by the iSCI impairments, few studies aimed to observe this outcome. We highlight the need for future studies to provide evidence of a-tDCS effects on the quality of life.

Moreover, the autonomic nervous system (ANS) impairments due to immobility postinjury and physical inactivity (Serra-Añó et al., 2015) have been aimed by a few studies with a-tDCS after iSCI. Findings pointed to the positive a-tDCS effects on ANS. A heart rate variability modulation regardless of gender, type of injury, and time of injury was suggested and related to an increased CE and reduction on ANS dysfunctions (Da Silva et al., 2017). However, these results cannot be generalized for the entire iSCI population because they were carried out with a mixed sample.

Although in recent years the a-tDCS has been increasingly studied, there is still a shortage of studies, especially in some specific outcomes. To facilitate monitoring the development of studies with a-tDCS after iSCI, Table 2 summarizes some clinical trials in progress registered at clinicaltrials.gov or not yet published, which aims to assess motor and/or functional effects, reinforcing that this has been the main focus of research.

Characteristics of the iSCI individuals under a-tDCS protocols

The a-tDCS protocols for the rehabilitation should consider the profile of iSCI individuals (de Araújo et al., 2020). Studies presented samples with men, cervical or thoracic traumatic injuries, B and C injuries levels by the American Spinal Injury

TABLE 2 Clinical trials registered at clinicaltrials.gov in the year 2020.

Study Title	Register Number	Status	Sponsor	Experimental Intervention
Association Between tDCS and Lokomat Training in Patients with Incomplete Spinal Cord Injury	NCT02562001	Not recruiting	University of Sao Paulo General Hospital	tDCS during 20 min, before robotic device to gait training.
Combined Robotic Training and tDCS in Chronic SCI	NCT03555838	Completed (in 2019)	Burke Medical Research Institute	tDCS (2 mA) on M1 of the more affected arm, before robotic training.
Improving Spinal Cord Injury Rehabilitation Interventions by Retraining the Brain with Stimulation	NCT01539109	Completed (in 2020), a pilot study published	The Cleveland Clinic	tDCS (2 mA) during rehabilitation exercises of weak upper limbs.
Improving Hand Recovery with Neuromodulation in Tetraplegia	NCT03954496	Recruiting	University of Kentucky	tDCS during 20 min (2,5 mA) followed by intensive motor therapy of the more affected UE.
Improving SCI Rehabilitation Interventions by Retraining the Brain	NCT03892746	Recruiting	The Cleveland Clinic	tDCS (2 mA) to the motor cortex of the weaker upper limb during task-oriented practice.
Conditioning Neural Circuits to Improve UE Function	NCT02611375	Completed (in 2020)	Shepherd Center	tDCS (2 mA) over the hand area of the M1 while completing a functional task practice.

Data were based on the ongoing protocols published in the clinicaltrials.gov but not published in a scientific journal yet. Unpublished.
tDCS, transcranial direct current stimulation; *SCI*, spinal cord injury; *UE*, upper extremity; *M1*, primary motor cortex; *mA*, milliampere.

Association Scale (ASIA) as B and C, and chronic stage, predominantly. Table 3 summarizes the characteristics of the iSCI sample from the current evidence. It is noticed that the profile of iSCI individuals was similar to indicated by the epidemiological global data. Overall, previous studies excluded individuals with drug instability, progressive neurodegenerative disorders, concomitant neurological conditions, inability to cooperate, individuals with absolute contraindication to a-tDCS (i.e., history of epilepsy, metallic implants in the head, pacemaker, and pregnant women) (Li, Stampas, et al., 2018; Murray et al., 2015; Potter-Baker et al., 2018).

TABLE 3 Profile of the iSCI individuals in the a-tDCS protocols and paired therapies.

Study (year)	Outcomes	Sample with iSCI (iSCI plus cSCI)	iSCI characteristics			a-tDCS paired therapies
			Mean age	Injury level	Postinjury stage	
Soler et al. (2010)[a]	Neuropathic Pain	8 (39)	45	Cervical and thoracic	Chronic	Visual illusion
Kumru et al. (2013)[a]	Neuropathic Pain	30 (52)	49.4	Cervical and thoracic	Chronic	Visual illusion
Yoon et al. (2014)[a]	Neuropathic Pain	6 (16)	44.1	Cervical and thoracic	Chronic	None
Ngernyam et al. (2015)[a]	Neuropathic Pain	11 (20)	44.5	Cervical and thoracic	Chronic	None
Li, Stampas, Frontera, and Davis, (2018); Li, Fan, Yang, He, and Li, (2018)	Neuropathic Pain	12	43.4	Cervical and thoracic	Chronic	Breathing-controlled electrical stimulation

TABLE 3 Profile of the iSCI individuals in the a-tDCS protocols and paired therapies—cont'd

Study (year)	Outcomes	Sample with iSCI (iSCI plus cSCI)	iSCI characteristics			a-tDCS paired therapies
			Mean age	Injury level	Postinjury stage	
Soler et al. (2020)[a]	Neuropathic Pain	70 (130)	49	Cervical and thoracic	Chronic	Visual illusion
Thibaut et al. (2017)	Neuropathic Pain/ Quality of life	33	51.1	–	Chronic	None
Salmon et al. (2014)	Motor Function	2	46	Cervical	Chronic	Task-oriented UE training
Murray et al. (2015)	Cortical excitability	9	40.7	Cervical	Chronic	None
Kumru et al. (2016)	Motor Function/ Functionality	24	51.2	Cervical and thoracic	Acute	Gait training
Raithatha et al. (2016)	Motor Function/ Functionality	15	47.5	Cervical, thoracic, and lumbar	Chronic	Gait training
Yamaguchi et al. (2016)[a]	Motor Function/ Functionality	11 (21)	51.8	Cervical and thoracic	Chronic	Patterned Electrical Stimulation
Yozbatiran et al. (2016)	Motor Function/ Functionality	9	52.7	Cervical	Chronic	Robotic-Assisted Arm Training
Yozbatiran et al. (2017)	Motor Function/ Functionality	4	49.7	Cervical	Chronic	Robotic-Assisted Arm Training
Cortes et al. (2017)	Motor Function/ Functionality	11	44.9	Cervical	Chronic	None
Potter-Baker (2017, 2018)	Motor Function/ Functionality	8	53.5	Cervical	Chronic	Massed practice training
da Silva et al. (2017)	Autonomic modulation	18	32.9	Thoracic	Chronic	None

Data of age and injury level were based on the mean and percentage, respectively. Unpublished.
iSCI, incomplete spinal cord injury; *cSCI*, complete spinal cord injury; –, not available; *a-tDCS*, anodal transcranial direct current stimulation; *UE*, upper extremities.
[a]*Mixed sample (cSCI plus iSCI).*

Parameters of the a-tDCS after iSCI

Overall, the skin impedance level, neuropathological status, concomitant medications or therapies, and anatomical characteristics can be factors related to the resultant a-tDCS effect (Fregni et al., 2020). Besides that, the a-tDCS parameters such as intensity, current density, stimuli duration, number of sessions, targeted brain area, electrode size, and the electrode site should be planned to improve the effectiveness of the stimulation for a specific neurological condition.

The intensity of a-tDCS reaches a range of 1–2 mA. Although the relationship between a-tDCS parameters and mechanisms associated is not fully understood and not necessarily linear, there is evidence that the magnitude of excitability promoted by the a-tDCS is intensity-dependent (Cortes et al., 2017; Murray et al., 2015). Despite some protocols with 4 mA have been applied in human studies, none of these were applied after iSCI.

The electrode type used in a-tDCS presented a rubber composition involved in sponges soaked in saline. Overall, the electrode size ranges from 25 to 35 cm^2. Previous studies pointed to a relationship between the electrode size and the

current density. The ratio between electrode size and current density (mA/cm^2) should be carefully observed to guarantee the correct quantity of direct current reaching the neuronal circuits (Elsner, Kugler, Pohl, & Mehrholz, 2019; Fregni et al., 2020). The most frequent densities to the a-tDCS in iSCI range from 0.05–0.63 mA/cm^2 and studies showed that high densities were related to feelings of discomfort (Fregni et al., 2020).

Regarding the stimuli duration, some studies reported the negative effect of the prolonged a-tDCS in the CE, therefore, the maximum stimuli duration should be between 10 and 20 min when applied for more than one session or 20–40 min in the case of a single session (Truong & Bikson, 2018). None of the protocols applied in iSCI reached a duration above 20 min. Also, a-tDCS sessions were observed ranging from one to 36 sessions in the current protocols (de Araújo et al., 2020; Mehta et al., 2015). However, there is not a consensus about the more effective number of sessions.

The electrode site was pointed in a range of studies as a variable responsible to change the current flow. The brain target has been defined by the International 10/20 Electroencephalogram System to find the brain target area (Rich & Gillick, 2019). In the 10/20 system, the target brain areas are found from the location of four individual anatomical landmarks: (a) nasion (lower depression between the forehead and the nose); (b) inion (the lowest point of the skull at the back of the head) and (c) preauricular points of each ear (Rich & Gillick, 2019). In general, the brain areas most stimulated after iSCI were located on the M1 (Fig. 3).

In the a-tDCS, the anode should be placed in a target brain area, while the cathode is placed over the supraorbital region (i.e., bicephalic montage) or on the trapezius muscle (i.e., monocephalic montage) (Elsner et al., 2019; Truong & Bikson, 2018). Bicephalic montages have been used in most a-tDCS studies in iSCI. The electrode site should be maintained through a safety electrode fixation because small deviations in the position can lead to significant changes in the current density (Fregni et al., 2020). The a-tDCS parameters applied to iSCI individuals based on the current evidence are summarized in Table 1.

Short and long-term effects of the a-tDCS

a-tDCS short-term effects have been referred to as immediate effects or in an early period, whereas the long-term effects corresponded to a prolonged effect after stimulation. One recent systematic review aiming to investigate the a-tDCS effects on MF and functionality on iSCI reported a lack of studies with assessments of long-term effects (de Araújo et al., 2020). Similarly, a systematic review of the a-tDCS effects on NP found a lack of adequate follow-up to observe the long-term effects (Mehta et al., 2015). Thus, the current findings of a-tDCS effects after iSCI have been restricted to last up to 3 months.

Overall, the a-tDCS effects appear to be reinforced when paired with other therapies. A systematic review found that prolonged effects were associated with a-tDCS paired with conventional therapies (de Araújo et al., 2020). Besides that, improvements on proximal arm movement and a higher amount of use to upper extremities with a lasting effect of at least 2 months were observed after a-tDCS paired with Robotic-Assisted Arm Training (Yozbatiran et al., 2016, 2017). The paired a-tDCS and Patterned Electrical Stimulation induced a significantly higher number of ankle movements 20 min after the interventions (Yamaguchi et al., 2016). Whereas a-tDCS with massed practice shows a trend in improving the strength of muscles last up to 3 months (Potter-Baker et al., 2018). Similarly, a-tDCS paired with lower extremity training, a significant improvement was evident for both lower extremities and gait velocity for at least 1 month (Raithatha et al., 2016). On the other hand, Kumru et al. (2016) performed a similar protocol but did not obtain positive results in the same outcomes (see Table 3).

A-tDCS safety and adverse effects (AEs)

AEs can be classified as the level of severity in a range of grades. Grade 1 corresponds to AEs without the need for medical intervention. In grade 2, AEs need noninvasive medical intervention. On the other hand, AEs into grades 3 and 4 are defined as serious. In these occurs the need for hospitalization or prolonged hospitalization, or life risk, respectively. AEs with a higher grade are associated with an event that results in death (Antal et al., 2017).

No serious AEs (i.e., 3, 4, or higher grade) were reported in the current evidence about the a-tDCS after iSCI. The AEs most observed were mild with grade 1 such as tingling, burning sensation, discomfort, headache, and itching (Kumru et al., 2016; Lefaucheur et al., 2017; Murray et al., 2015; Ngernyam et al., 2015). Some studies reported mild headache, redness, fatigue, dizziness, mild skin irritation, and somnolence also (Fregni et al., 2020; Lefaucheur et al., 2017; Yozbatiran et al., 2016). The AEs were related to electrode positioning, preexisting skin conditions, high impedance, long durations, and repeated sessions, or indiscriminate home use.

Thus, additional care during a-tDCS needs to be taken. First, to avoid skin irritation, by contact of metal or conductive rubber with the skin, the thickness of the sponge must be controlled (Truong & Bikson, 2018). Second, to prevent increased impedance on the scalp the patient should be advised to avoid using skin and/or hair products on stimulation days (Fregni et al., 2020). Moreover, the correct skin preparation, use of a suitable electrode, nonapplication on sensitive skin regions, and instructions for the patient not to perform skin abrasion and to report any discomfort quickly can prevent the appearance of AEs (Antal et al., 2017; Lefaucheur et al., 2017). A study reported the interference of AEs in the adherence rate to the a-tDCS protocol (Carvalho et al., 2018). Thus, the care to avoid the occurrence of AEs is important for better adherence to treatment as well as the correct identification.

Clinical practice based on the a-tDCS

The current evidence highlights a-tDCS as a promising therapy to induce a change in the nervous system excitability and, consequently, neuroplasticity. In addition to the initial evidence of positive a-tDCS effects, their use has been reported by the ease of administration, possibility of self-application, and relatively low price. A meta-analysis suggests the significant a-tDCS effect on MF on iSCI individuals, but the limited number of studies included in the study makes it necessary to carry out future studies (de Araújo et al., 2020). Similarly, a recommendation of a level C of evidence to a-tDCS effects in the NP reduction was made (Lefaucheur et al., 2017). Despite being identified as a potential therapy, there are still some questions unanswered about the a-tDCS effects after iSCI. Currently, there are no bases to support or refute the use of stimulation in daily clinical practice.

Some aspects highlighted regarding the paths for future studies were: evaluation of the neurophysiological mechanisms of a-tDCS through neuroimaging; a consensus of the protocol parameters related to a better response in the iSCI; definition of the time postinjury, lesion level, and type of injury affecting the a-tDCS results; designing of studies to evaluate the long-term effects; greater sample size; a combination of a-tDCS with standard therapies (Cortes et al., 2017; de Araújo et al., 2020; Jamil et al., 2020); AEs, cost-effectiveness, adherence level and factors contributing to the retention of the individuals in the protocols (Carvalho et al., 2018; Kim, 2011). Similar to the a-tDCS, other interventions experimentally have shown initial results of effects after iSCI (See Table 4).

Applications to other areas of neuroscience

The anodal transcranial direct current stimulation has been applied in a range of neurological conditions. In addition to the previously reported outcomes, some studies have shown the effects of the stimulation on depression. Prevalence of depression after incomplete spinal cord injury has been high and, therefore, it is important to discuss the effects in these cases (Williams & Murray, 2015). Borrione, Moffa, Martin, Loo, and Brunoni (2018) showed improvements in the depressive symptoms after anodal transcranial direct current stimulation and probable effectiveness when the anode is positioned in the left dorsolateral prefrontal cortex.

Considering neurological conditions with similar involvement to incomplete spinal cord injury, the postpolio syndrome appears to respond positively to anodal transcranial direct current stimulation with a reduction in muscle fatigue and improvements in quality of life (Matsushima, Hachisuka, Itoh, Sugimoto, & Saeki, 2019). Moreover, in the stroke, previous studies have shown a moderate increase in cortical excitability, improvements in the motor function, mobility, and muscle strength promoting effective short-term motor performance poststimulation, but not in reducing upper extremity spasticity, walking speed, and muscle endurance (Elsner et al., 2019; Li, Fan, Yang, He, & Li, 2018). The stimulation to Parkinson's disease also over M1 resulted in immediate motor gains, better walking performance, and decreased time to perform movements of the upper limbs with a sustained effect for 3 months (Broeder et al., 2015).

Dictionary of terms

American Spinal Injury Association Scale: Standardized scale for the classification of spinal cord injury by assessing motor skills and sensitivity.
Autonomic nervous system: System controlling vegetative functions such as breathing, blood circulation, temperature control, and digestion.
Cortical excitability: Changes in the cortical neuronal activation by the reduction of the depolarization threshold.
Corticospinal tract: Tract with nerve fibers from the central nervous system to the spinal cord to controls muscles.

TABLE 4 Experimental interventions similar to a-tDCS used after iSCI.

Experimental modality	Characteristics of the intervention	Outcomes
Transcutaneous Spinal Direct Current Stimulation (tSCS)	Electrodes are placed over the spinal process and other electrodes are placed abdominally. The devices work with biphasic pulses. Abdominal electrodes work as an anode in the first and as a cathode in the second phase	Voluntary locomotor activity, motor or sensory function, and cortical excitability
Transcranial Magnetic Stimulation (TMS)	Electrical transcranial stimuli are delivered to induce changes in brain activity through single or repetitive pulses varying between <1 Hz and 20 Hz. A coil is frequently placed over a targeted brain area	Spasticity, motor, and sensory function
Theta-burst stimulation (iTBS)	The magnetic stimuli are applied through a circular coil over a brain area. Three stimuli at 50 Hz repeated at 200 ms intervals for 2 s were applied	Spasticity and motor function
Spinal Associative Stimulation (Peripheral nerve stimulation plus TMS)	TMS applied through a coil to the brain area paired with electrical stimulation delivered with surface bipolar electrodes at single 200 μs rectangular pulses	Spinal excitability
Deep Brain Stimulation	The invasive technique is applied by a microelectrode surgically. The microelectrode is implanted and connected to a pulse generator—generally located in the clavicle, similarly a pacemaker—to induce current to the tissue	Neuropathic Pain
Pelvic neuromodulation	The invasive technique in which electrodes are inserted into the third sacral foramina and are stimulated by an external pulse generator. The pulse generator can be implanted in the patient's buttock	Pelvic function and global health

Data were based on the studies with positive effects in individuals with iSCI published until 2020. Unpublished.
a-tDCS, transcranial direct current stimulation; *iSCI,* incomplete spinal cord injury.

Direct current: A current with a flow of electrons in a single direction through the presence of a potential difference, from the negative pole to the positive pole.
Functionality: Ability of the motor function to respond correctly and to generate movements to assist the activities of daily living.
Long-term potentiation: Persistent increasements in synaptic strength, making it more effective and lasting.
Motor Evoked Potential. Electrical response evoked in a muscle or motor nerve by electrical stimulation.
Motor function. Ability to learn or to demonstrate the skillful, maintenance, modification, and control of voluntary postures and movement patterns.
Neuroplasticity. Ability to the adaptation to the nervous system, as a result of repetitive activations.
Neuropathic Pain. Pain that occurs along the course or distribution of a peripheral nerve or sensitive nerves.

Key facts of anodal transcranial direct current stimulation

- Direct current was created before Christ. However, it was the creation of a voltaic battery in 1800, that made viable transcranial stimulation.
- The brain area to be stimulated must be chosen based on the International 10/20 Electroencephalogram System, which allows the stimulation of specific areas related to the function that is to be improved.
- When applied on the motor primary cortex, anodal transcranial direct current stimulation activates cortical neurons, descending motor circuits, and spinal neurons, which makes possible the use as a potential intervention to improve rehabilitation.
- Long-term potentiation induced by the anodal transcranial direct current has been identified as one of the most important mechanisms of neuroplasticity.
- Simultaneous application of anodal transcranial direct current stimulation and standard therapies appears to produce more intense and longer effects.

Summary points

- Motor and sensory function impairments after an incomplete spinal cord injury cause a reduction in the functionality and quality of life, which should be targeted by effective rehabilitation.
- Transcranial direct current stimulation uses a low-intensity direct current distributed to the brain through two electrodes, anode, and cathode.
- Current flow depends on the electrode site, in which anodal stimulation occurs from the anode to the cathode causing a depolarization threshold reduction in the neuronal membrane.
- Neurophysiological effects of the anodal transcranial direct current stimulation are related to the modulation of neuronal excitability and long-term effects linked to neuroplasticity.
- Anodal transcranial direct current stimulation protocol parameters must be planned considering the desired neurophysiological effects. Thus, frequency, intensity, electrode size, and position must be specific for a targeted outcome.
- Effects on the cortical excitability, neuroplasticity, motor function, or functionality, and chronic neuropathic pain appear to be a potential effective rehabilitation to reduce impairments after incomplete spinal cord injury.
- Future studies should observe the short-, medium-, and long-term effects potentially related to the anodal transcranial direct current stimulation to define the therapy value to clinical practice, cost-effectiveness, and adherence level.

References

Antal, A., Alekseichuk, I., Bikson, M., Brockmöller, J., Brunoni, A. R., Chen, R., … Paulus, W. (2017). Low intensity transcranial electric stimulation: Safety, ethical, legal regulatory, and application guidelines. *Clinical Neurophysiology*, *128*(9), 1774–1809. https://doi.org/10.1016/j.clinph.2017.06.001.

Borrione, L., Moffa, A. H., Martin, D., Loo, C. K., & Brunoni, A. R. (2018). Transcranial direct current stimulation in the acute depressive episode: A systematic review of current knowledge. *The Journal of ECT*, *34*(3), 153–163. https://doi.org/10.1097/YCT.0000000000000512.

Broeder, S., Nackaerts, E., Heremans, E., Vervoort, G., Meesen, R., Verheyden, G., & Nieuwboer, A. (2015). Transcranial direct current stimulation in Parkinson's disease: Neurophysiological mechanisms and behavioral effects. *Neuroscience and Biobehavioral Reviews*, *57*, 105–117. https://doi.org/10.1016/j.neubiorev.2015.08.010.

Bunday, K. L., & Perez, M. A. (2012). Motor recovery after spinal cord injury is enhanced by strengthening corticospinal synaptic transmission. *Current Biology*, *22*(24), 2355–2361. https://doi.org/10.1016/j.cub.2012.10.046.

Carmel, J. B., Berrol, L. J., Brus-Ramer, M., & Martin, J. H. (2010). Chronic electrical stimulation of the intact corticospinal system after unilateral injury restores skilled locomotor control and promotes spinal axon outgrowth. *Journal of Neuroscience*, *30*(32), 10918–10926. https://doi.org/10.1523/JNEUROSCI.1435-10.2010.

Carvalho, S., Leite, J., Jones, F., Morse, L. R., Zafonte, R., & Fregni, F. (2018). Study adherence in a tDCS longitudinal clinical trial with people with spinal cord injury. *Spinal Cord*, *56*(5), 502–508. https://doi.org/10.1038/s41393-017-0023-5.

Cortes, M., Medeiros, A. H., Gandhi, A., Lee, P., Krebs, H. I., Thickbroom, G., & Edwards, D. (2017). Improved grasp function with transcranial direct current stimulation in chronic spinal cord injury. *NeuroRehabilitation*, *41*(1), 51–59. https://doi.org/10.3233/NRE-171456.

Da Silva, F. T. G., Browne, R. A. V., Pinto, C. B., Saleh Velez, F. G., Do Egito, E. S. T., Do Rêgo, J. T. P., … Fregni, F. (2017). Transcranial direct current stimulation in individuals with spinal cord injury: Assessment of autonomic nervous system activity. *Restorative Neurology and Neuroscience*, *35*(2), 159–169. https://doi.org/10.3233/RNN-160685.

De Araújo, A. V. L., Ribeiro, F. P. G., Massetti, T., Potter-Baker, K. A., Cortes, M., Plow, E. B., … de Mello Monteiro, C. B. (2020). Effectiveness of anodal transcranial direct current stimulation to improve muscle strength and motor functionality after incomplete spinal cord injury: A systematic review and meta-analysis. *Spinal Cord*, *58*(6), 635–646. https://doi.org/10.1038/s41393-020-0438-2.

Elsner, B., Kugler, J., Pohl, M., & Mehrholz, J. (2019). Transcranial direct current stimulation (tDCS) for improving aphasia in adults with aphasia after stroke. *Cochrane Database of Systematic Reviews*, *2019*(5). https://doi.org/10.1002/14651858.CD009760.pub4.

Erb, W. H. (1883). *Handbook of electro-therapeutics. Vol. 27*. Retrieved from https://books.google.com.br/books/about/Handbook_of_Electro_Therapeutics.html?id=vf1DswEACAAJ&redir_esc=y.

Fawcett, J. W., Curt, A., Steeves, J. D., Coleman, W. P., Tuszynski, M. H., Lammertse, D., … Short, D. (2007). Guidelines for the conduct of clinical trials for spinal cord injury as developed by the ICCP panel: Spontaneous recovery after spinal cord injury and statistical power needed for therapeutic clinical trials. *Spinal Cord*, *45*(3), 190–205. https://doi.org/10.1038/sj.sc.3102007.

Fregni, F., El-Hagrassy, M. M., Pacheco-Barrios, K., Carvalho, S., Leite, J., Simis, M., … Brunoni, A. R. (2020). Evidence-based guidelines and secondary meta-analysis for the use of transcranial direct current stimulation (tDCS) in neurological and psychiatric disorders. *The International Journal of Neuropsychopharmacology*. https://doi.org/10.1093/ijnp/pyaa051.

Horvath, J. C., Vogrin, S. J., Carter, O., Cook, M. J., & Forte, J. D. (2016). Effects of a common transcranial direct current stimulation (tDCS) protocol on motor evoked potentials was found to be highly variable within individuals over 9 testing sessions. *Experimental Brain Research*, *234*(9), 2629–2642. https://doi.org/10.1007/s00221-016-4667-8.

Jamil, A., Batsikadze, G., Kuo, H., Meesen, R. L. J., Dechent, P., Paulus, W., & Nitsche, M. A. (2020). Current intensity- and polarity-specific online and aftereffects of transcranial direct current stimulation: An fMRI study. *Human Brain Mapping*, *41*(6), 1644–1666. https://doi.org/10.1002/hbm.24901.

Khorasanizadeh, M. H., Yousefifard, M., Eskian, M., Lu, Y., Chalangari, M., Harrop, J. S., … Rahimi-Movaghar, V. (2019). Neurological recovery following traumatic spinal cord injury: A systematic review and meta-analysis. *Journal of Neurosurgery: Spine*, *30*(5), 683–699. https://doi.org/10.3171/2018.10.SPINE18802.

Kim, Y. (2011). Missing data handling in chronic pain trials. *Journal of Biopharmaceutical Statistics*, *21*(2), 311–325. https://doi.org/10.1080/10543406.2011.550112.

Kumru, H., Murillo, N., Benito-Penalva, J., Tormos, J. M., & Vidal, J. (2016). Transcranial direct current stimulation is not effective in the motor strength and gait recovery following motor incomplete spinal cord injury during Lokomat® gait training. *Neuroscience Letters*, *620*, 143–147. https://doi.org/10.1016/j.neulet.2016.03.056.

Kumru, H., Soler, D., Vidal, J., Navarro, X., Tormos, J. M., Pascual-Leone, A., & Valls-Sole, J. (2013). The effects of transcranial direct current stimulation with visual illusion in neuropathic pain due to spinal cord injury: An evoked potentials and quantitative thermal testing study. *European Journal of Pain*, *17*(1), 55–66. https://doi.org/10.1002/j.1532-2149.2012.00167.x.

Lefaucheur, J. P., Antal, A., Ayache, S. S., Benninger, D. H., Brunelin, J., Cogiamanian, F., … Paulus, W. (2017). Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). *Clinical Neurophysiology*, *128*(1), 56–92. https://doi.org/10.1016/j.clinph.2016.10.087.

Li, S. (2013). Breathing-controlled Electrical Stimulation (BreEStim) for management of neuropathic pain and spasticity. *Journal of Visualized Experiments*, *71*. https://doi.org/10.3791/50077.

Li, Y., Fan, J., Yang, J., He, C., & Li, S. (2018). Effects of transcranial direct current stimulation on walking ability after stroke: A systematic review and meta-analysis. *Restorative Neurology and Neuroscience*, *36*(1), 59–71. https://doi.org/10.3233/RNN-170770.

Li, S., Stampas, A., Frontera, J., & Davis, M. (2018). Combined transcranial direct current stimulation and breathing-controlled electrical stimulation for management of neuropathic pain after spinal cord injury. *Journal of Rehabilitation Medicine*, *50*(9), 814–820. https://doi.org/10.2340/16501977-2379.

Lippold, O. C., & Redfearn, J. W. (1964). Mental changes resulting from the passage of small direct currents through the human brain. *The British Journal of Psychiatry: The Journal of Mental Science*, *110*, 768–772. https://doi.org/10.1192/bjp.110.469.768.

Martin, J. H. (2016). Harnessing neural activity to promote repair of the damaged corticospinal system after spinal cord injury. *Neural Regeneration Research*, *11*(9), 1389–1391. https://doi.org/10.4103/1673-5374.191199.

Matsushima, Y., Hachisuka, A., Itoh, H., Sugimoto, K., & Saeki, S. (2019). Safety and feasibility of transcranial direct current stimulation for patients with post-polio syndrome. *Brain Stimulation*, *12*(2), 431. https://doi.org/10.1016/j.brs.2018.12.396.

Mehta, S., Mcintyre, A., Guy, S., Teasell, R. W., & Loh, E. (2015). Effectiveness of transcranial direct current stimulation for the management of neuropathic pain after spinal cord injury: A meta-analysis. *Spinal Cord*, *53*, 780–785. https://doi.org/10.1038/sc.2015.118.

Murray, L. M., Edwards, D. J., Ruffini, G., Labar, D., Stampas, A., Pascual-Leone, A., & Cortes, M. (2015). Intensity dependent effects of transcranial direct current stimulation on corticospinal excitability in chronic spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *96*(4), S114–S121. https://doi.org/10.1016/j.apmr.2014.11.004.

Ngernyam, N., Jensen, M. P., Arayawichanon, P., Auvichayapat, N., Tiamkao, S., Janjarasjitt, S., … Auvichayapat, P. (2015). The effects of transcranial direct current stimulation in patients with neuropathic pain from spinal cord injury. *Clinical Neurophysiology*, *126*(2), 382–390. https://doi.org/10.1016/j.clinph.2014.05.034.

Nitsche, M. A., & Paulus, W. (2000). Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *Journal of Physiology*, *527*(3), 633–639. https://doi.org/10.1111/j.1469-7793.2000.t01-1-00633.x.

Podda, M. V., Cocco, S., Mastrodonato, A., Fusco, S., Leone, L., Barbati, S. A., … Grassi, C. (2016). Anodal transcranial direct current stimulation boosts synaptic plasticity and memory in mice via epigenetic regulation of Bdnf expression. *Scientific Reports*, *6*(1), 1–19. https://doi.org/10.1038/srep22180.

Potter-Baker, K. A., et al. (2017). Transcranial direct current stimulation (tDCS) paired with massed practice training to promote adaptive plasticity and motor recovery in chronic incomplete tetraplegia: A pilot study. *Journal of Spinal Cord Medicine*, *41*(5), 503–517. https://doi.org/10.1080/10790268.2017.1361562.

Potter-Baker, K. A., et al. (2018). Variability of motor evoked potentials in stroke explained by corticospinal pathway integrity. *Brain Stimulation*, *11*(4).

Raithatha, R., Carrico, C., Powell, E. S., Westgate, P. M., Chelette, K. C., Lee, K., … Sawaki, L. (2016). Non-invasive brain stimulation and robot-assisted gait training after incomplete spinal cord injury: A randomized pilot study. *NeuroRehabilitation*, *38*(1), 15–25. https://doi.org/10.3233/NRE-151291.

Renga, V. (2020). Electricity, neurology, and noninvasive brain stimulation: Looking back, looking ahead. *Neurology Research International*. https://doi.org/10.1155/2020/5260820.

Rich, T. L., & Gillick, B. T. (2019). Electrode placement in transcranial direct current stimulation—How reliable is the determination of C3/C4? *Brain Sciences*, *9*(3). https://doi.org/10.3390/brainsci9030069.

Salmon, E., Carrico, C., Nichols, L., Reddy, L., Salles, S., & Sawaki, L. (2014). Transcranial direct current stimulation to enhance motor function in spinal cord injury: Pilot data. In *Vol. 2014. 2014 IEEE 16th international conference on E-health networking, applications and services* (pp. 1–6). Healthcom. https://doi.org/10.1109/HealthCom.2014.7001804.

Sarmiento, C. I., San-Juan, D., & Prasath, V. B. S. (2016). Letter to the Editor: Brief history of transcranial direct current stimulation (tDCS): From electric fishes to microcontrollers. *Psychological Medicine*, *46*, 3259–3261. https://doi.org/10.1017/S0033291716001926.

Serra-Añó, P., Montesinos, L. L., Morales, J., López-Bueno, L., Gomis, M., García-Massó, X., & González, L. M. (2015). Heart rate variability in individuals with thoracic spinal cord injury. *Spinal Cord*, *53*(1), 59–63. https://doi.org/10.1038/sc.2014.207.

Soler, M. D., Kumru, H., Pelayo, R., Vidal, J., Tormos, J. M., Fregni, F., … Pascual-Leone, A. (2010). Effectiveness of transcranial direct current stimulation and visual illusion on neuropathic pain in spinal cord injury. *Brain*, *133*(9), 2565–2577. https://doi.org/10.1093/brain/awq184.

Soler, D., Moriña, D., Kumru, H., Vidal, J., & Navarro, X. (2020). Transcranial direct current stimulation and visual illusion effect according to sensory phenotypes in patients with spinal cord injury and neuropathic pain. *The Journal of Pain*. https://doi.org/10.1016/j.jpain.2020.06.004.

Thibaut, A., Carvalho, S., Morse, L. R., Zafonte, R., & Fregni, F. (2017). Delayed pain decrease following M1 tDCS in spinal cord injury: A randomized controlled clinical trial. *Neuroscience Letters*, *658*, 19–26. https://doi.org/10.1016/j.neulet.2017.08.024.

Treede, R. D., Jensen, T. S., Campbell, J. N., Cruccu, G., Dostrovsky, J. O., Griffin, J. W., … Serra, J. (2008). Neuropathic pain: Redefinition and a grading system for clinical and research purposes. *Neurology*, *70*(18), 1630–1635. https://doi.org/10.1212/01.wnl.0000282763.29778.59.

Truong, D. Q., & Bikson, M. (2018). Physics of transcranial direct current stimulation devices and their history. *The Journal of ECT*, *34*(3), 137–143. https://doi.org/10.1097/YCT.0000000000000531.

Williams, R., & Murray, A. (2015). Prevalence of depression after spinal cord injury: A meta-analysis. *Archives of Physical Medicine and Rehabilitation*, *96*(1), 133–140. https://doi.org/10.1016/j.apmr.2014.08.016.

Yamaguchi, T., Fujiwara, T., Tsai, Y. A., Tang, S. C., Kawakami, M., Mizuno, K., … Liu, M. (2016). The effects of anodal transcranial direct current stimulation and patterned electrical stimulation on spinal inhibitory interneurons and motor function in patients with spinal cord injury. *Experimental Brain Research*, *234*(6), 1469–1478. https://doi.org/10.1007/s00221-016-4561-4.

Yoon, E. J., Kim, Y. K., Kim, H. R., Kim, S. E., Lee, Y., & Shin, H. I. (2014). Transcranial direct current stimulation to lessen neuropathic pain after spinal cord injury: A mechanistic PET study. *Neurorehabilitation and Neural Repair*, *28*(3), 250–259. https://doi.org/10.1177/1545968313507632.

Yozbatiran, N., Keser, Z., Davis, M., Stampas, A., O'Malley, M. K., Cooper-Hay, C., … Francisco, G. E. (2016). Transcranial direct current stimulation (tDCS) of the primary motor cortex and robot-assisted arm training in chronic incomplete cervical spinal cord injury: A proof of concept sham-randomized clinical study. *NeuroRehabilitation*, *39*(3), 401–411. https://doi.org/10.3233/NRE-161371.

Yozbatiran, N., Keser, Z., Hasan, K., Stampas, A., Korupolu, R., Kim, S., … Francisco, G. E. (2017). White matter changes in corticospinal tract associated with improvement in arm and hand functions in incomplete cervical spinal cord injury: Pilot case series. *Spinal Cord Series And Cases*, *3*(1), 1–5. https://doi.org/10.1038/scsandc.2017.28.

Yu, B., Qiu, H., Li, J., Zhong, C., & Li, J. (2020). Noninvasive brain stimulation does not improve neuropathic pain in individuals with spinal cord injury: Evidence from a meta-analysis of 11 randomized controlled trials. *American Journal of Physical Medicine and Rehabilitation*, *99*(9), 811–820. https://doi.org/10.1097/PHM.0000000000001421.

Further reading

Kashiwagi, F. T., El Dib, R., Gomaa, H., Gawish, N., Suzumura, E. A., Da Silva, T. R., … Bazan, R. (2018). Noninvasive brain stimulations for unilateral spatial neglect after stroke: A systematic review and meta-analysis of randomized and nonrandomized controlled trials. *Neural Plasticity*, *2018*. https://doi.org/10.1155/2018/1638763.

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Chapter 5

Neuromodulation and restoration of motor responses after severe spinal cord injury

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List of abbreviations

CNS	central nervous system
CPGs	central pattern generators
ILS	infralesional segment
IM	injured metamere
MRI	magnetic resonance imaging
NMES	neuromuscular electrical stimulation
SLSs	supralesional segments
TSS	transcutaneous spinal stimulation

Neuromodulation exploits intrinsic information processing

The term neuromodulation refers to any intervention that affects the strength of the information transfer within a neuronal circuit. Neuromodulation is also defined as a physiological processing of synaptic input that is sustained by endogenous chemicals, named neuromodulators, which activate metabotropic receptors, that in turn determine a cascade of molecules within the cell. Chemical neuromodulators target the membrane, the cytoplasm or the nucleus, and can, in turn, affect network excitability through both gene expression and plastic synaptic events (Marder, O'Leary, & Shruti, 2014). The importance of chemical neuromodulators in regulating neuronal transmission is largely exploited for pharmacotherapy, as confirmed by the wide range of pharmacological agents available to activate metabotropic receptors, ranking among the most represented classes of drugs available.

Similar modulatory actions can also be achieved through several physical forces supplied to the neuronal networks, in the form of mechanical, magnetic, and electrical pulses.

In particular, the intensity of electrical pulses can be strong enough to directly trigger an action potential in excitable cells, thus generating a stereotyped response (also called reflex) to each delivered input. In this case, we refer to the term of **electrical stimulation**. For instance, electrical stimulation of the limb surface is used in clinics to depolarize motor end-plates and elicit passive contractions for functional purposes (recently reviewed by Günter, Delbeke, & Ortiz-Catalan, 2019) and even to directly activate paralyzed muscles after denervation (recently reviewed by Kern & Carraro, 2020). Repetitive electrical stimulation has been applied to the spinal cord of spinalized animals to evoke the patterned sequence of activation of multiple muscles, enabling the automatic execution of rhythmic and coordinated motor tasks. Each task, e.g., stepping, corresponds to a defined rhythmic motor program that is driven by the activity of a remarkable ensemble of spinal neurons, named **central pattern generators** (CPGs, Kiehn, 2006). In particular, locomotor CPGs are responsible for the expression of rhythmic electrical discharges, alternating among pools of motoneurons, even in the absence of any input from either the supraspinal centres or sensory feedback from the periphery (Fig. 1).

Cellular, Molecular, Physiological, and Behavioral Aspects of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822427-4.00005-8

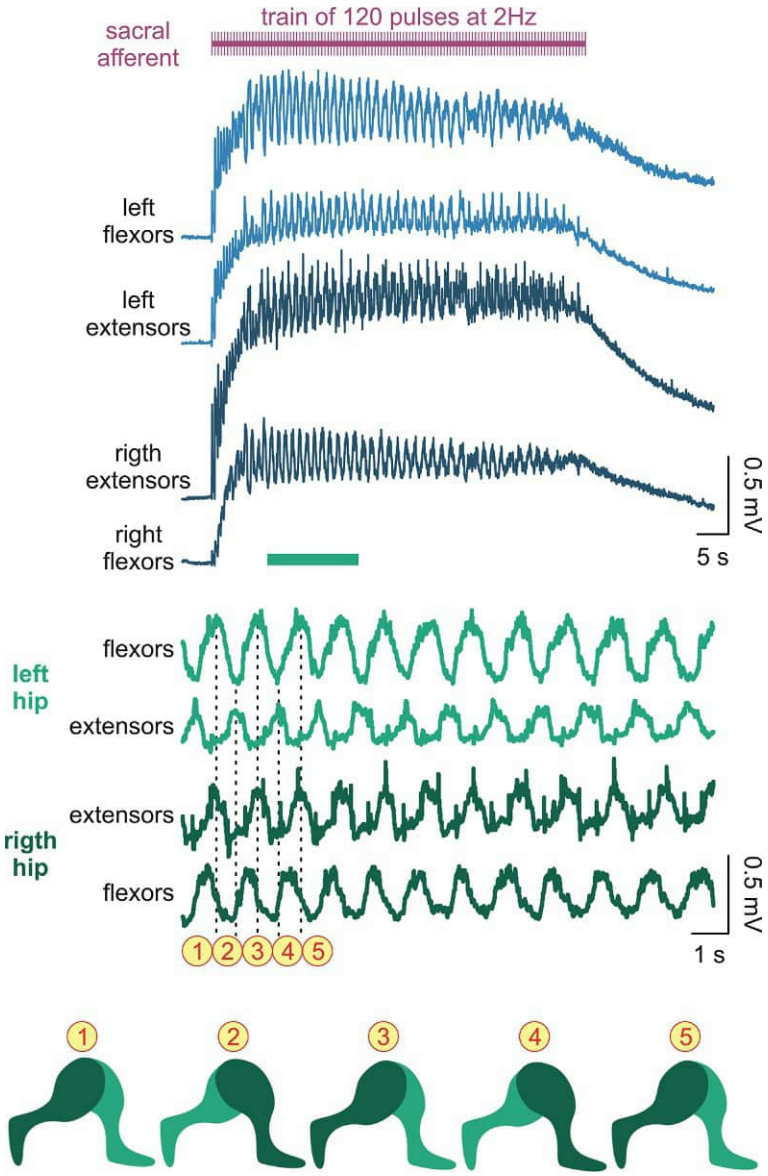

FIG. 1 Spinal central pattern generators for locomotion rhythmically drive the coordinated pattern of activation of motor pools during the locomotor program. A convincing proof of the existence of central pattern generators for locomotion comes from the isolated spinal cord of a neonatal rat, where an episode of rhythmic patterns is elicited in response to a nonpatterned stereotyped train of electrical pulses (120 stimuli at 2 Hz) applied to a single sacral afferent. The electrical activity of hip flexor and extensor motor pools is extracellularly derived from bilateral lumbar (L)2 and L5 ventral roots, respectively. A distinct feature of this locomotor-like episode is the appearance of a cumulative depolarization with superimposed rhythmic discharges that alternate between the two sides of the cord and between flexor- and extensor-related motor pools. The schematic representation at the bottom of the page visualizes how electrical oscillations derived from the motor pools of the neonatal cord in vitro correspond to the different phases of real gait (unpublished observations by GT).

Locomotor CPGs have finally been experimentally established in humans and electrical stimulation of the spinal cord generates episodes of coordinated EMG signals in lower limbs. However, this motor pattern alone was insufficient to enable persons with SCI to deambulate overground. Although electrical stimulation failed to recover automatic functional stepping in paraplegics, it has been shown to facilitate limited volitional motor control of paralyzed limbs, such as an increased volitional control of limb movement in the absence of load (Angeli et al., 2018; Gill et al., 2018, Harkema et al., 2011) and thereby has been proposed as a new rehabilitative practice termed **electrical neuromodulation**.

As opposed to electrical stimulation, electrical neuromodulation does not directly activate motoneurons. Rather, electrical neuromodulation modifies the probability for cells in spinal circuits to reach the threshold for triggering an action potential in response to any upcoming synaptic input. Thus, the spinal cord is more prone to integrate all afferent and propriospinal input with any spared descending commands.

For decades, spinal neuromodulation has been used to limit pain transmission, exploiting physiological gates that regulate pulse conduction along spinal *ascending* tracts (Shealy, Mortimer, & Reswick, 1967). It is noteworthy that a similar technique and the same implanted hardware at the dorsal spinal cord surface are used to generate the two opposite outcomes of pain inhibition vs motor recovery. In particular, the inhibition of pain tracts or, alternatively, the facilitation of motor

pathways, are obtained by varying the paradigms (mostly frequency) of trains of electrical pulses, without however significantly modifying the location of epidural electrodes on the spinal cord. Indeed, while high frequency is delivered for alleviating pain (above 100 Hz), 20–40 Hz have been traditionally supplied to facilitate the excitability of motor circuitry and improve volitional motor control. It could thus be inferred that pain and locomotion are both controlled by a group of cells with distinct membrane properties, which show a different responsivity to repetitive pulses delivered at different frequencies (Michelson, Eles, Vazquez, Ludwig, & Kozai, 2019).

Furthermore, when similar paradigms of stimulation are applied to adjacent sites of the spinal cord, multiple outcomes can be obtained. For example, identical electrical paradigms applied with similar electrode locations can modulate seemingly disparate modalities including muscular spasticity (Hofstoetter et al., 2019), bladder functions (Sysoev et al., 2020), standing posture (Sayenko et al., 2019), and volitional stepping activity (Gill et al., 2018). Likely, spinal networks responsible for these tasks are not strictly compartmentalized in the spinal cord, but are in fact largely overlapping. This interconnection can even represent a hurdle in the sequenced restoration of multiple functional deficits after a SCI represented by the challenge of conferring selectivity to electrical neuromodulation to evoke only distinct outcomes (e.g., locomotion or upright standing without micturition). On the other hand, this overlap in the function and structure of spinal networks can also be beneficial. Indeed, once properly targeted, the overlap can lead to a single therapeutic intervention, which can thus yield multiple clinical and functional outcomes and restore both somatosensory and autonomic functions.

A residual functional potential remains after SCI

The changes occurring following an SCI include the structural and functional reorganization of the CNS (Dimitrijevic, McKay, & Sherwood, 1997). These changes result from altered post-SCI motor and sensory control. In this new setting, the supralesional segments (SLSs) of the spinal cord sustain voluntary motor control, sensation and autonomic functions. However, sensory, motor, metabolic and autonomic system deprivation does occur at the injured metamere (IM) where the first impact occurred, as well as in the neighboring spinal cord or infralesional segment (ILS). Muscles corresponding to the IM may become denervated and atrophic. IM and ILS descending and ascending axonal tracts may be interrupted, although the circumferential white matter is often spared. In addition, at the IM, surviving local terminals derived from a different set of inputs can spontaneously form new synapses (Raisman, 1969). Although long debated, it is now clear that this type of synapse and circuit reorganization occurs spontaneously after all forms of CNS injury, including SCI, and that it can be associated with either adaptive or maladaptive functional changes. For instance, spontaneous synapse turnover and circuit reorganization can lead to maladaptive consequences, such as **spasticity** (Roy & Edgerton, 2012), **autonomic dysreflexia** (Hou & Rabchevsky, 2014), or **neuropathic pain** (Kramer et al., 2017; Tan & Waxman, 2012). In other cases, spontaneous circuit reorganization can be adaptive, supporting the restoration of function after incomplete SCI (i.e., **Brown Sequard Syndrome**), in spite of the permanent loss of descending supraspinal connections on the injured side (Ballermann & Fouad, 2006; Bareyre et al., 2004; Courtine et al., 2008; Filli, Zorner, Weinmann, & Schwab, 2011; Little & Halar, 1985; Rosenzweig et al., 2010). On the other hand, even at SLS, SCI leads to the death of cells, including neurons, oligodendrocytes, astrocytes, and precursor cells (Horky, Galimi, Gage, &, Horner, 2006) that can be compensated by various forms of cortical, brainstem, and spinal plasticity contributing to functional recovery (Raineteau & Schwab, 2001; Weidner, Ner, Salimi, & Tuszynski, 2001).

Central nervous system reorganization after SCI

The central nervous system of individuals with SCI is susceptible to substantial reorganization as cortical, subcortical, and much of the local spinal cord circuitry remain largely intact and partially interconnected through unlesioned nerve fibres (Kakulas, 1984; Raineteau & Schwab, 2001; Sherwood, Dimitrijevic, & Barry McKay, 1992). Although any of various adaptive reorganizations can contribute to the recovery of motor control, the role of cortical, as well as corticospinal reconfigurations seem to be crucial and potentially the most impactful among the mechanisms associated with the regaining of voluntary function.

Continuous cortical reorganization occurs during sensorimotor learning (Holtmaat & Svoboda, 2009) and is also commonly observed in humans after SCI, although it becomes particularly extreme after injuries that lead to massive deafferentation (Endo, Spenger, Tominaga, Brene, & Olson, 2007; Ghosh et al., 2010; Jain, Catania, & Kaas, 1997; Kokotilo, Eng, & Curt, 2009; Moxon, Oliviero, Aguilar, & Foffani, 2014). In particular, the decrease in the integrity of the corticospinal tract and in the volume of cortical gray matter is directly correlated to **spinal cord atrophy** (Freund et al., 2012; Freund, Curt, Friston, & Thompson, 2013), suggesting that trauma-induced spinal degenerative processes spread all the way to the brain. Human magnetic resonance imaging (MRI) studies confirm that SCI can cause progressive reduction in gray matter

volume, not only in the sensorimotor cortex, but also in brain regions not directly connected to spinal circuitry (Nicotra, Critchley, Mathias, & Dolan, 2005; Wrigley et al., 2008). Mapping studies with transcranial magnetic stimulation (TMS) and functional MRI reveal an enlargement of cortical sensorimotor areas that represent muscles preserved above the level of injury in individuals with quadriplegia (Kokotilo et al., 2009), as well as an enhanced excitability of motor pathways targeting muscles rostral to the level of a spinal lesion in persons with paraplegia (Topka, Cohen, Cole, & Hallett, 1991). In nonhuman primates, it has been shown that after complete cervical dorsal column transection, neurons in the deafferented contralateral primary somatosensory cortex become initially unresponsive to stimulation of the hand followed by innervation of cortical representation of the face (Jain, Qi, Collins, & Kaas, 2008). This is an example of how the cortical reorganization after a dorsal column transection is not limited to the primary somatosensory cortex, but also extends to the secondary somatosensory cortex and to the parietal ventral area (Kokotilo et al., 2009). From a translational viewpoint, the complexity of these interactions highlights the importance to better understand the anatomical level and degree of transection of spared pathways with the goal of designing approaches that minimize maladaptive plasticity and maximize functional recovery after SCI. Despite the heterogeneity in residual motor functions associated with human SCIs, little has been done so far to investigate the function undertaken by each specific neural structures after injury. It seems imperative to adopt training approaches aimed at reversing maladaptive **cortical remapping** when defining training programs for the recovery of voluntary motor control. The fact that the regaining of voluntary motor control can occur within a few sessions, and prior to repetitive training sessions (Angeli, Edgerton, Gerasimenko, & Harkema, 2014), indicates that the cortex is highly plastic and prepared for a "good" reorganization even months or years after an SCI.

Mechanisms of spinal neuromodulation

It is widely assumed that the mechanisms of spinal neuromodulation consist of reactivating dormant connections by mimicking afferent (mainly proprioceptive) input through the electrical activation of Aβ-fibres that are located in dorsal roots and represent low-threshold afferents characterized by a large diameter, high myelination and ability for rapid signal conduction (Holsheimer, 2002). Starting from this broad definition, some clarifications must be introduced to gain a better understanding of neuromodulation.

A first clarification must be made around the idea of *dormant* connections. Indeed, the activation of dormant connections would require the presence of **silent synapses**, which have not yet been reported in the spinal cord after injury. Indeed, silent synapses have been clearly identified so far in the hippocampus (Voronin & Cherubini, 2004), as a functional reserve of synapses that, at rest, are not engaged in information transfer but can be converted in functional ones, for example, in response to plastic events driven by a lesion (Zhang et al., 2018).

Second, although Aβ-fibres are inevitably activated by spinal neuromodulation due to their low threshold of activation, a selective stimulation of Aβ-fibbers in dorsal roots is likewise improbable. Indeed, the amount of current operatively applied to recover volitional control recruits many more types of dorsal root fibbers and passes across several spinal segments (Swiontek et al., 1976) that are populated by a myriad of excitable targets. As a result, spinal neuromodulation likely generates higher neuronal excitability, faster pulse conduction through axons, and an increased synaptic release with profound changes in the chemical composition of the extracellular fluid.

In spinal networks, the mechanism of neuromodulation can be mainly ascribed to the facilitation of the presynaptic input (Eccles, Kostyuk, & Schmidt, 1962) from peripheral afferents and from the cortical tracts spared by the lesion. Indeed, due to neuromodulation, network synapses depolarize and approach the threshold for activating calcium channels, in turn increasing the probability for any presynaptic input to activate neurotransmitter release onto postsynaptic targets. Moreover, for neuromodulation to be effective in allowing functional recovery after SCI, the presynaptic action requires that some functional synapses are spared by the injury and can be recruited in the presence of neuromodulation by the volitional attempt to move paralyzed limbs (Taccola, Sayenko, Gad, Gerasimenko, & Edgerton, 2018). Notably, strong electrical pulses can directly depolarize the resting membrane potential of postsynaptic targets (i.e., motoneurons and their axons), without recruiting any interneuronal circuitry, and thus lead to massive muscle activation. These stereotyped muscle responses rely on motoneuronal integrity, even in case of a large loss of premotoneuronal interneurons.

Fibre regeneration and sprouting of new synapses are both able to circumvent the interruption of descending tracts at the site of the lesion, and have been reported as the main mechanisms supporting functional recovery after SCI (Courtine et al., 2008). Indeed, functional anatomical changes are a consequence of activity-dependent plasticity triggered by repetitive sessions of neuromodulation, especially when associated with physical rehabilitation (Jack, Hurd, Martin, & Fouad, 2020). However, clinical benefits of neuromodulation have been reported as early as after one session (Gill et al., 2018), a time span theoretically too short to be accounted for by significant fibre remodeling but potentially indicating an acute functional reconfiguration of spared pathways including physiological or molecular changes to synaptic efficacy.

For the above-mentioned reasons, the present authors find it more rigorous to define electrical neuromodulation for the restoration of volitional motor control after a severe injury as a physical perturbation of many excitable structures in the spinal cord. As a result, neuromodulation profoundly affects the performance and organization of spared elements in injured networks by bringing them to a new homeostasis that, even if not necessarily physiological, is functionally beneficial for the expression of certain motor functions.

It is however questionable whether neuromodulation could generate a novel physiological state in spinal networks. For example, it is still to be demonstrated whether neuromodulation could also improve motor performances in neurologically intact subjects, thereby indicating potential to exploit the supraphysiological functionality of spinal networks.

Nevertheless, the broad activation of multiple neural structures during electrical neuromodulation might indeed alter the balance of injured networks by activating multiple plastic and compensatory events that, in sum, result in practical benefits for accomplishing the impaired motor tasks. A similar phenomenon, called **metaplasticity,** has been described for the conditioning of muscle reflexes elicited by repetitive electrical stimulation of peripheral nerves (Wolpaw, 2018).

Similar to the scrambling of pain fibre signals, also neuromodulation, at least when used acutely, likely "scrambles" the nonfunctional and aberrant motor patterns resulting from the injury, instead of adding new and previously missing sources of motor signals (Marineo, 2019).

The ideal candidate for the restoration of volitional motor responses through neuromodulation

Following the above interpretation, neuromodulation can be advantageous as long as at least some neural connections remain across the lesion. In this regard, Dimitrijevic et al. (Sherwood et al., 1992) have demonstrated that some individuals with a complete SCI are still capable of subclinical motor control below the level of injury and may even regain mastery of controlled movement when the spinal cord is appropriately stimulated. Neurophysiological evidence of subclinical brain influence on spinal cord function below the lesion has been found in "so-called" clinically **discomplete SCIs** (Sherwood et al., 1992). People with a discomplete SCI syndrome may have similar motor patterns in terms of brain control and/or the presence of subclinical motor activity as persons with incomplete SCIs (Tang, Tuel, McKay, & Dimitrijevic, 1994). A predictive neurophysiological assessment for the functional outcome of individuals with SCI is thus essential before defining any treatment to promote recovery (Tansey, 2012).

However, current diagnostic tools do not explicitly define the completeness of a SCI resulting in a rationale to test neuromodulation on the vast majority of persons with clinically diagnosed complete lesions in addition to those that maintain some residual anatomical connection.

A more sensitive surface EMG recording technology (Campanini, Disselhorst-Klug, Rymer, & Merletti, 2020), together with more detailed and advanced tools of spinal imaging (Kaushal, Shabani, Budde, & Kurpad, 2019), would clarify what extent of spared pathways is required to selectively address the benefits of neuromodulating therapies. Thus, the ideal candidate for the restoration of volitional motor responses using neuromodulation after a severe SCI, should be a subject with an incomplete and/or discomplete SCI, with minimal musculoskeletal atrophy below the level of injury, minimal joint limitations, and good trunk stability, as well as good cardiovascular reflex responses, cognitive and emotional stability, and strong motivation.

Neuromuscular electrical stimulation for the recovery of independent stepping

Neuromuscular electrical stimulation (NMES) has been intensively investigated in the 1980s (Cybulski, Penn, & Jaeger, 1984) with the intent to bypass the lesioned area by electrically stimulating certain paralyzed peripheral nerves, to regain some "artificial" motor control, recondition paralyzed limbs to muscle fatigue, reactivate the paralyzed muscle pump, and condition the cardiopulmonary and circulatory systems through muscle stimulation in nondenervated subjects with SCI. The Parastep walking NMES system, designed in Dr. Graupe's lab in Chicago, was the first system created for independent indoor and outdoor walking for persons with complete and nearly complete SCI at thoracic level (T1 to T12), having no motor function nor sensation below the lesion.

At the same time, allowing individuals with a complete SCI to stand and/or walk by means of NMES is a puzzle building procedure. Indeed, it allows, and increases over time, proper body alignment and functional range of motion, muscle strength, physiological cardio-pulmonary responses, and proper integration of the NMES activity with the body as a whole. The training methodology with Parastep was not univocal, so initially every rehabilitation centre came up with its own procedure to train Parastep users in walking. Cost and convenience were obviously an important factor. Hence, training

was attempted for a short period of time, but the overall walking performance was not good enough to sustain its use for functional walking for the vast majority of individuals with SCI.

Parastep users were trained to stand and walk against gravity only after participating in a well-structured task-oriented rehabilitation program. The program consisted in a multistep methodology (Fig. 2) aimed at: (1) strengthening upper body muscles and conditioning the cardio-pulmonary and circulatory system; (2) maintaining lower extremities within a functional range of motion for standing and walking; (3) reversing muscle atrophy, stopping muscle degeneration and increasing muscle force and endurance both through NMES and associated training that includes repetitive (and increasing) weight-lifting, kinematic exercise equipment and NMES cycling equipment; (4) learning to walk through a task-oriented-approach; (5) repetitive standing/walking exercise initially on a flat surface, followed by training on a treadmill; and (6) only then, progressing toward walking on diverse terrain surfaces (slope or obstacles, including stairs) and to building up confidence

E

Subjects	Height (m)	Weight (Kg)	SPWS (m/min)	**Work rate (watt)**
Parastep® (n = 5)	1.70 ± 0.04	63 ± 6.3	18.40 ± 0.89	**311.8 ± 62**
Controls (n = 5)	1.79 ± 0.09	75.2 ± 14	16.30 ± 2.30	**303.0 ± 51**

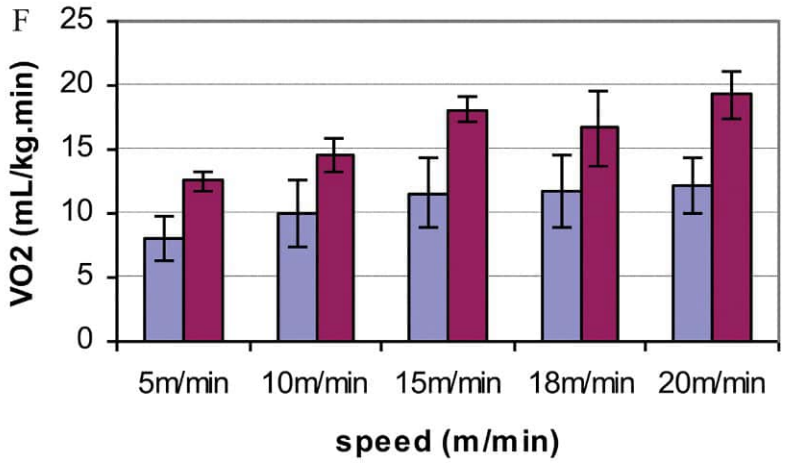

FIG. 2 Neuromuscular electrical stimulation (NMES) in persons with complete spinal cord injuries (SCIs). Training methodology with Parastep for the recovery of independent stepping in persons with complete SCIs at thoracic-level. The protocol progresses along several sessions, starting from repetitive standing exercises to improve trunk control and body re-alignment (A), strengthening leg muscles with NMES + cycling (B), walking initially over a controlled environment (C) and only then, progressing toward autonomously walking overground, showing the integration of electrically induced motor limb movements. (D) Characteristics of 10 research subjects (5 SCI + NMES; 5 able body controls) showing similar biomechanics and self-preferred walking speeds (SPWS). Although complete paralysis, the organism's work rate expressed during walking with NMES is equal to a physiological one. (E) Benefits of gait with NMES over traditional reciprocal gait orthosis on the cardio-pulmonary and circulatory systems is reported as volume of oxygen (VO_2) consumption per mL/Kg at different walking speeds (F). Ventilatory responses expressed during NMES trials ($n = 5$, *dark purple*) were higher than those pertaining to the group using traditional reciprocal gait orthosis ($n = 5$, *light purple*). Differences were statistically significant at $P \leq 0.01$ (unpublished observations by HACB).

in walking in the absence of direct feedback sensation from the NMES stimulated paralyzed limbs (Carmick, 1993; Graupe & Bazo, 2015; Waters, 1984). The methodology facilitated the physiological trunk posture and hip extension, properly integrating body systems above and below the level of injury to load or unload, to maximize the goal-oriented task of standing, balancing, and walking. The sequencing and timing of the movement thus became automatic, shifting from direct visual control to a more internalized form of control.

Rationale for combining NMES with other neuromodulation modalities

In individuals with a discomplete SCI, the NMES training methodology promoted sensorimotor integration and regaining of voluntary motor control for intentional cycling and/or walking. In individuals with a complete SCI, NMES promoted secure step, trunk control, and body re-alignment, showing the integration of electrically induced motor limb movements with SLS postural and voluntary motor control activity. It can be concluded that NMES can facilitate spinal integration of sensory afferent feedback coming from SLS and ILS to improve walking performance after SCI.

In summary, NMES can activate paralyzed muscles, although its use may present several disadvantages: (1) many of the key muscles lie deep in the legs and trunk and are not accessible with surface electrodes; (2) even with the percutaneous implantation system, multiple channels are required to stimulate all muscles; (3) peripheral neuromuscular stimulation inevitably results in significant fatigue because this stimulation paradigm recruits the fastest and most fatigable fibres first; and (4) complex motor tasks, such as standing and stepping, may require coordination by an external computer-controlled closed-loop system, when the body's position and velocity are continually monitored, and the level of stimulation is adjusted accordingly on a moment-to-moment basis (Ho et al., 2014). Therefore, while noninvasive NMES is preferred for therapeutic purposes, individual responses to this technique are generally not strong enough for individuals with SCI to regain sufficient motor functioning. Indeed, while NMES can reactivate paralyzed muscles, the effects may be insufficient to induce full body weight bearing during self-assisted stepping or standing. At the same time, a combinatory approach aimed at integrating, for instance, NMES and other neuromodulation modalities, may present an appealing and effective method to engage neural circuitries and regain robust self-assisted and weight-bearing activities in individuals with SCI. In particular, **transcutaneous spinal stimulation** (TSS), another noninvasive electrical stimulation technique, has recently drawn the attention of clinicians and researchers to activate and enable multiple paralyzed muscle groups at once (Sayenko et al., 2019). However, it has also been shown that individual responses to TSS can vary greatly, depending, for instance, on the strength, excitability or asymmetry of lower limb muscles due to SCI. For some participants, this can result in an insufficient bilateral muscle activation during activity. Therefore, the potential of combining various modalities to promote motor functions are worth being explored in future studies (Fig. 3).

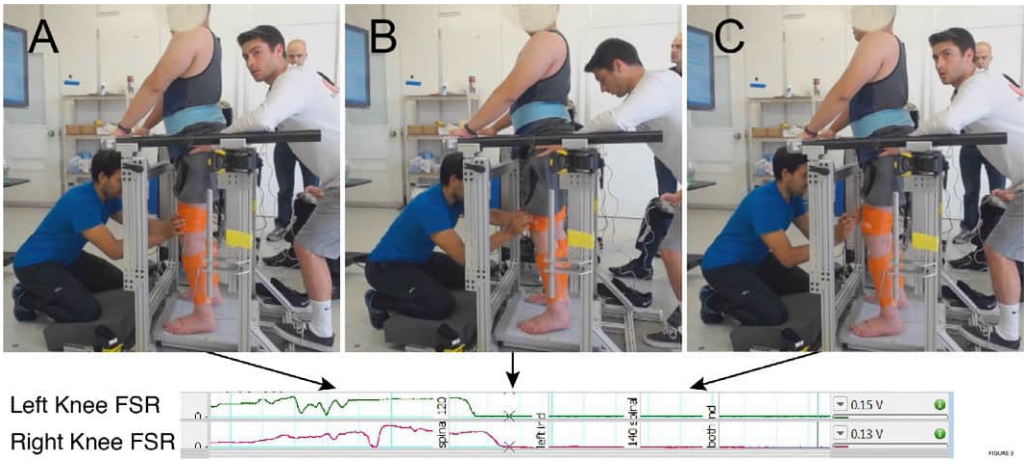

FIG. 3 An example of a combinatorial application of neuromuscular electrical stimulation (NMES) and transcutaneous spinal stimulation (TSS) in individual with complete spinal cord injury. (A) In a subject with chronic (4 years postinjury) thoracic (T2) SCI, only TSS was applied (L1, 15 Hz, and 120 mA). (B) TSS was combined with NMES on the plantarflexors (30 Hz and 70 mA). (C) TSS intensity was increased to 140 mA, with NMES on the plantarflexors (30 Hz and 70 mA). The traces at the bottom indicate the signals from two force sensitive resistance sensors on both knees. When TSS is combined with NMES, the load of the force sensors got reduced as well as the therapist's hands are detached from the knee shown on (B) and (C), indicating that manual assistance to the knees is no longer needed (unpublished observations by DGS).

Regaining of motor function after severe spinal cord injury

It has been implied that both daily training using epidural stimulation with stand training, and home-based voluntary training with **epidural stimulation** resulted in improvements, characterized by higher forces and lower stimulation voltages required to reach the thresholds that enable voluntary motor responses. Most recent studies of epidural spinal stimulation have revealed that neuromodulation of lumbosacral sensorimotor networks in combination with intensive training enables individuals with a chronic motor complete spinal cord injury (SCI) to perform self-assisted stepping utilizing paralyzed muscles (Angeli et al., 2018; Gill et al., 2018; Wagner et al., 2018).

Although these results demonstrate that spinal circuitries below a paralyzing injury have a functional potential that far exceeds what has ever been thought possible, two critical questions arise: (1) Is a repetitive activity-based training necessary to recover the voluntary motor control? and (2) Is there any specific training approach that can promote recovery of function-specific voluntary motor control?

Multimodal rehabilitation

It seems critical that approaches to regain voluntary motor control must engage the broadest variety of motor programs and neural networks, and not be limited to a single movement or function, to provide sufficient challenge of descending spinal tracts to activate spared supra- and intraspinal network. From this viewpoint, it is not surprising that somewhat limited clinical improvements can be seen following **conventional locomotor training**, primarily due to the limited spinal and supraspinal circuitry engagement during the intervention. Therefore, although positive physiological effects of locomotor training are indisputable (Dietz, Colombo, Jensen, & Baumgartner, 1995), this rehabilitative approach appears to target only rhythmogenic properties of the intrinsic spinal network, and may not promote, if applied alone, the volitional control of movement.

Postural verticalization is another conventional therapeutic modality that has been extensively adopted for decades in the rehabilitation of persons with a spinal lesion, though without being linked to any neurological recovery. It has been suggested that the standing posture has a number of therapeutic and functional benefits aimed at overcoming physiological problems, such as bladder infections, spasticity, and blood pressure homeostasis (Harkema, Ferreira, van den Brand, & Krassioukov, 2008). Surprisingly, minimally assisted verticalization of a subject with compromised sensorimotor control of the trunk or lower limbs may represent a comparable or even more dynamic experience (Sayenko et al., 2019) than locomotor training. Indeed, a sudden postural perturbation can trigger multiple sensorimotor signals and commands to recover equilibrium, which can result in a cascade of compelling ascending and descending inputs with a higher modulation frequency, compared to inputs evoked by stereotyped stepping on a treadmill, with passive weight bearing (Fig. 4). Based on these considerations, it can be proposed that stand training must engage all components of the postural sensorimotor network from supraspinal centres to spinal circuits (Sayenko et al., 2019). Stand training with visual feedback and voluntary

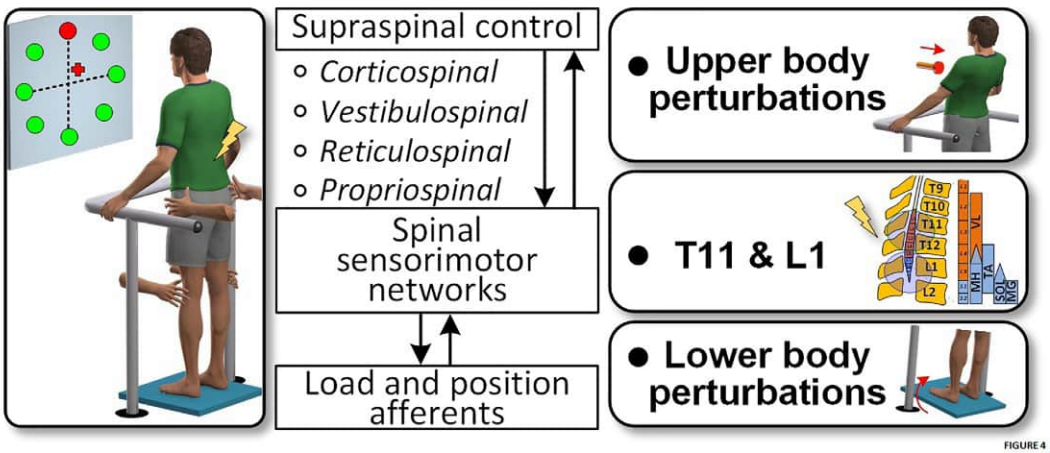

FIG. 4 Postural control and stand training. Main elements of stand training include spinal stimulation-induced minimally assisted standing, voluntary control of body position using visual feedback, and postural perturbations applied to upper and lower body. Multimodal approach activates sub-functional longitudinal fibres of the spinal cord and promotes the emerging responsiveness of spinal networks to descending commands and sensory inputs via corticospinal, vestibulospinal, reticulospinal, and propriospinal pathways (unpublished observations by DGS).

control of body movements, as well as postural perturbations, can provide a diffused background of descending and ascending somatosensory inputs that reach the spinal cord and can facilitate the activation of the corticospinal, vestibulospinal, reticulospinal, and propriospinal networks, all critical for postural regulation and motor control (Sayenko et al., 2019).

In this regard, the data by Gill et al. (2018) demonstrate that **multimodal rehabilitation**, which consists of the dynamic approach of stand-and-step training during each session, is highly efficient to enable both independent standing and stepping. Moreover, the authors observed that although task-specific epidural stimulation parameters enabled independent standing, when parameters were adjusted to enable stepping, standing was still possible. When the subject changed his intention from standing to stepping, he was able to independently step with both legs on a treadmill. Subsequent to stepping, spinal stimulation parameters were adjusted to enable optimal standing performance, and as a result of the dynamic training of spinal sensorimotor networks during multimodal rehabilitation, independent standing was achieved (Fig. 5).

To summarize, it is now clear that the majority of studies utilizing epidural spinal stimulation for motor recovery after motor complete SCI have been successful so far in generating an almost *immediate* regaining of muscle-specific control

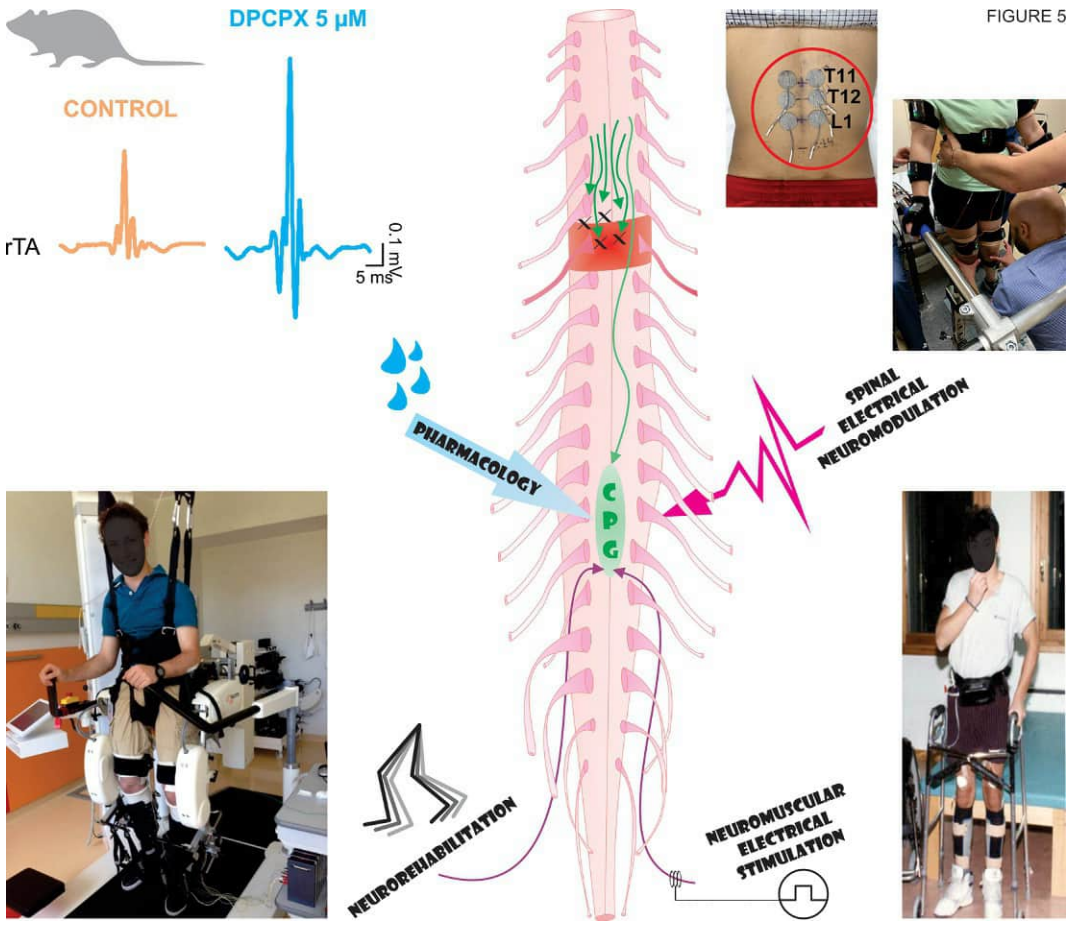

FIG. 5 Multilevel approach to the treatment of persons with spinal cord injury. The cartoon summarizes the different protocols that are experimentally or clinically used after spinal cord injury, including neuromodulation. A discomplete injury to the cord is depicted as a red segment, blocking (*black* "Xs") the majority of descending volitional commands (*green* downward arrows). A weak spared input passes the block (*pale green* downwards arrow) but is unable to activate the Central Pattern Generator (CPG) for locomotion located in upper lumbar segments. Sensory input from the periphery reaches the CPG from the sacrocaudal cord through ascending projections (*purple* upward arrows). CPG excitability might reach the threshold for motor control recovery by synergizing different approaches, which are schematized in clockwise order, as follows. Direct spinal cord neuromodulation is applied using transcutaneous electrodes placed on the back at the level of the thoracolumbar vertebrae (T11 to L1) to elicit standing posture in persons with chronic spinal cord injury. Neuromuscular electrical stimulation of peripheral afferents can be applied through surface electrode on the skin of lower limbs for the "artificial" control of standing and stepping. Robotic exoskeletons driving repetitive the passive motion of legs over a sliding treadmill generate afferent input that in turn modulate the CPG. Finally, in animal experiments, the direct application of neurochemicals (i.e., DPCPX, the selective pharmacological antagonist of adenosinergic A1 receptors; Taccola et al., 2020) modulates electrically-evoked motor responses from hindlimb muscles (i.e., *TA*, tibialis anterior; (unpublished materials by DGS, HACB, and GT).

below the lesion in the presence of stimulation. However, successful performance of more complex motor tasks, such as standing and stepping, most likely requires intensive training to promote integration of the *vast variety* of neural networks above, across, and below the level of neurological lesion.

Applications to other areas of neuroscience

Understanding of the neuromodulation mechanisms expands our knowledge on the basic rules pertaining to the recruitment of networks of neurons. In particular, the insights about the nonlinearity of neuronal circuits, according to which a quite stereotyped electrical input above a distinct threshold shapes a patterned motor output, could be exploited to design brain machine interfaces and robotics.

In this chapter, we reviewed the effects of electrical neuromodulation in restoring motor responses after spinal cord injury. Electrical spinal stimulation through transcutaneous or epidural electrodes is also an emerging practice in the treatment of several neuromotor disorders. Spinal stimulation for the recovery of motor control can been explored for lesions of upper motoneurons, such as stroke, cerebral palsy, Parkinson's disease and multiple sclerosis.

Noteworthy, spinal neuromodulation for the restoration of motor responses after severe spinal cord injury shares multiple features with epidural electrical stimulation for alleviating central pain, electrical stimulation of the peripheral nerve, and deep brain stimulation. Therefore, advancements in any of these closely related fields can potentially contribute to improving treatment of the other distinct neurological conditions, as well.

Although the neurophysiological processes at the base of electrical neuromodulation still need to be fully identified, advances in hardware design, rehabilitation training and pharmacological therapies might suggest new avenues on how electrical field interacts with a network of excitable neural targets.

Mini-dictionary of terms

Autonomic dysreflexia: Increased systolic blood pressure greater than 20–30 mmHg.

Brown-Sequard Syndrome: A partial damage to the cord, affecting half of a spinal segment and causing lateral sensory-motor deficits.

Central pattern generators: Networks of neurons that, due to their intrinsic membrane properties or their distinct synaptic wiring among the elements of the circuit, are able to express a rhythmic functional output even in the absence of any central or peripheral input.

Conventional locomotor training: Manually assisted stepping on a treadmill or overground with or without body weight support.

Cortical remapping: Changes in brain activation after spinal cord injury in terms of intensity, volume, and somatotopic localization, as well as preservation of activation during attempted and/or imagined movements.

Discomplete lesion: A clinically complete absence of motor activity after spinal cord injury, with or without any partial preservation of sensory functions, showing a subclinical brain influence on spinal cord functions below lesion.

Epidural stimulation: Electrical stimulation of the central nervous system through electrodes placed over the outmost meninges, which are called dura mater.

Metaplasticity: Homeostatic compensatory plastic events consequent to a rise in the excitability induced by the activation of previously nonresponsive injured networks.

Multimodal rehabilitation: Dynamic training of spinal stimulation-enabled functions in multiple environments, including stimulation-enabled stepping and standing.

Neuromuscular electrical stimulation: Electrical stimulation of motor endplates to induce muscle contraction for functional purposes.

Neuropathic pain: Chronic pain syndrome originated from the central nervous system.

Spasticity: A motor disorder with a velocity-dependent increase in tonic stretch reflexes and increased muscle activity during passive stretch, with clinical representation of hyperreflexia, spasms, and clonus.

Spinal cord atrophy: A reduction in the cross-sectional integrity of the cord.

Spinal metamere: A horizontal segment of the spinal cord that includes a pair of bilateral dorsal roots and a pair of bilateral ventral roots.

Transcutaneous spinal stimulation: A noninvasive electrical stimulation technique delivering pulses to the spinal cord through surface electrodes applied to the skin over the backbone.

Key facts of neuromodulation and restoration of motor responses after severe spinal cord injury

- Excitable cells use digital electrical input to transmit information.
- Rhythmic motor activities are automatically generated by distinct circuits of spinal neurons.
- Commands for the volitional control of motor tasks are generated by the brain.
- The spinal cord is not a simple tube of fibres, but contains networks of neurons that express smart decision-making properties.
- Sensory input from the periphery modulates the motor behavior mainly through unconscious mechanisms.
- The broad stimulation of spinal segments below the level of injury elicits the recovery of motor skills that require the sequenced activation of multiple motor pools.
- The rhythmic afferent feedback generated by physical training supports the reactivation of spinal networks through direct electrical stimulation.

Summary points

- A spinal cord injury determines a maladaptive reorganization of the motor cortex, which can be reverted by training programs aimed at regain voluntary motor control.
- Some individuals with a complete spinal cord injury are still capable of subclinical motor control below the level of injury and may regain motor control when the spinal cord is appropriately stimulated.
- Electric charges applied to the central nervous system affect the excitability of neuronal networks.
- Neuromodulation, as a direct physical perturbation of all excitable structures in the spinal cord, reconfigures spared elements in injured networks to restore the control of certain volitional motor functions after injury.
- The electrical stimulation of certain peripheral nerves facilitates spinal integration of sensory afferent feedback and allows some "artificial" motor control of paralyzed limbs after spinal cord injury.
- A multimodal intensive rehabilitation, which combines complex motor tasks with the electrical modulation of both spinal cord and peripheral nerves, restores motor control by exploiting the integration of multiple neural networks above, across, and below the level of a neurological lesion.

References

Angeli, C. A., Boakye, M., Morton, R. A., Vogt, J., Benton, K., Chen, Y., et al. (2018). Recovery of over-ground walking after chronic motor complete spinal cord injury. *The New England Journal of Medicine*, *379*, 1244–1250.

Angeli, C. A., Edgerton, V. R., Gerasimenko, Y. P., & Harkema, S. J. (2014). Altering spinal cord excitability enables voluntary movements after chronic complete paralysis in humans. *Brain*, *137*(Pt 5), 1394–1409. https://doi.org/10.1093/brain/awu038.

Ballermann, M., & Fouad, K. (2006). Spontaneous locomotor recovery in spinal cord injured rats is accompanied by anatomical plasticity of reticulospinal fibers. *The European Journal of Neuroscience*, *23*, 1988–1996.

Bareyre, F. M., Kerschensteiner, M., Raineteau, O., Mettenleiter, T. C., Weinmann, O., & Schwab, M. E. (2004). The injured spinal cord spontaneously forms a new intraspinal circuit in adult rats. *Nature Neuroscience*, *7*, 269–277.

Campanini, I., Disselhorst-Klug, C., Rymer, W. Z., & Merletti, R. (2020). Surface EMG in clinical assessment and neurorehabilitation: Barriers limiting its use. *Frontiers in Neurology*, *11*, 934.

Carmick, J. (1993). Clinical use of neuromuscular electrical stimulation for children with cerebral palsy. Part 1: Lower extremity. *Physical Therapy*, *73*, 514–522.

Courtine, G., Song, B., Roy, R. R., Zhong, H., Herrmann, J. E., Ao, Y., et al. (2008). Recovery of supraspinal control of stepping via indirect propriospinal relay connections after spinal cord injury. *Nature Medicine*, *14*, 69–74.

Cybulski, G. R., Penn, R. D., & Jaeger, R. J. (1984). Lower extremity functional neuromuscular stimulation in cases of spinal cord injury. *Neurosurgery*, *15*, 132–146.

Dietz, V., Colombo, G., Jensen, L., & Baumgartner, L. (1995). Locomotor capacity of spinal cord in paraplegic patients. *Annals of Neurology*, *37*, 574–582.

Dimitrijevic, M. R., McKay, W. B., & Sherwood, A. M. (1997). Motor control physiology below spinal cord injury: Residual volitional control of motor units in paretic and paralyzed muscles. *Advances in Neurology*, *72*, 335–345.

Eccles, J. C., Kostyuk, P. G., & Schmidt, R. F. (1962). The effect of electric polarization of the spinal cord on central afferent fibres and on their excitatory synaptic action. *The Journal of Physiology*, *162*, 138–150.

Endo, T., Spenger, C., Tominaga, T., Brene, S., & Olson, L. (2007). Cortical sensory map rearrangement after spinal cord injury: fMRI responses linked to Nogo signalling. *Brain*, *130*, 2951–2961.

Filli, L., Zorner, B., Weinmann, O., & Schwab, M. E. (2011). Motor deficits and recovery in rats with unilateral spinal cord hemisection mimic the Brown-Sequard syndrome. *Brain*, *134*, 2261–2273.

Freund, P., Curt, A., Friston, K., & Thompson, A. (2013). Tracking changes following spinal cord injury: Insights from neuroimaging. *The Neuroscientist*, *19*, 116–128.

Freund, P., Wheeler-Kingshott, C. A., Nagy, Z., Gorgoraptis, N., Weiskopf, N., Friston, K., et al. (2012). Axonal integrity predicts cortical reorganisation following cervical injury. *Journal of Neurology, Neurosurgery, and Psychiatry*, *83*, 629–637.

Ghosh, A., Haiss, F., Sydekum, E., Schneider, R., Gullo, M., Wyss, M. T., et al. (2010). Rewiring of hindlimb corticospinal neurons after spinal cord injury. *Nature Neuroscience*, *13*, 97–104.

Gill, M. L., Grahn, P. J., Calvert, J. S., Linde, M. B., Lavrov, I. A., Strommen, J. A., et al. (2018). Neuromodulation of lumbosacral spinal networks enables independent stepping after complete paraplegia. *Nature Medicine*, *24*, 1677–1682.

Graupe, D., & Bazo, H. A. C. (2015). Thoracic level complete paraplegia–walking performance, training and medical benefits with the PARASTEP FES system. *International Journal of Physical Medicine & Rehabilitation*, *3*, 5.

Günter, C., Delbeke, J., & Ortiz-Catalan, M. (2019). Safety of long-term electrical peripheral nerve stimulation: Review of the state of the art. *Journal of Neuroengineering and Rehabilitation*, *16*, 13.

Harkema, S., Gerasimenko, Y., Hodes, J., Burdick, J., Angeli, C., Chen, Y., et al. (2011). Effect of epidural stimulation of the lumbosacral spinal cord on voluntary movement, standing, and assisted stepping after motor complete paraplegia: A case study. *Lancet*, *377*, 1938–1947.

Harkema, S. J., Ferreira, C. K., van den Brand, R. J., & Krassioukov, A. V. (2008). Improvements in orthostatic instability with stand locomotor training in individuals with spinal cord injury. *Journal of Neurotrauma*, *25*(12), 1467–1475. https://doi.org/10.1089/neu.2008.0572.

Ho, C. H., Triolo, R. J., Elias, A. L., Kilgore, K. L., DiMarco, A. F., Bogie, K., et al. (2014). Functional electrical stimulation and spinal cord injury. *Physical Medicine and Rehabilitation Clinics of North America*, *25*, 631–654.

Hofstoetter, U. S., Freundl, B., Danner, S. M., Krenn, M. J., Mayr, W., Binder, H., et al. (2019). Transcutaneous spinal cord stimulation induces temporary attenuation of spasticity in individuals with spinal cord injury. *Journal of Neurotrauma*, *37*, 481–493.

Holsheimer, J. (2002). Which neuronal elements are activated directly by spinal cord stimulation. *Neuromodulation*, *5*, 25–31.

Holtmaat, A., & Svoboda, K. (2009). Experience-dependent structural synaptic plasticity in the mammalian brain. *Nature Reviews Neuroscience*, *10*, 647–658.

Horky, L. L., Galimi, F., Gage, F. H., & Horner, P. J. (2006). Fate of endogenous stem/progenitor cells following spinal cord injury. *The Journal of Comparative Neurology*, *498*, 525–538.

Hou, S., & Rabchevsky, A. G. (2014). Autonomic consequences of spinal cord injury. *Comprehensive Physiology*, *4*, 1419–1453.

Jack, A. S., Hurd, C., Martin, J., & Fouad, K. (2020). Electrical stimulation as a tool to promote plasticity of the injured spinal cord. *Journal of Neurotrauma*, *37*, 1933–1953.

Jain, N., Catania, K. C., & Kaas, J. H. (1997). Deactivation and reactivation of somatosensory cortex after dorsal spinal cord injury. *Nature*, *386*, 495–498.

Jain, N., Qi, H.-X., Collins, C. E., & Kaas, J. H. (2008). Large-scale reorganization in the somatosensory cortex and thalamus after sensory loss in macaque monkeys. *Journal of Neuroscience*, *28*, 11042–11060.

Kakulas, B. A. (1984). Pathology of spinal injuries. *Central Nervous System Trauma*, *1*, 117–129.

Kaushal, M., Shabani, S., Budde, M., & Kurpad, S. (2019). Diffusion tensor imaging in acute spinal cord injury: A review of animal and human studies. *Journal of Neurotrauma*, *36*, 2279–2286.

Kern, H., & Carraro, U. (2020). Home-based functional electrical stimulation of human permanent Denervated muscles: A narrative review on diagnostics, managements, results and byproducts revisited. *Diagnostics*, *10*, 529.

Kiehn, O. (2006). Locomotor circuits in the mammalian spinal cord. *Annual Review of Neuroscience*, *29*, 279–306.

Kokotilo, K. J., Eng, J. J., & Curt, A. (2009). Reorganization and preservation of motor control of the brain in spinal cord injury: A systematic review. *Journal of Neurotrauma*, *26*, 2113–2126.

Kramer, J. L., Minhas, N. K., Jutzeler, C. R., Erskine, E. L., Liu, L. J., & Ramer, M. S. (2017). Neuropathic pain following traumatic spinal cord injury: Models, measurement, and mechanisms. *Journal of Neuroscience Research*, *95*, 1295–1306.

Little, J. W., & Halar, E. (1985). Temporal course of motor recovery after Brown-Sequard spinal cord injuries. *Paraplegia*, *23*, 39–46.

Marder, E., O'Leary, T., & Shruti, S. (2014). Neuromodulation of circuits with variable parameters: Single neurons and small circuits reveal principles of state-dependent and robust neuromodulation. *Annual Review of Neuroscience*, *37*, 329–346.

Marineo, G. (2019). Inside the scrambler therapy, a noninvasive treatment of chronic neuropathic and cancer pain: From the gate control theory to the active principle of information. *Integrative Cancer Therapies*, *18*, 1–17.

Michelson, N. J., Eles, J. R., Vazquez, A. L., Ludwig, K. A., & Kozai, T. D. Y. (2019). Calcium activation of cortical neurons by continuous electrical stimulation: Frequency dependence, temporal fidelity, and activation density. *Journal of Neuroscience Research*, *97*, 620–638.

Moxon, K. A., Oliviero, A., Aguilar, J., & Foffani, G. (2014). Cortical reorganization after spinal cord injury: Always for good? *Neuroscience*, *283*, 78–94.

Nicotra, A., Critchley, H. D., Mathias, C. J., & Dolan, R. J. (2005). Emotional and autonomic consequences of spinal cord injury explored using functional brain imaging. *Brain*, *129*, 718–728.

Raineteau, O., & Schwab, M. E. (2001). Plasticity of motor systems after incomplete spinal cord injury. *Nature Reviews. Neuroscience*, *2*, 263–273.

Raisman, G. (1969). Neuronal plasticity in the septal nuclei of the adult rat. *Brain Research*, *14*, 25–48.

Rosenzweig, E. S., Courtine, G., Jindrich, D. L., Brock, J. H., Ferguson, A. R., Strand, S. C., et al. (2010). Extensive spontaneous plasticity of corticospinal projections after primate spinal cord injury. *Nature Neuroscience*, *13*, 1505–1510.

Roy, R. R., & Edgerton, V. R. (2012). Neurobiological perspective of spasticity as occurs after a spinal cord injury. *Experimental Neurology*, *35*, 116–122.

Sayenko, D. G., Rath, M., Ferguson, A. R., Burdick, J. W., Havton, L. A., Edgerton, V. R., et al. (2019). Self-assisted standing enabled by non-invasive spinal stimulation after spinal cord injury. *Journal of Neurotrauma*, *36*, 1435–1450.

Shealy, C. N., Mortimer, J. T., & Reswick, J. B. (1967). Electrical inhibition of pain by stimulation of the dorsal columns: Preliminary clinical report. *Anesthesia and Analgesia*, *46*, 489–491.

Sherwood, A. M., Dimitrijevic, M. R., & Barry McKay, W. (1992). Evidence of subclinical brain influence in clinically complete spinal cord injury: Discomplete SCI. *Journal of the Neurological Sciences*, *110*, 90–98.

Swiontek, T. J., Sances, A., Jr., Larson, S. J., Ackmann, J. J., Cusick, J. F., Meyer, G. A., et al. (1976). Spinal cord implant studies. *IEEE Transactions on Biomedical Engineering*, *23*, 307–312.

Sysoev, Y., Bazhenovam, E., Lyakhovetskii, V., Kovalev, G., Shkorbatova, P., Islamova, R., et al. (2020). Site-specific neuromodulation of detrusor and external urethral sphincter by epidural spinal cord stimulation. *Frontiers in Systems Neuroscience*, *14*, 47.

Taccola, G., Salazar, B. H., Apicella, R., Hogan, M. K., Horner, P. J., & Sayenko, D. (2020). Selective antagonism of A1 adenosinergic receptors strengthens the neuromodulation of the sensorimotor network during epidural spinal stimulation. *Frontiers in Systems Neuroscience*, *14*, 44.

Taccola, G., Sayenko, D., Gad, P., Gerasimenko, Y., & Edgerton, V. R. (2018). And yet it moves: Recovery of volitional control after spinal cord injury. *Progress in Neurobiology*, *160*, 64–81.

Tan, A. M., & Waxman, S. G. (2012). Spinal cord injury, dendritic spine remodeling, and spinal memory mecha- nisms. *Experimental Neurology*, *235*, 142–151.

Tang, S. F., Tuel, S. M., McKay, W. B., & Dimitrijevic, M. P. (1994). Correlation of motor control in the supine position and assistive device used for ambulation in chronic incomplete spinal cord-injured persons. *American Journal of Physical Medicine & Rehabilitation*, *73*, 268–274.

Tansey, K. E. (2012). Profiling motor control in spinal cord injury: Moving towards individualized therapy and evidence-based care progression. *The Journal of Spinal Cord Medicine*, *35*, 305–309.

Topka, H., Cohen, L. G., Cole, R. A., & Hallett, M. (1991). Reorganization of corticospinal pathways following spinal cord injury. *Neurology*, *41*, 1276–1283.

Voronin, L. L., & Cherubini, E. (2004). 'Deaf, mute and whispering' silent synapses: Their role in synaptic plasticity. *The Journal of Physiology*, *557*, 3–12.

Wagner, F. B., Mignardot, J. B., Le Goff-Mignardot, C. G., Demesmaeker, R., Komi, S., Capogrosso, M., et al. (2018). Targeted neurotechnology restores walking in humans with spinal cord injury. *Nature*, *563*, 65–71.

Waters, R. L. (1984). The enigma of "carry-over". *International Rehabilitation Medicine*, *6*, 9–12.

Weidner, N., Ner, A., Salimi, N., & Tuszynski, M. H. (2001). Spontaneous corticospinal axonal plasticity and functional recovery after adult central nervous system injury. *Proceedings. National Academy of Sciences. United States of America*, *98*, 3513–3518.

Wolpaw, J. R. (2018). The negotiated equilibrium model of spinal cord function. *The Journal of Physiology*, *596*, 3469–3491.

Wrigley, P. J., Gustin, S. M., Macey, P. M., Nash, P. G., Gandevia, S. C., Macefield, V. G., et al. (2008). Anatomical changes in human motor cortex and motor pathways following complete thoracic spinal cord injury. *Cerebral Cortex*, *19*, 224–232.

Zhang, Q., Li, S., Wong, H. C., He, X. J., Beirl, A., Petralia, R. S., et al. (2018). Synaptically silent sensory hair cells in zebrafish are recruited after damage. *Nature Communications*, *9*, 1388.

Further reading

Delattre, V., Denison, T., Lambert, H., Minassian, K., Bloch, J., & Courtine, G. (2018). Targeted neurotechnology restores walking in humans with spinal cord injury. *Nature*, *563*, 65–71.

Hachmann, J. T., Grahn, P. J., Calvert, J. S., Drubach, D. I., Lee, K. H., & Lavrov, I. A. (2017). Electrical neuromodulation of the respiratory system after spinal cord injury. *Mayo Clinic Proceedings*, *92*, 1401–1414.

McKay, W. B., Lim, H. K., Priebe, M. M., Stokic, D. S., & Sherwood, A. M. (2004). Clinical neurophysiological assessment of residual motor control in post-spinal cord injury paralysis. *Neurorehabilitation and Neural Repair*, *18*, 144–153.

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Chapter 6

Rehabilitation and wheelchair users after spinal cord injury: An overview

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List of abbreviations

AD	autonomic dysreflexia
HO	heterotopic ossification
NB	neurogenic bladder
PU	pressure ulcers
SCI	spinal cord injury

Introduction

Spinal cord injury (SCI) is one of the most complex clinical conditions that occur in humans. It involves motor, sensory, and autonomic changes with functional, emotional, economic, and social implications. This is a costly condition for the individual, his family and society. In Canada, it has been estimated to cost 1.47 to 3.03 million dollars per individual over a lifetime (Kang et al., 2018).

Numerous actions regarding clinical treatment and prevention of complications should be taken as soon as possible to facilitate clinical management and reduce morbidity and mortality (Riberto, Pinto, Sakamoto, & Battistella, 2005). These patients should be transferred to a specialized rehabilitation unit as soon as they are clinically stable (Bickenbach et al., 2013; Kirshblum & BrooksIn, 2010) where they must be assisted by a specialized interdisciplinary team to achieve desired therapeutic functional and clinical objectives (Nas, Yazmalar, Şah, et al., 2015).

Regarding mobility, robotic devices can offer highly repetitive training, coupled interactive strategies to enhance engagement, thus enhancing neuroplastic reorganization. Alternatively, powered exoskeletons are already commercially available and have proven their use in social activities and exercises.

Epidemiology

Incidence and prevalence of SCI have increased over the expansion of human activity. The epidemiological profile varies according to the region of the world and the most common etiologies are traumatic, with falls and traffic accidents prevailing, followed by sports accidents and violence. The incidence varies between 13 and 163.4/million and may be higher in some developing countries. There are few reports on the prevalence, but it is estimated to be between 490 and 526/million. Traumatic etiology predominates among younger men with ages varying between 14 and 68 years, but those figures are narrower in developing countries (between 29 and 46 years). The most common anatomical location is the cervical spine, therefore the neurological deficit is tetraplegia. There is a predominance of the most severe neurological lesions (AIS A and B) (Kang et al., 2018).

Other causes of SCI include infections, vascular injuries, genetic, and oncologic etiologies. This is a different group of patients, which include varied ages and certainly much more women. Nontraumatic SCI usually progresses slowly and causes incomplete harm to the spinal cord, which implies in varied clinic-functional pictures and prognosis (Almeida, Coelho, & Riberto, 2016). Mortality among patients with traumatic SCI was reported 28.8 times higher than in the Brazilian

Cellular, Molecular, Physiological, and Behavioral Aspects of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822427-4.00006-X

population without SCI and infectious causes were responsible for 55.3% of deaths (Leite, Souza, Imamura, & Battistella, 2019).

Classification and prognosis

The American Spinal Cord Injury Association (ASIA) recommends use of ASIA Impairment Scale (AIS) and a standardization of the physical examination of muscle strength and cutaneous sensibility to pain and touch to define motor and sensitive levels, respectively. This neurological examination should be repeated periodically to assess the evolution of the level and severity of the injury. In general, most patients will experience some degree of improvement after SCI, especially in the first six months, and may continue up to 2 years (Kirshblum, Burns, Biering-Sorensen, et al., 2011).

The initial classification after the end of spinal shock can provide the first prognostic information. The rate of neurological recovery is extremely low in patients with complete and incomplete sensory injuries, and some degree of gait recovery occurs in 0.9–8.3% of AIS A patients and can reach 67.2–97.3% in AIS D. Younger patients have better prognosis of neurological recovery but most patients will have permanent sequelae and will lose the ability to walk (van Middendorp et al., 2011).

The recovery of voiding control is also related to the motor recovery of lower limbs (Pavese et al., 2016). The prediction of manual functional recovery is even more uncertain. It is assumed that the earlier and more intense the motor and sensory recovery, the greater the chance of manual function recovery (Velstra et al., 2014).

Objectives in spinal cord rehabilitation

These objectives must be shared among all rehabilitation team members, who must establish a plan, considering the needs and patient perspectives:

- Education patients/families about SCI and its consequences for functioning.
- Emotional support for the patient and family.
- Promote autonomy and independence in activities of daily living and mobility, considering the functional capacity and adaptation of individual needs.
- Pain and spasticity management.
- Rehabilitation of neurogenic bladder and bowel.
- Sexual rehabilitation.
- Prevention of musculoskeletal deformities.
- Prescription of orthoses and other assistive technology.
- Support for social and family reorganization.

Robotic rehabilitation of movement

Mobility after SCI is the most expected aim of recovery and is believed to be responsible for the highest improvement in quality of life. Individuals with tetraplegia affirm hand function as their priority of recovery to regain their lives back, while those with paraplegia, rank walking as their preferences.

When SCI motor level is above C8, complete or not, hand function is extremely limited, thus emphasis in rehabilitation relies on accessing one's environmental factors, which includes technology and much support from caretakers for many daily activities. Subsequently, rehabilitation for the upper limbs stresses on strengthening any intact motor capacities to the arm and hand as well as bringing awareness to areas with impaired sensibility e proprioception, to prevent secondary skin and musculoskeletal injuries.

Several different robotic devices are currently used for neurorehabilitation of the upper extremities following SCI. The most striking aspect of robotic therapy is the possibility to deliver a high volume of high-quality movement repetitions, which promote functional recovery and may potentially facilitate adaptive plasticity, reducing therapist burden and cost of care (Mekki, Delgado, Fry, Putrino, & Huang, 2018). The most studied robotic devices for upper limb rehabilitation in the market are Armeo, InMotion ARM/WRIST, The Hand of Hope, ReoGo, and the Arm Light Exoskeleton (ALEx) (Fig. 1). They share the use of different support systems or exoskeletons to facilitate movement by the subject. These devices can initiate, drive, or finalize the strength efforts in the motor tasks. Alternatively, the hand and forearm may be strapped into a molded device and use electromyography sensors on the forearm to control the hand for several different tasks. Also, they engage the user with a visual feedback component and interactive games that can be used to improve the

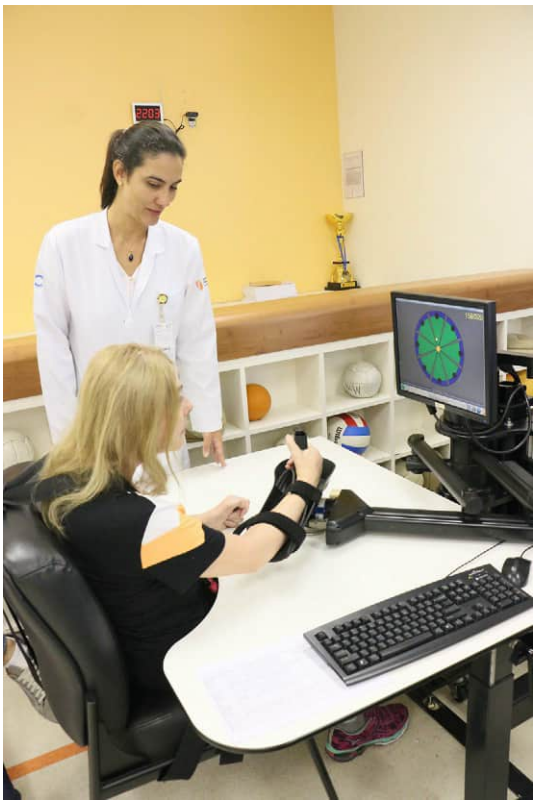


FIG. 1 Robotic rehabilitation upper limbs.

quality of therapeutic sessions. The Armeo Spring has been shown to be a reliable clinical tool to assess movement in the workplace (Rudhe, Albisser, Starkey, Curt, & Bolliger, 2012) and substitute other assessment tools (Zariffa et al., 2012), which added a novel use of robots as an extremely sensible measurement of functional achievements in SCI. Most of the published articles reporting their use so far are case reports or series with reports of motor improvements in chronic incomplete SCI subjects (Lu, Tong, Shin, Stampas, & Zhou, 2017; Siedziewski, Schaaf, & Mount, 2012).

In incomplete paraplegia, orthoses augment walking function, although they require a significant amount of strength and significantly increase energy expenditure (Mekki et al., 2018).

Moving around for AIS A or B paraplegic subjects, with motor levels above L3, has traditionally been limited to the wheelchair. While wheelchairs provide a modified level of independence and amplified access to the environment, wheelchair users continue to face difficulties in access and mobility. Usual rehabilitation with orthoses is highly demanding in physical aspects either on users, but also on therapists and caregivers (Fig. 2).

Body weight supported treadmill training may reduce this problem, but is not portable and therefore not recommended for community ambulation. In such scenarios, robotic gait rehabilitation can increase the amount of practice in a controlled system and may add an interactive engaging environment (Carpino, Pezzola, Urbano, & Guglielmelli, 2018) (Fig. 3).

Wearable exoskeletons are motorized or robotic devices that initiate or augment movement and may improve mobility and independence in nonambulatory people, thus possibly reducing secondary health conditions related to sedentariness. They facilitate recovery by delivering fully weight-bearing, repetitive, symmetric locomotor training efficiently and in high volume (Arazpour, Bani, Hutchins, & Jones, 2013).

Wearable lower limb exoskeletons for gait rehabilitation are still in their early stages of development and randomized control trials are needed to demonstrate their clinical efficacy. These robotic devices are used either for therapeutic purposes with repetitive, functional movement or as a mobility technology beyond wheelchairs and other walking aids. A recent report described the context in which one brand of exoskeletons have been used by 14 chronic complete SCI after an eight-week period of training. Subjects reported good satisfaction with the device in terms of comfort, adjustment, dimensions, durability and services, and less satisfaction with weight, effectiveness, and ease of use. The exoskeleton

FIG. 2 Transfer training in SCI.

FIG. 3 Robotic rehabilitation lower limbs.

was used primarily for exercises and social events, and 48% of times in outdoor environments (van Dijsseldonk, van Nes, Geurts, & Keijsers, 2020).

Bone fractures and falls are possible adverse effects of the use of powered exoskeletons in SCI. Bone fractures have been associated with decreased body mass density as well as the unfamiliar forces placed on the paralyzed limbs or misalignment and excessive torques of the exoskeleton during gait, coupled with a lack of pain response (Miller, Zimmermann, & Herbert, 2016).

Main clinical aspects for rehabilitation

Pain

Pain is a highly disabling and extremely frequent complication that can occur at any moment after SCI, interfering with rehabilitation and quality of life (Burke, Fullen, Stokes, et al., 2017).

Musculoskeletal pain is perceived in regions with preserved sensitivity. In the acute phase, it affects about 50% of patients and is related to the muscle, joint, tendon, and bone structures involved in spinal trauma, surgical manipulations, and posture. After 6 months, it affects 40–58% of patients with SCI (Siddal & Loeser, 2001). Myofascial pain, tendinitis and bursitis are frequent and generally related to poor positioning in bed, poor sitting posture, repetitive strain injury or degenerative-musculoskeletal processes. Subjects in wheelchairs and those with walking aids may overuse their upper extremities when moving around or during transfers. Although the muscles in their shoulders become stronger with time, this is a source of musculoskeletal injuries and pain (Freitas, Santana, Manoel, Serenza, & Riberto, 2019) (Fig. 4).

The diagnosis of musculoskeletal nociceptive pain is based on the anamnesis, physical exam, and complementary exams. Treatment consists of removing triggering factors, prescribing analgesics, opioids, antiinflammatories, and muscle relaxants in association with analgesic measures, such as acupuncture, blocking myofascial trigger points, massage, and physical means. Therapeutic exercises (physiotherapy and occupational therapy) are also recommended for muscle and postural rebalancing (Siddal & Loeser, 2001).

Neuropathic pain challenges the management of 50% SCI patients in the acute phase and rises to as much as 83% in the chronic phase and affects mostly the lower limbs, being characterized as burning, shock or pressure, present in patients (Burke et al., 2017). When it occurs above the level of the SCI, it is usually related to the root and peripheral nerve compression or with complex regional pain syndrome. Allodynia, which is the sensation of pain at any sensory stimulus such as touch, heat, or cold, is seen in 14% of acutely injured patients and tends to decrease in the first 6 months, being more frequent in incomplete injuries. A band-like pattern of neuropathic pain at the neurologic level is reported early after SCI in half of the patients. It is characterized by burning pain, shock, or pins-and-needles, which can be confused with visceral cramps when it is in the abdominal region. It can be associated with passive or active movement (Siddal & Loeser, 2001).

Drug treatment must consider the classification of pain and chronicity. Musculoskeletal nociceptive pain may respond to the use of analgesics, opioids, antiinflammatories, and muscle relaxants. Neuropathic pain should be addressed with the use of antidepressants (tricyclic antidepressants and duloxetine may be good options) and anticonvulsants (gabapentin and pregabalin are first-line options) (Mehta, McIntyre, Janzen, et al., 2016). Drug treatment of neuropathic pain offers several options, but with results it is not always satisfactory, justifying the combination of drugs. Their side effects should be considered as well as drug interactions since patients with SCI often receive multiple medications. Transcranial electrical stimulation in the motor cortex has been studied and appears to show satisfactory effects, with improvement in neurogenic pain (Fregni, Boggio, Lima, et al., 2006).

Selected cases, refractory to these previous interventions can be subjected to electrical stimulation of the spinal cord, with implantation of electrodes in the dorsal column, but pain improvement noticed in the initial phase loses effectiveness over time. Other surgical procedures include intrathecal pumps of morphine, lidocaine, and baclofen (Mehta et al., 2016), as

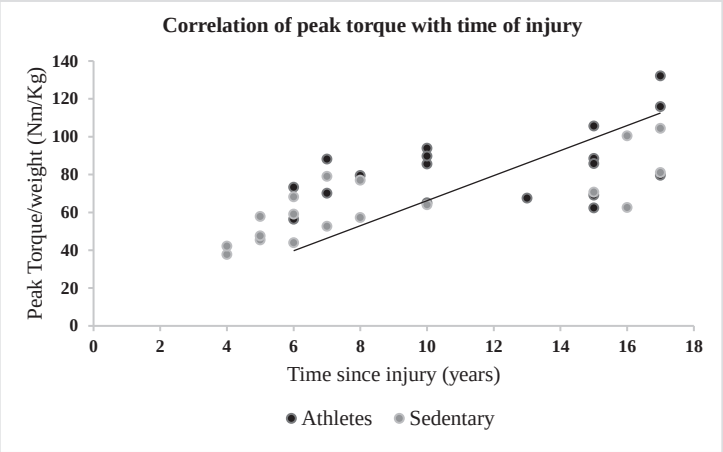


FIG. 4 Correlation between time (years) since injury and peak torque/weight (Nm/kg) of the internal rotators of the dominant shoulder of athletes and sedentary SCI subjects at 60°/s.

well as ablative surgeries—rhizotomy, cordotomy, and cordectomy with variable results. Complications of the most radical surgeries comprise loss of residual sensory, motor functions, urinary control, or sexual function (Mehta et al., 2016).

Spasticity

Spasticity is a motor dysfunction characterized by an involuntary, speed-dependent increase in muscle tone, as an exaggerated response to myotendinous stretching (exacerbation of the myotendinous reflex). It results from injuries to the pyramidal pathway leading to loss of inhibitory control of the medullary interneurons and modulation of cortical descending tracts. Spasticity is only observed in lesions above the medullary cone, after the phase of spinal shock (Elovic, Eisenberg, & Jasey Jr, 2010). The earlier the onset of spasticity, the greater its intensity. It is estimated that up to 80% of patients will have hypertonia and involuntary movements 1 year after the injury and 37% will need medications (Adams & Hicks, 2005).

Clinically, it is manifested by an increase in muscle resistance to sudden stretching (jackknife rigidity), clonus (rapid and repetitive involuntary muscle contractions), muscle automatisms (involuntary contractions) and deep tendon hyperreflexia. Muscle spasms can occur after any irritating nociceptive stimulus below the injury level, the most common are sudden movements, bladder repletion, intestinal constipation, urinary tract infection, pressure sores, ingrown nails, tight clothing, and inadequate positioning, among others (Elovic et al., 2010).

Spasticity can interfere in the control of movements of patients with partial motor control, worsening their mobility, namely in transfers, bed and chair positioning, standing and moving around. Muscle spasms and hypertonia hinder adequate positioning and activities such as clothing and bathing. In the long run, it can cause viscoelastic changes in the muscle leading to fibrosis, atrophy, and shortening and can cause deformities. However, mild to moderate spasticity can be useful as a facilitating factor for standing, sitting, handgrip, and postural changes (Elovic et al., 2010).

In the management of spasticity, the decision on the type of treatment to be performed depends on how much it interferes with functioning and quality of life (Taricco, Adone, Pagliacci, & Telaro, 2000). Treatment includes noninvasive therapeutic options, such as physiotherapy and oral medications, or more invasive techniques such as neurochemical blocks and orthopedic and neurosurgical procedures (Carvajal, Silva, Maeda, & Riberto, 2019; Elbasiouny, Moroz, Bakr, et al., 2010).

Drugs used in the systemic treatment may not guarantee the ideal control of spasticity and can cause systemic dose-dependent side effects like drowsiness and mental confusion. Most used drugs to treat spasticity are baclofen, benzodiazepines, and tizanidine. Anticonvulsants such as gabapentin can also be used, because of its gabaergic effect, as much as medications such as carbamazepine (which acts more by decreasing the frequency of spasms) (Taricco et al., 2000).

Regional treatment of spasticity can be performed with chemical neurolysis with phenol (5%) or alcohol (40–100%), which causes denaturation of the myelin sheath, leading to selective relaxation of target muscles. Muscle relaxation is immediate and can last up to 5 months. The procedure can be repeated when necessary, without restricting the interval between applications at the maximum dose of 15 mL with good results (Carvajal et al., 2019) (Fig. 5).

Botulinum toxin prevents the release of acetylcholine at the neuromuscular junction and successfully reduces spasticity. It is injected intramuscularly, in the motor plate, causing partial neurolysis. The effects are observed within 24–72 h. and can be temporary from 3 to 6 months, according to the range of complimentary treatment with psychical therapy or orthoses (Carvajal et al., 2019). When spasticity is refractory to drug and physical treatments, surgical procedures such as tenotomy, implantation of intrathecal baclofen or morphine infusion pumps, rhizotomies, cordotomies and cordectomies may be indicated (Elovic et al., 2010).

Heterotopic ossification

Heterotopic ossification (HO) is the pathological formation of ectopic bone in soft tissues. It occurs mainly in the first 12 months after the injury (with a peak up to months), always below the SCI level and close to the hips, knees, elbows and shoulders (Brady, Schultz, McDonald, & O'Brien, 2018). Clinical manifestations include low fever, regional oedema, hyperemia, pain in incomplete SCI, reduced range of motion and increased spasticity (Castro & Greve, 2003). Although physiopathology is not fully understood, an inflammatory modulation has been suggested to interfere on connective progenitor cells leading to differentiation into osteoblasts. Four to six weeks later there is calcification of the extracellular matrix produced by the newly differentiated cell (Ranganathan et al., 2015). Bone reabsorption is not noticed, and HO can only be removed surgically. The most striking impact of HO over functioning refers to the occurrence of deformities, which can further limit gait or adequate positioning in bed or wheelchair (Kirshblum & BrooksIn, 2010).

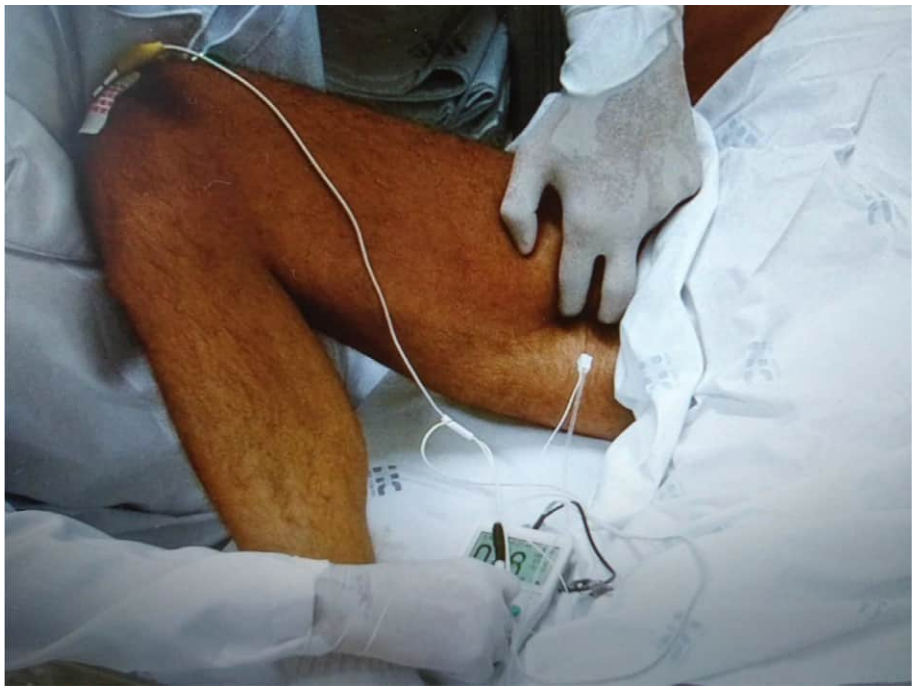
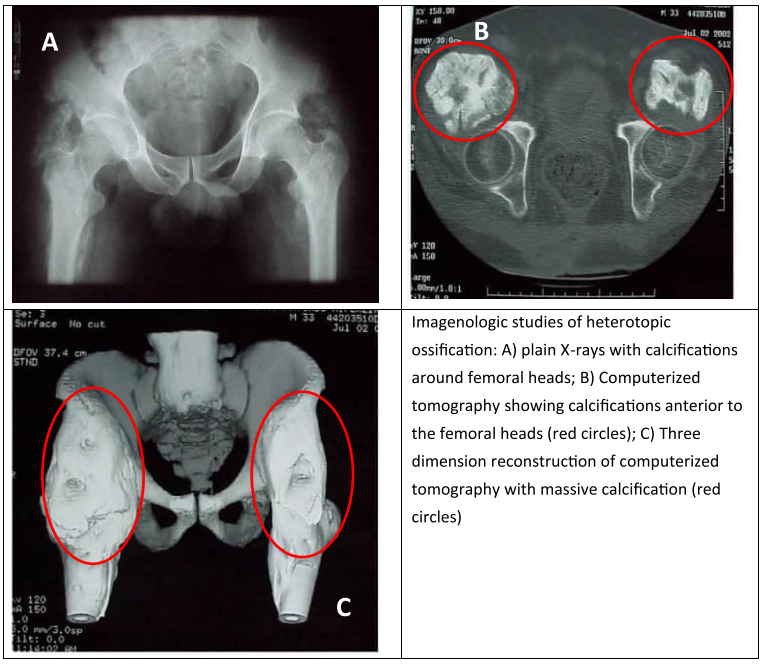


FIG. 5 Phenolic block of the anterior branch of the obturator nerve aiming to reduce adductor spasticity.

Early diagnosis is based on the clinical suspicion in a SCI subject with reduced range of motion and signal of limb oedema and hyperemia. Dosage of alkaline phosphatase, serum phosphorus, creatinophosfokinase (CPK) are sensitive, but nonspecific findings. Until a radiographic image is present after 6 weeks, bone scans are the only diagnostic resource available. Prophylactic use of nonsteroidal antiinflammatory agents or a single dose of 8 Grays radiation have been suggested and are routinely performed in some services (Popovic, Agarwal, Zhang, et al., 2014; Teasell, Mehta, Aubut, Ashe, et al., 2010) (Fig. 6).



Imagenologic studies of heterotopic ossification: A) plain X-rays with calcifications around femoral heads; B) Computerized tomography showing calcifications anterior to the femoral heads (red circles); C) Three dimension reconstruction of computerized tomography with massive calcification (red circles)

FIG. 6 Heterotopic ossification.

Autonomic dysreflexia

Autonomic dysreflexia (AD) is the sudden onset of arterial hypertension (increase of 20–40 mmHg in baseline blood pressure in adults or 15–20 mmHg in pediatric clinics) which occurs in patients with either complete or incomplete SCI above T6 associated with phenomena of cutaneous vasodilation in the head and neck (above the level of injury), characterized by facial flushing, nasal congestion and increased sweating, excruciating headaches, piloerection below the level of the lesion and, eventually, bradycardia (Cowan, Lakra, & Desai, 2020).

Early recognition is mandatory because of the risk of lethal complications such as acute myocardial infarction, pulmonary edema, hypertensive encephalopathy, seizures, and intracranial hemorrhage. Triggers of AD include nociceptive stimuli below the level of injury like the distention of hollow viscera, inflammatory and infectious processes, cutaneous injuries, or inadequate positioning (Eldahan & Rabchevisky, 2018). Chronic maintenance of repetitive episodes of AD are related with cardiovascular disease in people with SCI (Cragg, Noonan, Krassioukov, & Borisoff, 2013; Krassioukov, Warburton, Teasell, et al., 2009; West, Popok, Crawford, & Krassioukov, 2015).

Treatment of AD episodes starts with the correction of the triggering factors. Positioning of the patient to stimulate orthostatic hypotension, loosening of clothes and orthoses, as well as emptying the bladder and bowel are the recommended initial maneuvers. Other painful sources should be sought for and treated. If blood pressure remains elevated, with systolic values above 150 mmHg and/or diastolic values above 120 mmHg, antihypertensive pharmacological treatment with rapid-onset drugs—nitrates, channel blockers calcium (nifedipine) and alpha-blockers (hydralazine)—can be initiated, followed by the investigation of the triggering factors. If the hypertensive crisis is sustained and the triggering factor cannot be removed, the patient must be hospitalized and monitored until blood pressure normalizes (Cowan et al., 2020).

Neurogenic bladder

Urination is a process controlled by a complex neural network that involves multiple segments of the central nervous system (cerebral cortex, brainstem, spinal cord), peripheral nervous system and autonomic nervous system. In the SCI, ascending or descending tracts and the autonomic nervous system are compromised, altering the entire voiding cycle (Lisenmeyer, Bodner, Creasey, et al., 2006). Most common consequences of lesions in the upper motor neuron (i.e., above the medullary cone) are:

- Detrusor hyperreflexia: when the detrusor musculature contracts with minimal volumes of bladder repletion. These contractions can lead to hypertrophy of the detrusor musculature, formation of bladder diverticula and reduce bladder compliance.
- Voiding residue: the sphincter remains closed and opens momentarily at the expense of high intravesical pressure. Therefore, there is an accumulation of urine which predisposes the subject to infections and urinary stones.
- Vesical sphincter dyssynergy: under physiological conditions, the detrusor contracts as the urinary sphincter relaxes. In this pathologic condition, the detrusor contracts independently from sphincter opening and it is usual that paradoxical hypertonia of the sphincter is noticed (Lucas, 2019). Increased intravesical pressure that can lead to vesicoureteral reflux, elevation of pressure in the ureters and renal pelvis, causing dilation of the ureters and loss of renal function.

Periodic urodynamic study and urinary tract images are recommended after the acute phase of the SCI (Kreydin, Welk, Chung, Clemens, et al., 2018). Treatment of detrusor hyperreflexia requires tricyclic antidepressants, antimuscarinic drugs, or beta 3 agonists which differ among themselves in the frequency of side effects like blurry vision, impaired cognition, dry mouth, constipation, and tolerability (Milligan, Goetz, & Kennelly, 2020). The direct injection of botulinum toxin to the detrusor has been shown to significantly improve the bladder capacity without adverse effects, reducing the frequency of intermittent catheterization. Alpha-blockers reduce tension in sphincter and bladder neck muscles and can be combined in the treatment, especially in subjects with AD (Abreu-Mendes, Cruz, & Martins-Silva, 2020).

To guarantee an adequate bladder emptying, without post-voiding residue and low intravesical pressure, the most appropriate method is clean intermittent catheterization by the patient or a caregiver soon after the patient is clinically stable (Romo, Smith, Cox, et al., 2018). Complications comprise recurrent urinary tract infection and urethral trauma. For male patients with the condom catheter can use reflex voiding or bladder expression to push urine to the collector system, but recent systematic reviews (Groen, Pannek, Castro Diaz, et al., 2016; Kreydin et al., 2018) recommended clean intermittent catheterization as the primary method for bladder management, once theses maneuvers are associated with elevated intravesical pressure, vesicoureteral reflux, and upper tract disease (Wyndaele, Madersbacher, & Kovindha, 2001).

In lower motor neuron injuries, the biggest problem will be stress urinary incontinence, which occurs even with minimal movements. The detrusor musculature will be atonic and there will be great bladder capacity. Sometimes emptying

maneuvers (Crede, Valsalva or a combination of these) will be insufficient for the complete emptying of the bladder but emptying by clean intermittent catheterization is also stimulated (Romo et al., 2018).

Neurogenic bowel dysfunction

Neurogenic bowel dysfunction results from autonomic nervous system injury and lack of central nervous system control. These disorders are highly prevalent in SCI and involve constipation (prevalence ranging between 56% and 80%), fecal incontinence (range 42%–75%), hemorrhoids (36%) and bloating (31%) (Krassioukov, Eng, Claxton, et al., 2010). Typically, constipation will occur in injuries above T11/T12 region, whereas incontinence follows lesions below that level (Rodriguez, 2016). Because traumatic SCI usually occurs at the cervical or thoracic levels, the spinal defecation center, located in the sacral spinal cord, is intact (Callaghan, Furness, & Pustovit, 2018).

In lesions above the sacral segments (medullary cone), the connections between the spinal cord and the bowel are maintained, the external sphincter and pelvic floor are hypertonic, causing stool retention. Since nerve connections between the spinal cord and the colon are preserved, bowel movement can be triggered by reflexes, so an irritating suppository or digital stimulation are therapeutic strategies to stimulate defecation (Adriaansen, van Asbeck, & van Kuppevelt, 2015).

Lesions below the sacral segments or cauda equina are characterized by loss of spinal cord mediation of the peristalsis, the propulsion of the fecal bolus is sluggish, there is intestinal areflexia, decreased bowel transit and sphincter tone, leading constipation associated with fecal incontinence. Digital stool extraction is quite common (Krassioukov et al., 2010).

Guidelines on emptying maneuvers include diet recommendations (Bernardi et al., 2020), choosing the best position for defecation (sitting in a hygienic chair), digital rectal stimulation or suppository which triggers the defecation reflex, relaxes the external anal sphincter, and can facilitate digital stool extraction. Abdominal massage and Valsalva maneuver are also indicated. Drug treatment is based on the use of laxatives, preferably mass forming (natural or synthetic fibers). Osmotic laxatives (lactulose) and emollients (mineral oil) are also prescribed when intestinal emptying is unsatisfactory with previous methods. The use of stimulants (bisacodyl) or irritants (senna) is avoided because chronic use can cause damage to the myenteric plexus (Krassioukov et al., 2010). More invasive interventions include trans-anal irrigation, antegrade colonic irrigation, nerve stimulation of anterior sacral roots and, finally, a colostomy, which provides good results and greater independence, even having good acceptance by patients (Hultling, 2020).

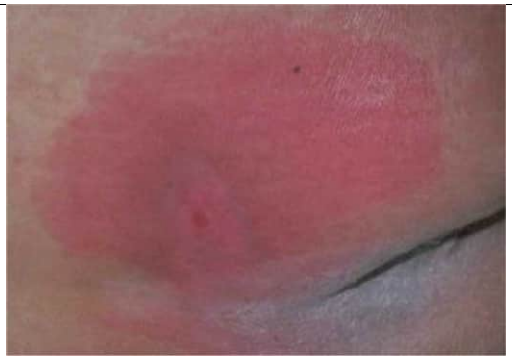
Pressure ulcers

Pressure ulcers (PU) are common complications with enormous impact on morbidity and mortality after SCI. They can be life-threatening and are a major economic burden, causing prolonged hospital stay, and compromised functional prognosis. They often occur over bony prominence in patients with altered sensitivity who remain in the same position for a long time (Atkinson & Cullum, 2018). Apparently, skin healing response to pressure differs in subjects with SCI as much as skin temperature, moistness, presence of feces and urine which interfere in the pathogenesis. A recent systematic review could not identify sufficient evidence for optimal bed or seated positions, or pressure relief maneuvers to prevent PUs in SCI persons (Groah, Schladen, Pineda, & Hsieh, 2015), although there is consensus that avoiding the 90° lateral position reduces PU risk over the trochanters. For wheelchair users, pressures are redistributed from the sitting area during recline and tilt, although reclining increases the risk of shear forces on the skin. Thus, technology with of cushions and wheelchairs is decisive in the prevention of PUs (He & Shi, 2020).

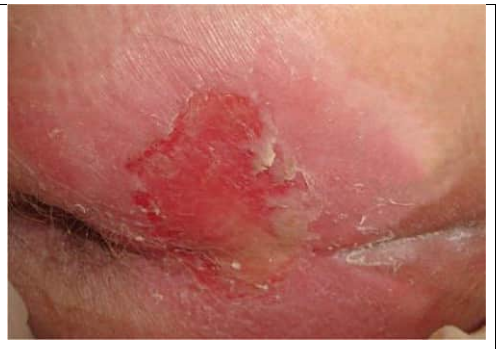
Facing an established PU, the treatment should focus on patient education to avoid any body support on the injured area, followed by local care to warrant a clean wound environment. Nutritional support is mandatory because of increased catabolic metabolism, risk of anemia and hypoalbuminemia (Bettex, Philandrianos, Jaloux, Bertrand, & Casanova, 2019). The control of automatisms, spasticity and prevention of deformities are key aspects to reduce pressure and shear forces (Atkinson & Cullum, 2018). The occurrence of infections on PUs is not rare, though swab cultures are often inconclusive and multi-bacterial (Dana & Bauman, 2015). If there is bony exposure, the recommendation is to collect bony material for culture and perform magnetic resonance studies to clarify the diagnosis of osteomyelitis and plan the surgical approach (Bettex et al., 2019) (Fig. 7).

Applications to other areas of neuroscience

Despite the enormous efforts of science, there is still no effective measure to cure SCI. The possibility of finding ways to provide neurological recovery depends on further clarifying the neurophysiological mechanisms related to SCI and recovery after trauma. We can say the same about the treatment of its main complications such as neuropathic pain,



Stage 1



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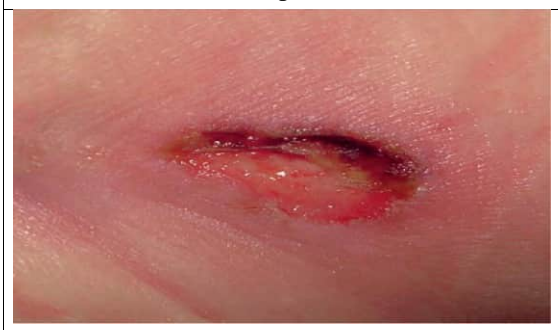

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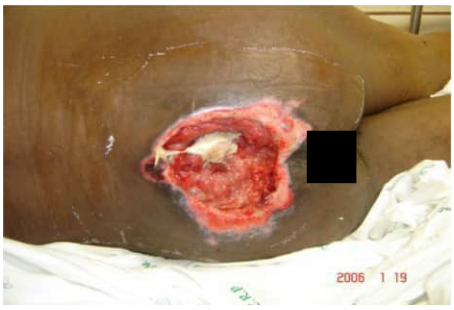

Stage 4

FIG. 7 Classification of pressure-induced skin injuries according to severity and deepness of the tissues involved.

spasticity, autonomic changes, and sphincter dysfunctions. The best management and reduction of their negative functional impacts also depends on a greater understanding of the complex mechanisms involved, knowing that structural and functional transformations of the neural axis and autonomic nervous system are involved. An improvement in the understanding of cellular and neurophysiological events may bring more effective treatments and greater possibilities of rehabilitation for patients with SCI.

Once structural and physiologic recovery are still not possible, rehabilitation is the main resource to attend the needs of these individuals. As much as in other central nervous system injuries, strategies to improve neuroplasticity based on the repetition are recommenced. This is particularly true in robotic therapy and use of powered exoskeletons for mobility or upper limb use. Future expectations rely on the crescent investigation of brain–machine interface. Also, alternative means of accomplishing the daily tasks should be texted and reinforced by a multi-professional rehabilitation team, considering the growing contribution of environmental facilitators and assistive technology to enhance social participation.

Mini-dictionary of terms

Activities of daily Living: term used to collectively describe fundamental skills that are required to independently care for oneself such as eating, bathing, and mobility.

Disability: The condition of being unable to perform an action because of an impairment in a specific environment and personal context.

Orthosis: an artificial or mechanical aid, such as a brace, to support or assist movement of a weak or injured part of the body.

Robotic devices: Powered instruments designed to help the subject to complete motor tasks or achieve better performance.

Urodynamic study: Clinical physiological study of the responses of the detrusor muscle to the accumulation of fluid in the bladder.

Key facts of clinical classification of SCI and mobility

- SCI is an extremely complex clinical condition that involves motor, sensory, and autonomic changes.
- The traumatic etiology responds for at least half of the cases, which affect mainly young adults and generate many costs to the individual, family, and society.
- The American Spinal Injury Association (ASIA) classification should be used to warrant standardization in diagnosis and comparison of treatments in different countries.
- Complete injuries are defined by the absence of sensitivity and motor skills in the last sacral roots and are less likely to have neurological recovery.
- Incomplete injuries manifest some motor or sensory preservation in the sacral levels and usually have better functional prognosis.
- Rehabilitation programs aim for improvement of functioning, prevention of secondary impairments, health promotion and education for patients and caregivers.
- The use of robotic equipment and powered exoskeletons are useful strategies in SCI because of a high volume of high-quality movement repetitions and reduced therapist burden.
- Access to orthoses and assistive technology allows people with spinal cord injuries to have greater independence and social participation.

Key facts on clinical complications of SCI

- Pain after SCI is frequent and may require centrally acting drugs or neurosurgical interventions in the most refractory cases.
- Spasticity treatments include physiotherapy, medications, neurolytic blocks, and the use of orthoses.
- The absence of sensitivity and movement in this population determines a high risk of pressure ulcers.
- Heterotopic ossification is the growth of an ectopic bone usually close to large joints which limits range of motion and hinders proper positioning and transfers and mobility.
- SCI usually results in loss of voluntary control of urination thus requiring bladder emptying through a catheter to prevent urinary loss and social restriction.
- Appropriate management of the neurogenic bladder prevents complications such as urinary stones or renal failure.
- Impairment of bowel and fecal sphincter control heightens the risk of constipation and eventual fecal incontinence.

Summary points

- Rehabilitation of SCI persons requires multi-professional skilled teams.
- Management of rehabilitation of SCI persons should use multi-dimensional assessment tools.
- Robotic devices promote high amounts of repetition and engage patients in motor tasks in interactive environments.
- Powered exoskeletons are already commercially available and can enhance exercise practice, social participation although there is still room for substantial improvement.
- Secondary complications of SCI may affect multiple systems and require the clinician to be aware of preventive and therapeutic interventions.

References

Abreu-Mendes, P., Cruz, F., & Martins-Silva, C. (2020). Treatment of neurogenic lower urinary tract symptoms: Main contributions from 2018 and 2019. *Current Opinion in Urology*, *30*(4), 486–490.

Adams, M. M., & Hicks, A. L. (2005). Spasticity after spinal cord injury. *Spinal Cord*, *43*, 577–586.

Adriaansen, J. J., van Asbeck, F. W., & van Kuppevelt, D. (2015). Outcomes of neurogenic bowel management in individuals living with a spinal cord injury for at least 10 years. *Archives of Physical Medicine and Rehabilitation*, *96*(5), 905–912.

Almeida, C., Coelho, J. C., & Riberto, M. (2016). Applicability, validation, and reproducibility of the spinal cord Independence measure version III (SCIM III) in patients with non-traumatic spinal cord lesions. *Disability and Rehabilitation*, *38*(22), 2229–2234.

Arazpour, M., Bani, M. A., Hutchins, S. W., & Jones, R. K. (2013). The physiological cost index of walking with mechanical and powered gait orthosis in patients with spinal cord injury. *Spinal Cord*, *51*(5), 356–359.

Atkinson, R. A., & Cullum, N. A. (2018). Interventions for pressure ulcers: A summary of evidence for prevention and treatment. *Spinal Cord*, *56*(3), 186–198.

Bernardi, M., Fedullo, A. L., Bernardi, E., Munzi, D., Peluso, I., Myers, J., et al. (2020). Diet in neurogenic bowel management: A viewpoint on spinal cord injury. *World Journal of Gastroenterology*, *26*(20), 2479–2497.

Bettex, Q., Philandrianos, C., Jaloux, C., Bertrand, B., & Casanova, D. (2019). La chirurgie secondaire des escarres chez le blessé médullaire [Surgical treatment of recurrent pressure ulcers in spinal cord injured patients]. *Annales de Chirurgie Plastique et Esthétique*, *64*(5–6), 674–684.

Bickenbach, J., Officer, A., Shakespeare, T., von Groote, P., World Health Organization, et al. (2013). *International perspectives on spinal cord injury: Summary*. World Health Organization. Available at https://apps.who.int/iris/handle/10665/94192.

Brady, R. D., Schultz, S. R., McDonald, S. J., & O'Brien, T. J. (2018). Neurological heterotopic ossification: Current understanding and future direction. *Bone*, *109*, 35–42.

Burke, D., Fullen, B. M., Stokes, D., et al. (2017). Neuropathic pain prevalence following spinal cord injury: A systematic review and meta-analysis. *European Journal of Pain*, *21*(1), 29–44.

Callaghan, B., Furness, J. B., & Pustovit, R. V. (2018). Neural pathways for colorectal control, relevance to spinal cord injury and treatment: A narrative review. *Spinal Cord*, *56*, 199–205.

Carpino, G., Pezzola, A., Urbano, M., & Guglielmelli, E. (2018). Assessing effectiveness and costs in robot-mediated lower limbs rehabilitation: A meta-analysis and state of the art. *Journal of Healthcare Engineering*, *2018*, 12.

Carvajal, D. V. T., Silva, N. O., Maeda, L. S., & Riberto, M. (2019). Phenol as a neurolytic agent in the treatment of focal and multifocal spasticity. *Acta Fisiatrica*, *26*(1), 1.

Castro, A. W., & Greve, J. M. D. (2003). Heterotopic ossification in patients with spinal cord injuries: Association with HLA-system antigens. *Acta Ortopedica Brasileira.*, *11*(2), 102–108.

Cowan, H., Lakra, C., & Desai, M. (2020). Autonomic dysreflexia in spinal cord injury. *BMJ*, *371*, m3596.

Cragg, J. J., Noonan, V. K., Krassioukov, A., & Borisoff, J. (2013). Cardiovascular disease and spinal cord injury: Results from a national population health survey. *Neurology*, *81*, 723–728.

Dana, A. N., & Bauman, W. A. (2015). Bacteriology of pressure ulcers in individuals with spinal cord injury: What we know and what we should know. *The Journal of Spinal Cord Medicine*, *38*(2), 147–160.

Elbasiouny, S. M., Moroz, D., Bakr, M. M., et al. (2010). Management of spasticity after spinal cord injury: Current techniques and future directions. *Neurorehabilitation and Neural Repair*, *24*(1), 23–33.

Eldahan, K. C., & Rabchevisky, A. G. (2018). Autonomic Dysreflexia after spinal cord injury: Systemic pathophysiology and methods of management. *Autonomic Neuroscience*, *209*(1), 59–70.

Elovic, E. P., Eisenberg, M. E., & Jasey, N. N., Jr. (2010). Spasticity and muscle Overactivity as components of the upper motor neuron syndrome. In *DeLisa's physical-medicine-rehabilitation: Principles and practice* (pp. 1319–1344). Philadelphia: Lippincott Williams & Wilkins.

Fregni, F., Boggio, P. S., Lima, M. C., et al. (2006). A sham-controlled, phase II trial of transcranial direct current stimulation for the treatment of central pain in traumatic spinal cord injury. *Pain*, *122*, 197–209.

Freitas, P. S., Santana, T. S., Manoel, L. S., Serenza, F. S., & Riberto, M. (2019). A comparison of isokinetic rotator cuff performance in wheelchair basketball athletes vs. non-athletes with spinal cord injury. *The Journal of Spinal Cord Medicine*, *16*, 1–6.

Groah, S. L., Schladen, M., Pineda, C. G., & Hsieh, C. H. (2015). Prevention of pressure ulcers among people with spinal cord injury: A systematic review. *PM & R: The Journal of Injury, Function, and Rehabilitation*, *7*(6), 613–636.

Groen, J., Pannek, J., Castro Diaz, D., et al. (2016). Summary of European Association of Urology (EAU) guidelines on neuro-urology. *European Urology*, *69*(2), 324–333.

He, C., & Shi, P. (2020). Interface pressure reduction effects of wheelchair cushions in individuals with spinal cord injury: A rapid review. *Disability and Rehabilitation*, *23*, 1–8.

Hultling, C. (2020). Neurogenic bowel management using trans anal irrigation by persons with spinal cord injury. *Physical Medicine and Rehabilitation Clinics of North America*, *31*, 305–318.

Kang, Y., Ding, H., Zhou, H., Wei, Z., Liu, L., Pan, L., et al. (2018). Epidemiology of worldwide spinal cord injury: A literature review. *Journal of Neurorestoratology.*, *6*, 1–9.

Kirshblum, S., & BrooksIn, M. (2010). Rehabilitation of spinal cord injury. In J. DeLisa (Ed.), *DeLisa's physical-medicine-rehabilitation: Principles and practice* (pp. 665–716). Philadelphia: Lippincott Williams & Wilkins.

Kirshblum, S. C., Burns, S. P., Biering-Sorensen, F., et al. (2011). International standards of neurological classification of spinal cord injury (revised 2001). *The Journal of Spinal Cord Medicine.*, *34*(6), 535–546.

Krassioukov, A., Eng, J., Claxton, G., et al. (2010). Neurogenic bowel management after spinal cord injury: A systematic review of the evidence. *Spinal Cord*, *48*(10), 718–733.

Krassioukov, A., Warburton, D. E. R., Teasell, R., et al. (2009). The SCIRE research team. A systematic review of the Management of Autonomic Dysreflexia Following Spinal Cord Injury. *Archives of Physical Medicine and Rehabilitation*, *90*(4), 682–695.

Kreydin, E., Welk, B., Chung, D., Clemens, Q., et al. (2018). Surveillance and management of urologic complications after spinal cord injury. *World Journal of Urology*, *36*(10), 1545–1553.

Leite, V. F., Souza, D. R., Imamura, M., & Battistella, L. R. (2019). Post-discharge mortality in patients with traumatic spinal cord injury in a Brazilian hospital: A retrospective cohort. *Spinal Cord*, *57*(2), 134–140.

Lisenmeyer, T. A., Bodner, D. R., Creasey, H. G., et al. (2006). The consortium for spinal cord medicine—Bladder Management for Adults with spinal cord injury: A clinical practice guideline for health-care providers. *The Journal of Spinal Cord Medicine*, *29*(5), 527–573.

Lu, Z., Tong, K. Y., Shin, H., Stampas, A., & Zhou, P. (2017). Robotic hand-assisted training for spinal cord injury driven by myoelectric pattern recognition: A case report. *American Journal of Physical Medicine & Rehabilitation*, *96*(10 Suppl 1), S146–s9.

Lucas, E. (2019). Medical Management of Neurogenic Bladder for children and adults: A review. *Topics in Spinal Cord Injury Rehabilitation*, *25*(3), 195–204.

Mehta, S., McIntyre, A., Janzen, S., et al. (2016). Systematic review of pharmacologic treatments of pain after spinal cord injury: An update. *Archives of Physical Medicine and Rehabilitation*, *97*(8), 1381–1391.

Mekki, M., Delgado, A. D., Fry, A., Putrino, D., & Huang, V. (2018). Robotic rehabilitation and spinal cord injury: A narrative review. *Neurotherapeutics*, *15*, 604–617.

Miller, L. E., Zimmermann, A. K., & Herbert, W. G. (2016). Clinical effectiveness and safety of powered exoskeleton-assisted walking in patients with spinal cord injury: Systematic review with meta-analysis. *Medical Devices (Auckland, N.Z.)*, *22*(9), 455–466.

Milligan, J., Goetz, L. L., & Kennelly, M. J. (2020). A primary care Provider's guide to management of neurogenic lower urinary tract dysfunction and urinary tract infection after spinal cord injury. *Topics in Spinal Cord Injury Rehabilitation*, *26*(2), 108–115.

Nas, K., Yazmalar, L., Şah, V., et al. (2015). Rehabilitation of spinal cord injuries. *World Journal of Orthopedics*, *6*(1), 8–16.

Pavese, C., Schneider, M. P., Schubert, M., Curt, A., Scivoletto, G., Finazzi-Agro, E., et al. (2016). Prediction of bladder outcomes after traumatic spinal cord injury: A longitudinal cohort study. *PLoS Medicine*, *13*(6), 1.

Popovic, M., Agarwal, A., Zhang, L., et al. (2014). Radiotherapy for prophylaxis of heterotopic ossification: A systematic review and meta-analysis of published data. *Radiotherapy and Oncology*, *113*(1), 10–17.

Ranganathan, K., Loder, S., Agarwal, S., Wong, V. W., Forsberg, J., Davis, T. A., et al. (2015). Heterotopic ossification: Basic-science principles and clinical correlates. *The Journal of Bone and Joint Surgery. American Volume*, *97*(13), 1101–1111.

Riberto, M., Pinto, P. P. N., Sakamoto, H., & Battistella, L. R. (2005). Functional independence of spinal cord injured patients. *Acta Fisiátrica*, *12*(2), 61–66.

Rodriguez, G. M. (2016). Bowel function after spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *97*, 339–340.

Romo, P. G. B., Smith, C. P., Cox, A., et al. (2018). Non-surgical urologic management of neurogenic bladder after spinal cord injury. *World Journal of Urology*, *36*(10), 1555–1568.

Rudhe, C., Albisser, U., Starkey, M. L., Curt, A., & Bolliger, M. (2012). Reliability of movement workspace measurements in a passive arm orthosis used in spinal cord injury rehabilitation. *Journal of Neuroengineering and Rehabilitation*, *9*, 37.

Siddal, P. J., & Loeser, J. D. (2001). Pain following spinal cord injury. *Spinal Cord*, *39*, 63–73.

Siedziewski, L., Schaaf, R. C., & Mount, J. (2012). Use of robotics in spinal cord injury: A case report. *The American Journal of Occupational Therapy*, *66* (1), 51–58.

Taricco, M., Adone, R., Pagliacci, C., & Telaro, E. (2000). Pharmacological interventions for spasticity following spinal cord injury. *Cochrane Database of Systematic Reviews*, *2*.

Teasell, R. W., Mehta, S., Aubut, J. L., Ashe, M. C., et al. (2010). A systematic review of the therapeutic interventions for heterotopic ossification after spinal cord injury. *Spinal Cord*, *48*, 512–521.

van Dijsseldonk, R. B., van Nes, I. J. W., Geurts, A. C. H., & Keijsers, N. L. W. (2020). Exoskeleton home and community use in people with complete spinal cord injury. *Scientific Reports*, *10*(1), 15600.

van Middendorp, J. J., Hasman, A. J. F., Danders, A. R. T., Pouw, N. H., Ditunno, J. F., Curt, A., et al. (2011). A clinical prediction rule for ambulation outcomes after traumatic spinal cord injury: A longitudinal cohort study. *The Lancet*, *377*, 1004–1010.

Velstra, I. M., Bolliger, M., Tanadini, L. G., Baumberger, M., Abel, R., Rietman, J. S., et al. (2014). Prediction e stratification of upper limb function and sef-care in acute cervical spinal cord injury with the graded redefined assessment of strength, sensibility and prehension (GRASSP). *Neurorehabilitation and Neural Repair*, *28*(7), 632–642.

West, C. R., Popok, D., Crawford, M. A., & Krassioukov, A. V. (2015). Characterizing the temporal development of cardiovascular dysfunction in response to spinal cord injury. *Journal of Neurotrauma*, *32*(12), 922–930.

Wyndaele, J. J., Madersbacher, H., & Kovindha, A. (2001). Conservative treatment of the neuropathic bladder in spinal cord injured patients. *Spinal Cord*, *39*, 294–300.

Zariffa, J., Kapadia, N., Kramer, J. L., Taylor, P., Alizadeh-Meghrazi, M., Zivanovic, V., et al. (2012). Relationship between clinical assessments of function and measurements from an upper-limb robotic rehabilitation device in cervical spinal cord injury. *IEEE transactions on Neural Systems and Rehabilitation Engineering: A Publication of the IEEE Engineering in Medicine and Biology Society*, *20*(3), 341–350.

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Section B

Cellular and molecular aspects of spinal injury

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Chapter 7

Gene expression and bone loss following spinal cord injury

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List of abbreviations

BMD	bone mineral density
BV/TV	fractional bone volume
CCL2	C—C motif chemokine ligand 2
CDC20	cell division cycle 20
CDK1	cyclin-dependent kinase 1
CCNA2	cyclin A2
CCNB1	cyclin B1
COL1a2	collagen type 1, alpha 2
Conn.D	connectivity density
CSA	cross-sectional area
CSF2	colony-stimulating factor 2
CTX	C-terminal telopeptide
DNA	deoxyribonucleic acid
DKK1	Dickkopf-1
EGR1	early growth response protein 1
FGF2	fibroblast growth factor
FOS	fos proto-oncogene
GFAP	glial fibrillary acidic protein
IL-β	interleukin 1 beta
IL6	interleukin 6
ITGAM	integrin subunit alpha M
JUN	jun proto-oncogene
lncRNA	long non-coding RNA
LRP-5	low-density lipoprotein receptor-related protein 5
LRP-6	low-density lipoprotein receptor-related protein 6
MBOAT4	membrane-bound O-acyltransferase domain containing 4
miRNA	micro RNA
mRNA	messenger RNA
MYC	MYC proto-oncogene
OPG	osteoprotegerin
OSX	osterixPOLE DNA polymerase epsilon, catalytic subunit
RANKL	receptor activator of NF-kB ligand
RNA	ribonucleic acid
RUNX2	runt-related transcription factor 2
SCI	spinal cord injury
sFRPs	secreted frizzled-related proteins
SMI	structure model index
STAT3	signal transducer and activator of transcription 3
Tb.Sp	trabecular separation
Tb.N	trabecular number

Cellular, Molecular, Physiological, and Behavioral Aspects of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822427-4.00007-1

TGFBR2	transforming growth factor β receptor 2
TNFα	tumor necrosis factor alpha
TOP2A	DNA topoisomerase II alpha
TRAP	tartrate-resistant acid phosphatase TNFtumor necrosis factor
Wnt/β-catenin	canonical Wnt or beta (β)-catenin pathway
VEGF	vascular endothelial growth factor
VEGFR2	vascular endothelial growth factor receptor 2

Introduction

If a spinal cord is injured, several molecular and cellular processes are impaired, resulting in systemic changes that affect several organs and tissues, and leads to a complex disease that requires multi-professional care treatment. Although the motor and sensory deficits are the most evident and life quality impacting changes due to spinal cord injury (SCI), autonomic and cardiovascular abnormalities occur and lead to several secondary complications (Eldahan & Rabchevsky, 2018). Aside from the immobility due to SCI, these individuals have a disconnection between autonomic circuits and supraspinal control, leading to significant liability in blood pressure and vascular injuries (Popa et al., 2010). Therefore, ranging from extreme hypotension during episodes of orthostatic hypotension to severe hypertension during episodes of autonomic dysreflexia (Cragg, Noonan, Krassioukov, & Borisoff, 2013; Karlsson, 1999). Of note, cardiovascular and respiratory complications secondary to SCI are among the most common underlying and contributing causes of death in this population (Myers, Lee, & Kiratli, 2007). In the past, renal failure was a leading cause of death in SCI individuals. However, proper care of the urological tract has decreased mortality rate, but require early, intense, and continuous care to avoid deterioration of renal function over time (Nseyo & Santiago-Lastra, 2017; Panicker, Fowler, & Kessler, 2015; Samson & Cardenas, 2007; Welk et al., 2018). Other complications include hepatic dysfunction (Goodus & McTigue, 2020), gastrointestinal and metabolic disorder (Kigerl, Zane, Adams, Sullivan, & Popovich, 2020), thermoregulation (Price & Trbovich, 2018), and pressure ulcer formation (Baron et al., 2018), not to mention the mental and emotional impact, as well as the economic burdens to individuals, families, and societies (Ramer, Ramer, & Bradbury, 2014). This chapter aims to gain a better understanding of the different mechanisms responsible for systemic changes following a spinal cord injury and to specifically underly the relation between gene expression and SCI-induced bone loss.

Incidence and pathophysiological mechanisms of spinal cord injury

Approximately half a million people damage their spinal cord every year worldwide (Holmes, 2017), being approximately 18,000 new SCI cases per year in the United States, excluding those whose death occurred immediately post-injury (National Spinal Cord Injury Statistical Center, 2020). Aside from the non-traumatic SCI, a recent study evidenced the global incidence of traumatic spinal injury as 10.5 cases per 100,000 persons, resulting in an estimated 768,473 new cases every year. Road traffic accidents, followed by falls, were the most common mechanisms of injury. Furthermore, SCI incidence has been shown to be higher in low- and middle-income countries (8.72 per 100,000 persons) compared with high-income countries (13.69 per 100,000 persons) (Kumar et al., 2018). Accordingly, previous studies have shown that the prevalence of SCI is estimated as much as 71 new cases per million in Brazil (de Campos et al., 2008) and 318 in Iran, annually (Soleyman-Jahi et al., 2018).

SCI is a highly debilitating disease and is increasingly being recognized as a significant global health priority. Yet, the mechanisms underlying SCI have not been fully elucidated, and effective therapies for SCI are lacking (Wang et al., 2019). What is known is that its pathophysiological mechanism has two phases. The primary damage is the mechanical injury itself, which occurs in response to the force directly impacted to the spinal cord during the mechanical injury, which leads to disruption in axons, blood vessels, and cell membranes (Venkatesh, Ghosh, Mullick, Manivasagam, & Sen, 2019). The secondary damage phase results from biochemical processes following the primary damage, and it is characterized by vascular dysfunction, edema, ischemia, excitotoxicity, electrolyte shifts, free radical production, inflammation, and cell death, representing an important therapeutic target at preventing injury progression (Rowland, Hawryluk, Kwon, & Fehlings, 2008). In the initial stage of the secondary phase, activation of microglia, T-cells, and astrocytes and upregulation of proinflammatory cytokines like the tumor necrosis factor alpha (TNFα) and interleukin 1 beta (IL-β) occur. As a result, it leads to disrupted endothelial cells, increased permeability of the blood–brain barrier during the inflammation, and hemorrhage

within the gray matter, thereby resulting in necrotic cell death or ischemia (Pineau & Lacroix, 2007). Another stage of the secondary phase refers to the Ca–dependent, glutamate-associated cell death and the formation of free radicals and nitric oxide, leading to impaired proteins, nucleic acids, lipids, and extracellular matrix proteins such as glycosaminoglycans. Consequently, resulting in neuronal cell death and function loss (Bao & Liu, 2002), as well as an overproduction of excitatory neurotransmitters such as glutamate and aspartate, which causes apoptosis of glial cells and neurons (Li & Stys, 2000; Park, Velumian, & Fehlings, 2004). Regeneration of the spinal cord does not occur after the injury due to intrinsic inhibitory factors expressed on central myelin and the extracellular matrix of the post-traumatic gliotic scar (Rowland et al., 2008).

Altered gene expression due to spinal cord injury

The expression of different genes has been identified in several diseases after the development of microarray and high-throughput sequence technologies (Venkatesh et al., 2019). Non-coding ribonucleic acid (RNA) genes, such as ribosomal RNAs, transfer RNAs, small nuclear RNAs, micro RNAs (miRNAs), and long non-coding RNAs (lncRNAs), have been identified in human and rodent genomes. MiRNAs are known to be differentially expressed after an SCI and may be a therapeutic target for the diagnosis, treatment, and prognosis of these lesions. Previous authors found that the serum *miR-9*, *miR-219*, and *miR-384-5p* levels may be promising biomarkers for predicting the severity of SCI (Hachisuka et al., 2014). LncRNAs constitute the largest portion of mammalian non-coding RNAs, with a critical role in the central nervous system, and that have risen as important regulators of several disease processes (Iyer et al., 2015). Specifically, previous authors reported that seven lncRNAs were found to be differentially expressed after an SCI, in which the *RGD1559747* (named as *lncSCIR1*) exhibited a significant downregulation at 1, 4, and 7 days following the injury (Wang et al., 2015). Recently, Zhou et al. have identified the expression of 772 lncRNA and 992 messenger RNA (mRNA) 2 h post-SCI, in which the interleukin 6 (IL6), membrane-bound o-acyltransferase domain containing 4 (MBOAT4), fos proto-oncogene (FOS), tumor necrosis factor (TNF), jun proto-oncogene (JUN), signal transducer and activator of transcription 3 (STAT3), colony-stimulating factor 2 (CSF2), MYC proto-oncogene (MYC), C—C motif chemokine ligand 2 (CCL2), and fibroblast growth factor 2 (FGF2) may be important targets in the immediate phase of SCI (Zhou et al., 2018). Changes in lncRNAs expression were also evidenced at the acute stages of SCI in a mouse model of spinal cord contusion. The authors detected few changes in the lncRNA expression levels at day 1 post-SCI, but the differential changes in LncRNA expression peaked 1 week after SCI and subsequently declined until 3 weeks post-SCI. The authors reported that differentially expressed mRNAs were involved in transport, cell adhesion, ion transport, and metabolic processes (Ding, Song, & Liu, 2016). In a very recent study, Shi et al. identified 3193 differentially expressed lncRNAs and 4308 differentially expressed mRNAs in an SCI rat model 2 days post-injury. The authors also detected 10 core genes, including interleukin 6 (IL6); deoxyribonucleic acid (DNA) topoisomerase II alpha (TOP2A); cyclin-dependent kinase 1 (CDK1); DNA polymerase epsilon, catalytic subunit (POLE); cyclin B1 (CCNB1); tumor necrosis factor (TNF); cyclin A2 (CCNA2); cell division cycle 20 (CDC20); integrin subunit alpha M (ITGAM); and MYC proto-oncogene (MYC), which may provide novel insights into the molecular mechanism of the early acute phase of SCI (Shi et al., 2019). In a recent and original study, Duran et al. detected critical pathways and networks that exhibit sustained alterations at the sub-chronic and chronic stages post-SCI. The authors identified 137 differentially expressed lncRNAs 1-month post-SCI, 239 in the third month, and 179 in the sixth month following injury, in which the molecules with the greatest number of interactions include transforming growth factor β receptor 2 (TGFBR2), glial fibrillary acidic protein (GFAP), signal transducer and activator of transcription 3 (STAT3), and early growth response protein 1 (EGR1), among others involved in astrogliosis and fibrosis. TGFBR2 exhibited a seven- to ninefold increase in gene expression from 1 month to 6 months post-SCI and had the most connections in the network, suggesting its essential roles in gliosis. The authors also identified several lncRNAs that may potentially be involved in the progression of SCI. These results indicate a high level of transcriptional abnormalities, which persisted in the sub-chronic and chronic stages, and the altered genes were related to several pathways such as immune and inflammatory responses (Duran et al., 2017).

Bone remodeling and osteometabolic dysfunction due to SCI

Bone remodeling corresponds to an ingenious mechanism, in which the bone contributes to the circulatory levels of calcium, and in parallel, ensures bone renewal. In ideal conditions, adult individuals restore bone resorption by an adequate amount of bone formation, guaranteeing bone strength maintenance (Zamarioli, de Andrade Staut, & Volpon, 2020). Any imbalance in bone turnover leads to osteometabolic dysfunction, and several mechanisms are involved according to each disease. Disuse osteoporosis is characterized by bone loss due to inactivity, and it is prevalent in several neurological disorders, including SCI, as well as in long-term bed rest and during microgravity exposure experienced by astronauts.

The osteocytes are bone cells embedded into the mineralized matrix, with the capability to sense mechanical stimuli and react to these loads by transducing these signals into biological responses, leading to the secretion of several factors, thus balancing bone turnover (Uda, Azab, Sun, Shi, & Pajevic, 2017). In able-bodied individuals, bone responds to its loading demand, in which higher mechanical load results in bone apposition and lower load results in bone resorption. SCI impairs motor function, thus resulting in immediate and permanent decrease of bone loading experienced by the lower extremities (Troy & Morse, 2015). The mechanisms underlying SCI-induced bone loss are complex and differ from other types of osteoporosis. Mechanical disuse in response to motor dysfunction, combined with post-injury neurogenic, vascular, and hormonal impairments, results in an imbalance of the natural resorption and formation of bone (Haider, Lobos, Simonian, Schnitzer, & Edwards, 2018).

Molecular mechanisms of SCI-induced bone loss

Although the mechanisms leading to SCI-induced bone loss are yet to be fully elucidated, the mechanical unloading may be a causative factor related to SCI-induced bone loss, mediated by osteocyte. Therefore, unloading conditions have not only been associated with osteocyte and osteoblast apoptosis but also with overactivity in bone resorption, providing a cellular mechanism for the suppressed bone formation and rapid bone loss (Gifre et al., 2015). The association between rapid bone loss and increased bone resorption rate, including increased alkaline phosphatase, urinary calcium, hydroxyproline, zinc, and constituents of bone matrix has been reported in the literature for a long time (Garland et al., 1992). Accordingly, a recent study with a rodent model of complete transection of the spinal cord evidenced an overactivity of bone resorption, parallel with a down expression of osteoblastic-related genes at different stages of cell maturation (Butezloff et al., 2019). Similarly, an uncoupled bone turnover was identified in SCI individuals as early as 2 days post-injury, with a predominance of resorption over formation, in which levels of serum C-terminal telopeptide (CTX) are increased by approximately 1.5-fold, in the absence of a coordinated change in serum osteocalcin (Peng et al., 2020). Bone resorption is stimulated by the release of receptor activator of NF-kB ligand (RANKL) by osteoblast lineage cells, thus stimulating differentiation and activity of osteoclasts. Osteocytes represent a major source of RANKL in unloaded bones, reflecting its fundamental role in mechanotransduction. The canonical Wnt or beta (β)-catenin pathway (Wnt/β-catenin) pathway regulates bone homeostasis by adjusting osteoblast function according to mechanical loading/unloading. Previous studies have reported upregulation of sclerostin, a Wnt inhibitor, in people with SCI (L. R. Morse et al., 2013). Consequently, leading to a decrease in Wnt/β-catenin signaling in osteoblasts, RANKL upregulation, osteoprotegerin (OPG) downregulation (Wijenayaka et al., 2011), therefore increasing bone resorption activity. Besides sclerostin, Dickkopf-1 (DKK1) and frizzled-related proteins (sFRPs) are Wnt inhibitors related to bone metabolism that exhibit important roles in the pathogenesis of disuse bone loss. Wnt binds to a co-receptor complex involving low-density lipoprotein receptor-related protein 5 or 6 (LRP-5 or LRP-6), present on osteoblasts, resulting in translocation of β-catenin, which activates gene transcription and promotes osteoblast proliferation, differentiation, and function, thereby leading to new bone formation. Sclerostin and DKK1 bind to LRP5/6 and suppress Wnt signaling, whereas sFRPs bind Wnts to reduce their biological activity (Peng et al., 2020).

Bone loss following SCI is certainly unique in its magnitude and rapidity, which may be explained by the concomitant effects of the absence of mechanical loading to the vascular changes, muscle atrophy, neural, and endocrine components. Appropriate vascular supply is essential for bone health, in which several pro-angiogenic factors, including vascular endothelial growth factor (VEGF) and its receptor VEGFR2, are crucial in the cross talk between bone cells and endothelial cells (Veeriah, Paone, Chatterjee, Teti, & Capulli, 2019). SCI-induced muscle atrophy also impairs bone homeostasis where the locoregional elastic deformation of the bone in response to muscle contraction is absent, thereby not leading to bone stimulation by means of mechanotransduction (Colaianni et al., 2017). Accordingly, a recent investigation in rats with muscle atrophy identified increased vascular porosity, with a reduction in osteocyte lacunar density, which resulted in increased intracortical porosity (Gatti et al., 2019), highly correlated to bone fragility (Iori et al., 2019). Bone–fat interactions are also involved in ongoing bone loss in chronic SCI. Of note, adiponectin, an adipokine produced by visceral fat, is negatively related to bone mass and strength in individuals with SCI, likely due to direct actions of adiponectin on bone cell receptors in regulating osteoblastogenesis and osteoclastogenesis (Doherty et al., 2014).

Acute and chronic stages of bone loss following SCI

SCI is known to cause rapid and intense osteoporosis, which is most severe below the level of injury (Morse et al., 2019) and may lead to a 5- to 23-fold increase in fracture risk. The mechanisms leading to SCI-induced bone loss involve two phases. A rapid and acute bone loss occurs in the first phase and reaches a plateau approximately 2 years post-injury. The second phase is characterized by a chronic and slower ongoing bone loss, which may continue for decades following SCI (Troy & Morse, 2015). It is also well recognized and reported in the literature that lower bone mass and skeletal

microarchitecture deterioration are consequences of SCI. Table 1 summarizes changes in bone quality in animals and patients with SCI, previously reported in the literature. As of note, bone loss starts acutely post-lesion and continues at a rate of nearly 4% per month in areas where the trabecular bone is dominant and 2% per month in regions mostly occupied by cortical bone (Wilmet, Ismail, Heilporn, Welraeds, & Bergmann, 1995). Recently, Peng et al. detected bone mass loss and microarchitectural deterioration of trabecular bone occurring as early as 2 days post-SCI, becoming more evident on

TABLE 1 Previous scientific evidence for bone loss following spinal cord injury.

Authors, year	Clinical or experimental design and time post-SCI	Assessed outcomes evidencing bone loss
Haider et al. (2018)	Computed tomography measures were obtained from 101 individuals, who experienced an SCI 30 days to 50 years prior to participation.	Bone loss showed an exponential decay over time until steady-state levels (3.6 years post-SCI). SCI also induced rapid and profound reductions in bone stiffness at the knee.
Gifre et al. (2015)	42 patients with a recent (<6 months) and complete SCI. Dickkopf-1 (DKK1), bone turnover marker C-terminal telopeptide (CTX), and bone mineral density (BMD) were assessed at baseline, at 6 and 12 months.	SCI patients exhibited a marked increase in CTX and DKK1 throughout the study, concomitant with important decrease in BMD. Patients with higher DKK1 values showed higher sublesional BMD loss.
Garland et al. (1992)	BMD of the knee was measured in 55 subjects. 10 were controls (non-SCI); 25 acutely injured (114 days post-SCI), with 12 reexamined 16 months after injury; and 20 chronic (>5 years post-SCI).	SCI-induced bone loss occurs throughout the entire skeleton, except the skull. Regression techniques demonstrated early, rapid, and linear decline of bone below the pelvis.
Butezloff et al. (2019)	Gene expression, bone quality and quantity were assessed in 36 rats, which sustained an SCI for 24 days prior to analysis.	SCI downregulated osteoblastic-related gene expression, associated with a twofold increase in osteoclasts and overexpression of receptor activator of NF-kB ligand (RANKL), resulting in lower bone mass, impaired microarchitecture, and weaker bones.
Peng et al. (2020)	20–24 rats were subjected to complete transection of the spinal cord. Blood, hindlimb bone samples, and bone marrows were collected at 2 and 7 days after SCI.	SCI-induced bone loss occurs as early as 2 days after injury and the skeletal defects become more evident at 7 days, with increased CTX levels.
Doherty et al. (2014)	The association between BMD and circulating adipokines (adiponectin and leptin) was investigated in 149 men with chronic SCI.	Adiponectin is negatively related to bone mass in individuals with SCI, likely due to direct actions of adiponectin on bone cell receptors in regulating osteoblastogenesis and osteoclastogenesis.
Wilmet et al. (1995)	One-year longitudinal study of bone mineral measurements and soft tissue composition in supra- and infra-lesional areas of 31 patients with SCI.	The authors observed a rapid decrease of bone mass in the paralyzed areas, (−4%/month during the first year in areas rich in trabecular bone and −2%/month in areas containing mainly compact bone).
Eser et al. (2004)	89 individuals between 2 months and 50 years post-SCI (24 tetraplegics and 65 paraplegics) were measured by peripheral quantitative computed tomography to quantify bone loss following SCI.	In the femur and tibia, bone mass, total and trabecular bone mineral density of the epiphyses, as well as bone mass and cortical cross-sectional area of the diaphyses showed an exponential decrease with time after injury in the SCI subjects. The decreasing bone parameters reached new steady states after 3–8 years, depending on the parameter.
Zamarioli et al. (2013)	Bone quality and quantity were assessed in 31 rats, which sustained an SCI for 33 days prior to analysis.	The authors observed lower mass, increased osteoclastic activity, and weaker bone integrity due to SCI.
Rodriguez et al. (2021)	The incidence of musculoskeletal morbidities was compared between adults with (9081) and without SCIs (1,474,232). Incidence estimates of common musculoskeletal morbidities (e.g., osteoporosis, sarcopenia, osteoarthritis, fractures, etc.) were compared at 5 years of enrollment.	Adults living with traumatic SCIs had a higher incidence of musculoskeletal morbidities (82% vs. 47%) as compared to adults without SCI, and differences were to a clinically meaningful extent.

Previous experimental and clinical studies reported bone changes in animals and individuals with spinal cord injury.

day 7 after injury. Specifically, the authors identified a rapid reduction of sublesional cancellous bone mineral density (BMD), a tridimensional structural disruption, including lower bone volume (BV/TV), increased trabecular separation (Tb.Sp), and higher structure model index (SMI) for rod-like geometry, as well as lower trabecular number (Tb.N) and connectivity density (Conn.D), which resulted in compromised structural integrity and reduced mechanical strength (Peng et al., 2020). Bone losses are more significant around the knee (distal femur and proximal tibia) and previous studies have documented reduction in bone mineral content (BMC) of up to 50% within the first 5 years post-SCI, reflecting important clinical implications as SCI individuals are more than twice as likely to fracture a sublesional bone at some point of their life compared to able-bodied controls (Haider et al., 2018). The chronic stage of bone loss following SCI (more than 2 years after injury) is poorly defined as ongoing bone loss is not usually assessed until a fracture occurs. Chronic SCI is associated with significant decreases in bone mass, microstructure, bone strength, and muscle mass in the lower limbs. As of note, previous investigations have identified reductions in femoral neck BMD of 27%–40%, knee BMD of 37%–70%, and tibia cortical diaphysis BMC of 7%–25%. Trabecular microarchitectural parameters such as BV/TV and Tb.N at the distal femur and proximal tibia are decreased by 20%–27% compared to able-bodied healthy individuals (Troy & Morse, 2015). Mean cortical thickness decreased at a loss rate of 0.23 mm/year in the femur and 0.28 mm/year in the tibia. The reduction of cortical cross-sectional area (CSA), concomitant with stable total CSA suggests mostly endocortical resorption of the femoral and tibial shaft (Eser et al., 2004), which leads to severe mechanical integrity impairment.

Changes in bone quality and quantity following SCI

Previous outcomes regarding bone loss following SCI have been published in the literature by the author's research group (Butezloff et al., 2019; Zamarioli et al., 2013, 2014; Zamarioli et al., 2020). Here, we illustrate bone changes in response to complete transection of the spinal cord at the vertebral T10 level in rats after 30 days of injury in comparison with age-matched, sham-operated rats. Fig. 1 represents the uncoupled turnover in SCI rats in which bone resorption exceeds formation, compared to a balanced bone turnover in sham-operated rats. The increased osteoclastic activity is demonstrated histologically by tartrate-resistant acid phosphatase (TRAP) staining that specifically identifies osteoclasts cells, in red (Fig. 2). As a result of the increased resorption activity over bone formation, Fig. 3 shows bone microarchitecture deterioration in rats sustaining a complete SCI compared to the shams. Accordingly, Fig. 4 evidences that such deterioration occurs both in trabecular and cortical bone. These tridimensional figures are outcomes obtained by microcomputed tomography. Assessments performed by means of scanning electron microscopy also detected a time-dependent behavior of SCI-induced bone loss, demonstrated in Fig. 5. In this image, a substantial bone loss may be seen in paraplegic rats at both 30 and 60 days after injury. However, bone loss is more intense on day 60 than 30 post-SCI. The rapid and intense bone loss following SCI will ultimately lead to secondary complications, including bone fracture. Recently, it has been demonstrated changes in bone healing in response to complete transection of the spinal cord, which may be related to a down expression

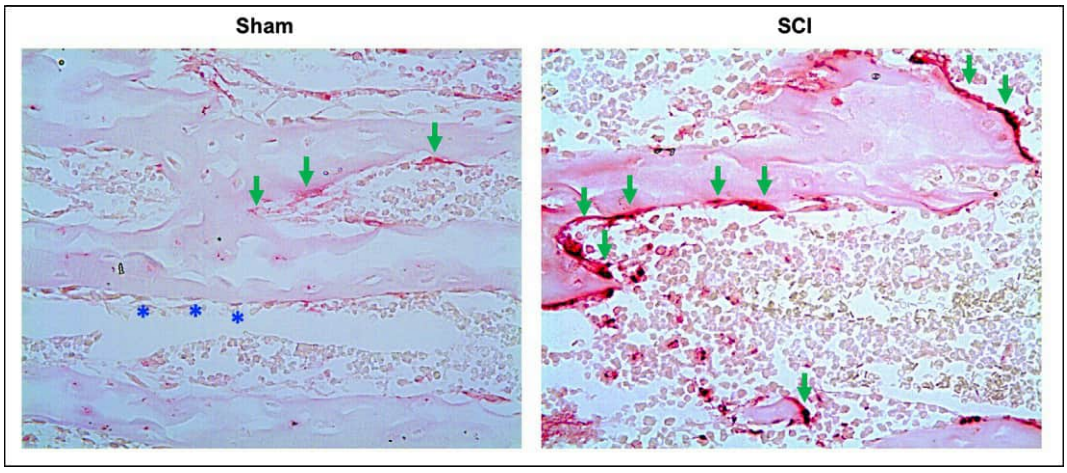

FIG. 1 Uncoupled bone in rats with spinal cord injury (SCI). A balanced turnover is observed in the sham images by a proportional activity between bone formation and resorption. Conversely, SCI images show an uncoupled bone turnover in which resorption exceeds formation, thereby leading to bone loss. Bone lining cells are represented by asterisks and indicate bone formation. The increased osteoclastic activity is demonstrated histologically by TRAP staining that specifically identifies osteoclast cells, in red (arrowheads), responsible for bone resorption. Magnification of 400×. Unpublished and original data.

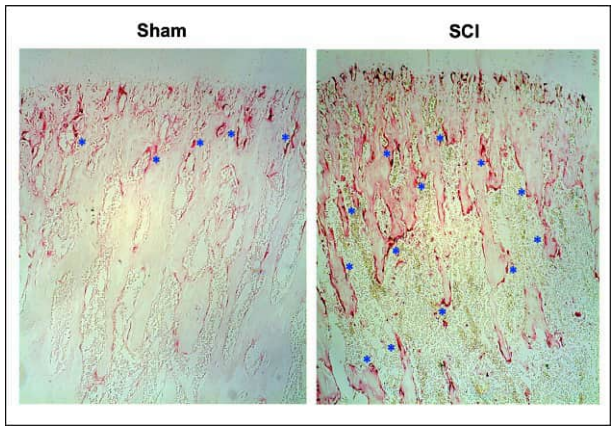

FIG. 2 Increased bone resorption activity in rats with spinal cord injury (SCI). TRAP histological slides specifically stain osteoclasts cells that may be identified as red cells (asterisks) and are responsible for bone resorption. The SCI group exhibited significantly more TRAP-positive cells per area of trabecular bone at the proximal tibial metaphysis than controls. Magnification of 100×. Unpublished and original data.

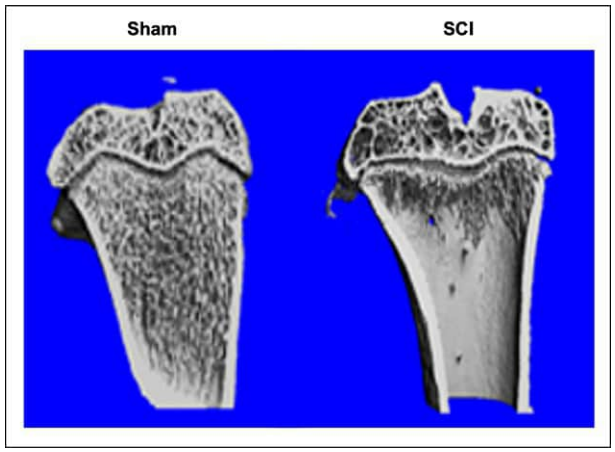

FIG. 3 Bone microarchitecture deterioration post-spinal cord injury. Fig. 3 shows tridimensional microarchitecture deterioration assessed by microcomputed tomography in response to increased resorption activity over bone formation. Unpublished and original data.

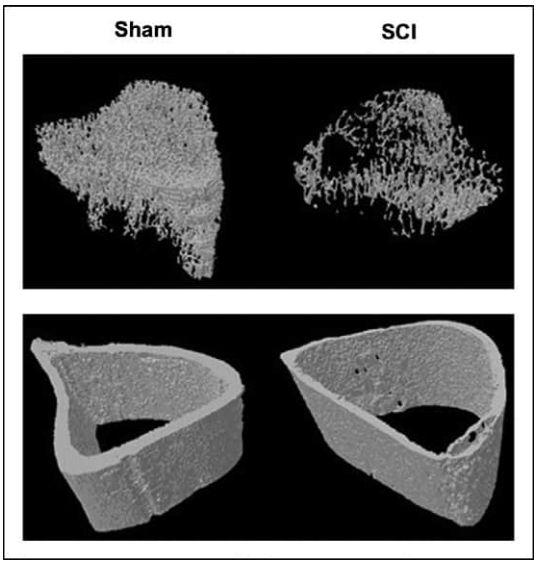

FIG. 4 Trabecular and cortical microstructure impairment due to paraplegia. Bone microstructure deterioration occurs both in trabecular and cortical bone following complete transection of the spinal cord, thus compromising its mechanical integrity. Unpublished and original data.

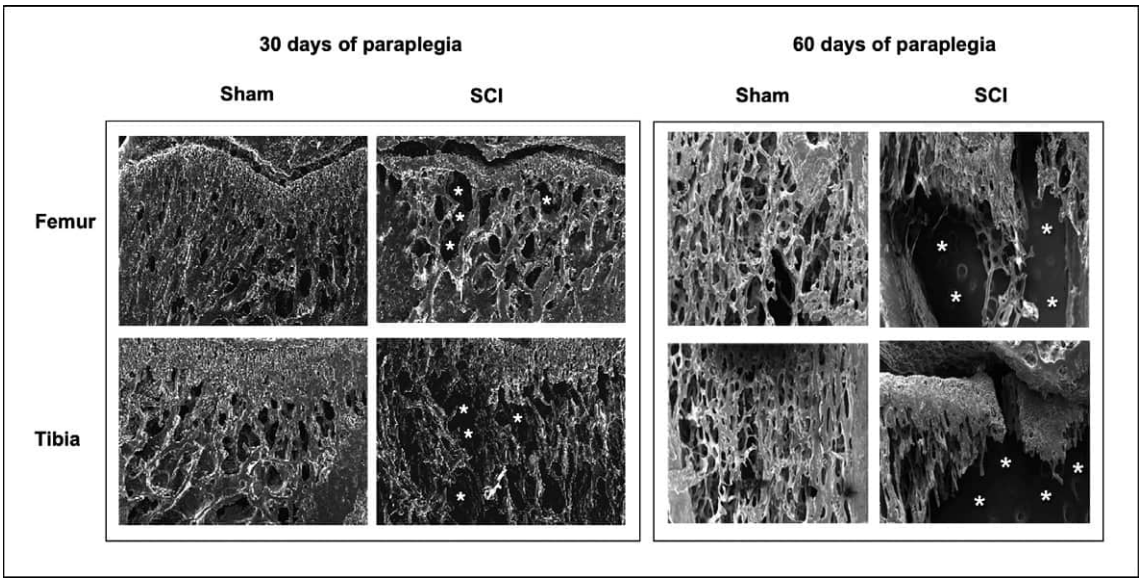

FIG. 5 Spinal cord injury (SCI)-induced bone loss is time-dependent on the injury. Scanning electron microscopy images detected a time-dependent behavior of SCI-induced bone loss. Although a substantial bone loss (asterisks) may be seen in paraplegic rats at both 30 and 60 days after injury, the loss is more intense on day 60 post-injury. Unpublished and original data.

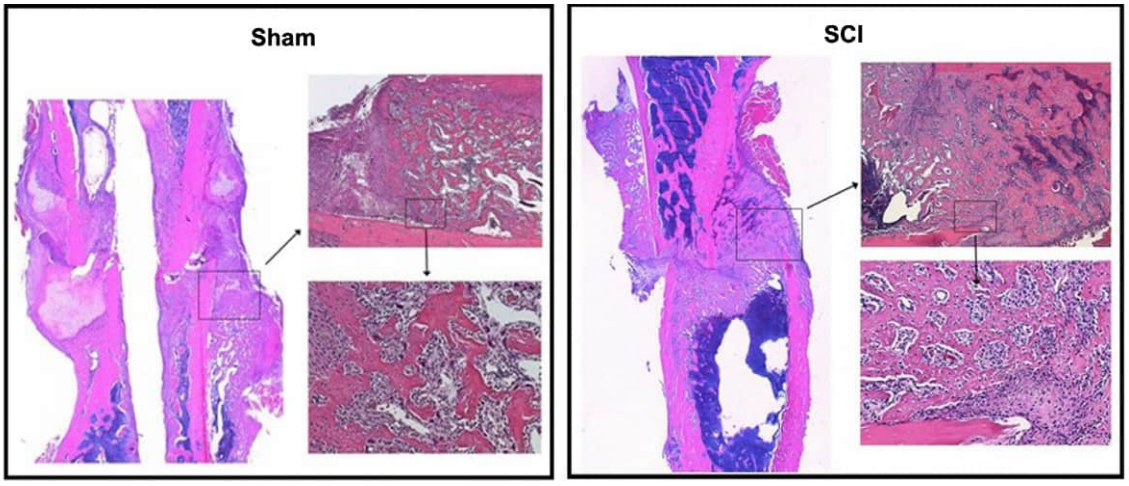

FIG. 6 Bone fragility in response to uncoupled turnover post-spinal cord injury (SCI). HE-stained histological images of the fracture evidencing a larger presence of woven bone and trabeculae than the sham rats, concomitant with lower cartilaginous tissue. Although bone healing may be accelerated in SCI rats, the newly formed callus is weaker, has thinner trabeculae, and has lower density. Magnifications of ×12.5, ×50, and ×200. Unpublished and original data.

in osteoblastic-related genes, including collagen type 1, alpha 2 (Col1a2), runt-related transcription factor 2 (Runx2), and osterix (Osx) (Butezloff et al., 2019). Butezloff et al. (2019) showed bone callus formation of lower quality in the SCI rats than the shams (Fig. 6), characterized by a lower density tissue, with thinner trabeculae and weaker at sustaining mechanical load until failure.

Secondary complication due to SCI-induced bone loss

Although mortality rates are declining for cancer, heart disease, stroke, arterial diseases, pulmonary embolus, urinary diseases, digestive diseases, and suicide among SCI individuals, these gains are being offset by increasing mortality rates for musculoskeletal disorders, accidents, endocrine, metabolic and nutritional conditions (National Spinal Cord Injury Statistical Center, 2020). In a very recent study, Rodriguez et al. reported that adults with SCI have a significantly higher

risk and incidence of musculoskeletal morbidities (e.g., osteoporosis, bone fractures, sarcopenia, etc.) in comparison with non-SCI adults (Rodriguez et al., 2021). Recently, the incidence of bone fracture has been reported as high as 7.4% per year (Troy & Morse, 2015), and has been estimated that more than 50% of SCI individuals will experience an osteoporotic fracture at some point in their life post-injury. The rates of fractures range from 1.2 to 3.4 per 100 patients per year (Morse et al., 2019). Both the distal femur and the proximal tibia seem to fracture at about the same rate. These fractures frequently occur from relatively minimal trauma, which would not cause any fracture in able-bodied individuals, and are known as low-energy/impact fractures. Causes of low-impact fractures include routine events such as rolling in bed, transferring from a wheelchair, being turned in bed, incorrect transfer maneuvers, as well as during rehabilitation techniques (e.g., passive stretching exercises). Another common cause of fracture is when the foot falls from the wheelchair, hits an obstacle, and the wheelchair conductor forces a torsional loading at the knee, causing a spiral fracture. The rate of secondary complications related to bone fracture after SCI is high, which impose devastating consequences for patient morbidity and mortality, including prolonged hospitalization, delayed union or non-union, cellulitis, skin breakdown with pressure ulcer formation, increased pain and spasticity, lower extremity amputation, and premature death (Haider et al., 2018; Troy & Morse, 2015). Therefore, any effort to maintain skeletal integrity and decrease secondary complications due to bone loss is imperative following SCI to fully benefit from future advances in paralysis cure research and robotic exoskeletons, brain–computer interfaces, and other evolving technologies (Morse et al., 2019).

Conclusions

Although the pathophysiology of SCI-induced bone loss remains inconclusive, studies are rapidly expanding with hopes of elucidating mechanisms and pathways responsible for this disorder and further therapies. SCI has a unique feature to cause a rapid and intense uncoupled bone turnover, with an increase in resorption activity synergistically with suppression in bone formation, resulting in a significant bone loss following injury. SCI-induced bone loss is linked to a high incidence of low-energy fracture, which may invariably result in healing complications, prolonged hospitalizations, increased morbidity and mortality, and a high cost for the medical system. Here, we discussed the mechanisms leading to SCI-induced bone loss, as well as the phenotypic consequences observed in the bone tissue.

Applications to other areas of neuroscience

In this chapter, we have reviewed the mechanisms and pathways responsible for bone loss due to spinal cord injury (SCI). Bone loss due to disuse also occurs in other conditions such as long-term bed rest (Rolvien et al., 2020), and microgravity exposure during spaceflight missions (Stavnichuk, Mikolajewicz, Corlett, Morris, & Komarova, 2020). However, the interconnection between neurological injury and the lack of mechanical loading (disuse osteoporosis) increases the speed and amount of bone loss, which may also be seen in other neurological conditions (e.g., cerebral palsy, stroke) (Lee, Varghese, Brooks, & Turpen, 2020; Shin, Yoon, Chung, Rhee, & Cho, 2017). Bone loss in neurologic disorders is dependent on the time from injury and extent of sequela. Accordingly, Shi et al. have shown that patients with ambulatory cerebral palsy have higher bone quality than patients with non-ambulatory neurological disorder. Likewise, SCI individuals with complete motor paralysis have lower bone mass than patients who can walk with orthosis and sustain load into their limbs (weight-bearing activity) (Karimi, Esrafilian, Esrafilian, Sadigh, & Amiri, 2013). Bone loss mainly occurs in the first year post-SCI, and fractures are more common around the knee. Due to the low bone quality in SCI individuals, a fracture does not require high force, and routine activities may lead to bone failure. Health professionals caring for individuals with neurological paralysis must be alert for fragility fractures and consider referral for surgical evaluation and management.

Mini-dictionary of terms

- SCI-induced bone loss: a loss in bone quality due to spinal cord injury.
- Low-energy fracture: fractures that occur from relatively minimal trauma, which would not cause any fracture in able-bodied individuals.
- Osteoporotic fracture: a fracture in an osteoporotic bone.
- Osteocytes: bone cells embedded in the bone matrix; derived from the osteoblast cell lineage; and the principal sensors for mechanical loading of bone.
- Mechanotransduction: is how the bone cells sense physical forces and translate them into biochemical and biological responses.

- Osteoblasts: bone cells primarily responsible for bone formation.
- Osteoclasts: bone cells primarily responsible for bone resorption.
- Bone turnover: is the process of resorption followed by replacement with new bone that occurs throughout a person's life. An imbalance in bone turnover where resorption exceeds formation and results in bone loss.
- Secondary disease: is a disease that is a sequela or complication of a primary disease. For example, osteoporosis is a secondary disease of the spinal cord injury (primary disease).

Key facts of gene expression, bone loss, and spinal cord injury

- Spinal cord injury (SCI) is a highly disabling condition, which commonly results in significant long-term disability as it deprives many patients of their arm and leg function, bowel, bladder, and sexual function.
- Bone loss is a secondary disease of SCI, which may severely decrease life quality and increase morbidity and mortality rate.
- Fractures may occur during daily routines, such as transferring from bed or wheelchair, rolling or being turned in bed, fall, incorrect transfer maneuvers, as well as during medical care or rehabilitation treatment.
- More than 50% of SCI individuals will sustain a bone fracture in a sublesional bone at some point of their life post-injury.
- Bone healing in SCI individuals commonly leads to several complications, including delayed union, prolonged hospitalization, and pressure ulcer formation.

Summary points

- Spinal cord injury (SCI) is a highly debilitating disease and is increasingly being recognized as an important global health priority.
- After the development of microarray and high-throughput sequence technologies, the expression of different genes has been identified in several diseases, including SCI.
- Non-coding and long non-coding ribonucleic acids (RNAs) have been identified to be differentially expressed after SCI and may be a therapeutic target for the diagnosis, treatment, and prognosis of these lesions.
- The mechanisms underlying SCI have not yet been fully elucidated, and effective therapies for SCI are lacking.
- Two phases characterize the damages following the injury.
- The primary damage is the mechanical injury itself, and the secondary damage phase results from biochemical processes following the primary damage.
- Bone loss following SCI is certainly unique in its magnitude and rapidity, which may be explained by the concomitant effects of the absence of mechanical loading to the vascular changes, muscle atrophy, neural, and endocrine components.
- Uncoupled bone turnover was identified in SCI individuals and animals, with a predominance of resorption over formation.
- The highly uncoupled bone turnover due to SCI, associated with muscle atrophy and vascular disorder, potentially increases the risk for low-impact fractures in the sublesional bones in these individuals.
- Maintaining bone integrity and preventing fractures are crucial for individuals with SCI in order to fully benefit from future advances in paralysis cure research and robotic exoskeletons, brain–computer interfaces, and other evolving technologies.

References

Bao, F., & Liu, D. (2002). Peroxynitrite generated in the rat spinal cord induces neuron death and neurological deficits. *Neuroscience*. https://doi.org/10.1016/S0306-4522(02)00506-7.

Baron, J. S., Sullivan, K. J., Swaine, J. M., Aspinall, A., Jaglal, S., Presseau, J., … Grimshaw, J. M. (2018). Self-management interventions for skin care in people with a spinal cord injury: Part 2—A systematic review of use of theory and quality of intervention reporting. *Spinal Cord*. https://doi.org/10.1038/s41393-018-0136-5.

Butezloff, M. M., Volpon, J. B., Ximenez, J. P. B., Astolpho, K., Correlo, V. M., Reis, R. L., … Zamarioli, A. (2019). Gene expression changes are associated with severe bone loss and deficient fracture callus formation in rats with complete spinal cord injury. *Spinal Cord*. https://doi.org/10.1038/s41393-019-0377-y.

Colaianni, G., Mongelli, T., Cuscito, C., Pignataro, P., Lippo, L., Spiro, G., … Grano, M. (2017). Irisin prevents and restores bone loss and muscle atrophy in hind-limb suspended mice. *Scientific Reports*. https://doi.org/10.1038/s41598-017-02557-8.

Cragg, J. J., Noonan, V. K., Krassioukov, A., & Borisoff, J. (2013). Cardiovascular disease and spinal cord injury results from a national population health survey. *Neurology*. https://doi.org/10.1212/WNL.0b013e3182a1aa68.

de Campos, M. F., Ribeiro, A. T., Listik, S., de Pereira, C. A. B., de Andrade Sobrinho, J., & Rapoport, A. (2008). Epidemiology of spine injuries. *Revista do Colégio Brasileiro de Cirurgiões*. https://doi.org/10.1590/s0100-69912008000200005.

Ding, Y., Song, Z., & Liu, J. (2016). Aberrant LncRNA expression profile in a contusion spinal cord injury mouse model. *BioMed Research International*. https://doi.org/10.1155/2016/9249401.

Doherty, A. L., Battaglino, R. A., Donovan, J., Gagnon, D., Lazzari, A. A., Garshick, E., … Morse, L. R. (2014). Adiponectin is a candidate biomarker of lower extremity bone density in men with chronic spinal cord injury. *Journal of Bone and Mineral Research*. https://doi.org/10.1002/jbmr.2020.

Duran, R. C. D., Yan, H., Zheng, Y., Huang, X., Grill, R., Kim, D. H., … Wu, J. Q. (2017). The systematic analysis of coding and long non-coding RNAs in the sub-chronic and chronic stages of spinal cord injury. *Scientific Reports*. https://doi.org/10.1038/srep41008.

Eldahan, K. C., & Rabchevsky, A. G. (2018). Autonomic dysreflexia after spinal cord injury: Systemic pathophysiology and methods of management. *Autonomic Neuroscience: Basic & Clinical*. https://doi.org/10.1016/j.autneu.2017.05.002.

Eser, P., Frotzler, A., Zehnder, Y., Wick, L., Knecht, H., Denoth, J., & Schiessl, H. (2004). Relationship between the duration of paralysis and bone structure: A pQCT study of spinal cord injured individuals. *Bone*. https://doi.org/10.1016/j.bone.2004.01.001.

Garland, D. E., Stewart, C. A., Adkins, R. H., Hu, S. S., Rosen, C., Liotta, F. J., & Weinstein, D. A. (1992). Osteoporosis after spinal cord injury. *Journal of Orthopaedic Research*. https://doi.org/10.1002/jor.1100100309.

Gatti, V., Ghobryal, B., Gelbs, M. J., Gerber, M. B., Doty, S. B., Cardoso, L., & Fritton, S. P. (2019). Botox-induced muscle paralysis alters intracortical porosity and osteocyte lacunar density in skeletally mature rats. *Journal of Orthopaedic Research*. https://doi.org/10.1002/jor.24276.

Gifre, L., Vidal, J., Carrasco, J. L., Filella, X., Ruiz-Gaspà, S., Muxi, A., … Peris, P. (2015). Effect of recent spinal cord injury on wnt signaling antagonists (Sclerostin and Dkk-1) and their relationship with bone loss. A 12-month prospective study. *Journal of Bone and Mineral Research*. https://doi.org/10.1002/jbmr.2423.

Goodus, M. T., & McTigue, D. M. (2020). Hepatic dysfunction after spinal cord injury: A vicious cycle of central and peripheral pathology? *Experimental Neurology*. https://doi.org/10.1016/j.expneurol.2019.113160.

Hachisuka, S., Kamei, N., Ujigo, S., Miyaki, S., Yasunaga, Y., & Ochi, M. (2014). Circulating microRNAs as biomarkers for evaluating the severity of acute spinal cord injury. *Spinal Cord*. https://doi.org/10.1038/sc.2014.86.

Haider, I. T., Lobos, S. M., Simonian, N., Schnitzer, T. J., & Edwards, W. B. (2018). Bone fragility after spinal cord injury: Reductions in stiffness and bone mineral at the distal femur and proximal tibia as a function of time. *Osteoporosis International*. https://doi.org/10.1007/s00198-018-4733-0.

Holmes, D. (2017). Spinal-cord injury: Spurring regrowth. *Nature*, *552*(7684), S49. https://doi.org/10.1038/d41586-017-07550-9.

Iori, G., Schneider, J., Reisinger, A., Heyer, F., Peralta, L., Wyers, C., … Raum, K. (2019). Large cortical bone pores in the tibia are associated with proximal femur strength. *PLoS One*. https://doi.org/10.1371/journal.pone.0215405.

Iyer, M. K., Niknafs, Y. S., Malik, R., Singhal, U., Sahu, A., Hosono, Y., … Chinnaiyan, A. M. (2015). The landscape of long noncoding RNAs in the human transcriptome. *Nature Genetics*. https://doi.org/10.1038/ng.3192.

Karimi, M. T., Esrafilian, O., Esrafilian, A., Sadigh, M. J., & Amiri, P. (2013). Determination of the influence of walking with orthosis on bone osteoporosis in paraplegic subjects based on the loads transmitted through the body. *Clinical Biomechanics*. https://doi.org/10.1016/j.clinbiomech.2013.01.001.

Karlsson, A. K. (1999). Autonomic dysreflexia. *Spinal Cord*. https://doi.org/10.1038/sj.sc.3100867.

Kigerl, K. A., Zane, K., Adams, K., Sullivan, M. B., & Popovich, P. G. (2020). The spinal cord-gut-immune axis as a master regulator of health and neurological function after spinal cord injury. *Experimental Neurology*. https://doi.org/10.1016/j.expneurol.2019.113085.

Kumar, R., Lim, J., Mekary, R. A., Rattani, A., Dewan, M. C., Sharif, S. Y., … Park, K. B. (2018). Traumatic spinal injury: Global epidemiology and worldwide volume. *World Neurosurgery*. https://doi.org/10.1016/j.wneu.2018.02.033.

Lee, J., Varghese, J., Brooks, R., & Turpen, B. J. (2020). A primary care provider's guide to accessibility after spinal cord injury. *Topics in Spinal Cord Injury Rehabilitation*. https://doi.org/10.46292/SCI2602-79.

Li, S., & Stys, P. K. (2000). Mechanisms of ionotropic glutamate receptor-mediated excitotoxicity in isolated spinal cord white matter. *Journal of Neuroscience*. https://doi.org/10.1523/jneurosci.20-03-01190.2000.

Morse, L. R., Biering-Soerensen, F., Carbone, L. D., Cervinka, T., Cirnigliaro, C. M., Johnston, T. E., … Craven, B. C. (2019). Bone mineral density testing in spinal cord injury: 2019 ISCD official position. *Journal of Clinical Densitometry*. https://doi.org/10.1016/j.jocd.2019.07.012.

Morse, L. R., Sudhakar, S., Lazzari, A. A., Tun, C., Garshick, E., Zafonte, R., & Battaglino, R. A. (2013). Sclerostin: A candidate biomarker of SCI-induced osteoporosis. *Osteoporosis International*. https://doi.org/10.1007/s00198-012-2072-0.

Myers, J., Lee, M., & Kiratli, J. (2007). Cardiovascular disease in spinal cord injury: An overview of prevalence, risk, evaluation, and management. *American Journal of Physical Medicine and Rehabilitation*. https://doi.org/10.1097/PHM.0b013e31802f0247.

National Spinal Cord Injury Statistical Center. (2020). *Facts and figures at a glance*. Birmingham, AL: University of Alabama at Birmingham, National Spinal Cord Injury Statistical Center.

Nseyo, U., & Santiago-Lastra, Y. (2017). Long-term complications of the neurogenic bladder. *Urologic Clinics of North America*. https://doi.org/10.1016/j.ucl.2017.04.003.

Panicker, J. N., Fowler, C. J., & Kessler, T. M. (2015). Lower urinary tract dysfunction in the neurological patient: Clinical assessment and management. *The Lancet Neurology*. https://doi.org/10.1016/S1474-4422(15)00070-8.

Park, E., Velumian, A. A., & Fehlings, M. G. (2004). The role of excitotoxicity in secondary mechanisms of spinal cord injury: A review with an emphasis on the implications for white matter degeneration. *Journal of Neurotrauma*. https://doi.org/10.1089/0897715041269641.

Peng, Y., Zhao, W., Hu, Y., Li, F., Guo, X. E., Wang, D., … Qin, W. (2020). Rapid bone loss occurs as early as 2 days after complete spinal cord transection in young adult rats. *Spinal Cord*. https://doi.org/10.1038/s41393-019-0371-4.

Pineau, I., & Lacroix, S. (2007). Proinflammatory cytokine synthesis in the injured mouse spinal cord: Multiphasic expression pattern and identification of the cell types involved. *Journal of Comparative Neurology*. https://doi.org/10.1002/cne.21149.

Popa, C., Popa, F., Grigorean, V. T., Onose, G., Sandu, A. M., Popescu, M., … Sinescu, C. (2010). Vascular dysfunctions following spinal cord injury. *Journal of Medicine and Life*, *3*(3), 275–285.

Price, M. J., & Trbovich, M. (2018). Thermoregulation following spinal cord injury. In *Handbook of clinical neurology*. https://doi.org/10.1016/B978-0-444-64074-1.00050-1.

Ramer, L. M., Ramer, M. S., & Bradbury, E. J. (2014). Restoring function after spinal cord injury: Towards clinical translation of experimental strategies. *The Lancet Neurology*. https://doi.org/10.1016/S1474-4422(14)70144-9.

Rodriguez, G., Berri, M., Lin, P., Kamdar, N., Mahmoudi, E., & Peterson, M. D. (2021). Musculoskeletal morbidity following spinal cord injury: A longitudinal cohort study of privately-insured beneficiaries. *Bone*. https://doi.org/10.1016/j.bone.2020.115700.

Rolvien, T., Milovanovic, P., Schmidt, F. N., von Kroge, S., Wölfel, E. M., Krause, M., … Busse, B. (2020). Long-term immobilization in elderly females causes a specific pattern of cortical bone and osteocyte deterioration different from postmenopausal osteoporosis. *Journal of Bone and Mineral Research*. https://doi.org/10.1002/jbmr.3970.

Rowland, J. W., Hawryluk, G. W. J., Kwon, B., & Fehlings, M. G. (2008). Current status of acute spinal cord injury pathophysiology and emerging therapies: Promise on the horizon. *Neurosurgical Focus*. https://doi.org/10.3171/FOC.2008.25.11.E2.

Samson, G., & Cardenas, D. D. (2007). Neurogenic bladder in spinal cord injury. *Physical Medicine and Rehabilitation Clinics of North America*. https://doi.org/10.1016/j.pmr.2007.03.005.

Shi, Z., Ning, G., Zhang, B., Yuan, S., Zhou, H., Pan, B., … Feng, S. (2019). Signatures of altered long noncoding RNAs and messenger RNAs expression in the early acute phase of spinal cord injury. *Journal of Cellular Physiology*. https://doi.org/10.1002/jcp.27560.

Shin, Y. K., Yoon, Y. K., Chung, K. B., Rhee, Y., & Cho, S. R. (2017). Patients with non-ambulatory cerebral palsy have higher sclerostin levels and lower bone mineral density than patients with ambulatory cerebral palsy. *Bone*. https://doi.org/10.1016/j.bone.2017.07.015.

Soleyman-Jahi, S., Yousefian, A., Maheronnaghsh, R., Shokraneh, F., Zadegan, S. A., Soltani, A., … Rahimi-Movaghar, V. (2018). Evidence-based prevention and treatment of osteoporosis after spinal cord injury: A systematic review. *European Spine Journal*. https://doi.org/10.1007/s00586-017-5114-7.

Stavnichuk, M., Mikolajewicz, N., Corlett, T., Morris, M., & Komarova, S. V. (2020). A systematic review and meta-analysis of bone loss in space travelers. *NPJ Microgravity*. https://doi.org/10.1038/s41526-020-0103-2.

Troy, K. L., & Morse, L. R. (2015). Measurement of bone: Diagnosis of SCI-induced osteoporosis and fracture risk prediction. *Topics in Spinal Cord Injury Rehabilitation*. https://doi.org/10.1310/sci2104-267.

Uda, Y., Azab, E., Sun, N., Shi, C., & Pajevic, P. D. (2017). Osteocyte mechanobiology. *Current Osteoporosis Reports*. https://doi.org/10.1007/s11914-017-0373-0.

Veeriah, V., Paone, R., Chatterjee, S., Teti, A., & Capulli, M. (2019). Osteoblasts regulate angiogenesis in response to mechanical unloading. *Calcified Tissue International*. https://doi.org/10.1007/s00223-018-0496-z.

Venkatesh, K., Ghosh, S. K., Mullick, M., Manivasagam, G., & Sen, D. (2019). Spinal cord injury: Pathophysiology, treatment strategies, associated challenges, and future implications. *Cell and Tissue Research*. https://doi.org/10.1007/s00441-019-03039-1.

Wang, J., Hu, B., Cao, F., Sun, S., Zhang, Y., & Zhu, Q. (2015). Down regulation of lncSCIR1 after spinal cord contusion injury in rat. *Brain Research*. https://doi.org/10.1016/j.brainres.2015.07.052.

Wang, F., Liu, J., Wang, X., Chen, J., Kong, Q., Ye, B., & Li, Z. (2019). The emerging role of lncRNAs in spinal cord injury. *BioMed Research International*. https://doi.org/10.1155/2019/3467121.

Welk, B., Schneider, M. P., Thavaseelan, J., Traini, L. R., Curt, A., & Kessler, T. M. (2018). Early urological care of patients with spinal cord injury. *World Journal of Urology*. https://doi.org/10.1007/s00345-018-2367-7.

Wijenayaka, A. R., Kogawa, M., Lim, H. P., Bonewald, L. F., Findlay, D. M., & Atkins, G. J. (2011). Sclerostin stimulates osteocyte support of osteoclast activity by a RANKL-dependent pathway. *PLoS One*. https://doi.org/10.1371/journal.pone.0025900.

Wilmet, E., Ismail, A. A., Heilporn, A., Welraeds, D., & Bergmann, P. (1995). Longitudinal study of the bone mineral content and of soft tissue composition after spinal cord section. *Paraplegia*. https://doi.org/10.1038/sc.1995.141.

Zamarioli, A., Battaglino, R. A., Morse, L. R., Sudhakar, S., Maranho, D. A. C., Okubo, R., … Shimano, A. C. (2013). Standing frame and electrical stimulation therapies partially preserve bone strength in a rodent model of acute spinal cord injury. *American Journal of Physical Medicine and Rehabilitation*, *92*(5). https://doi.org/10.1097/PHM.0b013e318287697c.

Zamarioli, A., de Andrade Staut, C., & Volpon, J. B. (2020). Review of secondary causes of osteoporotic fractures due to diabetes and spinal cord injury. *Current Osteoporosis Reports*. https://doi.org/10.1007/s11914-020-00571-w.

Zamarioli, A., Maranho, D. A., Butezloff, M. M., Moura, P. A., Volpon, J. B., & Shimano, A. C. (2014). Anatomic changes in the macroscopic morphology and microarchitecture of denervated long bone tissue after spinal cord injury in rats. *BioMed Research International*, *2014*. https://doi.org/10.1155/2014/853159.

Zhou, H., Shi, Z., Kang, Y., Wang, Y., Lu, L., Pan, B., … Feng, S. (2018). Investigation of candidate long noncoding RNAs and messenger RNAs in the immediate phase of spinal cord injury based on gene expression profiles. *Gene*. https://doi.org/10.1016/j.gene.2018.03.074.

Chapter 8

Sperm DNA fragmentation and its relevance to men with spinal cord injury

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List of abbreviations

ICSI	Intracytoplasmic sperm injection
PVS	Penile vibratory stimulation
ROS	Reactive oxygen species
SDF	Sperm DNA fragmentation
SCI	Spinal cord injury

Introduction

DNA integrity and stability are crucial for normal embryonic development leading to a successful pregnancy. However, as DNA is an active and dynamic molecule, it is constantly under pressure from physicochemical and biological forces that can induce changes or mutations to its native base-pair information. Of the adverse changes affecting the DNA molecule, one of the most profound and severe, is DNA fragmentation. DNA fragmentation is the separation or breaking of a continuous DNA strand into pieces such that genetic information and the control of effective replication and translation are compromised. To overcome this problem, somatic cells in eukaryotic organisms use mechanisms of DNA repair but these mechanisms are silent in mature spermatozoa (Gonzalez-Marin, Gosálvez, & Roy, 2012). Consequently, any breakage of the sperm DNA molecule is susceptible of being incorporated into the zygote following fertilization, unless it is repaired by the oocyte. If the damage is too severe, then this may result in potential errors during embryo development leading to failed pregnancy (García-Rodríguez, Gosálvez, Agarwal, Roy, & Johnston, 2019). In general, while all ejaculates possess a proportion of spermatozoa with damaged DNA, the higher the percentage of sperm with DNA fragmentation, the greater the probability of infertility (Deng et al., 2019). Human males presenting with a high proportion of sperm DNA fragmentation (SDF) are regarded as having impaired fertility once their SDF exceeds 30% (Esteves et al., 2020), whereas individuals considered fertile or presenting with acceptable levels of SDF typically present in the order of $\leq$20% (Gosálvez, Fernández, et al., 2015). Although the precise relationship between SDF and pregnancy outcome is still debatable, the extremely high incidence of sperm DNA damage reported in spinal cord injury (SCI) males (Vargas-Baquero et al., 2020) makes this condition, its causes and consequences, highly relevant to the SCI community. Consequently, understanding SDF in males with SCI is vital not only for establishing a clinical prognosis but also for developing effective therapies to overcome infertility. Given that the impact of SCI on male fertility is likely to be a complex synergistic combination of neural and lifestyle factors, it will also be important to compare how men with SCI differ from fertile and infertile males without SCI in terms of SDF and what elements of their medical condition might predispose them to high levels of SDF. This review will present the current status of information regarding SDF to males with SCI by analyzing the limited studies on this phenomenon and comparing these observations to other infertility etiologies associated with high levels of SDF. Additionally, we will define the primary mechanisms of SDF, discuss the possible etiologies of SDF that appear unique to SCI males, and finally propose clinical strategies designed to reduce SDF in SCI males to improve the probability of a successful pregnancy.

Cellular, Molecular, Physiological, and Behavioral Aspects of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822427-4.00008-3

How does SDF in men with SCI compare to other causes of infertility?

SDF in men with SCI has to date been limited to six studies, three using the sperm chromatin dispersion (SCD) test (Bartolomé-Nebreda et al., 2020; Qiu et al., 2012; Vargas-Baquero et al., 2020), one by means of the sperm chromatin structure assay (Brackett et al., 2008) and two using the terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assay procedure (Restelli et al., 2007; Talebi, Khalili, Vahidi, Ghasemzadeh, & Tabibnejad, 2013). Despite the methodology, the conclusion of all studies was that SDF in men with SCI is higher than in men without SCI. The next question then is how different are the levels of SDF in men with SCI compared to other clinical situations in men without SCI? To analyze this, we have selected data published by Esteves et al. (2015) in males without SCI (Fig. 1); to avoid differences based on the methodology, all cases were assessed for SDF using the SCD. In Fig. 1, we have included data from men without SCI that have experienced at least two failed assisted reproduction cycles, that have been diagnosed with leukocytospermia, *Chlamydia trachomatis* infection, testicular cancer, and varicocele and compared these to a control group (sperm donors) and men with SCI, previously published by Vargas-Baquero et al. (2020). Fig. 1 reveals that males without SCI but with other pathologies had SDF values approximately 2.5 × that of sperm donors but in the case of men with SCI their SDF values were 5 × higher than the sperm donors. Although these high SDF values position men with SCI as the most affected clinical group with SDF pathology, it should be noted that in almost every ejaculate of males with SCI, there is at least a small proportion of spermatozoa that were not affected by DNA damage, that theoretically, could be recovered to establish a pregnancy.

Molecular mechanisms of SDF

There are three fundamental theories thought to explain the presence of SDF in the ejaculate (Gosálvez, López-Fernández, Fernández, Esteves, & Johnston, 2015). The first hypothesis proposes that DNA breakage is associated with improper replacement of histone with protamine during spermiogenesis. Precise histone–protamine transition allows greater

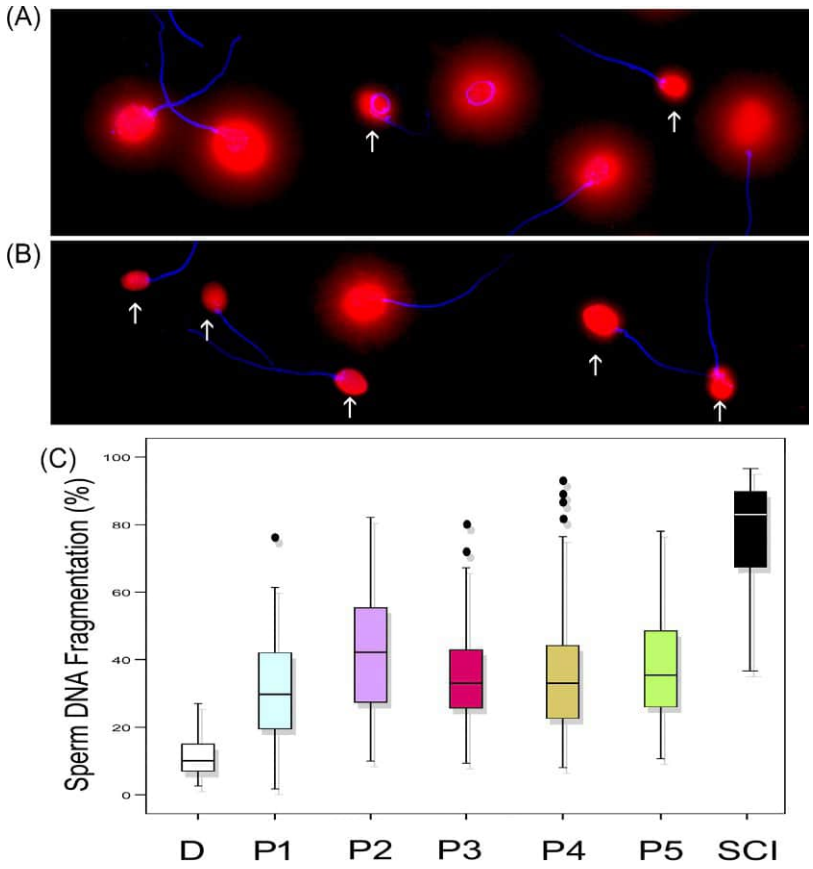

FIG. 1 Sperm DNA fragmentation as visualized with the Sperm Chromatin Dispersion test after dual fluorescence staining. (A) Normozoospermic non-SCI individual showing a high proportion of sperm presenting large haloes of chromatin dispersion (non-fragmented DNA). (B) SCI patients presenting absence of haloes (fragmented DNA: arrow). (C) Box and whisker plots in a series of males without SCI affected by infertility (colored). (P1: *blue*) failure to establish a pregnancy after two cycles of assisted reproduction, (P2: *pink*) leukocytospermia, (P3: *red*) *Chlamydia* infection, (P4: *yellow*) testicular cancer, and (P5: *green*) varicocele to be compared with sperm donors (D: *white*) and males with spinal cord injury (SCI: *black*).

compaction of the DNA molecule than that which occurs in the somatic cell line and facilitates protection of the DNA molecule to exist *ex soma*, for when it will experience external stressors associated with sperm transport in the female. García-Peiró et al. (2011) have shown misbalance in the ratio protamine-1/protamine-2 in human spermatozoa is associated with loss of DNA longevity, confirming that precise protamination is important for chromatin stability. Using animal models with a spinal contusion, Huang, Li, Wang, Wang, and Ottenweller (2003) showed a decrease in mRNA transcripts for spermatid-specific protamine-1 and transition protein-2. If this same phenomenon is also occurring in men with SCI, then it might explain the altered levels of chromatin condensation and low levels of chromatin stability in these individuals (Talebi et al., 2013). The second hypothesis suggests that SDF is a consequence of excessive oxidative stress acting at different levels of the male reproductive tract (Aitken, 2020); this hypothesis, will be analyzed in more detail later in the chapter. The third hypothesis highlights apoptotic events that occur during sperm maturation within the epididymis and are similar in mechanism to those described in somatic cells. Essentially, once caspase or annexin-V is detected at the sperm membrane, double-strand DNA breakage results, controlled by specific DNases (Gorczyca, Traganos, Jesionowska, & Darzynkiewicz, 1993). Some studies have referenced this mechanism as being operative in males with SCI (Restelli et al., 2007; Talebi et al., 2013) but have only used toluidine blue and chromomycin A or TUNEL to make this conclusion; specific protocols for apoptotic marker visualization or other molecular approaches have yet to be performed on the ejaculates of men with SCI. While all hypotheses that explain SDF in males without SCI are equally attributable to men with SCI, there are also likely to be additional effects associated with SCI that are potentially synergistically compounding SDF.

Etiologies of SDF in men with SCI

Hormone alterations

The relationship between altered hormone production and SDF is controversial, even in males without SCI. Some males without SCI show an increase in SDF when both extremely low and high levels of FSH and LH are diagnosed, with SDF being negatively correlated with testosterone concentration (Wdowiak, Raczkiewicz, Stasiak, & Bojar, 2014). In other cases, a direct role of FSH level has been implicated to affect SDF such that patients administered with recombinant FSH (150 IU) show a significant reduction in SDF and an improvement in gonadal function (Colacurci et al., 2018). Some of this variation may also be related to the fact that gonadotrophins associated with spermatogenesis are under homeostatic control such that both too high and too low levels of FSH and LH could have equally adverse effects on sperm production. Although Naderi and Safarinejad (2003) have reported lower reproductive hormones associated with hypothalamus-pituitary-gonadal function in men with SCI, any strong relationship between SDF and variable levels of hormones in SCI patients has yet to be established (Brackett, Nash, & Lynne, 1996), such that a direct role on SDF would be speculative. Odum, Sonksen, and Biering-Sorensen (1995) have also shown that somatostatin, which is important for the normal regulation of the endocrine system, is significantly reduced in the seminal plasma of males with SCI above thoracic vertebrate T6.

Elevated scrotal temperature

Men with scrotal temperatures above the normal range have elevated levels of sub or infertility associated with an increase in the proportion of abnormal and immature spermatozoa (Mieusset et al., 1987). Studies in mice have shown a direct link between heat stress and altered DNA quality, chromatin packaging and embryonic loss (e.g., Banks, King, Irvine, & Saunders, 2005); this damage may occur at the level of the testis (spermatogenesis) and/or the epididymis (sperm maturation). Hyperthermia can also result in decreased DNA synthesis and degradation of mRNAs and proteins necessary for cell survival (Durairajanayagam, Agarwal, & Ong, 2015). Increased SDF may also be associated with heat stress linked to gene expression changes, increased reactive oxygen species (ROS), and alterations in sperm DNA repair mechanisms during spermatogenesis (Durairajanayagam et al., 2015). Given that men with SCI spend many hours in a wheelchair, one might expect that testicular hyperthermia could represent a cause of poor sperm quality (Linsenmeyer & Perkash, 1991), potentially including elevated levels of SDF. While some studies have demonstrated men with SCI in wheelchairs have elevated scrotal temperature compared to men without SCI (Wang, Huang, & Lien, 1992), only one study found an inverse correlation of scrotal temperature with sperm motility and a further study found no difference (Brackett, Lynne, Weizman, Bloch, & Padron, 1994). In addition, men with SCI, but not bound to wheelchairs, still had poor semen quality, suggesting that there is likely to be some other underlying aspect of SCI contributing to lower sperm motility

(Brackett, 2012). As sperm DNA damage in mice can be induced with as little as 30 min exposure at 42 °C (Banks et al., 2005), further studies of men with SCI, examining SDF, might reveal more subtle differences in DNA damage not apparent in other semen parameters.

Ejaculation frequency

It has been suggested that anejaculation in men with SCI may lead to sperm accumulation and deterioration in the cauda epididymis (Vargas-Baquero et al., 2020) but the evidence is controversial. While studies report an improvement in sperm motility in men with SCI after frequent ejaculation (Hamid, Patki, Bywater, Shah, & Craggs, 2006), others have failed to demonstrate improvement (Das et al., 2006). Although there are currently no specific studies with respect to the effect of anejaculation in men with SCI on SDF, Gosálvez, Gonzalez-Martınez, López-Fernández, Fernández, and Sanchez-Martın (2011) have demonstrated a decrease in the level of SDF in ejaculates of normozoospermic men with a corresponding improvement in other semen characteristics and the rate of pregnancy (Sánchez-Martín, Sánchez-Martín, González-Martínez, & Gosálvez, 2013). A similar strategy for improving the DNA quality of the semen sample might be to use the first ejaculated sub-fraction; sperm quality in humans recovered from the first ejaculated fraction, compared to the second fraction show improved measures of sperm concentration, motility, and SDF (de la Torre, Sánchez-Martín, Gosálvez, & Crespo, 2016; Hebles, Dorado, Gallardo, González-Martínez, & Sánchez-Martín, 2015). Prolonged anejaculation may also induce anti-sperm antibodies but the role of these molecules on the fertility of men with SCI is still unresolved (Dimitriadis et al., 2010).

Sperm chromatin maturity

While Hou, Chen, and Jeyendran (1995) was unable to show any effect of SCI on sperm nuclear maturity, Engh, Clausen, Purvis, and Stien (1993) revealed a high degree of abnormal chromatin condensation and reduced binding of a fluorescent acrosomal marker in men with SCI. Investigation of the molecular biology of the rat testis associated with SCI has shown a reduction in the Sertoli cell protein transferrin-mRNA but no change in androgen binding protein-mRNA, or of the mRNA transcripts of spermatogenic cell-specific hemiferrin or spermatid transition protein-2 and protamine-1 and a decline in mRNA transcripts for spermatid-specific protamine-1 and transition protein-2 (Huang et al., 1997). Huang et al. (2003) also noted a precocious expression of CREM (cAMP-responsive element modulator) in early spermatocytes and an absence of it in young spermatids during the acute phase after SCI, which Dimitriadis et al. (2010) have suggested could disrupt spermiogenesis resulting in spermatozoa with abnormal morphology and/or function, including SDF.

Reactive oxygen species

The ejaculates of men with SCI appear to have increased levels of ROS, reduced levels of superoxide dismutase, and increased concentrations of cytokines (de Lamirande & Gagnon, 1993). ROS disequilibrium in the ejaculate is thought to have a significant effect on sperm membranes because in contrast to somatic cells, sperm cells are composed of a high percentage (50%) of fatty acids which are highly susceptible to lipid peroxidation (Henkel, 2011). While the plasma membrane is likely to be the first component of the sperm cell to be adversely affected by oxidative stress, this pathology likely facilitates subsequent ROS damage to the DNA molecule. Such a scenario is also consistent with the relatively high levels of necrozoospermia observed in the semen of SCI patients (Mallidis et al., 2000), where damage to the sperm membrane serves as a precursor to SDF. However, as the intensity of REDOX unbalance, as well as the capacity of the chromatin to be affected by this stressor, appears to be highly dependent on sperm protein composition (Gosálvez, López-Fernández, Fernández, Gouraud, & Holt, 2011), elevated SDF is also likely to be a consequence of the cooperative participation of ROS-related injury to the sperm membrane and incomplete sperm chromatin protamination (García-Peiró et al., 2011).

Leukocytospermia and ROS-related damage

In men with SCI, it is common to find an elevated leukocyte concentration in the semen samples (Jung et al., 2016) even without accompanying urogenital tract infection (UTI). Dimitriadis et al. (2010) have estimated that recurrent UTIs and subsequent leukocytospermia may affect up to 60–70% of men with SCI. Leucocytes can produce abnormally high levels of ROS generating an unbalance between the pro-oxidant and anti-oxidant capacity of the sperm environment (Henkel, 2011). However, although it is well established that ROS is directly involved in cell DNA damage (Poetsch, 2020), the adverse effect of leukocytospermia in men with SCI requires further investigation. For example, it has been reported that not all leucocytes present in the ejaculate of men with SCI show a high production of ROS (Vargas-Baquero et al., 2020). Given

the high incidence of SDF observed in the ejaculates of men with SCI, it would be interesting to examine the dynamic relationship between loss of sperm membrane quality and the increase of SDF during in vitro incubation. In men with SCI that have a high level of leukocytospermia, we might predict DNA damage to be accelerated associated with a loss of sperm membrane integrity (necrozoospermia).

Sperm concentration

Sperm concentration tends to be high in men with SCI but it is unlikely to have any benefit to overall semen quality; on the contrary, it may be detrimental to the other semen parameters. For example, a positive correlation between sperm concentration and SDF in the ejaculates of males with SCI has been reported by Vargas-Baquero et al. (2020). This effect has also been reported in human and animal species without spinal injury (López-Fernández, Johnston, Fernández, Wilson, & Gosálvez, 2010; Tvrdá, Arroyo, Ďuračka, López-Fernández, & Gosálvez, 2019). It is difficult to know whether this adverse effect is attributable to the accumulation of toxic metabolic products, active free enzymes such as those found in the acrosome, ROS initially present at the ejaculate, and/or additional ROS generated after sperm plasma membrane degradation.

Seminal vesicular secretions

El-Demiry and James (1988) and Harrison, Barratt, Robinson, Kessopoulou, and Cooke (1991) have referred to shielding components in the seminal fluids that protect the spermatozoa from the effects of leukocytospermia. As the ejaculates of men with SCI are characterized by high numbers of leukocytes compared to men without SCI, it has been proposed that dysfunction of compounds released from the seminal vesicles may interfere with the normal inhibition of leukocyte activation and accumulation (Dimitriadis et al., 2010). This would explain, in part at least, why some leukocytes do not show a large production of ROS (Vargas-Baquero et al., 2020). It is also possible this dysfunction subsequently interrupts the normal secretion of superoxide dismutase and catalase by the seminal vesicles leading to an increase in the adverse effects of ROS and thereby contributing to reduced motility, damaged sperm plasma membranes, and ultimately elevated SDF.

Immune function and cytokine production

Basu et al. (2002) have shown that semen samples of men with SCI have increased numbers of T-cells that co-express human leucocyte antigen HLA-DR and interleukin-2 receptor alpha chain (CD25). Basu, Aballa, Ferrell, Lynne, and Brackett (2004) have also shown that men with SCI typically have seminal plasma with elevated levels of the cytokines, with those with Th1 effector function (IL1β, IL12, IFNγ, TNFα, TNF) being predominant over those with Th2 effector function (IL4, IL6, IL10, TGFβ1) when compared to non-SCI healthy controls; these observations suggest a cell-mediated, rather than a humoral immunological basis for infertility (Dimitriadis et al., 2010). There is also evidence to suggest that the adverse effects of inflammation on sperm motility can be reduced (neutralized) with the use of monoclonal antibodies to cytokines in SCI men (Brackett, Cohen, Ibrahim, Aballa, & Lynne, 2007) but no such data currently exists for their effect on SDF. da Silva et al. (2013) have explored proteomic differences in the seminal plasma protein composition of men with and without SCI and revealed high levels of proteins in SCI patients that appeared to be related to a decrease in sperm motility. They also noted that proteins that initiate the cytokine cascade related to proinflammatory processes were enhanced in men with SCI, as well as elevated concentrations of the cytokines IL1β, IL6, IL12, IFNc, and TNFα but lower concentrations of IL4 and TGFβ1. An apoptosis-associated speck-like protein containing a caspase activation and recruitment domain (ASC) has been detected and found to be elevated in the seminal plasma of men with SCI (Zhang et al., 2013); this same study revealed caspase-1 to be amplified in men with SCI and that both proteins were correlated with increased expression of the proinflammatory cytokines IL1β and IL18. Elevated levels of ASC were also found in the semen of men with SCI almost free of leukocytes. Both ASC and caspase-1 expression were also found in the sperm cell, as was a negative correlation of these proteins with motility (Zhang et al., 2013) but its effect on sperm DNA has not yet been examined. Hirsch, Sedor, Callahan, and Staas (1992) have also reported elevated sperm antibodies in men with SCI.

Other seminal plasma biochemical compounds

Platelet-activating factor acetylhydrolase (PAFah) is derived from the prostate and seminal vesicles and has higher activity in the seminal plasma of men with SCI (Hirsch, Jeyendran, Sedor, Rosecrans, & Staas, 1991), and is negatively correlated with sperm motility (Dimitriadis et al., 2010). PAFah is known to catalyze hydrolysis of esterified PAF to give the

biologically active lyso-PAF which acts as an autocrine modulator of sperm motility and enhances both sperm capacitation and the acrosome reaction (Dimitriadis et al., 2010). While there are no current studies linking high PAFah in the semen of men with SCI and SDF, premature capacitation, and acrosome reaction could lead to detrimental plasma membrane changes that pre-dispose the DNA to early ROS degradation.

Based on rat studies, Huang et al. (1997) have shown a temporal impairment in autoregulation of the androgen receptor mRNA shortly after induction of SCI and an accompanying continuing elevation of testosterone repressed prostate message 2 m-RNA (TRPM-2); the gene product of TRPM-2 has a role in the control of apoptosis. Huang et al. (1997) found that elevation of TRPM-2 is associated with a decrease in prostate epithelial cell height and prostate weight in SCI rats. Men with SCI typically present with significantly smaller prostates and produce less prostatic fluid than fertile males without SCI (Hvarness, Jakobsen, & Biering-Sorensen, 2007; Pannek, Berges, Cubick, Meindl, & Senge, 2003). This reduction in prostate size appears to be related to secretory dysfunction and corresponds with lower concentrations of prostate-specific antigen (PSA) in the semen, but higher or equivalent levels systemically (Alexandrino, Rodrigues, & Matsuo, 2004; Lynne et al., 1999). Hirsch et al. (1991) have noted lower levels of the energy substrates fructose and albumin and of the enzymes glutamic oxaloacetic transaminase and alkaline phosphatase in the seminal plasma of men with SCI, along with a higher concentration of chloride. Alexandrino, Rodrigues, Matsuo, Gregório, and Santilli (2011) have reported lower levels of Zinc in the ejaculates of men with SCI. Dimitriadis et al. (2010) have suggested that decreased seminal PSA in men with SCI could result in reduced concentrations of citrate, zinc, and cholesterol in the seminal plasma; molecules which are thought to be important for motility. The relationship between seminal PSA and SDF is yet to be investigated.

The presence of cell-free DNA (cfDNA) has recently been described in the ejaculates of men with SCI (Bartolomé-Nebreda et al., 2020). Using standard gel electrophoresis, a cfDNA band of ~150 bp was observed in all SCI patients analyzed (Fig. 2); this band was occasionally accompanied by another band of ~90 bp but both these bands were not observed in normozoospermic donors. Despite these findings, no correlation was observed between the intensity of the two DNA bands and the level of SDF in males with SCI. Neither was there any correlation with the occurrence of DNase activity present in the seminal plasma?

Improving sperm DNA quality in men with SCI

Success rates for the recovery of spermatozoa from men with SCI have been summarized (See Table 1 in the review of Dimitriadis et al., 2010). Spermatozoa have been recovered nonsurgically using pharmaceuticals, by prostatic massage, but the most common approach for men with SCI is by penile vibratory stimulation (PVS) or electroejaculation. Spermatozoa may also be recovered surgically from the testis (testicular sperm extraction—TESE), epididymis, vas deferens, or

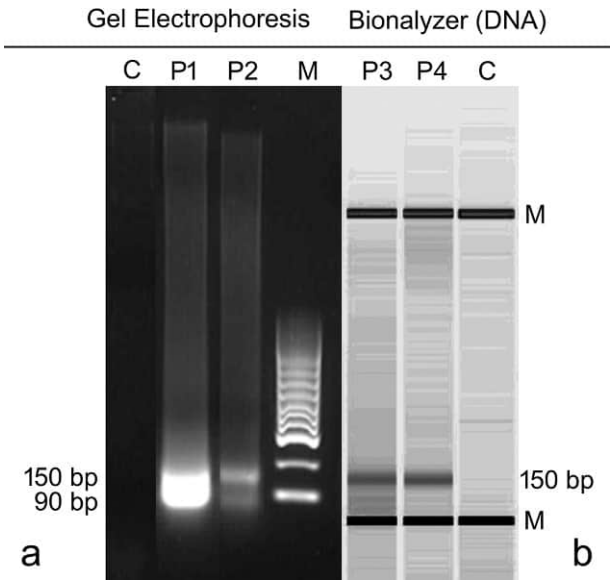

FIG. 2 (A) Gel electrophoresis showing cfDNA in the seminal plasma of two men with SCI (P1/P2) and the presence of two bands (150 bp and 90 bp) of cfDNA and its absence in normozoospermic a non-SCI individual (C). (B) High-resolution automated electrophoresis of cf-DNA from the seminal plasma of two SCI patients (P3/P4). M: DNA markers. In the middle 100 bp DNA ladder. C: control subjects.

TABLE 1 Summary of the differences in seminal plasma chemistry of men with and without SCI.

Seminal Plasma Chemistry	Relative difference in men with SCI	Physiological process impacted	References
Albumin	Lower	Energy substrate	Hirsch et al. (1991)
Chloride	Higher	Multiple functions	Hirsch et al. (1991)
DNase activity	Unchanged	Unknown	Bartolomé-Nebreda et al. (2020)
DNA—Free circulating	Higher	Unknown	Bartolomé-Nebreda et al. (2020)
Fructose	Lower	Energy substrate	Hirsch et al. (1991)
Glutamic oxaloacetic transaminase and alkaline phosphatase	Lower	Energetic metabolisms	Hirsch et al. (1991)
Hormones—Luteinising hormone, Follicle stimulating hormone, Testosterone, Prolactin	Lower	Hypothalamus-pituitary-gonad axis dysfunction	Naderi and Safarinejad (2003)
Interleukin-1b Interleukin-6, interleukin-12, and Tumor necrosis factor-A	Higher	Inflammatory cytokines	Basu et al. (2004) da Silva et al. (2013)
Interleukin-4 and Transforming growth factor-b	Lower	Inflammation	Basu et al. (2004) da Silva et al. (2013)
Interferon gamma	Higher	Reduce sperm motility	Basu et al. (2004) da Silva et al. (2013)
Immunoglobulin G immunoglobulin A	Higher	Anti-sperm antibodies	Hirsch et al. (1992)
Platelet activating factor acetyl hydrolase	Higher	Sperm motility	Hirsch et al. (1991)
Prostatic serum levels	Equivalent	Prostate and seminal vesicle function	Hirsch et al. (1991)
Prostate-specific antigen	Lower	Prostate and seminal vesicle function	Lynne et al. (1999) Alexandrino et al. (2004)
Somatostatin	Lower	Undefined role	Odum et al. (1995)
T-lymphocytes	Higher	Oxidative stress	Basu et al. (2002)
Zinc	Lower	Multiple functions	Alexandrino et al. (2011)

implanted sperm reservoirs. The advantage of TESE is that it can be applied regardless of the level of the spinal cord lesion, patient age, time-period post-injury, hormonal concentration, and semen analysis (Elliott et al., 2000).

The most efficient approach in obtaining a pregnancy in SCI patients is that of Intracytoplasmic Sperm Injection (ICSI), as this negates the need for sperm motility, which is a requirement of IVF, and only requires the selection of a single sperm cell. Under these conditions, a sperm cell free of fragmented DNA is essential. Therefore, there needs to be a reduction in the proportion of spermatozoa with SDF so the likelihood of accidentally selecting a spermatozoon with damaged DNA is

reduced. Consequently, we propose a strategy that draws together the combined use of preejaculation and postejaculation procedures to increase the proportion of spermatozoa without DNA damage in the semen of men with SCI for ICSI sperm selection (See Fig. 3).

Prior to semen collection, we suggest the use of recurrent ejaculation and/or use of the first ejaculated fraction to reduce the level of SDF in the ejaculate. Immediately after ejaculation, supportive sperm media (containing anti-oxidant compounds) should be added to reduce the high sperm concentration and the effect of oxidative stress, especially, if there is accompanying leukocytospermia. The semen sample can then be treated to remove immature sperm cells using Density-Gradient Centrifugation (DGC) to further reduce SDF (Gosálvez, Gonzalez-Martınez, et al., 2011). If the resulting number and relative motility of the reconstituted sample are suitable then it could be prepared for intrauterine insemination (IUI) or in vitro fertilization (IVF); if the sample is not suitable then ICSI would be employed.

There are a number of assisted reproductive strategies that can be used in association with the ICSI procedure to further improve the probability of selecting a sperm without fragmented DNA; these include magnetic-activated cell sorting (MACS) to remove apoptotic cells, Physiological-ICSI (PICSI) which differentially selects mature sperm based on hyaluronic acid-binding and intracytoplasmic morphologically selected sperm injection (IMSI) which selects sperm based on their morphological appearance; MACS and PICSI have both been developed to reduce the chance of selecting sperm with damaged DNA. If all this fails, then it is possible to harvest testicular sperm and use these cells in combination with ICSI. When used in men without SCI it has been shown to dramatically reduce the level of SDF (Esteves, Sanchez-Martín, Sanchez-Martín, Schneider, & Gosálvez, 2015); the technique has already resulted in successful pregnancies for men with SCI (Kanto et al., 2009).

Conclusion

This review has illustrated that men with SCI typically present with levels of SDF substantially higher than men without SCI, including those with male factor infertility and that the ultimate causes of this phenomenon are difficult to disentangle from the primary causes of high SDF in men without SCI. The etiologies of SDF in men with SCI are likely to be the result of synergistic pathologies so that the specifics of what causes the higher levels of SDF will require further investigation and are probably best suited to controlled studies involving animal models. Nevertheless, the take-home message of this review is that despite high SDF, the majority of men with SCI contain sufficient spermatozoa with an orthodox DNA molecule, that if clinically selected, could be used for successful assisted reproduction.

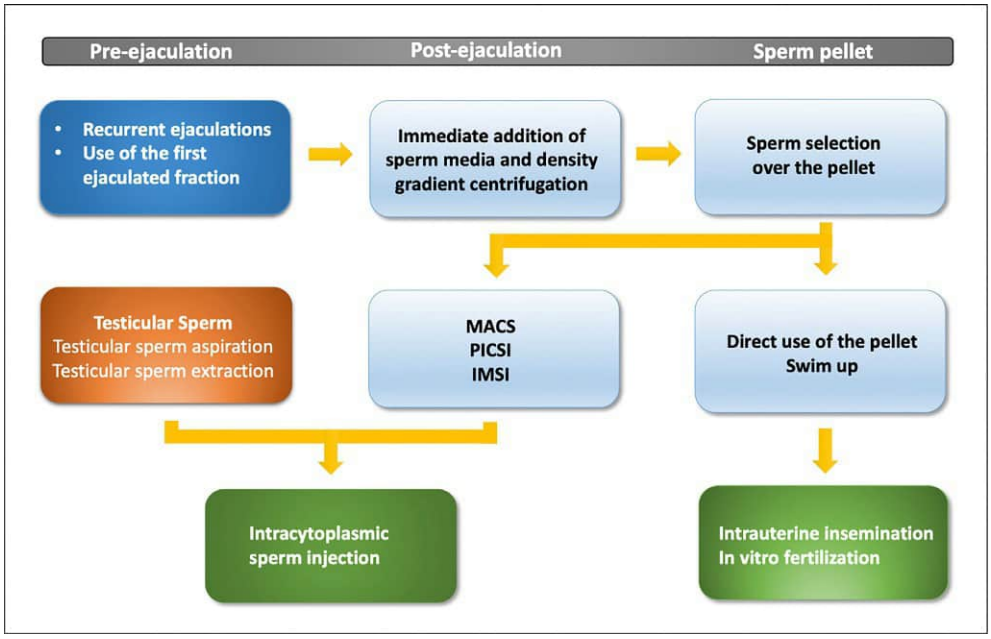

FIG. 3 Recommended protocol for an effective sperm DNA fragmentation reduction in SCI men. *TESE*, testicular sperm extraction; *TESA*, testicular sperm aspiration; *DCG*, density gradient centrifugation; *IVF*, in vitro fertilization; *ICSI*, intracytoplasmic sperm injection; *IUI*, intrauterine insemination; *MACS*, magnetic activated cell sorting; *PICSI*, physiological ICSI; *IMSI*, intracytoplasmic morphologically selected sperm injection.

Applications to other areas of neuroscience

As we have discovered in this chapter, the etiology of sperm DNA damage in the ejaculates of men with SCI is likely to be multifactorial and difficult to attribute to a specific neurophysiological pathology. The loss of sexual function and realization of the long-term impact of SCI can have a devastating impact on the male partner's psychological well-being (increased susceptibility to depression) and self-worth, not to mention the additional stress that the consequences of the injury may have on the female partner and the couple's desire to have a family. Nevertheless, most men with SCI have a proportion of spermatozoa in their ejaculate suitable for artificial reproductive technology procedures such as intracytoplasmic sperm injection that can be applied to obtain a successful pregnancy. Such fulfilment in establishing a family through assisted reproductive technology despite their injury is likely to be a powerful motivator in their recovery and rehabilitation process that should not be underestimated. In addition, some of the causes attributed to poor semen quality in men with SCI do not appear to be accounted for by their physiological dysfunction, suggesting that there are other subtle neural explanations and interactions (e.g., parasympathetic system) that we yet do not understand. In this respect studies of the effects of SCI on male fertility may also provide to be a useful research model for insights into SDF in men without SCI or the effects of oxidative damage on cellular function. SCI is typically accompanied by motor, vegetative, and sensitive dysfunction associated with the production of reactive oxygen species that can be extremely aggressive to surrounding tissues. We propose that sperm cells and sperm DNA fragmentation may serve as a useful bio-indicator for studying oxidative damage to better understand the pathophysiology of free radicals and for developing treatment protocols that reduce tissue necrosis, inflammation, infection, and apoptosis.

Mini-dictionary of terms

Apoptosis: a form of programmed cell death
Caspase: a family of protease enzymes essential to programmed cell death
Electroejaculation: method for collecting a semen sample
Histone: highly basic proteins that pack and order DNA into structural units called nucleosomes—in sperm replaced by protamine during spermiogenesis.
Leukocytospermia: abnormally high numbers of white cells in the semen
Necrozoospermia: ejaculate contains mainly dead spermatozoa
Normozoospermic: ejaculate which contains normal characteristics of seminogram
Oxidative stress: an imbalance between free radicals and anti-oxidants
Penile vibratory stimulation: method for collecting semen samples
Protamine: DNA binding proteins that facilitate the packaging of sperm chromatin
SCD assay: Sperm chromatin dispersal assay—simple rapid individual sperm assay to assess fragmented DNA in spermatozoa—based on the movement of fragmented DNA in a microgel
SCSA: Sperm chromatin structure assay—sperm assay based on flow cytometry to assay fragmented DNA in spermatozoa
TUNEL assay—Allows for the visualization and quantification of apoptotic cells
Varicocele—enlargement of the veins within pampiniform plexus

Key facts of sperm DNA fragmentation

- Sperm DNA Fragmentation (SDF) is a result of broken or fragmented DNA in the sperm nucleus without the capacity to be repaired.
- SDF has been shown to reduce reproductive outcome.
- SDF is high in ejaculates of men with spinal cord injury (SCI).
- The cause of elevated SDF in men with SCI is likely to be multifactorial.
- The high levels of SDF in men with SCI present problems in achieving pregnancy.
- Sperm selection reproductive technology can be used to increase the proportion of sperm with nonfragmented DNA in order to obtain a successful pregnancy.

Summary points

- Sperm DNA Fragmentation (SDF) occurs when the DNA molecule of the sperm cell is broken or fragmented in the form of single or double-stranded DNA breakages.

- SDF may arise in the testis during spermiogenesis, during sperm maturation and storage within the epididymis, iatrogenically during processing of the ejaculate for assisted fertilization or within the female reproductive tract.
- If not corrected by the oocyte following syngamy, SDF has been shown to result in embryonic failure and reduced pregnancy rate.
- Men with SCI have ejaculates that typically contain extremely high levels of SDF, up to 5 × higher than those of fertile men without SCI and 2 × higher than men without SCI but with evidence of male factor infertility.
- Previous reviews have identified etiologies in men with SCI that are thought to be associated with poor semen quality and which include alternations in the hormonal milieu of the testis, scrotal hyperthermia, anejaculation, differences in molecular biology of the testis, leukocytospermia, oxidative damage, abnormal seminal vesicular secretions, and abnormal seminal plasma chemistry.
- The majority of studies on the ejaculate of men with SCI have focused on classical sperm parameters (sperm motility and necrozoospermia) with little attention given to SDF; consequently, we explored the possible interaction with the etiologies indicated above and how these might influence the expression of SDF.
- We speculate that SDF is closely related to sperm plasma membrane damage linked to ROS formation leading to a secondary attack on sperm chromatin.
- The most efficient solution for overcoming infertility in men with SCI is likely to be through the use of intracytoplasmic sperm injection that requires the selection of a single spermatozoon without DNA damage.

References

Aitken, R. J. (2020). Impact of oxidative stress on male and female germ cells: Implications for fertility. *Reproduction*, *159*, 189–201.

Alexandrino, A. P., Rodrigues, M. A., & Matsuo, T. (2004). Evaluation of serum and seminal levels of prostate specific antigen in men with spinal cord injury. *Journal of Urology*, *171*, 2230–2232.

Alexandrino, A. P., Rodrigues, M. A. F., Matsuo, T., Gregório, E. P., & Santilli, J. C. (2011). Evaluation of seminal zinc levels by atomic absorption in men with spinal cord injury. *Spinal Cord*, *49*, 435–438.

Banks, S., King, S. A., Irvine, D. S., & Saunders, P. T. (2005). Impact of a mild scrotal heat stress on DNA integrity in murine spermatozoa. *Reproduction*, *129*, 505–514.

Bartolomé-Nebreda, J., Vargas-Baquero, E., López-Fernández, C., Fernández, J. L., Johnston, S. D., & Gosálvez, J. (2020). Free circulating DNA and DNase activity in the ejaculates of men with spinal cord injury. *Spinal Cord*. https://doi.org/10.1038/s41393-020-0518-3.

Basu, S., Aballa, T. C., Ferrell, S. M., Lynne, C. M., & Brackett, N. L. (2004). Inflammatory cytokine concentrations are elevated in seminal plasma of men with spinal cord injuries. *Journal of Andrology*, *25*, 250–254.

Basu, S., Lynne, C. M., Ruiz, P., Aballa, T. C., Ferrell, S. M., & Brackett, N. L. (2002). Cytofluorographic identification of activated T-cell subpopulations in the semen of men with spinal cord injuries. *Journal of Andrology*, *23*, 551–556.

Brackett, N. L. (2012). Infertility in men with spinal cord injury: Research and treatment. *Scientifica*, *12*. https://doi.org/10.6064/2012/578257, ID578257.

Brackett, N. L., Cohen, D. R., Ibrahim, E., Aballa, T. C., & Lynne, C. M. (2007). Neutralization of cytokine activity at the receptor level improves sperm motility in men with spinal cord injuries. *Journal of Andrology*, *28*, 717–721.

Brackett, N. L., Ibrahim, E., Grotas, J. A., Teodoro, C., Aballa, T. C., & Lynne, C. M. (2008). Higher sperm DNA damage in semen from men with spinal cord injuries compared with controls. *Journal of Andrology*, *29*, 93–99.

Brackett, N. L., Lynne, C. M., Weizman, M. S., Bloch, W. E., & Padron, O. F. (1994). Scrotal and oral temperatures are not related to semen quality or serum gonadotropin levels in spinal cord injured men. *Journal of Andrology*, *15*, 614–619.

Brackett, N. L., Nash, M. S., & Lynne, C. M. (1996). Male fertility following spinal cord injury: Facts and fiction. *Physical Therapy*, *76*, 1221–1231.

Colacurci, N., De Leo, V., Ruvolo, G., Piomboni, P., Caprio, F., Pivonello, R., et al. (2018). Recombinant FSH improves sperm DNA damage in male infertility: A phase II clinical trial. *Frontiers in Endocrinology*, *9*, 383.

Das, S., Dodd, S., Soni, B. M., Sharma, S. D., Gazvani, R., & Lewis-Jones, D. I. (2006). Does repeated electro-ejaculation improve sperm quality in spinal cord injured men? *Spinal Cord*, *44*, 753–756.

El-Demiry, M., & James, K. (1988). Lymphocyte subsets and macrophages in the male genital tract in health and disease. A monoclonal antibody-based study. *European Urology*, *14*, 226–235.

Deng, C., Li, T., Xie, Y., Guo, Y., Yang, Q., Liang, X., et al. (2019). Sperm DNA fragmentation index influences assisted reproductive technology outcome: A systematic review and meta-analysis combined with a retrospective cohort study. *Andrologia*, *51*, e13263.

Dimitriadis, F., Karakitsios, K., Tsounapi, P., Tsambalas, S., Loutradis, D., Kanakas, N., et al. (2010). Erectile function and male reproduction in men with spinal cord injury: A review. *Andrologia*, *42*, 139–165.

Durairajanayagam, D., Agarwal, A., & Ong, C. (2015). Causes, effects and molecular mechanisms of testicular heat stress. *Reproductive Biomedicine Online*, *30*, 14–27.

Elliott, S. P., Orejuela, F., Hirsch, I. H., Lipshultz, L. I., Lamb, D. J., & Kim, E. D. (2000). Testis biopsy findings in the spinal cord injured patient. *Journal of Urology*, *163*, 792–795.

Engh, E., Clausen, O. P., Purvis, K., & Stien, R. (1993). Sperm quality assessed by flow cytometry and accessory sex gland function in spinal cord injured men after repeated vibration-induced ejaculation. *Paraplegia*, *31*, 3–12.

Esteves, S. C., Cho, C. L., Majzoub, A., Zini, A., Coward, R. M., Evenson, D. P., et al. (2020). Clinical practice guidelines for sperm DNA fragmentation testing. *Andrologia*. https://doi.org/10.1111/and.13874.

Esteves, S. C., Gosálvez, J., López-Fernández, C., Núñez-Calonge, R., Caballero, P., Agarwal, A., et al. (2015). Diagnostic accuracy of sperm DNA degradation index (DDSi) as a potential noninvasive biomarker to identify men with varicocele-associated infertility. *International Urology and Nephrology*, *47*, 1471–1477.

Esteves, S. C., Sanchez-Martín, F., Sanchez-Martín, P. T., Schneider, D. T., & Gosálvez, J. (2015). Comparison of reproductive outcome in oligozoospermic men with high sperm DNA fragmentation undergoing intracytoplasmic sperm injection with ejaculated and testicular sperm. *Fertility and Sterility*, *104*, 1398–1405.

García-Peiró, A., Martínez-Heredia, J., Oliver-Bonet, M., Abad, C., Amengual, M. J., Navarro, J., et al. (2011). Protamine P1/P2 ratio correlates with dynamic aspects of DNA fragmentation in human sperm. *Fertility and Sterility*, *95*, 105–109.

García-Rodríguez, A., Gosálvez, J., Agarwal, A., Roy, R., & Johnston, S. (2019). DNA damage and repair in human reproductive cells. *International Journal of Molecular Sciences*, *20*, 31.

Gonzalez-Marin, C., Gosálvez, J., & Roy, R. (2012). Types, causes, detection and repair of DNA fragmentation in animal and human sperm cells. *International Journal of Molecular Sciences*, *13*, 14026–14052.

Gorczyca, W., Traganos, F., Jesionowska, H., & Darzynkiewicz, Z. (1993). Presence of DNA strand breaks and increased sensitivity of DNA in situ to denaturation in abnormal human sperm cells: Analogy to apoptosis of somatic cells. *Experimental Cell Research*, *207*, 202–205.

Gosálvez, J., Fernández, J. L., Yaniz, J., de la Casa, M., López-Fernández, C., & Johnston, S. D. (2015). A comparison of sperm DNA damage in the neat ejaculate of sperm donors and males presenting for their initial seminogram. *Austin Journal of Reproductive Medicine and Infertility*, *2*, 1014.

Gosálvez, J., Gonzalez-Martınez, M., López-Fernández, C., Fernández, J. L., & Sanchez-Martın, P. (2011). Shorter abstinence decreases sperm deoxyribonucleic acid fragmentation in ejaculate. *Fertility and Sterility*, *96*, 1083–1086.

Gosálvez, J., López-Fernández, C., Fernández, J. L., Gouraud, A., & Holt, W. V. (2011). Relationships between the dynamics of iatrogenic DNA damage and genomic design in mammalian spermatozoa from eleven species. *Molecular Reproduction and Development*, *78*, 951–961.

Gosálvez, J., López-Fernández, C., Fernández, J. L., Esteves, S. C., & Johnston, S. D. (2015). Unpacking the mysteries of sperm DNA fragmentation: Ten frequently asked questions. *Journal of Reproductive Biotechnology and Fertility*, *4*, 1–16.

Hamid, R., Patki, P., Bywater, H., Shah, P. J. R., & Craggs, M. D. (2006). Effects of repeated ejaculations on semen characteristics following spinal cord injury. *Spinal Cord*, *44*, 369–373.

Harrison, P. E., Barratt, C. L., Robinson, A. J., Kessopoulou, E., & Cooke, I. D. (1991). Detection of white blood cell populations in the ejaculates of fertile men. *Journal of Reproductive Immunology*, *19*, 95–98.

Hebles, M., Dorado, M., Gallardo, M., González-Martínez, M., & Sánchez-Martín, P. (2015). Seminal quality in the first fraction of ejaculate. *Systems Biology in Reproductive Medicine*, *61*, 113–116.

Henkel, R. R. (2011). Leukocytes and oxidative stress: Dilemma for sperm function and male fertility. *Asian Journal of Andrology*, *13*, 43–52.

Hirsch, I. H., Jeyendran, R. D., Sedor, J., Rosecrans, R. R., & Staas, W. E. (1991). Biochemical analysis of electroejaculates in spinal cord injured men: Comparison to normal ejaculates. *Journal of Urology*, *145*, 73–76.

Hirsch, I. H., Sedor, J., Callahan, H. J., & Staas, W. E. (1992). Antisperm antibodies in seminal plasma of spinal cord-injured men. *Urology*, *39*, 243–247.

Hou, J. W., Chen, D., & Jeyendran, R. S. (1995). Sperm nuclear maturity in spinal cord-injured men: Evaluation by acidic aniline blue stain. *Archives of Physical Medicine and Rehabilitation*, *76*, 444–445.

Huang, H. F., Li, M. T., Linsenmeyer, T. A., Ottenweller, J. E., Pogach, L. M., & Irwin, R. J. (1997). The effects of spinal cord injury on the status of messenger ribonucleic acid for TRPM 2 and androgen receptor in the prostate of the rat. *Journal of Andrology*, *18*, 250–256.

Huang, H. F., Li, M. T., Wang, S., Wang, G., & Ottenweller, J. E. (2003). Spinal cord contusion impairs sperm motility in the rat without disrupting spermatogenesis. *Journal of Andrology*, *24*, 371–380.

Hvarness, H., Jakobsen, H., & Biering-Sorensen, F. (2007). Men with spinal cord injury have a smaller prostate than men without. *Scandinavian Journal of Urology and Nephrology*, *41*, 120–123.

Jung, J. H., Kim, M. H., Kim, J., Baik, S. K., Koh, S. B., Park, H. J., et al. (2016). Treatment of leukocytospermia in male infertility: A systematic review. *World Journal of Mens Health*, *34*, 165–172.

Kanto, S., Uto, H., Toya, M., Ohnuma, T., Arai, Y., & Kyono, K. (2009). Fresh testicular sperm retrieved from men with spinal cord injury retains equal fecundity to that from men with obstructive azoospermia via intracytoplasmic sperm injection. *Fertility and Sterility*, *92*, 1333–1336.

de la Torre, J., Sánchez-Martín, P., Gosálvez, J., & Crespo, F. (2016). Equivalent seminal characteristics in human and stallion at first and second ejaculated fractions. *Andrologia*. https://doi.org/10.1111/and.12708.

de Lamirande, E., & Gagnon, C. (1993). A positive role for the superoxide anion in triggering hyperactivation and capacitation of human spermatozoa. *International Journal of Andrology*, *16*, 21–25.

Linsenmeyer, T. A., & Perkash, I. (1991). Infertility in men with spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *72*, 747–754.

López-Fernández, C., Johnston, S. D., Fernández, J. L., Wilson, R. J., & Gosálvez, J. (2010). Fragmentation dynamics of frozen-thawed ram sperm DNA is modulated by sperm concentration. *Theriogenology*, *74*, 1362–1370.

Lynne, C. M., Aballa, T. C., Wang, T. J., Rittenhouse, H. G., Ferrell, S. M., & Brackett, N. L. (1999). Serum and seminal plasma prostate specific antigen (PSA) levels are different in young spinal cord injured men compared to normal controls. *Journal of Urology*, *162*, 89–91.

Mallidis, C., Lim, T. C., Hill, S. T., Skinner, D. J., Brown, D. J., Johnston, W. I. H., et al. (2000). Necrospermia and chronic spinal cord injury. *Fertility and Sterility*, *74*, 221–227.

Mieusset, R., Bujan, L., Mondinat, C., Mansat, A., Pontonnier, F., & Grandjean, H. (1987). Association of scrotal hyperthermia with impaired spermatogenesis in infertile men. *Fertility and Sterility*, *48*, 1006–1011.

Naderi, A. R., & Safarinejad, M. R. (2003). Endocrine profiles and semen quality in spinal cord injured men. *Clinical Endocrinology*, *58*, 177–184.

Odum, L., Sonksen, J., & Biering-Sorensen, F. (1995). Seminal somatostatin in men with spinal cord injury. *Paraplegia*, *33*, 374–376.

Pannek, J., Berges, R. R., Cubick, G., Meindl, R., & Senge, T. (2003). Prostate size and PSA serum levels in male patients with spinal cord injury. *Urology*, *62*, 845–848.

Poetsch, A. R. (2020). The genomics of oxidative DNA damage, repair, and resulting mutagenesis. *Computational and Structural Biotechnology Journal*, *18*, 207–219.

Qiu, Y., Wang, L. G., Zhang, L. H., Li, J., Zhang, A. D., & Zhang, M. H. (2012). Sperm chromosomal aneuploidy and DNA integrity of infertile men with anejaculation. *Journal of Assisted Reproduction and Genetics*, *29*, 185–194.

Restelli, A. E., Borrelli, M., Jr., Spaine, D. M., Bertolla, R. P., Ortiz, V., & Cedenho, A. P. (2007). Sperm nuclear apoptotic DNA fragmentation in men with spinal cord injury. *Fertility and Sterility*, *88*(Suppl. 1), S374.

Sánchez-Martín, P., Sánchez-Martín, F., González-Martínez, M., & Gosálvez, J. (2013). Increased pregnancy after reduced male abstinence. *Systems Biology in Reproductive Medicine*, *59*, 256–260.

da Silva, B. F., Souza, G. H., Lo Turco, E. G., Del Giudice, P. T., Soler, T. B., Spaine, D. M., et al. (2013). Differential seminal plasma proteome according to semen retrieval in men with spinal cord injury. *Fertility and Sterility*, *100*, 959–969.

Talebi, A. R., Khalili, M. A., Vahidi, S., Ghasemzadeh, J., & Tabibnejad, N. (2013). Sperm chromatin condensation, DNA integrity, and apoptosis in men with spinal cord injury. *Journal of Spinal Cord Medicine*, *36*, 140–146.

Tvrdá, E., Arroyo, F., Ďuračka, M., López-Fernández, C., & Gosálvez, J. (2019). Dynamic assessment of human sperm DNA damage II: The effect of sperm concentration adjustment during processing. *Journal of Assisted Reproduction and Genetics*, *36*, 799–807.

Vargas-Baquero, E., Johnston, S., Sánchez-Ramos, A., Arévalo-Martin, A., Wilson, R., & Gosálvez, J. (2020). The incidence and etiology of sperm DNA fragmentation in the ejaculates of males with spinal cord injuries. *Spinal Cord*, *58*, 803–810.

Wang, Y. H., Huang, T. S., & Lien, I. N. (1992). Hormone changes in men with spinal cord injuries. *American Journal of Physical Medicine and Rehabilitation*, *71*, 328–332.

Wdowiak, A., Raczkiewicz, D., Stasiak, M., & Bojar, I. (2014). Levels of FSH, LH and testosterone, and sperm DNA fragmentation. *Neuro Endocrinology Letters*, *35*, 73–79.

Zhang, X., Ibrahim, E., de Rivero-Vaccari, J. P., Lotocki, G., Aballa, T. C., Dietrich, W. D., et al. (2013). Involvement of the inflammasome in abnormal semen quality of men with spinal cord injury. *Fertility and Sterility*, *99*, 118–124.

Chapter 9

Beneficial and detrimental effects of cytokines after spinal cord injury

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Abbreviations

CCL	chemokine (C-C motif) ligand
CSPGs	chondroitin sulfate proteoglycans
CXCL	chemokine (C-X-C motif) ligand
HDAC	histone deacetylase
IFN	interferon
IL	interleukin
MAG	myelin-associated glycoprotein
MCAO	middle cerebral artery occlusion
MCP	monocyte chemoattractant protein
M-CSF	macrophage colony-stimulating factor
MIP	macrophage inflammatory protein
miRNA	microRNA
MMPs	matrix metalloproteinases
MS	multiple sclerosis
NO	nitric oxide
NOS	nitric oxide synthase
OMgp	oligodendrocyte myelin glycoprotein
SCI	spinal cord injury
TGF	transforming growth factor
TNF	tumor necrosis factor
vMIPII	broad-spectrum chemokine receptor antagonist

Introduction

Cytokines are signaling proteins involved in intercellular communication, and mediate the regulation of a large variety of immune and nonimmune cells. These molecules have been mainly associated with an immune action, although they play pleiotropic effects such as proliferation, differentiation, growth, survival, and cell death. Thus, it is not surprising that cytokines play crucial roles in the pathophysiology after spinal cord injury (SCI). After SCI, there is an activation of resident glial cells, such as microglia and astrocytes, and infiltration of blood immune cells, such as macrophages, granulocytes, and lymphocytes. These cells produce sequential segregation of huge amounts of cytokines which stimulate diverse detrimental as well as beneficial processes after SCI.

After the primary impact on the spinal cord, within few hours after the lesion, there is an initial spike of proinflammatory cytokines secretion which promotes and exacerbates inflammation. This initial release of pro-inflammatory cytokines produces an increase of vascular permeability, cellular infiltration from peripheral blood, and enhances proliferation and hypertrophy of astrocytes. Then, activated astrocytes generate the glial scar which acts as a barrier for axonal regeneration. All these processes contribute to the secondary injury, where neuronal loss and functional outcomes are represented. Few hours after this initial spike, there is also a small expression of antiinflammatory cytokines which regulates the extent of

Cellular, Molecular, Physiological, and Behavioral Aspects of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822427-4.00009-5

peripheral cell infiltration, inhibits proinflammatory cytokine production, and provides trophic support to neurons allowing axonal growth. Therefore, to some extent, these antiinflammatory cytokines produce neuroprotection and functional recovery. However, the net imbalance toward antiinflammatory cytokine production drives to an extension of the secondary lesion and persisted inflammation which remains chronically impairing regeneration and functional recovery after SCI.

The main goal of this present book chapter is to describe the role of cytokines within the pathogenesis of SCI as well as to describe the main research findings that envisage them as therapeutic targets. Through the years, there has been important research that aims to alter the expression or activity of cytokines after neural trauma to modulate neurodegeneration, promote repair, and improve functional outcomes after SCI.

Cytokine expression after SCI

After the injury, cytokines are released by multiple different cells which proliferate or infiltrate into the spinal cord (Fig. 1A). Local glial cells (microglia and astrocytes) are the first to be activated after damage. In normal conditions, microglia display numerous cytoplasmic processes on their surface that extend and retract to monitor central nervous system (CNS) homeostasis. Minutes to hours after damage detection, microglial cells proliferate and their processes establish a dense network surrounding the lesion site. Macrophage colony-stimulating factor (M-CSF) is the main cytokine involved in the proliferation of microglia that peak at 7 days after injury (Francos-Quijorna et al., 2017). Meanwhile, the release of ATP from astrocytes promotes the rapid extension of microglia toward the injury site (Davalos et al., 2005). As they transition to the next step of phagocytosis, microglia retract their processes and adopt an amoeboid morphology in response to high levels of nitric oxide (NO) (Dibaj et al., 2010).

Then, neutrophils infiltrate from the peripheral blood followed by monocytes, which differentiate into macrophages. Neutrophils reach a maximum at 24 h, whereas macrophages and astrocytes have a delayed maximum peak number within the first week after injury. Chemokine (C—C motif) ligand (CCL)-2 is an important cytokine for the recruitment of these leukocytes since mice lacking CCL2 receptors showed a reduction in the infiltration of these cells after CNS damage (Conductier, Blondeau, Guyon, Nahon, & Rovere, 2010).

Lymphocytes are the last cells to be infiltrated reaching a plateau of infiltration by 3 days postinjury (Donnelly & Popovich, 2008). Studies describe that all these local and blood-infiltrated cells remain within the spinal cord parenchyma chronically after injury promoting a persistent and abnormal inflammation.

Regarding the analysis of released cytokines within the spinal cord parenchyma after traumatic injury, the majority of studies available have been performed in murine models of SCI (Fig. 1B). During the first hours after injury, there is an enhanced expression of proinflammatory cytokines, such as interleukin (IL)-6, chemokine (C-X-C motif) ligand (CXCL)-1, CXCL2, CCL-2, and CXCL10 (Francos-Quijorna, Amo-Aparicio, Martinez-Muriana, & Lopez-Vales, 2016; Stammers, Liu, & Kwon, 2012) (Fig. 1B). These cytokines increase between 100 and 800-fold, reaching their maximum expression by 6 h after the injury. Other proinflammatory cytokines are also highly expressed between 5 and 25-fold, such as CCL1,

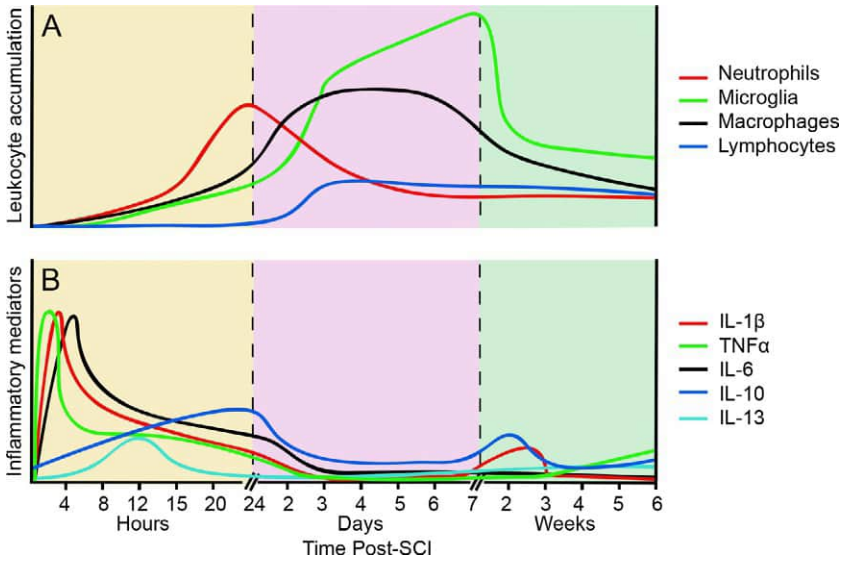

FIG. 1 Dynamics of the inflammatory response in the mouse spinal cord after injury. Immune cells (A) and inflammatory mediators (B) from hours to weeks after SCI. Values on the vertical axis represent relative changes and are not to scale. *Adapted from Donnelly, D. J., & Popovich, P. G. (2008). Inflammation and its role in neuroprotection, axonal regeneration and functional recovery after spinal cord injury*. Experimental Neurology, 209 *(2), 378–388. doi:10.1016/j.expneurol.2007.06.009 with data from Francos-Quijorna, I., Santos-Nogueira, E., Gronert, K., Sullivan, A. B., Kopp, M. A., Brommer, B., … Lopez-Vales, R. (2017). Maresin 1 promotes inflammatory resolution, neuroprotection, and functional neurological recovery after spinal cord injury*. The Journal of Neuroscience, 37*(48), 11731–11743. https://doi.org/10.1523/JNEUROSCI.1395-17.2017*.

CCL3, CCL4, CCL5 IL-1α, IL-9, IL-15, macrophage inflammatory protein (MIP)-1α, and tumor necrosis factor (TNF)-α with a peak between 6 and 24 h after injury. Contrasting, the number of antiinflammatory cytokines released is minimal. IL-13 and IL-10 increase by 5- to –15-fold between 12 and 24 h after lesion, respectively (Francos-Quijorna et al., 2016). Other antiinflammatory cytokines such as IL-4 do not alter their level of expression or even decrease. Therefore, a severe imbalance toward proinflammatory cytokine expression is described, which has a critical impact on the pathophysiology of SCI.

Several studies in humans correlate cytokine levels on the cerebrospinal fluid at 24 h after SCI with the level of the American Spinal Injury Association Impairment Scale (AIS) grade that patients reached. In addition, cytokine levels on human cerebrospinal fluid were also significantly different between those who improved an AIS grade over 6 months and those who did not improve (Dalkilic et al., 2018; Kwon et al., 2017). Therefore, the authors were able to predict the AIS grade progression through cerebrospinal fluid analyses of cytokines. These results emphasize the need to find therapeutic acute interventions to decrease the expression of inflammatory cytokines after lesion.

Cytokines promoting cell death and neurodegeneration after SCI

The initial trauma of the spinal cord produces massive necrosis of neurons and glial cells. Then, apoptosis plays an important role in the subsequent sustained loss of cells, which spreads tissue damage after the initial injury (Crowe, Bresnahan, Shuman, Masters, & Beattie, 1997). Several cytokines have been related to the activation of this secondary wave of cell death, mediated by apoptosis, and thus are related to the neurodegenerative events occurring after SCI.

Microglia, astrocytes, neurons, and infiltrating macrophages produce a rapid increase of TNFα expression in the lesion site, within 1 h after SCI, which remains significantly elevated up to 3 days posttrauma (Fig. 1B) (Harrington, Messier, Levine, Szmydynger-Chodobska, & Chodobski, 2005). The biological effects of TNFα are mediated by two receptors, the TNFR1 and TNFR2. Both receptors can mediate cell survival and cell death. However, after SCI, the balance is tipped toward cell death (Fig. 2). In fact, the initial peak of TNFα is followed by a significant increase on the expression of both receptors in neurons and oligodendrocytes at 3 and 6 h after the insult, which coincides with a high increment of apoptotic cells within the spinal cord parenchyma (Inukai et al., 2009). The accumulation of TNFα mediates apoptotic cell death of neurons and oligodendrocytes, in part, by inducing NO synthase (NOS) expression, and thus, NO production after injury (Lee et al., 2000).

Another important family of cytokines playing a key role in neurodegeneration is the IL-1 family. From this extensive family, IL-1α and IL-1β have been found to be important after SCI, exerting their pro-inflammatory actions by binding to the IL-1 type I receptor (IL-1R1). These cytokines are produced by resident spinal cells such as microglia, astrocytes, and neurons and promote tissue infiltration of neutrophils as well as astrogliosis. IL-1α protein expression in the injured spinal cord peaks at 4 h and it is mostly localized in microglia in the site of injury (Bastien et al., 2015). Its importance releases on studies that have shown that deletion of IL-1α gene protected against oligodendrocyte cell death and functional disabilities, but only at early stages after damage (Bastien et al., 2015). In contrast, IL-1β is upregulated later than IL-1α after SCI, peaking at 24 h and it is produced mainly by infiltrated neutrophils and macrophages (Bastien et al., 2015). IL-1β induces apoptosis, in part, by p38 MAPK induction and subsequent activation of caspase-3 (Wang, Kong, Qi, Ye, & Song, 2005).

Also, IL-17 mediates the recruitment and activation of mainly neutrophils, and stimulates chemokine and proinflammatory cytokine release, such as IL-1 and IL-6. In fact, a study with a knockout mice for IL-17 demonstrated that these injured mice have reduced cell infiltration in the injured spinal cord accompanied by reduced lesion size and enhanced functional performance (Hill, Kim, Gorrie, & Moalem-Taylor, 2011).

Finally, chemokines are a family of small cytokines which are able to induce chemotaxis in nearby responsive cells. Their importance after SCI is denoted by a study where they found that infusion of the broad-spectrum chemokine receptor antagonist (vMIPII) reduced monocyte infiltration into the spinal cord (Ghirnikar, Lee, & Eng, 2001). This reduction on infiltration was accompanied by a decrease on neuronal death, axonal degeneration, and demyelination within the injured spinal cord at 2 and 4 weeks after trauma.

Other studies also reflect the important role of specific chemokines, such as CXCL10, which has an important role in triggering T-lymphocyte and macrophage infiltration after trauma. CXCL10 expression peaks at 6 h after the trauma and remains elevated at 14 days after injury (Gonzalez, Glaser, Liu, Lane, & Keirstead, 2003). Inhibition of CXCL10 signaling by using specific neutralizing antibody results in a great reduction of lymphocyte and macrophage infiltration, tissue loss, and locomotor deficit (Gonzalez et al., 2003).

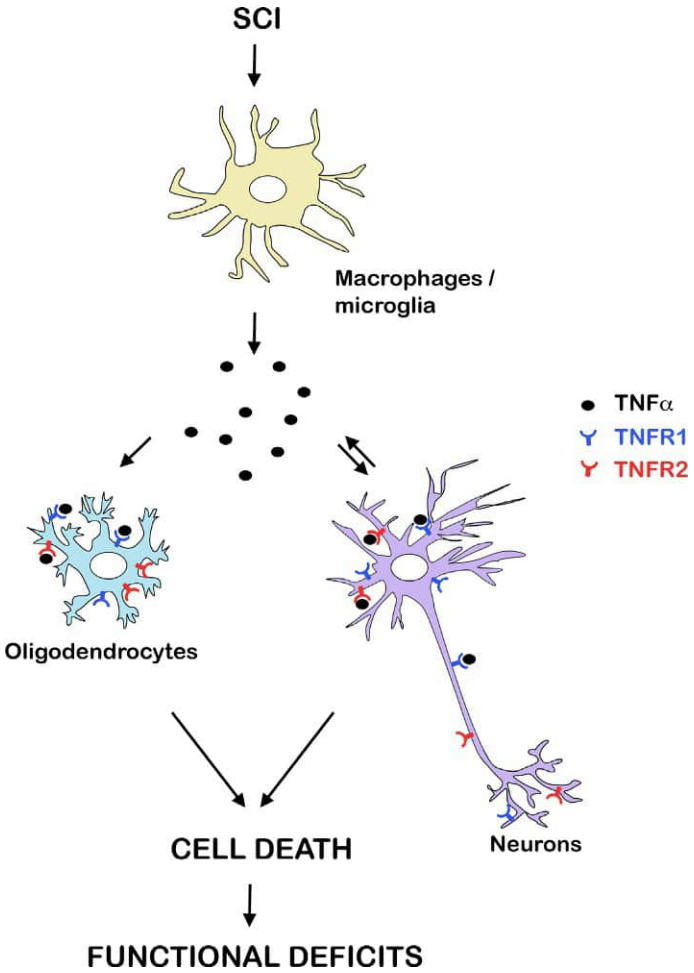

FIG. 2 TNFα effects after SCI. After the primary impact, resident cells such as microglia, neurons, and infiltrated macrophages secrete TNFα. Then TNFR1 and TNFR2 are upregulated in oligodendrocytes and neurons, promoting cell death after TNFα binding.

Cytokines in inflammation and glial scar formation

Macrophage and microglia polarization

Cytokines have an important role on macrophage and microglia functional state. Macrophages and microglia participate in the removal of cellular debris and the reestablishment of tissue homeostasis. However, there are many discrepancies about the contribution of these cells after injury. Several studies showed that the abolition of macrophages through different approaches could reduce the damage after SCI (Letellier et al., 2010; Lopez-Vales et al., 2005). Contrary, there are other lines of evidence showing that macrophages and microglia are protective and pro-regenerative (Yong, Rawji, Ghorbani, Xue, & Yong, 2019). These opposite actions of macrophages and microglia reflex a dual function that can be explained by their remarkable plasticity.

The term "polarization" refers to the plasticity of macrophages and microglia to acquire different and even opposite phenotypes (Fig. 3), and in which cytokines actively participate. Traditionally, two distinct polarization states have been described. Stimulation of macrophages and microglia with the prototypical Th1 cytokine Interferon (IFN)-γ or LPS induces M1 (or *classic*) polarization in which cells secrete pro-inflammatory cytokines (IL-1β, TNFα, and IL-6), cytotoxic mediators (iNOS and NO), and extracellular matrix-degrading enzymes (or matrix metalloproteinases, MMPs). On their surface, they express phagocytic receptors (CD16/32) and costimulatory molecules (CD86) (David & Kroner, 2011). They are therefore often referred to as pro-inflammatory cells. In contrast, stimulation with the Th2 cytokines, IL-4 or IL-13, induces the M2 (or *alternative*) polarization. This M2 phenotype is characterized by the upregulation of antiinflammatory cytokines (IL-10, transforming growth factor (TGF)-β), wound healing enzymes (Arg1), expression of clearance receptors (CD204 and CD206), and defective NF-κB activation (David & Kroner, 2011; Martinez, Helming, & Gordon, 2009). There are

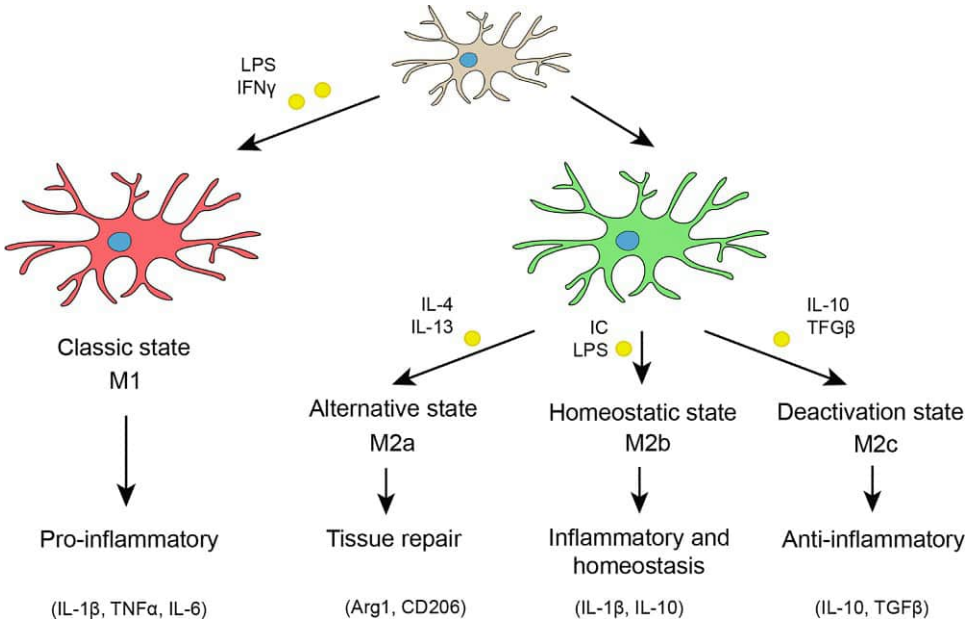

FIG. 3 Polarization of macrophages and microglia toward M1 and M2 phenotypes. M2 phenotype can be divided into M2a, M2b, and M2c profiles. Stimuli that induce polarization, general roles of these states, and produced factors are indicated.

therefore referred to as antiinflammatory cells. M2 polarization is more complex than M1 and, for some authors, it should be broken down into M2a, M2b, and M2c based on the specific profile of secreted cytokines (David, 2015).

M1 macrophages and microglia fight bacterial infections and remove cellular debris. Traditionally, they have been related to the detrimental effects of the inflammatory response since they secrete cytotoxic factors that could damage healthy tissue and contributes to secondary damage. M2 macrophages and microglia promote tissue healing and therefore they are related to the beneficial effects of the inflammatory response (David & Kroner, 2011). It is necessary to have in mind that the M1/M2 classification of macrophages and microglia is an experimental construct that was originally described using in vitro studies (Martinez et al., 2009). In vivo, cells are influenced by multiple additional factors leading to a wide spectrum of intermediate phenotypes where cells can express opposite markers at the same time (Morganti, Riparip, & Rosi, 2016).

Glial scar formation

Besides clearing up cellular debris and promote tissue healing, macrophages, and microglia also establish a burden of massive deposition of molecules called a glial scar. The glial scar is an evolving structure with different cells arriving and participating at different stages. At the first stages, the glial scar is formed by macrophages and microglia. However, the final structure is formed mainly by astrocytes (Fawcett & Asher, 1999). Although this glial structure delimitates the injury site avoiding its expansion, it also produces an inhibitory environment where axons fail to regenerate. Characterization of CNS myelin leads to the identification of several components that exert a potent inhibitory action on neurite outgrowth. These molecules include myelin-associated glycoprotein (MAG), oligodendrocyte myelin glycoprotein (OMgp), and chondroitin sulfate proteoglycans (CSPGs) (Fawcett & Asher, 1999). Astrocytes can express receptors and respond to a large variety of cytokines and growth factors involved in the proliferation and formation of the glial scar. From all the cytokines that participate in this process, TGF-β and IL-6 are the most important (Hamby & Sofroniew, 2010).

TGF-β is rapidly upregulated after CNS injury and promotes the activation and process extension of astrocytes, producing astrogliosis. TFG-β modulates the inflammatory response and induces the glial scar formation by stimulating the deposition of new matrix proteins (collagen, fibronectin, and proteoglycan) (Kohta, Kohmura, & Yamashita, 2009; Susarla et al., 2011). In agreement with these functions, intrathecal administration of neutralizing antibody to TGF-β into spinal cord injured rats reduced glial scar formation and enhanced axons growth (Kohta et al., 2009).

IL-6 is also involved in the formation of the glial scar. IL-6 shows an acute increase within the 12 h after injury (Francos-Quijorna et al., 2016), and induces astrogliosis through STAT3 signaling (Sofroniew, 2009). In vitro studies showed that IL-6 acts on neural stem cells to induce their differentiation into astrocytes (Bonni et al., 1997). Moreover, different authors

showed that astrogliosis can be targeted through excessive activation or blockade of IL-6/IL-6R pathways (Brunello et al., 2000; Okada et al., 2004).

Cytokines in neuroprotection and repair

During the first 2 weeks after SCI, macrophages and microglia display a predominant pro-inflammatory phenotype (Francos-Quijorna et al., 2016; Kroner et al., 2014). This unfavorable polarization can be explained by the low levels of antiinflammatory cytokines observed in the spinal epicenter. Aimed at modulating this injury environment, different cytokine-based strategies have been proposed.

Enhancement of antiinflammatory cytokine levels

Interleukin 4 (IL-4) is undetected in the spinal cord during the first 28 days after injury (Francos-Quijorna et al., 2016). Since this cytokine induces the M2 polarization of macrophages and microglia in vitro (Fig. 3) (David & Kroner, 2011; Martinez et al., 2009), promoting its levels after an injury has been used as a therapeutic approach. Single administration of recombinant IL-4 into the spinal cord at 48 h after injury resulted in the antiinflammatory polarization of macrophages and microglia based on the increased levels of Arg1 and CD206 (Francos-Quijorna et al., 2016) (Fig. 4A). At the histological level, recombinant IL-4 promoted tissue protection by increasing myelin sparing and preservation of central axonal pathways (Fig. 4B). All these changes translated into improved functional recovery after injury (Fig. 4C). Importantly, these results were not obtained with the acute administration of recombinant IL-4 within the first minutes after injury evidencing the unfavorable environment during the first days after damage (Francos-Quijorna et al., 2016).

IL-37 is a cytokine of the interleukin 1 family with antiinflammatory properties. Unlike other members of the IL-1 family, the open reading frame for the human *IL37* gene has not been found in the mouse genome yet (Taylor, Renshaw, Garka, Smith, & Sims, 2002). Besides that, transgenic mice expressing the human form of *IL37* gene exhibited reduced tissue damage and functional deficits after SCI in comparison with wild-type mice (Coll-Miro et al., 2016).

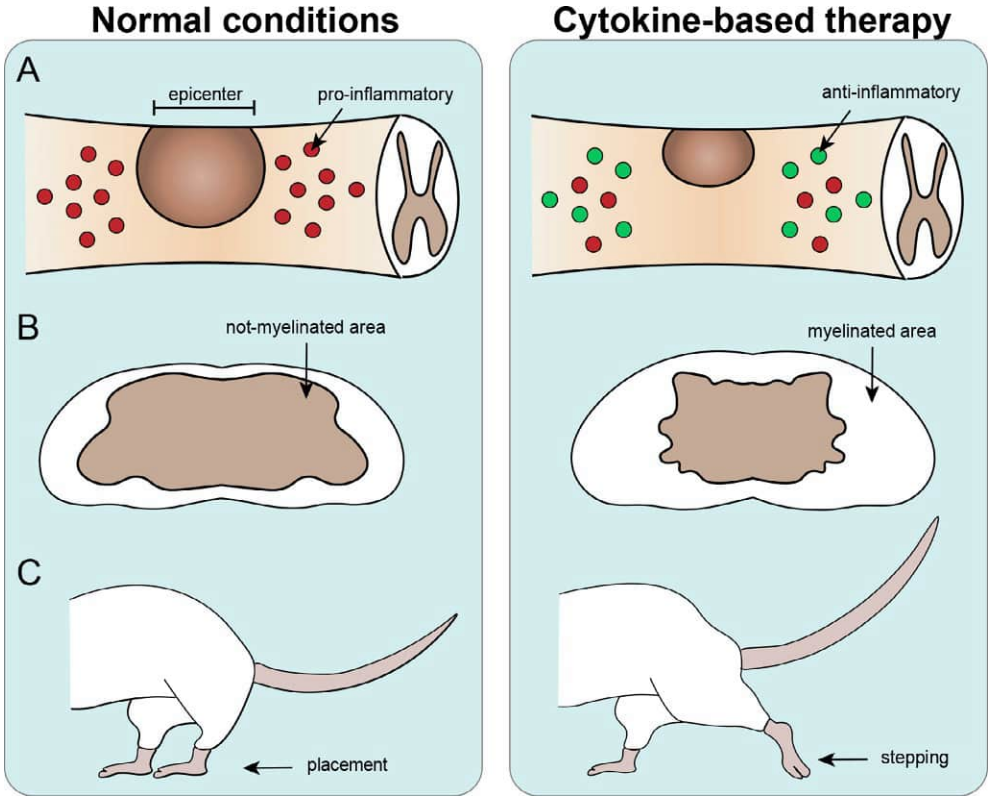

FIG. 4 Results of some cytokine-based therapies after SCI in animal models. Changes in the inflammatory environment (A), lesion volume (B), and locomotor recovery (C) due to the administration of antiinflammatory cytokines or blockade of proinflammatory cytokines.

This beneficial effect was associated with the moderated concentration of inflammatory cytokines and chemokines in the injury environment. Changes in axonal regeneration were not observed. Similar to transgenic expression, single administration of recombinant IL-37 protein in the spinal cord immediately after injury also resulted in functional recovery (Coll-Miro et al., 2016). Since recombinant IL-37 protein acts only through the extracellular pathway of this cytokine, it seems that this route is the main responsible for the beneficial effects of IL-37. Moreover, the abolition of an extracellular pathway in IL-37 transgenic mice resulted into the lack of protection after injury (Amo-Aparicio et al., 2020).

Inhibition of proinflammatory cytokine pathways

Not only promotion of antiinflammatory cytokines can be used to modulate the inflammatory environment after injury, strategies based on the inhibition of proinflammatory cytokines have also been studied. As one of the main proinflammatory cytokines after SCI, IL-1β has been targeted to promote protection. *Il1b* gene-deficient mice significantly improved locomotor recovery after SCI in comparison with wild-type mice (Boato et al., 2013). Histological analysis also revealed that the lack of *Il1b* gene produced smaller lesion size, reduced lesion width, and decreased glial scar. Moreover, the number of corticospinal tract fibers increased significantly in caudal regions (Boato et al., 2013). Despite these results, other publications using *Il1b* knockout mice showed no changes in the lesion volume or locomotor outcomes although proinflammatory macrophages and neutrophils in the spinal cord were reduced (Bastien et al., 2015).

Knocking out the *Tnf* gene in mice resulted in the amelioration of the proinflammatory environment after SCI (Kroner et al., 2014). Seven days after contusion injury, *Tnf* null mice showed a shift in macrophage polarization toward antiinflammatory phenotype based on the increase of Arg1 and CD206, and the reduction of CD16/32 markers. These changes resulted in improved tissue preservation and locomotor outcomes (Kroner et al., 2014). Similar results were observed with the intraperitoneal administration of TNF antagonist etanercept in spinal cord injured rats (Genovese et al., 2006).

Similarly, blockade of IL-6/IL-6R engagement through MR16-1, an antimouse IL-6R monoclonal antibody, resulted in protective effects. Single intraperitoneal dose of MR16-1 immediately after SCI increased the number of CD206-positive macrophages in the injury site (Guerrero et al., 2012). Moreover, the levels of IFNγ and TNFα in the lesioned area were reduced, whereas the levels of IL-4 and IL-13 were increased. All these changes correlated with the promotion of spared myelin, enhancement of the functional outcome (Guerrero et al., 2012), and reduction of astrogliosis (Okada et al., 2004). However, in contrast to expected, complete blockade of IL-6 through knockout mice showed detrimental effects on the regeneration after spinal cord injury suggesting a time-dependent dual effect (Cafferty et al., 2004).

Epigenetic regulation of cytokine expression

Epigenetics refers to inherited and reversible alterations to chromatin that alter gene expression without changing the DNA sequence. These mechanisms are regulated by two major epigenetic modifications: chemical modifications of DNA (DNA methylation) and covalent modification of histones associated with DNA (histone modification). From these, histone modifications, in particular acetylations, have been postulated to modulate cytokine expression after SCI. In addition, a third system included in epigenetic alterations is the expression of noncoding RNA (ncRNA)-associated with gene silencing.

Histone acetylation

Histone deacetylases (HDACs) belong to a family of enzymes that remove acetyl groups from lysine residues located on the amino-terminal tails of histone proteins, producing chromatin compaction, and thus, reduced gene expression. HDACs pan-inhibitors such as VPA and TSA promote antiinflammatory effects, reducing the expression of antiinflammatory cytokines from stimulated microglia/macrophages (Chen et al., 2018; Halili et al., 2010) and producing neuroprotection (Penas et al., 2011). Similarly, the class I HDAC inhibitor CI-994 tends to decrease pro-inflammatory cytokine production, inhibits the accumulation of neutrophils, reduces neuronal loss, and enhances functional recovery from SCI (Zhang, Fujita, Matsuzaki, & Yamashita, 2018). However, class IIa inhibition produces opposite effects, aggravating tissue damage, and impairing the functional recovery post-SCI (Qi & Wang, 2018).

There have been also some studies about epigenetic enzymes regarding these acetylated proteins. Bromodomain and extra-terminal domain (BET) proteins bind to acetylated lysine residues in both histone and nonhistone proteins, recruit transcriptional complexes to regulate gene expression. In particular, it has been observed that BET inhibition reduces proinflammatory cytokine expression and enhances antiinflammatory cytokine production after SCI (Rudman et al., 2018; Sanchez-Ventura, Amo-Aparicio, Navarro, & Penas, 2019) (Fig. 5). As a result, BET inhibition reduces inflammation, promotes neuroprotection, and enhances functional outcomes after SCI (Sanchez-Ventura et al., 2019). BET family

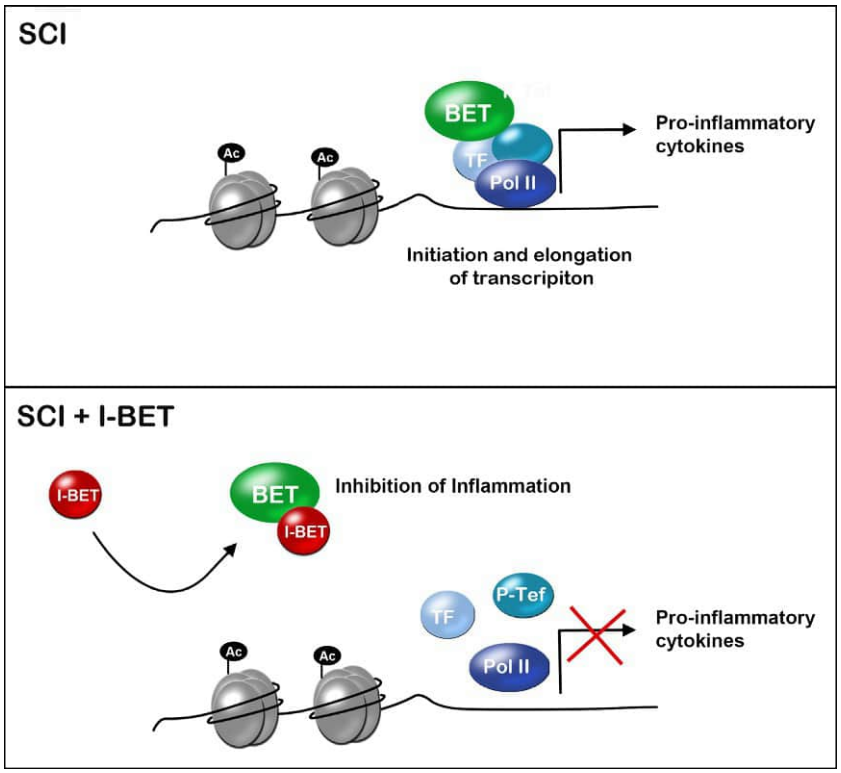

FIG. 5 Inhibition of BET proteins reduces inflammation after SCI. (Up) After the impact to the spinal cord, BET proteins recruit transcription factors (TF, P-Tef) and the RNA polymerase II (Pol II) to the chromatin, promoting the expression of proinflammatory cytokines. (Down) Treatment with a BET inhibitor (I-BET), displace BET proteins from the chromatin, inhibiting proinflammatory cytokine expression.

includes BRD2, BRD3, BRD4, and BRDT, and among them, BRD4 seems to be the main responsible for pro-inflammatory gene expression (Wang et al., 2019). Specific BRD4 knockdown suppresses inflammatory response via negatively modulating of NF-κB and MAPK signaling pathways (Wang et al., 2019).

Noncoding RNAs

Noncoding RNAs are diverse types of RNA molecules that are not translated into proteins. From these, microRNAs (miRNAs) have been deeply studied. miRNAs are small RNAs of about 22 nucleotides, which function in RNA silencing and posttranscriptional regulation of gene expression. These miRNAs function via complementary base-pairing sequences with mRNA molecules, which become silenced. After SCI, 138 miRNAs were found to be significantly expressed at 6 h postinjury, among which 87 miRNAs were upregulated and 51 miRNAs were downregulated (He et al., 2017). These altered miRNAs have opposite effects on inflammatory processes (Fig. 6). Literature shows that some decreased miRNAs

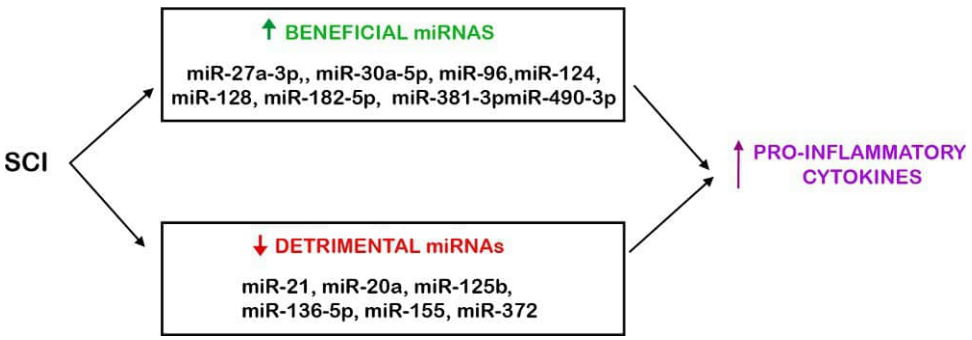

FIG. 6 MiRNAs affect the expression of cytokines after SCI. After trauma, there are several miRNAs that become upregulated and reduce the expression of proinflammatory cytokines, having a beneficial effect after SCI. Other miRNAs are downregulated, leading the expression of proinflammatory cytokines to become enhanced, and therefore, have a detrimental effect after SCI.

after SCI downregulate NF-κB pathway. Thus, its overexpression produces decreased cytokine expression and promotes reduced apoptosis, as well as enhanced functional recovery after SCI (Chen, Luo, Cao, Cheng, & He, 2018; Deng et al., 2018; He et al., 2017). Others, such as miR-21, which is increased after SCI, targets the PI3K/Akt/mTOR pathway and induces the expression of cytokines such as TGF-β, TNF-α, and IL-1β, promoting astrocytic and microglial immune response. Therefore, miR-21 has detrimental effects after SCI (Liu et al., 2018; Xie et al., 2018).

Applications to other areas of neuroscience

In addition, from spinal cord injury, some of the clinical approaches mentioned above have been demonstrated to be applicable to other neurological diseases.

Recent results showed that IL-37 exerts therapeutic effects in a mouse model of multiple sclerosis (MS). Similar to SCI, transgenic expression of IL-37 or recombinant protein administration protected against neurological deficits and myelin loss after MS. These changes were attributed to an attenuation in the inflammatory response on the spinal cord and lymph nodes. Authors also found that levels of IL-37 were ineffectively induced in the brain lesions of MS patients demonstrating the promising potential of this cytokine as a therapeutic approach (Sánchez-Fernández et al., 2020).

Regarding amyotrophic lateral sclerosis, using the mice model $SOD1^{G93A}$, a IL-4 lentiviral injection promoted microglia cell proliferation and modulated the inflammatory response by the reduction of pro-inflammatory cytokines and the increase on antiinflammatory cytokines (Rossi et al., 2018). All these changes translated into the slowed progression of motor impairments and delayed disease onset. Besides that, life span of $SOD1^{G93A}$ mice was not altered (Rossi et al., 2018).

For ischemic stroke, blockade of IL-1 β was shown to be protective in more than 25 publications (Banwell, Sena, & Macleod, 2009; McCann, Cramond, Macleod, & Sena, 2016). Rats and mice undergoing permanent or transient middle cerebral artery occlusion (MCAO) were treated with recombinant IL-1Ra (anakinra) by central or peripheral administration. Overall, anakinra reduced infarct volume by 38.2% (Banwell et al., 2009). Anakinra has also been studied in phase II clinical trials with ischemic stroke patients. Results showed a reduction of the inflammatory markers in plasma associated with worse outcomes after stroke (Smith et al., 2018). However, further studies are required to fully elucidate the efficacy and possible interaction of IL-1Ra with tissue plasminogen activator (Smith et al., 2018).

Finally, cytokines have been also found to have beneficial effects promoting axonal regeneration after nerve injury. Although peripheral axons are able to regenerate, peripheral regeneration is limited, especially in humans, due to the large distances that axons have to range. For instance, it has been demonstrated that the impairment of the inflammation via blockade of Toll-like receptor signaling impairs axonal outgrowth (Boivin et al., 2007) and that inhibition of TNF-α affects the survival and growth of sensory neurons (Fernyhough et al., 2005; Saleh et al., 2011). Importantly, antiinflammatory cytokines, secreted in the distal injured stump, have also a clear role in enhancing the capacity of proximal neurons to cross the critical zone. For example, it is known that animals lacking IL-10 regenerate worse than wild-type animals (Siqueira Mietto et al., 2015) and that the administration of IL-4 and IL-10 enhances axonal regeneration (Atkins et al., 2007; Vidal, Lemmens, Dooley, & Hendrix, 2013).

Mini-dictionary of terms

- Chemotaxis: Migration in response to stimuli. In the context of SCI, immune cells migrate toward the injury site in response to chemokines released by damaged tissue.
- Neurodegeneration: Progressive atrophy and loss of function of neurons.
- Neuroprotection: Preservation of neural structure and/or function.
- Secondary damage: Loss of neural tissue that takes weeks, and even months, after the initial trauma and expands the degenerative process of the lesion site through healthy neighboring areas.
- Polarization: Plasticity through macrophages and microglia acquire different, and even opposite, phenotypes. Traditionally, two opposite phenotypes have been described named M1 and M2.
- Proinflammatory cytokine: Cytokine that promotes the initiation or propagation of the inflammatory response
- Antiinflammatory cytokine: Cytokine that promotes the reduction of the inflammatory response

Key facts

Key facts of glial scar

- It is an evolving structure, cellularly composed by macrophages and microglia at the beginning and by astrocytes at late-stage
- Remains chronically after SCI
- Its extracellular matrix contains MAG, OMgp, and CSPGs
- Its major beneficial effect is to limit the propagation of tissue degeneration processes
- Its major detrimental effect is the inhibition of axonal regeneration

Key facts of inflammation after SCI

- Remains chronically after SCI
- It is imbalanced toward a proinflammatory environment
- Produces cytotoxic factors that damage healthy tissue
- Contributes to secondary damage
- Increases the lesion size and disabilities produced by the original trauma

Key facts on the major effects of cytokines

- Promotes chemotaxis of immune cells to the injury site
- Induces glial reactivity
- Promotes cell death and tissue damage
- Enhances vascular permeability allowing cell infiltration from blood
- Induces cell proliferation

Summary points

- Resident glial cells and blood-borne immune cells produce a high quantity of cytokines acutely after SCI.
- The major effects of cytokines after SCI are detrimental, including the promotion of cell infiltration from the blood, cell death, and glial scar formation.
- Cytokines have also beneficial effects including neuroprotection and axonal regeneration.
- Giving the importance of cytokines after SCI, they are being used as therapeutic targets after SCI.
- There are currently several lines of investigation studying the epigenetic mechanisms that regulate cytokine expression after SCI.

Acknowledgments

This work was supported by grant PID2019-108496RA-I00 from Ministerio de Ciencia e Innovación and Agencia Estatal de Investigación of Spain, CIBERNED (CB06/05/1105) and TERCEL (RD16/0011/0014) funds from the Instituto de Salud Carlos III of Spain, co-funded by European Union (ERDF/ESF, "Investing in your future").

References

Amo-Aparicio, J., Sanchez-Fernandez, A., Li, S., Eisenmesser, E. Z., Garlanda, C., Dinarello, C. A., et al. (2020). Extracellular and nuclear roles of IL-37 after spinal cord injury. *Brain, Behavior, and Immunity*, *91*, 194–201 (in press).

Atkins, S., Loescher, A. R., Boissonade, F. M., Smith, K. G., Occleston, N., O'Kane, S., et al. (2007). Interleukin-10 reduces scarring and enhances regeneration at a site of sciatic nerve repair. *Journal of the Peripheral Nervous System*, *12*(4), 269–276. https://doi.org/10.1111/j.1529-8027.2007.00148.x.

Banwell, V., Sena, E. S., & Macleod, M. R. (2009). Systematic review and stratified meta-analysis of the efficacy of interleukin-1 receptor antagonist in animal models of stroke. *Journal of Stroke and Cerebrovascular Diseases*, *18*(4), 269–276. https://doi.org/10.1016/j.jstrokecerebrovasdis.2008.11.009.

Bastien, D., Bellver Landete, V., Lessard, M., Vallieres, N., Champagne, M., Takashima, A., et al. (2015). IL-1alpha gene deletion protects oligodendrocytes after spinal cord injury through upregulation of the survival factor Tox3. *The Journal of Neuroscience*, *35*(30), 10715–10730. https://doi.org/10.1523/JNEUROSCI.0498-15.2015.

Boato, F., Rosenberger, K., Nelissen, S., Geboes, L., Peters, E. M., Nitsch, R., et al. (2013). Absence of IL-1beta positively affects neurological outcome, lesion development and axonal plasticity after spinal cord injury. *Journal of Neuroinflammation*, *10*, 6. https://doi.org/10.1186/1742-2094-10-6.

Boivin, A., Pineau, I., Barrette, B., Filali, M., Vallieres, N., Rivest, S., et al. (2007). Toll-like receptor signaling is critical for Wallerian degeneration and functional recovery after peripheral nerve injury. *The Journal of Neuroscience*, *27*(46), 12565–12576. https://doi.org/10.1523/JNEUROSCI.3027-07.2007.

Bonni, A., Sun, Y., Nadal-Vicens, M., Bhatt, A., Frank, D. A., Rozovsky, I., et al. (1997). Regulation of gliogenesis in the central nervous system by the JAK-STAT signaling pathway. *Science*, *278*(5337), 477–483. https://doi.org/10.1126/science.278.5337.477.

Brunello, A. G., Weissenberger, J., Kappeler, A., Vallan, C., Peters, M., Rose-John, S., et al. (2000). Astrocytic alterations in interleukin-6/soluble interleukin-6 receptor alpha double-transgenic mice. *The American Journal of Pathology*, *157*(5), 1485–1493. https://doi.org/10.1016/s0002-9440(10)64787-6.

Cafferty, W. B., Gardiner, N. J., Das, P., Qiu, J., McMahon, S. B., & Thompson, S. W. (2004). Conditioning injury-induced spinal axon regeneration fails in interleukin-6 knock-out mice. *The Journal of Neuroscience*, *24*(18), 4432–4443. https://doi.org/10.1523/JNEUROSCI.2245-02.2004.

Chen, W. C., Luo, J., Cao, X. Q., Cheng, X. G., & He, D. W. (2018). Overexpression of miR-381-3p promotes the recovery of spinal cord injury. *European Review for Medical and Pharmacological Sciences*, *22*(17), 5429–5437. https://doi.org/10.26355/eurrev_201809_15802.

Chen, S., Ye, J., Chen, X., Shi, J., Wu, W., Lin, W., et al. (2018). Valproic acid attenuates traumatic spinal cord injury-induced inflammation via STAT1 and NF-kappaB pathway dependent of HDAC3. *Journal of Neuroinflammation*, *15*(1), 150. https://doi.org/10.1186/s12974-018-1193-6.

Coll-Miro, M., Francos-Quijorna, I., Santos-Nogueira, E., Torres-Espin, A., Bufler, P., Dinarello, C. A., et al. (2016). Beneficial effects of IL-37 after spinal cord injury in mice. *Proceedings of the National Academy of Sciences of the United States of America*, *113*(5), 1411–1416. https://doi.org/10.1073/pnas.1523212113.

Conductier, G., Blondeau, N., Guyon, A., Nahon, J. L., & Rovere, C. (2010). The role of monocyte chemoattractant protein MCP1/CCL2 in neuroinflammatory diseases. *Journal of Neuroimmunology*, *224*(1–2), 93–100. https://doi.org/10.1016/j.jneuroim.2010.05.010.

Crowe, M. J., Bresnahan, J. C., Shuman, S. L., Masters, J. N., & Beattie, M. S. (1997). Apoptosis and delayed degeneration after spinal cord injury in rats and monkeys. *Nature Medicine*, *3*(1), 73–76. https://doi.org/10.1038/nm0197-73.

Dalkilic, T., Fallah, N., Noonan, V. K., Salimi Elizei, S., Dong, K., Belanger, L., et al. (2018). Predicting injury severity and neurological recovery after acute cervical spinal cord injury: A comparison of cerebrospinal fluid and magnetic resonance imaging biomarkers. *Journal of Neurotrauma*, *35*(3), 435–445. https://doi.org/10.1089/neu.2017.5357.

Davalos, D., Grutzendler, J., Yang, G., Kim, J. V., Zuo, Y., Jung, S., et al. (2005). ATP mediates rapid microglial response to local brain injury in vivo. *Nature Neuroscience*, *8*(6), 752–758. https://doi.org/10.1038/nn1472.

David, S. (2015). *Neuroinflammation: New insights into beneficial and detrimental functions*. John Wiley & Sons. ISBN: 1118732774, 9781118732779.

David, S., & Kroner, A. (2011). Repertoire of microglial and macrophage responses after spinal cord injury. *Nature Reviews. Neuroscience*, *12*(7), 388–399. https://doi.org/10.1038/nrn3053.

Deng, G., Gao, Y., Cen, Z., He, J., Cao, B., Zeng, G., et al. (2018). miR-136-5p regulates the inflammatory response by targeting the IKKbeta/NF-kappaB/A20 pathway after spinal cord injury. *Cellular Physiology and Biochemistry*, *50*(2), 512–524. https://doi.org/10.1159/000494165.

Dibaj, P., Nadrigny, F., Steffens, H., Scheller, A., Hirrlinger, J., Schomburg, E. D., et al. (2010). NO mediates microglial response to acute spinal cord injury under ATP control in vivo. *Glia*, *58*(9), 1133–1144. https://doi.org/10.1002/glia.20993.

Donnelly, D. J., & Popovich, P. G. (2008). Inflammation and its role in neuroprotection, axonal regeneration and functional recovery after spinal cord injury. *Experimental Neurology*, *209*(2), 378–388. https://doi.org/10.1016/j.expneurol.2007.06.009.

Fawcett, J. W., & Asher, R. A. (1999). The glial scar and central nervous system repair. *Brain Research Bulletin*, *49*(6), 377–391. https://doi.org/10.1016/s0361-9230(99)00072-6.

Fernyhough, P., Smith, D. R., Schapansky, J., Van Der Ploeg, R., Gardiner, N. J., Tweed, C. W., et al. (2005). Activation of nuclear factor-kappaB via endogenous tumor necrosis factor alpha regulates survival of axotomized adult sensory neurons. *The Journal of Neuroscience*, *25*(7), 1682–1690. https://doi.org/10.1523/JNEUROSCI.3127-04.2005.

Francos-Quijorna, I., Amo-Aparicio, J., Martinez-Muriana, A., & Lopez-Vales, R. (2016). IL-4 drives microglia and macrophages toward a phenotype conducive for tissue repair and functional recovery after spinal cord injury. *Glia*, *64*(12), 2079–2092. https://doi.org/10.1002/glia.23041.

Francos-Quijorna, I., Santos-Nogueira, E., Gronert, K., Sullivan, A. B., Kopp, M. A., Brommer, B., et al. (2017). Maresin 1 promotes inflammatory resolution, neuroprotection, and functional neurological recovery after spinal cord injury. *The Journal of Neuroscience*, *37*(48), 11731–11743. https://doi.org/10.1523/JNEUROSCI.1395-17.2017.

Genovese, T., Mazzon, E., Crisafulli, C., Di Paola, R., Muia, C., Bramanti, P., et al. (2006). Immunomodulatory effects of etanercept in an experimental model of spinal cord injury. *The Journal of Pharmacology and Experimental Therapeutics*, *316*(3), 1006–1016. https://doi.org/10.1124/jpet.105.097188.

Ghirnikar, R. S., Lee, Y. L., & Eng, L. F. (2001). Chemokine antagonist infusion promotes axonal sparing after spinal cord contusion injury in rat. *Journal of Neuroscience Research*, *64*(6), 582–589. https://doi.org/10.1002/jnr.1110.

Gonzalez, R., Glaser, J., Liu, M. T., Lane, T. E., & Keirstead, H. S. (2003). Reducing inflammation decreases secondary degeneration and functional deficit after spinal cord injury. *Experimental Neurology*, *184*(1), 456–463. https://doi.org/10.1016/s0014-4886(03)00257-7.

Guerrero, A. R., Uchida, K., Nakajima, H., Watanabe, S., Nakamura, M., Johnson, W. E., et al. (2012). Blockade of interleukin-6 signaling inhibits the classic pathway and promotes an alternative pathway of macrophage activation after spinal cord injury in mice. *Journal of Neuroinflammation*, *9*, 40. https://doi.org/10.1186/1742-2094-9-40.

Halili, M. A., Andrews, M. R., Labzin, L. I., Schroder, K., Matthias, G., Cao, C., et al. (2010). Differential effects of selective HDAC inhibitors on macrophage inflammatory responses to the Toll-like receptor 4 agonist LPS. *Journal of Leukocyte Biology*, *87*(6), 1103–1114. https://doi.org/10.1189/jlb.0509363.

Hamby, M. E., & Sofroniew, M. V. (2010). Reactive astrocytes as therapeutic targets for CNS disorders. *Neurotherapeutics*, *7*(4), 494–506. https://doi.org/10.1016/j.nurt.2010.07.003.

Harrington, J. F., Messier, A. A., Levine, A., Szmydynger-Chodobska, J., & Chodobski, A. (2005). Shedding of tumor necrosis factor type 1 receptor after experimental spinal cord injury. *Journal of Neurotrauma*, *22*(8), 919–928. https://doi.org/10.1089/neu.2005.22.919.

He, J., Zhao, J., Peng, X., Shi, X., Zong, S., & Zeng, G. (2017). Molecular mechanism of MiR-136-5p targeting NF-kappaB/A20 in the IL-17-mediated inflammatory response after spinal cord injury. *Cellular Physiology and Biochemistry*, *44*(3), 1224–1241. https://doi.org/10.1159/000485452.

Hill, F., Kim, C. F., Gorrie, C. A., & Moalem-Taylor, G. (2011). Interleukin-17 deficiency improves locomotor recovery and tissue sparing after spinal cord contusion injury in mice. *Neuroscience Letters*, *487*(3), 363–367. https://doi.org/10.1016/j.neulet.2010.10.057.

Inukai, T., Uchida, K., Nakajima, H., Yayama, T., Kobayashi, S., Mwaka, E. S., et al. (2009). Tumor necrosis factor-alpha and its receptors contribute to apoptosis of oligodendrocytes in the spinal cord of spinal hyperostotic mouse (twy/twy) sustaining chronic mechanical compression. *Spine (Phila Pa 1976)*, *34*(26), 2848–2857. https://doi.org/10.1097/BRS.0b013e3181b0d078.

Kohta, M., Kohmura, E., & Yamashita, T. (2009). Inhibition of TGF-beta1 promotes functional recovery after spinal cord injury. *Neuroscience Research*, *65*(4), 393–401. https://doi.org/10.1016/j.neures.2009.08.017.

Kroner, A., Greenhalgh, A. D., Zarruk, J. G., Passos Dos Santos, R., Gaestel, M., & David, S. (2014). TNF and increased intracellular iron alter macrophage polarization to a detrimental M1 phenotype in the injured spinal cord. *Neuron*, *83*(5), 1098–1116. https://doi.org/10.1016/j.neuron.2014.07.027.

Kwon, B. K., Streijger, F., Fallah, N., Noonan, V. K., Belanger, L. M., Ritchie, L., et al. (2017). Cerebrospinal fluid biomarkers to stratify injury severity and predict outcome in human traumatic spinal cord injury. *Journal of Neurotrauma*, *34*(3), 567–580. https://doi.org/10.1089/neu.2016.4435.

Lee, Y. B., Yune, T. Y., Baik, S. Y., Shin, Y. H., Du, S., Rhim, H., et al. (2000). Role of tumor necrosis factor-alpha in neuronal and glial apoptosis after spinal cord injury. *Experimental Neurology*, *166*(1), 190–195. https://doi.org/10.1006/exnr.2000.7494.

Letellier, E., Kumar, S., Sancho-Martinez, I., Krauth, S., Funke-Kaiser, A., Laudenklos, S., et al. (2010). CD95-ligand on peripheral myeloid cells activates Syk kinase to trigger their recruitment to the inflammatory site. *Immunity*, *32*(2), 240–252. https://doi.org/10.1016/j.immuni.2010.01.011.

Liu, R., Wang, W., Wang, S., Xie, W., Li, H., & Ning, B. (2018). microRNA-21 regulates astrocytic reaction post-acute phase of spinal cord injury through modulating TGF-beta signaling. *Aging (Albany NY)*, *10*(6), 1474–1488. https://doi.org/10.18632/aging.101484.

Lopez-Vales, R., Garcia-Alias, G., Fores, J., Udina, E., Gold, B. G., Navarro, X., et al. (2005). FK 506 reduces tissue damage and prevents functional deficit after spinal cord injury in the rat. *Journal of Neuroscience Research*, *81*(6), 827–836. https://doi.org/10.1002/jnr.20605.

Martinez, F. O., Helming, L., & Gordon, S. (2009). Alternative activation of macrophages: An immunologic functional perspective. *Annual Review of Immunology*, *27*, 451–483. https://doi.org/10.1146/annurev.immunol.021908.132532.

McCann, S. K., Cramond, F., Macleod, M. R., & Sena, E. S. (2016). Systematic review and meta-analysis of the efficacy of Interleukin-1 receptor antagonist in animal models of stroke: An update. *Translational Stroke Research*, *7*(5), 395–406. https://doi.org/10.1007/s12975-016-0489-z.

Morganti, J. M., Riparip, L. K., & Rosi, S. (2016). Call off the dog(ma): M1/M2 polarization is concurrent following traumatic brain injury. *PLoS One*, *11*(1). https://doi.org/10.1371/journal.pone.0148001, e0148001.

Okada, S., Nakamura, M., Mikami, Y., Shimazaki, T., Mihara, M., Ohsugi, Y., et al. (2004). Blockade of interleukin-6 receptor suppresses reactive astrogliosis and ameliorates functional recovery in experimental spinal cord injury. *Journal of Neuroscience Research*, *76*(2), 265–276. https://doi.org/10.1002/jnr.20044.

Penas, C., Verdu, E., Asensio-Pinilla, E., Guzman-Lenis, M. S., Herrando-Grabulosa, M., Navarro, X., et al. (2011). Valproate reduces CHOP levels and preserves oligodendrocytes and axons after spinal cord injury. *Neuroscience*, *178*, 33–44. https://doi.org/10.1016/j.neuroscience.2011.01.012.

Qi, X., & Wang, P. (2018). Class IIa HDACs inhibitor TMP269 promotes M1 polarization of macrophages after spinal cord injury. *Journal of Cellular Biochemistry*, *119*(4), 3081–3090. https://doi.org/10.1002/jcb.26446.

Rossi, C., Cusimano, M., Zambito, M., Finardi, A., Capotondo, A., Garcia-Manteiga, J. M., et al. (2018). Interleukin 4 modulates microglia homeostasis and attenuates the early slowly progressive phase of amyotrophic lateral sclerosis. *Cell Death & Disease*, *9*(2), 250. https://doi.org/10.1038/s41419-018-0288-4.

Rudman, M. D., Choi, J. S., Lee, H. E., Tan, S. K., Ayad, N. G., & Lee, J. K. (2018). Bromodomain and extraterminal domain-containing protein inhibition attenuates acute inflammation after spinal cord injury. *Experimental Neurology*, *309*, 181–192. https://doi.org/10.1016/j.expneurol.2018.08.005.

Saleh, A., Smith, D. R., Balakrishnan, S., Dunn, L., Martens, C., Tweed, C. W., et al. (2011). Tumor necrosis factor-alpha elevates neurite outgrowth through an NF-kappaB-dependent pathway in cultured adult sensory neurons: Diminished expression in diabetes may contribute to sensory neuropathy. *Brain Research*, *1423*, 87–95. https://doi.org/10.1016/j.brainres.2011.09.029.

Sánchez-Fernández, A., Zandee, S., Amo-Aparicio, J., Charabati, M., Prat, A., Garlanda, C., et al. (2020). IL-37 exerts therapeutic effects in experimental autoimmune encephalomyelitis through the receptor complex IL-1R5/IL-1R8. *Theranostic*, *11*, 1–13 (in press).

Sanchez-Ventura, J., Amo-Aparicio, J., Navarro, X., & Penas, C. (2019). BET protein inhibition regulates cytokine production and promotes neuroprotection after spinal cord injury. *Journal of Neuroinflammation*, *16*(1), 124. https://doi.org/10.1186/s12974-019-1511-7.

Siqueira Mietto, B., Kroner, A., Girolami, E. I., Santos-Nogueira, E., Zhang, J., & David, S. (2015). Role of IL-10 in resolution of inflammation and functional recovery after peripheral nerve injury. *The Journal of Neuroscience*, *35*(50), 16431–16442. https://doi.org/10.1523/JNEUROSCI.2119-15.2015.

Smith, C. J., Hulme, S., Vail, A., Heal, C., Parry-Jones, A. R., Scarth, S., et al. (2018). SCIL-STROKE (subcutaneous Interleukin-1 receptor antagonist in ischemic stroke): A randomized controlled phase 2 trial. *Stroke*, *49*(5), 1210–1216. https://doi.org/10.1161/STROKEAHA.118.020750.

Sofroniew, M. V. (2009). Molecular dissection of reactive astrogliosis and glial scar formation. *Trends in Neurosciences*, *32*(12), 638–647. https://doi.org/10.1016/j.tins.2009.08.002.

Stammers, A. T., Liu, J., & Kwon, B. K. (2012). Expression of inflammatory cytokines following acute spinal cord injury in a rodent model. *Journal of Neuroscience Research*, *90*(4), 782–790. https://doi.org/10.1002/jnr.22820.

Susarla, B. T., Laing, E. D., Yu, P., Katagiri, Y., Geller, H. M., & Symes, A. J. (2011). Smad proteins differentially regulate transforming growth factor-beta-mediated induction of chondroitin sulfate proteoglycans. *Journal of Neurochemistry*, *119*(4), 868–878. https://doi.org/10.1111/j.1471-4159.2011.07470.x.

Taylor, S. L., Renshaw, B. R., Garka, K. E., Smith, D. E., & Sims, J. E. (2002). Genomic organization of the interleukin-1 locus. *Genomics*, *79*(5), 726–733. https://doi.org/10.1006/geno.2002.6752.

Vidal, P. M., Lemmens, E., Dooley, D., & Hendrix, S. (2013). The role of "anti-inflammatory" cytokines in axon regeneration. *Cytokine & Growth Factor Reviews*, *24*(1), 1–12. https://doi.org/10.1016/j.cytogfr.2012.08.008.

Wang, J., Chen, J., Jin, H., Lin, D., Chen, Y., Chen, X., et al. (2019). BRD4 inhibition attenuates inflammatory response in microglia and facilitates recovery after spinal cord injury in rats. *Journal of Cellular and Molecular Medicine*, *23*(5), 3214–3223. https://doi.org/10.1111/jcmm.14196.

Wang, X. J., Kong, K. M., Qi, W. L., Ye, W. L., & Song, P. S. (2005). Interleukin-1 beta induction of neuron apoptosis depends on p38 mitogen-activated protein kinase activity after spinal cord injury. *Acta Pharmacologica Sinica*, *26*(8), 934–942. https://doi.org/10.1111/j.1745-7254.2005.00152.x.

Xie, W., Yang, S. Y., Zhang, Q., Zhou, Y., Wang, Y., Liu, R., et al. (2018). Knockdown of MicroRNA-21 promotes neurological recovery after acute spinal cord injury. *Neurochemical Research*, *43*(8), 1641–1649. https://doi.org/10.1007/s11064-018-2580-1.

Yong, H. Y. F., Rawji, K. S., Ghorbani, S., Xue, M., & Yong, V. W. (2019). The benefits of neuroinflammation for the repair of the injured central nervous system. *Cellular & Molecular Immunology*, *16*(6), 540–546. https://doi.org/10.1038/s41423-019-0223-3.

Zhang, S., Fujita, Y., Matsuzaki, R., & Yamashita, T. (2018). Class I histone deacetylase (HDAC) inhibitor CI-994 promotes functional recovery following spinal cord injury. *Cell Death & Disease*, *9*(5), 460. https://doi.org/10.1038/s41419-018-0543-8.

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Chapter 10

Neurovascular pathology following traumatic spinal cord injury

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Abbreviations

ASA	anterior spinal artery
ASIA	American Spinal Injury Association
BBB	blood–brain barrier
BSCB	blood–spinal cord barrier
CNS	central nervous system
CSPG	chondroitin sulfate proteoglycans
EC	endothelial cells
IgG	immunoglobulin G
IVIG	intravenous immunoglobulin G
MPSS	methylprednisolone sodium succinate
MSC	mesenchymal stem cell
NG2	nerve/glial antigen 2
NVU	neurovascular unit
SCI	spinal cord injury
SCI-IDS	injury-induced immune depression syndrome
TJ	tight junction
ZO	zona occludens

Introduction

Traumatic spinal cord injury (SCI) damages the local neuronal, glial, and vascular cells, which impairs the transmission and facilitation of autonomic and sensorimotor signals between the brain and peripheral organs (Zavvarian, Hong, & Fehlings, 2020). While the initial mechanical damage to the neuronal and glial cells directly impacts neurotransmission, vascular damage manifests in a prolonged pathology influencing the postinjury response and recovery (Tator & Fehlings, 1991). In the noninjured spinal cord, the spinal microvascular network maintains a steady supply of oxygen and nutrients to the neurons and adjacent glial cells, while excreting waste products. It also prevents the infiltration of harmful circulatory molecules and immune cells into the nervous system. The blood–spinal cord barrier (BSCB), and by extension the blood–brain barrier (BBB), form a tight seal between the central nervous system (CNS) and the bloodstream to regulate the passage of oxygen, nutrients, and waste products across the CNS microvasculature (Winkler et al., 2013). Recent studies have explored the interactions between vascular, glial, and neuronal cells, characterized as the neurovascular unit (NVU) model, to describe the BSCB function in both healthy and injured spinal cords (Xu et al., 2018).

The NVU damage following traumatic SCI stems from the direct disruption of vessels due to shear injury, leading to hemorrhage and vasospasm (Ahuja et al., 2017). This vascular disruption will subsequently result in the loss of autoregulation of spinal cord blood flow, which is exacerbated by damage to the descending sympathetic input into cardiac control centers in the upper thoracic cord. These mechanisms exacerbate ischemia. Furthermore, sympathetic nervous system impairment due to the loss of supraspinal input at the T6 level or higher injuries results in hypotension, autonomic dysreflexia, and cardiac arrhythmias (Sharif & Hou, 2017). Furthermore, traumatic SCI increases the risk of pulmonary

Cellular, Molecular, Physiological, and Behavioral Aspects of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822427-4.00010-1

embolism and deep venous thrombosis due to loss of mobility. Addressing these vascular-related complications is paramount for the mitigation of further spinal cord damage (Furlan & Fehlings, 2008).

Despite the high prevalence of SCI—ranging between 250 and 906 cases per million—our understanding of SCI-induced vascular damage and treatment options available to patients remains limited (Singh, Tetreault, Kalsi-Ryan, Nouri, & Michael, 2014). Although the first line of defense is the prevention of traumatic incidents, enhancing therapeutics aimed at restoring BSCB function would have a drastic impact on the patient's quality of life. Accordingly, this chapter will first provide an overview of the role of vascular damage following traumatic SCI and then explore therapeutic targets with the potential for clinical translation.

Secondary pathogenesis

The traumatic compression and contusion of the spinal cord cause immediate damage and long-term consequences, referred to as primary and secondary injury respectively (Fig. 1). Immediately following injury, the neuronal, glial, and vascular cells present at the injury site are damaged and result in the production of toxic cellular debris. Ischemia, hemorrhage, vasospasm, and edema are important consequences of vascular disruption in the injured spinal cord (Figley, Khosravi, Legasto, Tseng, & Fehlings, 2014). These lead to oxidative damage and the infiltration of reactive circulatory cells and molecules that induce the secondary injury pathogenesis. While the infiltrating immune cells are necessary to clear the cellular debris following injury, their continued presence is an important mediator of secondary SCI damage (Schwab, Zhang, Kopp, Brommer, & Popovich, 2014). Over the course of secondary injury, the injured spinal cord forms three distinct histological sections (Fig. 2), evident in both preclinical studies and postmortem analyses (O'Shea, Burda, & Sofroniew, 2017). The injury epicenter contains fibrotic scar and fluid-filled cavitations formed by cellular debris clearance. Immediately surrounding the lesion core, there is the astrocytic scar border which is formed from the proliferation of new astrocytes intermingled with extracellular molecules in order to encapsulate the immune cells in the lesion core. Expanding away from the astrocytic scar border is the spared neural tissue, which undergoes synaptic plasticity and axonal sprouting (Courtine & Sofroniew, 2019).

The secondary responses following ischemic-reperfusion damage due to traumatic SCI are classified into acute (48 h), subacute (2–14 days), intermediate (14–56 days), and chronic phases (more than 56 days) (Ahuja, Wilson, et al., 2017). In the acute phase of injury, the compromised microvascular network limits the blood supply at the lesion core, leading to the

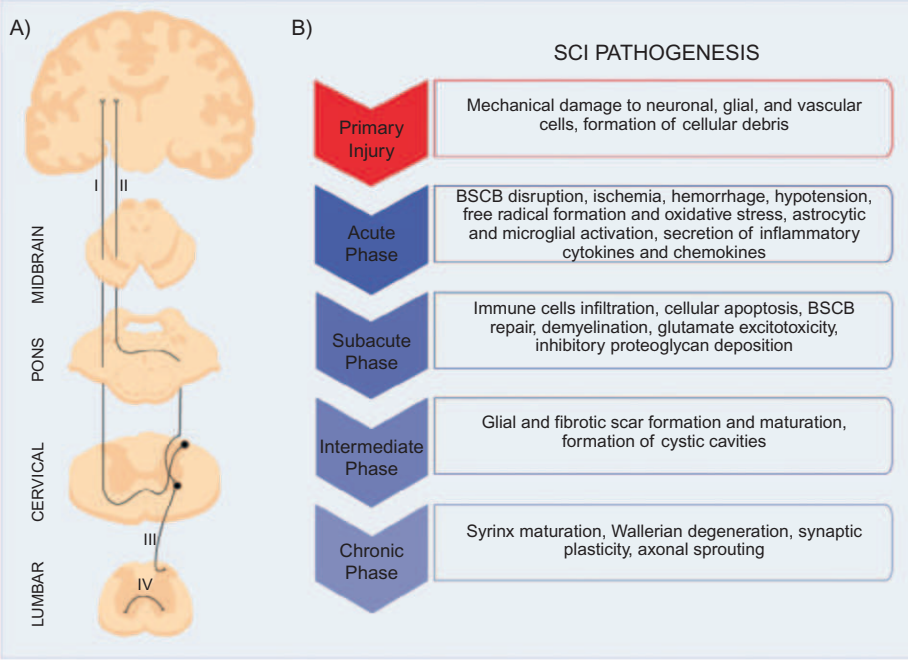

FIG. 1 Traumatic SCI hinders the ability of the spinal neural circuits to transmit and process autonomic and sensorimotor signals. (A) Representative schematic of spinal neural circuits; I: spinothalamic tract, II: corticospinal tract, III: propriospinal neurons, IV: commissural interneuron. (B) The secondary SCI pathogenesis is divided into four phases. The acute encompasses the first 48 h after injury. The sub-acute phase is a period between 48 h to 2 weeks postinjury. The intermediate phase refers to 2 weeks to 2 months after injury, and the chronic phase refers to greater than 2 months post-SCI.

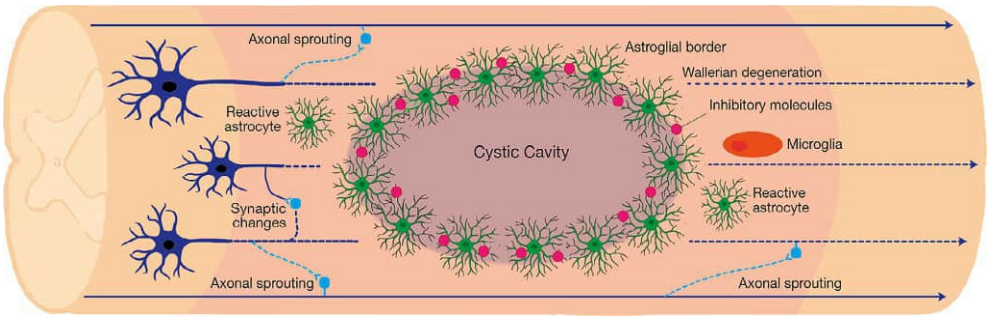

FIG. 2 The injured spinal cord consists of three distinct histological compartments, including a nonneuronal lesion core, a surrounding astroglial scar border, and pre-lesional tissue with spared but reactive neural tissue. Each compartment consists of unique cellular composition and exhibits distinct pathophysiology following traumatic SCI. *Pictures edited from Zavvarian, M.-M., Hong, J., & Fehlings, M. G. (2020). The functional role of spinal interneurons following traumatic spinal cord injury.* Frontiers in Cellular Neuroscience, 14, *127. doi:10.3389/fncel.2020.00127; Zavvarian, M.-M., Toossi, A., Khazaei, M., Hong, J., & Fehlings, M. (2020). Novel innovations in cell and gene therapies for spinal cord injury.* F1000Research, 9, *279. https://doi.org/10.12688/f1000research.21989.1*.

induction of hypoxia, ischemic injury, and hemorrhage (Mautes, Weinzierl, Donovan, & Noble, 2000). Moreover, reactive circulatory cells and molecules infiltrate the neural tissue, further complicating the injury pathology. In parallel, the produced cellular debris increases the proapoptotic signaling and triggers the activation of local microglia and astrocytes to clear the introduced debris and recruit additional blood-borne immune cells (Ahuja, Wilson, et al., 2017). In the subacute phase, the BSCB integrity is reestablished and the scar tissue begins to form in order to encapsulate the infiltrated immune cells. Ultimately, during the intermediate and chronic phase, the extended clearance of debris by microglia and macrophages leads to the development of the cystic cavity and continued axonal degradation. In many SCI cases, the formation of a longitudinal fluid-filled cavity occurs across many segments of the spinal cord (syringomyelia) and results in progressive myelopathy. The cause of syringomyelia occurrence is unknown, but it is affected by the gradual accumulation of intraparenchymal cerebrospinal fluid (Fig. 1B) (Siddiqui, Khazaei, & Fehlings, 2015).

SCI is a highly heterogeneous condition and the cellular response to trauma varies based on the severity and level of injury (Fig. 3) (Liu et al., 2019). The damage to the spinal cord can either be complete or incomplete (Raineteau & Schwab, 2001). The American Spinal Injury Association (ASIA) impairment scale uses a four-letter scheme to characterize the injury severity. Grade A refers to the complete loss of sensorimotor function below the site of injury. Grade B indicates

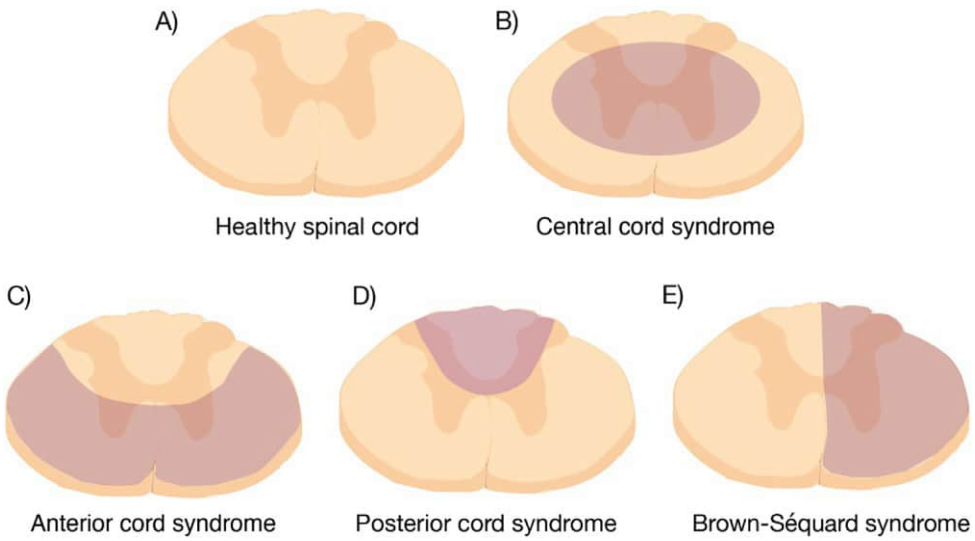

FIG. 3 SCI patients exhibit differential patterns of functional due to damage to specific spinal cord tracts while sparing other tracts. (A) A healthy spinal cord that consists of ascending and descending tracks. (B) Patients with central cord syndrome present with disproportionately greater upper limb motor impairment as compared to the lower limbs. (C) Patients with anterior cord syndrome suffer from complete motor paralysis and nociception loss due to damage to the corticospinal tract and spinothalamic tract, respectively. However, these patients continue to possess proprioception. (D) Posterior cord syndrome results in proprioception loss but preservation of sensorimotor function. (E) Brown-Séquard syndrome characterized by nociception loss contralateral to the lesion site and ipsilateral sensorimotor loss.

loss of motor function while sensation is still present. Grade C and D are indicative of preserved motor movement but differ from each other in the extent of mobility (Ahuja, Wilson, et al., 2017). Second, there are level-specific variations to SCI pathogenesis and the spinal cord varies in the degree of vascularization and myelination across different levels (Wilcox et al., 2017). While the most common level of injury is at the cervical level, the majority of preclinical studies have utilized a thoracic injury model. This introduces a knowledge gap in our understanding of cervical-specific vascular responses following SCI. This is a growing area of research as the majority of deaths following SCI are due to breathing dysfunction, which results from upper cervical injuries.

Hemodynamic response

The spinal cord is a highly vascularized organ, which requires an extensive network of blood vessels to maintain its ability to transmit and integrate signals between the brain and peripheral organs (Fig. 4). Traumatic damage to the spinal cord hinders this blood supply and results in areas of low perfusion (Mautes et al., 2000). The hemodynamic alterations to the injured spinal cord vary depending on the site of injury. This is due to the differences in the blood supply pattern across the spinal cord in order to account for necessary blood demands for each region. For instance, the anterior spinal artery (ASA) is largest in the cervical and lumbar regions, to correspond with the increased requirement for supplying the enlarged ganglions at these levels (Fig. 4). Additionally, the central sulcal arteries are both larger and increased in number in the cervical and lumbar regions, relative to the thoracic region. Furthermore, the significant narrowing of the spinal cord in the mid-thoracic region corresponds with the narrowing of its major longitudinal arteries and the reduced perfusion requirements from T4 to approximately the T9 level. The relatively reduced arterial supply renders this area more susceptible to ischemic damage upon vascular insult (Dommisse, 1974; Turnbull, 1971). However, the collateral circulation in any given area may be as relevant to the local blood supply as the number of arteries (Crosby & Lauer, 1962).

The hemodynamic disruption of the spinal cord vasculature results from the flattening of the spinal cord anteroposteriorly and it's widening laterally, as a direct consequence of a traumatic insult. This results in the lengthwise compression and shortening of perforant branches of the pial plexus running directly in the anteroposterior direction, which supplies the anterior and posterior columns. In contrast, the lateral perforant branches supplying the lateral columns are stretched lengthwise and flattened, decreasing their diameter. Hence, while the shortened anterior and posterior perforant branches do not alter blood supply, the flattened lateral perforant branches decrease the blood supply. The same effect is observed in the central arterial system, in which the lateral segments are flattened, and the anteroposterior segment in the anterior medial fissure is less dramatically affected (Turnbull, 1971). The varying hemodynamics among regions of the cord result

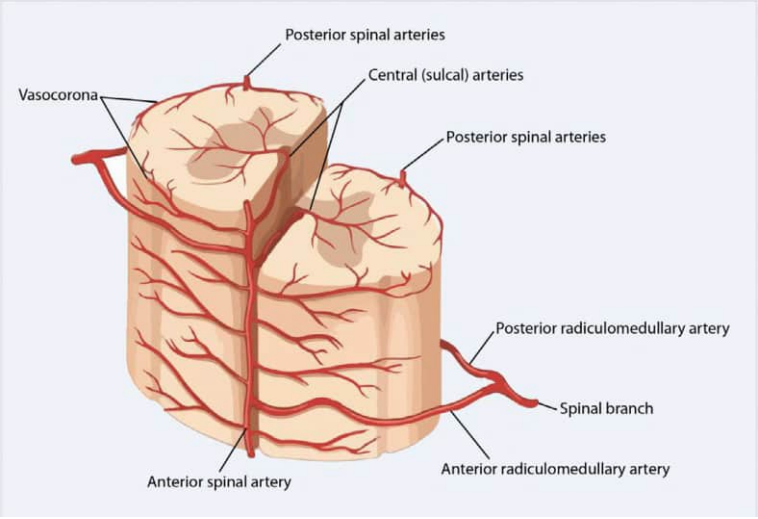

FIG. 4 An overview of the major spinal arteries. The vertebral arteries are the main source of blood to the spinal cord. However, the following figure shows the arteries that branch from the vertebral arteries to directly supply the spinal cord itself. It consists of one anterior spinal artery, the central sulcal arteries, two posterior spinal arteries, the anterior and posterior radiculomedullary arteries, and the arterial vasocorona—the anastomose between the spinal arteries. *Pictures edited from Santillan, A., Nacarino, V., Greenberg, E., Riina, H. A., Gobin, Y. P., & Patsalides, A. (2012). Vascular anatomy of the spinal cord.* Journal of NeuroInterventional Surgery, 4*(1), 67–74. https://doi.org/10.1136/neurintsurg-2011-010018.*

in several watershed regions with relatively low perfusion, such as the upper thoracic cord between the cervical and lumbar limb enlargements, the anterolateral surface between the coronary perimedullary arches, and the intramedullary gray–white junction between the centripetal and centrifugal arterial systems (Bosmia, Hogan, Loukas, Tubbs, & Cohen-Gadol, 2015). Previous studies demonstrate that the reduction in perfusion due to compression is associated with vessel distance from the dura mater and suggest that posterior compression may have a greater likelihood of producing ischemic injury when compared to anterior compression (Alshareef et al., 2014).

Neurovascular unit (NVU)

The NVU is an important tri-partite structure consisting of astrocytes, pericytes, and endothelial cells, which is involved in the coupling of local perfusion and neuronal activity (Cauli, 2004; Chio et al., 2019; Gordon, Mulligan, & Macvicar, 2007). It regulates the rate of blood flow to match the metabolic demands of active neurons (Fig. 5). The NVU's neural, glial, and vascular components work together to mediate the spinal blood flow and vascular permeability (McConnell, Kersch, Woltjer, & Neuwelt, 2017). The neurons and astrocytes signal to pericytes and endothelial cells (and vice versa) to modify the vascular tone, which affects the delivery of blood, oxygen, and glucose to the brain and spinal cord (Attwell et al., 2010; McConnell et al., 2017).

As blood flows from superficial to deeper regions in the CNS, the capillaries lose their smooth muscle cell and pia mater coverage between the endothelial cells and astrocytes (McConnell et al., 2017). Instead, they gain pericyte coverage between endothelial cells and astrocytes; the three cell constituents of the NVU. In close proximity to each other, neurons can release glutamate at the synapses, which can bind to metabotropic glutamate receptors on astrocytes. This induces a rise in intracellular calcium levels in astrocytes, which causes the release of vasoactive molecules such as prostaglandin, nitric oxide, serotonin, or neuropeptide Y) (McConnell et al., 2017). These compounds also induce changes in pericyte contractility (Itoh & Suzuki, 2012). Tight junction (TJ) proteins, such as occludin, zona occludens (ZO), and claudin protein families hold the NVU's cellular components together and allow them to communicate with each other (Kaplan, Chow, & Gu, 2020). In addition, these TJ proteins help form the BSCB, which is a regulated structure that partially separates the spinal cord from peripheral blood flow (Kaplan et al., 2020; Stamatovic, Johnson, Keep, & Andjelkovic, 2016). TJ proteins are associated with, but not entirely responsible for, the BSCB's integrity, as the knockout of occludin (Saitou et al., 1998, 2000), ZO (Katsuno et al., 2008) and claudin (Castro Dias, Coisne, Baden, et al., 2019; Castro Dias, Coisne, Lazarevic, et al., 2019) does not significantly increase permeability. Rather, the BSCB in these genetic models seems intact based on electron microscopy (Kaplan et al., 2020).

Pericytes are largely responsible for TJ protein expression (Thomsen, Burkhart, & Moos, 2015; Underly et al., 2017). While aforementioned studies have identified that the loss of TJ proteins does not result in significant increases in BSCB permeability (Castro Dias, Coisne, Baden, et al., 2019; Castro Dias, Coisne, Lazarevic, et al., 2019; Katsuno et al., 2008; Saitou et al., 1998, 2000; Umeda et al., 2006; Underly et al., 2017), pericytes are important members of the NVU for maintaining BSCB integrity and controlling blood flow in CNS tissue. After ischemia, the loss of BSCB integrity commonly originates in regions formerly covered by pericytes, as they die or migrate away from ischemic sites in a matrix

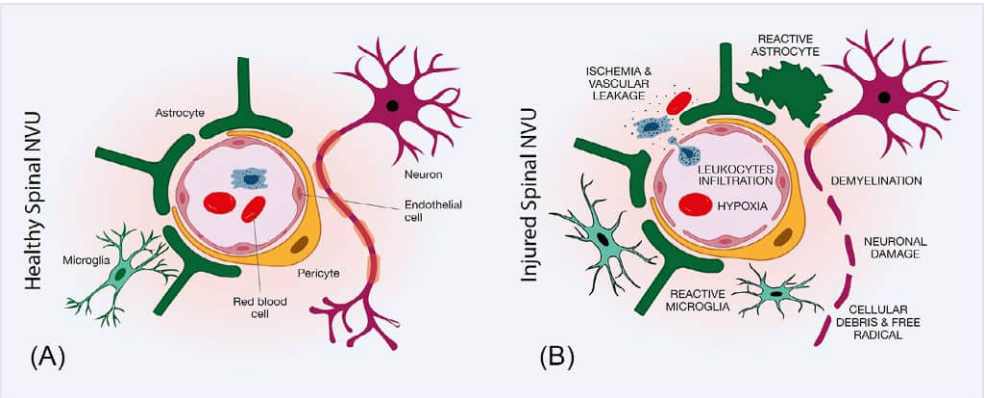

FIG. 5 Traumatic SCI impairs neurotransmission and NVU function. (A) The structure of a healthy spinal NVU comprised of endothelial cells, pericytes, astrocytes, and the surrounding cells. (B) The structure of an injured spinal NVU resulting in secondary SCI-induced pathologies. *Pictures edited from "biorender.com."*

metalloproteinase-dependent manner (Underly et al., 2017). Overall, regulation of BBB and BSCB integrity by the NVU is an active signaling process between NVU cells (Kaplan et al., 2020). The cell-specific responses that result in the loss of BSCB integrity are discussed below.

Endothelial cell (EC) response

ECs line up the arteries and capillaries, and are tightly associated with pericytes (Kaplan et al., 2020) to maintain homeostatic interactions with pericytes through numerous pathways (Park et al., 2017). ECs in the CNS have the highest pericyte coverage and markedly less fluid-phase transcytosis (Andreone et al., 2017; Ben-Zvi et al., 2014; Chow & Gu, 2017; McConnell et al., 2017), which are unique features that distinguish brain endothelium from peripheral tissues and allow ECs to adapt to the previously described unique requirements of the CNS (Li et al., 2011). As stated previously, ECs help to form the tri-partite BSCB, which regulates the entry and exit of molecules to and from the CNS. ECs have multiple signaling pathways that are integral to the proper formation and maintenance of the BSCB, such as retinoic acid (Mizee et al., 2013; Pollock, Xie, Bell, & Anand-Apte, 2018), N-cadherin-Notch (Li et al., 2011), Sonic Hedgehog-Sonic Hedgehog receptors (Alvarez et al., 2011), transforming growth factor-β (Vladimir, Dan, Jonathan, Rotem, & Adiel, 2019), and WNT-Frizzled receptors (Daneman et al., 2009; Kaplan et al., 2020). Outcomes stemming from a deficiency in these pathways are implicated in greater vascular permeability under pathological conditions.

Expressed on other cells, WNT ligands bind to Frizzled receptors on ECs and enable translocation of β-catenin to the nucleus (Kaplan et al., 2020). This allows transcription of genes associated with a less permeable BSCB. A rodent model of multiple sclerosis demonstrated that sub-optimal WNT-Frizzled receptor interactions, as mediated by secretion of WNT inhibitory factor 1 (Wif1), disrupts barrier integrity and triggers CNS inflammation (Niu et al., 2019). This results in ECs secreting less TJ proteins. Attempts to upregulate the expression of WNT and β-catenin in non-CNS tissues result in a greater presence of BBB-related genes and decreased barrier permeability, but still inferior to the integrity of native CNS tissues (Benz et al., 2019; Lengfeld et al., 2017; Wang et al., 2019; Wang et al., 2020). TGF-β is an anti-inflammatory cytokine that is upregulated after ischemia induced by SCI and other CNS injuries (Benton, Maddie, Dincman, Hagg, & Whittemore, 2009). SMADs are signal transducers for intracellular pathways mediated by TGF-β (Derynck & Zhang, 2003). TGF-β can cause ECs to be proliferative or quiescent (Kaplan et al., 2020), with proliferative and quiescent ECs associated with a leaky or non-porous BBB and BSCB, respectively. Binding between TGF-β and ALK1 causes phosphorylation of SMAD1 as well as SMAD5 and leads to proliferative ECs. On the contrary, interactions between TGF-β and ALK5 result in SMAD2 as well as SMAD3 phosphorylation and lead to quiescent ECs (ten Dijke & Arthur, 2007; van Meeteren & ten Dijke, 2012). ALK1 and ALK5 signals antagonize each other (Finnson, Parker, ten Dijke, Thorikay, & Philip, 2008). Intrathecal administration of TGF-β increases the protein expression of ZO-1 and occludin after nerve injury (Echeverry, Shi, Rivest, & Zhang, 2011). Overall, aberrant TGF-β signaling leads to vascular pathologies (Walshe et al., 2009).

The Notch-N-cadherin pathway is associated with pathologies due to aberrant TGF-β and WNT signaling (Li et al., 2011). The Notch pathway is important for angiogenic sprouting, vascular remodeling, and arteriovenous differentiation. N-cadherin mediates cell–cell adhesion through the formation of adherens junctions (Miyamoto, Sakane, & Hashimoto, 2015). Influence of the crosstalk between TGF-β and Notch pathways on vascular integrity was demonstrated when ECs deficient in SMAD4 had lower expression of Notch receptors and N-cadherin. Even though TJ proteins were detected in SMAD4 deficient ECs, the ECs adopted a proliferative state, which is a phenotype associated with a porous BBB. This substantiates findings that TJ proteins are associated with, but do not cause, a porous barrier. Furthermore, EC expression of N-cadherin occurs when ECs and pericytes are in contact with each other; with a lack of N-cadherin resulting in defective pericyte adhesion to the vasculature. Overall, these results indicate how a deficiency in SMAD4, TGF-β, and Notch pathways disrupts EC-pericyte interactions and leads to barrier disruptions.

Pericytic response

The role of pericytes in both the healthy and injured NVU was largely unknown and, until recently, was thought to only provide structural support to the vascular integrity. However, this view is being updated, particularly with the advent and wide-spread use of single-cells RNA-sequencing that enables the identification, classification, and expressional analysis of pericytes in the spinal cord (Dias et al., 2018). These studies demonstrate that not only are pericytes involved in secondary SCI pathogenesis, but they are also one of the key regulators of the acute secondary response.

Pericytes are composed of several subtypes, which differ in their functionality, expressional profile, distribution, and lineage. Common molecular and cellular markers to identify spinal pericytes include platelet-derived growth factor

receptor B and nerve/glial antigen 2 (NG2) proteoglycan (Picoli et al., 2019). Pericyte Type A is involved in the formation of fibrotic scar, which is found in the lesion core. These cells represent nearly 10% of all pericytes in the injured spinal cord. Fibrotic scar formation is important to regain tissue integrity after SCI. However, deposition of extracellular matrix proteins in the fibrotic scar limits regeneration and a moderate reduction of fibrotic scar-producing pericytes can increase axonal sprouting (Dias et al., 2018). In addition, pericytes regulate hemodynamics and capillary tone in the injured rat spinal cord through vasoconstriction (Picoli et al., 2019). Pericytes are also critical for regulating inflammation through lymphocyte activation, adhesion molecule expression, chemokine secretion, toxic cellular byproduct clearance, and phagocytosis (Picoli et al., 2019).

Astrocytic response

Astrocytes are among the early responders to the injury and play a diverse set of roles from immune modulation and scar formation to neuronal support. In the lesion core, astrocytes, along with microglia, initiate the early local response to the traumatic damage by releasing cytokines and chemokines to further advance the immune response to the injury (O'Shea et al., 2017). In the subacute phase of secondary SCI, hypertrophic astrocytes proliferate and intermingle with inhibitory molecules, which forms a barrier-like structure (Bradbury & Burnside, 2019).

This astrocytic barrier structure consists of several other cell types, including reactive oligodendrocyte precursor cells. These reactive glial cells release inhibitory molecules, such as tenascin and chondroitinase sulfate proteoglycans (CSPGs). CSPGs can be in the form of brevican, phosphacan, neurocan, versican, and neural/glial antigen 2 (NG2) proteoglycans. These inhibitory molecules are secreted from the reactive glia and activate the Rho–ROCK signaling pathway in neurons, which attenuates the repair and regeneration process (Zavvarian, Toossi, Khazaei, Hong, & Fehlings, 2020). Hence, the astrocytic scar was initially known as a barrier to recovery and regeneration. As such, the enzymatic degradation of inhibitory molecules in the astrocytic scar, such as CSPGs, resulted in significantly improved axonal sprouting and regeneration (Burnside et al., 2018). However, recent studies indicate that the astrocytic scar plays a diverse role in the injured spinal cord. Hence, it is difficult to identify it under a binary classification of either "good" or "bad" (Bradbury & Burnside, 2019). Namely, the genetic knockout of STAT3 to inhibit astrocytic scar formation results in reduced axonal growth and regeneration (Anderson et al., 2016).

Level-specific differences in the vascular architecture of the spinal cord

As stated previously, the vascular response to traumatic SCI varies according to the level of injury. The cervical region has a larger amount of gray as well as white matter and requires a greater blood supply compared to the thoracic region. The increased blood supply may correspond with greater vascular disruption in the cervical region following SCI. This is supported by greater cavitation and lesional area in cervical injuries when compared to thoracic injuries. Additionally, injury at the C5 level causes neuronal death and ventral horn atrophy over three segments (C6–C8), while injury at C6 impacts two segments (C8-T1) and C7 caused injury over one segmental level (T2) (Wilcox et al., 2017). These results are consistent with the higher vascular demands from elevated grey matter content in the limb enlargements, which would be disproportionately affected by secondary injury stemming from vascular disruption. Notably, due to a decreased amount of pericytes, the BSCB is inherently more permeable in the grey matter of the cervical region as compared to the thoracic region (Winkler, Sengillo, Bell, Wang, & Zlokovic, 2012).

Muradov et al. have shown that the extent of axonal and oligodendrocyte loss is associated with focal microvascular damage (Muradov, Ewan, & Hagg, 2013). Preclinical investigations indicate that the grey matter is more vulnerable to blood flow disturbances following SCI as compared to white matter, and typically contains relatively smaller vessels (Figley et al., 2014). The white matter adjacent to hemorrhagic grey matter is also especially prone to ischemic damage (Tator & Fehlings, 1991). Overall, the varying arterial and gray matter density throughout the cord has implications for primary and secondary injury after SCI. Regions with reduced vessel density, associated with regions of lesser gray matter, may display reduced focal hemorrhage and its associated secondary effects, including focal ischemic compromise. However, these regions may also be more susceptible to widespread ischemic compromise arising directly from the primary injury. In contrast, areas with increased arterial and microvascular density may display increased focal hemorrhage and secondary injury, while being less susceptible to widespread ischemic compromise from the primary injury.

The increased mobility, smaller vertebrae, and reduced stabilizing musculature of the cervical spine may make it more susceptible to injury (Fehlings, Ulndreaj, & Badner, 2017; Sekhon & Fehlings, 2001). The cervical region is also more susceptible to contusion injury due to the relatively smaller subdural space (Stokes & Jakeman, 2002). A recent study notes that the limited distance between components of the lower thoracic and lumbar spine may cause especially extended tissue

damage in this region (Liu et al., 2019). However, Vaccaro et al. report that a spinal canal with a larger transverse diameter was predictive of neurologic deficit after burst fractures, and thus that larger canals are not necessarily protective of the spinal cord (Vaccaro et al., 2001).

The level of injury also influences the systemic inflammatory response and, by extension, the local inflammatory environment. Notably, the expression of both proinflammatory and antiinflammatory compounds may be influenced by the level of injury. Hong, Chang, Liu, Wang, and Fehlings (2019) showed reductions in systemic circulatory levels of proinflammatory molecules with lesions in the cervical region when compared to other regions. SCI above the mid-thoracic level disrupts connections to sympathetic preganglionic neurons below that level, which control secondary lymphoid tissues and systemic immune function. While this dysfunction may lead to spinal cord injury-induced immune depression syndrome (SCI-IDS), it may also result in reduced chronic autoimmunity (Brommer et al., 2016; Fehlings, Ulndreaj, & Badner, 2017). Ibbara et al. demonstrated that the level of injury influences the functions of T cells, which are implicated in the severe infections accompanying SCI-IDS. The type of SCI (complete vs incomplete) may also be an important factor in the immunologic depression observed after SCI (Ibarra, Jiménez, Cortes, & Correa, 2007). As recently demonstrated by Hong et al., contusion injuries may increase splenic function (Hong et al., 2019). This contrasts with previous studies that used transection injuries and resulted in decreased peripheral immune function.

Therapeutic approach

Early intervention is crucial for improved recovery after traumatic SCI. Our multicenter investigation of surgical decompression following traumatic SCI demonstrates that the first 24–36 h after injury constitutes a critical time window to achieve optimal neurological recovery with decompressive surgery. Furthermore, the vascular complications following traumatic SCI require immediate attention to mitigate further damage (Badhiwala et al., 2021). The current guidelines recommend first monitoring the cardiac and hemodynamic parameters following injury, inotropic support to maintain a minimum mean arterial blood pressure of 85 mmHg, detection and treatment of neurogenic shock and cardiac arrhythmias, and immediate treatment of autonomic dysreflexia (Furlan & Fehlings, 2008). The current standard of care also involves the administration of methylprednisolone sodium succinate (MPSS) acutely to mitigate inflammation at the site of injury, improve spinal cord blood flow (SCBF), and enhance functional recovery (Fehlings et al., 2017).

Pharmacological interventions

Several pharmacological agents have been tested in both preclinical and clinical settings to attenuate secondary pathogenesis following SCI-induced vascular pathologies. Notable drug candidates include riluzole, which is a sodium channel blocker currently used in amyotrophic lateral sclerosis (ALS) (Fehlings et al., 2020). Riluzole was developed as an approach to address the consequences of ischemic damage. Preclinical studies examining the impact of riluzole following traumatic SCI reveal its ability to enhance tissue preservation and recovery (Nagoshi, Nakashima, & Fehlings, 2015). The current Phase2/3 clinical trial (ClinicalTrials.gov identifier: NCT01597518) will further examine riluzole as a promising pharmacological candidate for SCI patients.

Acute infusion of mesenchymal stromal cells to attenuate vascular disruption

Mesenchymal stem cells (MSCs) are an intensely studied population of multipotent mesodermal progenitors, which are relatively easy to isolate and display homing properties to the site of injury (Vawda et al., 2019). They differentiate quickly into chondrocytes, adipocytes, myocytes, and osteoblasts (Ahuja et al., 2017; Cofano et al., 2019). MSCs can be derived from various sources including bone-marrow (BM-MSC), umbilical cord (UC-MSC), and adipose-derived MSCs (AD-MSC). MSC treatments display both antiinflammatory properties, notably through macrophage phenotype modulation, and provide trophic support for neuroprotection and regeneration (Nakajima et al., 2012; Spejo et al., 2018). Interestingly, in both human and animal models, they also decrease peripheral inflammatory cell infiltration through protection of the BSCB (Ahuja, Nori, et al., 2017). Various factors have been reported to contribute to this function, notably IL-10, TSG-6, and TIMP-6 (Badner et al., 2016; Li et al., 2018; Watanabe et al., 2013). Recently, MSCs have been reported to reduce intraparenchymal hemorrhage and increase systemic levels of IL-10 in a spleen-dependent manner, which was further supported by altered splenic cytokine levels after MSC infusion (Badner et al., 2018). El-keir et al. report that in a phase I/II controlled single-blind trial (ID: NCT00816803) where chronic cervical and thoracic SCI patients were administered autologous adherent BM-BMCs, smaller lesions, and greater functional improvements were seen in thoracic SCI in comparison to cervical injuries (El-Kheir et al., 2014). There are several clinical trials currently assessing MSCs.

Notably, a phase II/II trial for BM-MSCs in chronic SCI (NCT01676441) and a phase I trial for AD-MSCs (NCT03308565). UC-MSCs are also being tested for use in sub-acute and chronic injury in phase I/II trials (NCT03521323, NCT03505034).

Acute IgG infusion for immunomodulation and rescue of BSCB disruption

Intravenous immunoglobulin G (IVIG) consists of pooled serum immunoglobulin G (IgG) from healthy donors. Despite a relatively uncertain mechanism of action, it is currently approved by the FDA for the treatment of autoimmune and immunodeficiency disorders, namely primary humoral deficiency idiopathic, thrombocytopenic purpura, and chronic inflammatory demyelinating polyneuropathy (Chio et al., 2019; Fehlings, Ulndreaj, & Badner, 2017). Brennan et al. report that IVIG decreased lesion enlargement and axonal degeneration after contusion SCI in a mouse model. This study also suggests that IVIG may achieve these effects through attenuation of the complement response and a decrease in the phagocytic activity of macrophages (Brennan et al., 2016). Nguyen et al. reported that in a rat model of cervical compression injury, IVIG administration reduced pro-inflammatory signaling (IL-1b and IL-6). This may have had neuroprotective effects via the BSCB, as demonstrated by the reduction in neutrophil infiltration and reductions in the level of BSCB-damaging metalloproteinase-9 (MMP-9) (Nguyen et al., 2012). This is further supported by reports of neurovascular protection through increases in tight junction protein expression and significant decreases in MMP-9. The improved BSCB integrity was associated with increased serum levels of inflammatory cytokines (IL-8, MIP-1α, CCL-2/MCP-1, and IL-5). IgG is also colocalized with vascular cell adhesion molecule 1 (VCAM-1) without reducing its expression. VCAM-1 is used by neutrophils in extravasation (Chio et al., 2019). Notably, IgG co-localized with astrocytes and pericytes, which suggests a role in modulating immune cell infiltration through the BSCB. Administration of 2 g/kg resulted in increased tissue preservation, blood flow, and behavioral recovery; effects comparable with MPSS treatment.

Conclusions

This chapter described a brief overview of the cellular and extracellular elements of the neurovascular unit, discussed their physiological functions, and reviewed their functional implications in the context of SCI. Traumatic SCI presents a complicated and heterogeneous condition, and this chapter emphasized the segmental anatomy of the neurovasculature of the spinal cord and discussed their implications on the region-specific pathophysiology of traumatic SCI. These are important considerations for the management of neurovascular pathology following traumatic SCI. Recent discoveries in vascular-related therapeutic strategies have greatly improved our ability to enhance protection against damage to the spinal neurovasculature and BSCB, and ultimately improve functional recovery.

Application to other areas of neuroscience

The secondary response following traumatic SCI is a complex process and involves a variety of cell types in the spinal cord. While the discussions provided in this chapter were primarily presented in the context of traumatic SCI, similar mechanisms are at play across the CNS. The endothelial, astrocytic, and pericytic responses demonstrated are active in other CNS-related neurovascular injuries. Therefore, the discussed vascular-mediated treatment strategies may be explored and considered for other neurological injuries and diseases, such as traumatic brain injuries, amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), and stroke. Many of the therapeutics discussed in this chapter are clinically approved for conditions other than SCI, which ease the clinical translation and repurposing for multiple conditions. Furthermore, the elucidation of vascular-related SCI pathogenesis will improve our understanding of the cellular structure and function of the spinal cord. This can have a significant impact for improving our understanding of non-traumatic SCI disorders, as these present the most common form of SCI in the clinic.

Mini-dictionary of terms

Autonomic dysreflexia: Sudden episodic elevation in blood pressure accompanied by bradycardia due to loss of supraspinal input into sympathetic preganglionic neurons.

Neurovascular unit: A model that characterizes the interaction between endothelial, astrocytic, pericytic, and other vascular cells to maintain the necessary oxygen and nutrient supply to the nervous system, while protecting it from foreign and toxic molecules.

Inotropic support: Altering the force of the heart's contraction to stabilize circulation.

Fibrotic scar: The deposition of stromal-derived fibroblasts and extracellular matrix molecules at the SCI epicenter.
Astrocytic scar: The accumulation of hypertrophic astrocytes intermingled with inhibitory molecules which surround the SCI lesion core.

Key facts

Key facts of the American Spinal Injury Association (ASIA) Impairment Scale

- ASIA impairment scale categorizes the SCI severity in the clinical setting ranging from Grade A to Grade E.
- Grade A indicates the complete loss of autonomic and sensorimotor functions distal to the site of injury.
- Grade B: Loss of motor function but not sensory function distal to the injury site. No motor function is present more than three levels below the neurological level, on either side of the body.
- Grade C: Preserved motor function distal to the neurological level of injury with more than half of the key muscles having a grade of <3 on the ASIA motor score.
- Grade D: Preserved motor function distal to the neurological level of injury with more than half of the key muscles having a grade of ≥ 3 on the ASIA motor score.
- Grade E: Neurologically intact sensorimotor function in all segments in patients with previous deficits due a suspected SCI.

Key facts of the spinal neurovascular unit (NVU)

- The neurovascular unit (NVU) is comprised of endothelial cells, pericytes, and astrocytes, which work alongside neurons to regulate spinal blood flow and vascular permeability.
- Occludin, zona occludens, and claudin are important tight junction (TJ) proteins forming the blood–spinal cord barrier (BSCB) and keeping NVU cells together.
- Molecular signaling cascades involving WNT, TGF-β, SMAD4, and Notch molecules regulate BSCB function and integrity.
- The full extent of pericytic and astrocytic responses to SCI continues to be under investigation. In addition to structural support, these cells play critical roles in scar formation.

Summary points

1. Aside from primary mechanical damage to neuronal, glial, and vascular cells, traumatic spinal cord injury impairs the local neuronal, glial, and vascular cells, which results in a cascade of secondary pathologies.
2. Vascular damage is a key mediator of this secondary response and exacerbates injury-induced tissue and functional loss, as it disrupts the homeostatic exchange of oxygen and essential nutrients.
3. Current clinically approved neuroprotective treatments that involve acute administration of MPSS have limited effectiveness to treat SCI patients.
4. The endothelial, pericytic, and astrocytic responses to injury continues to be under investigation, as they present promising therapeutic targets for SCI patients.
5. Recent advances in mesenchymal stromal cell administration or acute infusion of IgG demonstrate great efficacy to mitigate SCI-induced vascular pathologies and improve recovery.

References

Ahuja, C. S., Nori, S., Tetreault, L., Wilson, J., Kwon, B., Harrop, J., et al. (2017). Traumatic spinal cord injury—Repair and regeneration. *Clinical Neurosurgery*, *80*(3), S22–S90. https://doi.org/10.1093/neuros/nyw080.

Ahuja, C. S., Wilson, J. R., Nori, S., Kotter, M. R. N., Druschel, C., Curt, A., et al. (2017). Traumatic spinal cord injury. *Nature Reviews. Disease Primers*, *3* (1), 17018. https://doi.org/10.1038/nrdp.2017.18.

Alshareef, M., Krishna, V., Ferdous, J., Alshareef, A., Kindy, M., Kolachalama, V. B., et al. (2014). Effect of spinal cord compression on local vascular blood flow and perfusion capacity. *PLoS One*, *9*(9). https://doi.org/10.1371/journal.pone.0108820, e108820.

Alvarez, J. I., Dodelet-Devillers, A., Kebir, H., Ifergan, I., Fabre, P. J., Terouz, S., et al. (2011). The hedgehog pathway promotes blood-brain barrier integrity and CNS immune quiescence. *Science*, *334*(6063), 1727–1731. https://doi.org/10.1126/science.1206936.

Anderson, M. A., Burda, J. E., Ren, Y., Ao, Y., O'Shea, T. M., Kawaguchi, R., et al. (2016). Astrocyte scar formation aids central nervous system axon regeneration. *Nature*, *532*(7598), 195–200. https://doi.org/10.1038/nature17623.

Andreone, B. J., Chow, B. W., Tata, A., Lacoste, B., Ben-Zvi, A., Bullock, K., et al. (2017). Blood-brain barrier permeability is regulated by lipid transport-dependent suppression of caveolae-mediated transcytosis. *Neuron*, *94*(3), 581–594.e5. https://doi.org/10.1016/j.neuron.2017.03.043.

Attwell, D., Buchan, A. M., Charpak, S., Lauritzen, M., MacVicar, B. A., & Newman, E. A. (2010). Glial and neuronal control of brain blood flow. *Nature*, *468*(7321), 232–243. https://doi.org/10.1038/nature09613.

Badhiwala, J. H., Wilson, J. R., Witiw, C. D., Harrop, J. S., Vaccaro, A. R., Aarabi, B., et al. (2021). The influence of timing of surgical decompression for acute spinal cord injury: A pooled analysis of individual patient data. *The Lancet Neurology*, *20*(2), 117–126. https://doi.org/10.1016/S1474-4422(20)30406-3.

Badner, A., Hacker, J., Hong, J., Mikhail, M., Vawda, R., & Fehlings, M. G. (2018). Splenic involvement in umbilical cord matrix-derived mesenchymal stromal cell-mediated effects following traumatic spinal cord injury. *Journal of Neuroinflammation*, *15*(1). https://doi.org/10.1186/s12974-018-1243-0.

Badner, A., Vawda, R., Laliberte, A., Hong, J., Mikhail, M., Jose, A., et al. (2016). Early intravenous delivery of human brain stromal cells modulates systemic inflammation and leads to vasoprotection in traumatic spinal cord injury. *Stem Cells Translational Medicine*, *5*(8), 991–1003. https://doi.org/10.5966/sctm.2015-0295.

Benton, R. L., Maddie, M. A., Dincman, T. A., Hagg, T., & Whittemore, S. R. (2009). Transcriptional activation of endothelial cells by TGFβ coincides with acute microvascular plasticity following focal spinal cord ischaemia/reperfusion injury. *ASN Neuro*, *1*(3). https://doi.org/10.1042/AN20090008, AN20090008.

Benz, F., Wichitnaowarat, V., Lehmann, M., Germano, R. F., Mihova, D., Macas, J., et al. (2019). Low wnt/β-catenin signaling determines leaky vessels in the subfornical organ and affects water homeostasis in mice. *eLife*, *8*. https://doi.org/10.7554/eLife.43818, e43818.

Ben-Zvi, A., Lacoste, B., Kur, E., Andreone, B. J., Mayshar, Y., Yan, H., et al. (2014). Mfsd2a is critical for the formation and function of the blood–brain barrier. *Nature*, *509*(7501), 507–511. https://doi.org/10.1038/nature13324.

Bosmia, A. N., Hogan, E., Loukas, M., Tubbs, R. S., & Cohen-Gadol, A. A. (2015). Blood supply to the human spinal cord: Part I. Anatomy and hemodynamics. *Clinical Anatomy*, *28*(1), 52–64. https://doi.org/10.1002/ca.22281.

Bradbury, E. J., & Burnside, E. R. (2019). Moving beyond the glial scar for spinal cord repair. *Nature Communications*, *10*(1), 3879. https://doi.org/10.1038/s41467-019-11707-7.

Brennan, F. H., Kurniawan, N. D., Vukovic, J., Bartlett, P. F., Käsermann, F., Arumugam, T. V., et al. (2016). IVIg attenuates complement and improves spinal cord injury outcomes in mice. *Annals of Clinical Translational Neurology*, *3*(7), 495–511. https://doi.org/10.1002/acn3.318.

Brommer, B., Engel, O., Kopp, M. A., Watzlawick, R., Müller, S., Prüss, H., et al. (2016). Spinal cord injury-induced immune deficiency syndrome enhances infection susceptibility dependent on lesion level. *Brain*, *139*(3), 692–707. https://doi.org/10.1093/brain/awv375.

Burnside, E. R., De Winter, F., Didangelos, A., James, N. D., Andreica, E.-C., Layard-Horsfall, H., et al. (2018). Immune-evasive gene switch enables regulated delivery of chondroitinase after spinal cord injury. *Brain*, *141*(8), 2362–2381. https://doi.org/10.1093/brain/awy158.

Castro Dias, M., Coisne, C., Baden, P., Enzmann, G., Garrett, L., Becker, L., et al. (2019). Claudin-12 is not required for blood–brain barrier tight junction function. *Fluids and Barriers of the CNS*, *16*(1), 30. https://doi.org/10.1186/s12987-019-0150-9.

Castro Dias, M., Coisne, C., Lazarevic, I., Baden, P., Hata, M., Iwamoto, N., et al. (2019). Claudin-3-deficient C57BL/6J mice display intact brain barriers. *Scientific Reports*, *9*(1), 203. https://doi.org/10.1038/s41598-018-36731-3.

Cauli, B. (2004). Cortical GABA interneurons in neurovascular coupling: Relays for subcortical vasoactive pathways. *Journal of Neuroscience*, *24*(41), 8940–8949. https://doi.org/10.1523/JNEUROSCI.3065-04.2004.

Chio, J. C. T., Wang, J., Badner, A., Hong, J., Surendran, V., & Fehlings, M. G. (2019). The effects of human immunoglobulin G on enhancing tissue protection and neurobehavioral recovery after traumatic cervical spinal cord injury are mediated through the neurovascular unit. *Journal of Neuroinflammation*, *16*(1), 141. https://doi.org/10.1186/s12974-019-1518-0.

Chow, B. W., & Gu, C. (2017). Gradual suppression of transcytosis governs functional blood-retinal barrier formation. *Neuron*, *93*(6), 1325–1333.e3. https://doi.org/10.1016/j.neuron.2017.02.043.

Cofano, F., Boido, M., Monticelli, M., Zenga, F., Ducati, A., Vercelli, A., et al. (2019). Mesenchymal stem cells for spinal cord injury: Current options, limitations, and future of cell therapy. *International Journal of Molecular Sciences*, *20*(11). https://doi.org/10.3390/ijms20112698.

Courtine, G., & Sofroniew, M. V. (2019). Spinal cord repair: Advances in biology and technology. *Nature Medicine*, *25*(6), 898–908. https://doi.org/10.1038/s41591-019-0475-6.

Crosby, H., & Lauer. (1962). *Correlative Anatomy of the Nervous System*.

Daneman, R., Agalliu, D., Zhou, L., Kuhnert, F., Kuo, C. J., & Barres, B. A. (2009). Wnt/-catenin signaling is required for CNS, but not non-CNS, angiogenesis. *Proceedings of the National Academy of Sciences of the United States of America*, *106*(2), 641–646. https://doi.org/10.1073/pnas.0805165106.

Derynck, R., & Zhang, Y. E. (2003). Smad-dependent and Smad-independent pathways in TGF-b family signalling. *Nature*, *425*, 8.

Dias, D. O., Kim, H., Holl, D., Werne Solnestam, B., Lundeberg, J., Carlén, M., et al. (2018). Reducing pericyte-derived scarring promotes recovery after spinal cord injury. *Cell*, *173*(1), 153–165.e22. https://doi.org/10.1016/j.cell.2018.02.004.

Dommisse, G. F. (1974). The blood supply of the spinal cord. A critical vascular zone in spinal surgery. *Journal of Bone and Joint Surgery—Series B*, *56*(2), 225–235.

Echeverry, S., Shi, X. Q., Rivest, S., & Zhang, J. (2011). Peripheral nerve injury alters blood-spinal cord barrier functional and molecular integrity through a selective inflammatory pathway. *Journal of Neuroscience*, *31*(30), 10819–10828. https://doi.org/10.1523/JNEUROSCI.1642-11.2011.

El-Kheir, W. A., Gabr, H., Awad, M. R., Ghannam, O., Barakat, Y., Farghali, H. A. M. A., et al. (2014). Autologous bone marrow-derived cell therapy combined with physical therapy induces functional improvement in chronic spinal cord injury patients. *Cell Transplantation*, *23*(6), 729–745. https://doi.org/10.3727/096368913X664540.

Fehlings, M. G., Badhiwala, J. H., Ahn, H., Farhadi, H. F., Shaffrey, C. I., Nassr, A., et al. (2020). Safety and efficacy of riluzole in patients undergoing decompressive surgery for degenerative cervical myelopathy (CSM-protect): A multicentre, double-blind, placebo-controlled, randomised, phase 3 trial. *The Lancet Neurology*. https://doi.org/10.1016/S1474-4422(20)30407-5. S1474442220304075.

Fehlings, M. G., Ulndreaj, A., & Badner, A. (2017). Promising neuroprotective strategies for traumatic spinal cord injury with a focus on the differential effects among anatomical levels of injury. In *Vol. 6. F1000Research* Faculty of 1000 Ltd. https://doi.org/10.12688/f1000research.11633.1.

Fehlings, M. G., Wilson, J. R., Harrop, J. S., Kwon, B. K., Tetreault, L. A., Arnold, P. M., et al. (2017). Efficacy and safety of methylprednisolone sodium succinate in acute spinal cord injury: A systematic review. *Global Spine Journal*, *7*(3_suppl), 116S–137S. https://doi.org/10.1177/2192568217706366.

Figley, S. A., Khosravi, R., Legasto, J. M., Tseng, Y.-F. F., & Fehlings, M. G. (2014). Characterization of vascular disruption and blood-spinal cord barrier permeability following traumatic spinal cord injury. *Journal of Neurotrauma*, *31*(6), 541–552. https://doi.org/10.1089/neu.2013.3034.

Finnson, K. W., Parker, W. L., ten Dijke, P., Thorikay, M., & Philip, A. (2008). ALK1 opposes ALK5/Smad3 signaling and expression of extracellular matrix components in human chondrocytes. *Journal of Bone and Mineral Research*, *23*(6), 896–906. https://doi.org/10.1359/jbmr.080209.

Furlan, J. C., & Fehlings, M. G. (2008). Cardiovascular complications after acute spinal cord injury: Pathophysiology, diagnosis, and management. *Neurosurgical Focus*, *25*(5). https://doi.org/10.3171/FOC.2008.25.11.E13, E13.

Gordon, G. R. J., Mulligan, S. J., & Macvicar, B. A. (2007). Astrocyte control of the cerebrovasculature. *Glia*, *55*, 1214–1221.

Hong, J., Chang, A., Liu, Y., Wang, J., & Fehlings, M. G. (2019). Incomplete spinal cord injury reverses the level-dependence of spinal cord injury immune deficiency syndrome. *International Journal of Molecular Sciences*, *20*(15), 3762. https://doi.org/10.3390/ijms20153762.

Ibarra, A., Jiménez, A., Cortes, C., & Correa, D. (2007). Influence of the intensity, level and phase of spinal cord injury on the proliferation of T cells and T-cell-dependent antibody reactions in rats. *Spinal Cord*, *45*(5), 380–386. https://doi.org/10.1038/sj.sc.3101972.

Itoh, Y., & Suzuki, N. (2012). Control of brain capillary blood flow. *Journal of Cerebral Blood Flow & Metabolism*, *32*(7), 1167–1176. https://doi.org/10.1038/jcbfm.2012.5.

Kaplan, L., Chow, B. W., & Gu, C. (2020). Neuronal regulation of the blood–brain barrier and neurovascular coupling. *Nature Reviews Neuroscience*, *21*(8), 416–432. https://doi.org/10.1038/s41583-020-0322-2.

Katsuno, T., Umeda, K., Matsui, T., Hata, M., Tamura, A., Itoh, M., et al. (2008). Deficiency of zonula occludens-1 causes embryonic lethal phenotype associated with defected yolk sac angiogenesis and apoptosis of embryonic cells. *Molecular Biology of the Cell*, *19*(6), 2465–2475. https://doi.org/10.1091/mbc.e07-12-1215.

Lengfeld, J. E., Lutz, S. E., Smith, J. R., Diaconu, C., Scott, C., Kofman, S. B., et al. (2017). Endothelial Wnt/β-catenin signaling reduces immune cell infiltration in multiple sclerosis. *Proceedings of the National Academy of Sciences of the United States of America*, *114*(7), E1168–E1177. https://doi.org/10.1073/pnas.1609905114.

Li, F., Lan, Y., Wang, Y., Wang, J., Yang, G., Meng, F., et al. (2011). Endothelial Smad4 maintains cerebrovascular integrity by activating N-cadherin through cooperation with notch. *Developmental Cell*, *20*(3), 291–302. https://doi.org/10.1016/j.devcel.2011.01.011.

Li, R., Liu, W., Yin, J., Chen, Y., Guo, S., Fan, H., et al. (2018). TSG-6 attenuates inflammation-induced brain injury via modulation of microglial polarization in SAH rats through the SOCS3/STAT3 pathway. *Journal of Neuroinflammation*, *15*(1). https://doi.org/10.1186/s12974-018-1279-1.

Liu, S.-J., Wang, Q., Tang, H.-H., Bai, J.-Z., Wang, F.-Y., Lv, Z., et al. (2019). Heterogeneity among traumatic spinal cord injuries at the thoracolumbar junction: Helping select patients for clinical trials. *Spinal Cord*, *57*(11), 972–978. https://doi.org/10.1038/s41393-019-0317-x.

Mautes, A. E., Weinzierl, M. R., Donovan, F., & Noble, L. J. (2000). Vascular events after spinal cord injury: Contribution to secondary pathogenesis. *Physical Therapy*, *80*(7), 673–687. https://doi.org/10.1093/ptj/80.7.673.

McConnell, H. L., Kersch, C. N., Woltjer, R. L., & Neuwelt, E. A. (2017). The Translational significance of the neurovascular unit. *Journal of Biological Chemistry*, *292*(3), 762–770. https://doi.org/10.1074/jbc.R116.760215.

Miyamoto, Y., Sakane, F., & Hashimoto, K. (2015). N-cadherin-based adherens junction regulates the maintenance, proliferation, and differentiation of neural progenitor cells during development. *Cell Adhesion & Migration*, *9*(3), 183–192. https://doi.org/10.1080/19336918.2015.1005466.

Mizee, M. R., Wooldrik, D., Lakeman, K. A. M., van het Hof, B., Drexhage, J. A. R., Geerts, D., et al. (2013). Retinoic acid induces blood-brain barrier development. *Journal of Neuroscience*, *33*(4), 1660–1671. https://doi.org/10.1523/JNEUROSCI.1338-12.2013.

Muradov, J. M., Ewan, E. E., & Hagg, T. (2013). Dorsal column sensory axons degenerate due to impaired microvascular perfusion after spinal cord injury in rats. *Experimental Neurology*, *249*, 59–73. https://doi.org/10.1016/j.expneurol.2013.08.009.

Nagoshi, N., Nakashima, H., & Fehlings, M. (2015). Riluzole as a neuroprotective drug for spinal cord injury: From bench to bedside. *Molecules*, *20*(5), 7775–7789. https://doi.org/10.3390/molecules20057775.

Nakajima, H., Uchida, K., Guerrero, A. R., Watanabe, S., Sugita, D., Takeura, N., et al. (2012). Transplantation of mesenchymal stem cells promotes an alternative pathway of macrophage activation and functional recovery after spinal cord injury. *Journal of Neurotrauma*, *29*, 1614–1625. https://doi.org/10.1089/neu.2011.2109.

Nguyen, D. H., Cho, N., Satkunendrarajah, K., Austin, J. W., Wang, J., & Fehlings, M. G. (2012). Immunoglobulin G (IgG) attenuates neuroinflammation and improves neurobehavioral recovery after cervical spinal cord injury. *Journal of Neuroinflammation*, *9*. https://doi.org/10.1186/1742-2094-9-224.

Niu, J., Tsai, H.-H., Hoi, K. K., Huang, N., Yu, G., Kim, K., et al. (2019). Aberrant oligodendroglial–vascular interactions disrupt the blood–brain barrier, triggering CNS inflammation. *Nature Neuroscience*, *22*(5), 709–718. https://doi.org/10.1038/s41593-019-0369-4.

O'Shea, T. M., Burda, J. E., & Sofroniew, M. V. (2017). Cell biology of spinal cord injury and repair. *Journal of Clinical Investigation*, *127*(9), 3259–3270. https://doi.org/10.1172/JCI90608.

Park, D. Y., Lee, J., Kim, J., Kim, K., Hong, S., Han, S., et al. (2017). Plastic roles of pericytes in the blood–retinal barrier. *Nature Communications*, *8*(1), 15296. https://doi.org/10.1038/ncomms15296.

Picoli, C. C., Coimbra-Campos, L. M. C., Guerra, D. A. P., Silva, W. N., Prazeres, P. H. D. M., Costa, A. C., et al. (2019). Pericytes act as key players in spinal cord injury. *The American Journal of Pathology*, *189*(7), 1327–1337. https://doi.org/10.1016/j.ajpath.2019.03.008.

Pollock, L. M., Xie, J., Bell, B. A., & Anand-Apte, B. (2018). Retinoic acid signaling is essential for maintenance of the blood-retinal barrier. *The FASEB Journal*, *32*(10), 5674–5684. https://doi.org/10.1096/fj.201701469R.

Raineteau, O., & Schwab, M. E. (2001). Plasticity of motor systems after incomplete spinal cord injury. *Nature Reviews Neuroscience*, *2*(4), 263–273. https://doi.org/10.1038/35067570.

Saitou, M., Fujimoto, K., Doi, Y., Itoh, M., Fujimoto, T., Furuse, M., et al. (1998). Occludin-deficient embryonic stem cells can differentiate into polarized epithelial cells bearing tight junctions. *Journal of Cell Biology*, *141*(2), 397–408. https://doi.org/10.1083/jcb.141.2.397.

Saitou, M., Furuse, M., Sasaki, H., Schulzke, J.-D., Fromm, M., Takano, H., et al. (2000). Complex phenotype of mice lacking occludin, a component of tight junction strands. *Molecular Biology of the Cell*, *11*(12), 4131–4142. https://doi.org/10.1091/mbc.11.12.4131.

Schwab, J. M., Zhang, Y., Kopp, M. A., Brommer, B., & Popovich, P. G. (2014). The paradox of chronic neuroinflammation, systemic immune suppression, autoimmunity after traumatic chronic spinal cord injury. *Experimental Neurology*, *258*, 121–129. https://doi.org/10.1016/j.expneurol.2014.04.023.

Sekhon, L. H. S., & Fehlings, M. G. (2001). Epidemiology, demographics, and pathophysiology of acute spinal cord injury. *Spine*, *26*(24 Suppl), S2–12. https://doi.org/10.1097/00007632-200112151-00002.

Sharif, H., & Hou, S. (2017). Autonomic dysreflexia: A cardiovascular disorder following spinal cord injury. *Neural Regeneration Research*, *12*(9), 1390. https://doi.org/10.4103/1673-5374.215241.

Siddiqui, A. M., Khazaei, M., & Fehlings, M. G. (2015). Translating mechanisms of neuroprotection, regeneration, and repair to treatment of spinal cord injury. In *Vol. 218. Progress in brain research* (pp. 15–54). Elsevier. https://doi.org/10.1016/bs.pbr.2014.12.007.

Singh, A., Tetreault, L., Kalsi-Ryan, S., Nouri, A., & Michael, F. (2014). Global prevalence and incidence of traumatic spinal cord injury. *Clinical Epidemiology*, *309*. https://doi.org/10.2147/CLEP.S68889.

Spejo, A. B., Chiarotto, G. B., Ferreira, A. D. F., Gomes, D. A., Ferreira, R. S., Barraviera, B., et al. (2018). Neuroprotection and immunomodulation following intraspinal axotomy of motoneurons by treatment with adult mesenchymal stem cells. *Journal of Neuroinflammation*, *15*(1), 230. https://doi.org/10.1186/s12974-018-1268-4.

Stamatovic, S. M., Johnson, A. M., Keep, R. F., & Andjelkovic, A. V. (2016). Junctional proteins of the blood-brain barrier: New insights into function and dysfunction. *Tissue Barriers*, *4*(1). https://doi.org/10.1080/21688370.2016.1154641, e1154641.

Stokes, B., & Jakeman, L. (2002). Experimental modelling of human spinal cord injury: A model that crosses the species barrier and mimics the spectrum of human cytopathology. *Spinal Cord*, *40*(3), 101–109. https://doi.org/10.1038/sj.sc.3101254.

Tator, C. H., & Fehlings, M. G. (1991). Review of the secondary injury theory of acute spinal cord trauma with emphasis on vascular mechanisms. *Journal of Neurosurgery*, *75*(1), 15–26. https://doi.org/10.3171/jns.1991.75.1.0015.

ten Dijke, P., & Arthur, H. M. (2007). Extracellular control of TGFβ signalling in vascular development and disease. *Nature Reviews Molecular Cell Biology*, *8*(11), 857–869. https://doi.org/10.1038/nrm2262.

Thomsen, L. B., Burkhart, A., & Moos, T. (2015). A triple culture model of the blood-brain barrier using porcine brain endothelial cells, astrocytes and pericytes. *PLoS One*, *10*(8). https://doi.org/10.1371/journal.pone.0134765, e0134765.

Turnbull, I. M. (1971). Microvasculature of the human spinal cord. *Journal of Neurosurgery*, *35*(2), 141–147. https://doi.org/10.3171/jns.1971.35.2.0141.

Umeda, K., Ikenouchi, J., Katahira-Tayama, S., Furuse, K., Sasaki, H., Nakayama, M., et al. (2006). ZO-1 and ZO-2 independently determine where claudins are polymerized in tight-junction strand formation. *Cell*, *126*(4), 741–754. https://doi.org/10.1016/j.cell.2006.06.043.

Underly, R. G., Levy, M., Hartmann, D. A., Grant, R. I., Watson, A. N., & Shih, A. Y. (2017). Pericytes as inducers of rapid, matrix metalloproteinase-9-dependent capillary damage during ischemia. *The Journal of Neuroscience*, *37*(1), 129–140. https://doi.org/10.1523/JNEUROSCI.2891-16.2016.

Vaccaro, A. R., Nachwalter, R. S., Klein, G. R., Sewards, J. M., Albert, T. J., & Garfin, S. R. (2001). The significance of thoracolumbar spinal canal size in spinal cord injury patients. *Spine*, *26*(4), 371–376. https://doi.org/10.1097/00007632-200102150-00013.

van Meeteren, L. A., & ten Dijke, P. (2012). Regulation of endothelial cell plasticity by TGF-β. *Cell and Tissue Research*, *347*(1), 177–186. https://doi.org/10.1007/s00441-011-1222-6.

Vawda, R., Badner, A., Hong, J., Mikhail, M., Lakhani, A., Dragas, R., et al. (2019). Early intravenous infusion of mesenchymal stromal cells exerts a tissue source age-dependent beneficial effect on neurovascular integrity and neurobehavioral recovery after traumatic cervical spinal cord injury. *Stem Cells Translational Medicine*, *8*(7), 639–649. https://doi.org/10.1002/sctm.18-0192.

Vladimir, S., Aaron, F., Dan, M., Jonathan, O., Rotem, S.-A., & Adiel, C. (2019). Blood-brain barrier dysfunction in aging induces hyperactivation of TGF signaling and chronic yet reversible neural dysfunction. *Science Translational Medicine*, *11*, 15.

Walshe, T. E., Saint-Geniez, M., Maharaj, A. S. R., Sekiyama, E., Maldonado, A. E., & D'Amore, P. A. (2009). TGF-β is required for vascular barrier function, endothelial survival and homeostasis of the adult microvasculature. *PLoS One*, *4*(4). https://doi.org/10.1371/journal.pone.0005149, e5149.

Wang, Z., Liu, C.-H., Huang, S., Fu, Z., Tomita, Y., Britton, W. R., et al. (2020). Wnt signaling activates MFSD2A to suppress vascular endothelial transcytosis and maintain blood-retinal barrier. *Science Advances*, *6*(35). https://doi.org/10.1126/sciadv.aba7457, eaba7457.

Wang, Y., Sabbagh, M. F., Gu, X., Rattner, A., Williams, J., & Nathans, J. (2019). Beta-catenin signaling regulates barrier-specific gene expression in circumventricular organ and ocular vasculatures. *eLife*, *8*. https://doi.org/10.7554/eLife.43257, e43257.

Watanabe, J., Shetty, A. K., Hattiangady, B., Kim, D. K., Foraker, J. E., Nishida, H., et al. (2013). Administration of TSG-6 improves memory after traumatic brain injury in mice. *Neurobiology of Disease*, *59*, 86–99. https://doi.org/10.1016/j.nbd.2013.06.017.

Wilcox, J. T., Satkunendrarajah, K., Nasirzadeh, Y., Laliberte, A. M., Lip, A., Cadotte, D. W., et al. (2017). Generating level-dependent models of cervical and thoracic spinal cord injury: Exploring the interplay of neuroanatomy, physiology, and function. *Neurobiology of Disease*, *105*, 194–212. https://doi.org/10.1016/j.nbd.2017.05.009.

Winkler, E. A., Sengillo, J. D., Bell, R. D., Wang, J., & Zlokovic, B. V. (2012). Blood-spinal cord barrier pericyte reductions contribute to increased capillary permeability. *Journal of Cerebral Blood Flow and Metabolism*, *32*(10), 1841–1852. https://doi.org/10.1038/jcbfm.2012.113.

Winkler, E. A., Sengillo, J. D., Sullivan, J. S., Henkel, J. S., Appel, S. H., & Zlokovic, B. V. (2013). Blood–spinal cord barrier breakdown and pericyte reductions in amyotrophic lateral sclerosis. *Acta Neuropathologica*, *125*(1), 111–120. https://doi.org/10.1007/s00401-012-1039-8.

Xu, J., Long, H., Chen, W., Cheng, X., Yu, H., Huang, Y., et al. (2018). Ultrastructural features of neurovascular units in a rat model of chronic compressive spinal cord injury. *Frontiers in Neuroanatomy*, *11*, 136. https://doi.org/10.3389/fnana.2017.00136.

Zavvarian, M.-M., Hong, J., & Fehlings, M. G. (2020). The functional role of spinal interneurons following traumatic spinal cord injury. *Frontiers in Cellular Neuroscience*, *14*, 127. https://doi.org/10.3389/fncel.2020.00127.

Zavvarian, M.-M., Toossi, A., Khazaei, M., Hong, J., & Fehlings, M. (2020). Novel innovations in cell and gene therapies for spinal cord injury. *F1000Research*, *9*, 279. https://doi.org/10.12688/f1000research.21989.1.

Chapter 11

Protein degradome in spinal cord injury

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Abbreviations

BDPs	breakdown products
CSPGs	chondroitin sulfate proteoglycans
GFAP	glial fibrillary acidic protein
HA	hyaluronan
I-NaP	increased persistent sodium current
MMPs	matrix metalloproteinases
Nav	voltage-gated sodium
NF200	neurofilament
SBDPs	αII-spectrin breakdown product
SCI	spinal cord injury
UPS	ubiquitin-proteasome system
USP4	ubiquitin-specific protease 4

Introduction

Degradomics is a subdiscipline of proteomics, it refers to the study of proteases, the enzymes responsible for the hydrolysis of peptide bonds, and the study of breakdown products (BDPs) ensuing from the targeted substrates (Overall & Dean, 2006) (Fig. 1). Among the techniques that were used to decipher the degradomic profiling in neurotrauma, mass spectrometry has proved to be the most efficacious in conveying the precise measurements of BDPs, proteases, and substrates (Lopez-Otin & Overall, 2002). Several disease states produce an array of BDPs resulting from an uncontrolled protease-substrate repertoire, that could be further used in the diagnosis, assessment, treatment, and follow-up (Savickas & Keller, 2017).

Spinal Cord Injury (SCI) can be divided into a primary injury, where the shear forces of the direct trauma disrupt the axonal relays, causing disability (McKinley, Santos, Meade, & Brooke, 2007), and a secondary injury, where neurotoxicity plays a key role (Tator & Fehlings, 1991). The latter can exacerbate the former injury and slows the recovery, which will lead to a downward spiral of cellular and molecular activation (Tator & Fehlings, 1991), alterations of proteolytic enzymes, upregulation of cytotoxic neurotransmitters (Veeravalli, Dasari, & Rao, 2012), and impairment of blood–CNS barrier (Nasser et al., 2016).

The mechanism of spinal cord injury is complex and interrelated. This chapter sheds light on the degradomics implicated in SCI, it uncovers hidden pathophysiological processes after the identification and characterization of BDPs, resulting from the overactivation of proteases. It describes signature substrates and their BDPs involved in SCI, including ion channels, cytoskeletal proteins, cellular junction proteins, and others. Different enzymes responsible for the proteolysis will be discussed, such as caspases, calpains, cathepsins, and Matrix Metalloproteinases (MMPs). Taken together, it can improve our understanding of the secondary injury, and guide new therapeutic approaches.

Protease-substrate repertoires

Proteolysis of specific substrates during SCI was extensively studied in the past few years (Fig. 2). Circulating cytokines after SCI activate the proteolytic cascade in the spinal cord (Supinski, Wang, & Callahan, 2009), this was evident when

Cellular, Molecular, Physiological, and Behavioral Aspects of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822427-4.00011-3

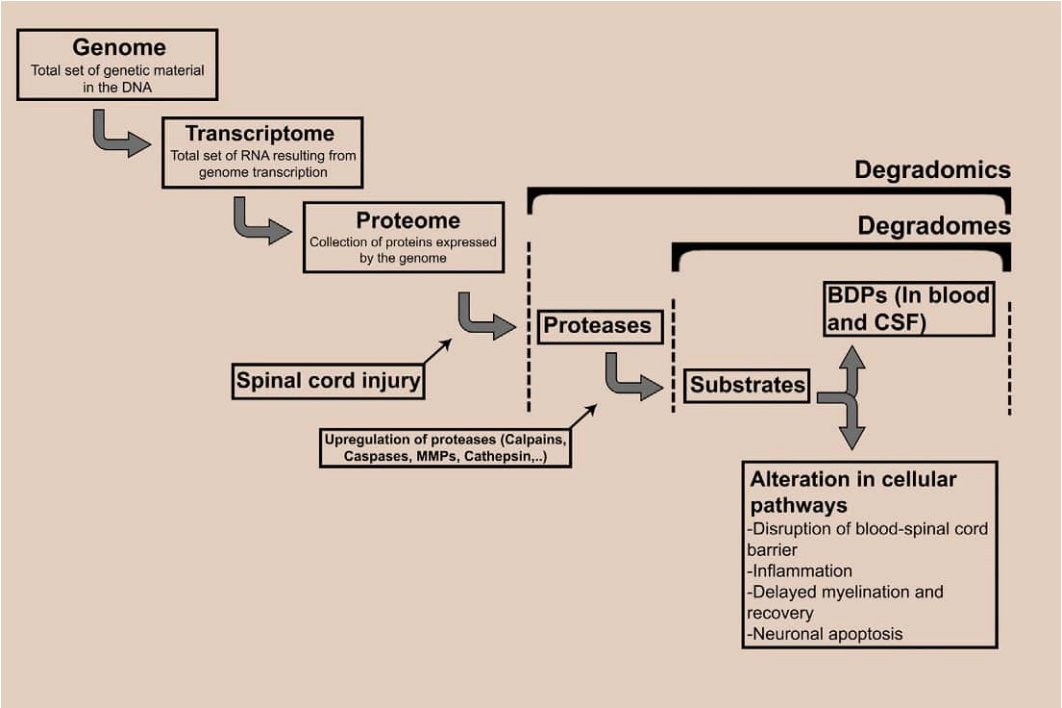

FIG. 1 Showing protease-substrate repertoires during cellular injury after spinal cord injury. *aSAH*, aneurysmal subarachnoid hemorrhage; *BDPs*, breakdown products; *MMPs*, matrix metalloproteinase.

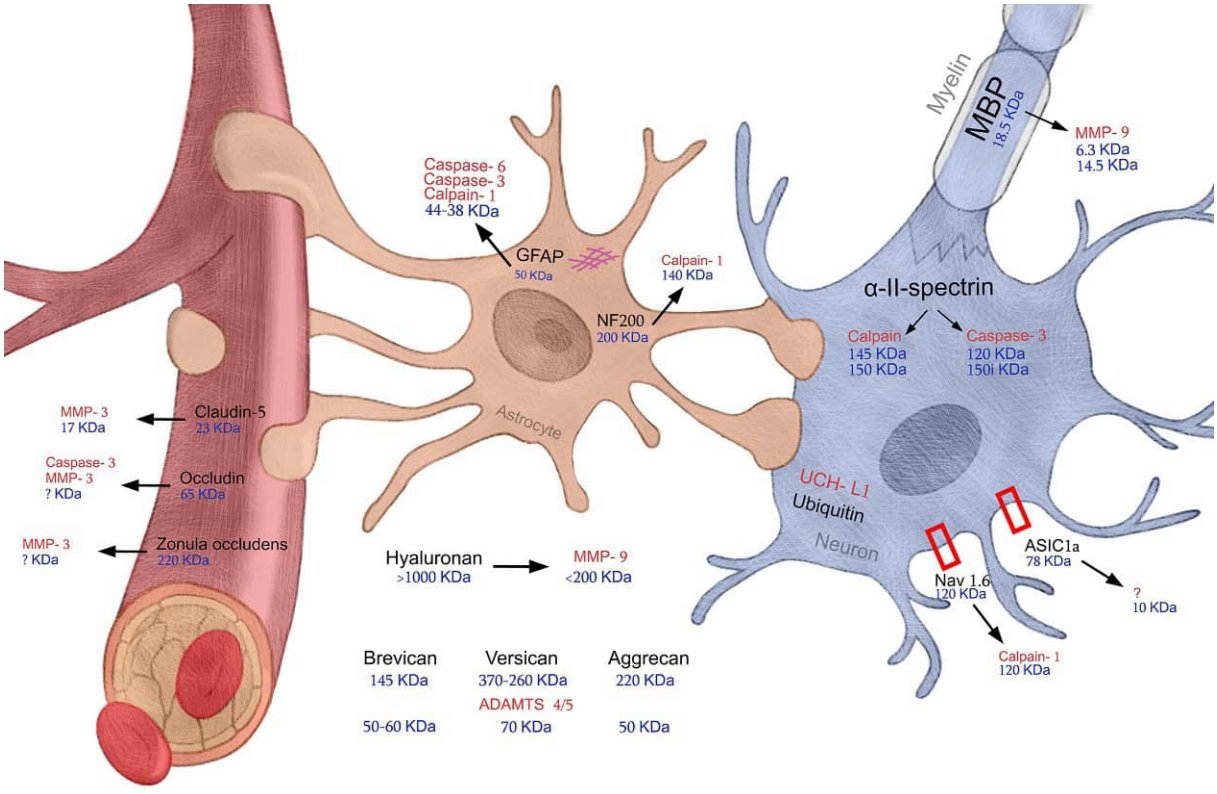

FIG. 2 Showing the location of different substrates, their proteases, and the resulting BDPs implicated in spinal cord injury. *ASIC1a*, mAcid-sensing ion channel 1a; *GFAP*, glial fibrillary acidic protein; *KDa*, kilodalton; MMP, matrix metalloproteinase; UCH-L1, ubiquitin C terminal hydrolase 1.

caspase-3, a cysteine aspartic protease, was found elevated at 1-day post-SCI, and calpain-3, a nonlysosomal cysteine protease, was elevated at day 7 post-SCI, as the extent of injury progressed (Banik et al., 1998; Gill et al., 2014).

Cathepsin-B and cathepsin-D are aspartyl proteases that were linked to SCI (Ellis, Earnhardt, Hayes, Wang, & Anderson, 2004; Hashimoto et al., 2005). 37-kDa cathepsin-B proenzyme was increased at 48, 72, and 168 h, in SCI post-contusion in rats (Ellis et al., 2004), and 31-kDa cathepsin-D were detected at 3 and 7 days in microglia post-SCI (Hashimoto et al., 2005). This contributed to the increased phagocytosis and lysosomal activation during the spinal cord insult (Moon et al., 2008). The endoplasmic reticulum injury was also studied as one of the reasons for apoptosis following injury, where caspase-12 and caspase-3 are expressed to accelerate the process (Liu et al., 2015).

Matrix Metalloproteinases (MMPs) are proteases that have an important vital function, including wound healing, neuronal growth and plasticity, and other physiological functions. Cytokines and growth factors are considered the main regulators of MMPs (Nagase & Woessner, 1999). An increase in MMP-1 and MMP-2 levels was found in macrophages of traumatized human spinal cords at the site of injury (Buss et al., 2007). Interestingly, MMP-2 had a major contribution to the extent of glial scarring (Veeravalli et al., 2009). In a study involving MMP-9 null mice vs wild-type mice with SCI, MMP-9 null mice were associated with a more stable blood–spinal cord barrier, decreased neutrophils at the site of injury, and a better locomotor activity (Noble, Donovan, Igarashi, Goussev, & Werb, 2002). A similar effect on locomotor activity was also seen in MMP-12 null mice compared with wild-type controls, as well as a higher motor strength days after SCI (Wells et al., 2003). MMPs are major contributors to the secondary damage after SCI, and a crucial cause of disability, where cell apoptosis exacerbates the underlying neuronal damage. Furthermore, when rats with SCI were injected intrathecally with SB-3CT (MMP-2/MMP-9 inhibitor), apoptotic cell death was inhibited, thus reducing secondary damage (Yu, Kamada, Niizuma, Endo, & Chan, 2008). This can guide further human clinical trials, to prevent MMPs' remodeling effect of the spinal cord, and prevent superimposed injuries.

Membrane type 1-MMP (MT1-MMP) and Glutamine Synthetase (GS) share an intimate correlation during SCI (Zou et al., 2011). This study noted a decreased GS levels acutely post-SCI. It is degraded by MT1-MMP, which amplifies glial scar formation and increases neurotoxicity, given that GS is highly expressed in astrocytes and plays a paramount protective effect by eliminating cytotoxic agents such as glutamate and ammonia (Zou et al., 2011).

Other proteases had a positive role in reducing injury and improving functional recovery, this is the case of few serine proteases like tissue-type Plasminogen Activator (tPA) and Urokinase PA (uPA). They reduce immune cell activation, soothe the destructive process, and promote recovery following the traumatic injury (Seeds et al., 2011). In contrast, neuropsin (kallikrein-like serine protease) promotes oligodendrocyte death, demyelination, and axonal degeneration after spinal cord injury (Terayama et al., 2007).

The Ubiquitin-Proteasome System (UPS) includes the proteasome and ubiquitin ligases, hydrolases, and ubiquitin itself (Gong, Radulovic, Figueiredo-Pereira, & Cardozo, 2016), which organizes many aspects of cellular behavior and function (Gong et al., 2016). It is found to be upregulated during acute SCI. The phosphorylation of Ubiquitin Carboxyl-terminal hydrolase L1 (UCH-L1) and conjugated ubiquitin is increased, which in turn, regulates neurogenesis and promotes neuronal progenitor cells (Sakurai et al., 2006). On the other hand, Ubiquitin-specific protease 4 (USP4) belongs to the deubiquitinase family which inhibits the NF-κB pathway. During SCI, USP4 is downregulated, which promotes the NF-κB pathway and increases microglial proliferation and amplifies the inflammatory process (Jiang et al., 2017).

Recently, UPS activation post-SCI was found to be the origin of the decline of heart function in terms of contractility and cardiomyocyte size weeks after the initial injury to the spinal cord, and preclinical trials targeting the UPS activation yielded promising results, using phosphodiesterase-4 inhibitors and dibutyryl-cAMP (Myeku, Wang, & Figueiredo-Pereira, 2012; Squair et al., 2018).

Extensive data analysis showed increased Presenilin (PS1) expression, the catalytic subunit of gamma-secretase, on day 1 after SCI (Kobayashi et al., 2010). PS1 is responsible for the formation of amyloid plaque due to its action on amyloid precursor protein involved in synaptogenesis and iron transport, and it is highly implicated in Alzheimer's disease (Murphy & LeVine, 2010). Theoretically, the development of gamma-secretase inhibitors would probably be of great interest to decrease secondary injury caused by B-amyloid plaque deposition.

Other protease inhibitors showed promising results in rats, but none has reached clinical or preclinical studies. Carfilzomib is a proteasome inhibitor that interacts with PSMB10, improved SCI injury in rats (Sharma et al., 2015). As previously stated, caspase-3 mediates apoptosis of neurons and glial cells after SCI which exacerbates the initial insult (Gill et al., 2014), few protease inhibitors such as nafamostat mesilate and Mesencephalic astrocyte-derived Neurotrophic Factor (MANF) reduced caspase-3-mediated apoptosis and showed improved functional recovery after SCI in rats (Gao et al., 2018). Due to the similarity of molecular changes after SCI between rats and humans, it is crucial to transfer these findings into human clinical trials to minimize the damage of proteolytic reactions and reduce neurotoxicity.

Degradomes in SCI

Degradomes constitute the substrates which the proteases act upon and the breakdown products generated from these proteolytic reactions. These degradomes modulate the cellular behavior in a number of ways, they carry important structural and functional cellular roles, including cytoskeleton, signaling pathways, enzymes, and mitotic or apoptotic properties (Rawlings, Barrett, & Finn, 2016).

Cytoskeletal proteins

Calpains are responsible for the neurochemical cascade that ends with glutamate neurotoxicity and degradation of the cytoskeleton (Veeravalli et al., 2012). αII-spectrin breakdown product (SBDP150) was found to increase at 3 and 6 h post-SCI in the thoracic spine in mice after high-pressure air blast injury, due to the action of calpains on αII-spectrin (280 kDa) (del Mar et al., 2015). In addition, 145- and 150-kDa SBDPs generated from the activity of calpain-1 were also found in rats with spinal cord contusion at T-10 level (Xiong, Rabchevsky, & Hall, 2007). Recently, SBDP120 was also detected at day 7 postspinal cord trauma (Yang et al., 2018).

Neurofilament (NF200) is an important 200,000 molecular weight protein that stabilizes and maintains neuronal structure (Banik, Matzelle, Gantt-Wilford, Osborne, & Hogan, 1997). Calpain-1 elevated levels at 2 h post-SCI cleave NF200 generating 140,000 fragments (Banik et al., 1997). In ovariectomized rats, Gonadotropin-releasing hormone treatment improves locomotor activity, 160- and 200-kDa neurofilament protein expression, and urinary function after spinal cord injury (Calderon-Vallejo & Quintanar, 2012).

Glial Fibrillary Acidic Protein (GFAP) is an intermediate filament located in astrocytes and Schwann cells, it has a molecular weight of 50 kDa. It is acutely cleaved during SCI into 38–44-kDa fragments by calpain-1 (Abou-El-Hassan et al., 2017). GFAP is found elevated during SCI, mainly due to protease-activated receptor 2 (PAR2) (Radulovic et al., 2015). PAR2 is a suppressor of myelin, its inhibition by lipopeptide inhibitors reduced ERK1/2 signaling, and the upcoming neurotoxicity (Yoon et al., 2013).

Other cytoskeletal proteins fluctuated after 12 h of SCI, there's an increase of α-tubulin and decrease of both dynamin 1 and the novel fascin, but they return to normal after 24 h of the primary injury (Zhu et al., 2013).

The clinical effect of the cytoskeletal protein degradation by the upregulated proteases is referred to the structural importance of these proteins in maintaining the stability of neuronal and glial cells. The inhibition of this proteolysis can lead to a decrease in neuronal loss and subsequent injury. A summary of cytoskeletal proteins is found in Table 1.

TABLE 1 Cytoskeletal proteins in SCI.

Precursor	Weight (kDa)	Location	Role	Proteolytic enzyme	Proteolytic product
αII-spectrin	280	Cytoplasm	Cytoskeletal protein, maintains cellular integrity, and stabilizes axons	Calpain-1	150-kDa SBDP
				Calpain-2	150-kDa SBDP 145-kDa SBDP
				Calpain-3	150i-kDa SBDP 120-kDa SBDP
NF200	200	Cytoplasm	Intermediate filaments, neuronal, and axonal structure	Calpain-1 cathepsin	140 kDa
GFAP	50	Cytoplasm	Intermediate filament, glial cell cytoskeleton	Calpain-1 Caspase-3 Caspase-6	38–44 kDa

GFAP, glial fibrillary acidic protein; *NF200*, neurofilament.

Extracellular matrix

After the initial SCI, there's a blood–spinal cord barrier damage that paves the way for a massive neuroinflammatory response. Extracellular matrix deposition is deemed one of the most important factors that regulate the entry of inflammatory cells and amplify the immune response (Deng et al., 2014). It is regulated by releasing and presenting peptides to increase cellular response and produce further tissue damage (Deng et al., 2014).

MMPs, as previously stated, are found in higher levels during SCI (Buss et al., 2007). They play an important role in Degrading Hyaluronan (HA), which produces sulfated Proteoglycans (PG) and tenascin fragments (Gaudet & Popovich, 2014). Further studies have shown a significant recovery of SCI in rats after adding HA, this has led to a decrease in macrophage density and reactive gliosis, with improved myelination and nerve regeneration. It also prevented the further deposition of proteoglycans with the ensuing inflammatory reactions (Park et al., 2009).

Axonal growth following SCI is inhibited mostly by Chondroitin Sulfate Proteoglycans (CSPGs), which increase perineuronal scarring. The proposed mechanism is narrowed down to the axonal tips being wedged and embedded within the inhibitory matrix (Nazari-Robati, Golestani, & Asadikaram, 2016). Aggrecan (220 kDa), versican (260–370 kDa), and brevican (145 kDa) are all considered parts of CSPGs (Nazari-Robati et al., 2016). Many successful attempts were used to inhibit CSPGs and showed promising results that can be further translated into the clinical routine in the management of SCI, aiming to improve neuroplasticity and nerve regeneration.

Myelin Basic Protein (MBP) is considered a key factor for proper neuro-regeneration and the restoration of normal nerve function. Adenovirus-mediated delivery of intact MBP improved neurological function when compared with inactive MBP that is cleaved after SCI (Lutz et al., 2016).

Extracellular matrix changes during SCI provide an early insight into the vast molecular pathways that intervene with neuro-regeneration. It is also a target for several therapeutic agents that can modulate the axonal myelination and decrease further neuronal damage. A summary of the extracellular matrix is found in Table 2.

Cell junction proteins

MMPs emerged to play a very important role in blood–spinal cord barrier breakdown, through their action on junction proteins. Specifically, 48-kDa MMP-3 peaks at 1-day postspinal cord injury, causing a decrease of zonula occludens-1 (220 kDa) at 4–8 h, occludin (65 kDa) at day 1, and claudin-5 (23 kDa) at 4–8 h (Lee, Choi, Ahn, Ju, & Yune, 2014). Hence, higher levels of junction proteins were detected with MMP-3 inhibition (Lee et al., 2014). Similarly, another study showed a protective role of metformin on the blood–spinal cord barrier by shutting down the breakdown of junctional proteins, by decreasing AMP-activated protein kinase (AMPK)-dependent MMP-9, ICAM-1, and neutrophil infiltration (Zhang et al., 2017). Likewise, mithramycin (an anticancer drug) and anti-Ly6G inhibited MMP-9 expression and thus decreased tight junction proteins degradation and blood–spinal cord barrier instability (Lee, Choi, Park, Ju, & Yune, 2018; Lee, Rosen, Weinstein, van Rooijen, & Noble-Haeusslein, 2011). In another study, MMP-8 inhibitor reduced significantly the

TABLE 2 Extracellular matrix in SCI.

Precursor	Weight (kDa)	Location	Role	Proteolytic enzyme	Proteolytic product
Hyaluronan	>1000	ECM	ECM, maintains CNS structure	MMP-9	Sulfated proteoglycan < 200 kDa Tenascin fragments < 200 kDa
Aggrecan	220	ECM	ECM-Chondrocyte function, part of CSPGs	ADAMTS4/5	50 kDa
Versican	260–370	ECM	Cell adhesion and migration, part of CSPGs		70 kDa
Brevican	145	ECM	Neuronal growth Part of CSPGs		50–60 kDa
Myelin basic protein	18.5	Myelin membrane	Myelination of nervous tissue	MMP-9	6.3, 7.0, 7.3, 8.3, 10.2, 14.5 kDa

proteolysis of occluding and zonula occludens-1 protein (Kumar et al., 2018). In brief, MMPs play a crucial role in destabilizing junction proteins, allowing the entry of inflammatory cells through the breakage of the blood–spinal cord barrier, further decapacitating the healing process and exacerbating the injury. A summary of cell junction proteins is found in Table 3.

Ion channels

In the past few years, ion channelopathies have taken a huge role in explaining many of the cellular injuries following ischemic insults. Neuron transmembrane potential and ion gradients are highly influenced by the alteration of ion channels, resulting in pericellular blebbing and plasma membrane damage (Liu et al., 2012). Proteolytic enzyme activation by calcium influx in SCI is one of the proposed mechanisms of neurotoxic injuries (Oliveira et al., 2014). Administration of calcium channel inhibitors had major neuroprotective properties in rat models. For example, Omega-conotoxin, attenuated neuronal death, by inhibiting voltage-dependent calcium channels, hence decreasing caspase-3 activation (Oliveira et al., 2014). Similarly, inhibition of sodium–calcium exchanger enhanced recovery and protected spectrin proteins from degradation by calpains, using bepridil and KB-R7943 (Li, Jiang, & Stys, 2000).

mAcid-sensing ion channel 1a (ASIC1a) allows sodium and calcium influx. It is upregulated in acute hypoxia in SCI, causing mitochondrial dysfunction and apoptosis, therefore amplifying the secondary injury (Yermolaieva, Leonard, Schnizler, Abboud, & Welsh, 2004). Its inhibition using spider-venom peptide PcTx1 leads to a better functional outcome (Koehn et al., 2016).

Another serious disability following SCI is spasticity. Molecular studies showed that calpain-mediated proteolysis of 250-kDa voltage-gated sodium (Nav) 1.6 channels increased persistent sodium current (I-NaP), the origin of increased spasticity (Brocard et al., 2016). Inhibition of calpain-mediated proteolysis of Nav was achieved using MDL28170, which downregulated I-NaP and relieved spasticity (Plantier & Brocard, 2017).

The pathophysiology of neuropathic pain following SCI was considerably studied, revealing an electric instability of the neuronal membrane, and a disruption of the structural and functional integrity of myelin (Dubin & Patapoutian, 2010). This activates the nociceptive circuitry in the small unmyelinated C-nociceptive and thinly myelinated Aδ afferents. This mechanism is mediated by MMPs' action on MBP (Dubin & Patapoutian, 2010). The severity of demyelination was reduced by tamoxifen, a selective estrogen receptor modulator, which also had a positive effect on upregulating aquaporin 4 (AQP4) water channels, decreasing edema, and improving recovery. It emphasized the positive effect of estrogen as a mediator of neuroprotection (Guptarak et al., 2014). A summary of ion channels is found in Table 4.

Clinical perspectives

Since the development of sophisticated methods and analytical tools to discover the molecular pattern of various medical conditions, new standards of characterizing patients suffering from SCI have emerged. Treatment can be personalized depending on each case based on the clinical symptomatology and severity, enabling specific targeted treatment that aims to reduce the secondary injury following SCI. Discoveries in animal models can be translated to humans via clinical trials and molecular studies that acknowledge the molecular and cellular behavior of neurons following the primary injury. Protein's identification is now available due to the advancement in proteomic studies, including quantitative high-resolution two-dimensional (2D-PAGE-isoelectric focusing and SDSPAGE) protein separation technique, matrix-assisted laser

TABLE 3 Cellular junction proteins in SCI.

Precursor	Weight (kDa)	Location	Role	Proteolytic enzyme	Proteolytic product
Zonula occludens-1	220 65 23	Cell membrane	Close paracellular pathway	MMP-3	?
Occluding	65	Cell membrane	Close paracellular pathway	MMP-3	?
Claudin-5	23	Cell membrane	Close paracellular pathway	MMP-3	17 kDa

TABLE 4 Ion channels in SCI.

Precursor	Weight (kDa)	Location	Role	Proteolytic enzyme	Proteolytic product
ASIC1a	78	Cell membrane	Sodium and calcium influx	?	10 kDa
Nav1.6	250	Cell membrane	Voltage-gated channel	Calpain-1	120 kDa

ASIC1a, mAcid-sensing ion channel 1a; *Nav*, voltage-gated sodium.

desorption/ionization (MALDI) TOF mass spectrometry, and nano ESI-MS/MS (Abou-El-Hassan et al., 2020). The protease-substrate repertoire was evident using a two-hybrid screening assay and high-throughput protein microarrays, which was considered a step further toward a better understanding of secondary injury (Abou-El-Hassan et al., 2020).

Application to other neuroscience areas

Degradomics' impact on CNS injury was also studied in traumatic brain injury (Abou-El-Hassan et al., 2017). The activation of proteases following the calcium influx and mitochondrial dysfunction leads to disruption of key components of cellular recovery, such as cytoskeleton integrity, synaptic transmissions, and neuronal survival (Zhou, Xu, Liao, Bi, & Baudry, 2009). In addition, brain ischemia and the subsequent neurotoxicity were also linked to calpain activation (Sharma et al., 2015).

Lately, emerging biomarkers involving aneurysmal subarachnoid hemorrhage were studied (Bsat et al., 2020, 2021). The early classification of patients according to the complications and severity of the aneurysmal rupture can guide an early and aggressive treatment to prevent further ischemic damage. Cerebral vasospasm is considered the main complication of aneurysmal subarachnoid hemorrhage, and the proposed mechanism is also related to calcium influx and a proteolytic cascade that ends with apoptosis (Abou-El-Hassan et al., 2017). Breakdown products of many cellular components can then be detected in blood, following proteolysis and apoptosis. The BDPs poured in blood and CSF reflect the severity of the damage and can predict the outcome. As an example, higher levels of SBDP150, SBDP145, and SBDP120 levels were significantly linked to higher WFNS (World federation of neurological surgeons) grades of severity and Glasgow coma scale (Papa et al., 2018).

Degradomics remains a new material for neurosurgeons, but it opens a variety of molecular patterns that can be the target of newer treatment after SCI. Further studies need to assess the efficacy of treating secondary injury in humans, but promising results are already coming to light.

Mini-dictionary of terms

Proteomics: The study of proteins, the vital parts of the living organisms, on a system-wide scale.
Degradomics: A subdiscipline in biology involving the analysis of proteases and their targeted substrates, their inhibitors, and the breakdown product.
Breakdown products: Peptides resulting from the action of proteases on their targeted substrates.
Channelopathy: The dysregulation of ion channel subunits, or the disturbance of proteins that regulate them.
Ubiquitin-proteasome system: Eukaryotic system concerned in the degradation and turnover of intracellular proteins through the action of proteases. Proteins destined for proteolysis are marked and linked by ubiquitin.

Key facts of spinal cord degradomics

- Degradomics constitutes a subdiscipline of proteomics.
- It is the study of proteases and their target substrates, that generate breakdown products.
- Breakdown products can be detected in serum or CSF of patients with SCI.
- Proteases play a key role in exacerbating spinal cord injury.
- Substrate's degradation influences neuronal and axonal metabolism, leading to demyelination and apoptosis.
- Targeted treatment can be implemented, to decrease the molecular cascade and inhibit neuronal apoptosis.

Summary points

- This chapter focuses on the secondary injury following spinal cord injury, induced by degradomics.
- Proteases such as caspase-3, calpains, cathepsins, and matrix metalloproteinases (MMPs) are found elevated after spinal cord injury.
- Ubiquitin-proteasome system (UPS) is considered protective, improving myelination, and nerve regeneration.
- Calpain degrades cytoskeletal proteins such as αII-spectrin, glial fibrillary acidic protein (GFAP), and neurofilament.
- Hyaluronan, a key component of extracellular matrix, increase myelination. and decrease inflammation. It is cleaved by MMPs after SCI.
- Chondroitin sulfate proteoglycans (CSPGs) decrease axonal regeneration and increase perineuronal scarring. Its inhibition potentiates neuroplasticity.
- Ion channelopathies increase neurotoxicity after spinal cord injury. Increased persistent sodium current (I-NaP) after calpains induced proteolysis of voltage-gated sodium (Nav) causes spasticity.
- Neuropathic pain after the axonal injury is exacerbated by myelin disruption through the action of MMPs on myelin basic protein (MBP), in addition to the electrical instability.

References

Abou-El-Hassan, H., Bsat, S., Sukhon, F., Assaf, E. J., Mondello, S., Kobeissy, F., et al. (2020). Protein degradome of spinal cord injury: Biomarkers and potential therapeutic targets. *Molecular Neurobiology*, *57*(6), 2702–2726. https://doi.org/10.1007/s12035-020-01916-3.

Abou-El-Hassan, H., Sukhon, F., Assaf, E. J., Bahmad, H., Abou Abbass, H., Jourdi, H., et al. (2017). Degradomics in neurotrauma: Profiling traumatic brain injury. *Methods in Molecular Biology*, *1598*, 65–99. https://doi.org/10.1007/978-1-4939-6952-4_4.

Banik, N. L., Matzelle, D. C., Gantt-Wilford, G., Osborne, A., & Hogan, E. L. (1997). Increased calpain content and progressive degradation of neurofilament protein in spinal cord injury. *Brain Research*, *752*(1–2), 301–306. https://doi.org/10.1016/S0006-8993(96)01488-6.

Banik, N. L., Shields, D. C., Ray, S., Davis, B., Matzelle, D., Wilford, G., et al. (1998). Role of calpain in spinal cord injury: Effects of calpain and free radical inhibitors(a). *Annals of the New York Academy of Sciences*, *844*(1), 131–137. https://doi.org/10.1111/j.1749-6632.1998.tb08228.x.

Brocard, C., Plantier, V., Boulenguez, P., Liabeuf, S., Bouhadfane, M., Viallat-Lieutaud, A., et al. (2016). Cleavage of Na(+) channels by calpain increases persistent Na(+) current and promotes spasticity after spinal cord injury. *Nature Medicine*, *22*(4), 404–411. https://doi.org/10.1038/nm.4061.

Bsat, S., Chanbour, H., Alomari, S., Moussalem, C., Houshiemy, M. N. E., & Sunna, T. (2020). Can we improve the prediction of complications and outcome in aneurysmal subarachnoid hemorrhage? The clinical implications of serum proteomics. *Journal of Integrative Neuroscience*, *19*(4), 711–717. https://doi.org/10.31083/j.jin.2020.04.370.

Bsat, S., Chanbour, H., Bsat, A., Alomari, S., Moussalem, C., Houshiemy, M. N. E., et al. (2021). Clinical utility of degradomics as predictors of complications and clinical outcome in aneurysmal subarachnoid hemorrhage. *Journal of Integrative Neuroscience*, *20*(2), 489–497. https://doi.org/10.31083/j.jin2002052.

Buss, A., Pech, K., Kakulas, B. A., Martin, D., Schoenen, J., Noth, J., et al. (2007). Matrix metalloproteinases and their inhibitors in human traumatic spinal cord injury. *BMC Neurology*, *7*, 17. https://doi.org/10.1186/1471-2377-7-17.

Calderon-Vallejo, D., & Quintanar, J. L. (2012). Gonadotropin-releasing hormone treatment improves locomotor activity, urinary function and neurofilament protein expression after spinal cord injury in ovariectomized rats. *Neuroscience Letters*, *515*(2), 187–190. https://doi.org/10.1016/j.neulet.2012.03.052.

del Mar, N., von Buttlar, X., Yu, A. S., Guley, N. H., Reiner, A., & Honig, M. G. (2015). A novel closed-body model of spinal cord injury caused by high-pressure air blasts produces extensive axonal injury and motor impairments. *Experimental Neurology*, *271*, 53–71. https://doi.org/10.1016/j.expneurol.2015.04.023.

Deng, W. P., Yang, C. C., Yang, L. Y., Chen, C. W., Chen, W. H., Yang, C. B., et al. (2014). Extracellular matrix-regulated neural differentiation of human multipotent marrow progenitor cells enhances functional recovery after spinal cord injury. *The Spine Journal*, *14*(10), 2488–2499. https://doi.org/10.1016/j.spinee.2014.04.024.

Dubin, A. E., & Patapoutian, A. (2010). Nociceptors: The sensors of the pain pathway. *The Journal of Clinical Investigation*, *120*(11), 3760–3772. https://doi.org/10.1172/JCI42843.

Ellis, R. C., Earnhardt, J. N., Hayes, R. L., Wang, K. K., & Anderson, D. K. (2004). Cathepsin B mRNA and protein expression following contusion spinal cord injury in rats. *Journal of Neurochemistry*, *88*(3), 689–697. https://doi.org/10.1046/j.1471-4159.2003.02197.x.

Gao, L., Xu, W., Fan, S., Li, T., Zhao, T., Ying, G., et al. (2018). MANF attenuates neuronal apoptosis and promotes behavioral recovery via Akt/MDM-2/p53 pathway after traumatic spinal cord injury in rats. *BioFactors*. https://doi.org/10.1002/biof.1433.

Gaudet, A. D., & Popovich, P. G. (2014). Extracellular matrix regulation of inflammation in the healthy and injured spinal cord. *Experimental Neurology*, *258*, 24–34. https://doi.org/10.1016/j.expneurol.2013.11.020.

Gill, L. C., Ross, H. H., Lee, K. Z., Gonzalez-Rothi, E. J., Dougherty, B. J., Judge, A. R., et al. (2014). Rapid diaphragm atrophy following cervical spinal cord hemisection. *Respiratory Physiology & Neurobiology*, *192*, 66–73. https://doi.org/10.1016/j.resp.2013.12.006.

Gong, B., Radulovic, M., Figueiredo-Pereira, M. E., & Cardozo, C. (2016). The ubiquitin-proteasome system: Potential therapeutic targets for Alzheimer's disease and spinal cord injury. *Frontiers in Molecular Neuroscience*, *9*, 4. https://doi.org/10.3389/fnmol.2016.00004.

Guptarak, J., Wiktorowicz, J. E., Sadygov, R. G., Zivadinovic, D., Paulucci-Holthauzen, A. A., Vergara, L., et al. (2014). The cancer drug tamoxifen: A potential therapeutic treatment for spinal cord injury. *Journal of Neurotrauma*, *31*(3), 268–283. https://doi.org/10.1089/neu.2013.3108.

Hashimoto, M., Koda, M., Ino, H., Yoshinaga, K., Murata, A., Yamazaki, M., et al. (2005). Gene expression profiling of cathepsin D, metallothioneins-1 and -2, osteopontin, and tenascin C in a mouse spinal cord injury model by cDNA microarray analysis. *Acta Neuropathologica*, *109*(2), 165–180. https://doi.org/10.1007/s00401-004-0926-z.

Jiang, X., Yu, M., Ou, Y., Cao, Y., Yao, Y., Cai, P., et al. (2017). Downregulation of USP4 promotes activation of microglia and subsequent neuronal inflammation in rat spinal cord after injury. *Neurochemical Research*, *42*(11), 3245–3253. https://doi.org/10.1007/s11064-017-2361-2.

Kobayashi, S., Sasaki, T., Katayama, T., Hasegawa, T., Nagano, A., & Sato, K. (2010). Temporal-spatial expression of presenilin 1 and the production of amyloid-beta after acute spinal cord injury in adult rat. *Neurochemistry International*, *56*(3), 387–393. https://doi.org/10.1016/j.neuint.2009.11.005.

Koehn, L. M., Noor, N. M., Dong, Q., Er, S. Y., Rash, L. D., King, G. F., et al. (2016). Selective inhibition of ASIC1a confers functional and morphological neuroprotection following traumatic spinal cord injury. *F1000Research*, *5*, 1822. https://doi.org/10.12688/f1000research.9094.2.

Kumar, H., Jo, M. J., Choi, H., Muttigi, M. S., Shon, S., Kim, B. J., et al. (2018). Matrix metalloproteinase-8 inhibition prevents disruption of blood-spinal cord barrier and attenuates inflammation in rat model of spinal cord injury. *Molecular Neurobiology*, *55*(3), 2577–2590. https://doi.org/10.1007/s12035-017-0509-3.

Lee, J. Y., Choi, H. Y., Ahn, H. J., Ju, B. G., & Yune, T. Y. (2014). Matrix metalloproteinase-3 promotes early blood-spinal cord barrier disruption and hemorrhage and impairs long-term neurological recovery after spinal cord injury. *The American Journal of Pathology*, *184*(11), 2985–3000. https://doi.org/10.1016/j.ajpath.2014.07.016.

Lee, J. Y., Choi, H. Y., Park, C. S., Ju, B. G., & Yune, T. Y. (2018). Mithramycin A improves functional recovery by inhibiting BSCB disruption and hemorrhage after spinal cord injury. *Journal of Neurotrauma*, *35*(3), 508–520. https://doi.org/10.1089/neu.2017.5235.

Lee, S. M., Rosen, S., Weinstein, P., van Rooijen, N., & Noble-Haeusslein, L. J. (2011). Prevention of both neutrophil and monocyte recruitment promotes recovery after spinal cord injury. *Journal of Neurotrauma*, *28*(9), 1893–1907. https://doi.org/10.1089/neu.2011.1860.

Li, S., Jiang, Q., & Stys, P. K. (2000). Important role of reverse Na(+)Ca(2+) exchange in spinal cord white matter injury at physiological temperature. *Journal of Neurophysiology*, *84*(2), 1116–1119. https://doi.org/10.1152/jn.2000.84.2.1116.

Liu, S., Sarkar, C., Dinizo, M., Faden, A. I., Koh, E. Y., Lipinski, M. M., et al. (2015). Disrupted autophagy after spinal cord injury is associated with ER stress and neuronal cell death. *Cell Death & Disease*, *6*. https://doi.org/10.1038/cddis.2014.527, e1582.

Liu, H., Shiryaev, S. A., Chernov, A. V., Kim, Y., Shubayev, I., Remacle, A. G., et al. (2012). Immunodominant fragments of myelin basic protein initiate T cell-dependent pain. *Journal of Neuroinflammation*, *9*, 119. https://doi.org/10.1186/1742-2094-9-119.

Lopez-Otin, C., & Overall, C. M. (2002). Protease degradomics: A new challenge for proteomics. *Nature Reviews. Molecular Cell Biology*, *3*(7), 509–519. https://doi.org/10.1038/nrm858.

Lutz, D., Kataria, H., Kleene, R., Loers, G., Chaudhary, H., Guseva, D., et al. (2016). Myelin basic protein cleaves cell adhesion molecule L1 and improves regeneration after injury. *Molecular Neurobiology*, *53*(5), 3360–3376. https://doi.org/10.1007/s12035-015-9277-0.

McKinley, W., Santos, K., Meade, M., & Brooke, K. (2007). Incidence and outcomes of spinal cord injury clinical syndromes. *The Journal of Spinal Cord Medicine*, *30*(3), 215–224. https://doi.org/10.1080/10790268.2007.11753929.

Moon, C., Lee, T. K., Kim, H., Ahn, M., Lee, Y., Kim, M. D., et al. (2008). Immunohistochemical study of cathepsin D in the spinal cords of rats with clip compression injury. *The Journal of Veterinary Medical Science*, *70*(9), 937–941. https://doi.org/10.1292/jvms.70.937.

Murphy, M. P., & LeVine, H., 3rd. (2010). Alzheimer's disease and the amyloid-beta peptide. *Journal of Alzheimer's Disease*, *19*(1), 311–323. https://doi.org/10.3233/JAD-2010-1221.

Myeku, N., Wang, H., & Figueiredo-Pereira, M. E. (2012). cAMP stimulates the ubiquitin/proteasome pathway in rat spinal cord neurons. *Neuroscience Letters*, *527*(2), 126–131. https://doi.org/10.1016/j.neulet.2012.08.051.

Nagase, H., & Woessner, J. F., Jr. (1999). Matrix metalloproteinases. *The Journal of Biological Chemistry*, *274*(31), 21491–21494. https://doi.org/10.1074/jbc.274.31.21491.

Nasser, M., Bejjani, F., Raad, M., Abou-El-Hassan, H., Mantash, S., Nokkari, A., et al. (2016). Traumatic brain injury and blood-brain barrier cross-talk. *CNS & Neurological Disorders Drug Targets*, *15*(9), 1030–1044.

Nazari-Robati, M., Golestani, A., & Asadikaram, G. (2016). Improvement of proteolytic and oxidative stability of chondroitinase ABC I by cosolvents. *International Journal of Biological Macromolecules*, *91*, 812–817. https://doi.org/10.1016/j.ijbiomac.2016.06.030.

Noble, L. J., Donovan, F., Igarashi, T., Goussev, S., & Werb, Z. (2002). Matrix metalloproteinases limit functional recovery after spinal cord injury by modulation of early vascular events. *The Journal of Neuroscience*, *22*(17), 7526–7535. https://doi.org/10.1523/jneurosci.22-17-07526.2002.

Oliveira, K. M., Lavor, M. S., Silva, C. M., Fukushima, F. B., Rosado, I. R., Silva, J. F., et al. (2014). Omegaconotoxin MVIIC attenuates neuronal apoptosis in vitro and improves significant recovery after spinal cord injury in vivo in rats. *International Journal of Clinical and Experimental Pathology*, *7*(7), 3524–3536.

Overall, C. M., & Dean, R. A. (2006). Degradomics: Systems biology of the protease web. Pleiotropic roles of MMPs in cancer. *Cancer Metastasis Reviews*, *25*(1), 69–75. https://doi.org/10.1007/s10555-006-7890-0.

Papa, L., Rosenthal, K., Silvestri, F., Axley, J. C., Kelly, J. M., & Lewis, S. B. (2018). Evaluation of alpha-II-spectrin breakdown products as potential biomarkers for early recognition and severity of aneurysmal subarachnoid hemorrhage. *Scientific Reports*, *8*(1). https://doi.org/10.1038/s41598-018-31631-y.

Park, J., Lim, E., Back, S., Na, H., Park, Y., & Sun, K. (2009). Nerve regeneration following spinal cord injury using matrix metalloproteinase-sensitive, hyaluronic acid-based biomimetic hydrogel scaffold containing brain-derived neurotrophic factor. *Journal of Biomedical Materials Research Part A*, *9999A*. https://doi.org/10.1002/jbm.a.32519.

Plantier, V., & Brocard, F. (2017). Calpain as a new therapeutic target for treating spasticity after a spinal cord injury. *Medical Science*, *33*(6–7), 629–636. https://doi.org/10.1051/medsci/20173306020.

Radulovic, M., Yoon, H., Wu, J., Mustafa, K., Fehlings, M. G., & Scarisbrick, I. A. (2015). Genetic targeting of protease activated receptor 2 reduces inflammatory astrogliosis and improves recovery of function after spinal cord injury. *Neurobiology of Disease*, *83*, 75–89. https://doi.org/10.1016/j.nbd.2015.08.021.

Rawlings, N. D., Barrett, A. J., & Finn, R. (2016). Twenty years of the MEROPS database of proteolytic enzymes, their substrates and inhibitors. *Nucleic Acids Research*, *44*, D343–D350. https://doi.org/10.1093/nar/gkv1118.

Sakurai, M., Ayukawa, K., Setsuie, R., Nishikawa, K., Hara, Y., Ohashi, H., et al. (2006). Ubiquitin C-terminal hydrolase L1 regulates the morphology of neural progenitor cells and modulates their differentiation. *Journal of Cell Science*, *119*(Pt. 1), 162–171. https://doi.org/10.1242/jcs.02716.

Savickas, S., & Keller, U. A. D. (2017). Targeted degradomics in protein terminomics and protease substrate discovery. *Biological Chemistry*. https://doi.org/10.1515/hsz-2017-0187.

Seeds, N., Mikesell, S., Vest, R., Bugge, T., Schaller, K., & Minor, K. (2011). Plasminogen activator promotes recovery following spinal cord injury. *Cellular and Molecular Neurobiology*, *31*(6), 961–967. https://doi.org/10.1007/s10571-011-9701-6.

Sharma, H. S., Muresanu, D. F., Lafuente, J. V., Sjoquist, P. O., Patnaik, R., & Sharma, A. (2015). Nanoparticles exacerbate both ubiquitin and heat shock protein expressions in spinal cord injury: Neuroprotective effects of the proteasome inhibitor carfilzomib and the antioxidant compound H-290/51. *Molecular Neurobiology*, *52*(2), 882–898. https://doi.org/10.1007/s12035-015-9297-9.

Squair, J. W., DeVeau, K. M., Harman, K. A., Poormasjedi-Meibod, M. S., Hayes, B., Liu, J., et al. (2018). Spinal cord injury causes systolic dysfunction and cardiomyocyte atrophy. *Journal of Neurotrauma*, *35*(3), 424–434. https://doi.org/10.1089/neu.2017.4984.

Supinski, G. S., Wang, W., & Callahan, L. A. (2009). Caspase and calpain activation both contribute to sepsis-induced diaphragmatic weakness. *Journal of Applied Physiology*, *107*(5), 1389–1396. https://doi.org/10.1152/japplphysiol.00341.2009.

Tator, C. H., & Fehlings, M. G. (1991). Review of the secondary injury theory of acute spinal cord trauma with emphasis on vascular mechanisms. *Journal of Neurosurgery*, *75*(1), 15–26. https://doi.org/10.3171/jns.1991.75.1.0015.

Terayama, R., Bando, Y., Murakami, K., Kato, K., Kishibe, M., & Yoshida, S. (2007). Neuropsin promotes oligodendrocyte death, demyelination and axonal degeneration after spinal cord injury. *Neuroscience*, *148*(1), 175–187. https://doi.org/10.1016/j.neuroscience.2007.05.037.

Veeravalli, K. K., Dasari, V. R., & Rao, J. S. (2012). Regulation of proteases after spinal cord injury. *Journal of Neurotrauma*, *29*(13), 2251–2262. https://doi.org/10.1089/neu.2012.2460.

Veeravalli, K. K., Dasari, V. R., Tsung, A. J., Dinh, D. H., Gujrati, M., Fassett, D., et al. (2009). Human umbilical cord blood stem cells upregulate matrix metalloproteinase-2 in rats after spinal cord injury. *Neurobiology of Disease*, *36*(1), 200–212. https://doi.org/10.1016/j.nbd.2009.07.012.

Wells, J. E., Rice, T. K., Nuttall, R. K., Edwards, D. R., Zekki, H., Rivest, S., et al. (2003). An adverse role for matrix metalloproteinase 12 after spinal cord injury in mice. *The Journal of Neuroscience*, *23*(31), 10107–10115. https://doi.org/10.1523/jneurosci.23-31-10107.2003.

Xiong, Y., Rabchevsky, A. G., & Hall, E. D. (2007). Role of peroxynitrite in secondary oxidative damage after spinal cord injury. *Journal of Neurochemistry*, *100*(3), 639–649.

Yang, Z., Bramlett, H. M., Moghieb, A., Yu, D., Wang, P., Lin, F., et al. (2018). Temporal profile and severity correlation of a panel of rat spinal cord injury protein biomarkers. *Molecular Neurobiology*, *55*(3), 2174–2184. https://doi.org/10.1007/s12035-017-0424-7.

Yermolaieva, O., Leonard, A. S., Schnizler, M. K., Abboud, F. M., & Welsh, M. J. (2004). Extracellular acidosis increases neuronal cell calcium by activating acid-sensing ion channel 1a. *Proceedings of the National Academy of Sciences of the United States of America*, *101*(17), 6752–6757. https://doi.org/10.1073/pnas.0308636100.

Yoon, H., Radulovic, M., Wu, J., Blaber, S. I., Blaber, M., Fehlings, M. G., et al. (2013). Kallikrein 6 signals through PAR1 and PAR2 to promote neuron injury and exacerbate glutamate neurotoxicity. *Journal of Neurochemistry*, *127*(2), 283–298. https://doi.org/10.1111/jnc.12293.

Yu, F., Kamada, H., Niizuma, K., Endo, H., & Chan, P. H. (2008). Induction of MMP-9 expression and endothelial injury by oxidative stress after spinal cord injury. *Journal of Neurotrauma*, *25*(3), 184–195. https://doi.org/10.1089/neu.2007.0438.

Zhang, D., Tang, Q., Zheng, G., Wang, C., Zhou, Y., Wu, Y., et al. (2017). Metformin ameliorates BSCB disruption by inhibiting neutrophil infiltration and MMP-9 expression but not direct TJ proteins expression regulation. *Journal of Cellular and Molecular Medicine*, *21*(12), 3322–3336. https://doi.org/10.1111/jcmm.13235.

Zhou, M., Xu, W., Liao, G., Bi, X., & Baudry, M. (2009). Neuroprotection against neonatal hypoxia/ischemia-induced cerebral cell death by prevention of calpain-mediated mGluR1alpha truncation. *Experimental Neurology*, *218*, 75–82. https://doi.org/10.1016/j.expneurol.2009.04.006.

Zhu, B., Li, Y., Li, M., Yang, X., Qiu, B., Gao, Q., et al. (2013). Dynamic proteome analysis of spinal cord injury after ischemia reperfusion in rabbits by two-dimensional difference gel electrophoresis. *Spinal Cord*, *51*(8), 610–615. https://doi.org/10.1038/sc.2013.24.

Zou, J., Wang, Y. X., Mu, H. J., Xiang, J., Wu, W., Zhang, B., et al. (2011). Down-regulation of glutamine synthetase enhances migration of rat astrocytes after in vitro injury. *Neurochemistry International*, *58*(3), 404–413. https://doi.org/10.1016/j.neuint.2010.12.018.

Chapter 12

Proteomics of pressure ulcers in spinal cord injury

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List of abbreviations

IMS	imaging mass spectrometry
LC-MS/MS	liquid chromatography tandem mass spectrometry
MS	mass spectrometry
PTMs	post-translational modifications
PBS	phosphate buffered saline
PUs	pressure ulcers
SCI	spinal cord injury
SRM	selected reaction monitoring
TMT	tandem mass tags
WB	Western blot

Background

Spinal cord injury (SCI) is the result of trauma at any level of the spinal cord causing temporary or permanent damage, with a significant effect on the patient's physical and psychosocial well-being (Van Middendorp, Goss, Urquhart, et al., 2011). SCI is related to considerable healthcare costs, morbi-mortality, especially when it reaches advanced stages. The most common medical classification to characterize SCI is the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) to classify subjects using the ASIA Impairment Scale (AIS) and the neurological level of SCI. ISNCSCI categorizes injuries by severity into complete (patient without sacral preservation; defined as ASIA A), and incomplete (patients with sensorimotor sacral preservation) injuries, which is further subdivided into different degrees of involvement (B, C, D, and E) (Schuld et al., 2016). Currently, there is no treatment available for SCI once it is established, and rehabilitation is the only therapy for functional improvement. The life-changing consequences, along with the high social cost and the lack of treatment options, make the study of SCI and its adjacent pathologies an important scientific and medical objective (Alizadeh, Dyck, & Karimi-Abdolrezaee, 2019).

Even with advances in healthcare, pressure ulcers (PUs) remain a more common complication in patients with SCI. PU formation is a complex process, and its incidence significantly grows with time post-injury (Charlifue, Jha, & Lammertse, 2010; Chen, DeVivo, & Jackson, 2005). Pressure ulcers are defined as lesions on any skin surface that result from localized shear and/or compression for a prolonged period over bony prominences at certain anatomic locations (Black, Baharestani, Cuddigan, et al., 2007). This occurrence leads to ischemia of overlying soft tissues, which can finally result in necrosis (Bogie, Nuseibeh, & Bader, 1995). Frequently, severe PUs do not respond to traditional wound therapy and surgery is required to avoid further tissue damage (Bhattacharya & Mishra, 2015). These limitations in the therapeutic strategies used for PUs highlight the urgent need for new treatments for this grave public health problem.

While enormous efforts have been expended to better understand the main risk factors for PUs and to improve prevention, the course of these lesions hampers an accurate and individualized evaluation (Martin-Rojas et al., 2020). Accordingly, new tools are desirable to further our knowledge on the cellular/molecular subjacent mechanisms of PU development (Baldan-Martin et al., 2020).

Cellular, Molecular, Physiological, and Behavioral Aspects of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822427-4.00012-5

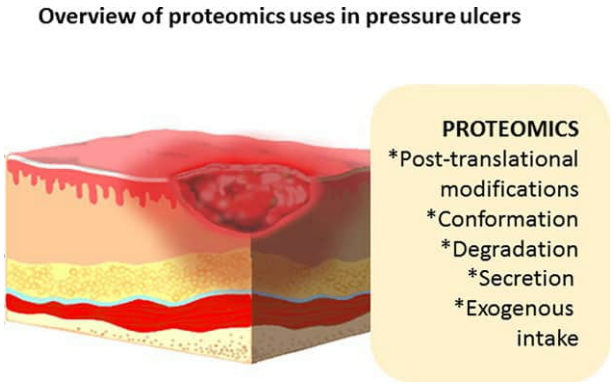


FIG. 1 Overview of proteomics uses: Proteomics gives an insight into the estate of a system, as affected by stimulus. In the case of pressure ulcers in spinal cord injury patients, researchers hope to observe the effect of these pressure ulcers on the types and quantities of proteins.

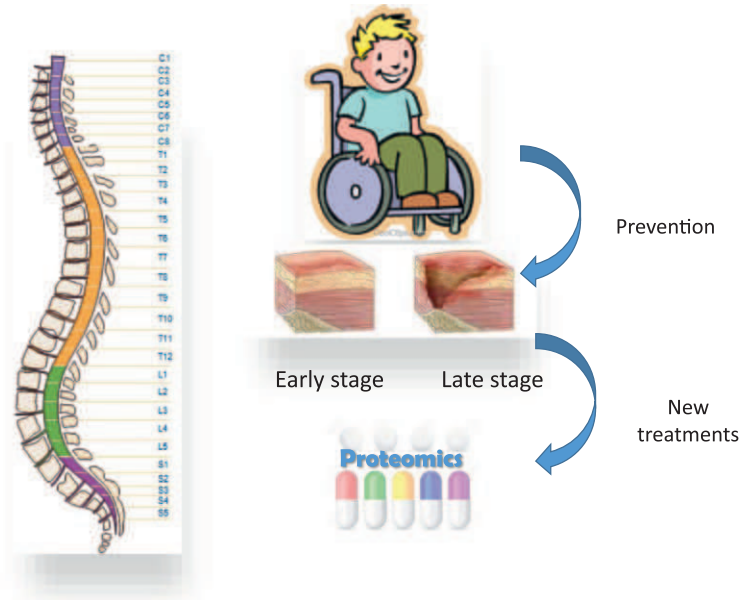
Proteomics technologies offer considerable chances to identify significant changes in protein abundance (Pandey et al., 2015) during the progression of PU formation in an unbiased manner. Improvements in proteomics technology allow the molecular determinants of complex samples like tissue to be analyzed using mass spectrometry (MS) (Marshall & Williams, 2002). The use of these methods can permit the identification of important biological processes that are altered in PU and may enable the discovery of new therapeutic options to improve clinical management of these patients (Fig. 1).

Patient's management

PUs are complex and chronic wounds in patients with SCI and no gold standard has yet been established for their prevention and treatment. PUs are difficult to prevent and manage and can lead to a decline in the overall well-being of patients in SCI (Dwivedi et al., 2017) (Fig. 2).

Chronic wounds place the person with SCI at high risk of infections, sepsis, and death. Skin health and disruption is individual and multifactorial, thus prevention requires personalized education direct to patient predilections and objectives (Rosin, Tabibi, Trimbath, & Henzel, 2020). Assessment requires a correct description of wound-type/PUs stage, location, size, wound bed, wound margin, epithelialization, exudate, and peri-wound condition (Canadian Agency for Drugs and Technologies in Health, 2013). PUs should be staged using the National Pressure Injury Advisory Panel (NPIAP) staging system. Successful treatment requires optimal wound bed preparation, pressure off-loading, and access to surgical specialists if needed (Medical Advisory Secretariat. Pressure ulcer prevention, 2009). People with spinal cord injury, due

FIG. 2 Pressure ulcers are a more common complication in patients with SCI: The use of proteomics can permit the identification of important biological processes that are altered in PU and may enable the discovery of new therapeutic options to improve clinical management of these patients.



to impaired mobility, are most vulnerable to PUs. Furthermore, and taking into account the Canadian Agency for Drugs and Technologies in Health guides, conditions such as poor nutrition, poor sensation, urinary and fecal incontinence, and poor overall physical and mental health are predisposing factors to PU formation.

Prevalence of PUs is considered as an indicator of quality for long-term care facilities, and develop of PUs in hospitalized patients is often considered an unnecessary complication defining failure of inpatient management. Normally, higher prevalence is reported for the elderly, the acutely ill, and those who have sustained SCI (O'Meara, Cullum, Majid, & Sheldon, 2000).

Exits several paths that may be employed in PU wound care: (i) reduction or elimination of underlying contributing conditions such as modifying support surfaces and providing nutritional support; (ii) provision of local wound care, including but not limited to wound dressing and topical applications to promote healing; (iii) surgical repair of the ulcer, where appropriate (Jaul, 2010).

The main objective of therapy in most cases consists of complete healing with the restoration of functional integrity of skin to the highest extent possible. Sometimes the goal of therapy may be palliative for certain patients such as the terminally ill, focusing on reducing discomfort, and/or deterioration of the PU (Evans, Andrews, Chutka, Fleming, & Garness, 1995). In any case, dressing a specific PU wound care could help protect PU contamination and improve the quality of life of these kinds of patients. A wide variety of dressings are available; including many with various combinations of properties such as wound bed preparation (debridement), antimicrobial activity, and moisture control (Lachenbruch, Ribble, Emmons, & Van Gilder, 2016).

Clinical proteomics

Clinical proteomics is based on the application of proteomics technologies to diagnosis, prognosis, treatment, and course of human diseases (Dominguez, Lopes, & Torres, 2007). It is predicted that the 20,300 protein-coding genes enclosed in the human genome are responsible for more than 1 million different protein isoforms derived by DNA recombination, alternative splicing, and diverse post-translational modifications (PTMs) that vary across time and location, and are impacted by different kinds of perturbations (Chambers, Lawrie, Cash, & Murray, 2000; Hooff et al., 2011; Legrain et al., 2011). These isoforms and PTMs are detectable only by studying the proteins directly and can be indicative of specific protein functions.

The proteomics strategy is somehow "blind" at the discovery phase. This means that no key target is pre-selected, all the protein found in the discovery phase are investigated as a whole (Fig. 3). In this way, not only particular pathways or

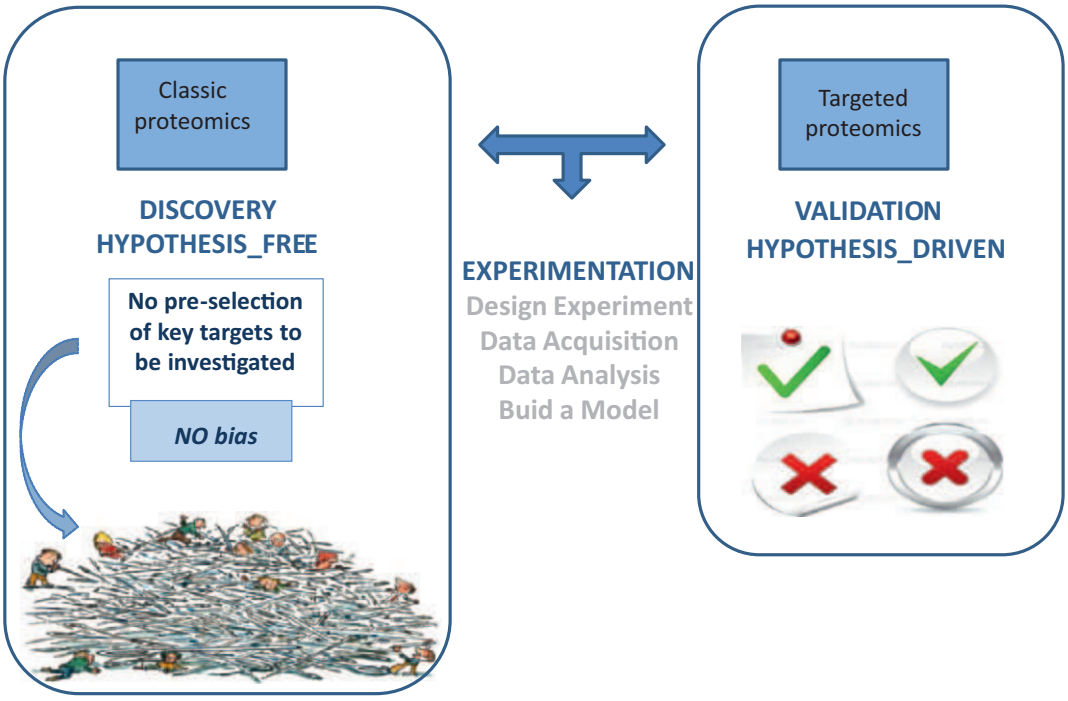


FIG. 3 The proteomics strategy: In the discovery phase, no potential marker, no key target is pre-selected, but all the protein sets are investigated as a whole. In the validation phase, the discovery phase makes all sense, confirming previous results in wider cohorts and setting valid conclusions for the clinical practice.

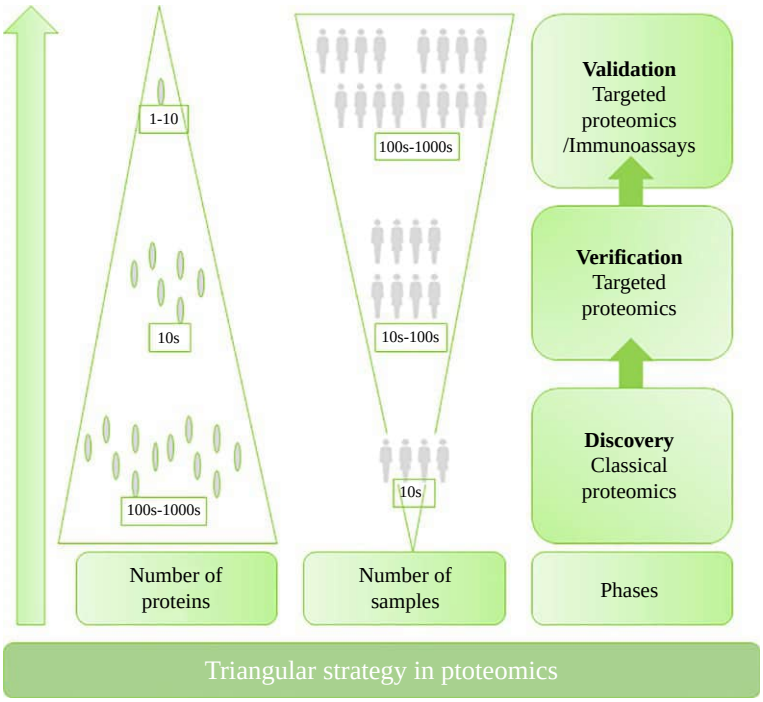


FIG. 4 The inverted triangle strategy: The inverted triangle strategy is a very visual concept to easily understand the phases that make up a clinical proteomics study. In the discovery phase, we start with an "n" of very small subjects, dozens, and we will have a very high number of identified proteins. In the verification phase and with an independent cohort of patients, the "n" will be increased to hundreds. In this case, dozens of proteins could be verified. Finally, in the validation phase, the "n" will be of several miles of subjects, and we could validate 1 to 10 proteins as pathology markers.

responding molecules commonly measured in routine biochemical patient's analysis are being investigated but also those whose relationship with the pathophysiological processes taking place are still unknown.

The action for identifying new decisive biomarkers of disease is based on three steps: (1) discovery, where the differential expression of specific proteins between states is defined; (2) verification, where hundreds of patients with environmental, genetic, and biological differences are analyzed; and (3) validation, where the discovery phase makes all the sense and it is then when candidate makers are further investigated, confirming previous results in wider cohorts and setting valid conclusions for the clinical practice (Paulovich et al., 2008. Rifai, Gillette, & Carr, 2006) (Fig. 4).

Proteomics in pressure ulcers

Since the growth development of mass spectrometry (MS) during the past 20 years, proteomics has become a powerful tool in biomedical research (Lindsey, Mayr, Gomes, Delles, et al., 2015). Proteomics has enabled the measurement of multiple properties of thousands of proteins, including their abundance, subcellular localization, post-translational modifications, and interactions (Wilhelm et al., 2014). While traditional molecular biology methods detect a limited number of proteins based on signaling or metabolic pathways, proteomics has become a systematic approach to qualitative and quantitative localization of entire proteomes in large-scale research (Yates, Ruse, & Nakorchevsky, 2009). In the area of traumatology, proteomics for comparing protein expression profiles between normal and disease states has seldom been applied to obtain unique protein-expression profiles of PUs, let alone deep tissues. Furthermore, recent advances in proteomic approaches have allowed the study of proteins to understand pathophysiological mechanisms in SCI disease and PUs (Albayar et al., 2019; Baldan-Martin et al., 2020; Liu, Cui, Hu, & Zhang, 2020; Martin-Rojas et al., 2020). Nevertheless, the search for biomarkers for clinical implementation by high-throughput proteomics requires multiple stages, from shotgun to targeted approaches, and nowadays, there is a lack of clinically useful protein biomarkers due to sample optimization and technological limitation not only in PUs but also in other diseases. Despite this, proteome analysis is currently helping to better understand and define the pathophysiology of PUs, contributing to the clinical needs of treatment of PUs in SCI patients (Baldan-Martin et al., 2020).

A recent investigation by Baldan-Martin et al. (2020) performed tissue proteomics from PUs obtained from SCI patients. They identified a total of 4504 proteins, of which 76 were differentially expressed in cases from controls using TMT-based multiplexed isobaric labeling followed by LC-MS/MS (Fig. 5). According to the molecular function, it was remarkable that a substantial number of proteins were implicated in enzyme regulator activity, including peptidase regulator or lipase inhibitor activity categories.

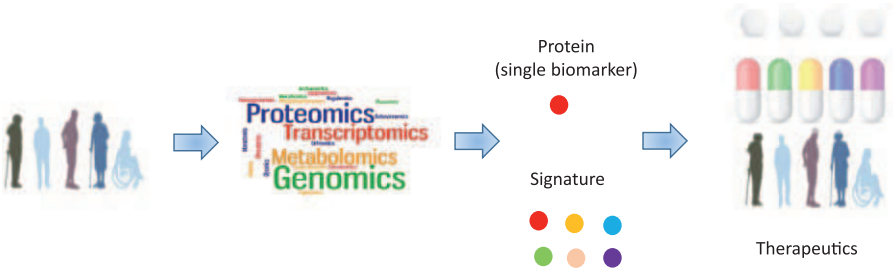


FIG. 5 Precision medicine is fundamentally changing the way therapies are being developed. Personalized medicine is directed toward personalized treatment. Patients are different and so their treatment. Personalized medicine aims to give the right treatment to the right patients. For example, make subgroups of patients to try to identify those who are more likely to benefit from a specific treatment, identify those who may suffer side effects, etc.

Following the analysis of tissue samples, another study performed in the muscle of patients with PUs (Liu et al., 2018) identified 2558 proteins, 520 of which were identified with differential expression between samples from patients with deep PU and normal muscle tissues by iTRAQ LC-MS/MS, particularly, JAK2 was downregulated. These results demonstrated that JAK2 may play an important protective role in muscular ischemia and reperfusion injury during DTI development by inhibition of autophagy and apoptosis through the AKT and ERK1/2 pathways. Furthermore, Liu et al. (2020), using ITRAQ LC-MS/MS, found a number of proteins that were differentially expressed in PU muscle samples compared with the normal and identified unique proteins expression patterns between these two groups. Importantly, cathepsin B and D were identified, which indicated that they might be key drug targets for PUs.

Another proteomics technique, imaging mass spectrometry (IMS), was employed for the analysis of frozen skin biopsies to investigate the differences between stage IV pressure ulcers that remain stalled, stagnant, and unhealed versus those exhibiting clinical and histological signs of improvement. Taverna, Pollins, Sindona, Caprioli, and Nanney (2015) revealed a rich diversity of proteins that are dynamically modulated, and they selectively highlight a family of calcium-binding proteins (S-100 molecules) including calcyclin (S100-A6), calgranulins A (S100-A8) and B (S100-A9), and calgizzarin (S100-A11). IMS allowed defining three discrete regions of interest: the wound bed, adjacent dermis, and hypertrophic epidermis. The discovery-based approach with IMS augments current knowledge of the molecular signatures within PUs while providing a rationale for a focused examination of the role of calcium modulators within the context of impaired wound healing.

All in all, integration of biomarker information coming from several proteomic strategies is still a challenge. Nonetheless, once we get an integrative approach we will be able to develop a "multimarker" approach which may achieve higher sensitivity and specificity to therapy which, probably, would be more appropriate than a single marker for complex conditions such as Pus (Table 1).

The importance of precision medicine

The objectives of clinical practice, both in PUs from patients with SCI and in other diseases, have always been addressed to the patients, to aid from pain, to treat the disease, and to help prevent illness from occurring. Normally, reductionism in medicine presupposes that patients with common signs and symptoms share the same disease pathophenotype and will respond similarly to medical interventions tested in groups of similar subjects (Leopold & Loscalzo, 2018).

Contrarily, precision medicine is dedicated to selecting the proper treatment for each patient according to their personal pathophenotype. Consequently, precision medicine combines standard clinical evaluation, including synthesis of data, imaging, or laboratory tests, with different -omics approaches such as genomics, transcriptomics, proteomics, or metabolomics, for deep phenotyping (Antman & Loscalzo, 2016; Lee et al., 2012) (Fig. 6). Defining the phenotype before disease onset may help risk stratification, which are procedures used for risk assessment that regulate individuals based on the probability of developing a specific outcome. Identifying distinct risk phenotypes would allow the screening in patients with high risk, or avoid gratuitous treatments with corresponding side effects. Precision medicine, in the treatment of patients, aims to select the best therapy for each individual, considering that different groups of patients may respond differently to the same drug in terms of dose, length, or side effects (Garmaroudi et al., 2016; Manrai et al., 2016).

It is hoped that the application of precision medicine in PUs generally, but in SCI patients, principally, will improve patient management by promoting adequate prevention and treatment options, which should reduce the number of surgeries as well as the economic costs (Fuster, 2014; Mirnezami, Nicholson, & Darzi, 2012). Indeed, PUs in SCI patients is a perfect candidate for precision medicine.

TABLE 1 Compilation of studies reported so far in the field of proteomics in pressure ulcers.

Most relevant proteins (validated)	Abbreviation	Methodology	Reference
ANTITHROMBIN III	ANT3	TMT-LC/MS-MS	Baldan-Martin et al. (2020)
ALPHA-A-ANTITRYPSIN	A1AT	TMT-LC/MS-MS	Baldan-Martin et al. (2020)
KININOGEN-1	KNG1	TMT-LC/MS-MS	Baldan-Martin et al. (2020)
ALPHA-2-MACROGLOBULIN	A2MG	TMT-LC/MS-MS	Baldan-Martin et al. (2020)
FIBRONECTIN	FINC	TMT-LC/MS-MS	Baldan-Martin et al. (2020)
APOLIPROTEIN AI	APOA1	TMT-LC/MS-MS	Baldan-Martin et al. (2020)
COLLAGEN ALPHA-1 (XII) CHAIN	COCA	TMT-LC/MS-MS	Baldan-Martin et al. (2020)
HAPTOGLOBIN	HPT	TMT-LC/MS-MS	Baldan-Martin et al. (2020)
APOLIPROTEIN B-100	APOB	TMT-LC/MS-MS	Baldan-Martin et al. (2020)
COMPLEMENT FACTOR B	CFAB	TMT-LC/MS-MS	Baldan-Martin et al. (2020)
CATHEPSIN B	CTSB	iTRAQ LC/MS-MS	Liu et al. (2020)
CATHEPSIN D	CTSD	iTRAQ LC/MS-MS	Liu et al. (2020)
JANUS KINASE 2	JAK2	iTRAQ LC/MS-MS	Liu et al. (2018)
CALGRANULINS A	S100A8	IMAGING-MS	Taverna et al. (2015)
CALGRANULINS B	S100A9	IMAGING-MS	Taverna et al. (2015)
CALCICYN	S100A6	IMAGING-MS	Taverna et al. (2015)
CALGIZZARIN	S100A11	IMAGING-MS	Taverna et al. (2015)

Limitations of proteomics

Despite the progressively realized power of proteomics, several problems exist for the above-mentioned methods. In MS, the cost of equipment is a determinant, and separation and ionization techniques may affect findings. To overcome this, proteomics can be used to discover novel proteins, and orthogonal techniques such as SRM or immunoassays are used to quantitate larger sample sets even in platforms capable of absolute quantification (Jiang, Zhang, Yu, et al., 2014). Although all platforms provide insights into relative protein regulation, absolute quantification is only possible in MS and, in a proximity extension assay, these assays require the use of labeled standards that may not be feasible in untargeted experiments (Jarchum, 2016; Pan, Aebersold, Chen, et al., 2009; Van de Merbel, 2019).

It is also important to consider the sample source when designing experiments. Although peripheral blood sera samples are readily collected, the blood proteome may be influenced by a large number of systemic issues that may or may not be related to the system of interest. Proteomics conducted on tissue samples, although more difficult to obtain, may better reflect the proteome of the system of interest.

Conclusions

The study of PUs through proteomic approach, and the subsequent integration of data, can provide molecular-level information of the molecular pathways that are more active in that tissue. The characterization of physiological proteins in this tissue and the creation of a complete database with the results from the descriptive studies may serve as a reference material for further studies. This makes it easier the search for new therapeutic options by supplementation, which may enhance the physiological response of wound healing.

Application to other areas of neuroscience

- Great efforts have been made in recent years to understand the mechanisms leading to the development of different neurological diseases.
- Proteomics techniques are widely applied in most areas of biology and medicine.

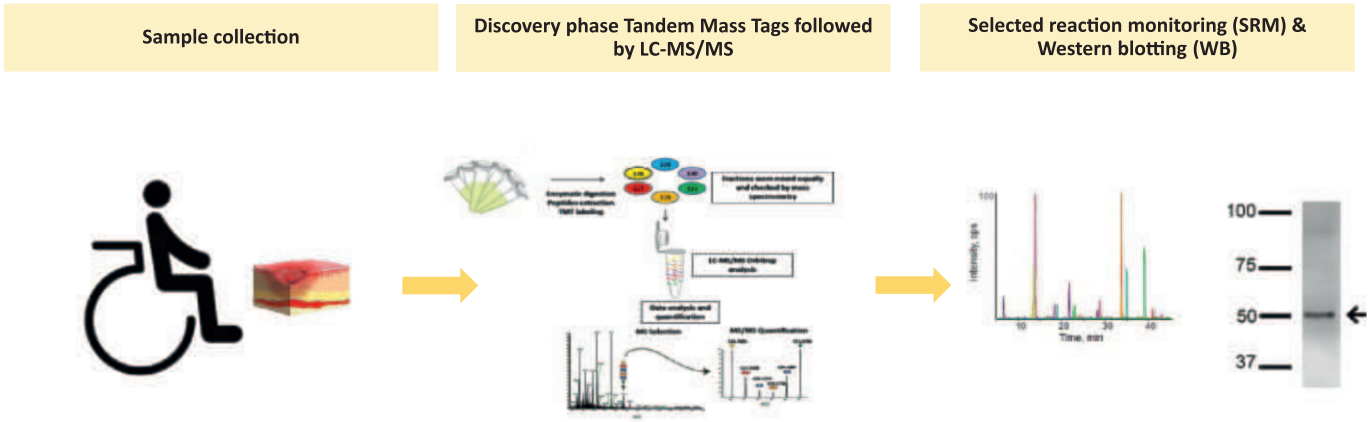


FIG. 6 Schematic representation of proteomics analysis in PUs of SCI patients. (A) Samples collection. Tissue samples were collected from subjects with SCI who were scheduled for PU surgery. (B) Discovery phase using Tandem Mass Tags (TMT) labeling followed by liquid chromatography tandem mass spectrometry (LC-MS/MS). TMT are isobaric chemical tags that provide multiplexing capabilities for relative quantitative proteomics analysis. This ability to perform concurrent MS analysis of multiple samples increases throughput and enables relative quantitation of up to 16 different samples derived from cells, tissues, or biological fluids. The tags consist of an MS/MS reporter group, a spacer arm, and an amine-reactive group. The amine-reactive group binds to the N-terminus of a peptide or to a lysine residue during labeling. In relative quantitation experiments, different isobaric tags are used to label different systemic conditions. Once labeled, all samples are mixed and analyzed in a single liquid chromatography-mass spectrometry (LC-MS) experiment. Because the isobaric tags possess the same chemical properties, all peptides from different TMT-labeled samples co-elute during LC separation. Once the peptides enter the mass spectrometer, they are detected simultaneously as a single and indistinguishable precursor ion peak. (C) Verification phase employing two orthogonal techniques, selected reaction monitoring (SRM) and western blotting (WB). SRM is a method used in tandem mass spectrometry in which an ion of a particular mass is selected in the first stage of a tandem mass spectrometer and an ion product of a fragmentation reaction of the precursor ion is selected in the second mass spectrometer stage for detection. Using a WB, researchers are able to identify specific proteins from a complex mixture of proteins extracted from cells. The technique uses three elements to accomplish this task: (1) separation by size, (2) transfer to a solid support, and (3) marking target protein using proper primary and secondary antibodies to visualize.

- The powerful "omic" technologies (mass spectrometry (MS)-based proteomics, focusing on the analysis of whole proteomes, protein-based interactions, and post-translational modifications) have provided an important amount of results in different diseases including neurological diseases.
- Complexity of the nervous system at the molecular level remains one of the central challenges in neuroscience.
- Proteomic tools offer a new platform for studies of complex biological functions involving large numbers and networks of proteins. Intracellular networks of proteins perform key functions in neurons and glia.
- Proteomics has applications in neurology and neurosciences, for example, studying neurotoxicology, neuroendocrinology, neuropsychiatric, neurodegenerative disorders, neurometabolism among others.
- Proteomics studies the determination of specific proteomic aspects of individual brain areas and body fluids in neurodegeneration too.
- The identification of new protein patterns involved in the pathogenesis of this kind of disease may lead to better treatment and new therapeutic interventions.
- In this innovative chapter, we explained how proteomics could have utility in therapy by supplementation, which may enhance the physiological response of neurological diseases.
- Although numerous challenges still exist, proteomics approach will increase the understanding of pathological mechanisms involved in different areas of neurosciences.

Key facts of proteomics in PUs of spinal cord patients

- Proteomics technologies offer considerable chances to identify significant changes in protein abundance during the progression of PU formation in an unbiased manner.
- Proteomics technologies allow the molecular determinants of complex samples like tissue obtained of PUs to be analyzed using mass spectrometry.
- Proteomics methods can permit the identification of important biological processes that are altered in PU.
- Proteomics may enable the discovery of new therapeutic options to improve clinical management of these kinds of patients.
- Proteomics helps to identify distinct risk phenotypes which would allow the screening in patients with high risk or to avoid gratuitous treatments with corresponding side effects.

Mini-dictionary of terms

- Spinal cord injury (SCI) is the result of trauma at any level of the spinal cord causing temporary or permanent damage, with a significant effect on the patient's physical and psychosocial well-being.
- International Standards for Neurological Classification of Spinal Cord Injury is the most common medical classification to characterize SCI.
- Pressure ulcers are defined as lesions on any skin surface that result from localized shear and/or compression for a prolonged period over bony prominences at certain anatomic locations.
- Proteomics is the large-scale study of proteomes. Proteomics can provide significant biological information for many biological problems.
- Proteome is a set of proteins produced in an organism, system, or biological context. The proteome is not constant; it differs from cell to cell and changes over time.
- MS proteomic methods provide important information by identifying many proteins and detecting post-translational modifications.
- Liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) is an analytical chemistry technique that combines the physical separation capabilities of liquid chromatography (or HPLC) with the mass analysis capabilities of mass spectrometry (MS).
- Selected reaction monitoring (SRM) is a method used in tandem mass spectrometry in which an ion of a particular mass is selected in the first stage of a tandem mass spectrometer and an ion product of a fragmentation reaction of the precursor ion is selected in the second mass spectrometer stage for detection.
- iTRAQ LC-MS/MS isobaric tags for relative and absolute quantitation (iTRAQ) is an isobaric labeling method used in quantitative proteomics by tandem mass spectrometry to determine the amount of proteins from different sources in a single experiment (Gafken & Lampe, 2006; Ross et al., 2004; Zieske, 2006). It uses stable isotope-labeled molecules that can be covalent bonded to the N-terminus and side chain amines of proteins.
- TMT-based, multiplexed isobaric labeling followed by LC-MS/MS. The Thermo Scientific Tandem Mass Tag Reagents are designed to enable identification and quantitation of proteins in different samples using tandem mass

spectrometry (MS). All mass tagging reagents within a set have the same nominal mass (i.e., are isobaric) and a chemical structure composed of an amine-reactive NHS ester group, a spacer arm (mass normalizer), and a mass reporter.

- Precision medicine is an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person.

Summary points

- Proteomic study of tissue, cells, and/or biological fluids will transform the diagnostic methods currently used in medicine.
- Advancements in proteomics allow researchers to measure a multitude of proteins simultaneously with excellent sensitivity and selectivity to detect low abundance proteins.
- This chapter focuses on the identification of important biological processes that are altered in pressure ulcers.
- These identifications of proteins may enable the discovery of new therapeutic options to improve clinical management of patients with spinal cord injury.
- A deeper understanding of the pathophysiology of disease would allow us to develop a precision medicine based on each patient, optimizing the effectiveness of pharmacological treatments.

Acknowledgments and sources of funding

This work was supported by grants from the Instituto de Salud Carlos III (PI14/01917, PI18/00995). Sociedad Española de Cardiología para la Investigación Básica 2017. Grant PRB3 (IPT17/0019—ISCIII-SGEFI/ERDF).

References

Albayar, A. A., Roche, A., Swiatkowski, P., Antar, S., Ouda, N., Emara, E., et al. (2019). Biomarkers in spinal cord injury: Prognostic insights and future potentials. *Frontiers in Neurology*, *10*, 27. Jan 29.

Alizadeh, A., Dyck, S. M., & Karimi-Abdolrezaee, S. (2019). Traumatic spinal cord injury: An overview of pathophysiology, models and acute injury mechanisms. *Frontiers in Neurology*, *10*, 282.

Antman, E. M., & Loscalzo, J. (2016). Precision medicine in cardiology. *Nature Reviews. Cardiology*, *13*(10), 591–602.

Baldan-Martin, M., Martin-Rojas, T., Corbacho-Alonso, N., Lopez, J. A., Sastre-Oliva, T., Gil-Dones, F., et al. (2020). Comprehensive proteomic profiling of pressure ulcers in patients with spinal cord injury identifies a specific protein pattern of pathology. *Advances in Wound Care (New Rochelle)*, *9*(5), 277–294. May 1.

Bhattacharya, S., & Mishra, R. K. (2015). Pressure ulcers: Current understanding and newer modalities of treatment. *Indian Journal of Plastic Surgery*, *48* (1), 4–16.

Black, J., Baharestani, M. M., Cuddigan, J., et al. (2007). National Pressure Ulcer Advisory Panel's updated pressure ulcer staging system. *Advances in Skin & Wound Care*, *20*(5), 269–274.

Bogie, K. M., Nuseibeh, I., & Bader, D. L. (1995). Early progressive changes in tissue viability in the seated spinal cord injured subject. *Paraplegia*, *33*, 141.

Canadian Agency for Drugs and Technologies in Health. (2013). *Dressing materials for the treatment of pressure ulcers in patients in long-term care facilities: A review of the comparative clinical effectiveness and guidelines*. Ottawa, ON: Canadian Agency for Drugs and Technologies in Health. [Internet]. Nov 18.

Chambers, G., Lawrie, L., Cash, P., & Murray, G. I. (2000). Proteomics: A new approach to the study of disease. *The Journal of Pathology*, *192*(3), 280–288. Nov.

Charlifue, S., Jha, A., & Lammertse, D. (2010). Aging with spinal cord injury. *Physical Medicine and Rehabilitation Clinics of North America*, *21*(2), 383–402.

Chen, Y., DeVivo, M. J., & Jackson, A. B. (2005). Pressure ulcer prevalence in people with spinal cord injury: Age-period-duration effects. *Archives of Physical Medicine and Rehabilitation*, *86*(6), 1208–1213.

Dominguez, D. C., Lopes, R., & Torres, M. L. (2007). Proteomics: Clinical applications. *Clinical Laboratory Science*, *20*(4), 245–248.

Dwivedi, M. K., Bhagat, A. K., Srivastava, R. N., Jain, A., Baghel, K., & Raj, S. (2017). Expression of MMP-8 inpressure injuries in spinal cord injury patients managed by negative pressure wound therapyor conventional wound care: A randomized controlled trial. *Journal of Wound, Ostomy, and Continence Nursing*, *44*, 343–349.

Evans, J. M., Andrews, K. L., Chutka, D. S., Fleming, K. C., & Garness, S. L. (1995). Pressure ulcers: Prevention and management. *Mayo Clinic Proceedings*, *70*(8), 789–799. Aug.

Fuster, V. (2014). A first dilemma in cardiovascular medicine: Adherence versus personalized therapy. *Journal of the American College of Cardiology*, *64* (10), 1059–1060.

Gafken, P. R., & Lampe, P. D. (2006). Methodologies for characterizing phosphoproteins by mass spectrometry. *Cell Communication & Adhesion*, *13*(5–6), 249–262.

Garmaroudi, F. S., et al. (2016). Systems pharmacology and rational polypharmacy: Nitric oxide-cyclic GMP signaling pathway as an illustrative example and derivation of the general case. *PLoS Computational Biology*, *12*(3), e1004822.

Hooff, G. P., van Huizen, N. A., Meesters, R. J., Zijlstra, E. E., Abdelraheem, M., Abdelraheem, W., et al. (2011). Analytical investigations of toxic p-phenylenediamine (PPD) levels in clinical urine samples with special focus on MALDI-MS/MS. *PLoS One*, *6*(8), e22191.

Jarchum, I. (2016). Proteomics: Proteome quantification compared. *Nature Methods*, *13*, 972.

Jaul, E. (2010). Assessment and management of pressure ulcers in the elderly: Current strategies. *Drugs & Aging*, *27*(4), 311–325. Apr 1.

Jiang, H., Zhang, L., Yu, Y., et al. (2014). A pilot study of angiogenin in heart failure with preserved ejection fraction: A novel potential biomarker for diagnosis and prognosis? *Journal of Cellular and Molecular Medicine*, *18*, 2189–2197.

Lachenbruch, C., Ribble, D., Emmons, K., & Van Gilder, C. (2016). Pressure ulcer risk in the incontinent patient: Analysis of incontinence and hospital-acquired pressure ulcers from the International Pressure Ulcer Prevalence™ Survey. *Journal of Wound, Ostomy, and Continence Nursing*, *43*(3), 235–241. May-Jun.

Lee, M.-S., et al. (2012). Personalized medicine in cardiovascular diseases. *Korean Circulation Journal*, *42*(9), 583–585.

Legrain, P., et al. (2011). The human proteome project: Current state and future direction. *Molecular & Cellular Proteomics*, *10*(7), M111.009993.

Leopold, J. A., & Loscalzo, J. (2018). Emerging role of precision medicine in cardiovascular disease. *Circulation Research*, *122*(9), 1302–1315.

Lindsey, M. L., Mayr, M., Gomes, A. V., Delles, C., et al. (2015). Transformative impact of proteomics on cardiovascular health and disease: A scientific statement from the American Heart Association. *Circulation*, *132*(9), 852–872.

Liu, Z., Cui, X., Hu, Y., & Zhang, P. (2020). Quantitative iTRAQ LC-MS/MS reveals muscular proteome profiles of deep pressure ulcers. *Bioscience Reports*, *40*(6). Jun 26. BSR20200563.

Liu, Z., Ren, L., Cui, X., Guo, L., Jiang, B., Zhou, J., et al. (2018). Muscular proteomic profiling of deep pressure ulcers reveals myoprotective role of JAK2 in ischemia and reperfusion injury. *American Journal of Translational Research*, *10*(11), 3413–3429. Nov 15.

Manrai, A. K., et al. (2016). Genetic misdiagnoses and the potential for health disparities. *The New England Journal of Medicine*, *375*(7), 655–665.

Marshall, T., & Williams, K. M. (2002). Proteomics and its impact upon biomedical science. *British Journal of Biomedical Science*, *59*(1), 47–64.

Martin-Rojas, T., Sastre-Oliva, T., Esclarín-Ruz, A., Gil-Dones, F., Mourino-Alvarez, L., Corbacho-Alonso, N., et al. (2020). Effects of growth hormone treatment and rehabilitation in incomplete chronic traumatic spinal cord injury: Insight from proteome analysis. *Journal of Personalized Medicine*, *10*(4), 183.

Medical Advisory Secretariat. (2009). Pressure ulcer prevention: An evidence-based analysis. *Ontario Health Technology Assessment Series*, *9*(2), 1–104.

Mirnezami, R., Nicholson, J., & Darzi, A. (2012). Preparing for precision medicine. *The New England Journal of Medicine*, *366*(6), 489–491.

O'Meara, S., Cullum, N., Majid, M., & Sheldon, T. (2000). Systematic reviews of wound care management: Antimicrobial agents for chronic wounds; diabetic foot ulceration. *Health Technology Assessment*, *4*(21), 1–237.

Pan, S., Aebersold, R., Chen, R., et al. (2009). Mass spectrometry based targeted protein quantification: Methods and applications. *Journal of Proteome Research*, *8*, 787–797.

Pandey, A., Garg, S., Khunger, M., Darden, D., Ayers, C., Kumbhani, D. J., et al. (2015). Dose-response relationship between physical activity and risk of heart failure: A meta-analysis. *Circulation*, *132*(19), 1786–1794. 10.

Paulovich, A. G., et al. (2008). The interface between biomarker discovery and clinical validation: The tar pit of the protein biomarker pipeline. *Proteomics. Clinical Applications*, *2*(10 – 11), 1386–1402.

Rifai, N., Gillette, M. A., & Carr, S. A. (2006). Protein biomarker discovery and validation: The long and uncertain path to clinical utility. *Nature Biotechnology*, *24*(8), 971–983.

Rosin, N. R., Tabibi, R. S., Trimbath, J. D., & Henzel, M. K. (2020). A primary care provider's guide to prevention and management of pressure injury and skin breakdown in people with spinal cord injury. *Topics in Spinal Cord Injury Rehabilitation*, *26*(3), 177–185. Summer.

Ross, P. L., Huang, Y. N., Marchese, J. N., Williamson, B., Parker, K., Hattan, S., et al. (2004). Multiplexed protein quantitation in *Saccharomyces cerevisiae* using amine-reactive isobaric tagging reagents. *Molecular & Cellular Proteomics*, *3*(12), 1154–1169.

Schuld, C., Franz, S., Brüggemann, K., Heutehaus, L., Weidner, N., Kirshblum, S. C., et al. (2016). International standards for neurological classification of spinal cord injury: Impact of the revised worksheet (revision 02/13) on classification performance. *The Journal of Spinal Cord Medicine*, *39*, 504–512.

Taverna, D., Pollins, A. C., Sindona, G., Caprioli, R. M., & Nanney, L. B. (2015). Imaging mass spectrometry for assessing cutaneous wound healing: Analysis of pressure ulcers. *Journal of Proteome Research*, *14*(2), 986–996. Feb 6.

Van de Merbel, N. C. (2019). Protein quantification by LC–MS: A decade of progress through the pages of bioanalysis. *Bioanalysis*, *11*, 629–644.

Van Middendorp, J. J., Goss, B., Urquhart, S., et al. (2011). Diagnosis and prognosis of traumatic spinal cord injury. *Global Spine Journal*, *1*(1), 1–8.

Wilhelm, M., Schlegl, J., Hahne, H., Gholami, A. M., Lieberenz, M., Savitski, M. M., et al. (2014). Mass-spectrometry-based draft of the human proteome. *Nature*, *509*, 582–587.

Yates, J. R., Ruse, C. I., & Nakorchevsky, A. (2009). Proteomics by mass spectrometry: Approaches, advances, and applications. *Annual Review of Biomedical Engineering*, *11*, 49–79.

Zieske, L. R. (2006). A perspective on the use of iTRAQ reagent technology for protein complex and profiling studies. *Journal of Experimental Botany*, *57*(7), 1501–1508.

Chapter 13

Innate immune responses of glia and inflammatory cells in spinal cord injury

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Abbreviations

AQP4	aquaporin-4
ASC	apoptosis-associated speck-like protein containing a CARD
ATP	adenosine triphosphate
bFGF	basic fibroblast growth factor
CARD	caspase activation and recruitment domain
CLR	C-type lectin receptor
CNS	central nervous system
CpG-ODN	cytosine-phosphate-guanine oligodeoxynucleotides
CSPG	chondroitin sulfate proteoglycan
DAMP	danger-associated molecular pattern
ECM	extracellular matrix
HA	hyaluronan
HMGB1	high-mobility group box 1
HSP	heat shock protein
IL	interleukin
Mincle	macrophage-inducible C-type lectin
NLR	NOD-like receptor
NLRP	NLR with pyrin domain
NLRC	NLR with CARD
NOD	nucleotide-binding oligomerization domain
ODN	oligodeoxynucleotides
OPC	oligodendrocyte progenitor cell
P2X7	P2X purinoreceptor 7
PAMP	pathogen-associated molecular pattern
Panx1	pannexin 1
PRR	pattern recognition receptor
RLR	retinoic acid-inducible gene 1 (RIG-1)-like receptor
ROS	reactive oxygen species
SC	spinal cord
SCI	spinal cord injury
TGF-β	transforming growth factor-beta
TIR	toll/interleukin-1 receptor
TLR	toll-like receptor
TnC	tenascin-C
TnR	tenascin-R

* Equal contribution.

Cellular, Molecular, Physiological, and Behavioral Aspects of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822427-4.00013-7

Introduction

The central nervous system (CNS) was historically considered an immune-privileged organ. However, this concept has changed as compelling evidence demonstrates that CNS infections and injuries as well as neurodegenerative diseases provoke innate immune responses in the brain and spinal cord (SC). Signals derived from infectious agents, pathogenic proteins in neurodegenerative diseases, and danger signals released by stressed and damaged cells following neural injuries activate innate immunity in the CNS via engagement of pattern recognition receptors (PRRs) (Russo & McGavern, 2015). Both neurons and glia express PRRs. Stimulation of PRR signaling in resident CNS cells leads to neuroinflammation, with beneficial and detrimental outcomes that are context-, CNS region-, cell type-, PRR-, and ligand-dependent. Microglia and astrocytes are the principal innate immune cells of the CNS. However, PRRs in neurons and oligodendrocytes mediate non-immune functions and contribute to the overall functional outcomes.

During traumatic spinal cord injury (SCI), a cascade of deleterious mechanisms follows the initial mechanical damage and inflicts secondary injury to the adjacent spared tissue. SCI elicits microglial activation and astrocyte reactivity at the lesion site and in regions remote from the injury epicenter (Pallottie et al., 2018). Activated/reactive glia play both protective and detrimental roles that are context-dependent. Glial activation encompasses morphological, molecular and functional changes, increased proliferation and migration to the affected site, and altered gene expression (Sofroniew, 2015). Stimulation of PRR signaling in activated microglia and reactive astrocytes leads to cytokine and chemokine release, which initiates neuroinflammation and promotes chemotaxis of immune cells to the injury site. The breaching of the blood-spinal cord barrier and the release of interleukin 1β (IL-1β) by activated microglia and reactive astrocytes enhances vascular permeability and the extravasation of immune cells (Fahey & Doyle, 2019). Reactive astrocytes foster the formation of a glial scar around the lesion (Burda & Sofroniew, 2014). The glial scar limits secondary tissue damage by confining toxic molecules released by damaged cells to the lesion site, and by restricting the infiltration of immune cells. The glial scar is also considered as an impediment to axonal regeneration. The heterogeneity and phenotypic plasticity of astrocytes and microglia, as well as the crosstalk between these glial subtypes influence neuroinflammation and neural dysfunction (Liddelow, Marsh, & Stevens, 2020).

Monocytes and neutrophils are the first cells that infiltrate the lesion site followed by macrophages and T-lymphocytes (Stirling & Yong, 2008). Neutrophils have also been implicated in secondary tissue loss in SCI (Anwar, Al Shehabi, & Eid, 2016). However, following SCI, depletion of neutrophils impairs the wound-healing response of astrocytes, reduces white matter sparing and axonal preservation, and impairs functional recovery. This suggests that neutrophils could help recovery and repair. Neutrophils and macrophages express PRRs (Thomas & Schroder, 2013). It is highly probable that activation of PRRs on these cells contributes to the neuroinflammatory response in SCI.

Toll-like receptors (TLRs), nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), retinoic acid-inducible gene 1 (RIG-1)-like receptors (RLRs), and the C-type lectin receptors (CLRs) are among the PRR families (Takeuchi & Akira, 2010). This chapter will provide a brief overview of the major PRRs expressed in the CNS. As TLRs are the first identified and best-characterized PRRs, their role in SCI will be discussed.

Overview of PRRs

PRRs are highly conserved among species and recognize molecules derived from pathogens, collectively called pathogen-associated molecular patterns (PAMPs). PRRs are also activated by endogenous ligands released by damaged or dead cells, namely, danger-associated molecular patterns (DAMPs) (Amarante-Mendes et al., 2018). The PAMPs that activate PRRs, include bacterial lipopolysaccharides, lipoproteins and lipopeptides, flagellin, single-or double-stranded RNA, unmethylated CpG DNA, and zymosan. DAMPs include high-mobility group box 1 (HMGB1), adenosine triphosphate (ATP), heat shock proteins (HSPs), mitochondrial DNA, histones, interleukin 1α (IL-1α), IL-33, amyloid β, uric acid, crystallin, and extracellular matrix (ECM) components such as hyaluronic acid, fibronectin, and fibrinogen.

TLRs

TLRs are the mammalian homologs of Toll receptors, which were first identified in *Drosophila melanogaster*. To date, 10 functional TLRs (TLR1–10) have been identified in humans and 12 TLRs (TLR1–9 and TLR11–13) in the mouse. TLRs 1, 2, 4–6, 11–12 are localized at the cell surface whereas TLRs 3, 7–9, and 13 are intracellular receptors found in endosomal compartments and endoplasmic reticulum (Fig. 1; (Heiman, Pallottie, Heary, & Elkabes, 2014). The initiation of TLR signaling necessitates the formation of either homodimers or heterodimers. TLR2 forms heterodimers with TLR1 or TLR6.

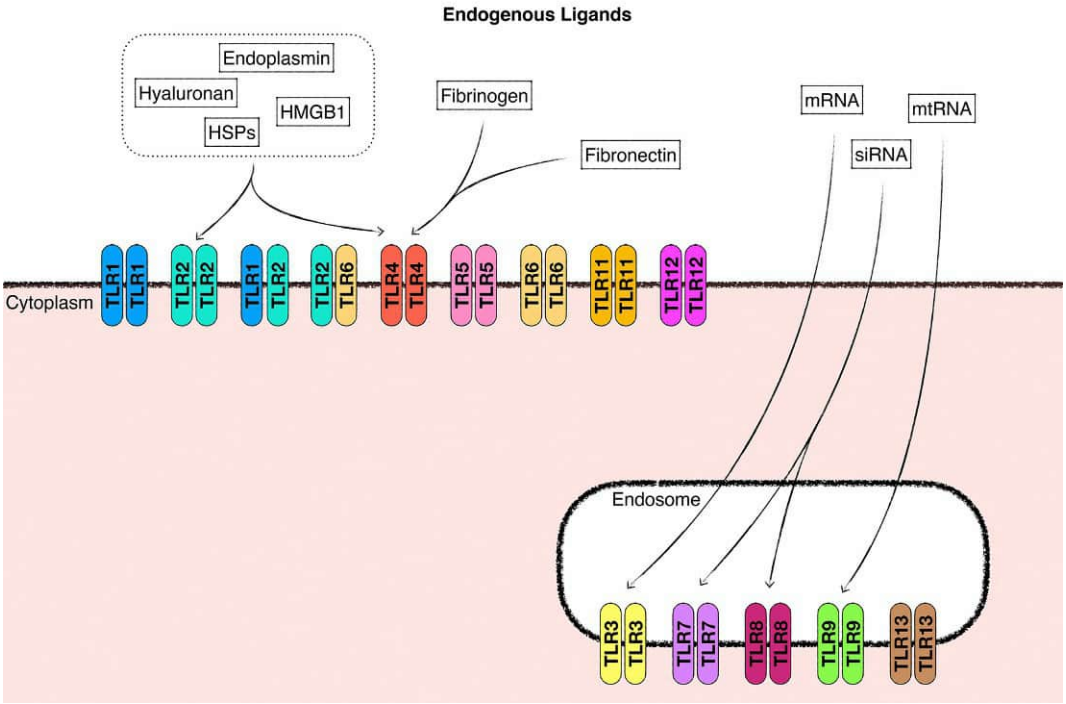

FIG. 1 Cell surface and intracellular Toll-like receptors (TLRs) in the mouse. Toll-like receptors form homodimers or heterodimers. The heterodimers are exemplified by TLR2/TLR1 and TLR2/TLR6. Humans express only TLR1–10. Mice do not express functional TLR10. Examples of endogenous ligands are provided. HSPs, heat shock proteins; HMGB1, high-mobility group box 1.

The type of heterodimer formed influences the response elicited by specific stimuli. Some TLRs also utilize co-receptors. CD14 is one of the best-known co-receptors and it interacts with TLR4.

All TLRs, except TLR3, utilize the MyD88-signaling pathway. TLR3 signals through the Toll/interleukin-1 receptor (TIR)-domain-containing adapter-inducing interferon-β (TRIF)-dependent signaling pathway. TLR4 utilizes both the MyD88-dependent and TRIF-dependent signaling pathways. Activation of TLR signaling leads to the transcription of inflammatory cytokines and type I interferons (Heiman et al., 2014). Synergy and counteractions between different TLRs have been reported (Rosenberger et al., 2014).

NLRs, inflammasome complexes, and TLR-inflammasome cooperation

NOD-like receptors are cytoplasmic PRRs that detect a wide range of PAMPs and DAMPs. Members of the NLR family have a C-terminal leucine-rich repeat (LRR) domain, a central nucleotide-binding oligomerization domain (NACHT), and a variable interaction domain at the amino terminus. The NLR family is divided into various sub-families distinguishable by their N-terminal effector domains. Two NLR families, NLR with pyrin domain (NLRP) and NLR with caspase activation and recruitment domain (CARD) (NLRC), will be further discussed, as they form inflammasomes (Walsh, Muruve, & Power, 2014).

Inflammasomes are cytoplasmic multi-protein complexes that regulate inflammation. The complex contains a cytoplasmic PRR, pro-caspase-1, and an adaptor protein such as apoptosis-associated speck-like protein containing a CARD (ASC), which mediates the interaction between the PRR and pro-caspase-1. In some inflammasome complexes, the PRR and pro-caspase-1 do not require an adaptor protein and interact directly. The assembly of the inflammasome complex leads to the auto-proteolytic cleavage of pro-caspase-1, which results in caspase-1 activation. Active caspase-1 cleaves pro-IL-1β and pro-IL-18 to generate mature IL-1β and IL-18. Upon release, IL-1β initiates neuroinflammation and neuronal death, whereas caspase-1 induces pyroptosis (Walsh et al., 2014). Although inflammasome signaling has been predominantly studied in microglia, neurons, astrocytes, and oligodendrocytes also express the components of inflammasome complexes. NLRP1, NLRP3, and NLRC4 are primarily found in microglia, whereas NLRP2 is mostly localized in astrocytes. Neurons express NLRP1 (Mamik & Power, 2017). NLRP1 forms an inflammasome by interacting directly with pro-caspase-1, and its expression is increased following SCI (de Rivero Vaccari, Lotocki, Marcillo, Dietrich, & Keane, 2008). The NLRP2

inflammasome has been detected in human primary astrocyte cultures and is activated by ATP. The effects of ATP are mediated by the P2X purinoreceptor 7 (P2X7) and the membrane channel pannexin 1 (Panx1). Inhibition of Panx1 and P2X7 attenuates ATP-dependent NLRP2 inflammasome activation. Studies suggest that astrocytic NLRP2 inflammasome is an important component of the inflammatory response following CNS injuries (Minkiewicz, de Rivero Vaccari, & Keane, 2013). The NLRP3 inflammasome is the most widely studied and best-characterized inflammasome. Activation of the NLRP3 inflammasome requires a two-step process. A first signal, e.g., a TLR ligand, primes the cell and enhances pro-IL-1β and NLRP3 expression. Subsequently, a second signal triggers the assembly and activation of the NLRP3 inflammasome complex. Increased K^+ efflux, ATP, and release of reactive oxygen species (ROS) by damaged mitochondria are among the triggers that activate NLRP3 inflammasome (Voet, Srinivasan, Lamkanfi, & van Loo, 2019; Walsh et al., 2014). The cooperation between TLRs and NLRP3 inflammasome is essential for IL-1β production and the initiation of inflammation (Fig. 2). Although the role of the NLRP3 inflammasome in neurodegenerative diseases and CNS infections is well established, its contribution to SCI remains inadequately investigated. NLRP3 expression is increased in neurons, microglia, and astrocytes following SCI. Inhibition of the NLRP3 inflammasome attenuates neuroinflammation, microglial activation, motor neuron death, and tissue damage, and improves recovery of locomotor function in mice with SCI (Jiang, Li, He, Zhou, & Zhu, 2017). NLRC4 has also been implicated in sterile inflammation associated with CNS injury and diseases (Voet et al., 2019). Although DAMPs that activate NLRC4 have not been fully identified, lysophosphatidylcholine, a major component of the low-density protein, induces NLRP4 inflammasome activation in microglia and astrocytes leading to sterile inflammation (Freeman et al., 2017).

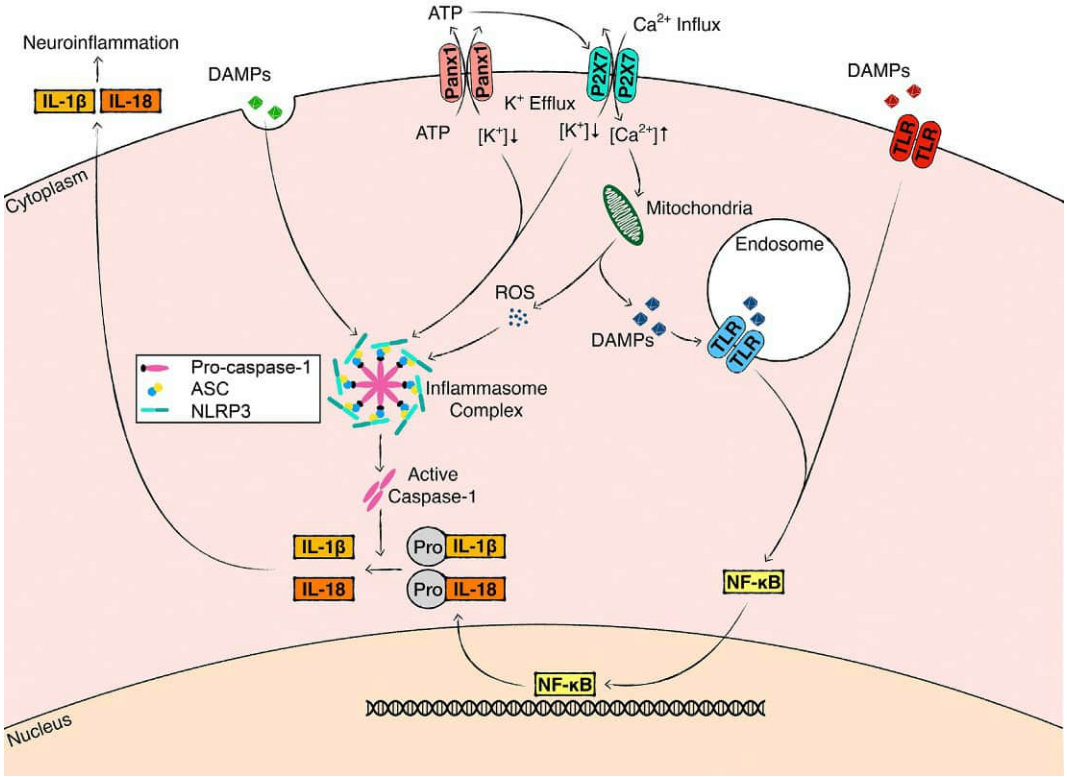

FIG. 2 Cooperation between NLRP3 inflammasome and TLRs in macrophages. Activation of TLR signaling promotes transcription of pro-IL-1β and pro-IL-18. Extracellular ATP, released by damaged cells or through Panx1 channels, activates P2X7 purinergic receptors, and enhances K^+ efflux. The drop in intracellular K^+, ROS released by damaged mitochondria, and other DAMPs initiate the assembly of the inflammasome complex. This is followed by cleavage of pro-caspase-1 and activation of caspase-1. Active caspase-1 cleaves pro-IL-1β and pro-IL-18. Mature IL-1β and IL-18 are released and promote neuroinflammation. ATP, adenosine triphosphate; ASC, apoptosis-associated speck-like protein containing a CARD; DAMPs, danger-associated molecular patterns; NLRP3, nucleotide-binding oligomerization domain-like receptor with pyrin domain; IL, interleukin; P2X7, P2X purinoreceptor 7; Panx1, pannexin 1; ROS, reactive oxygen species.

CLRs and RLRs

C-type lectin receptors are a family of transmembrane and soluble receptors that bind carbohydrates. They trigger multiple intracellular signaling pathways leading to nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)-mediated type I interferon and cytokine production. Dectin-1 is a CLR subtype. Stimulation of dectin-1 in the intact rodent SC promotes macrophage activation, demyelination, and axonal injury. Accordingly, axonal dieback is lower in dectin-1-knockout mice sustaining a SCI compared to injured wild type controls. These negative effects of dectin-1 are alleviated by simultaneous activation of TLR2 (Gensel et al., 2015), suggesting crosstalk between TLR2 and dectin-1. Another CLR, macrophage-inducible C-type lectin (Mincle), is expressed in brain microglia and neurons, and SC neurons (Yang, Dai, Chen, & Cui, 2020). However, in Mincle-deficient mice sustaining a SCI, locomotor recovery and lesion size are not different than in injured wild-type controls (Arumugam et al., 2017). Nevertheless, further studies are needed to determine whether ligand-induced activation of Mincle impacts the outcomes of SCI. Even though synergy between TLRs and Mincle has been reported (van Haren et al., 2016), it is still unknown whether such synergistic interactions occur in SCI.

In the CNS, both neurons and glia express RLRs, which are cytoplasmic receptors that recognize RNA viruses and self-RNA. SCI and stretch injury of cultured astrocytes activate RLR signaling, whereas ligand-induced stimulation of RLRs upregulates markers of reactive astrocytes (de Rivero Vaccari et al., 2012). These studies indicate that RLRs modulate the innate immune response of astrocytes.

It is possible that multiple PRRs are simultaneously activated in SCI. The interactions between different TLRs, the crosstalk between TLRs and other PRRs (Pashenkov, Murugina, Budikhina, & Pinegin, 2019), and the cooperation between innate immune receptor signaling pathways (Vajjhala, Ve, Bentham, Stacey, & Kobe, 2017) likely modulate the inflammatory reaction, glial reactivity, and cell death in SCI.

Role of TLRs in SCI

Even though all TLRs are expressed in the SC, TLR2, TLR4, and TLR9 are the best studied in pre-clinical rodent models of traumatic SCI (Li, Acioglu, Heary, & Elkabes, 2020). The expression of cell surface TLRs and the intracellular TLR7 is increased following SCI (Kigerl et al., 2007). In a mouse model of mid-thoracic SC contusion injury, TLR9 transcript levels progressively increase within 7-days post-injury (dpi) and remain high even at 35 dpi (Fig. 3).

TLR2 in SCI

Initial studies on the roles of TLR2 in SCI were performed on whole body TLR2 knockout mice sustaining a SCI. These investigations revealed that the recovery of gait and motor coordination was impaired in TLR2 knockout mice as compared to wild-type controls (Kigerl et al., 2007). Axonal dieback was also more pronounced in TLR2 knockout mice (Stirling et al., 2014). These findings suggested that TLR2 plays beneficial roles in SCI. In fact, in an ex vivo laser-induced SCI model, stimulation of TLR2 by use of the agonist Pam2CSK4 mitigated axonal dieback and secondary degeneration of axons by promoting the microglial neuroprotective properties (Stirling et al., 2014). The protective role of TLR2 was

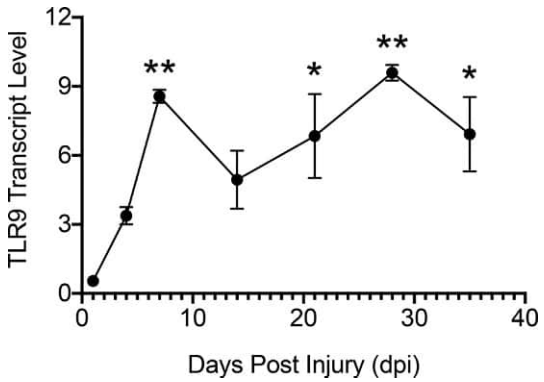

FIG. 3 Expression of Toll-like receptor 9 (TLR9) at the injury epicenter following spinal cord injury in the mouse. TLR9 transcript levels significantly increase by 7 days post-injury (dpi) and remain high until 35 dpi. Significantly different from 1 dpi by one-way ANOVA followed by Tukey's post hoc test, $^{*}P < 0.05$, $^{**}P < 0.01$. Values represent fold increase compared to the housekeeping gene and are presented as mean ± S.E.M. $n = 3$–4 (unpublished data).

further corroborated by the use of another TLR2-specific agonist, Pam3CSK4, in a similar SCI model (Stivers et al., 2017). In a rat model of SC crush injury, intraspinal injection of Pam2CSK4 increased macrophage activation, reduced axonal dieback, and decreased lesion size (Gensel et al., 2015). Since earlier investigations showed that activated macrophages promote axonal dieback (Evans et al., 2014), the simultaneous occurrence of enhanced macrophage reactivity and reduced axonal dieback raised the possibility that the TLR2 agonist attenuates axonal dieback by altering macrophage effector function.

TLR4 in SCI

Early investigations on the contribution of TLR4 to SCI were performed on TLR4-mutant mice that sustained a moderate SC contusion injury. Recovery of locomotor coordination was inferior in the TLR4-mutant mice compared to injured wild-type controls, suggesting that expression of TLR4 supports functional recovery (Kigerl et al., 2007). Increased demyelination and oligodendrocyte loss, reduced oligodendrogenesis, delayed myelin debris clearance, enhanced astrogliosis, and altered regulation of cytokine and growth factor expression were also observed in TLR4-mutant mice following SCI (Church, Kigerl, Lerch, Popovich, & McTigue, 2016; Kigerl et al., 2007). Although intraspinal injection of TLR4 agonists into the intact SC resulted in acute oligodendrocyte loss, this was attributed to the toxicity of activated microglia/macrophages at the injection site. This initial oligodendrocyte loss was followed by proliferation of oligodendrocyte progenitor cells (OPCs) and oligodendrogenesis (Church et al., 2016; Schonberg, Popovich, & McTigue, 2007), supporting the idea that TLR4 signaling can induce repair mechanisms. Studies have also shown that TLR4 positive astrocytes are found in the vicinity of the injury epicenter but not at distant locations or in the intact controls (Nishimura et al., 2013), indicating that astrocytes upregulate TLR4 expression in response to local changes elicited by SCI. It is possible that the endogenous TLR4 ligand HMGB1, which is dramatically increased at the lesion site (Kigerl, Lai, Wallace, Yang, & Popovich, 2018), is one of the triggers that increase astroglial TLR4 expression, as suggested by in vitro investigations (Famakin et al., 2020). In astrocyte cultures, which were maintained under conditions that simulate hypoxic injury, activation of TLR4 by HMGB1 resulted in the upregulation of the water channel Aquaporin-4 (AQP4) and astrocyte swelling. These findings suggest that TLR4 modulates a key mechanism underlying CNS edema (Sun et al., 2017). TLR4 and MyD88 have also been implicated in the necroptosis of reactive astrocytes located around the lesion core following SCI. The expression of TLR4 and MyD88 increased in reactive astrocytes undergoing necroptosis in vivo, and in a model of astrocyte necroptosis in vitro. Inhibition of MyD88-dependent signaling attenuated necroptosis in cultured astrocytes (Fan et al., 2016). The aforementioned findings, taken together, support the notion that TLR4 signaling influences various mechanisms following SCI. Some of these mechanisms foster repair whereas others contribute to secondary injury. However, the net effect of TLR4 signaling in SCI appears to be beneficial.

TLR9 in SCI

In contrast to TLR2 and TLR4, stimulation of TLR9 by the agonist ODN 1826 increases the number of inflammatory cells and the expression of the pro-inflammatory cytokine TNF-α at the injury epicenter following a severe SC contusion injury (David et al., 2013). The agonist also exacerbates bladder dysfunction (unpublished results). Therefore, it was hypothesized that inhibition of TLR9 signaling could positively impact the outcomes of SCI by preventing the activation of TLR9 by endogenous ligands. Indeed, intrathecal administration of a TLR9 antagonist, ODN 2088, to mice sustaining a SCI, decreased inflammatory cell number and the expression of pro-inflammatory mediators at the injury epicenter, reduced proliferation of reactive astrocytes at the glial scar, preserved injured proximal axons, increased the percentage of the anti-inflammatory M2 macrophages, ameliorated tissue sparing, and decreased the levels of chondroitin sulfate proteoglycans (CSPGs), ECM proteins which have been implicated in the inhibition of axonal regeneration (David et al., 2013; David et al., 2014; Li, Ni, Eugenin, Heary, & Elkabes, 2019; Li, Ni, Heary, & Elkabes, 2020). At the functional level, intrathecal treatment with the TLR9 antagonist alleviated urinary retention and pain hypersensitivity but did not improve locomotor function (David et al., 2013, 2014).

In summary, the studies on TLR2, TLR4, and TLR9 indicate that TLR signaling can lead to both beneficial or deleterious effects following SCI depending on the TLR involved and the cell-type engaged (Fig. 4). Some of these effects could be the result of overall changes in the inflammatory milieu, whereas others could be due to alterations in glial and neuronal function via direct activation of TLR signaling in these cells.

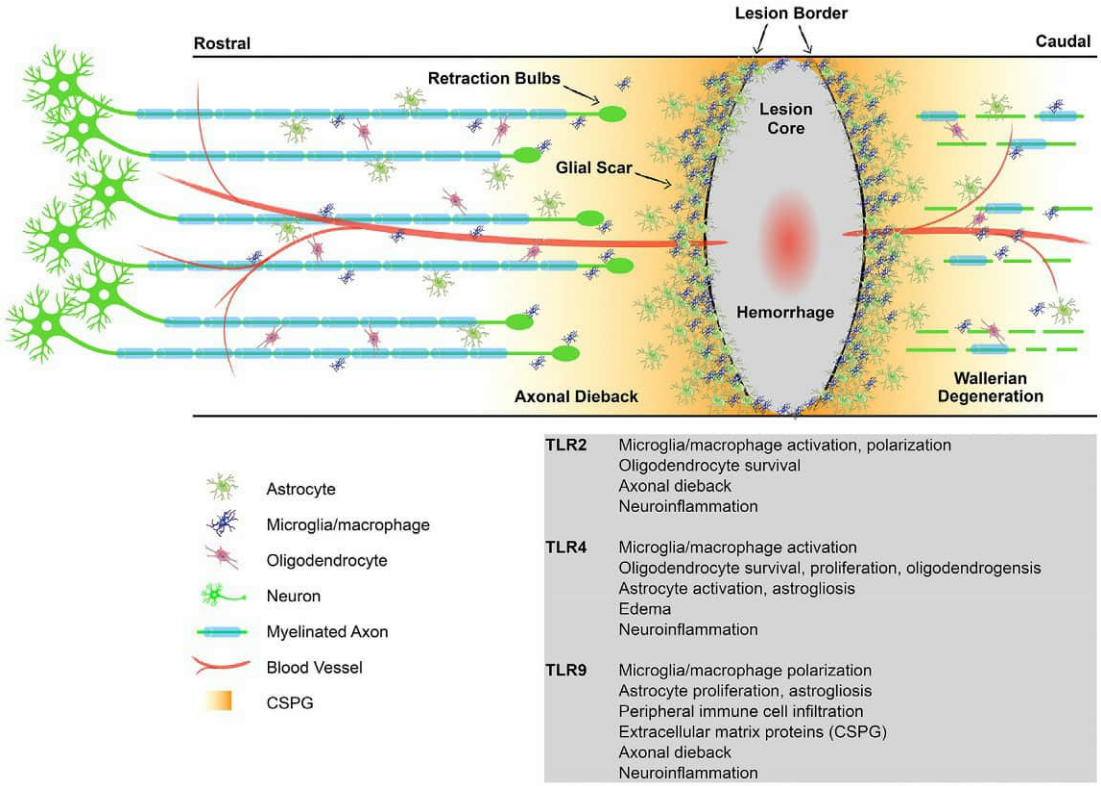

FIG. 4 Role of Toll-like receptors (TLRs) in secondary injury mechanisms following spinal cord injury. Injured proximal axons retract from the injury site (axonal dieback). A glial scar forms around the lesion core. Chondroitin sulfate proteoglycans (CSPGs) increase at the lesion site. The mechanisms influenced by TLR2, TLR4, and TLR9 are listed.

Non-immune functions of TLRs in neurons: Relevance to SCI

Mouse neurons express TLR2–4 and TLR7–9 (Acioglu et al., 2016; Carty & Bowie, 2011; Liu et al., 2013; Ma et al., 2006). This raises the possibility that TLRs exert non-immune functions in the CNS. In fact, neuronal TLR signaling modulates neurite outgrowth and neuronal survival, in vitro, processes that have relevance to SCI as well as CNS development. TLR3 and TLR8 are highly expressed in growth cones. Agonist-elicited activation of TLR3 and TLR8 causes growth cone collapse and irreversible inhibition of neurite outgrowth, followed by neuronal apoptosis in vitro (Cameron et al., 2007; Liu et al., 2013; Ma et al., 2006). It is plausible that inhibition of neuronal TLR3 and TLR8 signaling facilitates axonal regrowth or sprouting following SCI, a possibility that has not been investigated. Interestingly, neuronal TLR9 antagonism protects against excitotoxic death, in vitro, through the modulation of the endoplasmic reticulum stress response (Acioglu et al., 2016). Moreover, TLR2- and TLR4-deficiency renders neurons more resistant to death provoked by energy deprivation, suggesting that TLR2 and TLR4 increase the vulnerability of neurons to insults. Even though TLR2 and TLR4 agonists play an overall positive role in SCI by fostering microglia/macrophage-mediated neuroprotection, it is conceivable that they also induce neuronal death through direct effects on these cells (Fig. 5). These reparative versus neurodegenerative effects of TLR2 and TLR4 signaling could occur in parallel. This possibility has not been addressed and warrants further investigations.

Modulation of ECM proteins by TLRs: Relevance to SCI

The ECM regulates cell proliferation, survival, migration, and differentiation (Bonnans, Chou, & Werb, 2014). In the adult CNS, the ECM is primarily composed of hyaluronan (HA), sulfated proteoglycans, which include CSPGs, and Tenascin-R (TnR) (Haggerty, Marlow, & Oudega, 2017). However, after SCI, the molecular composition of the ECM is altered. Hyaluronan is degraded, CSPG expression is increased, and de novo synthesis of Tenascin-C (TnC) is induced (Yang et al., 2020). These changes influence both injury and repair mechanisms. Reactive astrocytes are an abundant source of CSPGs. In CNS pathologies, CSPGs modulate inflammation by acting on immune cells and by binding cytokines and chemokines

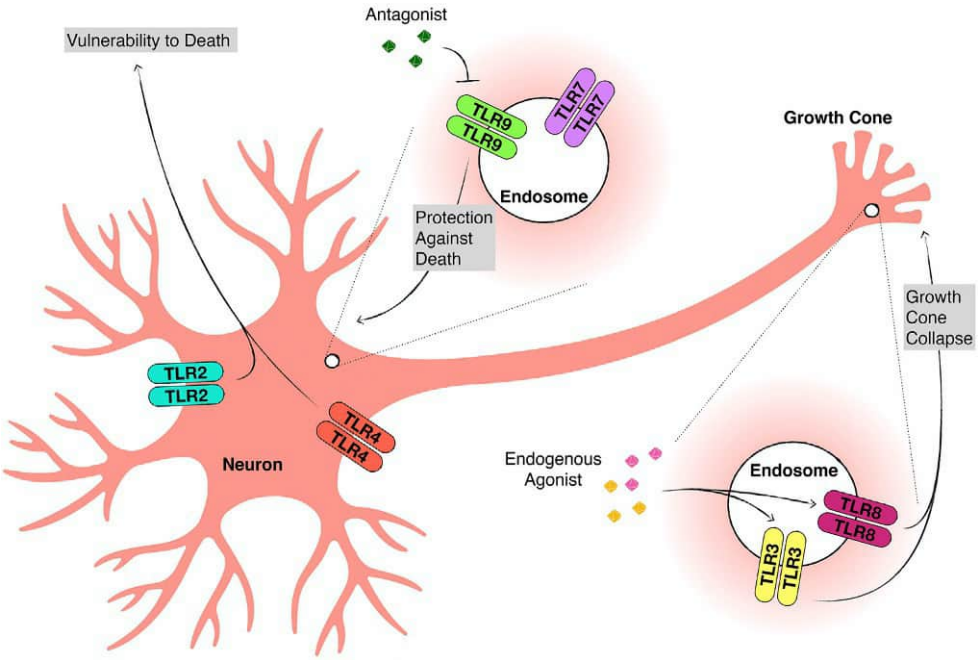

FIG. 5 Non-immune functions of neuronal Toll-like receptors (TLRs). Activation of neuronal TLR2 and TLR4 signaling has been associated with neuronal death whereas inhibition of TLR9 increases the resistance of spinal cord neurons to excitotoxic death. In addition, TLR3 accumulates in growth cones and causes growth cone collapse, whereas activation of TLR8 inhibits neurite outgrowth, in vitro.

(Stephenson & Yong, 2018). CSPGs inhibit axonal regeneration by excessive adhesion and immobilization of regenerating axons (Yang et al., 2020). Elimination of CSPGs at the glial scar promotes axonal regeneration and functional recovery following SCI (Bradbury et al., 2002). As indicated above, the TLR9 antagonist reduces CSPG levels at the glial scar following SCI (Li et al., 2019).

Tenascin-C is expressed during CNS development but is downregulated in adulthood (Wiese, Karus, & Faissner, 2012). However, after SCI, there is de novo synthesis of TnC around the lesion site (Zhang, Winterbottom, Schachner, Lieberman, & Anderson, 1997). TnC-deficient mice exhibit poor axonal regrowth and sprouting, and impaired locomotor recovery following SCI, suggesting that TnC facilitates axonal regeneration (Chen et al., 2010). Astrocyte TnC expression is increased by TGF-β and bFGF (Smith & Hale, 1997). Both growth factors are robustly upregulated at the injury epicenter following SCI (Smith & Strunz, 2005). Interestingly, TLR9 antagonism in astrocytes regulates the TGF-β and bFGF-elicited increase in TnC expression in an opposite manner (Fig. 6). The antagonist suppresses TGF-β-elicited increase

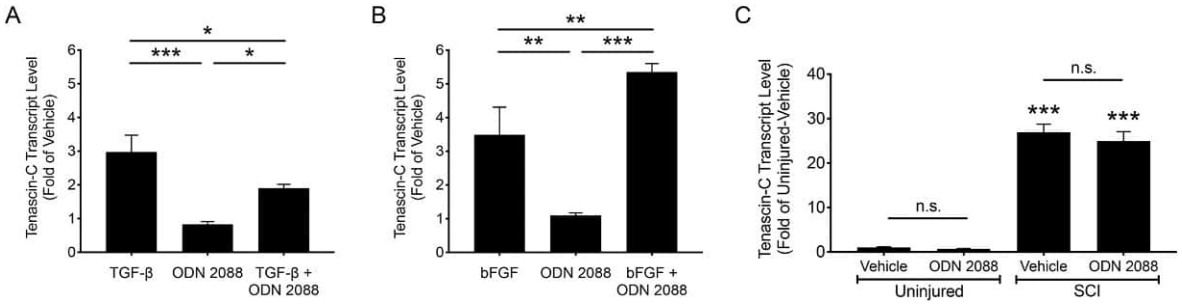

FIG. 6 Effects of a TLR9 antagonist on Tenascin (TnC) expression in spinal cord astrocytes, in vitro, and at the lesion site following spinal cord injury (SCI). (A) TnC transcript levels are increased in Transforming growth factor-beta (TGF-β)-treated spinal cord astrocytes, in vitro. The TLR9 antagonist, ODN 2088, inhibits the TGF-β-elicited increase. (B) TnC transcript levels are increased when astrocytes are treated with basic fibroblast growth factor (bFGF). TLR9 antagonism enhances the increase elicited by bFGF. (C) TnC levels are significantly increased at the lesion site following SCI. Intrathecal ODN 2088 treatment does not alter the increase in TnC expression. It is likely, that in vivo, ODN 2088 exerts opposite effects on TnC expression, depending on the stimuli that induce an increase, as indicated by the studies shown in A and B. The net outcome could be unaltered TnC expression at the injury site. The graphs in A and B show the mean of three independent experiments ± S.E.M. The graph in C shows a representative experiment with $n = 4$/group. Significantly different by one-way ANOVA followed by Tukey's post-hoc test $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$. n.s. = not significant. The figure shows previously unpublished data.

in TnC transcript levels, whereas it enhances the bFGF-elicited increase in TnC expression, in vitro (Fig. 6A and B). Therefore, it is not surprising that ODN 2088 does not alter SCI-induced increase in TnC transcript levels in mice, since this could be the net outcome of such opposite effects (Fig. 6C).

Applications to other areas of neuroscience

TLRs have been implicated in a broad range of CNS pathologies (Li, Acioglu, et al., 2020) including injury, epilepsy, Alzheimer's disease, Parkinson's disease, multiple sclerosis, and neuropathic pain (Deerhake, Biswas, Barclay, & Shinohara, 2019; Gesuete, Kohama, & Stenzel-Poore, 2014; Gross et al., 2017; Kouli, Horne, & Williams-Gray, 2019; Momtazmanesh, Perry, & Rezaei, 2020; Shi, Hua, Kong, Stein, & Hua, 2019). In the majority of these pathological conditions, TLRs have been investigated in the context of neuroinflammation and glial activation. Although in each of these disorders, the affected brain or spinal cord regions and the neuronal sub-populations are distinct, and the stimuli that activate TLRs are different, there could be commonalities in the way that TLRs drive the innate immune reaction. Therefore, deciphering the cellular and molecular mechanisms underlying TLR-dependent innate immunity in SCI could provide insights into events that lead to sterile inflammation in neurodegenerative diseases and other pathologies.

TLRs also modulate neural progenitor cell proliferation, cell differentiation, and neurite outgrowth (Okun et al., 2012). These processes are important for CNS development. Therefore, aberrant TLR function could play a role in developmental disorders of the CNS. The impairment of sensory-motor function in TLR9 knockout mice (Khariv et al., 2013) and the alterations in learning and memory in TLR4 deficient mice (Okun et al., 2012) highlight the importance of TLRs in development.

Conclusions

The studies described above, collectively show that TLRs modulate the functional and histopathological outcomes of SCI. However, further investigations are needed to elucidate the complex cellular and molecular mechanisms underlying the effects of TLRs in SCI. This is an important, yet challenging question to address in vivo, given the fact that neurons and all glial subtypes express TLRs. The net outcome of activating or inhibiting a TLR in the injured SC is likely to reflect the combination of responses mounted by various cell types. In addition, the crosstalk among different TLRs and the interactions between TLRs and other PRRs further compound this complexity. The simultaneous use of in vitro and in vivo approaches, and the generation of mice with cell-type-specific TLR deletion could facilitate the delineation of distinct molecular and cellular mechanisms. As stated before, studies on TLRs in SCI have been primarily focused on TLR2, TLR4, and TLR9. Further investigations are needed to interrogate the role of other TLRs in SCI.

There is also a need for advancing the understanding of the non-immune role of TLRs in CNS cells. The modulation of neuronal viability and function through the direct effects of TLR agonists or antagonists on neurons (Acioglu et al., 2016; Korgaonkar et al., 2020; Li et al., 2015) and the regulation of astrocyte (Li et al., 2019; Li, Ni, et al., 2020) and oligodendrocyte function by direct activation of TLR signaling warrant further investigations.

It is worth noting that the development of TLR modulators has been an active research field primarily for the treatment of cancers and infectious diseases (Anwar, Shah, Kim, & Choi, 2019). The availability of such TLR modulators could also be useful as therapeutic agents in SCI.

Mini-dictionary of terms

- **Axonal dieback:** The progressive retraction of injured proximal axons from the lesion site.
- **Astrogliosis:** The changes observed in astrocytes in response to injury, which include alterations in gene expression, proliferation, and morphology.
- **Chemotaxis:** Migration of cells in response to extracellular signals.
- **Dystrophic axons:** Axons that show pathological changes such as swellings in disease and injury.
- **Retraction bulbs:** The oval or round swellings that form at the end of injured proximal axons.
- **Microglia and macrophage polarization:** The acquisition of pro-inflammatory and detrimental (M1 phenotype) versus anti-inflammatory and beneficial (M2 phenotype) properties under the influence of various stimuli.
- **Necroptosis:** Programmed necrotic cell death induced by inflammation.
- **Proximal axons:** Injured axons which remain connected to the cell body.

- **Pyroptosis:** A form of inflammatory programmed cell death.
- **Wallerian degeneration:** The mechanism by which injured distal axons, disconnected from the cell body, degenerate following SCI.

Key facts of innate immunity in central nervous system injury

- Injury provokes innate immune responses in the CNS.
- PRRs are the principal mediators of innate immunity and are activated by self-ligands released by damaged or stress cells following injury.
- Cells intrinsic to the spinal cord and immune cells that infiltrate the injury site express functional PRRs and release inflammatory effectors in response to activation of these receptors.
- TLRs are the best-characterized family of PRRs.
- Reactive astrocytes and activated microglia are key players in TLR-mediated innate immunity in the injured CNS.

Summary points

- TLRs modulate the innate immune and non-immune functions of glia and neurons following SCI.
- Stimulation of TLRs leads to enhanced production of type I interferons, cytokines, and chemokines, which initiate neuroinflammation.
- The crosstalk between TLRs and other PRRs, and the interactions between different TLRs are important determinants of neuroinflammation.
- TLR2, TLR4, and TLR9 are the best-studied TLRs in SCI.
- TLR2 and TLR4 are associated with improvement of function, protection, and repair in SCI.
- In contrast, TLR9 antagonism protects injured axons, alters astrocyte function, polarizes macrophages into a beneficial phenotype, and improves the functional outcomes of SCI.
- Elucidating the contribution of TLRs to SCI could provide insights into their roles in pathogenic mechanisms associated with neurodegenerative diseases, brain injuries, and potentially developmental disorders of the CNS.

Acknowledgments

The work in the authors' laboratory was supported by New Jersey Commission on Spinal Cord Research Grants CSCR12IRG007 and CSCR17IRG007 and the Reynolds Family Spine Laboratory funds.

References

Acioglu, C., Mirabelli, E., Baykal, A. T., Ni, L., Ratnayake, A., Heary, R. F., et al. (2016). Toll like receptor 9 antagonism modulates spinal cord neuronal function and survival: Direct versus astrocyte-mediated mechanisms. *Brain, Behavior, and Immunity*, *56*, 310–324.

Amarante-Mendes, G. P., Adjemian, S., Branco, L. M., Zanetti, L. C., Weinlich, R., & Bortoluci, K. R. (2018). Pattern recognition receptors and the host cell death molecular machinery. *Frontiers in Immunology*, *9*, 2379.

Anwar, M. A., Al Shehabi, T. S., & Eid, A. H. (2016). Inflammogenesis of secondary spinal cord injury. *Frontiers in Cellular Neuroscience*, *10*, 98.

Anwar, M. A., Shah, M., Kim, J., & Choi, S. (2019). Recent clinical trends in Toll-like receptor targeting therapeutics. *Medicinal Research Reviews*, *39*, 1053–1090.

Arumugam, T. V., Manzanero, S., Furtado, M., Biggins, P. J., Hsieh, Y. H., Gelderblom, M., et al. (2017). An atypical role for the myeloid receptor Mincle in central nervous system injury. *Journal of Cerebral Blood Flow and Metabolism*, *37*, 2098–2111.

Bonnans, C., Chou, J., & Werb, Z. (2014). Remodelling the extracellular matrix in development and disease. *Nature Reviews. Molecular Cell Biology*, *15*, 786–801.

Bradbury, E. J., Moon, L. D., Popat, R. J., King, V. R., Bennett, G. S., Patel, P. N., et al. (2002). Chondroitinase ABC promotes functional recovery after spinal cord injury. *Nature*, *416*, 636–640.

Burda, J. E., & Sofroniew, M. V. (2014). Reactive gliosis and the multicellular response to CNS damage and disease. *Neuron*, *81*, 229–248.

Cameron, J. S., Alexopoulou, L., Sloane, J. A., DiBernardo, A. B., Ma, Y., Kosaras, B., et al. (2007). Toll-like receptor 3 is a potent negative regulator of axonal growth in mammals. *The Journal of Neuroscience*, *27*, 13033–13041.

Carty, M., & Bowie, A. G. (2011). Evaluating the role of Toll-like receptors in diseases of the central nervous system. *Biochemical Pharmacology*, *81*, 825–837.

Chen, J., Joon Lee, H., Jakovcevski, I., Shah, R., Bhagat, N., Loers, G., et al. (2010). The extracellular matrix glycoprotein tenascin-C is beneficial for spinal cord regeneration. *Molecular Therapy*, *18*, 1769–1777.

Church, J. S., Kigerl, K. A., Lerch, J. K., Popovich, P. G., & McTigue, D. M. (2016). TLR4 deficiency impairs oligodendrocyte formation in the injured spinal cord. *The Journal of Neuroscience*, *36*, 6352–6364.

David, B. T., Ratnayake, A., Amarante, M. A., Reddy, N. P., Dong, W., Sampath, S., et al. (2013). A Toll-like receptor 9 antagonist reduces pain hypersensitivity and the inflammatory response in spinal cord injury. *Neurobiology of Disease*, *54*, 194–205.

David, B. T., Sampath, S., Dong, W., Heiman, A., Rella, C. E., Elkabes, S., et al. (2014). A Toll-like receptor 9 antagonist improves bladder function and white matter sparing in spinal cord injury. *Journal of Neurotrauma*, *31*, 1800–1806.

Deerhake, M. E., Biswas, D. D., Barclay, W. E., & Shinohara, M. L. (2019). Pattern recognition receptors in multiple sclerosis and its animal models. *Frontiers in Immunology*, *10*, 2644.

Evans, T. A., Barkauskas, D. S., Myers, J. T., Hare, E. G., You, J. Q., Ransohoff, R. M., et al. (2014). High-resolution intravital imaging reveals that blood-derived macrophages but not resident microglia facilitate secondary axonal dieback in traumatic spinal cord injury. *Experimental Neurology*, *254*, 109–120.

Fahey, E., & Doyle, S. L. (2019). IL-1 family cytokine regulation of vascular permeability and angiogenesis. *Frontiers in Immunology*, *10*, 1426.

Famakin, B. M., Tsymbalyuk, O., Tsymbalyuk, N., Ivanova, S., Woo, S. K., Kwon, M. S., et al. (2020). HMGB1 is a potential mediator of astrocytic TLR4 signaling activation following acute and chronic focal cerebral ischemia. *Neurology Research International*, *2020*.

Fan, H., Zhang, K., Shan, L., Kuang, F., Chen, K., Zhu, K., et al. (2016). Reactive astrocytes undergo M1 microglia/macrohpages-induced necroptosis in spinal cord injury. *Molecular Neurodegeneration*, *11*.

Freeman, L., Guo, H., David, C. N., Brickey, W. J., Jha, S., & Ting, J. P. (2017). NLR members NLRC4 and NLRP3 mediate sterile inflammasome activation in microglia and astrocytes. *The Journal of Experimental Medicine*, *214*, 1351–1370.

Gensel, J. C., Wang, Y., Guan, Z., Beckwith, K. A., Braun, K. J., Wei, P., et al. (2015). Toll-like receptors and dectin-1, a c-type lectin receptor, trigger divergent functions in CNS macrophages. *The Journal of Neuroscience*, *35*, 9966–9976.

Gesuete, R., Kohama, S. G., & Stenzel-Poore, M. P. (2014). Toll-like receptors and ischemic brain injury. *Journal of Neuropathology and Experimental Neurology*, *73*, 378–386.

Gross, A., Benninger, F., Madar, R., Illouz, T., Griffioen, K., Steiner, I., et al. (2017). Toll-like receptor 3 deficiency decreases epileptogenesis in a pilocarpine model of SE-induced epilepsy in mice. *Epilepsia*, *58*, 586–596.

Haggerty, A. E., Marlow, M. M., & Oudega, M. (2017). Extracellular matrix components as therapeutics for spinal cord injury. *Neuroscience Letters*, *652*, 50–55.

van Haren, S. D., Dowling, D. J., Foppen, W., Christensen, D., Andersen, P., Reed, S. G., et al. (2016). Age-specific adjuvant synergy: Dual TLR7/8 and mincle activation of human newborn dendritic cells enables Th1 polarization. *Journal of Immunology*, *197*, 4413–4424.

Heiman, A., Pallottie, A., Heary, R. F., & Elkabes, S. (2014). Toll-like receptors in central nervous system injury and disease: A focus on the spinal cord. *Brain, Behavior, and Immunity*, *42*, 232–245.

Jiang, W., Li, M., He, F., Zhou, S., & Zhu, L. (2017). Targeting the NLRP3 inflammasome to attenuate spinal cord injury in mice. *Journal of Neuroinflammation*, *14*, 207.

Khariv, V., Pang, K., Servatius, R. J., David, B. T., Goodus, M. T., Beck, K. D., et al. (2013). Toll-like receptor 9 deficiency impacts sensory and motor behaviors. *Brain, Behavior, and Immunity*, *32*, 164–172.

Kigerl, K. A., Lai, W., Rivest, S., Hart, R. P., Satoskar, A. R., & Popovich, P. G. (2007). Toll-like receptor (TLR)-2 and TLR-4 regulate inflammation, gliosis, and myelin sparing after spinal cord injury. *Journal of Neurochemistry*, *102*, 37–50.

Kigerl, K. A., Lai, W., Wallace, L. M., Yang, H., & Popovich, P. G. (2018). High mobility group box-1 (HMGB1) is increased in injured mouse spinal cord and can elicit neurotoxic inflammation. *Brain, Behavior, and Immunity*, *72*, 22–33.

Korgaonkar, A. A., Li, Y., Sekhar, D., Subramanian, D., Guevarra, J., Swietek, B., et al. (2020). Toll-like receptor 4 signaling in neurons enhances calcium-permeable alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor currents and drives post-traumatic epileptogenesis. *Annals of Neurology*, *87*, 497–515.

Kouli, A., Horne, C. B., & Williams-Gray, C. H. (2019). Toll-like receptors and their therapeutic potential in Parkinson's disease and α-synucleinopathies. *Brain, Behavior, and Immunity*, *81*, 41–51.

Li, Y., Korgaonkar, A. A., Swietek, B., Wang, J., Elgammal, F. S., Elkabes, S., et al. (2015). Toll-like receptor 4 enhancement of non-NMDA synaptic currents increases dentate excitability after brain injury. *Neurobiology of Disease*, *74*, 240–253.

Li, L., Acioglu, C., Heary, R. F., & Elkabes, S. (2020). Role of astroglial Toll-like receptors (TLRs) in central nervous system infections, injury and neurodegenerative diseases. *Brain, Behavior, and Immunity*, *91*, 740–755.

Li, L., Ni, L., Eugenin, E. A., Heary, R. F., & Elkabes, S. (2019). Toll-like receptor 9 antagonism modulates astrocyte function and preserves proximal axons following spinal cord injury. *Brain, Behavior, and Immunity*, *80*, 328–343.

Li, L., Ni, L., Heary, R. F., & Elkabes, S. (2020). Astroglial TLR9 antagonism promotes chemotaxis and alternative activation of macrophages via modulation of astrocyte-derived signals: Implications for spinal cord injury. *Journal of Neuroinflammation*, *17*, 73.

Liddelow, S. A., Marsh, S. E., & Stevens, B. (2020). Microglia and astrocytes in disease: Dynamic duo or partners in crime? *Trends in Immunology*, *41*, 820–835.

Liu, H. Y., Hong, Y. F., Huang, C. M., Chen, C. Y., Huang, T. N., & Hsueh, Y. P. (2013). TLR7 negatively regulates dendrite outgrowth through the Myd88-c-Fos-IL-6 pathway. *The Journal of Neuroscience*, *33*, 11479–11493.

Ma, Y., Li, J., Chiu, I., Wang, Y., Sloane, J. A., Lu, J., et al. (2006). Toll-like receptor 8 functions as a negative regulator of neurite outgrowth and inducer of neuronal apoptosis. *The Journal of Cell Biology*, *175*, 209–215.

Mamik, M. K., & Power, C. (2017). Inflammasomes in neurological diseases: Emerging pathogenic and therapeutic concepts. *Brain*, *140*, 2273–2285.

Minkiewicz, J., de Rivero Vaccari, J. P., & Keane, R. W. (2013). Human astrocytes express a novel NLRP2 inflammasome. *Glia*, *61*, 1113–1121.
Momtazmanesh, S., Perry, G., & Rezaei, N. (2020). Toll-like receptors in Alzheimer's disease. *Journal of Neuroimmunology*, *348*, 577362.
Nishimura, Y., Natsume, A., Ito, M., Hara, M., Motomura, K., Fukuyama, R., et al. (2013). Interferon-β delivery via human neural stem cell abates glial scar formation in spinal cord injury. *Cell Transplantation*, *22*, 2187–2201.
Okun, E., Barak, B., Saada-Madar, R., Rothman, S. M., Griffioen, K. J., Roberts, N., et al. (2012). Evidence for a developmental role for TLR4 in learning and memory. *PLoS One*, *7*, e47522.
Pallottie, A., Ratnayake, A., Ni, L., Acioglu, C., Li, L., Mirabelli, E., et al. (2018). A Toll-like receptor 9 antagonist restores below-level glial glutamate transporter expression in the dorsal horn following spinal cord injury. *Scientific Reports*, *8*, 8723.
Pashenkov, M. V., Murugina, N. E., Budikhina, A. S., & Pinegin, B. V. (2019). Synergistic interactions between NOD receptors and TLRs: Mechanisms and clinical implications. *Journal of Leukocyte Biology*, *105*, 669–680.
de Rivero Vaccari, J. P., Lotocki, G., Marcillo, A. E., Dietrich, W. D., & Keane, R. W. (2008). A molecular platform in neurons regulates inflammation after spinal cord injury. *The Journal of Neuroscience*, *28*, 3404–3414.
de Rivero Vaccari, J. P., Minkiewicz, J., Wang, X., De Rivero Vaccari, J. C., German, R., Marcillo, A. E., et al. (2012). Astrogliosis involves activation of retinoic acid-inducible gene-like signaling in the innate immune response after spinal cord injury. *Glia*, *60*, 414–421.
Rosenberger, K., Derkow, K., Dembny, P., Kruger, C., Schott, E., & Lehnardt, S. (2014). The impact of single and pairwise Toll-like receptor activation on neuroinflammation and neurodegeneration. *Journal of Neuroinflammation*, *11*, 166.
Russo, M. V., & McGavern, D. B. (2015). Immune surveillance of the CNS following infection and injury. *Trends in Immunology*, *36*, 637–650.
Schonberg, D. L., Popovich, P. G., & McTigue, D. M. (2007). Oligodendrocyte generation is differentially influenced by Toll-like receptor (TLR) 2 and TLR4-mediated intraspinal macrophage activation. *Journal of Neuropathology and Experimental Neurology*, *66*, 1124–1135.
Shi, H., Hua, X., Kong, D., Stein, D., & Hua, F. (2019). Role of Toll-like receptor mediated signaling in traumatic brain injury. *Neuropharmacology*, *145*, 259–267.
Smith, G. M., & Hale, J. H. (1997). Macrophage/microglia regulation of astrocytic tenascin: Synergistic action of transforming growth factor-β and basic fibroblast growth factor. *The Journal of Neuroscience*, *17*, 9624–9633.
Smith, G. M., & Strunz, C. (2005). Growth factor and cytokine regulation of chondroitin sulfate proteoglycans by astrocytes. *Glia*, *52*, 209–218.
Sofroniew, M. V. (2015). Astrogliosis. *Cold Spring Harbor Perspectives in Biology*, *7*, a020420.
Stephenson, E. L., & Yong, V. W. (2018). Pro-inflammatory roles of chondroitin sulfate proteoglycans in disorders of the central nervous system. *Matrix Biology*, *71–72*, 432–442.
Stirling, D. P., Cummins, K., Mishra, M., Teo, W., Yong, V. W., & Stys, P. (2014). Toll-like receptor 2-mediated alternative activation of microglia is protective after spinal cord injury. *Brain*, *137*, 707–723.
Stirling, D. P., & Yong, V. W. (2008). Dynamics of the inflammatory response after murine spinal cord injury revealed by flow cytometry. *Journal of Neuroscience Research*, *86*, 1944–1958.
Stivers, N. S., Pelisch, N., Orem, B. C., Williams, J., Nally, J. M., & Stirling, D. P. (2017). The Toll-like receptor 2 agonist Pam3CSK4 is neuroprotective after spinal cord injury. *Experimental Neurology*, *294*, 1–11.
Sun, L., Li, M., Ma, X., Feng, H., Song, J., Lv, C., et al. (2017). Inhibition of HMGB1 reduces rat spinal cord astrocytic swelling and AQP4 expression after oxygen-glucose deprivation and reoxygenation via TLR4 and NF-κB signaling in an IL-6-dependent manner. *Journal of Neuroinflammation*, *14*, 231.
Takeuchi, O., & Akira, S. (2010). Pattern recognition receptors and inflammation. *Cell*, *140*, 805–820.
Thomas, C. J., & Schroder, K. (2013). Pattern recognition receptor function in neutrophils. *Trends in Immunology*, *34*, 317–328.
Vajjhala, P. R., Ve, T., Bentham, A., Stacey, K. J., & Kobe, B. (2017). The molecular mechanisms of signaling by cooperative assembly formation in innate immunity pathways. *Molecular Immunology*, *86*, 23–37.
Voet, S., Srinivasan, S., Lamkanfi, M., & van Loo, G. (2019). Inflammasomes in neuroinflammatory and neurodegenerative diseases. *EMBO Molecular Medicine*, *11*, e10248.
Walsh, J. G., Muruve, D. A., & Power, C. (2014). Inflammasomes in the CNS. *Nature Reviews. Neuroscience*, *15*, 84–97.
Wiese, S., Karus, M., & Faissner, A. (2012). Astrocytes as a source for extracellular matrix molecules and cytokines. *Frontiers in Pharmacology*, *3*, 120.
Yang, T., Dai, Y., Chen, G., & Cui, S. (2020). Dissecting the dual role of the glial scar and scar-forming astrocytes in spinal cord injury. *Frontiers in Cellular Neuroscience*, *14*, 78.
Zhang, Y., Winterbottom, J. K., Schachner, M., Lieberman, A. R., & Anderson, P. N. (1997). Tenascin-C expression and axonal sprouting following injury to the spinal dorsal columns in the adult rat. *Journal of Neuroscience Research*, *49*, 433–450.

Chapter 14

The role of oxidative stress in spinal cord injury animal models: A focus on nuclear factor erythroid-2 related factor 2

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Abbreviations

3-NT	3-nitrotyrosine
4-HNE	4-hidroxinonenal
ARE	antioxidant response element
ATP	adenosine triphosphate
Bax	Bcl-2-like protein 4
BBB	Basso, Beattie, and Bresnahan
Bcl-2	anti-apoptotic B-cell lymphoma
BDNF	brain-derived neurotrophic factor
BMS	Basso mouse scale
CAT	catalase
CK2	casein kinase 2
DNA	deoxyribonucleic acid
EAAT1	excitatory amino acids transport
EAAT2	excitatory amino acids transport
ERK	extracellular signal-regulated kinase
GPx	peroxidase glutathione
GSH	reduced glutathione
GSK-3	glycogen synthase kinase
GSSG	oxidized glutathione
HO-1	hemeoxygenase 1
IL-6	interleukin-6
JNK	c-jun N-terminal kinase
KEAP1	Kelch-like ECH-associated protein 1
MAF	musculo aponeurotic fibrosarcoma
MDA	malondialdehyde
mRNA	messenger RNA
NADH	nicotinamine adenine dinucleotide
NF-κB	nuclear factor kappa B
NLRP3	Nod-like receptor pyrin domain-containing 3 complex
NMDA	N-metil-D-aspartate
NQO1	NA(*D*)PH quinone oxidoreductase 1
Nrf2	nuclear factor erythroid-2 related factor 2
P38 MAPK	p38 mitogen-activated protein kinase
PI3K:phosphoinositide 3-kinase	
PKC	protein kinase C

Cellular, Molecular, Physiological, and Behavioral Aspects of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822427-4.00014-9

RNS	reactive nitrogen species
ROS	reactive oxidative species
SCI	spinal cord injury
SOD	superoxide dismutase
TBARS	thiobarbituric acid reactive substances
TLR-4	toll-like receptor 4
TNF-α	tumoral necrosis factor-α

Introduction

Paraplegia and tetraplegia are major consequences induced by spinal cord trauma and affect many young adults (Jia et al., 2012). Movement loss, sensory deficits, and autonomic dysfunction are common aggravating factors after spinal cord injury (SCI), and numerous pre-clinical studies have been performed to better understand the mechanisms underlying the lesion in order to improve rehabilitation programs. Tissue lesions can occur by compression, contusion, or laceration of the spinal cord, leading to transitory tissue disruption associated with primary cellular mechanisms, including acute neuronal loss by necrosis immediately after trauma (Beattie, Farooqui, & Bresnahan, 2000).

Primary lesions are followed by molecular and cellular cascades in the damage site, such as glutamatergic excitotoxicity, ischemia/reperfusion, inflammatory processes, edema, and oxidative stress (Table 1) that are classified in the secondary mechanism of the lesion and can cause late cell apoptosis (Beattie et al., 2000). Indeed, the molecular and cellular alterations that accompany initial tissue disruption can hinder recovery and are directly involved with social problems and debilities in the injured individuals' quality of life.

Regarding SCI pathophysiology, it is important to note that the spared nerve fibers are essential in the functional recovery process. However, the number of fibers remaining depends on the volume of axonal bundles lost at the time of injury and Wallerian degeneration in response to secondary mechanisms. Free radical and reactive oxygen species and reactive nitrogen species (ROS/RNS) production are part of normal metabolisms in the physiological systems because, under normal conditions, these compounds are kept under control by cellular defense mechanisms. Moreover, oxidative molecules are necessary for several biochemical reactions in physiological systems during homeostasis (Droge, 2002). On the other hand, the excessive increase of oxidant molecules is part of many secondary mechanisms that accompany SCI (from minutes to weeks) and may be associated with tissue degeneration and inhibited recovery (Woźniak, Woźniak, Mila-Kierzenkowska, & Kasprzak, 2016). This process can begin in the spinal cord by excessive calcium (Ca^{2+}) influx through *N*-methyl-D-aspartate (NMDA) receptors mediated by glutamate neurotransmitters, damaging the mitochondrial matrix and increasing free radicals and ROS (Ma et al., 2020; Springer et al., 1997).

Excessive oxidant molecules and mitochondrial damage cause cell apoptosis by cytochrome C release and neuronal loss. Although most of these cell characteristics occur after compression, contusion, or laceration of the spinal cord, further knowledge on the effects of oxidants and antioxidant molecules after SCI is still necessary. Therefore, the present chapter describes the main oxidants released in the medullary lesion and antioxidant interventions in pre-clinical research that should be useful for future therapeutic treatments.

TABLE 1 Secondary damage after spinal cord injury.

Spinal cord injury
Secondary damage
Excitotoxicity
Ischemia/reperfusion
Oxidative stress
Edema
Inflammation

Molecular and cellular cascades in the damage site.
Source: Authors.

Oxidative stress characteristics and mechanisms

Oxidative stress is characterized by the oxidation of biomolecules that may lead to the loss of biological functions in healthy tissues (Halliwell & Whiteman, 2004). This process occurs when the production of free radicals or ROS/RNS is higher than the antioxidant defenses present in the physiological system. Free radicals are atoms or molecules that, when formed, have one or more unpaired electrons in their valence shell (Halliwell, 1989), while ROS and RNS are equally reactive compounds but do not have unpaired electrons (Droge, 2002). Even though the electrons are unpaired, ROS and RNS are highly reactive and seek stability during their brief existence, reacting with other molecules and damaging cell membranes, proteins, and deoxyribonucleic acid (DNA) of cells (Halliwell, 2012).

Oxidative phosphorylation is the principal ROS generator, in which the first free radical formed is superoxide ($O_2^{-\bullet}$), mainly in complex I (NADH dehydrogenase) and complex III (ubiquinone cytochrome C oxidase) of the respiratory chain, where Flavin's mononucleotide coenzyme and ubiquinol reduce molecular oxygen (O_2) and form the free radical (Navarro & Boveris, 2007). Reactive oxygen species such as hydrogen peroxide (H_2O_2) and other free radicals, including hydroxyl radical ($^{-}OH^{\bullet}$), which is the most reactive radical, can be formed from $O_2^{-\bullet}$. In addition, H_2O_2 can react with metals such as copper (Cu^{+1}) and iron (Fe^{+2}) in the so-called "Fenton reaction," forming $^{-}OH^{\bullet}$ (Jia et al., 2012). This dangerous molecule can act as an electrophile or nucleophile and attack organic molecules by hydrogen abstraction or coupling in double bonds and aromatic rings (hydroxylation), even in substituted positions, causing reactions such as deamination (Fukushima, Tatsumi, & Morimoto, 2000) and decarboxylation (Chen, Ma, He, & Zhao, 2002). Additionally, H_2O_2 can also react with $O_2^{-\bullet}$ itself in the so-called "Haber-Weiss reaction," forming $^{-}OH^{\bullet}$(Jia et al., 2012). Moreover, $O_2^{-\bullet}$ can react with nitric oxide (NO) formed by nitric oxide synthase (NOS) and form peroxynitrite ($ONOO^{-}$), an RNS that damages membranes, proteins, and cellular DNA (Lau & Tymianski, 2010).

The excessive formation of these ROS is controlled by an antioxidant defense system composed of enzymatic antioxidants, such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). All antioxidant defenses are involved with a system of auxiliary molecules. There are also non-enzymatic antioxidants [vitamins A, C, D, and E and reduced glutathione (GSH)] (Halliwell & Gutteridge, 1995). Among enzymatic antioxidants, SOD is found in two isoforms (SOD1 or CuZinSOD)and uses copper and zinc as cofactors, being located mainly in the cell cytoplasm, although it is also present in peroxisomes, lysosomes, and the mitochondrial intermembrane space. Other isoforms such as SOD2 or MnSODuse manganese as a cofactor and are located in the mitochondrial matrix (Jia et al., 2012). These two isoforms catalyze the $O_2^{-\bullet}$ dismutation reaction to form H_2O_2. Following these reactions, the enzymes CAT and GPx catalyze the degradation reaction of H_2O_2 into H_2O and O_2. The GPx enzyme is found in two isoforms: one is present in mitochondria and cytosol and uses selenium as a cofactor, while the other is only located in the cytosol and does not use selenium as a cofactor. For the GPx reaction, the reduced glutathione substrate (GSH) is required for the enzyme, forming oxidized glutathione (GSSG) and the reaction product of the hydroperoxide. To restore the GSH molecule, the GPx enzyme works coupled with glutathione reductase (GR), which is an enzyme that reduces the GSSG molecule to GSH using nicotinamide adenine dinucleotide phosphate (NADPH) (Maiorino, Gregolin, & Ursini, 1990). Thus, the antioxidant system can reduce the action of oxidant molecules (Fig. 1).

However, excitotoxicity is directly related to the excessive free radical formation (ROS and RNS) caused by mitochondrial damage (Navarro & Boveris, 2007) and calcium-dependent enzyme activation, such as phospholipase A2 (Miller et al., 2010) and xanthine oxidase (Allen et al., 2012), which hinder the blockage of the antioxidant system. Among the damage resulting from the exacerbated production of free radicals, lipid peroxidation also stands out (Allen et al., 2012). Lipid peroxidation produces aldehydes, hydrocarbon gases, and various chemical residues, including malondialdehyde (MDA), conjugated dienes, and 4-hydroxynonenal (4-HNE) (Hotz, Hoet, & Lauwerys, 1987). In this sense, the cell membranes are composed of lipids, and research has shown that soon after the SCI model (1–24 h), there is an increase in lipid peroxidation that inhibits glutamate uptake, causing excitotoxicity in injured spinal cords (Springer et al., 1997).

Nonetheless, it is important to note that the overstimulation of glutamatergic receptors also represents the main mediator of oxidative stress in several neurological disease models (Kumar, Kalonia, & Kumar, 2011). In this scenario, reducing antioxidant enzymes in the brain, such as SOD, CAT, and GPx, contributes to developing various neurodegenerative diseases through free radicals in pathological conditions. Therefore, experimental findings have described the protective role of antioxidants in animal models of traumatic injury, strokes, Huntington's, Parkinson's, and Alzheimer's diseases (Halliwell, 1989).

Different isoforms of glutamate transporters show sensitivity to biological oxidants and may share one or more vulnerable sites to oxidants. Oxidants also inhibit the transport activity of the principal excitatory amino acid transports (EAAT1 and EAAT2) by directly affecting glutamate transport proteins. A common primary target for $O_2^{-\bullet}$, H_2O_2, $ONOO^{-}$, and the by-product $^{-}OH^{\bullet}$ is the oxidation of sulfhydryl cysteine groups (Radi, Beckman, Bush, & Freeman,

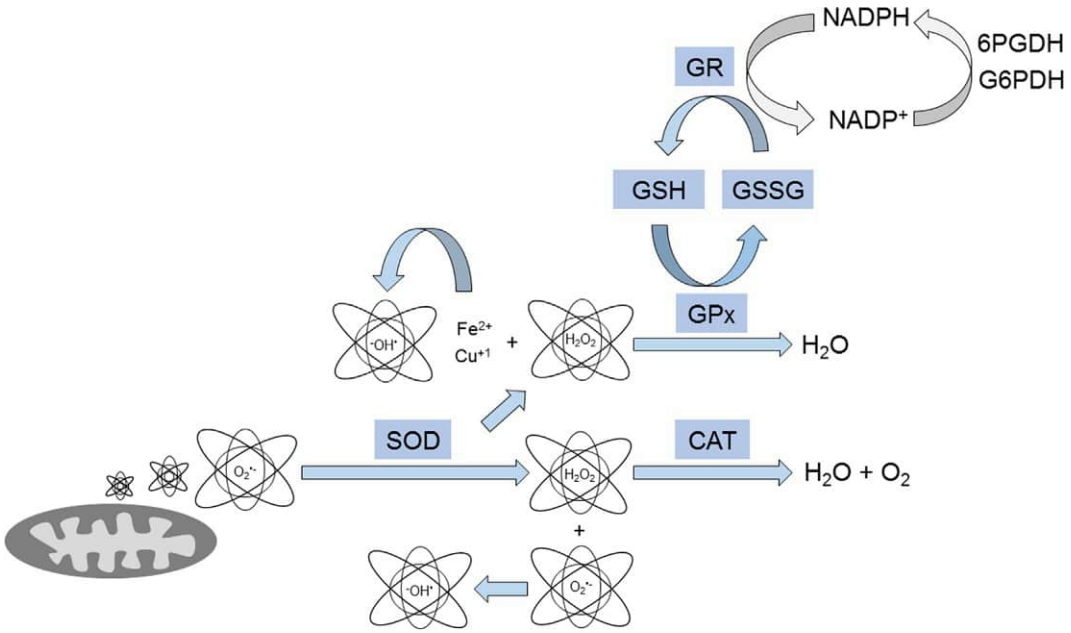

FIG. 1 Oxidant and antioxidant actions in cellular homeostasis. Oxidative phosphorylation generates the free radical $O_2^{-\bullet}$; SOD form H_2O_2 from $O_2^{-\bullet}$; H_2O_2 can react with $O_2^{-\bullet}$ and generate $^{-}OH^{\bullet}$ (Haber-Weiss reaction) or react with Cu^{+1} or Fe^{+2} ions to form $^{-}OH^{\bullet}$ (Fenton reaction); CAT and GPx degrade H_2O_2 in H_2O and O_2; GPx uses GSH as a substrate for the enzyme, forming GSSG; GR reduces GSSG to GSH using NADPH, forming $NADP^{+}$; NADPH is restored from G6PDH, forming 6GPDH. $O_2^{-\bullet}$: superoxide radical; GPx: peroxidase glutathione; H_2O_2: hydrogen peroxide; $^{-}OH^{\bullet}$: hydroxyl radical; SOD: superoxide dismutase; GSH: reduced glutathione; GSSG: oxidized glutathione; GR: reductase glutathione; NADPH: reduced nicotinamide adenine dinucleotide phosphate; $NADP^{+}$: oxidized nicotinamide adenine dinucleotide phosphate; G6PDH: Glycose 6 phosphate dehydrogenase; 6GPDH: 6-phosphogluconate dehydrogenase; H_2O: water; O_2: oxygen. *(Source: Authors.)*

1991). In addition, by decomposing it in neutral pH, $ONOO^{-}$ generates nitronium ion and nitrogen dioxide, which promote nitrosylation and nitration of tyrosine residues and alter the phosphorylation processes in these residues (Radi et al., 1991). However, the physiological system may protect the cells in some situations in which homeostasis is disrupted. This protection system occurs via endogenous cascades of transcription of defense molecules, which can be exogenously stimulated.

The implications of oxidative damage in SCI pathophysiology

One of the leading causes of motor deficits after SCI is the irreversible loss of motor neurons during primary damage. However, sensorimotor recovery is also impaired by fiber loss associated with late degeneration processes. Regarding SCI pathophysiology, white matter injury occurs due to primary and secondary damage, and it is important to note that therapeutic intervention and attenuation in such late secondary phases is still possible to reduce the white matter loss (Hayta & Elden, 2018). In this sense, from a translational perspective for motor recovery, which is a primary need for SCI patients, in rodents, at least 10% of white matter must be spared to improve the motor system after SCI (Kloos, Fisher, Detloff, Hassenzahl, & Basso, 2005).

Furthermore, oxidative and antioxidative balance marked by reactive substances such as thiobarbituric acid reactive substances (TBARS), conjugated dienes concentrations, and enzymatic antioxidant system (SOD, CAT, and GPx) is deregulated in the blood of individuals with cervical SCI (Woźniak et al., 2016). Reactive oxygen species-induced protein oxidation immediately after injury is a critical secondary SCI pathophysiology marked by protein carbonyl formation and 3-nitrotyrosine (3-NT) in spinal cord tissues (Visavadiya, Patel, VanRooyen, Sullivan, & Rabchevsky, 2016). Severe SCI increases $O_2^{-\bullet}$, H_2O_2, and NO levels in isolated mitochondria and decreases GSH content with continuous production of NO levels in cell parameters (Visavadiya et al., 2016). Consequently, NO can react with $O_2^{-\bullet}$ to form $ONOO^{-}$, causing nitration and the oxidation and nitrosylation of several mitochondrial compounds that cause drastic consequences in proteins, lipids, and nucleic acid formation (Szabó, Ischiropoulos, & Radi, 2007).

Several biological degradation products are released during oxidative stress and bring characteristics that allow establishing which intracellular tissue organelles were affected. In this scenario, lipid peroxidation and protein carbonyls are

relevant biochemical markers and indications of oxidative damage in lipids and proteins, respectively (Luo, Borgens, & Shi, 2004; Visavadiya et al., 2016). Although the oxidative process is more intense in damage epicenter in experimental models, adjacent segments can also suffer degradation in plasmatic membrane lipids. For instance, experimental data by Luo et al. (2004) revealed that a rat thoracic compression model with SCI in the T10–T11 segments presented spread lipid peroxidation in rostral and caudal segments T6–T7, T8–T9, T12–T13, and L1–L2, respectively, in addition to the epicenter (T10–T11).

Membrane degradation can deregulate Na^+/K^+ homeostasis in axoplasm and mitochondria (LoPachin et al., 1999), leading to higher Ca^{2+} influx inside cells and mitochondrial matrix that consequently cause over-production of ROS (Luo et al., 2004). Additionally, mitochondrial swelling is involved with ROS production and lipid peroxidation after experimental SCI in rats (Luo et al., 2004). Besides inducing higher production of free radicals, the mitochondria are also targeted by oxidant molecules, leading to loss of function in transport electrons and reduced ATP synthesis. The constant opening of the mitochondrial membrane permeability transition pore and transport of cytochrome C to cell cytosol induce caspase activation with consequent cell apoptosis (Ma et al., 2020). In this sense, the intrasynaptosomal Ca^{2+} influx soon after SCI increases in the lesion area, which is associated with reduced synaptosomal function (Luo et al., 2004). Moreover, Ca^{2+} and H_2O_2 cause permeability transition and mitochondrial swelling in isolated mitochondria, similar to what happened in synaptosomes of injured tissues in a compression SCI model (Luo et al., 2004). Thus, oxidative stress can cause degeneration of remaining neurons and oligodendrocytes (Wallerian degeneration), leading to impairment in ascending and descending (sensorimotor) information of axons of the injured spinal cord and proximal segments (Beattie et al., 2000).

This way, tissue protection in secondary phases of SCI is vital for maintaining cell survival of sensory and motor tracts and simultaneously provide better conditions for rehabilitating injured individuals. Hence, the transcription factor Nrf2 should be a target to reduce the continuous damage caused by oxidative stress in tracts of the spinal cord and contribute to patient recovery.

Protection mechanisms by endogenous antioxidants via Nrf2-ARE system

During evolution, cells developed defense systems against harmful endogenous processes and exogenous substances. Several transcription factors are involved in increasing cell defenses. A complex system of phase I, II, and III genes involves antioxidant enzyme activation. The main regulator of phase II genes and some phase III genes of antioxidant enzymes is the nuclear factor erythroid-2-related factor 2 (Nrf2) (Itoh et al., 1997). The principle of the system is to keep the Nrf2 protein low under normal cellular conditions, with the possibility of rapid induction in the event of increased cellular oxidation. Furthermore, Nrf2 is a member of the family of transcription factors that includes Nrf1, Nrf3, p45 NF-E2, Bach1, and Bach2 (Motohashi, O'Connor, Katsuoka, Engel, & Yamamoto, 2002). Nrf2 is composed of six functional domains known as Nrf2-ECH homologies (Neh) and classified as Neh1–6, with each Neh domain having its own designated function (Baird & Dinkova-Kostova, 2011). Under quiescent conditions, Nrf2 is maintained by a cytosolic repressor, Keap1 (Kelch-like ECH-associated protein 1), a cytoskeletal protein that anchors and suppresses transcription activity (Itoh et al., 1999; Tong et al., 2007). Keap1 promotes rapid proteasomal degradation of Nrf2 through ubiquitination and acts as an oxidative and electrophilic stress sensor (Itoh et al., 1999).

Research has suggested that changes in the structure of Keap1 lead to the dissociation of the Nrf2-Keap1 complex (Motohashi & Yamamoto, 2004), although a specific modification in the Keap1 site may also alter ubiquitin ligase E3 function and consequently reduce Nrf2 degradation (Tong et al., 2007). Additionally, a pathway for ubiquitination and degradation of Nrf2 independent of Keap1 is also proposed (Rojo et al., 2012). In this model, GSK-3 phosphorylates serine residues in the Neh 6 domain in Nrf2 (Rada et al., 2012), and phosphorylated Neh 6 can be recognized by a ubiquitin ligase E3. The dissociation of the Nrf2-Keap1 complex in the cytoplasm is a widely accepted mechanism for Nrf2 activation. In summary, the oxidation of cysteine residues modifies the conformation of Keap1, thus initiating Nrf2 activation (Tong et al., 2007). In this way, oxidative products improve Nrf2 stability and increase phase II gene expression (McMahon, Thomas, Itoh, Yamamoto, & Hayes, 2006). The phosphorylation in the serine/threonine residues in Nrf2 may be a distinct mechanism that Nrf2 dissociates from Keap1 (Surh, Kundu, & Na, 2008). Protein kinases including protein kinase C (PKC), c-jun N-terminal kinase (JNK), extracellular signal-regulated kinase (ERK), casein kinase 2 (CK2), p38 mitogen-activated protein kinase (p38 MAPK), and phosphoinositide 3-kinase (PI3K) appear to modulate the import and export of Nrf2 from the nucleus (Jain & Jaiswal, 2007; Surh et al., 2008). Therefore, the oxidation of cysteine residues that are sensitive to the redox state in Keap1 constitutes the molecular basis for Nrf2 activation (Tong et al., 2007).

The induction of phase II antioxidant defense enzymes by Nrf2 is regulated by the antioxidant response element (ARE) or electrophile response element (EpRE) (Itoh et al., 1997; Venugopal & Jaiswal, 1998). The Nrf2-ARE bond can initiate the transcription of hundreds of cytoprotective genes, including SOD, CAT (Cho et al., 2011), and a series of phase II

antioxidants that include the glutathione defense system, NA(*D*)PH quinone oxidoreductase 1 (NQO1), and heme oxygenase-1 (HO-1) (Zhang et al., 2012).

Notably, Nrf2 is a transcription factor able to induce the expression of other types of protective proteins in the CNS. Among them are the brain-derived neurotrophic factor (BDNF) (Sakata et al., 2012) and anti-apoptotic B-cell lymphoma (Bcl-2) (Niture & Jaiswal, 2012), which are extremely important proteins for cell maintenance and survival.

Hence, Nrf2 in the brain can act as one of the most decisive defenses against oxidative stress by modulating microglia (Rojo et al., 2010), protecting astrocytes (Vargas & Johnson, 2009) and neurons (Lee, Shih, Murphy, & Johnson, 2003) from toxic insults, and regulating the expression of inflammatory markers (Innamorato et al., 2008) and antioxidant enzymes (Shah et al., 2007; Yan et al., 2009). In this context, it is clear that Nrf2 plays a protective role in neurodegenerative disorders, including Parkinson's (Cuadrado, Moreno-Murciano, & Pedraza-Chaverri, 2009), Alzheimer's (Kanninen et al., 2008), and Huntington's diseases (Stack et al., 2010). Moreover, Nrf2 is also a regulator in secondary mechanisms of lesions in traumatic brain injury (Yan et al., 2009) and SCI (Ma et al., 2020).

Involvement of Nrf2 in blockage of oxidative stress post-SCI induced by exogenous stimuli

Many studies have attempted to reduce neurodegenerative processes and improve functionality in rat SCI models, including treatments that decrease oxidative stress and inflammation via Nrf2 signaling pathway activation (Table 2). It is important to note that damage in the CNS, such as traumatic brain injury, can elevate p-Nrf2/Nrf2 ratio and Nrf2 levels in a "compensation system" due to higher ROS production after injury (da Silva Fiorin et al., 2016; Yan et al., 2009). However, Nrf2 activation is unable to prevent prolonged pathophysiologic cascades after the damage that leads to behavioral deficits and brain cell loss (da Silva Fiorin et al., 2016). Nevertheless, increased Nrf2 in spinal cord damage is accompanied by increased Bax apoptotic protein expression, decreased Bcl-2 anti-apoptotic protein expression, and elevated apoptosis rates compared to non-injured tissues (Liu et al., 2020; Lv et al., 2019). After the contusion SCI model, the increased Nrf2 levels were unable to reduce inflammatory markers, such as interleukin-6 (IL-6), tumoral necrosis factor-α (TNF-α), and lesion-induced ROS production, in addition to there being no protection in the antioxidant system due to the lower SOD expression levels (Liu et al., 2020). On the other hand, when physical stimuli or pharmacological treatments increased p-Nrf2/Nrf2 ratio or Nrf2 levels in injured animals, the antioxidant system was able to induce protection of the injured nervous tissues (da Silva Fiorin et al., 2016; Liu et al., 2020; Lv et al., 2019) (Fig. 2).

In this sense, Ma et al. (2020) reported significant motor recovery during 28 days of rosmarinic acid (RA) administration after compression of the spinal cord in rats. Interestingly, an integration between oxidative and inflammatory mechanisms leads to degenerative processes through apoptosis (Ma et al., 2020). Furthermore, the authors also proposed that high nuclear factor kappa B (NF-κB) activation is induced by toll-like receptor 4 (TLR4) activation (Ma et al., 2020). The consequent inflammatory process leads to apoptosis caused by mitochondrial damage and caspase 3, 8, and 9 activation that are blocked due to musculoaponeurotic fibrosarcoma (MAF), HO-1, and NQO1 dependents of Nrf2 (Ma et al., 2020). In fact, crosstalk was observed between NF-κB and Nrf2 after white matter injury caused by hypoxia with reduced NF-κB signaling pathway via Nrf2-induced antioxidant response (Daverey & Agrawal, 2020).

The NFκB-TLR4 pathway is up-regulated after SCI, and this signaling pathway appears to be modulated by phosphorylation in p38 (p-p38) and JNK (p-JNK) proteins (Guan, Chen, Zhong, Liu, & Chen, 2020). Hence, higher phosphorylation was observed in the p-IKKα/β, p-Iκβα, and nuclear p65 subunits after experimental SCI showing active NF-κB signaling pathway and inducing transcription of pro-inflammatory mediators. On the other hand, antioxidant treatment up-regulated Nrf2 and decreased the NF-κB signaling pathway with increased p65 subunit expression in the cell cytoplasm, indicating lower activation and less nuclear transcription (Ma et al., 2020). Furthermore, p-NF-κB decreased after the ketogenic diet in SCI rats associated with less synthesis and release of pro-inflammatory mediators and increased Nrf2 levels (Lu et al., 2018). Corroborating such data, the compression SCI model has already been reported to cause pro-inflammatory cytokine release for 28 days after injury with spread systemic inflammation (do Espírito Santo et al., 2019).

Although many mechanisms of Nrf2-activation by antioxidant and anti-inflammatory compounds are unclear, many of those molecules can induce protective effects via Nrf2 at the cellular level, including reduced apoptosis, lower loss of ventral motor neurons at rostral, caudal, and epicenter segments, and more preserved tissue (Zhang et al., 2019). Therefore, it is important to note that after the severe SCI model, the Nrf2/HO-1 pathway activation in neurons and astrocytes promotes functional recovery through Basso, Beattie, and Bresnahan (BBB) locomotor rating scale (Lin et al., 2019). On the other hand, Li et al. (2019) reported that the motor effects did not improve, despite the coenzyme Q10 suppressing oxidative

TABLE 2 Effects of various antioxidants composed in biochemical mechanisms in SCI animal models.

Author	SCI model	Animal species	Proposed treatment	Biochemical outcomes
Wang et al., 2020	Compression (T9 vertebra)	Adult female Sprague-Dawley rats	Metformin	Increased Nrf2; Improved mitochondrial function; Decreased apoptosis
Ma et al., 2020	Compression (T9 vertebra)	Adult female Sprague-Dawley rats	Rosmarinic acid	Increased Nrf2 and HO-1; Inhibited NF-kB-p65 translocation to the nucleus; Reduced apoptosis
Liu et al., 2020	Contusion (T10 vertebra)	Adult male and female Sprague-Dawley rats	Imatinib	Increased Nrf2, HO-1, and SOD; Decreased IL-6, TNF-α, and ROS; Reduced apoptosis
Li et al., 2020	Contusion (T9 vertebra)	Adult C57BL/6 J mice	Zinc	Increased Nrf2 and HO-1; Decreased NLRP3 (inflammation-associated protein) and caspase-1
Mao et al., 2020	Weight drop (T8 vertebra)	Adult male Sprague-Dawley rats	Eriodictyol	Increased Nrf2 and HO-1; Decreased p-NF-kB/NF-kB
Dai, Tang, Zhao, Dai, & Huang, 2020	Compression (unspecified vertebra)	Adult female C57BL/6 J mice	Electroacupuncture	Increased Nrf2, HO-1, and NQO1
Zhang et al., 2019	Contusion (T9 vertebra)	Adult female Sprague-Dawley rats	Sinomenine	Increased Nrf2; Decreased inflammation and oxidative stress
Lv et al., 2019	Weight drop (T8 vertebra)	Adult male Sprague-Dawley rats	Polydatin	Increased Nrf2; Decreased oxidative stress; Reduced apoptosis
Lin et al., 2019	Compression (between T10 and T12 vertebrae)	Adult male Sprague-Dawley rats	2-(-2-Benzofuranyl)-2-imidazoline	Increased Nrf2, HO-1, SOD, GPx, and Bcl-2; Decreased Bax and caspase-3; Reduced apoptosis
Li et al., 2019	Weight drop (between T9 and T10 vertebra)	Adult male Sprague-Dawley rats	Coenzyme Q10	Increase Nrf2, NQO-1, SOD, GSH, and Bcl-2; Decreased Bax and caspase-3; Reduced apoptosis
Lu et al., 2018	Hemi-contusion (C7 vertebra)	Adult male Sprague-Dawley rats	Ketogenic diet	Increased Nrf2 and SOD; Decreased p-NF-κB and pro-inflammatory markers

T: thoracic; p: phosphorylation; p65: phosphorylation on the 65 subunit; NLRP3: Nod-like receptor pyrin domain-containing 3 complex; SOD: superoxide dismutase; GSH: reduced glutathione; Nrf2: nuclear factor erythroid-2 related factor 2; HO-1: hemeoxygenase 1; NQO1: NA(*D*)PH quinone oxidoreductase 1; GPx: peroxidase glutathione; NF-κB: nuclear factor kappa B; Bcl-2: anti-apoptotic B-cell lymphoma; Bax: Bcl-2-like protein 4; ROS: reactive oxygen species; IL-6: interleukin-6; TNF-α: tumor necrosis factor alpha.
Source: Authors.

stress and apoptosis after SCI in rats. However, it is important to note the differences in the SCI model that may explain some discrepancies (Table 2).

Using the Basso mouse scale (BMS) after experimental SCI, Li et al. (2020) demonstrated that zinc improved motor function in injured animals during 28 days of evaluation. After the injury, the levels of both Nrf2/HO-1 and Nod-like receptor pyrin domain-containing 3 complex (NLRP3) increase, although after treatment, only Nrf2/HO-1 continues to

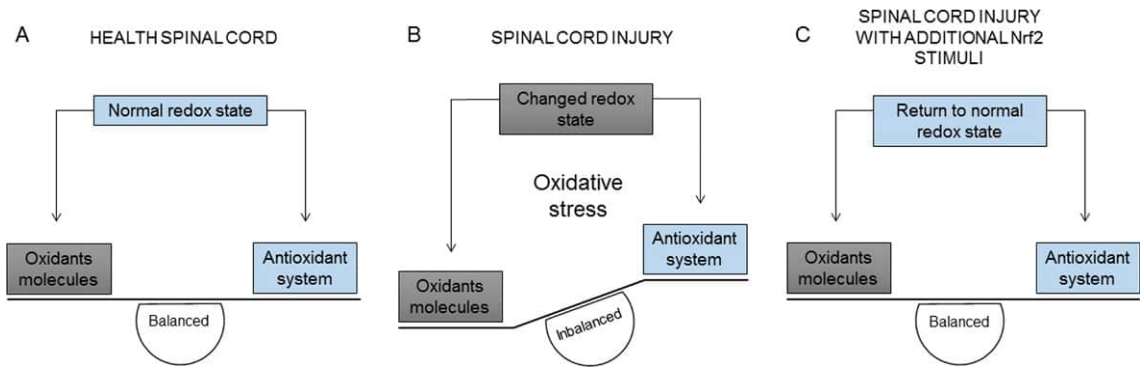

FIG. 2 Balanced and imbalanced redox state before and after SCI. (A) the oxidant and antioxidant molecules are in balance in the healthy spinal cord. (B) SCI increases oxidant molecules and causes a redox state imbalance, leading to oxidative stress. (C) Additional stimuli increase the antioxidant system via Nrf2 and balance redox state after SCI. SCI: spinal cord injury; Nrf2: nuclear factor erythroid-2-related factor 2. *(Source: Authors.)*

increase while NLRP3 decreases (Li et al., 2020). Intervention soon after SCI appears to be promising and beneficial for reorganizing and protecting the cellular microenvironment. Hence, the elevated Nrf2 mRNA expression levels presented in rats treated with antioxidants after spinal cord damage corroborates increased Nrf2 protein levels (Liu et al., 2020). Moreover, decreased pro-inflammatory cytokine release, antioxidant improvement, ROS reduction, and apoptosis protection via down-regulation of Bax, and up-regulation of Bcl-2 proteins were also observed (Liu et al., 2020). After SCI in animals, electroacupuncture stimulates Nrf2 levels, reduces pathological scores evaluated by histomorphology near the epicenter of damage, and induces protection in axons 28 days after injury (Dai, Tang, Zhao, Dai, & Huang, 2020). Reduced oxidative and inflammatory processes improved the BMS scale during the evaluation periods and electroacupuncture treatment (Dai, Tang, Zhao, Dai, & Huang, 2020).

In summary, when the up-regulation of Nrf2 is stimulated, this transcription factor can act against oxidative and inflammatory crosstalk at the cellular level after injury of the spinal cord characterized by several markers of oxidative damage, antioxidant system, and inflammatory pathway. The blockage of the oxidant and inflammatory signaling pathway improves neuronal and glial cell protection, reducing the loss of the remaining ascending and descending fibers. This protection occurs at the epicenter of damage and at the rostral and caudal segments and may lead to motor recovery in some SCI rat models (Fig. 3).

Concluding remarks

Regarding the complexity of SCI pathophysiology, many points still need to be clarified. Oxidative stress is only one of them, and the protection in targets of this secondary complication may accompany technological development to improve therapeutic treatments. Moreover, oxidative damage is a debilitating factor to the cellular environment, although it can be an "alert system" for tissue prevention or damage compensation. Furthermore, it is not yet clear if oxidative stress is caused or a consequence of tissue degeneration; therefore, additional studies are required.

In view of this, further comprehensive scientific research on cellular mechanisms, signaling pathways, and treatments are crucial and may contribute to the maintenance of cells in injured tissue. Despite advances in this research area, oxidative stress is still not a promising treatment in clinical studies due to difficult motor recovery, even with improved therapies. Nevertheless, the role of oxidative stress in injured tissues may hamper the evolution of the injured individual, and more knowledge on oxidative processes may help improve the effectiveness of current technological therapies, such as neuromodulation and brain-machine interface for the sensorimotor recovery of SCI patients.

Application to others areas of neuroscience

This chapter focuses on describing the effects of oxidative stress after SCI. Oxidative stress comprises a complex process of reactive molecules implicated in cell degeneration. Here, we also associated oxidative and inflammatory events after SCI. However, it is accepted that oxidant processes and inflammation are involved in the pathogenesis of diseases and tissue injury of the central nervous system, leading to cell loss. For example, in Parkinson's (Cuadrado et al., 2009), Alzheimer's (Kanninen et al., 2008), and Huntington's diseases (Stack et al., 2010), the reduction of oxidative damage by antioxidants can reduce brain tissue damage. Brain areas that are significantly involved in normal processes are debilitated by oxidative

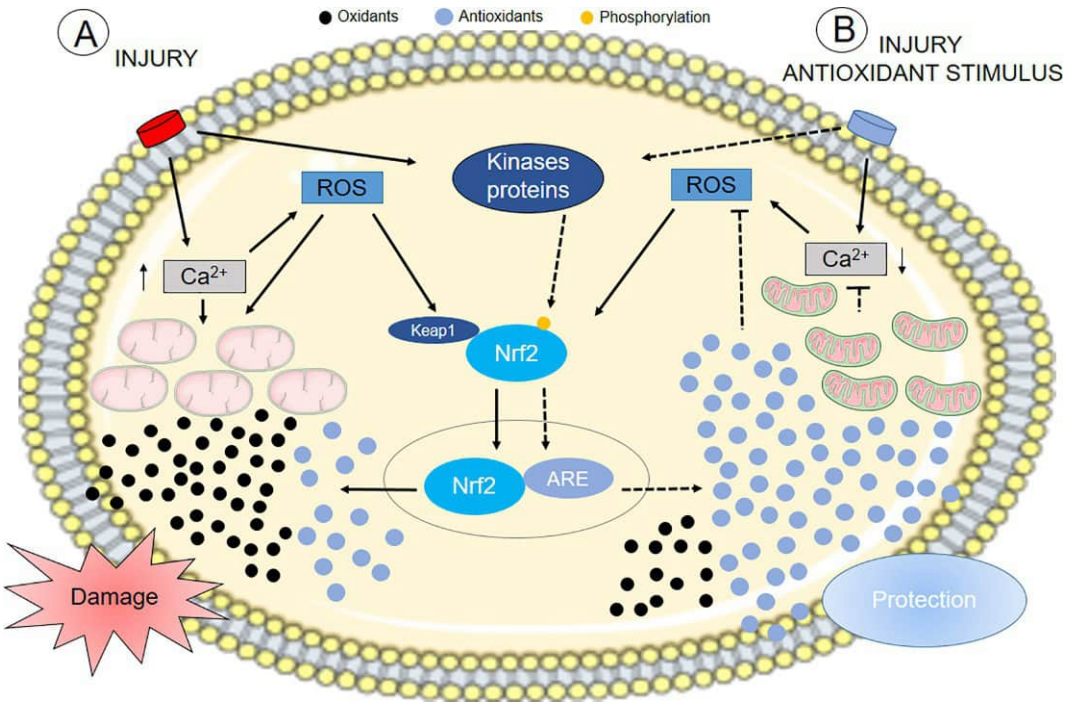

FIG. 3 Schematic representation of the redox signaling pathway after SCI and antioxidant treatment. (A) Injury causes an elevation in intracellular Ca^{2+} levels that induce ROS production through Ca^{2+}-dependent enzymes and mitochondrial damage. Oxidation of cysteine residues modifies the conformation of Keap1 and, together with phosphorylation, initiates the activation of Nrf2. The Nrf2-ARE system is activated but is not effective due to excessive ROS synthesis that causes increased Ca^{2+} influx and cellular and mitochondrial damage. (B) Antioxidant stimuli soon after the injury potentializeNrf2-ARE system activation and increase antioxidant molecule expression against oxidative molecules, decreasing intracellular Ca^{2+} influx and maintaining the tissue and mitochondrial protection. ROS: reactive oxygen species; Keap1: Kelch-like ECH-associated protein 1; Nrf2: nuclear factor erythroid-2-related factor 2; ARE: antioxidant response element; Ca^{2+}: calcium; Continuous arrows: dangerous; Dotted arrows: protective. *(Source: Authors.)*

stress in neurodegenerative disorders. Additionally, reduced dopaminergic pathways in motor areas in Parkinson's disease (Cuadrado et al., 2009) and beta amyloid accumulation in essential memory areas in Alzheimer's disease (Kanninen et al., 2008)also occur due to oxidative stress. Moreover, endogenous and exogenous injuries such as stroke (Halliwell, 1989) and traumatic brain injury (Yan et al., 2009) lead to cascades of signaling events by excessive production of oxidant molecules with consequent functional deficits. The progressive damage induced by oxidative stress appears to play a critical role in axonal degeneration and cell apoptosis after several central nervous system disorders.

Mini-dictionary of terms

Apoptosis: the phenomenon of programmed cell death.
Axoplasm: a cytoplasmic portion of neural axons.
Compression SCI model: compression of the spinal cord using a neurovascular clip, forceps, or balloon.
Contusion SCI model: an impact on the spinal cord using an impactor apparatus.
Excitotoxicity: overstimulation of glutamatergic receptors causing higher calcium influx inside the cells.
Mitochondrial swelling: a marker of mitochondrial damage.
Oxidants: reactive molecules that seek stability during their brief existence through electron attraction.
Oxidative stress: when oxidant molecules are higher than antioxidants, causing cell damage.
Redox state: relative changes in oxidation and reduction state of molecules that are not well defined or quantified.
Wallerian degeneration: a process of axon degeneration associated with the disruption of the myelin sheath.

Key facts of oxidative stress

Oxidative stress causes cell damage by oxidization in proteins, lipids, and nucleic acids after SCI.
In several neurodegenerative disorders and tissue damage, there is oxidative stress-induced cell damage.

Oxidative stress activates the cascade of events that leads to cell apoptosis.
Wallerian degeneration is caused by secondary damage after tissue injury, including oxidative stress.
Nuclear factor erythroid-2-related factor 2 stimulation can increase endogenous antioxidant defenses that may protect cells from oxidative stress damage.

Summary points

This chapter focuses on degeneration mechanisms and protection of nervous fibers after SCI.
Oxidative damage is involved in nervous fiber degeneration after SCI.
The transcription factor nuclear factor erythroid-2 related factor 2 can protect ascending and descending fibers from degeneration by inducing AREs.
Nuclear factor erythroid-2-related factor 2 induces the activation of protective molecules, such as anti-apoptotic B-cell lymphoma and BDNF.
Inflammatory processes reduce with nuclear factor erythroid-2-related factor 2 activation through crosstalk between antioxidant and anti-inflammatory systems.

References

Allen, M., Zou, F., Chai, H. S., Younkin, C. S., Miles, R., Nair, A. A., et al. (2012). Glutathione S-transferase omega genes in Alzheimer and Parkinson disease risk, age-at-diagnosis and brain gene expression: an association study with mechanistic implications. *Molecular Neurodegeneration*, *7*(1), 1–12.

Baird, L., & Dinkova-Kostova, A. T. (2011). The cytoprotective role of the Keap1-Nrf2 pathway. *Archives of Toxicology*, *85*(4), 241–272.

Beattie, M. S., Farooqui, A. A., & Bresnahan, J. C. (2000). Review of current evidence for apoptosis after spinal cord injury. *Journal of Neurotrauma*, *17*(10), 915–925.

Chen, F., Ma, W., He, J., & Zhao, J. (2002). Fenton degradation of malachite green catalyzed by aromatic additives. *The Journal of Physical Chemistry A*, *106*(41), 9485–9490.

Cho, B. O., Ryu, H. W., Jin, C. H., Choi, D. S., Kang, S. Y., Kim, D. S., … Jeong, I. Y. (2011). Blackberry extract attenuates oxidative stress through up-regulation of Nrf2-dependent antioxidant enzymes in carbon tetrachloride-treated rats. *Journal of Agricultural and Food Chemistry*, *59*(21), 11442–11448.

Cuadrado, A., Moreno-Murciano, P., & Pedraza-Chaverri, J. (2009). The transcription factor Nrf2 as a new therapeutic target in Parkinson's disease. *Expert Opinion on Therapeutic Targets*, *13*(3), 319–329.

da Silva Fiorin, F., de Oliveira Ferreira, A. P., Ribeiro, L. R., Silva, L. F., de Castro, M. R., da Silva, L. R., … Franco, J. L. (2016). The impact of previous physical training on redox signaling after traumatic brain injury in rats: A behavioral and neurochemical approach. *Journal of Neurotrauma*, *33*(14), 1317–1330.

Dai, N., Tang, C., Zhao, H., Dai, P., & Huang, S. (2020). *Effect of electroacupuncture on spinal cord injury in mice: Inhibition of inflammatory response and oxidative stress via ApoE and Nrf2* (pp. 1–25). Research Square. https://doi.org/10.21203/rs.3.rs-22504/v1.

Daverey, A., & Agrawal, S. K. (2020). Curcumin protects against white matter injury through NF-κB and Nrf2 cross talk. *Journal of Neurotrauma*, *37*(10), 1255–1265.

do Espírito Santo, C. C., da Silva Fiorin, F., Ilha, J., Duarte, M. M. M. F., Duarte, T., & Santos, A. R. S. (2019). Spinal cord injury by clip-compression induces anxiety and depression-like behaviours in female rats: The role of the inflammatory response. *Brain, Behavior, and Immunity*, *78*, 91–104.

Droge, W. (2002). Free radicals in the physiological control of cell function. *Physiological Reviews*, *82*(1), 47–95.

Fukushima, M., Tatsumi, K., & Morimoto, K. (2000). The fate of aniline after a photo-Fenton reaction in an aqueous system containing iron (III), humic acid, and hydrogen peroxide. *Environmental Science & Technology*, *34*(10), 2006–2013.

Guan, B., Chen, R., Zhong, M., Liu, N., & Chen, Q. (2020). Protective effect of oxymatrine against acute spinal cord injury in rats via modulating oxidative stress, inflammation and apoptosis. *Metabolic Brain Disease*, *35*(1), 149–157.

Halliwell, B. (1989). Oxidants and the central nervous system: Some fundamental questions. Is oxidant damage relevant to Parkinson's disease, Alzheimer's disease, traumatic injury or stroke? *Acta Neurologica Scandinavica*, *80*, 23–33.

Halliwell, B. (2012). Free radicals and antioxidants: Updating a personal view. *Nutrition Reviews*, *70*(5), 257–265.

Halliwell, B., & Gutteridge, J. M. (1995). The definition and measurement of antioxidants in biological systems. *Free Radical Biology & Medicine*, *18*(1), 125.

Halliwell, B., & Whiteman, M. (2004). Measuring reactive species and oxidative damage in vivo and in cell culture: How should you do it and what do the results mean? *British Journal of Pharmacology*, *142*(2), 231–255.

Hayta, E., & Elden, H. (2018). Acute spinal cord injury: A review of pathophysiology and potential of non-steroidal anti-inflammatory drugs for pharmacological intervention. *Journal of Chemical Neuroanatomy*, *87*, 25–31.

Hotz, P., Hoet, P., & Lauwerys, R. (1987). Lipid peroxidation in human pathology: Evaluation of data in literature. *Pathologie Biologie*, *35*(7), 1067–1073.

Innamorato, N. G., Rojo, A. I., García-Yagüe, Á. J., Yamamoto, M., De Ceballos, M. L., & Cuadrado, A. (2008). The transcription factor Nrf2 is a therapeutic target against brain inflammation. *The Journal of Immunology*, *181*(1), 680–689.

Itoh, K., Chiba, T., Takahashi, S., Ishii, T., Igarashi, K., Katoh, Y., … Yamamoto, M. (1997). An Nrf2/small Maf heterodimer mediates the induction of phase II detoxifying enzyme genes through antioxidant response elements. *Biochemical and Biophysical Research Communications*, *236*(2), 313–322.

Itoh, K., Wakabayashi, N., Katoh, Y., Ishii, T., Igarashi, K., Engel, J. D., & Yamamoto, M. (1999). Keap1 represses nuclear activation of antioxidant responsive elements by Nrf2 through binding to the amino-terminal Neh2 domain. *Genes & Development*, *13*(1), 76–86.

Jain, A. K., & Jaiswal, A. K. (2007). GSK-3β acts upstream of Fyn kinase in regulation of nuclear export and degradation of NF-E2 related factor 2. *Journal of Biological Chemistry*, *282*(22), 16502–16510.

Jia, Z., Zhu, H., Li, J., Wang, X., Misra, H., & Li, Y. (2012). Oxidative stress in spinal cord injury and antioxidant-based intervention. *Spinal Cord*, *50*(4), 264–274.

Kanninen, K., Malm, T. M., Jyrkkänen, H. K., Goldsteins, G., Keksa-Goldsteine, V., Tanila, H., … Koistinaho, J. (2008). Nuclear factor erythroid 2-related factor 2 protects against beta amyloid. *Molecular and Cellular Neuroscience*, *39*(3), 302–313.

Kloos, A. D., Fisher, L. C., Detloff, M. R., Hassenzahl, D. L., & Basso, D. M. (2005). Stepwise motor and all-or-none sensory recovery is associated with nonlinear sparing after incremental spinal cord injury in rats. *Experimental Neurology*, *191*(2), 251–265.

Kumar, P., Kalonia, H., & Kumar, A. (2011). Expression of concern: Role of LOX/COX pathways in 3-nitropropionic acid-induced Huntington's disease-like symptoms in rats: Protective effect of licofelone. *British Journal of Pharmacology*, *164*(2b), 644–654.

Lau, A., & Tymianski, M. (2010). Glutamate receptors, neurotoxicity and neurodegeneration. *Pflügers Archiv: European Journal of Physiology*, *460*(2), 525–542.

Lee, J. M., Shih, A. Y., Murphy, T. H., & Johnson, J. A. (2003). NF-E2-related factor-2 mediates neuroprotection against mitochondrial complex I inhibitors and increased concentrations of intracellular calcium in primary cortical neurons. *Journal of Biological Chemistry*, *278*(39), 37948–37956.

Li, D., et al. (2020). Zinc promotes functional recovery after spinal cord injury by activating Nrf2/HO-1 defense pathway and inhibiting inflammation of NLRP3 in nerve cells. *Life Sciences*, *245*, 117351.

Li, X., et al. (2019). Coenzyme Q10 suppresses oxidative stress and apoptosis via activating the Nrf-2/NQO-1 and NF-κB signaling pathway after spinal cord injury in rats. *American Journal of Translational Research*, *11*(10), 6544.

Lin, X., et al. (2019). Treatment with 2-BFI attenuated spinal cord injury by inhibiting oxidative stress and neuronal apoptosis via the Nrf2 signaling pathway. *Frontiers in Cellular Neuroscience*, *13*, 567.

Liu, L., et al. (2020). Imatinib inhibits oxidative stress response in spinal cord injury rats by activating Nrf2/HO-1 signaling pathway. *Experimental and Therapeutic Medicine*, *19*(1), 597–602.

LoPachin, R. M., Gaughan, C. L., Lehning, E. J., Kaneko, Y., Kelly, T. M., & Blight, A. (1999). Experimental spinal cord injury: Spatiotemporal characterization of elemental concentrations and water contents in axons and neuroglia. *Journal of Neurophysiology*, *82*(5), 2143–2153.

Lu, Y., Yang, Y. Y., Zhou, M. W., Liu, N., Xing, H. Y., Liu, X. X., & Li, F. (2018). Ketogenic diet attenuates oxidative stress and inflammation after spinal cord injury by activating Nrf2 and suppressing the NF-κB signaling pathways. *Neuroscience Letters*, *683*, 13–18.

Luo, J., Borgens, R., & Shi, R. (2004). Polyethylene glycol improves function and reduces oxidative stress in synaptosomal preparations following spinal cord injury. *Journal of Neurotrauma*, *21*(8), 994–1007.

Lv, R., et al. (2019). Polydatin attenuates spinal cord injury in rats by inhibiting oxidative stress and microglia apoptosis via Nrf2/HO-1 pathway. *Life Sciences*, *217*, 119–127.

Ma, Z., et al. (2020). Rosmarinic acid exerts a neuroprotective effect on spinal cord injury by suppressing oxidative stress and inflammation via modulating the Nrf2/HO-1 and TLR4/NF-κB pathways. *Toxicology and Applied Pharmacology*, 115014.

Maiorino, M., Gregolin, C., & Ursini, F. (1990). [47] phospholipid hydroperoxide glutathione peroxidase. *Methods in Enzymology*, *186*, 448–457.

Mao, X., et al. (2020). Eriodictyol attenuates spinal cord injury by activating Nrf2/HO-1 pathway and inhibiting NF-κB pathway. *Tropical Journal of Pharmaceutical Research*, *19*(8).

McMahon, M., Thomas, N., Itoh, K., Yamamoto, M., & Hayes, J. D. (2006). Dimerization of substrate adaptors can facilitate cullin-mediated ubiquitylation of proteins by a "tethering" mechanism a two-site interaction model for the Nrf2-Keap1 complex. *Journal of Biological Chemistry*, *281*(34), 24756–24768.

Miller, J. P., Holcomb, J., Al-Ramahi, I., De Haro, M., Gafni, J., Zhang, N., … Botas, J. (2010). Matrix metalloproteinases are modifiers of huntingtin proteolysis and toxicity in Huntington's disease. *Neuron*, *67*(2), 199–212.

Motohashi, H., O'Connor, T., Katsuoka, F., Engel, J. D., & Yamamoto, M. (2002). Integration and diversity of the regulatory network composed of Maf and CNC families of transcription factors. *Gene*, *294*(1–2), 1–12.

Motohashi, H., & Yamamoto, M. (2004). Nrf2-Keap1 defines a physiologically important stress response mechanism. *Trends in Molecular Medicine*, *10*(11), 549–557.

Navarro, A., & Boveris, A. (2007). Brain mitochondrial dysfunction in aging: Conditions that improve survival, neurological performance and mitochondrial function. *Frontiers in Bioscience*, *12*, 1154–1163.

Niture, S. K., & Jaiswal, A. K. (2012). Nrf2 protein up-regulates antiapoptotic protein Bcl-2 and prevents cellular apoptosis. *Journal of Biological Chemistry*, *287*(13), 9873–9886.

Rada, P., Rojo, A. I., Evrard-Todeschi, N., Innamorato, N. G., Cotte, A., Jaworski, T., … Hayes, J. D. (2012). Structural and functional characterization of Nrf2 degradation by the glycogen synthase kinase 3/β-TrCP axis. *Molecular and Cellular Biology*, *32*(17), 3486–3499.

Radi, R., Beckman, J. S., Bush, K. M., & Freeman, B. A. (1991). Peroxynitrite-induced membrane lipid peroxidation: The cytotoxic potential of superoxide and nitric oxide. *Archives of Biochemistry and Biophysics*, *288*(2), 481–487.

Rojo, A. I., Innamorato, N. G., Martín-Moreno, A. M., De Ceballos, M. L., Yamamoto, M., & Cuadrado, A. (2010). Nrf2 regulates microglial dynamics and neuroinflammation in experimental Parkinson's disease. *Glia*, *58*(5), 588–598.

Rojo, A. I., Medina-Campos, O. N., Rada, P., Zúñiga-Toalá, A., López-Gazcón, A., Espada, S., … Cuadrado, A. (2012). Signaling pathways activated by the phytochemical nordihydroguaiaretic acid contribute to a Keap1-independent regulation of Nrf2 stability: Role of glycogen synthase kinase-3. *Free Radical Biology and Medicine*, *52*(2), 473–487.

Sakata, H., Niizuma, K., Yoshioka, H., Kim, G. S., Jung, J. E., Katsu, M., … Chan, P. H. (2012). Minocycline-preconditioned neural stem cells enhance neuroprotection after ischemic stroke in rats. *Journal of Neuroscience*, *32*(10), 3462–3473.

Shah, Z. A., Li, R. C., Thimmulappa, R. K., Kensler, T. W., Yamamoto, M., Biswal, S., & Doré, S. (2007). Role of reactive oxygen species in modulation of Nrf2 following ischemic reperfusion injury. *Neuroscience*, *147*(1), 53–59.

Springer, J. E., Azbill, R. D., Mark, R. J., Begley, J. G., Waeg, G., & Mattson, M. P. (1997). 4-Hydroxynonenal, a lipid peroxidation product, rapidly accumulates following traumatic spinal cord injury and inhibits glutamate uptake. *Journal of Neurochemistry*, *68*(6), 2469–2476.

Stack, C., Ho, D., Wille, E., Calingasan, N. Y., Williams, C., Liby, K., … Beal, M. F. (2010). Triterpenoids CDDO-ethyl amide and CDDO-trifluoroethyl amide improve the behavioral phenotype and brain pathology in a transgenic mouse model of Huntington's disease. *Free Radical Biology and Medicine*, *49*(2), 147–158.

Surh, Y. J., Kundu, J. K., & Na, H. K. (2008). Nrf2 as a master redox switch in turning on the cellular signaling involved in the induction of cytoprotective genes by some chemopreventive phytochemicals. *Planta*, *74*(13), 1526–1539.

Szabó, C., Ischiropoulos, H., & Radi, R. (2007). Peroxynitrite: Biochemistry, pathophysiology and development of therapeutics. *Nature Reviews Drug Discovery*, *6*(8), 662–680.

Tong, K. I., Padmanabhan, B., Kobayashi, A., Shang, C., Hirotsu, Y., Yokoyama, S., & Yamamoto, M. (2007). Different electrostatic potentials define ETGE and DLG motifs as hinge and latch in oxidative stress response. *Molecular and Cellular Biology*, *27*(21), 7511–7521.

Vargas, M. R., & Johnson, J. A. (2009). The Nrf2-ARE cytoprotective pathway in astrocytes. *Expert Reviews in Molecular Medicine*, *11*.

Venugopal, R., & Jaiswal, A. K. (1998). Nrf2 and Nrf1 in association with Jun proteins regulate antioxidant response element-mediated expression and coordinated induction of genes encoding detoxifying enzymes. *Oncogene*, *17*(24), 3145–3156.

Visavadiya, N. P., Patel, S. P., VanRooyen, J. L., Sullivan, P. G., & Rabchevsky, A. G. (2016). Cellular and subcellular oxidative stress parameters following severe spinal cord injury. *Redox Biology*, *8*, 59–67.

Wang, H., et al. (2020). Metformin promotes axon regeneration after spinal cord injury through inhibiting oxidative stress and stabilizing microtubule. *Oxidative Medicine and Cellular Longevity*, *2020*.

Woźniak, B., Woźniak, A., Mila-Kierzenkowska, C., & Kasprzak, H. A. (2016). Correlation of oxidative and antioxidative processes in the blood of patients with cervical spinal cord injury. *Oxidative Medicine and Cellular Longevity*, *2016*.

Yan, W., Wang, H. D., Feng, X. M., Ding, Y. S., Jin, W., & Tang, K. (2009). The expression of NF-E2-related factor 2 in the rat brain after traumatic brain injury. *Journal of Trauma and Acute Care Surgery*, *66*(5), 1431–1435.

Zhang, F., Wang, S., Zhang, M., Weng, Z., Li, P., Gan, Y., … Sporn, M. B. (2012). Pharmacological induction of heme oxygenase-1 by a triterpenoid protects neurons against ischemic injury. *Stroke*, *43*(5), 1390–1397.

Zhang, L., et al. (2019). Sinomenine attenuates traumatic spinal cord injury by suppressing oxidative stress and inflammation via Nrf2 pathway. *Neurochemical Research*, *44*(4), 763–775.

Chapter 15

Novel agent ONO-2506 suppresses astrocytic activation and attenuates post-spinal cord injury pain

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Abbreviations

CNS	central nervous system
CSPGs	chondroitin sulfate proteoglycans
EAAT	excitatory amino acid transporter
GABA	γ-aminobutyric acid
GAD	glutamic acid decarboxylase
GFAP	glial fibrillary acidic protein
GLAST	glutamate aspartate transporter
GLT	glutamate transporter
IL	interleukin
iNOS	inducible nitric oxide synthase
pMCAO	permanent middle cerebral artery occlusion
SCI	spinal cord injury
TNF	tumor necrosis factor

Introduction

Neuropathic pain occurs in 53% of traumatic spinal cord injury (SCI) patients (Burke, Fullen, Stokes, & Lennon, 2017). Post-SCI neuropathic pain is characterized by burning, stabbing, or electric-like pain and often persists chronically (Siddall, McClelland, Rutkowski, & Cousins, 2003). This severe pain markedly affects patients' activities of daily living (ADL) and quality of life (QOL) and can be a cause of depression and even suicide (Cairns, Adkins, & Scott, 1996; Harris, Barraclough, Grundy, Bamford, & Inskip, 1996).

Post-SCI neuropathic pain includes peripherally evoked pain such as hyperalgesia (exaggerated pain evoked by noxious stimuli), allodynia (pain evoked by non-noxious stimuli), and spontaneous pain. Pain is classified into three regions: above-level pain, at-level pain, and below-level pain (Siddall, Taylor, & Cousins, 1997). Despite a variety of pharmacological, surgical, and behavioral therapeutic strategies, it remains challenging to treat post-SCI neuropathic pain effectively (Hatch, Cushing, Carlson, & Chang, 2018; Hulsebosch, Hains, Crown, & Carlton, 2009).

In SCI, an immune reaction represented by astrocytic activation, characterized by the aberrant proliferation and phenotypic change of astrocytes, occurs after mechanical damage. Several studies have demonstrated that astrocytic activation plays important role in post-SCI neuropathic pain (Kramer et al., 2017; Putatunda, Hala, Chin, & Lepore, 2014), and inhibition of this activation has attracted attention as a new therapeutic target for post-SCI neuropathic pain (Nakagawa & Kaneko, 2010).

Cellular, Molecular, Physiological, and Behavioral Aspects of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822427-4.00015-0

Secondary injury of the spinal cord and astrocytic activation

Primary and secondary injury of the spinal cord

Traumatic spinal injury results in various patterns of mechanical damage to the spinal cord tissue, including compression, contusion, and laceration. After these primary injuries, the invasion of immune cells through the damaged blood-spinal cord barrier occurs. These cells induce secondary injury of the spinal cord by causing an immune reaction (inflammation). Neutrophils, macrophages, T-lymphocytes, and microglia are reported to invade the injured spinal cord and release pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-1β, oxidative and proteolytic enzymes, nitric oxide (NO), and free radicals. This secondary injury expands the injured area through the necrosis and apoptosis of neurons and glial cells around the focal region and results in further neurological deterioration. In addition, a fluid-filled cystic cavity that is formed after clearance of the injured area by microglia can be a barrier for axonal regrowth (Ahuja et al., 2017; Fleming et al., 2006; Macaya & Spector, 2012). Currently, the administration of high-dose methylprednisolone sodium succinate is the only available treatment for secondary injury although its use is not recommended because of the limited effectiveness and risk of complications (Hurlbert, 2000) (Table 1).

Astrocytes and their activation

Astrocytes comprise the largest population of glial cells and play a critical role in the secondary injury of the spinal cord. Astrocytes have various important functions, such as maintaining the physical structure of the central nervous system (CNS), formation of the blood-spinal cord barrier, maintaining the extracellular homeostasis of the ionic environment, the release of various neurotrophic factors and cytokines, and uptake of neurotransmitters. Inflammation around the injured site can activate astrocytes and change their phenotype to reactive astrocytes. Reactive astrocytes upregulate glial fibrillary acidic protein (GFAP), key intermediate filaments as astrocyte markers, and exhibit morphologic characteristics such as expanded cytoplasm and extended processes. They produce various pro-inflammatory cytokines (such as IL-1β, IL-6, and TNF-α) to induce further inflammation and neurotoxic agents (such as cyclooxygenase [COX]-2, inducible nitric oxide synthase [iNOS], S100B, and glutamate), which induce neuronal hyperexcitability and apoptosis (Gaudet & Fonken, 2018).

Reactive astrocytes and glial scarring

Reactive astrocytes migrate to the injured site, accumulate around the cystic cavities, and form high-density scar tissue, called glial scars (Fig. 1). Glial scars create physical barriers for axonal regeneration and inhibit the recovery of motor and sensory functions (Silver & Miller, 2004). During scar formation, the reactive astrocytes upregulate the production of chondroitin sulfate proteoglycans (CSPGs; aggrecan, brevican, neurocan, versican, phosphacan, and NG2) (Yiu & He, 2006). CSPGs are extracellular matrix molecules composed of a protein core with glycosaminoglycan (GAG) side chains, which inhibit axonal regrowth. Treatment using chondroitinase ABC (ChABC), an enzyme that removes GAG chains from CSPGs, improved the axonal regeneration and recovery of sensorimotor function in a rat SCI model (Bradbury et al., 2002), and the administration of ChABC is thought to be a potential treatment option for SCI by modulating glial scar formation. The significance of glial scar formation is controversial, however, because recent reports have suggested that

TABLE 1 Pharmacological treatments for post-SCI neuropathic pain.

Clinically available drugs	
Pregabalin, Gabapentin, Lamotrigine	Antiepileptics
Amitriptyline	Tricyclics
Tramadol	Opioids
Duloxetine	Serotonin noradrenaline reuptake inhibitors (SNRI)
Potential therapeutic agents	
ONO-2506 (Ishiguro et al., 2019)	Inhibitor of astrocytic activation
Propentofylline (Gwak et al., 2008)	Inhibitor of microglial and astrocytic activation

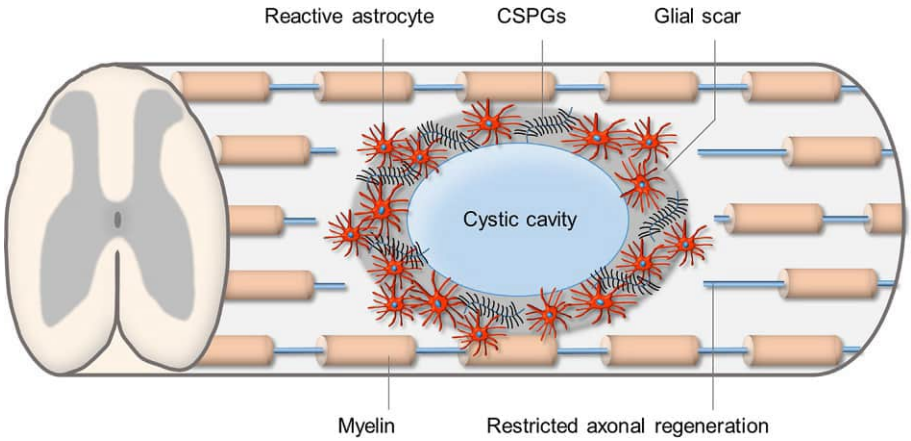

FIG. 1 Glial scar and cystic cavity at the injured site of the spinal cord. Reactive astrocytes form a glial scar with deposition of chondroitin sulfate proteoglycans (CSPGs) around a cystic cavity at the injured site of the spinal cord. The scar tissue creates physical barriers for axonal regeneration.

glial scars might have beneficial functions in neural protection, inhibiting the migration of immune cells and localizing tissue degeneration (Anderson et al., 2016; Faulkner et al., 2004).

Astrocytic activation and post-SCI neuropathic pain

Recent evidence indicates that astrocytic activation plays a major role in post-SCI neuropathic pain. The reduction of reactive astrocytes by the viral overexpression of IL-10 attenuated hindlimb hyperalgesia and allodynia in a rat SCI model (Lau et al., 2012). Below-level allodynia after SCI was alleviated in connexin-43 (a gap junction protein predominantly expressed by astrocytes) knockout mice (Chen et al., 2012). Several studies have reported that reactive astrocytes are observed in the below-level dorsal horn as well as at the regional level after SCI. These findings indicate that astrocytic activation at each level of the spinal cord may alter synaptic activity at the dorsal horn (Carlton et al., 2009; Gwak, Kang, Unabia, & Hulsebosch, 2012). The absence of reactive astrocytes at the below-level dorsal horn after SCI was also reported, however (Ishiguro et al., 2019).

Mechanisms of post-SCI neuropathic pain by astrocytic activation

The detailed mechanisms of post-SCI neuropathic pain associated with astrocytic activation remain largely unknown. Possible causes of the pain include changes in extracellular glutamate and extracellular γ-aminobutyric acid (GABA).

Increase in extracellular glutamate

Glutamate is a neurotransmitter that is released from the presynaptic terminal of primary afferent neurons to secondary neurons. Increased extracellular glutamate concentration in the CNS not only has a harmful influence on synaptic transport but also has the potential to induce neuronal death due to excessive activation of glutamate receptors, which is termed excitotoxicity (Choi, 1988). The glutamate release to extracellular fluid is mediated by excitatory amino acid transporters (EAATs). Among the variety of EAATs, EAAT1 (glutamate aspartate transporter; GLAST) and EAAT2 (glutamate transporter-1; GLT-1), which are selectively expressed by astrocytes, are the main pathways of glutamate uptake (Zhou & Danbolt, 2014) (Fig. 2).

Increased extracellular glutamate concentration at the spinal dorsal horn leads to excitation of the spinothalamic tract neurons (Gwak & Hulsebosch, 2011). The inhibition of glutamate uptake through the intrathecal injection of glutamate transporter blockers DL-threo-beta-benzyloxyaspartate to an intact spinal cord induced post-SCI pain-related behaviors (Liaw et al., 2005).

Post-SCI astrocytic activation causes an elevation in extracellular glutamate concentration in the spinal cord. Thermal hyperalgesia in a rat cervical contusion SCI model demonstrated that the activation of astrocytes was accompanied by the reduced expression of GLT-1 at the dorsal horn (Putatunda et al., 2014; Watson, Hala, Putatunda, Sannie, & Lepore, 2014). In contrast, the viral overexpression of GLT-1 in astrocytes attenuated thermal hyperalgesia in this model (Falnikar, Hala, Poulsen, & Lepore, 2016). These findings suggest that neuropathic pain is caused by the dysregulation of extracellular

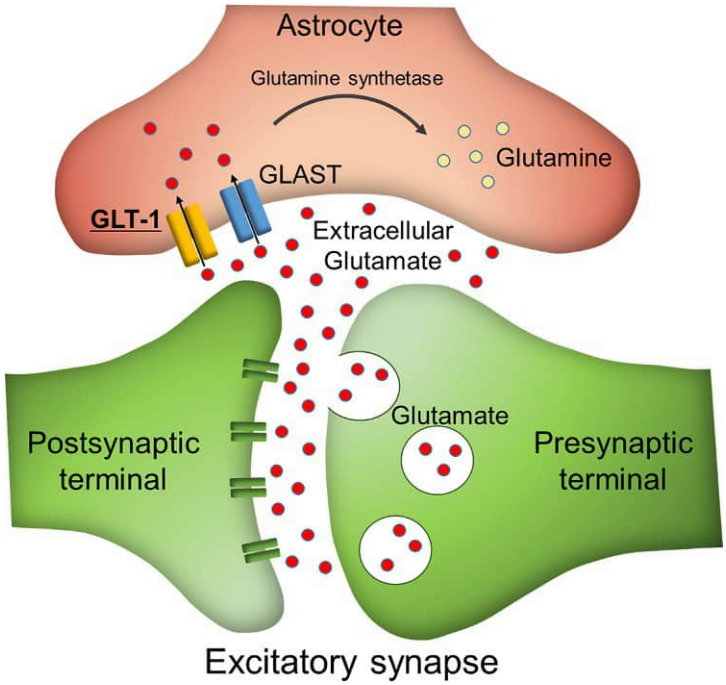

FIG. 2 The uptake of extracellular glutamate by astrocyte glutamate transporters. The glutamate released into an extracellular fluid is mainly mediated by glutamate aspartate transporter (GLAST) and glutamate transporter-1 (GLT-1), which are expressed in astrocytes. Astrocytic activation causes the reduction of GLT-1 expression at the dorsal horn and induces neuropathic pain through the elevation of extracellular glutamate concentration in the spinal cord. GLAST: glutamate aspartate transporter; GLT: glutamate transporter.

glutamate uptake and the subsequent increase of extracellular glutamate concentration. The enhanced release of glutamate from the reactive astrocytes also contributes to the increase in the concentration (Chao, Hu, & Peterson, 1995).

Decrease in extracellular GABA

GABA is a neurotransmitter that plays a crucial role in inhibitory synaptic transmission in the CNS. GABA is produced from glutamate through decarboxylation by glutamic acid decarboxylase (GAD), which is expressed by GABAergic inhibitory neurons. GABA released from the presynaptic terminal to the synaptic cleft acts via ionotropic $GABA_A$ receptors or G-protein-coupled $GABA_B$ receptors. Astrocytes modulate extracellular GABA concentration through the uptake of released GABA via GABA transporter (GAT) (Fig. 3). Gwak et al. reported that astrocytic activation was accompanied by reduced expression of GAD_{65} at the dorsal horn in a rat thoracic SCI model with below-level allodynia. They also demonstrated that the intrathecal administration of propentophylline, a glial modulator that inhibits phosphodiesterase and adenosine uptake, prevented the decrease of GAD_{65} expression at the lumbar dorsal horn and attenuated the astrocytic activation and mechanical allodynia following SCI. These findings suggest that astrocytic activation induces the decreases of GABA production via the reduction of GAD_{65} expression, suppresses the GABAergic inhibitory tone, and induces the sensitization of secondary afferent neurons (Gwak, Crown, Unabia, & Hulsebosch, 2008; Gwak & Hulsebosch, 2011).

Attenuation of post-SCI neuropathic pain by ONO-2506

S100B

The S100 proteins are a family of 8–14 kDa EF-hand Ca^{2+}-binding proteins that have more than 20 subfamilies (Heizmann, Fritz, & Schäfer, 2002). S100B, a homodimer of the S100β subunits, is a member of the S100 protein family that is produced by astrocytes. Reactive astrocytes in the injured CNS due to ischemia or trauma enhance S100B production and secretion, resulting in elevation of the blood and tissue concentration of S100B. This protein is widely used as a reliable clinical biomarker that reflects the volume of cerebral infarction (Missler, Wiesmann, Friedrich, & Kaps, 1997; Thelin, Nelson, & Bellander, 2017). The correlation between serum and cerebrospinal fluid levels of S100B and the severity of SCI has also been reported (Cao et al., 2008). An animal study using S100B overexpressing transgenic mice showed the exacerbation of the infarct volume and neuronal deficit after cerebral ischemia (Mori et al., 2008). In contrast, the neuronal dysfunction due to cerebral infarction was attenuated in S100B knockout mice (Wainwright et al., 2004). Thus, S100B is considered to play an important role in central nerve injury.

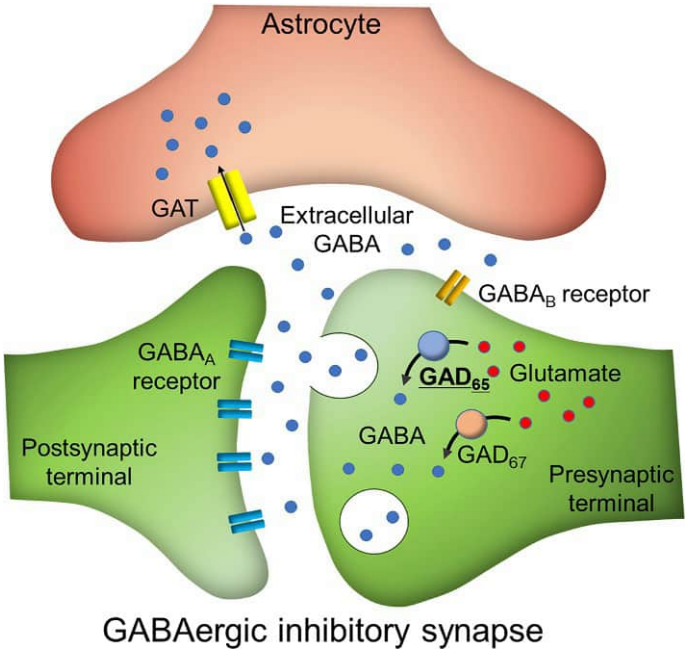

FIG. 3 The GABAergic system in the inhibitory synapse. γ-aminobutyric acid (GABA) is produced from glutamate through decarboxylation by glutamic acid decarboxylase (GAD), which is expressed by GABAergic inhibitory neurons. Astrocytic activation reduces the expression of GAD_{65} at the dorsal horn, which decreases GABA production and induces the sensitization of secondary afferent neurons.

S100B is known to exert both positive and negative effects according to the concentration. Under physiological conditions of low concentration (nanomolar level), S100B exhibit neurotrophic effects, such as the prevention of neuron death, promotion of synapse formation, enhancement of neurite extension, and modulation of long-term neuronal synaptic plasticity (Iwasaki, Shiojima, & Kinoshita, 1997; Kligman & Marshak, 1985; Nishiyama, Knopfel, Endo, & Itohara, 2002). In contrast, a high concentration (micromolar level) of S100B exhibits neurotoxic and pro-inflammatory effects, including the induction of glutamate-induced excitotoxicity and NO-dependent neuronal death (Hu, Ferreira, & Van Eldik, 1997). In addition, S100B promotes astrocytic activation through the receptor for advanced glycation endproducts (RAGE) in astrocytes. This mechanism configures an amplification loop of astrocytic activation and enhances the production of iNOS and pro-inflammatory factors, such as COX-2, IL-1β, IL-6, and TNF-α (Michetti et al., 2019; Villarreal et al., 2014) (Fig. 4).

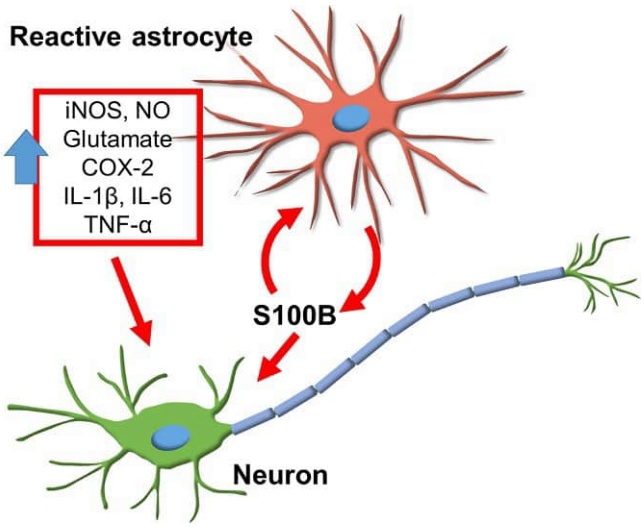

FIG. 4 The effects of S100B secreted by reactive astrocytes. S100B secreted by reactive astrocytes exhibits neurotoxic effects. In addition, S100B promotes astrocytic activation and enhances the production of iNOS, glutamate, and pro-inflammatory factors, such as cyclooxygenase (COX)-2, interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α, which induce neuronal hyperexcitability and apoptosis.

ONO-2506

ONO-2506 (arundic acid, [R]-[−]-2-npropyloctanoic acid) is an agent that inhibits spontaneous S100B expression in cultured astrocytes (Fig. 5). ONO-2506 selectively inhibits S100B production and suppresses astrocytic activation. In this respect, ONO-2506 differs from other antiastrocytic agents such as pentamidine, which blocks the interaction between S100B and p53 (Cirillo et al., 2015), and propentofylline, which inhibits adenosine reuptake (Tawfik et al., 2008). No significant side effects of ONO-2506 on other functions of the central nervous, cardiopulmonary, renal, or digestive systems were observed in animal experiments (Asano et al., 2005).

Action mechanisms of ONO-2506

ONO-2506 suppresses the expression of iNOS and COX-2 in astrocytes by inhibiting the excessive production of S100B in vitro. In a co-culture system of astrocytes and neurons, ONO-2506 attenuated NO-induced neuronal death through the suppression of iNOS expression in astrocytes (Asano et al., 2005). Furthermore, ONO-2506 improves glutamate uptake through the enhancement of GLAST and GLT-1 expression in astrocytes and suppresses glutamate excitotoxicity (Karki et al., 2018; Mori et al., 2004).

The positive effects of ONO-2506 on cerebral ischemia have been confirmed in several studies. In cerebral ischemia, astrocytic activation is known to affect the expansion of the infarct region and the subsequent neurological deterioration. In a rat permanent middle cerebral artery occlusion (pMCAO) model, the administration of ONO-2506 significantly suppressed the delayed expansion of the infarct region. In this model, the increase of S100B at the peri-infarct area and in the cerebrospinal fluid was significantly suppressed by the administration of ONO-2506. Moreover, better neurological recovery within 24 h following the administration of ONO-2506 was observed (Tateishi et al., 2002). In another animal study using a rat transient middle cerebral artery occlusion model, ONO-2506 prevented the reduction of the mRNA expression of glial glutamate transporters (GLT-1 and GLAST) and promoted neurological recovery (Mori et al., 2004). This effect was also confirmed in a monkey model of pMCAO (Asano et al., 2005).

As for the effects of ONO-2506 on SCI, Hanada et al. reported that the administration of ONO-2506 suppressed the astrocytic expression of S100 protein at the injured site and improved motor function after SCI (Hanada et al., 2014).

Effects of ONO-2506 on post-SCI neuropathic pain

Recently, we investigated the effects of ONO-2506 on post-SCI neuropathic pain in a rat model of SCI (Ishiguro et al., 2019). The daily administration of ONO-2506 or saline was continued for 1 week following SCI, and the below-level mechanical and thermal allodynia were evaluated. At post-SCI week 6, the injured site and the dorsal horn at L4/5 were evaluated by fluorescent immunohistochemical analysis using S100B and GFAP antibodies.

The below-level mechanical and thermal allodynia were significantly attenuated by the administration of ONO-2506 throughout the entire 6 weeks after SCI. Fluorescent immunohistochemical assessment at the injured site revealed a significant reduction in the cross-sectional area of the cysts, and a high fluorescence intensity area of S100B and GFAP were confirmed in the ONO-2506 group (Fig. 6). The morphological changes, including cytoplasm expansion and cell process extension in GFAP-positive astrocytes in the saline group, were markedly reduced in the ONO-2506 group. These findings indicate that ONO-2506 attenuates post-SCI neuropathic pain by suppressing secondary injury at the injured site, which occurs within 1 week after SCI. In contrast, reactive astrocytes were not observed at the L4/5 dorsal horn in either group, which suggests that incomplete SCI does not induce below-level astrocytic activation at the dorsal horn. Therefore, the changes at the injured site are the key components in post-SCI neuropathic pain rather than the changes at the lumbar dorsal horn. In addition, a strong correlation was found between the severity of allodynia and the area of the S100B high-intensity lesion at the injured site. These findings suggest that ONO-2506, an inhibitor of S100B production in astrocytes, may be a promising therapeutic agent for post-SCI neuropathic pain.

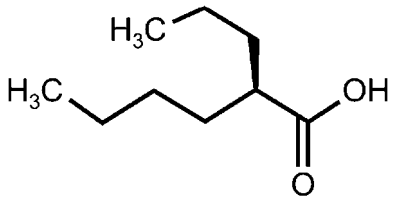

FIG. 5 Chemical structure of ONO-2506.

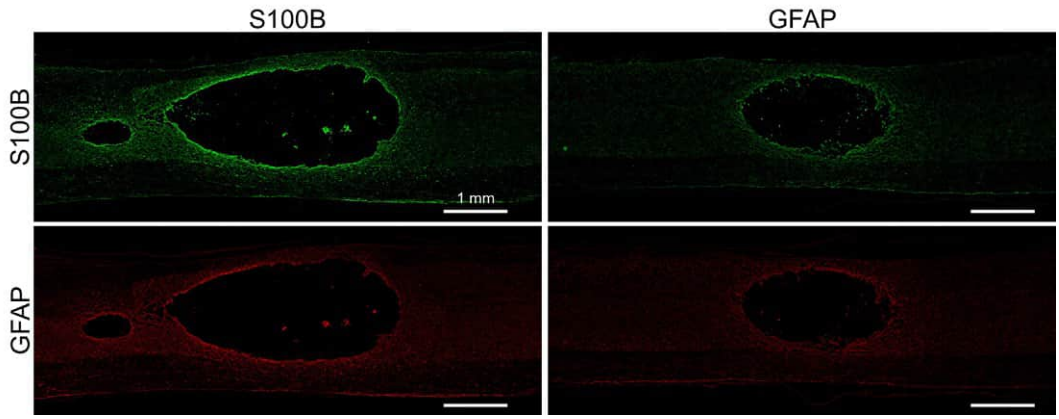

FIG. 6 Immunohistochemical images at the injured site. Fluorescent immunostaining for S100B (red) and glial fibrillary acidic protein (GFAP; green) in the sagittal section of the spinal cord at the injured level. A significant reduction in the cross-sectional area of the cysts and a high fluorescence intensity area of S100B and GFAP were confirmed in the ONO-2506 group. GFAP: glial fibrillary acidic protein.

As mentioned above, astrocytic activation at the dorsal horn has been regarded as the main cause of post-SCI neuropathic pain in previous studies. However, in our study, astrocytic activation was not detected at the below-level dorsal horn. Although the relatively low contusion energy applied to the spinal cord may contribute to this difference, this finding offers a new perspective. First, the reduction of glial scar formation around the lesion by ONO-2506 could have led to the alleviation of neuropathic pain. Since glial scarring prevents neuronal regeneration, this effect may have promoted the regeneration of secondary afferent nociceptive neurons or descending inhibitory neurons. Second, the increase in S100B at the injured site may be critically involved in the development of sensory nervous system disorder after SCI. Further studies are required to identify the detailed underlying mechanisms of astrocytic activation and S100B on post-SCI neuropathic pain.

Post-SCI neuropathic pain due to SCI is a serious disorder that significantly affects patients' ADL and QOL. To develop an effective treatment for post-SCI pain relief, a more detailed understanding of the pathology is essential. As described in this chapter, it is clear that astrocytic activation plays a crucial role in the development of post-SCI neuropathic pain. Although the detailed mechanisms of astrocytic activation on neuropathic pain remain unclear, ONO-2506 may be a promising candidate for the attenuation of post-SCI neuropathic pain by the suppression of astrocytic activation.

Applications to other areas of neuroscience

In this chapter, we have reviewed the mechanisms of post-SCI neuropathic pain, focusing on astrocytic activation associated with secondary injury of the spinal cord. Astrocytic activation causes hyperexcitability of afferent neurons through alteration of the environment of glutamate and gamma-aminobutyric acid (GABA) in the spinal cord, resulting in neuropathic pain such as allodynia and hyperalgesia. Administration of ONO-2506, an agent that suppresses astrocytic activation by inhibition of S100B production, maybe a novel treatment option for post-SCI neuropathic pain.

Enhancement of S100B production in astrocytes is observed not only in cerebral ischemia (Tateishi et al., 2002) and traumatic brain injury (Kleindienst et al., 2005; Sandhir, Onyszchuk, & Berman, 2008), but also in epilepsy (Yang & Sun, 2008); neurodegenerative disorders such as Alzheimer's disease (Doraiswamy & Xiong, 2006; Mori et al., 2006), Parkinson's disease (Kato, Kurosaki, Oki, & Araki, 2004; Sathe et al., 2012), and amyotrophic lateral sclerosis (Serrano et al., 2017; Traynor et al., 2006); and psychological disorders such as schizophrenia (Katsel et al., 2011; Steiner et al., 2014), major or minor depressive disorder, and bipolar disorder (Gos et al., 2013). Further studies using agents that modulate astrocytic S100B production, including ONO-2506, are expected to provide effective treatment options for a variety of neurological and psychological disorders.

Mini-dictionary of terms

- **Allodynia:** Pain evoked by non-noxious stimuli.
- **Astrocytic activation:** A reaction with morphological and functional changes of astrocytes.

- **Excitotoxicity:** A pathological process triggered by the overactivation of receptors for glutamate that induces neuronal death.
- **Gamma-aminobutyric acid (GABA):** A neurotransmitter that plays a crucial role in inhibitory synaptic transmission in the CNS.
- **Glial fibrillary acidic protein (GFAP):** The key intermediate filament as an astrocyte marker. Reactive astrocytes upregulate this protein.
- **Glial scar:** High-density scar tissue formed by reactive astrocytes that creates physical barriers to axonal regeneration.
- **Glutamate:** An excitatory neurotransmitter in the CNS. An elevated concentration of extracellular glutamate is toxic to neurons.
- **Hyperalgesia:** Exaggerated pain evoked by noxious stimuli.
- **Secondary injury:** An expansion of the injured region due to an immune reaction after mechanical damage to the spinal cord.
- **S100B:** A member of the S100 protein family that is produced by astrocytes. Reactive astrocytes in the injured CNS enhance S100B production.

Key facts of ONO-2506

- ONO-2506 is a novel agent that suppresses astrocytic activation by inhibiting S100B production from astrocytes.
- ONO-2506 suppresses nitric oxide-induced neuronal death through the reduction of the inducible nitric oxide synthase expression of astrocytes.
- ONO-2506 ameliorates the reduction of glutamate transporters in reactive astrocytes.
- Studies on cerebral ischemia suggest that ONO-2506 significantly suppresses the delayed expansion of the infarct region due to astrocytic activation.
- The attenuation of post-SCI neuropathic pain by ONO-2506 is demonstrated in animal models of SCI.

Summary points

- Post-SCI neuropathic pain is an important problem that markedly affects patients' ADL and QOL.
- Studies suggest that astrocytic activation plays important role in post-SCI neuropathic pain.
- Changes in the extracellular concentration of glutamate and γ-aminobutyric acid (GABA) have been reported to be involved in astrocytic activation associated post-SCI neuropathic pain.
- ONO-2506 is a novel agent that suppresses astrocytic activation by inhibiting the S100B production from astrocytes.
- Recently, ONO-2506 was reported to attenuate post-SCI neuropathic pain in a rat model of SCI.
- ONO-2506 is a promising candidate for attenuating post-SCI neuropathic pain.

CSPGs: chondroitin sulfate proteoglycans.

GABA: γ-aminobutyric acid, GAD: glutamic acid decarboxylase, GAT: GABA transporter.

iNOS: inducible nitric oxide synthase, NO: nitric oxide, COX: cyclooxygenase, IL: interleukin, TNF: tumor necrosis factor.

References

Ahuja, C. S., Wilson, J. R., Nori, S., Kotter, M. R. N., Druschel, C., Curt, A., et al. (2017). Traumatic spinal cord injury. *Nature Reviews. Disease Primers*, *3*, 17018.

Anderson, M. A., Burda, J. E., Ren, Y., Ao, Y., O'Shea, T. M., Kawaguchi, R., et al. (2016). Astrocyte scar formation aids central nervous system axon regeneration. *Nature*, *532*(7598), 195–200.

Asano, T., Mori, T., Shimoda, T., Shinagawa, R., Satoh, S., Yada, N., et al. (2005). Arundic acid (ONO-2506) ameliorates delayed ischemic brain damage by preventing astrocytic overproduction of S100B. *Current Drug Targets. CNS and Neurological Disorders*, *4*(2), 127–142.

Bradbury, E. J., Moon, L. D., Popat, R. J., King, V. R., Bennett, G. S., Patel, P. N., et al. (2002). Chondroitinase ABC promotes functional recovery after spinal cord injury. *Nature*, *416*(6881), 636–640.

Burke, D., Fullen, B. M., Stokes, D., & Lennon, O. (2017). Neuropathic pain prevalence following spinal cord injury: A systematic review and meta-analysis. *European Journal of Pain*, *21*(1), 29–44.

Cairns, D. M., Adkins, R. H., & Scott, M. D. (1996). Pain and depression in acute traumatic spinal cord injury: Origins of chronic problematic pain? *Archives of Physical Medicine and Rehabilitation*, *77*(4), 329–335.

Cao, F., Yang, X. F., Liu, W. G., Hu, W. W., Li, G., Zheng, X. J., et al. (2008). Elevation of neuron-specific enolase and S-100beta protein level in experimental acute spinal cord injury. *Journal of Clinical Neuroscience*, *15*(5), 541–544.

Carlton, S. M., Du, J., Tan, H. Y., Nesic, O., Hargett, G. L., Bopp, A. C., et al. (2009). Peripheral and central sensitization in remote spinal cord regions contribute to central neuropathic pain after spinal cord injury. *Pain*, *147*(1–3), 265–276.

Chao, C. C., Hu, S., & Peterson, P. K. (1995). Glia, cytokines, and neurotoxicity. *Critical Reviews in Neurobiology*, *9*(2–3), 189–205.

Chen, M. J., Kress, B., Han, X., Moll, K., Peng, W., Ji, R. R., et al. (2012). Astrocytic CX43 hemichannels and gap junctions play a crucial role in development of chronic neuropathic pain following spinal cord injury. *Glia*, *60*(11), 1660–1670.

Choi, D. W. (1988). Glutamate neurotoxicity and diseases of the nervous system. *Neuron*, *1*(8), 623–634.

Cirillo, C., Capoccia, E., Iuvone, T., Cuomo, R., Sarnelli, G., Steardo, L., et al. (2015). S100B inhibitor pentamidine attenuates reactive gliosis and reduces neuronal loss in a mouse model of Alzheimer's disease. *BioMed Research International*, *2015*, 508342.

Doraiswamy, P. M., & Xiong, G. L. (2006). Pharmacological strategies for the prevention of Alzheimer's disease. *Expert Opinion on Pharmacotherapy*, *7*(1), 1–10.

Falnikar, A., Hala, T. J., Poulsen, D. J., & Lepore, A. C. (2016). GLT1 overexpression reverses established neuropathic pain-related behavior and attenuates chronic dorsal horn neuron activation following cervical spinal cord injury. *Glia*, *64*(3), 396–406.

Faulkner, J. R., Herrmann, J. E., Woo, M. J., Tansey, K. E., Doan, N. B., & Sofroniew, M. V. (2004). Reactive astrocytes protect tissue and preserve function after spinal cord injury. *The Journal of Neuroscience*, *24*(9), 2143–2155.

Fleming, J. C., Norenberg, M. D., Ramsay, D. A., Dekaban, G. A., Marcillo, A. E., Saenz, A. D., et al. (2006). The cellular inflammatory response in human spinal cords after injury. *Brain*, *129*(Pt. 12), 3249–3269.

Gaudet, A. D., & Fonken, L. K. (2018). Glial cells shape pathology and repair after spinal cord injury. *Neurotherapeutics*, *15*(3), 554–577.

Gos, T., Schroeter, M. L., Lessel, W., Bernstein, H. G., Dobrowolny, H., Schiltz, K., et al. (2013). S100B-immunopositive astrocytes and oligodendrocytes in the hippocampus are differentially afflicted in unipolar and bipolar depression: A postmortem study. *Journal of Psychiatric Research*, *47*(11), 1694–1699.

Gwak, Y. S., Crown, E. D., Unabia, G. C., & Hulsebosch, C. E. (2008). Propentofylline attenuates allodynia, glial activation and modulates GABAergic tone after spinal cord injury in the rat. *Pain*, *138*(2), 410–422.

Gwak, Y. S., & Hulsebosch, C. E. (2011). GABA and central neuropathic pain following spinal cord injury. *Neuropharmacology*, *60*(5), 799–808.

Gwak, Y. S., Kang, J., Unabia, G. C., & Hulsebosch, C. E. (2012). Spatial and temporal activation of spinal glial cells: Role of gliopathy in central neuropathic pain following spinal cord injury in rats. *Experimental Neurology*, *234*(2), 362–372.

Hanada, M., Shinjo, R., Miyagi, M., Yasuda, T., Tsutsumi, K., Sugiura, Y., et al. (2014). Arundic acid (ONO-2506) inhibits secondary injury and improves motor function in rats with spinal cord injury. *Journal of the Neurological Sciences*, *337*(1–2), 186–192.

Harris, E. C., Barraclough, B. M., Grundy, D. J., Bamford, E. S., & Inskip, H. M. (1996). Attempted suicide and completed suicide in traumatic spinal cord injury. Case reports. *Spinal Cord*, *34*(12), 752–753.

Hatch, M. N., Cushing, T. R., Carlson, G. D., & Chang, E. Y. (2018). Neuropathic pain and SCI: Identification and treatment strategies in the 21st century. *Journal of the Neurological Sciences*, *384*, 75–83.

Heizmann, C. W., Fritz, G., & Schäfer, B. W. (2002). S100 proteins: Structure, functions and pathology. *Frontiers in Bioscience*, *7*, d1356–d1368.

Hu, J., Ferreira, A., & Van Eldik, L. J. (1997). S100beta induces neuronal cell death through nitric oxide release from astrocytes. *Journal of Neurochemistry*, *69*(6), 2294–2301.

Hulsebosch, C. E., Hains, B. C., Crown, E. D., & Carlton, S. M. (2009). Mechanisms of chronic central neuropathic pain after spinal cord injury. *Brain Research Reviews*, *60*(1), 202–213.

Hurlbert, R. J. (2000). Methylprednisolone for acute spinal cord injury: An inappropriate standard of care. *Journal of Neurosurgery*, *93*(1 Suppl), 1–7.

Ishiguro, H., Kaito, T., Hashimoto, K., Kushioka, J., Okada, R., Tsukazaki, H., et al. (2019). Administration of ONO-2506 suppresses neuropathic pain after spinal cord injury by inhibition of astrocytic activation. *The Spine Journal*, *19*(8), 1434–1442.

Iwasaki, Y., Shiojima, T., & Kinoshita, M. (1997). S100 beta prevents the death of motor neurons in newborn rats after sciatic nerve section. *Journal of the Neurological Sciences*, *151*(1), 7–12.

Karki, P., Hong, P., Johnson, J., Jr., Pajarillo, E., Son, D. S., Aschner, M., et al. (2018). Arundic acid increases expression and function of astrocytic glutamate transporter EAAT1 via the ERK, Akt, and NF-κB pathways. *Molecular Neurobiology*, *55*(6), 5031–5046.

Kato, H., Kurosaki, R., Oki, C., & Araki, T. (2004). Arundic acid, an astrocyte-modulating agent, protects dopaminergic neurons against MPTP neurotoxicity in mice. *Brain Research*, *1030*(1), 66–73.

Katsel, P., Byne, W., Roussos, P., Tan, W., Siever, L., & Haroutunian, V. (2011). Astrocyte and glutamate markers in the superficial, deep, and white matter layers of the anterior cingulate gyrus in schizophrenia. *Neuropsychopharmacology*, *36*(6), 1171–1177.

Kleindienst, A., McGinn, M. J., Harvey, H. B., Colello, R. J., Hamm, R. J., & Bullock, M. R. (2005). Enhanced hippocampal neurogenesis by intraventricular S100B infusion is associated with improved cognitive recovery after traumatic brain injury. *Journal of Neurotrauma*, *22*(6), 645–655.

Kligman, D., & Marshak, D. R. (1985). Purification and characterization of a neurite extension factor from bovine brain. *Proceedings of the National Academy of Sciences of the United States of America*, *82*(20), 7136–7139.

Kramer, J. L., Minhas, N. K., Jutzeler, C. R., Erskine, E. L., Liu, L. J., & Ramer, M. S. (2017). Neuropathic pain following traumatic spinal cord injury: Models, measurement, and mechanisms. *Journal of Neuroscience Research*, *95*(6), 1295–1306.

Lau, D., Harte, S. E., Morrow, T. J., Wang, S., Mata, M., & Fink, D. J. (2012). Herpes simplex virus vector-mediated expression of interleukin-10 reduces below-level central neuropathic pain after spinal cord injury. *Neurorehabilitation and Neural Repair*, *26*(7), 889–897.

Liaw, W. J., Stephens, R. L., Jr., Binns, B. C., Chu, Y., Sepkuty, J. P., Johns, R. A., et al. (2005). Spinal glutamate uptake is critical for maintaining normal sensory transmission in rat spinal cord. *Pain*, *115*(1–2), 60–70.

Macaya, D., & Spector, M. (2012). Injectable hydrogel materials for spinal cord regeneration: A review. *Biomedical Materials*, *7*(1), 012001.

Michetti, F., D'Ambrosi, N., Toesca, A., Puglisi, M. A., Serrano, A., Marchese, E., et al. (2019). The S100B story: From biomarker to active factor in neural injury. *Journal of Neurochemistry*, *148*(2), 168–187.

Missler, U., Wiesmann, M., Friedrich, C., & Kaps, M. (1997). S-100 protein and neuron-specific enolase concentrations in blood as indicators of infarction volume and prognosis in acute ischemic stroke. *Stroke*, *28*(10), 1956–1960.

Mori, T., Tan, J., Arendash, G. W., Koyama, N., Nojima, Y., & Town, T. (2008). Overexpression of human S100B exacerbates brain damage and periinfarct gliosis after permanent focal ischemia. *Stroke*, *39*(7), 2114–2121.

Mori, T., Tateishi, N., Kagamiishi, Y., Shimoda, T., Satoh, S., Ono, S., et al. (2004). Attenuation of a delayed increase in the extracellular glutamate level in the peri-infarct area following focal cerebral ischemia by a novel agent ONO-2506. *Neurochemistry International*, *45*(2–3), 381–387.

Mori, T., Town, T., Tan, J., Yada, N., Horikoshi, Y., Yamamoto, J., et al. (2006). Arundic acid ameliorates cerebral amyloidosis and gliosis in Alzheimer transgenic mice. *The Journal of Pharmacology and Experimental Therapeutics*, *318*(2), 571–578.

Nakagawa, T., & Kaneko, S. (2010). Spinal astrocytes as therapeutic targets for pathological pain. *Journal of Pharmacological Sciences*, *114*(4), 347–353.

Nishiyama, H., Knopfel, T., Endo, S., & Itohara, S. (2002). Glial protein S100B modulates long-term neuronal synaptic plasticity. *Proceedings of the National Academy of Sciences of the United States of America*, *99*(6), 4037–4042.

Putatunda, R., Hala, T. J., Chin, J., & Lepore, A. C. (2014). Chronic at-level thermal hyperalgesia following rat cervical contusion spinal cord injury is accompanied by neuronal and astrocyte activation and loss of the astrocyte glutamate transporter, GLT1, in superficial dorsal horn. *Brain Research*, *1581*, 64–79.

Sandhir, R., Onyszchuk, G., & Berman, N. E. (2008). Exacerbated glial response in the aged mouse hippocampus following controlled cortical impact injury. *Experimental Neurology*, *213*(2), 372–380.

Sathe, K., Maetzler, W., Lang, J. D., Mounsey, R. B., Fleckenstein, C., Martin, H. L., et al. (2012). S100B is increased in Parkinson's disease and ablation protects against MPTP-induced toxicity through the RAGE and TNF-α pathway. *Brain*, *135*(Pt. 11), 3336–3347.

Serrano, A., Donno, C., Giannetti, S., Perić, M., Andjus, P., D'Ambrosi, N., et al. (2017). The astrocytic S100B protein with its receptor RAGE is aberrantly expressed in SOD1(G93A) models, and its inhibition decreases the expression of proinflammatory genes. *Mediators of Inflammation*, *2017*, 1626204.

Siddall, P. J., McClelland, J. M., Rutkowski, S. B., & Cousins, M. J. (2003). A longitudinal study of the prevalence and characteristics of pain in the first 5 years following spinal cord injury. *Pain*, *103*(3), 249–257.

Siddall, P. J., Taylor, D. A., & Cousins, M. J. (1997). Classification of pain following spinal cord injury. *Spinal Cord*, *35*(2), 69–75.

Silver, J., & Miller, J. H. (2004). Regeneration beyond the glial scar. *Nature Reviews. Neuroscience*, *5*(2), 146–156.

Steiner, J., Schmitt, A., Schroeter, M. L., Bogerts, B., Falkai, P., Turck, C. W., et al. (2014). S100B is downregulated in the nuclear proteome of schizophrenia corpus callosum. *European Archives of Psychiatry and Clinical Neuroscience*, *264*(4), 311–316.

Tateishi, N., Mori, T., Kagamiishi, Y., Satoh, S., Katsube, N., Morikawa, E., et al. (2002). Astrocytic activation and delayed infarct expansion after permanent focal ischemia in rats. Part II: Suppression of astrocytic activation by a novel agent (R)-(−)-2-propyloctanoic acid (ONO-2506) leads to mitigation of delayed infarct expansion and early improvement of neurologic deficits. *Journal of Cerebral Blood Flow and Metabolism*, *22*(6), 723–734.

Tawfik, V. L., Regan, M. R., Haenggeli, C., Lacroix-Fralish, M. L., Nutile-McMenemy, N., Perez, N., et al. (2008). Propentofylline-induced astrocyte modulation leads to alterations in glial glutamate promoter activation following spinal nerve transection. *Neuroscience*, *152*(4), 1086–1092.

Thelin, E. P., Nelson, D. W., & Bellander, B. M. (2017). A review of the clinical utility of serum S100B protein levels in the assessment of traumatic brain injury. *Acta Neurochirurgica*, *159*(2), 209–225.

Traynor, B. J., Bruijn, L., Conwit, R., Beal, F., O'Neill, G., Fagan, S. C., et al. (2006). Neuroprotective agents for clinical trials in ALS: A systematic assessment. *Neurology*, *67*(1), 20–27.

Villarreal, A., Seoane, R., Gonzalez Torres, A., Rosciszewski, G., Angelo, M. F., Rossi, A., et al. (2014). S100B protein activates a RAGE-dependent autocrine loop in astrocytes: Implications for its role in the propagation of reactive gliosis. *Journal of Neurochemistry*, *131*(2), 190–205.

Wainwright, M. S., Craft, J. M., Griffin, W. S., Marks, A., Pineda, J., Padgett, K. R., et al. (2004). Increased susceptibility of S100B transgenic mice to perinatal hypoxia-ischemia. *Annals of Neurology*, *56*(1), 61–67.

Watson, J. L., Hala, T. J., Putatunda, R., Sannie, D., & Lepore, A. C. (2014). Persistent at-level thermal hyperalgesia and tactile allodynia accompany chronic neuronal and astrocyte activation in superficial dorsal horn following mouse cervical contusion spinal cord injury. *PLoS One*, *9*(9), e109099.

Yang, L., & Sun, R. (2008). ONO-2506 may both prevent and treat epilepsy. *Medical Hypotheses*, *71*(3), 465–466.

Yiu, G., & He, Z. (2006). Glial inhibition of CNS axon regeneration. *Nature Reviews. Neuroscience*, *7*(8), 617–627.

Zhou, Y., & Danbolt, N. C. (2014). Glutamate as a neurotransmitter in the healthy brain. *Journal of Neural Transmission (Vienna)*, *121*(8), 799–817.

Chapter 16

Neural tissue loss after spinal cord injury

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List of abbreviations

ASA	anterior spinal artery
BSCB	blood–spinal cord barrier
CSF	cerebrospinal fluid
FLA	fluorescein-labeled albumin
ISP	intraspinal pressure
MAP	mean arterial pressure
PSAs	posterior spinal arteries
SCBF	spinal cord blood flow
SCI	spinal cord injury

Introduction

Even if the spinal cord is naturally well protected by the spine, cerebrospinal fluid (CSF) buffering the dural sac movements, and epidural fat unevenly distributed along the spinal canal, spinal trauma can induce a sudden or slow and gradual pressure on the spinal cord resulting in the interruption of information that transfer between brain and periphery. The severity and duration of compression determine the manifestation of clinical symptoms. The progress of histopathological changes arising from the initial insult (primary injury) and following secondary injury can be classified into a distinct, but in certain degree overlapping periods: immediate phase (initial 1–2 h), acute phase (early acute 2–48 h, subacute 48 h to 14 days), intermediate phase (14 days to 6 months), and chronic injury phase (>6 months) (Rowland, Hawryluk, Kwon, & Fehlings, 2008). Following pathological events of acute traumatic injury occurring during early and/or late phases significantly contribute to the progressive degeneration and subsequently to the neural tissue loss of the spinal cord.

Dysfunction of vascular system

The spinal cord is equipped with rich, highly variable, and extensively anastomotic vascular network providing continuous delivery of oxygen and nutrients that are necessary for the maintenance of high metabolic demands. Therefore, systemic and local dysfunction of vascular system, resulting in post-traumatic ischemia and subsequent spinal cord infarction, represents a crucial factor affecting the extent of secondary injury.

The reduced blood supply of spinal cord

Since the spinal cord is vulnerable to suboptimal perfusion, it is therefore equipped with pressure autoregulatory capacity, also called *vascular autoregulation*. The synergy between sympathetic and parasympathetic nervous systems plays an important role in the control of cardiovascular system. While parasympathetic outflow is preserved, the direct mechanical insult to the spinal cord can cause the disruption of efferent pathways from the cardiovascular center in the brainstem to the spinal sympathetic centers resulting in failure of short-term blood pressure regulation. It is dependent on injury level, with more severe in cervical and high thoracic SCI. Sudden loss of autonomic tone due to the SCI can typically lead to *neurogenic shock*. Its typical symptoms are bradycardia and hypotension with decreased peripheral resistance and depressed cardiac output (Kiss & Tator, 1993). Persisted hypotension as a manifestation of impairment to the neuraxial blood flow autoregulation markedly increases the risk of secondary ischemia. Experimental study of autoregulation of spinal cord

Cellular, Molecular, Physiological, and Behavioral Aspects of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822427-4.00016-2

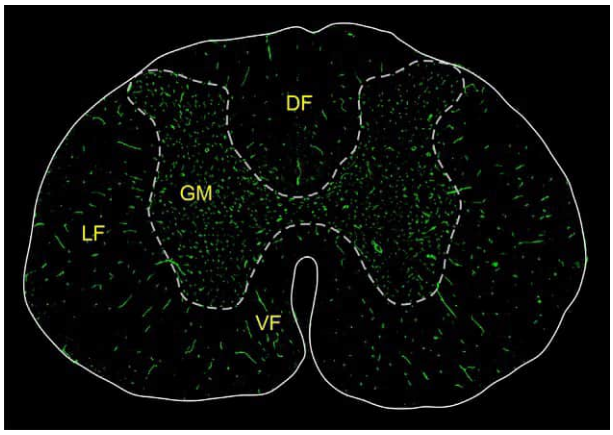

FIG. 1 Vascular density in the spinal cord. Vascular network is much denser in the gray matter (GM) than in the white one. Although blood flow in the dorsal (DF), lateral (LF), and ventral funiculus (VF) of the white matter is relatively similar, blood flow in the gray matter regions is approximately 2–5 times higher.

blood flow (SCBF) in rats at the lesion site demonstrated that vascular autoregulatory mechanisms are maintained after mild SCI, but were lost in the severe SCI (Guha, Tator, & Rochon, 1989).

Measurement of SCBF during experimental SCI revealed significant post-traumatic ischemia at the injury site and adjacent segments, and the blood flow reduction correlated with the severity of the injury (Koyanagi, Tator, & Lea, 1993). Interestingly, utilizing 3D model demonstrated that anterior SCI results in the least reduction of SCBF, while posterior SCI contributes to the greatest reduction of SCBF (Alshareef et al., 2014). Detailed study of blood flow following SCI in rats revealed a severe reduction of SCBF 15 min after injury that lasted for at least 24 h in both white and gray matter, but predominantly in the gray one (Fig. 1) (Rivlin & Tator, 1978). Similarly, pathological changes in vascular endothelium can lead to progressive deterioration of SCBF. Ultrastructural studies of injured spinal cord revealed the integrity loss of endothelial tight junctions in capillaries and larger vessels with smooth muscle cells (Goodman, Bingham Jr, & Hunt, 1976). Other factors associated with spinal vasculature disruption, such as tissue swelling and hemorrhages, can substantially support the development of secondary ischemia. Besides, since venous blood return usually promoted by the skeletal muscle pumping effect is disrupted due to motor deficit, the venous stasis can be one of the factors contributing to the risk of deep vein thrombosis.

Recently, real-time monitoring of microvascular SCBF using laser speckle contrast imaging in human patients after the SCI determined three distinct patterns of SCBF: (1) *the necrosis-penumbra SCBF pattern* characterized by a central region of very low SCBF (necrosis, defined as <25% of maximum flux), intermediate SCBF above and below (penumbra, defined as 25%–75% of maximum flux), and normal SCBF more distally; (2) *the hyperperfusion SCBF pattern* characterized by very high SCBF throughout the injury site, and was only seen in cervical SCI; and (3) *the patchy-perfusion SCBF pattern* characterized by irregular regions of ischemic and hyperemic SCBF (Gallagher, Hogg, Zoumprouli, Papadopoulos, & Saadoun, 2019). Interestingly, the intervention to elevate mean arterial pressure (MAP) by 20 mmHg, in order to normalize perfusion of injured spinal cord, increased overall SCBF at injury site only in some patients, and blood flow increased in some regions but decreased in the others (phenomenon termed as *blood pressure-induced local steal*). Moreover, some parts of the injured spinal cord were well perfused in systole, but inadequately perfused in diastole (known as *diastolic ischemia*). These findings suggested that intervention to increase MAP may induce detrimental responses in post-traumatic SCBF, at least, in some cases.

Intraparenchymal hemorrhages

The instant traumatic event causes mechanical damage to spinal parenchyma at the lesion center, including the direct disruption of local vascular integrity. The rupture of vessel results in *primary hemorrhage,* a leakage of blood that pressurizes on surrounding spinal parenchyma. The size of hemorrhage is maximal at the lesion epicenter, and is directly proportional to the severity of initial insult (Mautes, Weinzierl, Donovan, & Noble, 2000). Intraparenchymal hemorrhage occupies predominantly the gray matter and extends radially into the adjacent white matter in a variable proportion (Losey, Young, Krimholtz, Bordet, & Anthony, 2014). The extent of hemorrhage within injured spinal cord is commonly associated with the formation of intraparenchymal cavities. Resulting from progressive failure of structural capillary integrity, there is an

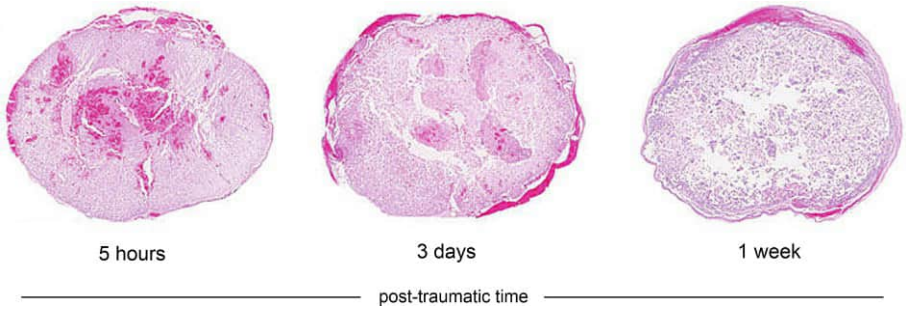

FIG. 2 Petechial hemorrhages. Coronal sections demonstrating numerous discrete petechial hemorrhages observed early after SCI that disappeared over time. *(Reproduced from Leonard, A. V., Thornton, E., & Vink, R. (2015). The relative contribution of edema and hemorrhage to raised intrathecal pressure after traumatic spinal cord injury*. Journal of Neurotrauma, 32*(6), 397–402.)*

early observed formation of small *petechial hemorrhages* (Fig. 2) in the spinal cord tissue surrounding the site of primary lesion, which within time increase in number and coalesce into a hemorrhagic lesion (Gerzanich et al., 2009). A marked reduction of microcirculation in both gray and white matter, especially in hemorrhagic regions and in adjacent zones, was observed (Tator & Fehlings, 1991). Since the predominance of hemorrhage, gray matter was considered to be the origin of the spinal tissue damage, which slowly spreads to the surrounding white matter. However, it was suggested that initial trauma also disrupts the functional ability of white matter and the injury is not simply a result of spreading from gray to white matter (Martirosyan et al., 2011).

Previous microangiographic studies showed that the vascular damage in human SCI occurs primarily in the intramedullary vascular system (Tator & Koyanagi, 1997). Contrary, traumatic occlusion or thrombosis of major superficial arteries after trauma, including the anterior spinal artery (ASA) and posterior spinal arteries (PSAs), is extremely rare (Jellinger, 1976). A physical modeling of spinal cord contusion revealed that compression force on spinal cord produces longitudinal stress being most intense in the center (Blight & Decrescito, 1986). Thus, it explains why the superficial vessels of the spinal cord are relatively spared from initial insults, whereas microvasculature in the central gray matter is subjected to stretching and shear stress. Additionally, the spinal cord is anisotropic and the elasticity of white and gray matter is different (Popovich, Lemeshow, Gensel, & Tovar, 2012).

It seems that central (sulcal) arteries are the most frequently affected by traumatic insult, especially in acute compression-induced SCI. Since they represent the main blood supply of the spinal cord, their disruption and occlusion subsequently interrupt the blood supply to the capillary beds and cause extensive spinal cord ischemia (Fig. 3). Regular narrowed sulcal arteries at the injury site and sporadic mild narrowing of the ASA were observed by scanning electron microscopy technique after the application of aneurysm clip compression (Koyanagi et al., 1993). Fibrinoid necrosis of sulcal arteries at the lesion site immediately and aneurysmal dilatation and rupture of intramedullary arteries in the lateral spinal cord columns at 4 and 8 h were described after experimental traumatic insult (Balentine, 1978). The sulcal arteries supplying area closely correspond with the distribution of both hemorrhagic necroses in the acute phase and the central myelomalacia and cavitation in later phases (Tator & Koyanagi, 1997). The results published by Tator and Koyanagi (1997) showed that the gray matter at the lesion site is more prone to be hemorrhagic, whereas non-hemorrhagic degenerative changes, including decreased staining, periaxonal and axonal swelling, and myelin disruption on most of the white matter are distributed around these hemorrhagic gray matter and extended rostrally and caudally from the lesion site, especially in the posterior white columns. Thus, the surrounding white matter lesions can be partially explained by disrupted sulcal centrifugal arterial system in gray matter that leads to a subsequent interruption of blood flow to the inner half of the white matter.

The initial trauma affects arterial as well as venous system. Electron microscopy studies showed the distention of muscular venules in the gray matter within 5 min after injury (Dohrmann, Wagner Jr., & Bucy, 1971). Small hemorrhages with extravasation of erythrocytes into the perivascular spaces of post-capillary and muscular venules are observed between 15 and 30 min post-traumatic period. In addition, it was suggested that the disruption of venous drainage by either direct mechanical or secondary to arterial or capillary occlusion can markedly contribute to the non-hemorrhagic lesions of the white matter.

The formation of intraparenchymal hemorrhage in lesioned spinal cord can substantially contribute to the following secondary injury at least by (1) direct compression of surrounding tissue resulting in reduced blood flow (secondary ischemia) and (2) toxicity of extravascular blood components such as elevated thrombin (Hua et al., 2006), erythrocyte lysis, and iron toxicity (Garton, Keep, Hua, & Xi, 2016).

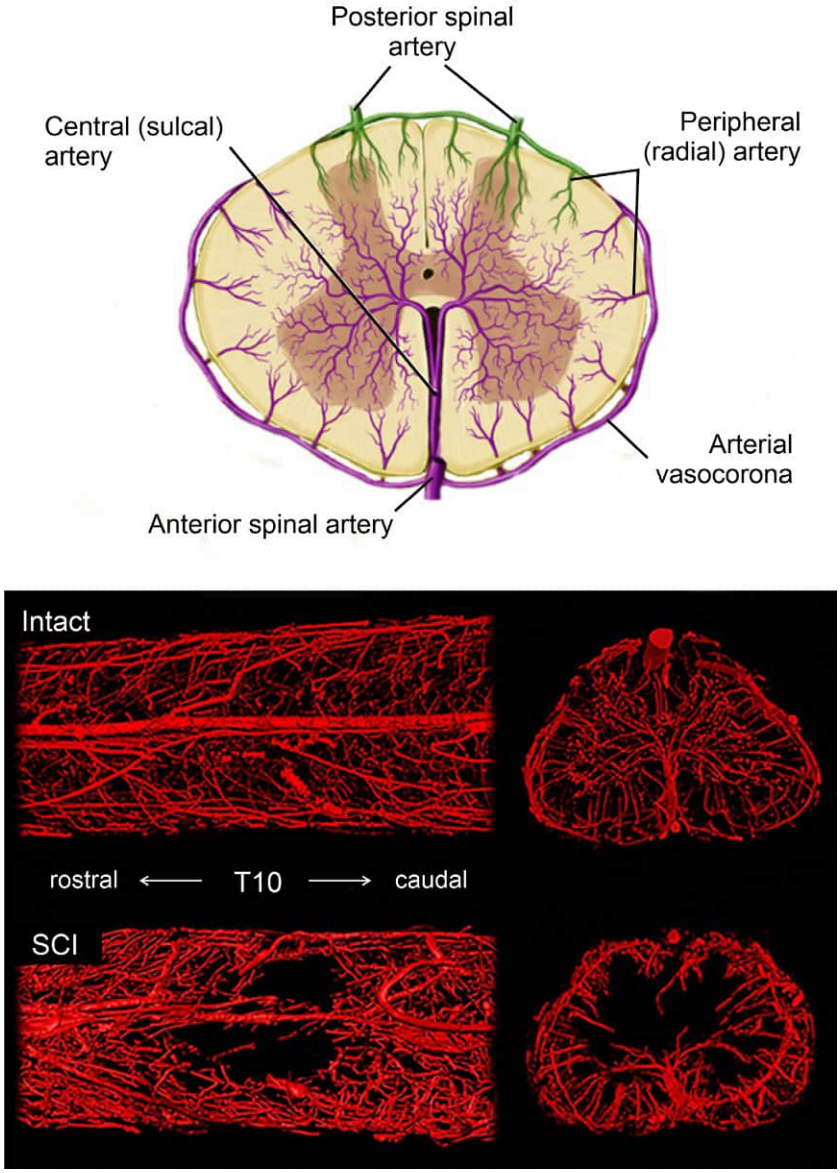

FIG. 3 Intramedullary arterial system after the SCI. *Upper:* The spinal cord parenchyma is instantly supplied by two types of intramedullary feeding arteries: the central (sulcal) arteries arising from the ASA and the penetrating peripheral (radial) arteries arising from the vasocorona, which are formed by branches of the PSAs. In humans, the central arteries centrifugally supply the major part of the spinal cord, which consists of all anterior gray matter, the anterior half of the posterior gray matter, approximately the inner half of the anterior and lateral white matter columns, and the anterior half of the posterior white columns. The peripheral arteries centripetally supply the outer part of the ventral and lateral columns, and dorsal columns in white matter, and the dorsal part of the dorsal gray matter. *Lower*: 3D morphology (longitudinal and transverse views) of the rat spinal cord vasculature of intact and injured spinal cord 1 day after trauma. Mechanical impact was applied dorsally at the T10 segmental level. It can be noted on the transverse section that avascular area predominantly corresponds with the area supplied by central (sulcal) artery. *Upper: Modified from Martirosyan, N. L., Feuerstein, J. S., Theodore, N., Cavalcanti, D.D., Spetzler, R. F., & Preul, M. C. (2011). Blood supply and vascular reactivity of the spinal cord under normal and pathological conditions*. Journal of Neurosurgery: Spine, 15*(3), 238–251. Lower: Reproduced from Cao, Y., Wu, T., Yuan, Z., Li, D., Ni, S., Hu, J. et al. (2015). Three-dimensional imaging of microvasculature in the rat spinal cord following injury*. Scientific Reports, 5*, 12643*.

Spinal cord edema

Direct vascular damage by initial trauma as well as ischemia-induced changes in capillary permeability combined with inflammatory response can result in edema causing spinal cord tissue swelling. Post-traumatic edema is clinically considered as a serious complication markedly contributing to the secondary injury. The precise pathology of edema formation is still not very well understood. Spinal cord edema develops during early acute phase and generally resolves within 14 days when the initiation of astroglial scar and blood–spinal cord barrier (BSCB) repair occurs (Rowland et al., 2008). It seems that long-lasting, post-traumatic edema is independent of ischemia, because although experimental studies performed on primates showed that spinal cord edema persisted for 15 days, ischemic conditions were prominent only up to 18 h following injury (Locke, Yashon, Feldman, & Hunt, 1971; Yashon, Bingham Jr, Faddoul, & Hunt, 1973). The degree of edema formation and its longitudinal extension is directly related to the severity of initial trauma (Wagner Jr & Stewart, 1981). In the model of permanent focal ischemia, magnetic resonance imaging (MRI) technique demonstrated the presence of edema first in peri-infarct regions that are still perfused, suggesting that tissue swelling requires active blood flow providing a

source of water, ions, and blood (Simard, Kent, Chen, Tarasov, & Gerzanich, 2007). Driving force for the movement of edema fluid into the unperfused tissue is the concentration gradient for moving constituents, such as Na^+, Cl^-, and water.

Traumatic spinal cord injury results in edema formation ultrastructurally showing both vasogenic and cytotoxic features (Goodman et al., 1976). V*asogenic edema* characterized by increased vascular permeability associated with BSCB breakdown is primarily due to direct traumatic impact and secondary due to release of endogenous vasoactive agents such as bradykinin, pro-inflammatory cytokines/chemokines, histamines, and prostaglandins (Abbott, 2000). In case that vascular leakage resulting from partial disconnection of endothelial cells, the basement membrane serves as a filter allowing passive diffusion of water, but retains serum proteins. White matter seems to be more vulnerable to vasogenic edema development than gray one (Kimelberg, 1995).

On contrary, the *cytotoxic edema*, otherwise known as cellular edema, is characterized by intracellular accumulation of Na^+ (primary driver), Cl^- and water (secondary participants), mainly due to post-traumatic depletion of ATP that leads to failure of the Na^+-K^+ ATPase (Simard et al., 2007). Cytotoxic edema itself does not result in spinal cord swelling, but the extravasation of fluid is evoked by the disruption of osmotic pressure gradient resulting from depletion of the extracellular Na^+, Cl^-, and water (Michinaga & Koyama, 2015). Its formation accelerates intravascular Na^+ outflow inducing extravasation of fluid without BSCB disruption, and it leads to extracellular fluid accumulation that is known as *ionic edema*.

The formation and recovery of vasogenic and cytotoxic edema are different in time. Even if both events are equally common during post-traumatic period, cytotoxic edema is considered as more prominent during the early phases (Hudak et al., 2014). Cellular swelling begins early after induction of focal ischemia particularly around capillaries (Liang, Bhatta, Gerzanich, & Simard, 2007). The most likely mediators of glial cell swelling are acidosis and elevated extracellular K^+ (Sykova, Svoboda, Polak, & Chvatal, 1994). Swelling of astrocytes is considered as much more prominent than neuronal ones, since they are involved in the clearance of K^+ and glutamate from extracellular space which promotes water inflow (Liang et al., 2007). When compensatory mechanisms in the plasma membrane fail, swollen cell undergoes the *oncosis*, a necrotic cell death mediated by ATP depletion and cell swelling. In clinical practice, the presence of post-traumatic hematoma and/or edema provides clinicians information regarding the severity and extent of injury and helps predict functional recovery (Chandra et al., 2012). Intradural MRI findings supported the concept that an edematous spinal cord has more potential in functional recovery than hemorrhagic (Tarawneh, D'Aquino, Hilis, Eisa, & Quraishi, 2020).

Raised intraspinal pressure

Since the spinal cord is located in rigid spinal canal and relative inelasticity of dura mater, the abnormal increase of spinal cord tissue volume due to post-traumatic hemorrhages and edema elevates the *intraspinal pressure* (ISP). Under normal conditions, a small increase in intraspinal volume does not greatly increase ISP, because of the elasticity of spinal cord, blood, and CSF. However, when capacity of compensatory mechanisms is exceeded, further increase in volume of spinal tissue due to post-traumatic hemorrhage and edema elevates ISP and causes a secondary compression of neurovascular structures resulting in a profound reduction of SCBF and subsequent ischemic tissue damage. Real-time monitoring of ISP after SCI in rats revealed dynamic changes (Dong et al., 2016). The ISP fluctuated over time and peaked at 1 and 48 h after mild and moderate SCI, but remained at high level during severe injury. It was demonstrated its positive correlation with the injury degree. Elevated intraspinal pressure after the SCI is initially driven by hemorrhage, however, latter is driven by edema (Leonard, Thornton, & Vink, 2015).

Breakdown of BSCB

BSCB provides a stable microenvironment that is necessary for the physiological function of the nervous system. Structurally, the BSCB is composed of tight junction-connected endothelial cell layer and its basement membrane that are surrounded by astrocytes foot processes and pericytes. Around small penetrating vessels are interstitial fluid-filled cavities, known as *perivascular spaces* or Virchow–Robin spaces (Fig. 4), which function as spinal drainage system. The preferential presence of spinal cord edema in white matter can be partially explained by a lower vascular density, and thus smaller capacity of fluid outflow via perivascular spaces occurring in the spinal white matter as compared with gray one. Using weight-drop SCI model in cats, it was detected a centrifugal spreading of extravasated fluorescein-labeled albumin (FLA) from gray to white matter (Wagner Jr & Stewart, 1981). It well corresponds with the disruption of central (sulcal) arteries that centrifugally supply the major part of the spinal cord. Extravasated FLA extended rostro-caudally from lesioned site along white matter columns, but the greatest longitudinal extent was usually seen in the lateral columns. It is likely associated with the development of tissue pressure gradients between epicenter and rostral and caudal areas.

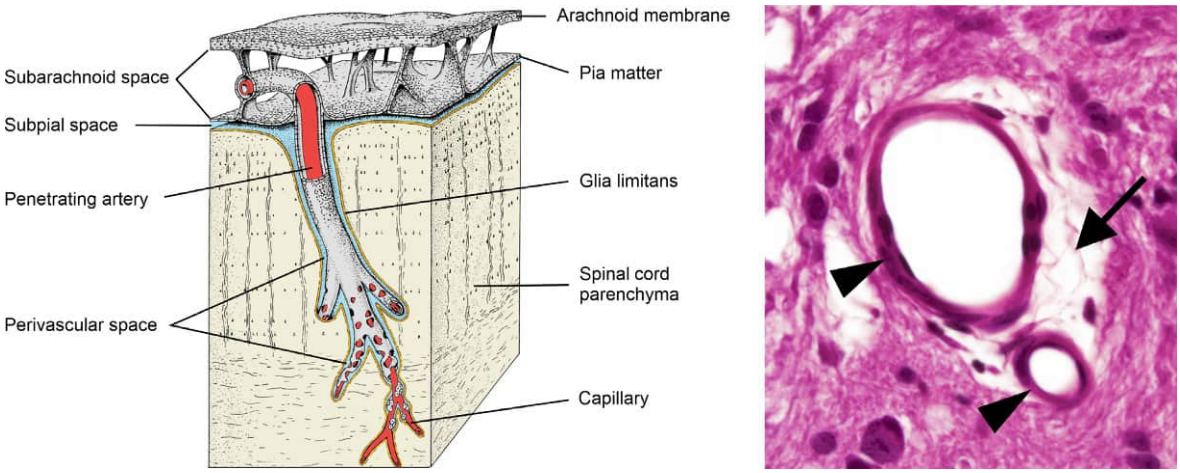

FIG. 4 Perivascular spaces and fluid exchange. *Left:* Anatomical illustration demonstrating a pivotal role of the perivascular (Virchow–Robin) spaces in the fluid exchange between the spinal cord tissue (interstitial fluid) and surrounding subarachnoid spaces (CSF). *Right:* Photomicrograph of coronal section from ischemia-injured spinal cord in rabbit stained with hematoxylin-eosin showing vessels (arrowheads) with surrounding enlarged perivascular space (arrow). *Left: Modified from Zhang, E. T., Inman, C. B., & Weller, R. O. (1990). Interrelationships of the pia mater and the perivascular (Virchow-Robin) spaces in the human cerebrum.* Journal of Anatomy, 170, *111–123.*

It was reported that the SCI induces a biphasic opening of the BSCB (Whetstone, Hsu, Eisenberg, Werb, & Noble-Haeusslein, 2003). The first abnormal leaking occurs within the first several hours after the injury, whereas a second one is evident within 3–7 days, a time period corresponding to marked post-traumatic revascularization. The authors expect that first robust leakage reflects direct damage to blood vessels and activated inflammatory processes can contribute to the more delayed second phase of barrier breakdown. It is assumed that the prolonged vascular permeability observed after the SCI is an inherent part of normal wound-healing response and reflects ongoing angiogenesis.

The inflammatory response and elimination of necrotic debris

The clearance of cellular debris and extravasated blood is indispensably required to maintain the homeostasis of surrounding spared neuronal and glial cells. Comprehensive post-mortem analysis of human spinal cord after traumatic injury provided valuable knowledge of cell types participating in the *post-traumatic inflammation* (Fleming et al., 2006). It showed a correlation between necrotic areas and the presence of inflammatory cells. Surprisingly, they often extended into more intact tissue adjacent to the lesion epicenter suggesting their role in the expansion of the lesion size. First immune cells coming very early from the ruptured blood vessels into lesioned tissue where phagocyte and clear tissue debris are *neutrophils*. In these human studies, extravascular neutrophils were found in the areas of hemorrhage, necrosis, and tissue fragmentation. It looks that these immune cells can initiate the secondary injury, because their maximal prevalence occurring 1–3 days corresponded with abrupt tissue damage. Neutrophil infiltration of lesion site ceased after 10 days. Perivascular neutrophils are an important source of inflammatory matrix metalloproteinase-9 (Rosell et al., 2008), the enzyme specifically degrading components of basal lamina of the BSCB. Therefore, it is likely that they contribute to the early secondary tissue damage and hemorrhagic injury.

Predominant inflammatory cells at and beyond 5–10 days are *activated microglia* and *macrophages* considered as another part of phagocytic population (Popovich et al., 2002). Phagocytic macrophages were detected in necrotic areas and along the border of cystic cavities, whereas activated microglia surrounded necrotic area and lesion site. The phagocytic activity of macrophages decreases within weeks after human SCI. The primary role of macrophages is to remove tissue and cellular debris, which enable spinal cord repair. It was demonstrated that decreased number of macrophages accumulating at the lesion site of SCI resulted in reduced cavitation and myelin damage (Popovich et al., 1999). Besides phagocytic function, macrophages also play an important role in wound healing. Macrophages can be classified into two main groups: M1 contributing to the tissue inflammation and damage and M2 contributing to wound healing and tissue remodeling. Predominant macrophages/microglial cells in the lesioned spinal cord are the M1 subtype, and the M2 subtype occurs transiently and in small amounts (Kigerl et al., 2009). Recent study investigating the phagocytic response of infiltrating macrophages and resident microglia and their viability at lesioned spinal cord concluded that (1) activated microglia contact and engulf degenerating axons early after SCI, before the infiltration of peripheral macrophages; (2) infiltrating macrophages are more susceptible than microglia to phagocytosis of myelin-induced apoptosis after the SCI; and

(3) microglial proliferation is about sevenfold greater than peripheral macrophages (Greenhalgh & David, 2014). It has been shown that infiltrating macrophages after injury become resident cells of CNS (Simard et al., 2007). Experimental SCI studies in rats comparing gray and white matter showed that macrophages and activated microglia were predominantly found in degenerating white matter tracts (Popovich, Wei, & Stokes, 1997), demonstrating a more extensive inflammatory response in the white matter regions and probable involvement of these cells in the initial phases of Wallerian degeneration. Majority of gray matter loss after the SCI occurs within hours and is mostly complete by 24 h, however, loss of white matter extends over several days post-injury (Ek et al., 2010). Despite progress in the last decades, a better understanding of the role of resident and peripheral immune cells in beneficial and detrimental processes of post-traumatic inflammatory response is still necessary.

Development of cysts/cavities and syrinx

An initial mechanical insult followed by secondary degenerative processes can initiate a serious chronic complication of SCI associated with delayed neurological deterioration known as *post-traumatic syringomyelia* (PTS). It is characterized by the presence of fluid-filled cysts (called syrinxes) that can expand over time, resulting in additional compression. Its time of onset after trauma ranges from months to decades, and it is developed in up to one-third of SCI patients (Berliner et al., 2020). Typical histological features of PTS are a cavity with a thick gliotic wall and enlarged perivascular spaces. MRI scanning of many SCI patients demonstrates fluid-filled cysts or microcysts that do not represent PTS, but rather myelomalacia, "softening" of the injured spinal cord (Shields, Zhang, & Shields, 2012). Retrospective MRI analysis of the compressive myelomalacia in humans suggested that early stage is most frequently characterized by the presence of cord edema, intermediate stage by varying degrees of cystic necrosis of the central gray matter following prolonged cord edema, and central cystic degeneration of the spinal cord and syrinx formation was typical for late stage (Ramanauskas, Wilner, Metes, Lazo, & Kelly, 1989). Moreover, it was concluded that early stage may be reversible (depends on severity of initial injury), but intermediate and late stages are progressive and most likely irreversible. Despite progress in research, there is still no explanation why in some SCI patients is PTS developed and in others not. Even if its pathogenesis is still not completely understood, the post-traumatic formation of spinal cord cysts can be divided into two following steps: (1) initial cavity formation and (2) cyst extension. The changes resulting from primary and secondary injuries, such as hemorrhagic necrosis, ischemic damage, and formation and coalescence of microcysts, are factors that predispose the syrinx formation.

The presence of small cavities at the injury level is very common (Fig. 5), but not all of them enlarge to form syrinxes. The syrinxes developed in spinal parenchyma after the SCI are usually extracanalicular (separated from the central canal)

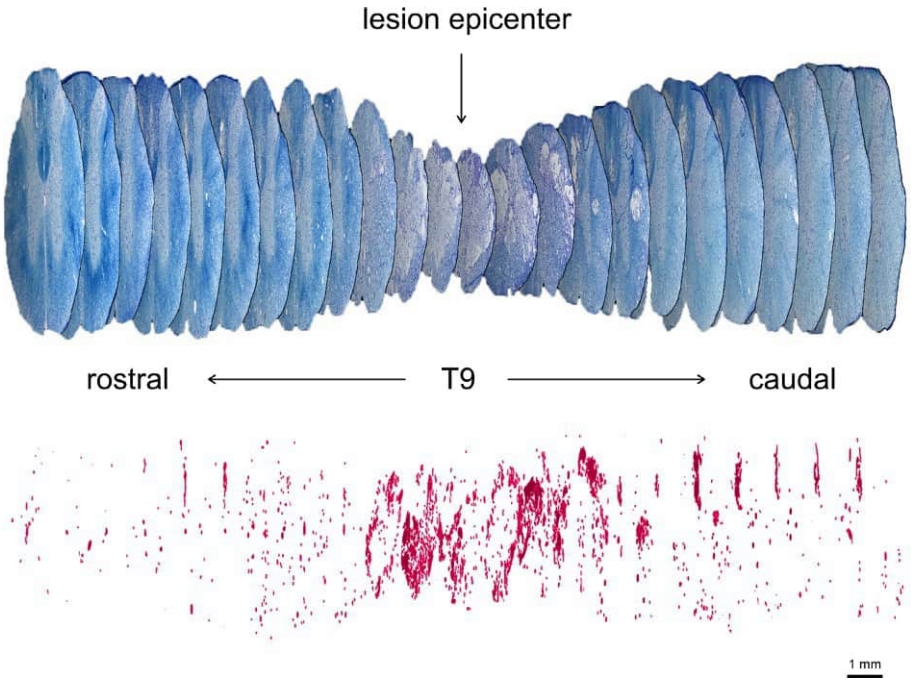

FIG. 5 Post-traumatic spinal cord degeneration and formation of cavities. 3D reconstructions demonstrating the longitudinal development of secondary tissue damage (*upper image*) and corresponding cavity formation (*lower image*) 28 days after severe spinal cord trauma at T9 segmental level in rats.

and are typically found in spinal watershed zones (Milhorat, 2000). Despite many theories, it seems that severe inflammatory response, arachnoiditis, and the impairment of CSF flow are the most probable factors in the development of PTS. According to current prevailing theory, the increased pulse pressure of CSF in the subarachnoid space above tethering of the spinal cord at the lesion site can force CSF through perivascular spaces toward syrinx (Greitz, 2006). The detailed experimental study of rat PTS model revealed perivascular microcavities or entirely enlarged spaces around venules, arterioles, and capillaries (Berliner et al., 2020). Spinal cord tissue surrounding cavities was characterized by integrity loss and enlarged extracellular spaces in the gray and white matter, consistent with severe parenchymal edema. In addition to that, the impairment of BSCB can increase the extracellular fluid and provide a potential source for fluid flow into post-traumatic syrinxes. It is supported by previous experimental study that suggests the impaired BSCB in the spinal cord tissue adjacent to a cyst (Josephson, Greitz, Klason, Olson, & Spenger, 2001).

The histological analysis of human cadavers with tubular cavitations of spinal cord revealed that most of the primary parenchymal cavitations were detected in central and dorsolateral gray matter, the watershed zone of the spinal cord (Milhorat, Capocelli Jr, Anzil, Kotzen, & Milhorat, 1995). Extracanalicular syrinx consisted mostly of irregularly shaped tubular cavities lined by densely packed glial or fibroglial tissue, with the presence of hemosiderin-laden macrophages and microglia in their wall. They were also associated with various degrees of focal necrosis and Wallerian degeneration. Cavitations in spinal gray matter displayed central chromatolysis, neuronophagia, and gliosis. Demyelinization in the white matter columns was accompanied by gliosis and the infiltration of foamy fat-laden macrophages. Cavitations present in the anterior horn of gray matter were associated with denervation atrophy in the diaphragm and segmental muscles. Atrophic cavitations do not propagate, and they can be related to degenerative changes leading to the formation of microcysts, intramedullary clefts, and localized dilations of the central spinal canal (Milhorat, 2000).

The post-traumatic spinal cord shrinkage

Predominantly damaging processes of progressive secondary injury involving a wide range of pathological events and initiated by mechanical insult lead to spinal cord tissue destruction. Therefore, the major target of SCI research is to develop effective and clinically acceptable therapeutic intervention that could reverse the destructive processes or reduce the final damage of spinal cord tissue. One of the common experimental parameters characterizing the severity and extent of SCI as well as determining the effectiveness of therapeutic approach in correlation with functional motor deficits is the amount of lost or spared neural tissue. However, removal of tissue debris can cause an extensive reduction of neural tissue at lesioned site that can be seen as spinal cord shrinkage, especially during later phases of SCI (Fig. 6). Therefore, the assessment of spared or lost tissue by direct measurement of total cross-sectional area without knowing pre-injury area in lesioned region

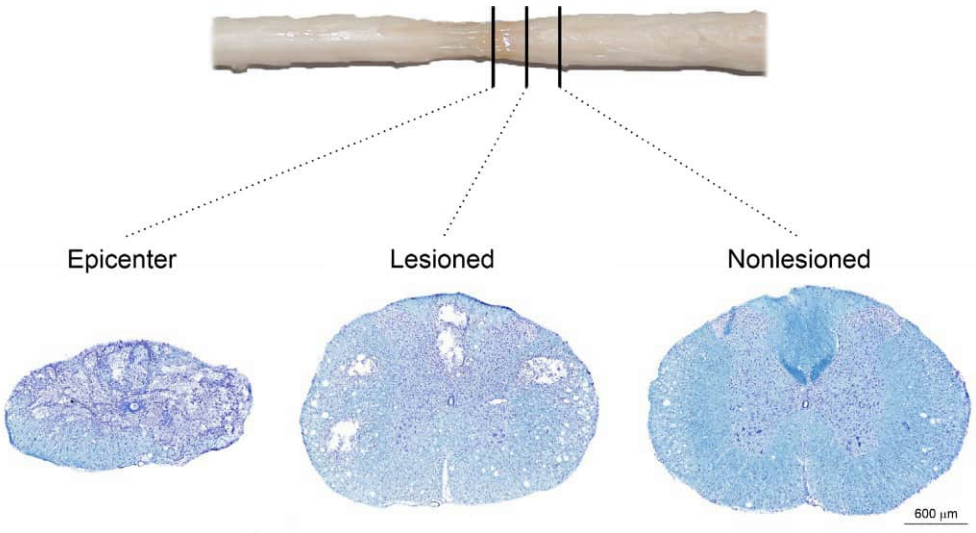

FIG. 6 The neural tissue loss after SCI. Demonstration of spinal cord tissue loss after severe posterior compression in rat detected 28 days post-injury (*upper image*). Progress of damage can be observed as longitudinal tissue shrinkage peaking at the lesion epicenter. Transverse sections stained with the Luxol fast blue and Cresyl Violet from three differently injured regions demonstrate various degrees of tissue damage resulting in spinal cord tissue loss (*lower images*). Numerous cysts and cavities can be noted predominantly in the white matter columns of lesioned region.

may result in an underestimation of tissue loss or an overestimation of tissue sparing. Recently, it was suggested that the new quantification approach overcomes the issue of post-traumatic spinal cord shrinkage and is relatively fast, accurate, and optimally reproducible (Fedorova & Pavel, 2019).

Applications to other areas of neuroscience

In this chapter, we have briefly reviewed the major pathological changes that substantially can contribute to post-traumatic neural tissue loss of the spinal cord. Some non-traumatic SCI related to metabolic, vascular, and inflammatory causes can share same neuropathological aspects, such as ischemia, hemorrhages, and edema. However, it is necessary to be aware of several important facts.

Ischemic injuries to the spinal cord are very uncommon since the spinal cord is equipped with a longitudinally continuous, highly variable, and extensively collateral vascular network. The incidence of spinal cord infarction usually results from ischemia originating in feeding extravertebral arteries. Since a loss of local vascular integrity, intervention to increase blood pressure to prevent persisted hypotension applied generally in human SCI patients is controversial. Intramedullary spinal cord hemorrhages are most commonly found in association with spinal cord trauma. Non-traumatic intramedullary spinal cord hemorrhages are rare and are often caused by spinal vascular malformations. According to clinical experience, spinal cord swelling indicates a severe spinal cord damage. If swelling is not apparent, neurological improvement can be expected even if severe deficits are initially apparent. Elimination of causal factors of increased intraspinal pressure has beneficial effects. In addition, post-traumatic spinal cord shrinkage should be taken into account during the assessment of lesion volumes in experimental studies.

Mini-dictionary of terms

Vascular autoregulation. The intrinsic ability of the spinal cord through arteries (specifically arterioles) to maintain a constant blood flow despite changes in perfusion pressure.

Neurogenic shock. A life-threatening condition associated with autonomic dysregulation resulting in inadequate spinal tissue perfusion.

Petechial hemorrhage. Capillary bleeding into spinal cord parenchyma manifested as tiny red spots.

Vasogenic edema. A pathophysiological process characterized by extravasation and extracellular accumulation of fluid with high protein content in spinal cord parenchyma caused by the BSCB breakdown.

Cytotoxic edema. A pathophysiological process that involves cellular swelling due to the movement of osmotically active molecules from the extracellular to intracellular space.

Ionic edema. A form of edema associated with cytotoxic edema, and represents the transcapillary movement of sodium ions and water into the extracellular space of spinal cord parenchyma.

Watershed zone. Spinal cord region vulnerable in case of vascular obstruction and do not receive a direct blood supply, but is supplied by overlapping vascular fields coming from neighboring arteries.

Key facts of post-traumatic loss of spinal cord tissue

The dysfunction of blood supply after traumatic SCI represents a crucial factor affecting the extent of secondary injury and subsequent tissue loss.

Vascular damage in human SCI occurs primarily in the intramedullary vascular system involving central (sulcal) arteries.

Primary hemorrhages are maximal at lesion center, whereas petechial hemorrhages predominantly surround the site of primary lesion.

Although post-traumatic edema shows both vasogenic and cytotoxic features, cytotoxic edema is considered as more prominent during the early phases.

Hemorrhages are responsible for raised intraspinal pressure initially, latter is driven by edema.

Both hemorrhages and edema cause additional compression of trauma-injured spinal cord and with inflammatory response result in more profound tissue damage.

First immune cells infiltrating lesioned tissue are neutrophils, whereas phagocytic microglia and macrophages are predominant later.

Majority of gray matter loss occurs within hours after the SCI, but loss of white matter extends over several days.

Summary points

- Final damage of spinal cord is highly variable and depends on aspects of traumatic insult as well as on local metabolic demands and morphological arrangement, including specific neuronal groups and local vascular characteristics.
- Major post-traumatic events contributing to neural tissue loss involve a systemic and local dysfunction of vascular system (including neurogenic shock, hemorrhage, impairment of blood flow autoregulation), edema formation, elevation of intraspinal pressure, BSCB breakdown, the inflammatory response associated with the elimination of necrotic debris, and the development of cysts/cavities and syrinx.
- Adequate vascular perfusion and regulated inflammatory response are essential factors for survival of reversibly injured spinal cord tissue.
- Hemorrhage early and edema later after SCI are major factors that are responsible for raised ISP. Therefore, its clinical monitoring is needed to ensure adequate vascular perfusion in post-traumatic period.
- The underestimation of lesion volume due to progressive shrinkage of the spinal cord represents a risk of consistent and reproducible quantification.

Acknowledgment

The authors would like to thank Dr. Ivo Vanicky for providing stained histological sections. Supported by APVV-18-0163 (J.P.).

References

Abbott, N. J. (2000). Inflammatory mediators and modulation of blood-brain barrier permeability. *Cellular and Molecular Neurobiology*, *20*(2), 131–147.

Alshareef, M., Krishna, V., Ferdous, J., Alshareef, A., Kindy, M., Kolachalama, V. B., et al. (2014). Effect of spinal cord compression on local vascular blood flow and perfusion capacity. *PLoS One*, *9*(9), e108820.

Balentine, J. D. (1978). Pathology of experimental spinal cord trauma. I. The necrotic lesion as a function of vascular injury. *Laboratory Investigation*, *39*(3), 236–253.

Berliner, J., Hemley, S., Najafi, E., Bilston, L., Stoodley, M., & Lam, M. (2020). Abnormalities in spinal cord ultrastructure in a rat model of post-traumatic syringomyelia. *Fluids and Barriers of the CNS*, *17*(1), 11.

Blight, A. R., & Decrescito, V. (1986). Morphometric analysis of experimental spinal cord injury in the cat: The relation of injury intensity to survival of myelinated axons. *Neuroscience*, *19*(1), 321–341.

Chandra, J., Sheerin, F., Lopez de Heredia, L., Meagher, T., King, D., Belci, M., et al. (2012). MRI in acute and subacute post-traumatic spinal cord injury: Pictorial review. *Spinal Cord*, *50*(1), 2–7.

Dohrmann, G. J., Wagner, F. C., Jr., & Bucy, P. C. (1971). The microvasculature in transitory traumatic paraplegia. An electron microscopic study in the monkey. *Journal of Neurosurgery*, *35*(3), 263–271.

Dong, X., Yang, D., Li, J., Liu, C., Yang, M., Du, L., et al. (2016). Intramedullary pressure changes in rats after spinal cord injury. *Spinal Cord*, *54*(11), 947–950.

Ek, C. J., Habgood, M. D., Callaway, J. K., Dennis, R., Dziegielewska, K. M., Johansson, P. A., et al. (2010). Spatio-temporal progression of grey and white matter damage following contusion injury in rat spinal cord. *PLoS One*, *5*(8), e12021.

Fedorova, J., & Pavel, J. (2019). An accurate method for histological determination of neural tissue loss/sparing after compression-induced spinal cord injury with optimal reproducibility. *Journal of Neurotrauma*, *36*(18), 2665–2675.

Fleming, J. C., Norenberg, M. D., Ramsay, D. A., Dekaban, G. A., Marcillo, A. E., Saenz, A. D., et al. (2006). The cellular inflammatory response in human spinal cords after injury. *Brain*, *129*(Pt 12), 3249–3269.

Gallagher, M. J., Hogg, F., Zoumprouli, A., Papadopoulos, M. C., & Saadoun, S. (2019). Spinal cord blood flow in patients with acute spinal cord injuries. *Journal of Neurotrauma*, *36*(6), 919–929.

Garton, T., Keep, R. F., Hua, Y., & Xi, G. (2016). Brain iron overload following intracranial haemorrhage. *Stroke and Vascular Neurology*, *1*(4), 172–184.

Gerzanich, V., Woo, S. K., Vennekens, R., Tsymbalyuk, O., Ivanova, S., Ivanov, A., et al. (2009). De novo expression of Trpm4 initiates secondary hemorrhage in spinal cord injury. *Nature Medicine*, *15*(2), 185–191.

Goodman, J. H., Bingham, W. G., Jr., & Hunt, W. E. (1976). Ultrastructural blood-brain barrier alterations and edema formation in acute spinal cord trauma. *Journal of Neurosurgery*, *44*(4), 418–424.

Greenhalgh, A. D., & David, S. (2014). Differences in the phagocytic response of microglia and peripheral macrophages after spinal cord injury and its effects on cell death. *The Journal of Neuroscience*, *34*(18), 6316–6322.

Greitz, D. (2006). Unraveling the riddle of syringomyelia. *Neurosurgical Review*, *29*(4), 251–263.

Guha, A., Tator, C. H., & Rochon, J. (1989). Spinal cord blood flow and systemic blood pressure after experimental spinal cord injury in rats. *Stroke*, *20*(3), 372–377.

Hua, Y., Wu, J., Keep, R. F., Nakamura, T., Hoff, J. T., & Xi, G. (2006). Tumor necrosis factor-alpha increases in the brain after intracerebral hemorrhage and thrombin stimulation. *Neurosurgery*, *58*(3), 542–550.

Hudak, A. M., Peng, L., Marquez de la Plata, C., Thottakara, J., Moore, C., Harper, C., et al. (2014). Cytotoxic and vasogenic cerebral oedema in traumatic brain injury: Assessment with FLAIR and DWI imaging. *Brain Injury*, *28*(12), 1602–1609.

Jellinger, K. (1976). Neuropathology of cord injuries. In P. J. Vinken, & G. W. Bruyn (Eds.), *Handbook of clinical neurology Vol. 25, injuries of the spine and spinal cord part 1* (pp. 43–121). Amsterdam: North-Holland Publishing Co.

Josephson, A., Greitz, D., Klason, T., Olson, L., & Spenger, C. (2001). A spinal thecal sac constriction model supports the theory that induced pressure gradients in the cord cause edema and cyst formation. *Neurosurgery*, *48*(3), 636–646.

Kigerl, K. A., Gensel, J. C., Ankeny, D. P., Alexander, J. K., Donnelly, D. J., & Popovich, P. G. (2009). Identification of two distinct macrophage subsets with divergent effects causing either neurotoxicity or regeneration in the injured mouse spinal cord. *The Journal of Neuroscience*, *29*(43), 13435–13444.

Kimelberg, H. K. (1995). Current concepts of brain edema. Review of laboratory investigations. *Journal of Neurosurgery*, *83*(6), 1051–1059.

Kiss, Z. H. T., & Tator, C. H. (1993). Neurogenic shock. In E. R. Geller (Ed.), *Shock and resuscitation* (pp. 421–440). New York: McGraw-Hill Education.

Koyanagi, I., Tator, C. H., & Lea, P. J. (1993). Three-dimensional analysis of the vascular system in the rat spinal cord with scanning electron microscopy of vascular corrosion casts. Part 2: Acute spinal cord injury. *Neurosurgery*, *33*(2), 285–292.

Leonard, A. V., Thornton, E., & Vink, R. (2015). The relative contribution of edema and hemorrhage to raised intrathecal pressure after traumatic spinal cord injury. *Journal of Neurotrauma*, *32*(6), 397–402.

Liang, D., Bhatta, S., Gerzanich, V., & Simard, J. M. (2007). Cytotoxic edema: Mechanisms of pathological cell swelling. *Neurosurgical Focus*, *22*(5), E2.

Locke, G. E., Yashon, D., Feldman, R. A., & Hunt, W. E. (1971). Ischemia in primate spinal cord injury. *Journal of Neurosurgery*, *34*(5), 614–617.

Losey, P., Young, C., Krimholtz, E., Bordet, R., & Anthony, D. C. (2014). The role of hemorrhage following spinal-cord injury. *Brain Research*, *1569*, 9–18.

Martirosyan, N. L., Feuerstein, J. S., Theodore, N., Cavalcanti, D. D., Spetzler, R. F., & Preul, M. C. (2011). Blood supply and vascular reactivity of the spinal cord under normal and pathological conditions. *Journal of Neurosurgery: Spine*, *15*(3), 238–251.

Mautes, A. E., Weinzierl, M. R., Donovan, F., & Noble, L. J. (2000). Vascular events after spinal cord injury: Contribution to secondary pathogenesis. *Physical Therapy*, *80*(7), 673–687.

Michinaga, S., & Koyama, Y. (2015). Pathogenesis of brain edema and investigation into anti-edema drugs. *International Journal of Molecular Sciences*, *16*(5), 9949–9975.

Milhorat, T. H. (2000). Classification of syringomyelia. *Neurosurgical Focus*, *8*(3), E1.

Milhorat, T. H., Capocelli, A. L., Jr., Anzil, A. P., Kotzen, R. M., & Milhorat, R. H. (1995). Pathological basis of spinal cord cavitation in syringomyelia: Analysis of 105 autopsy cases. *Journal of Neurosurgery*, *82*(5), 802–812.

Popovich, P. G., Guan, Z., McGaughy, V., Fisher, L., Hickey, W. F., & Basso, D. M. (2002). The neuropathological and behavioral consequences of intraspinal microglial/macrophage activation. *Journal of Neuropathology and Experimental Neurology*, *61*(7), 623–633.

Popovich, P. G., Guan, Z., Wei, P., Huitinga, I., van Rooijen, N., & Stokes, B. T. (1999). Depletion of hematogenous macrophages promotes partial hindlimb recovery and neuroanatomical repair after experimental spinal cord injury. *Experimental Neurology*, *158*(2), 351–365.

Popovich, P. G., Lemeshow, S., Gensel, J. C., & Tovar, C. A. (2012). Independent evaluation of the effects of glibenclamide on reducing progressive hemorrhagic necrosis after cervical spinal cord injury. *Experimental Neurology*, *233*(2), 615–622.

Popovich, P. G., Wei, P., & Stokes, B. T. (1997). Cellular inflammatory response after spinal cord injury in Sprague-Dawley and Lewis rats. *The Journal of Comparative Neurology*, *377*(3), 443–464.

Ramanauskas, W. L., Wilner, H. I., Metes, J. J., Lazo, A., & Kelly, J. K. (1989). MR imaging of compressive myelomalacia. *Journal of Computer Assisted Tomography*, *13*(3), 399–404.

Rivlin, A. S., & Tator, C. H. (1978). Regional spinal cord blood flow in rats after severe cord trauma. *Journal of Neurosurgery*, *49*(6), 844–853.

Rosell, A., Cuadrado, E., Ortega-Aznar, A., Hernández-Guillamon, M., Lo, E. H., & Montaner, J. (2008). MMP-9-positive neutrophil infiltration is associated to blood-brain barrier breakdown and basal lamina type IV collagen degradation during hemorrhagic transformation after human ischemic stroke. *Stroke*, *39*(4), 1121–1126.

Rowland, J. W., Hawryluk, G. W., Kwon, B., & Fehlings, M. G. (2008). Current status of acute spinal cord injury pathophysiology and emerging therapies: Promise on the horizon. *Neurosurgical Focus*, *25*(5), E2.

Shields, C. B., Zhang, Y. P., & Shields, L. B. (2012). Post-traumatic syringomyelia: CSF hydrodynamic changes following spinal cord injury are the driving force in the development of PTSM. *Handbook of Clinical Neurology*, *109*, 355–367.

Simard, J. M., Kent, T. A., Chen, M., Tarasov, K. V., & Gerzanich, V. (2007). Brain oedema in focal ischaemia: Molecular pathophysiology and theoretical implications. *The Lancet Neurology*, *6*(3), 258–268.

Sykova, E., Svoboda, J., Polak, J., & Chvatal, A. (1994). Extracellular volume fraction and diffusion characteristics during progressive ischemia and terminal anoxia in the spinal cord of the rat. *Journal of Cerebral Blood Flow and Metabolism*, *14*(2), 301–311.

Tarawneh, A. M., D'Aquino, D., Hilis, A., Eisa, A., & Quraishi, N. A. (2020). Can MRI findings predict the outcome of cervical spinal cord injury? A systematic review. *European Spine Journal*, *29*(10), 2457–2464.

Tator, C. H., & Fehlings, M. G. (1991). Review of the secondary injury theory of acute spinal cord trauma with emphasis on vascular mechanisms. *Journal of Neurosurgery*, *75*(1), 15–26.

Tator, C. H., & Koyanagi, I. (1997). Vascular mechanisms in the pathophysiology of human spinal cord injury. *Journal of Neurosurgery*, *86*(3), 483–492.

Wagner, F. C., Jr., & Stewart, W. B. (1981). Effect of trauma dose on spinal cord edema. *Journal of Neurosurgery*, *54*(6), 802–806.

Whetstone, W. D., Hsu, J. Y., Eisenberg, M., Werb, Z., & Noble-Haeusslein, L. J. (2003). Blood-spinal cord barrier after spinal cord injury: Relation to revascularization and wound healing. *Journal of Neuroscience Research*, *74*(2), 227–239.

Yashon, D., Bingham, W. G., Jr., Faddoul, E. M., & Hunt, W. E. (1973). Edema of the spinal cord following experimental impact trauma. *Journal of Neurosurgery*, *38*(6), 693–697.

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Chapter 17

Remodeling mitochondrial transport and cellular energetics in axonal regeneration and spinal cord injury

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List of abbreviations

ATP	adenosine triphosphate
CNS	central nervous system
CST	corticospinal tract
DH	dorsal hemisection
EMG	electromyography
FRET	Försterresonance energy transfer
MT	microtubule
OMM	outer mitochondrial membrane
ROS	reactive oxygen species
SCI	spinal cord injury
SNPH	syntaphilin
TMRE	tetramethylrhodamine ethyl ester

Introduction

While young neurons possess the capacity for robust axon growth and synaptogenesis, mature neurons in the central nervous system (CNS) typically fail to survive and regenerate after injury, leading to permanent neurological impairment. Many studies have suggested that mature CNS neurons have lost their regrowth capacity due to an intrinsic decline in permissive conditions for regeneration (Bradbury & McMahon, 2006; Case & Tessier-Lavigne, 2005; Harel & Strittmatter, 2006). Neuronal regeneration is a highly energy-demanding process. To succeed in regeneration following an injury, mature neuronal axons must reseal injured terminals, reform growth cones, reorganize the cytoskeleton network, synthesize and transport raw building materials, assemble axon components, and make new synaptic connections (He & Jin, 2016). All of these cellular events require a high level of energy consumption. However, injury is an acute insult that damages local mitochondria leading to an energy crisis, thus raising a fundamental question as to whether injury-induced energetic deficits contribute to the intrinsic restriction that accounts for regeneration failure in the mature CNS.

Mitochondria are the main cellular bioenergetic organelles that convert glucose and pyruvate into adenosine triphosphate (ATP) through the electron transport chain and oxidative phosphorylation (Mattson, Gleichmann, & Cheng, 2008). In the brain, ~93% of ATP is produced in mitochondria, while glycolysis generates ~7% of total ATP (Harris, Jolivet, & Attwell, 2012). Thus, a constant energy supply by mitochondria in the brain is essential to power neuronal growth, function, and regeneration. Mitochondrial biogenesis and turnover primarily take place in the cell body of neurons. Due to the polarized structures and high-energy demand in axons, ATP diffusion capacity through long axons is rather limited to maintain energy homeostasis (Sun, Qiao, Pan, Chen, & Sheng, 2013). Given the far distance between injured axons and their cell body, neurons face exceptional challenges in maintaining energy supply in injured axons and growth cones. Injury-damaged mitochondria not only fail to produce ATP but also release toxic reactive oxygen species (ROS) to induce neuronal degeneration. It is essential for neurons to adopt specialized mechanisms that efficiently deliver the appropriate

Cellular, Molecular, Physiological, and Behavioral Aspects of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822427-4.00017-4

number of healthy mitochondria into regenerative tips and remove damaged mitochondria to meet the enhanced energy consumption for ensuring neuronal survival and axonal regeneration where energy is in high demand (Sheng, 2017).

Although mitochondria transplantation and enhanced mitochondrial biogenesis have surfaced as possible avenues for therapeutic development for CNS injuries including spinal cord injury (SCI), genetic and cellular remodeling of enhanced delivery of healthy mitochondria into injured axons has emerged as one of the robust mechanisms for boosting local energy supply and thus facilitating axon regeneration in various CNS injury models (Cartoni et al., 2016; Han et al., 2020; Han, Baig, & Hammarlund, 2016; Zhou et al., 2016). In this chapter, we first briefly introduce the microtubule (MT)-based trafficking and anchoring mechanisms that control mitochondrial delivery and distribution into distal axons. Next, we provide an in-depth discussion of recent emerging findings on how genetic and cellular regulation of axonal mitochondrial transport promotes the energy-demanding axon regeneration and functional recovery in various injury models. In the final part of this chapter, we provide perspective views on the potential therapeutic strategies by remodeling mitochondrial transport and/or by elevating cellular energetic metabolism for SCI. For additional insights into mitochondrial trafficking and neuronal energy maintenance, we refer readers to other reviews (Devine & Kittler, 2018; Misgeld & Schwarz, 2017; Sheng & Cai, 2012).

Complex motility patterns of axonal mitochondria

To monitor mitochondrial transport in live neurons, expression of mitochondria-tagged proteins (e.g., DsRed-Mito) or loading mitochondrial dyes (e.g., Mitotracker Green) have routinely been applied to label mitochondria for time-lapse imaging. Axonal mitochondria display complex motility patterns: they move bi-directionally over long distances, pause and change direction frequently, and can be re-mobilized and re-distributed in axons in response to changes in metabolic needs and growth status (Fig. 1). Given frequent pauses and changes in direction, the mean velocities of axonal mitochondrial motility are highly variable ranging from ~0.2 to 2.0 μm per second (Sheng, 2014). We and others consistently observed a significant difference in the total motility of axonal mitochondria between young and mature neurons. Approximately 30%–45% of axonal mitochondria are mobile and the remaining two-thirds are stationary in young developing neurons. These motility profiles decline and become relatively stable after neurons mature. These complex motility patterns indicate a unique mechanistic interplay between anterograde and retrograde motors in driving mitochondria bi-directional transport along with anchoring proteins in positioning mitochondria in distal axons or at synapses.

Molecular motors driving mitochondrial bi-directional transport in axons

Long-distance mitochondrial transport along MT-tracks is driven by ATP-hydrolyzing molecular motors. MTs within axons display uniform polarity: their plus-ends are directed to distal axons and their minus-ends toward the soma. Thus,

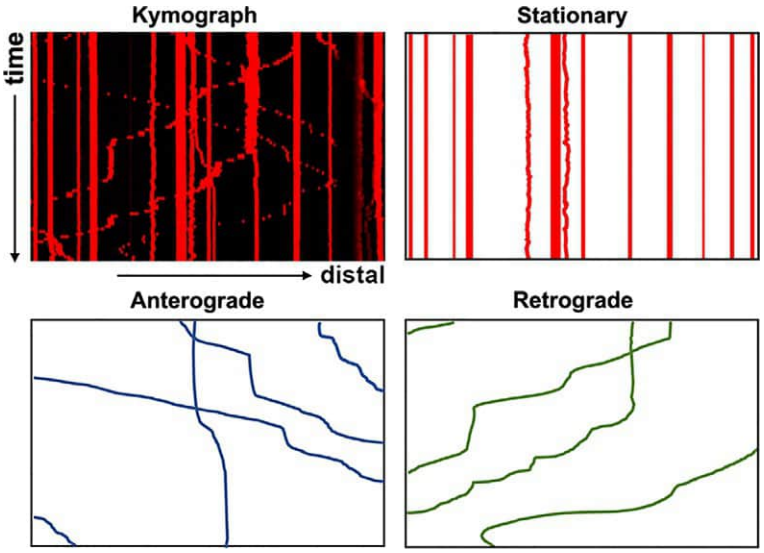

FIG. 1 Complex motility patterns of axonal mitochondria. Representative kymograph showing bi-directional motility patterns of axonal mitochondria. In the kymograph, vertical lines (upper panels) represent stationary mitochondria; oblique lines or curves to the right (lower panels, *blue*) indicate anterograde transport toward distal terminals, whereas those to the left (lower panels, *green*) denote retrograde transport toward the cell body.

kinesin motors drive anterograde transport from the soma toward distal axons, while dynein motors mediate retrograde transport back toward the soma. Kinesin-1 family members, also known as KIF5A, KIF5B, and KIF5C, are the primary motors driving neuronal mitochondrial transport (Pilling, Horiuchi, Lively, & Saxton, 2006; Tanaka et al., 1998). Kinesin-1 motors are a hetero tetramerized complex composed of two heavy chains (KHC) and two light chains (KLC). The KHC contains a motor domain at the N-terminal region that has ATPase activity and is directly engaged with MTs, whereas the C-terminal domain of KHC binds to KLC or directly associates with cargoes (Hirokawa, Niwa, & Tanaka, 2010). Cytoplasmic dynein motors contain two motor-containing dynein heavy chains (DHC) and several other chains including dynein intermediate chains (DIC), light chains (DLC), and dynactin that mainly regulate motility or associate with their cargoes. In *Drosophila*, dynein motors are recruited on mitochondria and mediate retrograde trafficking along axons (Pilling et al., 2006).

Mitochondrial motor adaptors and receptors

Mitochondria recruit molecular motors through their specific adaptors and/or receptors that associate with the outer mitochondrial membrane (OMM). Mitochondrial adaptor proteins help to connect kinesin-1 motors and mitochondria, thus regulating mitochondrial transport. In *Drosophila*, Milton is the adaptor that bridges KIF5 motors with Miro, an OMM receptor (Glater, Megeath, Stowers, & Schwarz, 2006). *Milton* mutation impairs anterograde transport of mitochondria without affecting other axonal cargoes. Extracellular glucose alters axonal mitochondrial transport through GlcNAcylation modification of Milton (Pekkurnaz, Trinidad, Wang, Kong, & Schwarz, 2014). Two mammalian Milton orthologs, Trak1 and Trak2, regulate axonal and dendritic mitochondrial trafficking and outgrowth (van Spronsen et al., 2013). Trak1 facilitates bi-directional mitochondrial trafficking along axons through interacting with both kinesin-1 and dynein motors, while Trak2 mediates dendritic mitochondrial transport via preferentially binding to dynein motors.

Miro is a Rho-GTPase with two GTPase domains and two Ca^{2+}-binding EF-hand motifs, which allows mitochondrial transport to be regulated by Ca^{2+} signaling and synaptic activity (Fransson, Ruusala, & Aspenstrom, 2006). In *Drosophila*, *Miro* mutation alters anterograde mitochondrial transport (Guo et al., 2005). In mammals, there are two Miro isoforms: Miro1 and Miro2. By using a*miro1* deletion mouse model, Lopez-Domenech et al. revealed that Miro1, but not Miro2, mediates mitochondrial trafficking (Lopez-Domenech et al., 2016). Recent studies revealed that Miro1 expression is facilitated by two Parkinson's disease (PD)-related kinases PINK1 and LRRK2 (Hsieh et al., 2016). Interestingly, a new splicing variant of Miro1 was found to localize to peroxisomes and mediate long-distance peroxisome trafficking together with Trak2 (Okumoto et al., 2018). Miro1 and Miro2 have also been suggested to play a role in the peroxisomal fission process, supporting the crosstalk between peroxisomes and mitochondria (Covill-Cooke et al., 2020). Together, KIF5 (motor), Milton/Trak (adaptor), and Miro (receptor) comprise the mitochondrial transport machinery that drives anterograde transport.

Syntabulin is an attractive motor-adaptor that targets the OMM via its carboxyl-terminal mitochondria-targeting domain and interacts with and thus recruits KIF5 motors to mitochondria (Cai, Gerwin, & Sheng, 2005). In hippocampal neurons, knocking down syntabulin with siRNA or interfering with syntabulin-KIF5 interaction impairs mitochondrial transport from the soma into axons. Several other KIF5 adaptors, such as FEZ1 and RanBP2, have also been reported to mediate neuronal mitochondrial transport (Cho et al., 2007; Fujita et al., 2007). The existence of multiple pairs of motor-adaptor complexes may suggest diverse mechanisms in coordinating mitochondrial trafficking and positioning in response to various physiological conditions or axonal injury.

Compared to the well-characterized kinesin-adaptor transport complexes, dynein-adaptor complexes are less well-defined. Several studies suggest that Miromay also associates with dynein motors for mediating retrograde transport. While the loss of *dmiro* in *Drosophila* neurons impairs bi-directional mitochondrial transport (Guo et al., 2005), overexpressing dMiro enhances axonal mitochondrial transport in both directions (Russo et al., 2009). Consistent with findings in *Drosophila*, mammalian Trak1/2 have the binding capacity for both KIF5B and dynein/dynactin (van Spronsen et al., 2013). Based on these findings, an attractive model was proposed: bi-directional mitochondrial transport is driven by opposing motors kinesin-1 and dynein likely through the same adaptor and receptor complexes (Fig. 2).

Declined axonal mitochondrial transport in mature neurons

During early neuronal development, axon outgrowth, branching, and synaptogenesis require bulk synthesis and delivery of cellular proteins and organelles into growing tips. These developmental events are highly energy demanding, and thus require robust mitochondrial transport from the soma into distal axons (Morris & Hollenbeck, 1993; Ruthel & Hollenbeck, 2003). In young developing neurons, we and others consistently found that ~30%–45% of axonal

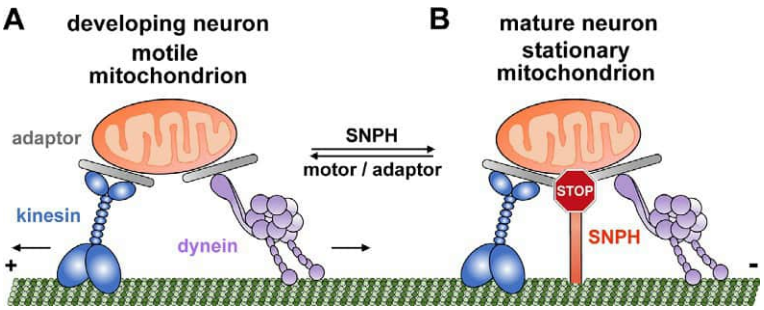

FIG. 2 Mechanistic interplay between mitochondrial trafficking and anchoring proteins. Schematic models showing motor-adaptor complexes and anchoring protein SNPH in regulating axonal mitochondrial motility. (A) Long-distance axonal mitochondrial transport is driven by MT-based motors: the plus-end directed kinesin and the minus-end directed dynein. Axonal MTs are uniformly arranged so that their plus-ends are directed distally. (B) SNPH acts as a "static anchor" that arrests axonal mitochondrial transport by anchoring them to MTs. The balance of motile versus stationary mitochondria pools depends on the relative action of the motor/adaptor and SNPH to axonal mitochondria. Progressive elevation of SNPH expression with neuron maturation contributes to declined motility of axonal mitochondria in mature neurons and adult brains.

mitochondria are mobile and the remaining two-thirds are stationary. When neurons fully mature, the majority of axonal mitochondria enter a steady phase and remain stationary (Zhou et al., 2016). Given that synaptic transmission and action potential propagation are two major functional features in mature neurons, axonal mitochondria, instead of maintaining a uniform distribution, display increased density at synapses and nodes of Ranvier, two active sites of energy metabolism. An increasing majority of axonal mitochondria remain stationary in matured axonal branches or axonal terminals, which were consistently observed in rodent nervous systems in vitro and in vivo from several independent studies (Lewis Jr., Turi, Kwon, Losonczy, & Polleux, 2016; Smit-Rigter et al., 2016; Takihara et al., 2015; Zhou et al., 2016). These studies suggest that axonal mitochondrial motility undergoes a progressive regulation from developing neurons (or brains) to mature neurons (or adult brains). This declined axonal mitochondrial motility raises an interesting and fundamental question as to whether mitochondrial trafficking or its anchoring mechanisms are progressively regulated with neuronal maturation and age.

SNPH immobilizes axonal mitochondria in mature neurons and adult brains

Mitochondrial anchoring mechanisms are essential for arresting mobile mitochondria within axons. This anchoring mechanism was recently revealed by our series of studies demonstrating that syntaphilin (SNPH) acts as a "static anchor" for axonal mitochondria (Chen & Sheng, 2013; Kang et al., 2008; Zhou et al., 2016). SNPH selectively associates with axonal mitochondria through its OMM-insertion domain and axon-sorting sequence and anchors mitochondria on MTs through its MT-binding domain. Deleting *snph* robustly enhances axonal mitochondrial transport (by increasing the total motility up to ~78%) in mature neurons in vitro and adult brains in vivo; overexpressing SNPH in mouse cortical and hippocampal neurons abolishes axonal mitochondrial motility. Recent optogenetic analysis further confirmed that the balance between mobile vs stationary pools of axonal mitochondria is controlled by selective recruitment of the KIF5 motor vs SNPH onto axonal mitochondria, respectively (van Bergeijk, Adrian, Hoogenraad, & Kapitein, 2015) (Fig. 2).

SNPH-mediated anchoring is the key mechanism contributing to this maturation-associated decline of axonal mitochondrial motility. Our recent parallel study of axonal mitochondrial motility and SNPH expression in mouse cortical neurons demonstrated that axonal mitochondria display progressively reduced motility from young developing neurons at DIV7 ($47.60 \pm 4.60\%$) to well-matured neurons at DIV18 ($22.88 \pm 3.09\%$, $p < 0.001$) (Fig. 3A). In contrast, SNPH expression is hardly detectable in neurons before DIV3, and in mouse embryonic brains, becomes readily detectable after DIV9 in culture and gradually reaches its peak at DIV22 and in adult mouse brains (Fig. 3B) (Zhou et al., 2016). This progressively elevated expression is specific for SNPH; as other mitochondrial trafficking motor-adaptor proteins including KIF5, DIC, Miro1/2, and Trak2 show consistent levels of expression throughout neuronal development and maturation. The elevated SNPH expression pattern was also confirmed in rat brains: it is undetectable at embryonic stages, gradually increases during brain maturation, and peaks in adulthood (Das, Boczan, Gerwin, Zald, & Sheng, 2003). Such progressively elevated SNPH expression with neuron and brain maturation supports the notion that SNPH-mediated anchoring contributes to declined motility of axonal mitochondria in mature neurons and adult brains. Therefore, motile mitochondria in developing neurons are recruited to the stationary pool during neuronal maturation, thus maintaining energy metabolism to sustain key neuronal activities by positioning mitochondria at synapses and nodes of Ranvier. Deleting *snph* in mice disrupts this anchoring mechanism, thus robustly increasing axonal mitochondria in motile pools: 78% of axonal mitochondria are motile in cultured hippocampal neurons at DIV14, and 71% of axonal mitochondria are motile in axonal bundles of sciatic nerves in 2-month-old adult mice (Chen & Sheng, 2013; Kang et al., 2008; Zhou et al., 2016). Given

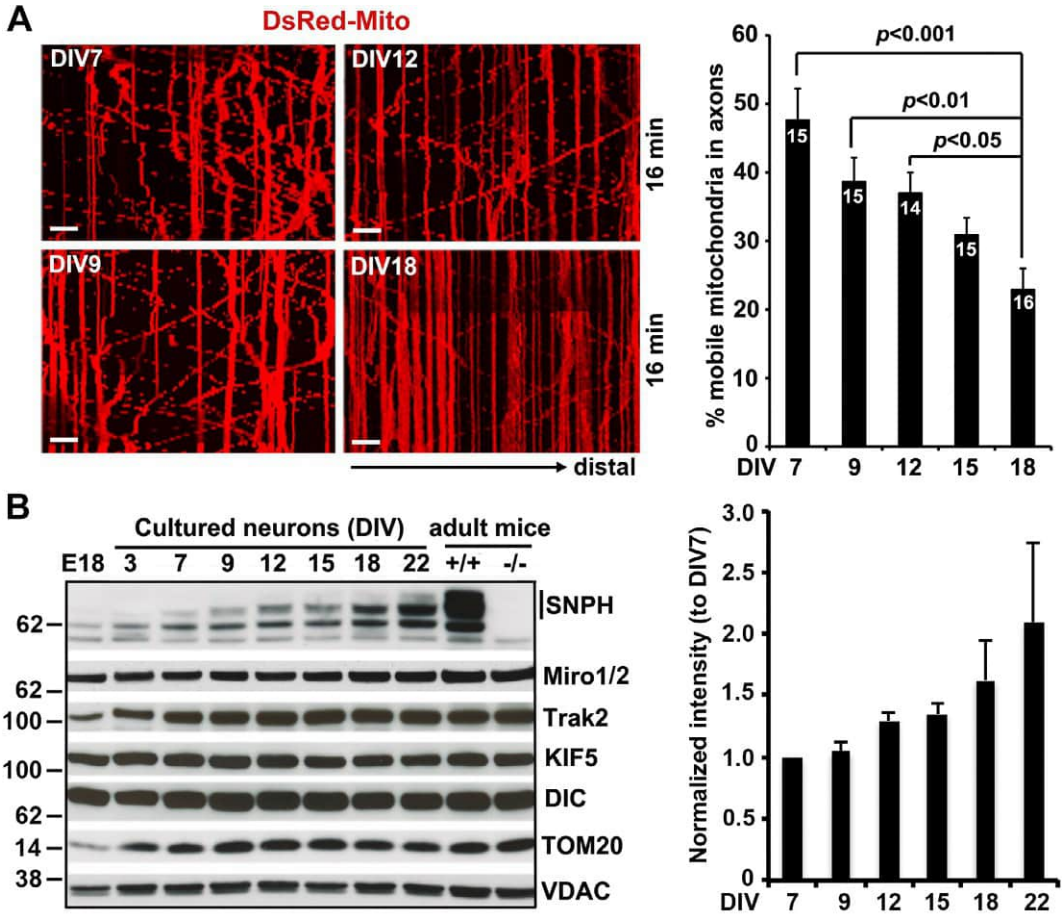

FIG. 3 SNPH contributes to declined motility of axonal mitochondria in mature neurons. (A) Kymographs showing a progressive decline of axonal mitochondrial motility with neuron maturation. Cortical neurons were transfected with DsRed-Mito, followed by time-lapse images at DIV7, 9, 12, or 18. Data were analyzed from the total number of neurons indicated within bars and expressed as mean ± SEM. Bars, 10 μm. (B) Progressive increase in SNPH expression with neuron maturation. Cortical neurons isolated from E18 mouse brains were cultured for 3, 7, 9, 12, 15, 18, and 22 days. Equal amounts of lysates were sequentially immunoblotted with various antibodies. Brain lysates from E18 WT, adult WT, and *snph* KO mouse brain homogenates were used as controls. The intensity of SNPH bands was quantified from three repeats, calibrated to TOM20 levels, and then normalized to SNPH expression at DIV7. *(Adapted with permission from Zhou, B., Yu, P., Lin, M. Y., Sun, T., Chen, Y., & Sheng, Z. H. (2016). Facilitation of axon regeneration by enhancing mitochondrial transport and rescuing energy deficits.* Journal of Cell Biology, 214*(1), 103–119. https://doi.org/10.1083/jcb.201605101.)*

the fact that SNPH plays a major role in anchoring the majority of axonal mitochondria in mature neurons and adult mouse brains, *snph* knockout (KO or $snph^{-/-}$) mice serve as an ideal genetic model for investigations into whether genetically enhanced transport of axonal mitochondria ensures matured neurons and adult brains regain regenerative capacity by reversing the injury-induced energy crisis.

Deleting SNPH anchoring boosts axon regeneration in vitro and in vivo

While developing neurons possess robust axon growth and dynamic mitochondrial transport, mature neurons in the CNS display a declined mitochondrial motility and typically fail to regrow after injury. A widely accepted concept is that the limited regrowth capacity of the mature CNS is due to an intrinsic decline of permissive conditions. Thus, it is critical to elucidate these intrinsic mechanisms accounting for declined regrowth capacity in mature neurons. As we discussed above, neural regeneration is a highly energy-demanding process starting from resealing axonal terminals, reorganizing the cytoskeleton, synthesizing and delivering building materials into new growth cones, and finally re-connecting synapses and restoring functions (He & Jin, 2016). Given that (1) the majority of axonal mitochondria in the mature CNS remain stationary (Lewis Jr. et al., 2016; Smit-Rigter et al., 2016; Takihara et al., 2015; Zhou et al., 2016), and (2) brain injury is an acute insult that damages local mitochondria leading to an energy crisis (Cavallucci et al., 2014; O'Donnell, Vargas, &

Sagasti, 2013), proper delivery of healthy mitochondria into injured axons ensures an adequate supply of ATP. Two fundamental questions emerge: (1) do energetic deficits, caused by impaired ATP production combined with high ATP consumption, contribute to one of the intrinsic restrictions that account for regeneration failure in mature CNS neurons? If this is the case, then (2) does reversing declined mitochondrial transport enable mature neurons to regain regrowth capacity following in vitro and in vivo injury?

Our recent study addressed these two issues by live imaging mitochondrial transport, mitochondrial membrane potential, and local ATP levels within injured axons of mature cortical neurons cultured in a microfluidic chamber system (Zhou et al., 2016). The study demonstrated that axon injury is an acute stress signal that rapidly depolarizes mitochondria, leading to a local energy crisis in the vicinity of the injured site. We further applied *snph*$^{-/-}$ mice as a genetic model to investigate whether enhanced mitochondrial transport in mature neurons regains their regenerative capacity after injury. Surprisingly, robustly enhancing mitochondrial transport in mature *snph*$^{-/-}$ axons helps remove damaged mitochondria from injured axons and replenish with healthy ones, thus effectively reversing local energy deficits. Thus, maintaining ATP supply in injured axons via recruiting healthy mitochondria is critical to meeting enhanced energy requirements during regeneration. Significantly, such enhanced mitochondrial trafficking not only facilitates axonal regeneration in mature cortical neurons after axotomy in vitro (Fig. 4A and B), but also boosts regeneration of dorsal root ganglion (DRG) neurons in vivo after crush injury of sciatic nerves in adult mice (Fig. 4E). Alternatively, manipulating an enhanced axonal mitochondrial motility in wild-type neurons by overexpressing motor receptor Miro1, instead of deleting anchoring protein SNPH, also promotes axon regeneration. As a negative control, our study further confirmed that re-expressing SNPH arrests almost all mitochondria and thus abolishes axon regeneration (Fig. 4C and D). This study provides mechanistic insights into how elevated SNPH expression in the mature CNS neurons and an injury-induced energy crisis contribute to regeneration failure.

Enhanced mitochondrial transport facilitates axon regeneration

SNPH and Miro1 become attractive candidate targets for investigations into the roles of mitochondrial trafficking and anchoring and thus recovery of energy metabolism in the regeneration capacity of the adult CNS. The enhanced axonal regeneration found in *snph*$^{-/-}$ mice was supported by three recent in vitro and in vivo studies demonstrating that enhanced mitochondrial transport and recruitment play critical roles in nerve regeneration in both worm and mouse models. By studying an enhanced regeneration mouse model with SOCS3 and PTEN double dKO, Cartoni et al. reported that a mitochondria-targeted protein named Armcx1 promotes mitochondrial transport in mouse retinal ganglion cells (RGCs) likely through its interaction with mitochondrial motor receptor Miro1 (Cartoni et al., 2016). Interestingly, Armcx1 expression is elevated in RGCs with high regenerative capacity. Overexpressing Armcx1 enhances axonal mitochondrial transport in RGCs and supports the survival and regeneration of axotomized neurons. Conversely, depleting Armcx1 in this dKO model decreases its regeneration capacity. This study highlighted a regeneration-relevant mitochondrial protein that enhances axonal mitochondrial transport in response to injury, thus adding an additional line of evidence showing a critical role of mitochondrial transport in nerve regeneration. A second study by Kalinski et al. revealed an unexpected role of histone deacetylase 6 (HDAC6) that is thought to deacetylate α-tubulin. HDAC6-mediated deacetylation of Miro1 decreases axonal mitochondrial transport and thus inhibits DRG neuron axon growth (Kalinski et al., 2019). Thus, this study provided a new line of evidence demonstrating that proper mitochondrial trafficking is crucial for maintaining neural regeneration capacity. In a third study using *C. elegans* as a model organism, Han et al. revealed that axotomy in GABA motor neurons induces axonal energy stress that triggers an enhanced mitochondrial density within injured axons, thus meeting the increased ATP demand to support axon survival and regeneration. Interestingly, they found the dual leucine zipper kinase 1 (DLK-1) as a candidate signaling pathway that is able to recruit mitochondria to the injury site (Han et al., 2016).

The notion that enhanced mitochondrial transport benefits nerve regeneration after injury is also supported by several earlier in vivo studies in different nervous systems. By examining the proximal segments of transected intercostal nerves, Misgeld et al. found that injury induces mitochondrial anterograde transport and re-distribution at the growth cone (Misgeld, Kerschensteiner, Bareyre, Burgess, & Lichtman, 2007). In the *C. elegans ric-7* mutant where mitochondrial transport is impaired, degeneration of injured axons is inhibited by delivering mitochondria into axons (Rawson et al., 2014). The axon-protective Wld^{S} protein reduces the decline of axonal ATP levels by partially rescuing glycolysis and mitochondrial respiration after axonal injury (Godzik & Coleman, 2015). It was also reported that Wld^{S}-induced mitochondrial flux protects axons from Wallerian degeneration after injury in both *Drosophila* and mouse models (Avery et al., 2012).

In addition, several regeneration-associated signaling pathways have been reported to crosstalk with the mechanisms that drive mitochondrial transport. In zebrafish, pharmacologically activating cyclic adenosine monophosphate (cAMP)

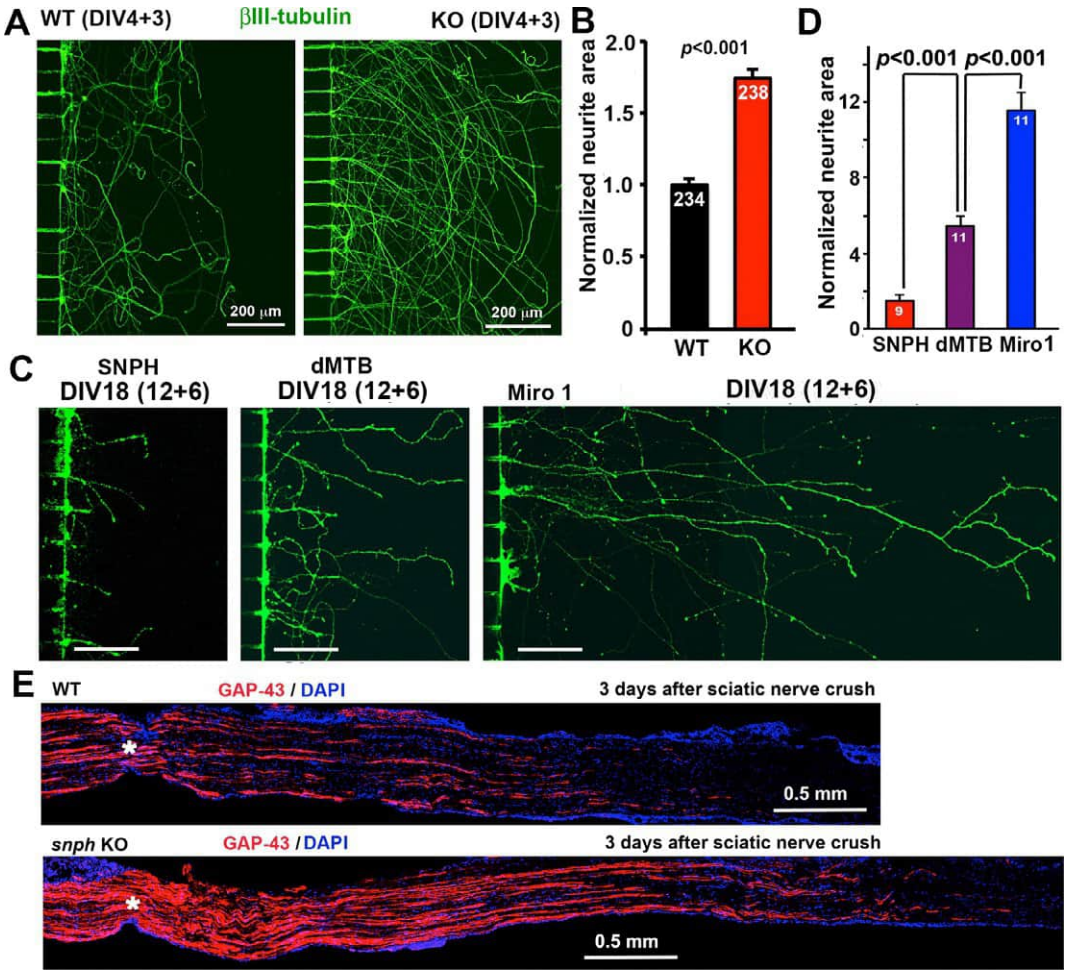

FIG. 4 Enhancing mitochondrial transport boosts axon regrowth capacity after injury in vitro and in vivo. (A, B) Enhancing axonal mitochondrial transport in *snph* KO cortical neurons facilitates axon regrowth after axotomy. Neurons cultured in microfluidic chambers were axotomized at DIV4 and allowed to regrow for 3 days. Axons were stained with βIII-tubulin at DIV7. (C, D) Mature neurons regain regrowth capacity by enhancing axonal mitochondrial transport. Neurons expressing SNPH, SNPH mutant dMTB, or Miro1 were grown in microfluidic chambers for 12 days before axotomy. Regeneration was evaluated 6 days after axotomy (DIV18). Note that abolishing mitochondrial transport by overexpressing SNPH shows failed axon regrowth, whereas enhancing mitochondrial transport by overexpressing Miro1 boosts axon regrowth after injury. (E) SNPH KO mice display enhanced regenerative capacity of sciatic nerves after crush injury in vivo. Adult WT and *snph* KO mice were subjected to a sciatic nerve crush and sacrificed at 3 days post-injury. Regenerating axons were visualized by expressing GAP-43 (*red*) on sciatic nerve longitudinal sections (*crush site). Total number of microgroove channels (B) or chambers (D) are indicated within bars. Scale bars: 200 μm (A), 100 μm (C), 500 μm (E). *(Adapted with permission from Zhou, B., Yu, P., Lin, M. Y., Sun, T., Chen, Y., & Sheng, Z. H. (2016). Facilitation of axon regeneration by enhancing mitochondrial transport and rescuing energy deficits.* Journal of Cell Biology, 214*(1), 103–119. https://doi.org/10.1083/jcb.201605101.)*

enhances axonal mitochondrial trafficking and axon regrowth in Mauthner cells (Xu, Chen, Hu, Huang, & Hu, 2017). Furthermore, the cAMP-PKA-Kinesin1 axis was reported to regulate mitochondrial flux in an aging *Drosophila* model (Vagnoni & Bullock, 2018). A second PI3K-AKT axis was found to negatively regulate PTEN, thus playing an opposite role in mitochondrial motility and axon regeneration (Huang et al., 2019; Park et al., 2008). Although mechanisms as to how these signaling pathways facilitate mitochondrial transport have not been fully elucidated, these studies support an emerging concept: activating an intrinsic "regeneration program" requires the recovery of energy supply by reprogramming mitochondrial transport and recruitment.

Remodeling mitochondrial transport promotes regeneration after SCI

CNS injury and particularly SCI are often characterized by the initial traumatic injury, followed by a secondary injury cascade that could last progressively over weeks (Ahuja et al., 2017). While the primary injury ruptures the axon plasma membrane and elevates intracellular calcium leading to acute mitochondrial damage (Bradke, Fawcett, & Spira, 2012),

widespread secondary injury may also cause progressive mitochondrial dysfunction due to chronic inflammation, excitotoxicity, and oxidative response. Although restoring local energy supply by enhancing mitochondrial transport has proven to be arobust strategy in promoting axon survival and regeneration in cultured neurons and the peripheral nerve system (Zhou et al., 2016), it is rather challenging to reverse the axonal energy crisis and support regeneration and synaptic re-connection in injured long-projection corticospinal tract (CST) neurons, and thus restore motor functions after SCI. By collaborating with Xiao-Ming Xu's group at the University of Indiana, we recently established that SCI-induced mitochondrial dysfunction and the local energy crisis are intrinsic restrictions linked to regeneration failure. Using three different murine CNS injury models, we provided in vivo evidence that reversing energy deficits by enhancing mitochondrial transport using *snph*$^{-/-}$ micerepresents a promising therapeutic direction to stimulate axonal regeneration and functional recovery after SCI (Han et al., 2020).

First, Han et al. (2020) used a 5th cervical (C5) dorsal hemisection (DH) injury model to study CST regeneration. While WT mice showed little axonal regrowth beyond the lesion, *snph*$^{-/-}$ mice exhibited robust axon regeneration past the lesion, extending into the caudal spinal cord (Fig. 5). SCI impairs synaptic connections between CST axons and their postsynaptic targets, and thus disrupts the cortico-motoneuronal circuit. By combing light and electron microscopy imaging along with electromyography (EMG) recording, the study demonstrated that these regenerated CSTs in *snph*$^{-/-}$ mice are able to establish cortico-spinal motor connections and conduct synaptic transmission caudal to the injury (Fig. 6). One of the most promising findings was that *snph*$^{-/-}$ mice display notable forelimb dexterous improvement in the single-pellet retrieval test after the C5 SCI. Second, Han et al. (2020) utilized a unilateral pyramidotomy model in which CST axons were severed unilaterally, leading to complete loss of CST innervation on the contralesional spinal cord. WT mice display no change in the termination pattern of CST collaterals after pyramidotomy; most axons remain ipsilateral to the lesion at cervical, thoracic, and lumbar spinal cord levels. In contrast, after pyramidotomy, *snph*$^{-/-}$ mice showed enhanced CST sprouting across the midline and extend into the denervated side at cervical, thoracic, and lumbar spinal cord levels. This striking difference indicates that enhancing axonal mitochondrial transport by deleting *snph* in mice facilitates robust CST sprouting to the denervated contralesional hemicord after a unilateral pyramidotomy. To explore whether increased regrowth could be applied to other CNS pathways, the study applied the third injury model of a thoracic 8 (T8) spinal complete transection to investigate regeneration of both CST and monoaminergic pathways. CST axons dramatically died back from the rostral lesion border in all WT mice. Notably, such typical retraction did not occur in *snph*$^{-/-}$ mice. Instead, CST axon terminals

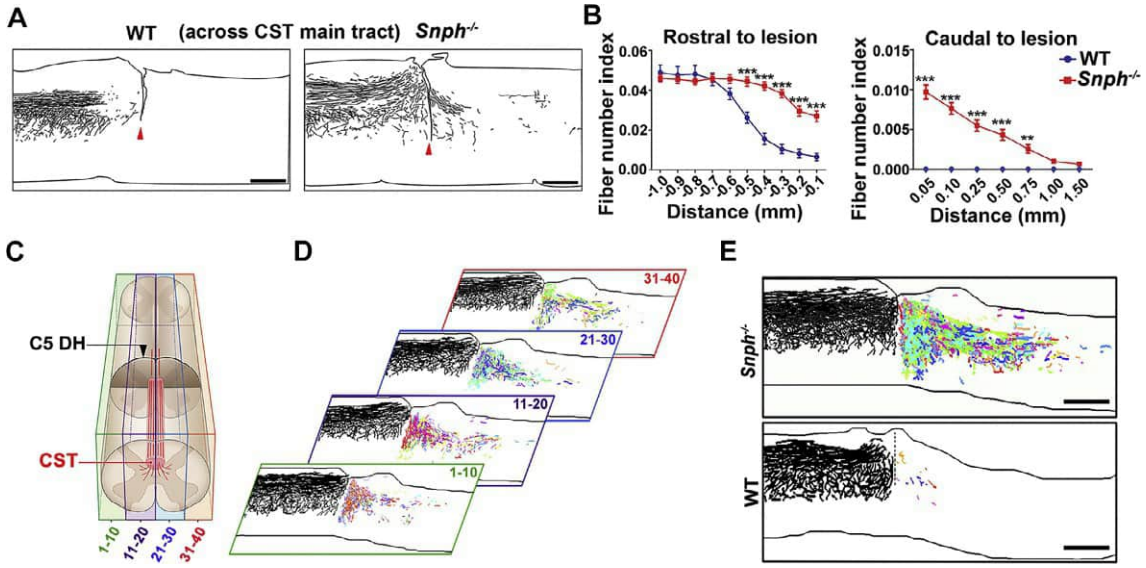

FIG. 5 *Snph*$^{-/-}$ mice display enhanced CST axonal regeneration after SCI. (A) Representative images of BDA-labelled CST main tract in the dorsal column after C5 DH in WT and *Snph*$^{-/-}$ mice. (B) Quantification of CST axon number index at different distances rostral (left) and caudal (right) to the C5 DH. (C, D) Schematic images showing a spinal cord segment divided into four longitudinal blocks, each containing 10 sections (C). BDA-labelled CST axons in each section were traced and color-coded with Imaris software (D). Each of the four color-coded blocks on the right was generated by overlaying 10 consecutive sections. Each color represents a trace of BDA-labeled axons caudal to the lesion in a single section of one block. (E) Reconstruction of a stack of all 40 color-coded images showing CST regeneration across and beyond the lesion in WT and *Snph*$^{-/-}$ mice at 8 weeks post SCI. *(Adapted with permission from Han, Q., Xie, Y., Ordaz, J. D., Huh, A. J., Huang, N., Wu, W., Liu, N., Chamberlain, K. A., Sheng, Z. H., & Xu, X. M. (2020). Restoring cellular energetics promotes axonal regeneration and functional recovery after spinal cord injury.* Cell Metabolism, 31*(3), 623–641 e628. https://doi.org/10.1016/j.cmet.2020.02.002.)*

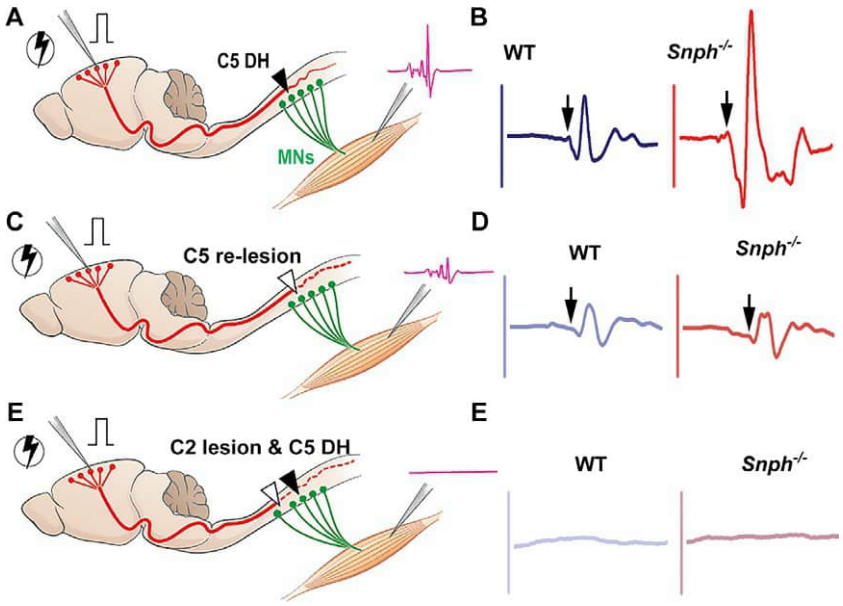

FIG. 6 *Snph*$^{-/-}$ mice display enhanced corticomotoneuron connection after SCI. Schematic model and sample traces of electromyography (EMG) in WT and *Snph*$^{-/-}$ mice recorded from forelimb biceps in response to motor cortex single-pulse stimulation after the C5 DH (A, B). The increased EMG responses in *Snph*$^{-/-}$ mice were abolished after the C5 re-lesion (C, D). EMG activity in both WT and *Snph*$^{-/-}$ mice was completely abolished after a second C2 lesion rostral to the C5 DH in mice (E, F). Scale: 400 μm. *(Adapted with permission from Han, Q., Xie, Y., Ordaz, J. D., Huh, A. J., Huang, N., Wu, W., Liu, N., Chamberlain, K. A., Sheng, Z. H., & Xu, X. M. (2020). Restoring cellular energetics promotes axonal regeneration and functional recovery after spinal cord injury.* Cell Metabolism, 31*(3), 623–641 e628. https://doi.org/10.1016/j.cmet.2020.02.002.)*

were sustained at the rostral lesion border. In addition, we provided in vivo evidence that enhancing mitochondrial transport helps deliver healthy mitochondria from the motor cortex into the injured and regenerating CST axons, thus recovering local axonal mitochondrial integrity. Altogether, restored CNS regeneration in vivo in the three injury models (Han et al., 2020), combined with our findings in in vitro cortical neuron injury and in vivo DRG neurons after crush injury of sciatic nerves (Zhou et al., 2016), supports an emerging concept: enhancing mitochondrial transport via deleting mitochondrial anchoring protein SNPH enables a robust regenerative response to injury in both the PNS and CNS in adult mice.

Boosting energetic metabolism promotes regeneration after SCI

Instead of enhancing mitochondrial transport, boosting energy metabolism in injury neurons represents an alternative promising therapeutic direction. To further test the "injury-induced energy crisis" model, we elevated energy metabolism using creatine, an FDA-approved blood-brain-barrier permeable bioenergetic compound that regenerates ATP from ADP independent of the mitochondrial transport chain (Tarnopolsky & Beal, 2001). While saline-treated WT mice showed no CST axon regeneration after C5 DH, creatine-treated WT mice exhibited significant regeneration of CSTs past the lesion site. However, most regenerated CST axons in creatine-treated WT mice stopped at 0.5 mm caudal to the lesion. In contrast, regenerated axons in *snph*$^{-/-}$ mice extended further up to 1.5 mm in the caudal spinal cord. One explanation is that creatine may induce a rather limited recovery of energy metabolism because of the majority of damaged mitochondria stay within injured axons. Thus, enhanced delivery of healthy mitochondria into injured axons by deleting *snph* likely plays a more persistent and predominant role in recovering axonal energy supply. This hypothesis was supported by the combination of *snph*$^{-/-}$ mice with creatine treatment, which offers even greater effects to boost axon regeneration and functional improvement after SCI (Han et al., 2020).

These regeneration studies in *snph*$^{-/-}$ mice (Han et al., 2020; Zhou et al., 2016) reveal for the first time an "injury-induced energy crisis" model and provide new mechanistic insights as to how enhancing mitochondrial transport enables the mature CNS to regain regenerative capacity after both PNS and CNS injury. However, such genetic manipulation is rather artificial and not suitable for translational development and clinical application in treating SCI. Thus, it is urgent to develop a therapeutic strategy that specifically targets energetic signaling pathways that could either enhance mitochondrial transport and/or elevate energetic metabolism in local axons in response to the brain and spinal injury. Several signaling pathways, including LKB1-Nuak1, cAMP-PKA, and PTEN, have been reported to recruit axonal mitochondria by enhancing their motility in response to various physiological and pathological conditions (Cartoni et al., 2016; Courchet et al., 2013; Vagnoni & Bullock, 2018). A recent high-content screen on mitochondrial motility revealed that pharmacological inhibition of Tripeptidyl peptidase 1 (TPP1) or Aurora Kinase B (AurKB) enhances axonal mitochondrial motility

in rat hippocampal neurons and iPSC-derived human cortical neurons (Shlevkov et al., 2019), which provides therapeutic potential in mobilizing axonal mitochondria after SCI.

Creatine is one of the therapeutic compounds that have been applied in rodent SCI models and SCI patients (Tarnopolsky & Beal, 2001). In vertebrates, creatine is converted into phosphocreatine for rapid ATP generation through creatine kinase (CK) independent of the mitochondrial transport chain, and thus CK activity is critical to maintaining creatine concentration and energy demand in tissues (Wyss & Kaddurah-Daouk, 2000). Oral creatine supplementation elevates the phosphocreatine level in the rat nervous system. After SCI, creatine supplementation significantly reduced the scar tissue surrounding the lesion and promoted locomotor capacity (Hausmann, Fouad, Wallimann, & Schwab, 2002). In patients with complete cervical-level SCI, creatine supplementation was reported to enhance their exercise capacity (Jacobs, Mahoney, Cohn, Sheradsky, & Green, 2002), although it remains unknown whether this is the effect of creatine-enhanced regeneration and/or muscle strength. Han et al. (2020) demonstrated that creatine treatment helps astrocytes bridge the lesion gap and promotes CST axon regeneration passing through the lesion in the C5 DH SCI model. However, creatine-induced CST axon regeneration in WT mice is rather limited after SCI when compared to enhanced mitochondrial transport in *snph*$^{-/-}$ mice. Thus, enhanced delivery of healthy mitochondria into injured axons would play a more persistent and predominant role in recovering energy supply than systemic administration of creatine.

Conclusions and new challenges

Mitochondria are the main cellular powerhouses that produce ATP essential for neuronal survival and regeneration. Since injury triggers acute mitochondrial dysfunction, the "injury-induced energy crisis" model has emerged as a new concept of intrinsic restriction that accounts for regeneration failure in SCI and other CNS injuries. Recent studies demonstrate that enhancing mitochondrial transport and replacing damaged mitochondria could reverse these energy deficits and promote axon regeneration and functional recovery, thus providing an emerging therapeutic target for treating SCI. While recent preclinical SCI studies have focused on cell-to-cell mitochondrial transfer and/or enhancement of mitochondrial biogenesis (Simmons, Scholpa, & Schnellmann, 2020), future investigations into the energy-sensing regulation of axonal mitochondrial trafficking and anchoring is a new and promising frontier in neurobiology and neurology (Sheng, 2017). These self-regulation pathways within injured neurons and local axons seem more effective and robust to reverse the energy crisis following acute injury. However, there are many fundamental questions that remain to be addressed. Specifically, while the majority of axonal mitochondria are in the stationary status in mature neurons and adult or aging brains, how could mitochondrial trafficking and anchoring mechanisms be reprogrammed by energetic repairing signals in order to sense the local energetic crisis and regrowth status after SCI and brain injury? Revealing and reprogramming such intrinsic "energy repairing programs" is an emerging frontier for therapeutic investigations. In addition, it remains largely unknown whether bioenergetic compounds could be efficiently delivered into injured axons to elevate local mitochondrial energetic metabolism. Given our findings that creatine-induced axon regeneration after SCI is rather limited when compared to enhanced mitochondrial transport in *snph*$^{-/-}$ mice (Han et al., 2020), future development of more effective bioenergetic compounds would be beneficial to quickly reverse the energy crisis following CNS injuries. Technically, a more sensitive ATP sensor suitable for in vivo real-time tracking of energy levels in the CNS needs to be developed. The current available ATP reporters or biosensors such as Perceval HR, which monitors intracellular ATP/ADP ratios (Tantama, Martinez-Francois, Mongeon, & Yellen, 2013), and GO-ATeam 2, a Förster Resonance Energy Transfer (FRET)-based fluorescent probe to measure cytosolic ATP levels (Nakano, Imamura, Nagai, & Noji, 2011), have been widely applied to examine intracellular ATP levels in live neurons. However, these ATP imaging tools have limited capacity for directly assessing in vivo energy deficits, thus preventing the evaluation of therapeutic strategies in rescuing the energy crisis after SCI.

Applications to other areas of neuroscience

In this chapter, we focused on providing updates on recent studies into how enhanced axonal mitochondrial transport promotes the highly energy-demanding axon regeneration and functional recovery in in vitro and in vivo injury models, and provide prospective views on the potential therapeutic strategy of remodeling mitochondrial transport and elevating cellular energetic metabolism for SCI. In fact, acute mitochondrial damage and altered mitochondrial transport has also been observed in other CNS injury models including traumatic brain injury (Simmons et al., 2020) and ischemia (Yang, Mukda, & Chen, 2018). Preclinical trials that restore axonal mitochondrial integrity and/or local energy homeostasis through exogenous mitochondrial transplantation or pharmacological treatment have surfaced as mitochondrial therapeutic strategies against these CNS injuries. Mitochondrial transplantation is a cellular surgical approach that replaces damaged mitochondria through in situ injections of exogenously isolated healthy ones. The concept of mitochondrial transplantation

comes from the fact that after CNS ischemia-reperfusion injury, astrocyte mitochondria are released into the extracellular space, and transferred into injured neurons to support oxidative phosphorylation. Recent studies suggest that such mitochondrial transplantation could increase total ATP levels, oxygen uptake, and expression of key mitochondrial proteins in injected tissues without inducing an inflammatory response. However, mitochondrial transplantation in SCI models is quite challenging given the very limited efficiency in transferring mitochondria into the injured spinal cord axons. Thus, pharmacological activation of the signaling pathways that elevate local mitochondrial biogenesis within injury sites is an attractive direction for future preclinical studies against CNS injury. Several studies have reported that increased mitochondrial biogenesis could slow injury progression and promote functional recovery. Furthermore, pharmacological compounds that enhance mitochondrial biogenesis have already been approved by the FDA for the treatment in rodent SCI models. Thus, these compounds benefit therapeutic development against traumatic brain injury, ischemia, and other CNS injuries. In addition, chronic mitochondrial dysfunction and impaired transport have also been implicated in major neurodegenerative diseases and neurological disorders. Aging-associated accumulation of chronically damaged mitochondria not only produces energy less efficiently but also releases harmful reactive oxygen species. The removal of defective mitochondria from axons and synapses by enhancing their transport constitutes a critical step of mitochondrial quality control (Lin et al., 2017). Therefore, revealing and reprogramming "energy repairing programs" in SCI also benefits the therapeutic development of aging-associated neurodegeneration and neurological disorders.

Mini-dictionary of terms

Adenosine triphosphate (ATP): An organic compound that provides energy to support cellular processes. In the brain, ~93% of ATP is supplied by mitochondria, and the remaining ~7% of ATP is generated through glycolysis.

Mitochondria: The main cellular powerhouses that convert glucose and pyruvate into cellular energy ATP through the electron transport chain and oxidative phosphorylation, and also buffers cytosol calcium.

Axonal mitochondrial motility: Axonal mitochondria move bi-directionally along axonal microtubules; they can pause and change direction frequently and re-mobilize and re-distribute in axons. The mean velocities of axonal mitochondrial motility are highly variable ranging from ~0.2 to 2.0 μm per second. In developing neurons, ~30%–45% of axonal mitochondria are mobile and the remaining two-thirds are stationary. These motility profiles decline and become relatively stable after neurons mature.

Mitochondrial adaptors: A class of mitochondria-associated proteins that connect mitochondria with their transport motor proteins.

Kinesin-1: A class of the plus-end directed and microtubule-based motor proteins that hydrolyze ATP to power anterograde axonal transport of membrane cargoes from the soma toward distal axons in neurons.

Cytosolic dynein: A family of the minus-end directed and microtubule-based motor proteins that hydrolyze ATP to power retrograde axonal transport of membrane cargoes from distal axons back toward the soma in neurons.

Microtubules: A class of cytoskeleton that is formed by polymerized tubulin. Axonal mitochondrial trafficking and anchoring machineries are mainly based on axonal MT tracks.

Mitochondrial membrane potential: An essential functional component of mitochondria that maintains ATP generation and storage capacity during oxidative phosphorylation and is widely used as a marker of mitochondrial integrity.

ROS: Reactive oxygen species are produced by mitochondria during oxidative phosphorylation. High levels of mitochondrial ROS induce cellular stress and apoptosis as well as neuronal degeneration.

Local energy homeostasis: An energetic status that maintains cytosolic ATP to fully power various cellular processes in local areas.

Energy deficits: An insufficient ATP supply status when mitochondria are damaged and/or during increased energy consumption such as after axonal injury and during regeneration.

Creatine: An FDA-approved blood–brain barrier permeable bioenergetic compound that is converted into phosphocreatine for rapid ATP generation from ADP through creatine kinase (CK) independent of the mitochondrial transport chain.

SNPH-mediated axonal mitochondrial anchoring: Syntaphilin (SNPH) acts as a 'static anchor' that selectively associates with axonal mitochondria through its OMM-insertion domain and axon-sorting sequence, and anchors mitochondria on MTs through its MT-binding domain.

Mitochondrial transplantation: A cellular surgical approach that replaces damaged mitochondria through in situ injections of exogenously isolated healthy ones.

Key facts of SNPH-mediated decline of axonal mitochondrial transport in mature neurons

- Axonal mitochondrial motility progressively declines from developing neurons (brains) to mature neurons or adult brains.
- In developing neurons, 30%–45% of axonal mitochondria are mobile and the remaining two-thirds are stationary; when neurons mature, axonal mitochondria largely remain stationary.
- Mitochondrial anchoring mechanisms are essential for arresting mobile axonal mitochondria.
- SNPH acts as a "static anchor" for axonal mitochondria and immobilizes axonal mitochondria.
- Progressive elevation of SNPH expression with neuron maturation contributes to declined motility of axonal mitochondria in mature neurons and adult brains.

Key facts of the energy crisis that accounts for regeneration failure

- Neural regeneration is a highly energy-demanding process, while brain injury is an acute insult that damages local mitochondria.
- An insufficient ATP supply when mitochondria are damaged and increased energy consumption during regeneration collectively contribute to the energy crisis in local injured axons.
- Enhancing mitochondrial transport in *snph*$^{-/-}$ axons helps remove damaged mitochondria from injured axons and replenish with healthy ones, thus reversing local energy deficits.
- Reversing the energy crisis by deleting *snph* enables mature neurons to regain regrowth capacity following in vitro and in vivo injury.
- Enhancing mitochondrial transport and replacing damaged mitochondria reverse the energy deficits and promote axon regeneration and functional recovery after SCI.

Key facts of boosting local energy supply in injured axons

- In addition to enhancing mitochondrial transport, boosting energy metabolism in injured neurons represents an alternative therapeutic direction for stimulating regeneration after SCI.
- Boosting energy metabolism using the bioenergetic compound creatine modestly facilitates CST axon regeneration after SCI.
- The combination of enhanced mitochondrial transport in *snph*$^{-/-}$ mice with creatine treatment offers even greater effects at boosting axon regeneration and functional improvement after SCI.
- Reprogramming intrinsic "energy repairing programs" that enhance mitochondrial transport in response to the brain and spinal injury is an emerging frontier for therapeutic investigations.
- Pharmacological activation of the signaling pathways that elevate mitochondrial biogenesis within injured axons is an attractive direction for future preclinical studies against CNS injury.

Summary points

- The mature CNS typically fails to regenerate after injury leading to permanent neurological impairment.
- Regeneration requires high-energy consumption in the form of ATP that is mainly produced in mitochondria.
- Injury is an acute insult that damages local mitochondria leading to an energy crisis.
- The "injury-induced energy crisis" concept has emerged as one of the intrinsic restrictions that accounts for regeneration failure in SCI and other CNS injuries.
- Axonal mitochondrial transport progressively declines from developing neurons to mature neurons or adult brains.
- SNPH acts as a "static anchor" contributing to declined motility of axonal mitochondria in mature neurons and adult brains.
- Enhancing mitochondrial transport in *snph*$^{-/-}$ axons helps remove damaged mitochondria and replenish them with healthy ones, thus reversing the local energy crisis.
- Reversing this energy crisis enables mature neurons to regain regrowth capacity and promote axon regeneration and functional recovery after SCI.

- Boosting energy metabolism using the bioenergetic compound creatine facilitates CST axon regeneration after SCI.
- Remodeling the delivery of healthy mitochondria into injured axons has emerged as one of the robust mechanisms for boosting axon regeneration after SCI.

Acknowledgment

This work was supported by the Intramural Research Program of NINDS, NIH ZIA NS003029 and ZIA NS002946 (Z-H. Sheng).

References

Ahuja, C. S., Wilson, J. R., Nori, S., Kotter, M. R. N., Druschel, C., Curt, A., et al. (2017). Traumatic spinal cord injury [Primer]. *Nature Reviews. Disease Primers*, *3*, 17018.

Avery, M. A., Rooney, T. M., Pandya, J. D., Wishart, T. M., Gillingwater, T. H., Geddes, J. W., et al. (2012). WldS prevents axon degeneration through increased mitochondrial flux and enhanced mitochondrial Ca2+ buffering. *Current Biology*, *22*(7), 596–600.

Bradbury, E. J., & McMahon, S. B. (2006). Spinal cord repair strategies: Why do they work? *Nature Reviews. Neuroscience*, *7*(8), 644–653.

Bradke, F., Fawcett, J. W., & Spira, M. E. (2012). Assembly of a new growth cone after axotomy: The precursor to axon regeneration [review article]. *Nature Reviews. Neuroscience*, *13*(3), 183–193.

Cai, Q., Gerwin, C., & Sheng, Z. H. (2005). Syntabulin-mediated anterograde transport of mitochondria along neuronal processes. *The Journal of Cell Biology*, *170*(6), 959–969.

Cartoni, R., Norsworthy, M. W., Bei, F., Wang, C., Li, S., Zhang, Y., et al. (2016). The mammalian-specific protein Armcx1 regulates mitochondrial transport during axon regeneration. *Neuron*, *92*(6), 1294–1307.

Case, L. C., & Tessier-Lavigne, M. (2005). Regeneration of the adult central nervous system. *Current Biology*, *15*(18), R749–R753.

Cavallucci, V., Bisicchia, E., Cencioni, M. T., Ferri, A., Latini, L., Nobili, A., et al. (2014). Acute focal brain damage alters mitochondrial dynamics and autophagy in axotomized neurons. *Cell Death & Disease*, *5*, e1545.

Chen, Y., & Sheng, Z. H. (2013). Kinesin-1-syntaphilin coupling mediates activity-dependent regulation of axonal mitochondrial transport. *The Journal of Cell Biology*, *202*(2), 351–364.

Cho, K. I., Cai, Y., Yi, H., Yeh, A., Aslanukov, A., & Ferreira, P. A. (2007). Association of the kinesin-binding domain of RanBP2 to KIF5B and KIF5C determines mitochondria localization and function. *Traffic*, *8*(12), 1722–1735.

Courchet, J., Lewis, T. L., Jr., Lee, S., Courchet, V., Liou, D. Y., Aizawa, S., et al. (2013). Terminal axon branching is regulated by the LKB1-NUAK1 kinase pathway via presynaptic mitochondrial capture. *Cell*, *153*(7), 1510–1525.

Covill-Cooke, C., Toncheva, V. S., Drew, J., Birsa, N., Lopez-Domenech, G., & Kittler, J. T. (2020). Peroxisomal fission is modulated by the mitochondrial Rho-GTPases, Miro1 and Miro2. *EMBO Reports*, *21*(2), e49865.

Das, S., Boczan, J., Gerwin, C., Zald, P. B., & Sheng, Z. H. (2003). Regional and developmental regulation of syntaphilin expression in the brain: A candidate molecular element of synaptic functional differentiation. *Brain Research. Molecular Brain Research*, *116*(1–2), 38–49.

Devine, M. J., & Kittler, J. T. (2018). Mitochondria at the neuronal presynapse in health and disease. *Nature Reviews. Neuroscience*, *19*(2), 63–80.

Fransson, S., Ruusala, A., & Aspenstrom, P. (2006). The atypical Rho GTPases Miro-1 and Miro-2 have essential roles in mitochondrial trafficking. *Biochemical and Biophysical Research Communications*, *344*(2), 500–510.

Fujita, T., Maturana, A. D., Ikuta, J., Hamada, J., Walchli, S., Suzuki, T., et al. (2007). Axonal guidance protein FEZ1 associates with tubulin and kinesin motor protein to transport mitochondria in neurites of NGF-stimulated PC12 cells. *Biochemical and Biophysical Research Communications*, *361*(3), 605–610.

Glater, E. E., Megeath, L. J., Stowers, R. S., & Schwarz, T. L. (2006). Axonal transport of mitochondria requires milton to recruit kinesin heavy chain and is light chain independent. *The Journal of Cell Biology*, *173*(4), 545–557.

Godzik, K., & Coleman, M. P. (2015). The axon-protective WLD(S) protein partially rescues mitochondrial respiration and glycolysis after axonal injury. *Journal of Molecular Neuroscience*, *55*(4), 865–871.

Guo, X., Macleod, G. T., Wellington, A., Hu, F., Panchumarthi, S., Schoenfield, M., et al. (2005). The GTPase dMiro is required for axonal transport of mitochondria to Drosophila synapses. *Neuron*, *47*(3), 379–393.

Han, S. M., Baig, H. S., & Hammarlund, M. (2016). Mitochondria localize to injured axons to support regeneration. *Neuron*, *92*(6), 1308–1323.

Han, Q., Xie, Y., Ordaz, J. D., Huh, A. J., Huang, N., Wu, W., et al. (2020). Restoring cellular energetics promotes axonal regeneration and functional recovery after spinal cord injury. *Cell Metabolism*, *31*(3), 623–641. e628.

Harel, N. Y., & Strittmatter, S. M. (2006). Can regenerating axons recapitulate developmental guidance during recovery from spinal cord injury? *Nature Reviews. Neuroscience*, *7*(8), 603–616.

Harris, J. J., Jolivet, R., & Attwell, D. (2012). Synaptic energy use and supply. *Neuron*, *75*(5), 762–777.

Hausmann, O. N., Fouad, K., Wallimann, T., & Schwab, M. E. (2002). Protective effects of oral creatine supplementation on spinal cord injury in rats. *Spinal Cord*, *40*(9), 449–456.

He, Z., & Jin, Y. (2016). Intrinsic control of axon regeneration. *Neuron*, *90*(3), 437–451.

Hirokawa, N., Niwa, S., & Tanaka, Y. (2010). Molecular motors in neurons: Transport mechanisms and roles in brain function, development, and disease. *Neuron*, *68*(4), 610–638.

Hsieh, C. H., Shaltouki, A., Gonzalez, A. E., Bettencourt da Cruz, A., Burbulla, L. F., St Lawrence, E., et al. (2016). Functional impairment in miro degradation and mitophagy is a shared feature in familial and sporadic Parkinson's disease. *Cell Stem Cell*, *19*(6), 709–724.

Huang, H., Miao, L., Yang, L., Liang, F., Wang, Q., Zhuang, P., et al. (2019). AKT-dependent and -independent pathways mediate PTEN deletion-induced CNS axon regeneration. *Cell Death & Disease*, *10*(3), 203.

Jacobs, P. L., Mahoney, E. T., Cohn, K. A., Sheradsky, L. F., & Green, B. A. (2002). Oral creatine supplementation enhances upper extremity work capacity in persons with cervical-level spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *83*(1), 19–23.

Kalinski, A. L., Kar, A. N., Craver, J., Tosolini, A. P., Sleigh, J. N., Lee, S. J., et al. (2019). Deacetylation of Miro1 by HDAC6 blocks mitochondrial transport and mediates axon growth inhibition. *The Journal of Cell Biology*, *218*(6), 1871–1890.

Kang, J. S., Tian, J. H., Pan, P. Y., Zald, P., Li, C., Deng, C., et al. (2008). Docking of axonal mitochondria by syntaphilin controls their mobility and affects short-term facilitation. *Cell*, *132*(1), 137–148.

Lewis, T. L., Jr., Turi, G. F., Kwon, S. K., Losonczy, A., & Polleux, F. (2016). Progressive decrease of mitochondrial motility during maturation of cortical axons in vitro and in vivo. *Current Biology*, *26*(19), 2602–2608.

Lin, M. Y., Cheng, X. T., Tammineni, P., Xie, Y., Zhou, B., Cai, Q., et al. (2017). Releasing syntaphilin removes stressed mitochondria from axons independent of mitophagy under pathophysiological conditions. *Neuron*, *94*, 595–610.

Lopez-Domenech, G., Higgs, N. F., Vaccaro, V., Ros, H., Arancibia-Carcamo, I. L., MacAskill, A. F., et al. (2016). Loss of dendritic complexity precedes neurodegeneration in a mouse model with disrupted mitochondrial distribution in mature dendrites. *Cell Reports*, *17*(2), 317–327.

Mattson, M. P., Gleichmann, M., & Cheng, A. (2008). Mitochondria in neuroplasticity and neurological disorders. *Neuron*, *60*(5), 748–766.

Misgeld, T., Kerschensteiner, M., Bareyre, F. M., Burgess, R. W., & Lichtman, J. W. (2007). Imaging axonal transport of mitochondria in vivo. *Nature Methods*, *4*(7), 559–561.

Misgeld, T., & Schwarz, T. L. (2017). Mitostasis in neurons: Maintaining mitochondria in an extended cellular architecture. *Neuron*, *96*(3), 651–666.

Morris, R. L., & Hollenbeck, P. J. (1993). The regulation of bidirectional mitochondrial transport is coordinated with axonal outgrowth. *Journal of Cell Science*, *104*(Pt 3), 917–927.

Nakano, M., Imamura, H., Nagai, T., & Noji, H. (2011). Ca(2)(+) regulation of mitochondrial ATP synthesis visualized at the single cell level. *ACS Chemical Biology*, *6*(7), 709–715.

O'Donnell, K. C., Vargas, M. E., & Sagasti, A. (2013). WldS and PGC-1alpha regulate mitochondrial transport and oxidation state after axonal injury. *The Journal of Neuroscience*, *33*(37), 14778–14790.

Okumoto, K., Ono, T., Toyama, R., Shimomura, A., Nagata, A., & Fujiki, Y. (2018). New splicing variants of mitochondrial Rho GTPase-1 (Miro1) transport peroxisomes. *The Journal of Cell Biology*, *217*(2), 619–633.

Park, K. K., Liu, K., Hu, Y., Smith, P. D., Wang, C., Cai, B., et al. (2008). Promoting axon regeneration in the adult CNS by modulation of the PTEN/mTOR pathway. *Science*, *322*(5903), 963–966.

Pekkurnaz, G., Trinidad, J. C., Wang, X., Kong, D., & Schwarz, T. L. (2014). Glucose regulates mitochondrial motility via Milton modification by O-GlcNAc transferase. *Cell*, *158*(1), 54–68.

Pilling, A. D., Horiuchi, D., Lively, C. M., & Saxton, W. M. (2006). Kinesin-1 and Dynein are the primary motors for fast transport of mitochondria in Drosophila motor axons. *Molecular Biology of the Cell*, *17*(4), 2057–2068.

Rawson, R. L., Yam, L., Weimer, R. M., Bend, E. G., Hartwieg, E., Horvitz, H. R., et al. (2014). Axons degenerate in the absence of mitochondria in *C. elegans*. *Current Biology*, *24*(7), 760–765.

Russo, G. J., Louie, K., Wellington, A., Macleod, G. T., Hu, F., Panchumarthi, S., et al. (2009). Drosophila Miro is required for both anterograde and retrograde axonal mitochondrial transport. *The Journal of Neuroscience*, *29*(17), 5443–5455.

Ruthel, G., & Hollenbeck, P. J. (2003). Response of mitochondrial traffic to axon determination and differential branch growth. *The Journal of Neuroscience*, *23*(24), 8618–8624.

Sheng, Z. H. (2014). Mitochondrial trafficking and anchoring in neurons: New insight and implications. *The Journal of Cell Biology*, *204*(7), 1087–1098.

Sheng, Z. H. (2017). The interplay of axonal energy homeostasis and mitochondrial trafficking and anchoring. *Trends in Cell Biology*, *27*(6), 403–416.

Sheng, Z. H., & Cai, Q. (2012). Mitochondrial transport in neurons: Impact on synaptic homeostasis and neurodegeneration. *Nature Reviews. Neuroscience*, *13*(2), 77–93.

Shlevkov, E., Basu, H., Bray, M. A., Sun, Z., Wei, W., Apaydin, K., et al. (2019). A high-content screen identifies TPP1 and Aurora B as regulators of axonal mitochondrial transport. *Cell Reports*, *28*(12), 3224–3237.e3225.

Simmons, E. C., Scholpa, N. E., & Schnellmann, R. G. (2020). Mitochondrial biogenesis as a therapeutic target for traumatic and neurodegenerative CNS diseases. *Experimental Neurology*, *329*, 113309.

Smit-Rigter, L., Rajendran, R., Silva, C. A., Spierenburg, L., Groeneweg, F., Ruimschotel, E. M., et al. (2016). Mitochondrial dynamics in visual cortex are limited in vivo and not affected by axonal structural plasticity. *Current Biology*, *26*(19), 2609–2616.

Sun, T., Qiao, H., Pan, P. Y., Chen, Y., & Sheng, Z. H. (2013). Motile axonal mitochondria contribute to the variability of presynaptic strength. *Cell Reports*, *4*(3), 413–419.

Takihara, Y., Inatani, M., Eto, K., Inoue, T., Kreymerman, A., Miyake, S., et al. (2015). In vivo imaging of axonal transport of mitochondria in the diseased and aged mammalian CNS. *Proceedings of the National Academy of Sciences of the United States of America*, *112*(33), 10515–10520.

Tanaka, Y., Kanai, Y., Okada, Y., Nonaka, S., Takeda, S., Harada, A., et al. (1998). Targeted disruption of mouse conventional kinesin heavy chain, kif5B, results in abnormal perinuclear clustering of mitochondria. *Cell*, *93*(7), 1147–1158.

Tantama, M., Martinez-Francois, J. R., Mongeon, R., & Yellen, G. (2013). Imaging energy status in live cells with a fluorescent biosensor of the intracellular ATP-to-ADP ratio. *Nature Communications*, *4*, 2550.

Tarnopolsky, M. A., & Beal, M. F. (2001). Potential for creatine and other therapies targeting cellular energy dysfunction in neurological disorders. *Annals of Neurology*, *49*(5), 561–574.

Vagnoni, A., & Bullock, S. L. (2018). A cAMP/PKA/Kinesin-1 axis promotes the axonal transport of mitochondria in aging drosophila neurons. *Current Biology*, *28*(8), 1265–1272.e1264.

van Bergeijk, P., Adrian, M., Hoogenraad, C. C., & Kapitein, L. C. (2015). Optogenetic control of organelle transport and positioning. *Nature*, *518*(7537), 111–114.

van Spronsen, M., Mikhaylova, M., Lipka, J., Schlager, M. A., van den Heuvel, D. J., Kuijpers, M., et al. (2013). TRAK/Milton motor-adaptor proteins steer mitochondrial trafficking to axons and dendrites. *Neuron*, *77*(3), 485–502.

Wyss, M., & Kaddurah-Daouk, R. (2000). Creatine and creatinine metabolism. *Physiological Reviews*, *80*(3), 1107–1213.

Xu, Y., Chen, M., Hu, B., Huang, R., & Hu, B. (2017). In vivo imaging of mitochondrial transport in single-axon regeneration of zebrafish mauthner cells. *Frontiers in Cellular Neuroscience*, *11*, 4.

Yang, J. L., Mukda, S., & Chen, S. D. (2018). Diverse roles of mitochondria in ischemic stroke. *Redox Biology*, *16*, 263–275.

Zhou, B., Yu, P., Lin, M. Y., Sun, T., Chen, Y., & Sheng, Z. H. (2016). Facilitation of axon regeneration by enhancing mitochondrial transport and rescuing energy deficits. *The Journal of Cell Biology*, *214*(1), 103–119.

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Chapter 18

Neurotrophins and their role in axonal outgrowth following spinal cord injury

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List of abbreviations

BDNF	brain-derived neurotrophic factor
BSCB	blood-spinal-cord barrier
CST	corticospinal tract
CNS	central nervous system
GC	growth cone
k_d	receptor-neurotrophin dissociation constant
NGF	nerve growth factor
NT-3	neurotrophin-3
NT-4/5	neurotrophin-4/5
SCI	spinal cord injury
Trk	tropomyosin-regulated kinase

Introduction

Throughout neuronal development, neurotrophic expression is essential for the survival of growing axonal projections. Following the discovery of the prototypic neurotrophic factor, nerve growth factor (NGF) (Levi-Montalcini & Hamburger, 1951), researchers have identified a family of structurally related molecules termed "neurotrophins" including NGF, brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and neurotrophin-4/5 (NT-4/5). A repertoire of experimental studies have since established these biomolecules as key modulators of neuronal differentiation (Berkemeier et al., 1991), growth (Boyd & Gordon, 2003) plasticity (Brock et al., 2010), and axonal guidance (Gundersen & Barrett, 1979). However, contrary to embryonic development, neurotrophin production is drastically reduced within the adult spinal cord (Widenfalk, Lundströmer, Jubran, Brené, & Olson, 2001). Amongst other factors, this deficiency in trophic support contributes to the absence of spontaneous axonal regeneration following traumatic spinal cord injury (SCI) (Fawcett, 2020). However, despite limited endogenous production, adult neurons still express neurotrophin receptors and retain their capacity to respond. Hence, exogenous stimulation has been explored as a potential avenue to promote regeneration after an SCI (Widenfalk et al., 2001). As receptor expression differs across ascending and descending spinal populations, each neurotrophin has been shown to vary in effect on distinct spinal tracts (Keefe, Sheikh, & Smith, 2017).

The initial traumatic insult associated with SCI, precedes a secondary injury cascade, cystic cavitation, and the formation of a growth-inhibitory lesion known as a "glial scar" (Fitch & Silver, 2008). Supporting spared axons to bridge this injury zone and innervate existing neuronal targets is a challenge to restoring function after injury (McCall, Weidner, & Blesch, 2012). Although propriospinal relay connections have been attributed to some spontaneous functional recovery (Courtine et al., 2008), re-establishment of original synaptic connections requires spared axons to grow beyond the injury site and re-enter the host spinal cord towards denervated targets (McCall et al., 2012). In anatomically incomplete injuries, this path can either be through or around the lesion. Although localized neurotrophin administration has been

Cellular, Molecular, Physiological, and Behavioral Aspects of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822427-4.00018-6

shown to support the extension of injured axons through the lesion, it is now understood that delivery in the form of a spatiotemporal concentration gradient is a key strategy for promoting axons to exit the lesion zone and grow towards pre-injury targets (Lu, Yang, Jones, Filbin, & Tuszynski, 2004).

This chapter discusses the role of neurotrophins in stimulating axonal outgrowth following SCI, with a focus on the application of neurotrophin concentration gradients. We detail the structure and function of the neurotrophins with respect to the spinal cord, followed by an explanation of growth cone navigation in response to neurotrophin gradients. Finally, we outline current progress and future considerations towards clinically appropriate neurotrophin delivery in *in vivo* settings.

Structure and function of the neurotrophins

The neurotrophins are an endogenously produced group of polypeptides and the most investigated growth factors in SCI studies. This family consists of NGF, BDNF, NT-3, and NT-4/5, all sharing near 50% homology in their primary structure (Hauburger, Kliemannel, Madsen, Rudolph, & Schwarz, 2007). The neurotrophins are synthesized on the rough endoplasmic reticulum as a "pre-pro-neurotrophin" precursor form (Al-Qudah & Al-Dwairi, 2016). Subsequent translocation to the Golgi apparatus and cleavage of the "pre-region" produces the ~30 kDa pro-neurotrophin precursor which is known to exert apoptotic effects (Chao & Bothwell, 2002; Kowiański et al., 2018). Further proteolytic cleavage of the pro-neurotrophin occurs intracellularly and extracellularly by plasmin and furin molecules to generate the final mature neurotrophin – a 13 kDa non-covalently linked homodimer molecule (Bibel & Barde, 2000) which is responsible for neurotrophic activity.

Neurotrophin function is mediated by the transmembrane tropomyosin-regulated kinase (Trk) and p75 neurotrophin receptors ($p75^{NTR}$). The low-affinity $p75^{NTR}$, a member of the tumor necrosis superfamily group, non-selectively binds to all the neurotrophins in the mature and uncleaved pro-neurotrophin form (Meeker & Williams, 2015). On the other hand, each isoform of the Trk family, consisting of TrkA, TrkB, and TrkC, exhibits selective, high-affinity binding for a specified mature neurotrophin (Fig. 1). Namely, NGF binds TrkA; BDNF and NT-4/5 both bind TrkB; while NT-3 binds primarily to TrkC, and a lesser degree with TrkA and TrkB (Chao & Bothwell, 2002). Neurotrophin binding results in autophosphorylation of intracellular tyrosine residues of the Trk receptor. This, in turn, initiates key downstream signaling cascades such as the phosphatidylinositol 3-kinase/protein kinase B (PI3K-Akt), mitogen-activated protein kinase (MAPK), extracellular signal-regulated kinases (ERK), and phospholipase C-γ (PLCγ) pathways (Meeker & Williams, 2015) which are responsible for neurite outgrowth, cell survival, cell differentiation, and synaptic plasticity. In contrast, $p75^{NTR}$ receptor binding results in cellular apoptosis through Jun N-terminal kinase (JNK) and p53 activation (Dechant & Barde, 2002).

Receptor distribution of the Trk isoforms varies between the different neuronal subpopulations within the spinal cord. Hence, each neurotrophin differs in the extent to which it affects distinct spinal tracts (Dravid, Parittotokkaporn, Aqrawe, O'Carroll, & Svirskis, 2020; Keefe et al., 2017), as illustrated in Fig. 2. Knowledge about Trk receptor expression in the injured spinal cord is still developing. Liebl et al. have previously investigated Trk expression in a contusion rat model, observing reduced levels within the first week of trauma at and near the injury site, but not within the proximal and distal spinal cord (Liebl, Huang, Young, & Parada, 2001). Similarly, King et al. have also reported a reduction of receptor expression at the lesion site of a hemisection rat model, while expression in the undamaged regions of the cord remained

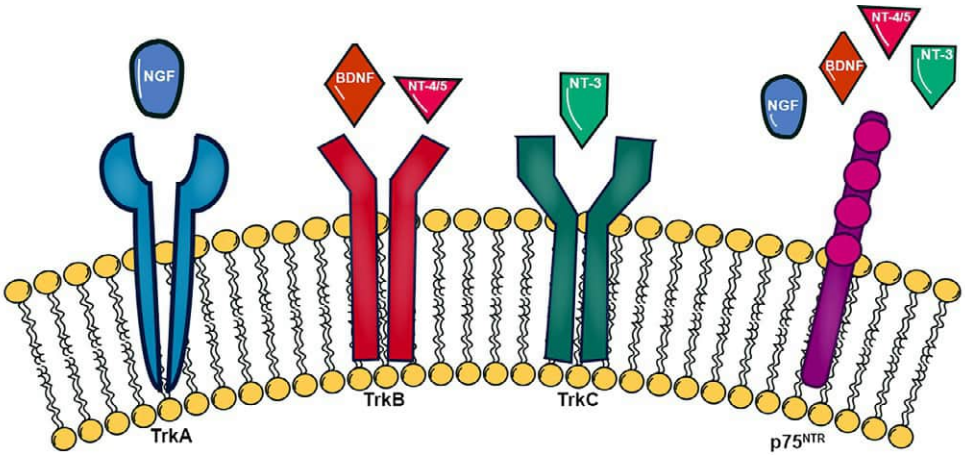

FIG. 1 Schematic illustration of neurotrophin-Trk receptor preferential binding interactions. Each neurotrophin binds with high affinity to a specific Trk receptor isoform. The $p75^{NTR}$ binds all neurotrophins with low affinity. NGF, nerve growth factor; BDNF, brain-derived neurotrophic factor; NT-3, neurotrophin-3; NT-4/5, neurotrophin-4/5.

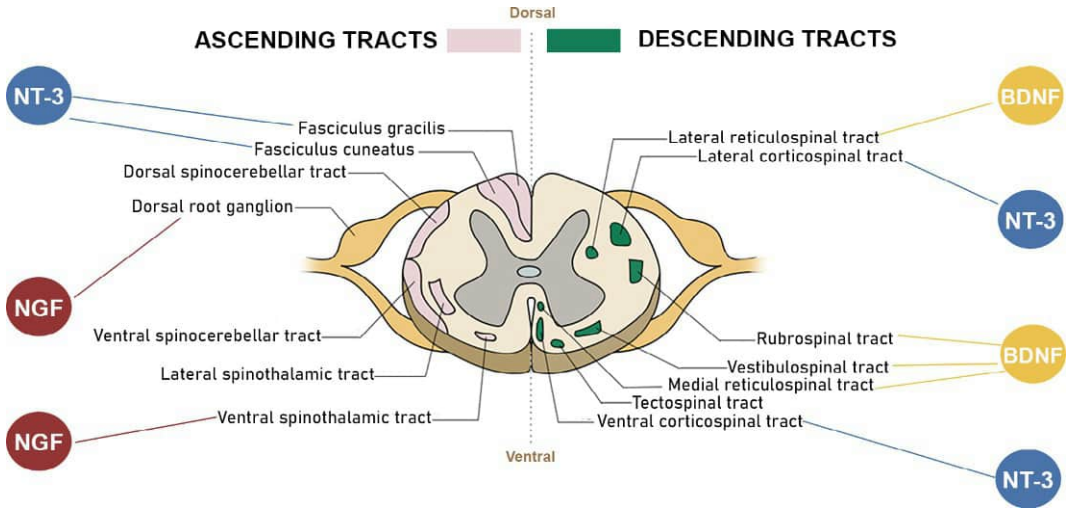

FIG. 2 Spinal cord segment highlighting neurotrophin sensitivities. NGF, nerve growth factor; BDNF, brain-derived neurotrophic factor; NT-3, neurotrophin-3; NT-4/5, neurotrophin-4/5. *(Adapted with permission from Dravid, A., Parittotokkaporn, S., Aqrawe, Z., O'Carroll, S. J., & Svirskis, D. (2020). Determining neurotrophin gradients in vitro to direct axonal outgrowth following spinal cord injury*. ACS Chemical Neuroscience, 11*(2), 121–132. doi:10.1021/acschemneuro.9b00565. Copyright (2020) American Chemical Society.)*

normal (King, Bradbury, McMahon, & Priestley, 2000). These observations support the application of a neurotrophin gradient, with the highest concentrations delivered near uninjured regions of the cord where Trk receptors are expressed after injury, as a strategy to encourage growth towards pre-injury targets.

Nerve growth factor

The findings of a soluble, diffusible factor enhancing the outgrowth of adjacent sympathetic and sensory neuronal populations led to the discovery and isolation of NGF, a pivotal moment in modern neurobiology (Levi-Montalcini & Hamburger, 1951). As the oldest member of the neurotrophin family, numerous studies have aimed to harness its neurotrophic effects for therapeutic outcomes. NGF is a robust promoter of sensory neuron survival and growth following injury (Oudega & Hagg, 1996, 1999; Tuszynski et al., 1994), with the TrkA receptor expressed widely across the ventral and lateral spinothalamic neuron population groups. Additionally, growth of small diameter $CGRP^+$ sensory and TH^+ cerulospinal neurons after an injury has been observed in response to NGF (Grill, Blesch, & Tuszynski, 1997).

Brain-derived neurotrophic factor

The discovery of NGF initiated a pursuit for other nerve growth factors, achieving success decades later in 1982 with the identification of BDNF. Demonstrating an ability to evoke neuroprotective and growth responses in a diversity of cell populations, including those unaffected by NGF, the neurotrophin BDNF has become one of the most investigated growth factor therapies in SCI models (Weishaupt, Blesch, & Fouad, 2012). The BDNF receptor, TrkB, is widely distributed in spinal populations involved in producing motor function (Kishino, Ishige, Tatsuno, Nakayama, & Noguchi, 1997). Specifically, the $5\text{-}HT^+$ raphaespinal, reticulospinal, rubrospinal, vestibulospinal, and TH^+ cerulospinal have all exhibited axonal growth in response to BDNF stimulation (Hollis 2nd & Tuszynski, 2011; Koda et al., 2004; Lu, Jones, & Tuszynski, 2005).

Neurotrophin-3

NT-3 has also been widely investigated in experimental SCI, as the only factor to demonstrate significant growth-promoting effects in the corticospinal tract (CST) (Blits, Dijkhuizen, Boer, & Verhaagen, 2000) (Tuszynski et al., 2003). Unlike the other neurotrophins, NT-3 has a more versatile binding capacity, demonstrating low-affinity binding to the TrkA and TrkB isoforms alongside its preferential binding with TrkC. NT-3 has also been shown to promote regeneration of dorsal column proprioceptive sensory axons and the $5\text{-}HT^+$ raphaespinal neuron populations (Taylor, Jones, Tuszynski, & Blesch, 2006).

Neurotrophin-4/5

As with BDNF, the neurotrophin NT-4/5 also signals through the TrkB receptor, affecting the same spinal populations based on receptor expression. Despite binding to the same receptor, some studies have alluded to the possibility of axonal growth differing in response to BDNF and NT-4/5 due to the presence of TrkB splice variants or variations in downstream signaling cascades (Blesch, Yang, Weidner, Hoang, & Otero, 2004). Thorough investigations of this factor in experimental SCI models are still wanting, with current studies suggesting roles in promoting sensory and motor neuron outgrowth (Kobayashi et al., 1997) (Schmalbruch & Rosenthal, 1995) (Stucky, Shin, & Lewin, 2002).

Neurotrophic gradients for guiding regenerating axons

In 1892 neuroscientist Ramón y Cajal proposed his "neurotropic hypothesis", detailing the ability of the growth cone (GC) to be guided by diffusible chemotactic gradients secreted by target cells. A body of *in vitro* gradient-based assays have validated this theory, demonstrating how axons alter their trajectory when presented with a chemotactic stimulus. The GC is a dynamic sensory feature located at the terminal end of elongating axons. We now know these actin-rich structures to be responsible for (i) detecting spatial gradients of chemical stimuli in the extracellular environment and (ii) navigating axonal trajectory towards the direction of the chemoattractive stimulus.

Amongst well-established roles in axonal outgrowth and survival, the neurotrophins have been shown to act as axonal guidance cues for developing and regenerating neurons. Early investigations with chick dorsal root ganglion (DRG) first elicited the chemotactic effects of NGF in vitro, with the axons reorienting their growth towards the direction of the NGF source (Gundersen & Barrett, 1979). Similarly, BDNF and NT-3 demonstrated the ability to influence GC-mediated turning of *Xenopus* spinal neurons (Ming, Lohof, & Zheng, 1997). Following Trk receptor activation at the GC, the downstream signaling cascades involved in survival and outgrowth have also been thought to contribute to axonal guidance. In fact, Ming et al. have previously ascribed the effect of NGF on *Xenopus* spinal neuron turning to the co-activation of the PI3K-Akt and PLCγ signaling pathways at the GC (Ming et al., 1999).

Delivery of the neurotrophins in the form of a concentration gradient (Fig. 3) has increasingly presented itself as an attractive approach to encourage axonal bridging of the injury lesion (McCall et al., 2012). For severed axons to regenerate

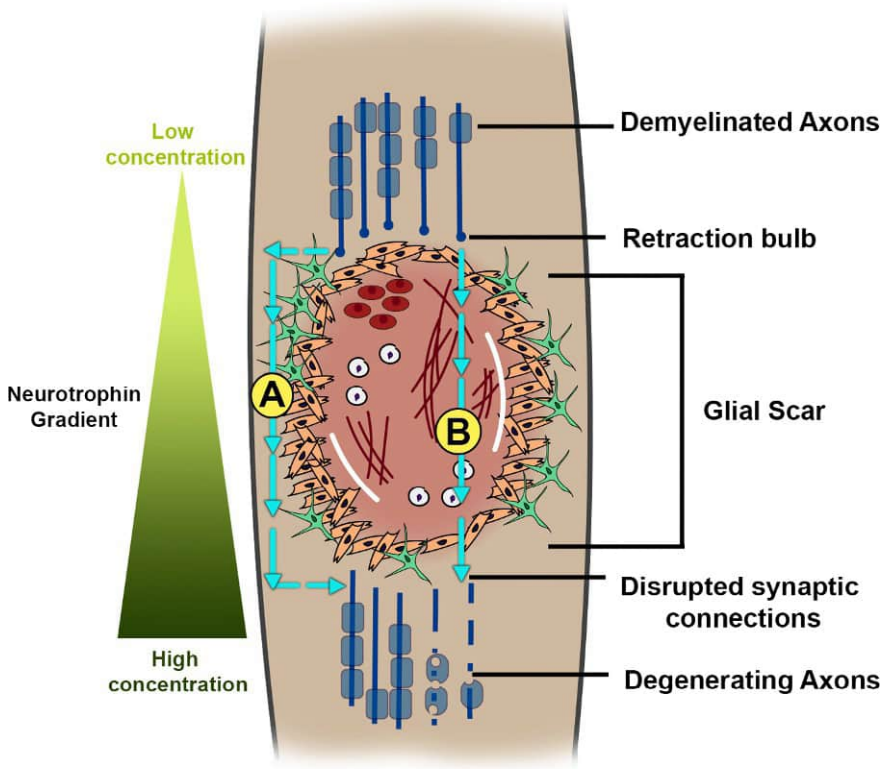

FIG. 3 Schematic illustration depicting the effect of a neurotrophin gradient on axonal guidance of descending projections through glial scar. A neurotrophic gradient may facilitate the growth of severed axons either (A) around or (B) through the lesion towards denervated targets.

TABLE 1 Receptor-neurotrophin dissociation constants for the three key neurotrophins investigated in experimental SCI studies.

Receptor-neurotrophin	k_d	References
TrkA + NGF	2.3×10^{-11} M	Rodríguez-Tébar, Dechant, Götz, and Barde (1992), Sutter, Riopelle, Harris-Warrick, and Shooter (1979)
TrkB + BDNF	1.7×10^{-11} M	Rodriguez-Tébar, Dechant, and Barde (1990), Sakuragi, Tominaga-Yoshino, and Ogura (2013)
TrkC + NT-3	1.8×10^{-11} M	Rodríguez-Tébar et al. (1992)

NGF, nerve growth factor; *BDNF*, brain-derived neurotrophic factor; *NT-3*, neurotrophin-3; *NT-4/5*, neurotrophin-4/5.
Adapted with permission from Dravid, A., Parittotokkaporn, S., Aqrawe, Z., O'Carroll, S. J., & Svirskis, D. (2020). Determining neurotrophin gradients in vitro to direct axonal outgrowth following spinal cord injury. *ACS Chemical Neuroscience, 11*(2), 121–132. https://doi.org/10.1021/acschemneuro.9b00565. Copyright (2020) American Chemical Society.

and re-connect with denervated pre-injury targets, the neurotrophins must be delivered in a dynamic pattern. Initially, this would require a sufficient concentration delivered within the lesion, to promote growth within this inhibitory region (Jones, Oudega, Bunge, & Tuszynski, 2001). Following this, the neurotrophins should then be applied in the form of a concentration gradient, with the highest concentrations expressed beyond the injury site (Jones et al., 2001). This gradient may be able to guide the growing axons over a length of several millimeters (Giger, Hollis 2nd, & Tuszynski, 2010).

For a GC to respond to a concentration gradient, it must be able to detect a significant location-dependent concentration difference of the ligand across its width. The width of a GC has commonly been assumed as 10 μm–20 μm in existing gradient-based axonal guidance assays. Further, the absolute concentration (i.e., the amount of neurotrophin per unit of volume) must be within a suitable range with respect to the receptor–neurotrophin dissociation constant (k_d) (Table 1). A concentration higher than the k_d may lead to receptor saturation across both sides of the GC, impeding its directional sensing (Goodhill & Baier, 1998). However, a concentration too low may not overcome noise created by thermal fluctuations in ligand number, nor will a sufficient number of receptors be activated to initiate downstream signaling pathways (Goodhill & Baier, 1998). Within the current literature, two models have been reported to describe the mechanism of GC detection (Goodhill, 1998; Goodhill & Baier, 1998). The first model proposes that the GC responds to the absolute change across its width (ΔC), while the second model suggests that the fractional or relative change ($\Delta C/C$) is detected by the GC. In the latter model, "C" refers to the concentration at the GC midpoint. The fractional change can also be represented as a percentage, known as the steepness. While *in vivo* quantification of such gradient parameters are complicated, *in vitro* studies have focused on determining optimal gradient steepness values to promote axonal turning over biased outgrowth.

Preclinical models of neurotrophin delivery to promote axonal outgrowth and regeneration following SCI

The effect of various neurotrophin delivery approaches (Fig. 4) has been widely investigated using in vivo SCI models. To date, few studies have aimed to achieve a gradient release profile for guiding axonal outgrowth beyond the lesion. Delivery of trophic support to the lesion site has been explored in animal models using direct protein injections, osmotic mini-pumps, viral-vector mediated gene therapy, and biomaterial-based approaches. Selected studies and key outcomes using these approaches have been summarised in Table 2.

Acute localized injections and continuous infusions

Traditional approaches of neurotrophin delivery involved acute localized injections or continuous osmotic pump infusions to administer the neurotrophins as recombinant proteins and bypass the blood–spinal cord barrier (BSCB). These injections have previously been administered via intravenous, intrathecal, and intraparenchymal routes. Schnell et al. investigated the effects of NGF, BDNF, and NT-3 injected locally on the CST (Schnell et al., 1994) observing sprouting of the projections in response to NT-3, but not BDNF. Similarly, Bradbury et al. used a mini-osmotic pump to deliver BDNF and NT-3, noting a growth response of the lesioned dorsal column axons only to NT-3 (Bradbury et al., 1999). The invasive nature of this

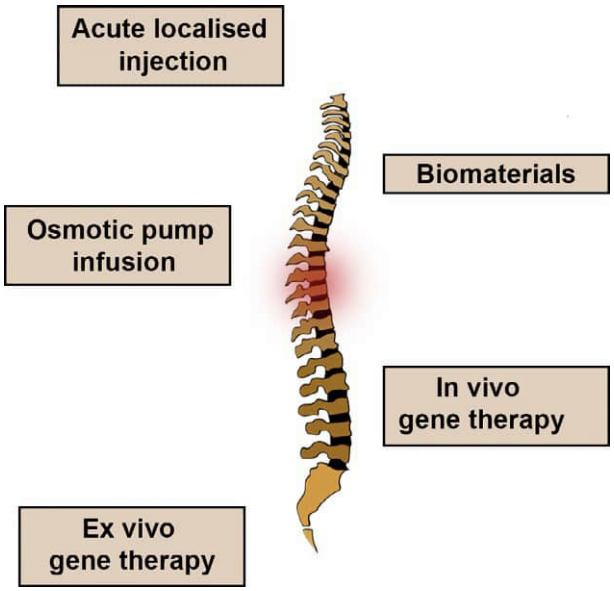

FIG. 4 Current approaches for neurotrophin delivery to the injured spinal cord. Each approach has been investigated in animal models for delivering the neurotrophins to the spinal cord.

TABLE 2 Overview of selected studies investigating neurotrophin delivery in preclinical models.

Neurotrophin	Delivery mode	Animal	Injury	Key results	Reference
NGF BDNF NT-3	Direct protein injection	Rat (P2) Lewis	Bilateral transection of the dorsal halves of the lower thoracic spinal cord	BDNF had no effect; NT-3 increased regenerative sprouting of transected CST axons although the distance of growth was limited; NT-3 combined with antibody against myelin-associated inhibitory protein improved elongation distance	Schnell, Schneider, Kolbeck, Barde, and Schwab (1994)
BDNF NT-3	Mini-osmotic pump	Rat (Adult) Wistar	T6 dorsal column crush	BDNF had no growth-promoting effects on dorsal column axons;NT-3 significantly promoted growth of dorsal column axons after injury with fibers extending into and beyond the epicenter of the injury	Bradbury et al. (1999)
NGF	Mini-osmotic pump	Rat (Adult) Sprague Dawley	T10 contusion injury	NGF delivered directly at injury site. Zone of injury reduced in response to NGF, however, this was not statistically significant	Lee, Green, Dietrich, and Yezierski (1999)
NGF	Ex-vivo gene therapy (Fibroblasts)	Rat (Adult) Fischer 344	T7 dorsal hemi section lesion	By 2 weeks, significant penetration of CGRP+ sensory neurites was observed in response to NGF secretion; only 46.2% of ChAT+ motor neurons penetrated the NGF-secreting graft	Tuszynski et al. (1996)

TABLE 2 Overview of selected studies investigating neurotrophin delivery in preclinical models—cont'd

Neurotrophin	Delivery mode	Animal	Injury	Key results	Reference
BDNF	Ex-vivo gene therapy (bone marrow stromal cells)	Rat (Adult) Fischer 344	Dorsal column bilateral transection	Axonal penetration into BDNF grafts was 2.8 greater than the control at 3 months post-surgery, however, was not greater than the growth observed in BDNF grafts at 1 month; axons in the graft were TH+ coerulospinal, 5-HT+ raphaespinal, CGRP+ sensory and ChAT motor; despite axonal growth into the grafts, no functional recovery was observed	Lu et al. (2005)
BDNF	In vivo gene therapy (AAV vector)	Rat (Adult) Wistar	T8 complete transection	Partial regrowth of transected descending rubrospinal axons and some functional recovery observed in response to BDNF; Highest Basso, Beattie, and Bresnahan (BBB) score in BDNF treated groups was 7, compared to 1 in control	Koda et al. (2004)
NT-3	In vivo gene therapy (LV vector)	Rat (Adult) Fischer 344	C1 dorsal partial laminectomy	LV vector used in combination with mesenchymal stem cell grafts; LV-NT-3 injected into the nucleus gracilis promoted regeneration and synaptic formation	Alto et al. (2009)
NT-3	Biomaterial (Collagen)	Rat (Adult) Wistar	T9 dorsal laminectomy	NT-3 containing collagen fibers promoted the directional growth of CST fibers ($22 \pm 6\%$) compared to the control ($7 \pm 2\%$). No fibers seen caudal to the lesion. NT-3 treated animals exhibited functional recovery in the gridwalk test, although this was not due to the regeneration of CST axons	Houweling, Lankhorst, Gispen, Bär, and Joosten (1998)
BDNF	Biomaterial (Agarose)	Rat (Adult) Fischer 344	C4 dorsal column aspiration lesion	Hydrogel scaffolds support the linear growth of injured axons, compared to disorganized growth observed in non-scaffold controls; BDNF increases the density of axonal penetration; fibrin-filled scaffolds with BDNF-MSCs had a greater density (1.5 ×) of axons compared to Matrigel	Stokols et al. (2006)

The method of neurotrophin delivery, animal and injury model used and key outcomes have been summarised in the columns. *NGF*, nerve growth factor; *BDNF*, brain-derived neurotrophic factor; *NT-3*, neurotrophin-3; *NT-4/5*, neurotrophin-4/5; *CST*, corticospinal tract.

delivery approach in conjunction with limited protein stability and the need for repetitive injections has limited its progression as a potential intervention. Hence, the development of other delivery strategies has now superseded direct protein injections and infusions.

Ex-vivo gene therapy

Using this approach, cells are first genetically modified in vitro to express a neurotrophin and subsequently transplanted within the injury lesion site. Fibroblasts, Schwann cells, bone marrow stromal cells, and neural stem cells have previously been genetically modified to express neurotrophins in SCI models. Grill et al. reported an increase in corticospinal growth in response to NT-3 secreting fibroblasts (Grill, Murai, Blesch, Gage, & Tuszynski, 1997). Neurite outgrowth of sensory and noradrenergic populations has been observed in response to NGF-secreting fibroblasts grafted into a hemisection lesion (Tuszynski et al., 1996). Schwann cell grafts secreting BDNF improved the regenerative response of reticulospinal and

raphaespinal neurons (Menei, Montero-Menei, Whittemore, Bunge, & Bunge, 1998). While this approach can provide a supportive environment for axonal extension into the graft, axons seldom exit the lesion and long-distance regeneration is unlikely to be observed.

In vivo gene therapy

The *in vivo* gene therapy approach involves the use of viral vectors to directly transduce host cell populations in vivo in the region of interest to express a specific gene. The adenovirus (AV), lentivirus (LV), adeno-associated virus (AAV), and herpes simplex virus (HSV) are commonly used to express neurotrophins in SCI models. Zhang et al. observed that by administering AV containing NT-3 cDNA into the ventral horn of the spinal cord, the transgenes could be strongly expressed in glial cells with dorsal root axonal regeneration observed (Zhang, Dijkhuizen, Anderson, Lieberman, & Verhaagen, 1998). Koda et al. used AAV gene transfer of BDNF in a rat transection model, observing a regenerative response in descending rubrospinal axons and recovery of hindlimb function (Koda et al., 2004). Chemotropic guidance of regenerating axons was investigated using LV expressing NT-3 in C1 lesioned rats (Alto et al., 2009). Notably, re-innervation of brainstem targets was reported in response to NT-3 delivery.

Biomaterial-based approaches

Biomaterials are materials engineered to interface with biological tissue. They are attractive candidates for neurotrophin delivery due to their biocompatibility and tuneable properties which permit the fabrication of sustained drug delivery systems. However, ensuring the stability of the neurotrophin within a polymeric drug delivery system during fabrication and application is important for maintaining bioactivity. NT-3 released from fibrin scaffolds 2 weeks following injury was shown to enhance neural fiber sprouting (Johnson, Parker, & Sakiyama-Elbert, 2009). Similarly, Nguyen et al. sustained NT-3 release from collagen scaffolds integrated with poly (ε-caprolactone-*co*-ethyl ethylene phosphate) (PCLEEP) nanofibers (Nguyen et al., 2017), observing regeneration 1 week after injury.

Challenges and considerations for neurotrophin delivery and clinical translation

Development of a clinically translatable neurotrophin delivery system has been a problematic pursuit, demonstrating limited efficacy in human clinical trials. Current preclinical investigations have been conducted using rodent and mice animal models, which possess several anatomical and functional discrepancies compared to nonhuman primates and other large animals (Nardone et al., 2017). Hence, optimal safe and effective dosages determined on cellular and animal models may not accurately translate to humans. Although no animal model can completely recapitulate what is expected in humans, further investigations of motor and sensory outcomes in primates would hold a great benefit in determining the safety and efficacy of the neurotrophins and delivery systems in vivo for subsequent human translation (Hollis 2nd & Tuszynski, 2011).

As the cellular response to an SCI occurs over extended time periods (i.e., months) an ideal platform would enable localized and sustained delivery of therapeutic concentrations to produce the desired biological effects. Overcoming the challenges associated with delivering these factors into the CNS is still a work in progress. The neurotrophins are large molecules, cationic in nature, and poor permeability across the BSCB (Weissmiller & Wu, 2012). This issue is further complicated by a short biological half-life, poor pharmacokinetic properties, enzymatic degradation, and off-target effects. NGF is known to regulate nociceptive pathways, with acute pain and hyperalgesia reported as a common and significant adverse effect in clinical trials and rodent models (Eriksdotter Jönhagen et al., 1998). Similarly, systemic administration of BDNF has been linked to chronic pain (Boudes & Menigoz, 2009) and weight gain (Lin et al., 2008). Systemic routes typically require high doses to be administered to attain therapeutic levels at the target region. Additionally, suboptimal neurotrophin dose and release kinetics can lead to aberrant axonal growth (Madduri & Gander, 2012). Hence, a focus on localized and smart drug delivery systems may be one approach to mitigate such off-target effects and improve permeability across the BSCB. Any delivery system designed to release neurotrophins over an extended time period would be required to maintain the stability of the bioactive payload. As previously mentioned, the spatial availability of these growth factors in the form of a gradient is central to directing axonal growth towards pre-injury targets. In addition, the size and position of the gradient must be flexible to change over time (i.e. temporal availability). The requirement of such precise release patterns necessitates the development of smart drug delivery platforms.

Finally, the pathophysiological progression of an SCI involves several distinct stages (i.e. acute, sub-acute, and chronic) each with distinct features that can affect the efficacy of therapeutic interventions. Administration within the acute stage

may have benefits for minimizing axonal retraction, neuronal atrophy, and supporting neuronal survival (Awad, Carmody, & Steinmetz, 2015). However, this may not be the most pragmatic approach in a clinical setting, where there is a time delay between the occurrence of the initial injury, stabilization, and treatment initiation (Lee, Ryu, & Vig, 2019). As such, there would be significant value in investigating the efficacy of these factors delivered at the chronic stage of injury.

Concluding remarks

Exogenous application of the neurotrophins demonstrates promise in promoting axonal regeneration, outgrowth, and survival within the growth-inhibitory injured CNS environment. While the complexity of an SCI will undoubtedly require a combinatorial therapeutic approach to target the various facets of injury, the provision of trophic support could help encourage neuronal survival and re-innervation of natural post-synaptic targets when delivered as a concentration gradient. Additionally, knowledge of receptor expression and distribution on impacted cellular populations can inform which neurotrophins should be applied for delivery. Improvements are still needed in the delivery of these growth factors and further studies conducted using nonhuman primate animal models may be more informative about the human response, increasing the chances of successful translation for human therapy in the future.

Applications to other areas of neuroscience

In this chapter, we have explored the application of neurotrophins on axonal outgrowth in spinal neurons. We describe the structure and function of the neurotrophins and detail their role as chemotactic and regenerative factors for application following spinal cord injury. Further, we outline current progress and challenges associated with neurotrophin delivery to the spinal cord.

As the neurotrophins are essential to neuronal growth and survival, their therapeutic potential is applicable to other neurotraumatic and neurodegenerative conditions where the neuronal function is perturbed (Nagahara & Tuszynski, 2011). Such conditions include Stroke (Ploughman et al., 2009), Traumatic Brain Injury (Marshall et al., 2017), cochlear neuron survival in deafness (Ramekers, Versnel, Grolman, & Klis, 2012), Alzheimer's Disease (Mitra, Behbahani, & Eriksdotter, 2019), Amyotrophic Lateral Sclerosis (Henriques, Pitzer, & Schneider, 2010), Parkinson's Disease (Siegel & Chauhan, 2000), Huntington's disease (Alberch, Pérez-Navarro, & Canals, 2004) and Peripheral Neuropathy (Apfel et al., 1998). As with SCI, one of the factors affecting the progression of neurotrophin-based therapies for these other conditions has been the challenges associated with drug delivery to the CNS. Doses and delivery durations may also vary between SCI and neurodegenerative diseases, with the latter potentially requiring more prolonged periods of neurotrophin delivery based on disease pathology. An understanding of neurotrophin structure, function, and challenges for therapeutic translation can help inform the development of novel drug delivery systems to treat various neuronal diseases.

Mini-dictionary of terms

Absolute change ($\Delta C/x$): Defined as the change in concentration over the average width of a growth cone (typically $x = 10$ μm).

Fractional change ($\Delta C/C$): Defined as the change in concentration (ΔC) over the concentration at the midpoint of the growth cone (C).

Gradient: Occurs when the concentration of a factor is higher in one region compared to another. The gradient is the gradual difference in concentration between the two regions.

Growth Cone: A "fan-shaped" actin structure present at the tip of elongating axons, responsible for navigating axonal growth.

Neurotrophic stimulation: Neurotrophin-induced activation of the Trk receptor and downstream signaling pathways which increase neurite outgrowth and axonal regeneration.

Steepness: The slope of the gradient. It can be described using the absolute change or fractional change model.

Key facts of neurotrophins in spinal cord injury

- Neurotrophins are chemotrophic growth factors that are essential to the regeneration, growth, and survival of neurons after a spinal cord injury.
- Discovery of the first neurotrophin, nerve growth factor, was a pivotal moment in neurobiology—receiving the 1986 Nobel Prize in Physiology or Medicine.

- Each neurotrophin targets a different population of spinal neurons based on Trk receptor expression.
- Ramón y Cajal proposed his "neurotropic hypothesis" in 1892, describing how the axon growth cone can be navigated towards a certain target.
- Neurotrophic gradients delivered to the injured spinal cord could help to regenerate axons grow beyond the site of the lesion and re-connect with host targets.

Summary points

- To re-establish original functional connectivity regenerating axons should extend beyond the injury lesion and re-connect with pre-injury targets.
- The neurotrophins are chemoattractive growth factors with a demonstrated role in axonal outgrowth and survival following spinal cord injury.
- Delivery of the neurotrophins in the form of a concentration gradient could be used to direct axonal outgrowth.
- *In vivo* neurotrophin delivery has been explored using intrathecal injections, osmotic pumps, *ex vivo* gene therapy, and biomaterial-based approaches. However, limited studies have achieved spatiotemporal gradient delivery.
- Sustained, localized delivery of the neurotrophins must be achieved to mitigate off-target adverse effects.

References

Alberch, J., Pérez-Navarro, E., & Canals, J. M. (2004). Neurotrophic factors in Huntington's disease. *Progress in Brain Research*, *146*, 195–229. https://doi.org/10.1016/s0079-6123(03)46014-7.

Al-Qudah, M. A., & Al-Dwairi, A. (2016). Mechanisms and regulation of neurotrophin synthesis and secretion. *Neurosciences (Riyadh, Saudi Arabia)*, *21*(4), 306–313. https://doi.org/10.17712/nsj.2016.4.20160080.

Alto, L. T., Havton, L. A., Conner, J. M., Hollis Ii, E. R., Blesch, A., & Tuszynski, M. H. (2009). Chemotropic guidance facilitates axonal regeneration and synapse formation after spinal cord injury. *Nature Neuroscience*, *12*(9), 1106–1113. https://doi.org/10.1038/nn.2365.

Apfel, S. C., Kessler, J. A., Adornato, B. T., Litchy, W. J., Sanders, C., & Rask, C. A. (1998). Recombinant human nerve growth factor in the treatment of diabetic polyneuropathy. NGF Study Group. *Neurology*, *51*(3), 695–702. https://doi.org/10.1212/wnl.51.3.695.

Awad, B. I., Carmody, M. A., & Steinmetz, M. P. (2015). Potential role of growth factors in the management of spinal cord injury. *World Neurosurgery*, *83*(1), 120–131. https://doi.org/10.1016/j.wneu.2013.01.042.

Berkemeier, L. R., Winslow, J. W., Kaplan, D. R., Nikolics, K., Goeddel, D. V., & Rosenthal, A. (1991). Neurotrophin-5: A novel neurotrophic factor that activates trk and trkB. *Neuron*, *7*(5), 857–866. https://doi.org/10.1016/0896-6273(91)90287-A.

Bibel, M., & Barde, Y. A. (2000). Neurotrophins: Key regulators of cell fate and cell shape in the vertebrate nervous system. *Genes & Development*, *14*(23), 2919–2937. https://doi.org/10.1101/gad.841400.

Blesch, A., Yang, H., Weidner, N., Hoang, A., & Otero, D. (2004). Axonal responses to cellularly delivered NT-4/5 after spinal cord injury. *Molecular and Cellular Neuroscience*, *27*(2), 190–201. https://doi.org/10.1016/j.mcn.2004.06.007.

Blits, B., Dijkhuizen, P. A., Boer, G. J., & Verhaagen, J. (2000). Intercostal nerve implants transduced with an adenoviral vector encoding neurotrophin-3 promote regrowth of injured rat corticospinal tract fibers and improve Hindlimb function. *Experimental Neurology*, *164*(1), 25–37. https://doi.org/10.1006/exnr.2000.7413.

Boudes, M., & Menigoz, A. (2009). Non-neuronal BDNF, a key player in development of central sensitization and neuropathic pain. *The Journal of Physiology*, *587*(Pt 10), 2111–2112. https://doi.org/10.1113/jphysiol.2009.172130.

Boyd, J. G., & Gordon, T. (2003). Neurotrophic factors and their receptors in axonal regeneration and functional recovery after peripheral nerve injury. *Molecular Neurobiology*, *27*(3), 277–324. https://doi.org/10.1385/mn:27:3:277.

Bradbury, E. J., Khemani, S., Von, R., King, Priestley, J. V., & McMahon, S. B. (1999). NT-3 promotes growth of lesioned adult rat sensory axons ascending in the dorsal columns of the spinal cord. *European Journal of Neuroscience*, *11*(11), 3873–3883. https://doi.org/10.1046/j.1460-9568.1999.00809.x.

Brock, J. H., Rosenzweig, E. S., Blesch, A., Moseanko, R., Havton, L. A., Edgerton, V. R., et al. (2010). Local and remote growth factor effects after primate spinal cord injury. *Journal of Neuroscience*, *30*(29), 9728–9737. https://doi.org/10.1523/JNEUROSCI.1924-10.2010.

Chao, M. V., & Bothwell, M. (2002). Neurotrophins: To cleave or not to cleave. *Neuron*, *33*(1), 9–12. https://doi.org/10.1016/S0896-6273(01)00573-6.

Courtine, G., Song, B., Roy, R. R., Zhong, H., Herrmann, J. E., Ao, Y., et al. (2008). Recovery of supraspinal control of stepping via indirect propriospinal relay connections after spinal cord injury. *Nature Medicine*, *14*(1), 69–74. https://doi.org/10.1038/nm1682.

Dechant, G., & Barde, Y.-A. (2002). The neurotrophin receptor p75NTR: Novel functions and implications for diseases of the nervous system. *Nature Neuroscience*, *5*(11), 1131–1136. https://doi.org/10.1038/nn1102-1131.

Dravid, A., Parittotokkaporn, S., Aqrawe, Z., O'Carroll, S. J., & Svirskis, D. (2020). Determining neurotrophin gradients in vitro to direct axonal outgrowth following spinal cord injury. *ACS Chemical Neuroscience*, *11*(2), 121–132. https://doi.org/10.1021/acschemneuro.9b00565.

Eriksdotter Jönhagen, M., Nordberg, A., Amberla, K., Bäckman, L., Ebendal, T., Meyerson, B., et al. (1998). Intracerebroventricular infusion of nerve growth factor in three patients with Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders*, *9*(5), 246–257. https://doi.org/10.1159/000017069.

Fawcett, J. W. (2020). The struggle to make CNS axons regenerate: Why has it been so difficult? *Neurochemical Research*, *45*(1), 144–158. https://doi.org/10.1007/s11064-019-02844-y.

Fitch, M. T., & Silver, J. (2008). CNS injury, glial scars, and inflammation: Inhibitory extracellular matrices and regeneration failure. *Experimental Neurology*, *209*(2), 294–301. https://doi.org/10.1016/j.expneurol.2007.05.014.

Giger, R. J., Hollis, E. R., 2nd, & Tuszynski, M. H. (2010). Guidance molecules in axon regeneration. *Cold Spring Harbor Perspectives in Biology*, *2*(7), a001867. https://doi.org/10.1101/cshperspect.a001867.

Goodhill, G. J. (1998). Mathematical guidance for axons. *Trends in Neurosciences*, *21*(6), 226–231. https://doi.org/10.1016/s0166-2236(97)01203-4.

Goodhill, G. J., & Baier, H. (1998). Axon guidance: Stretching gradients to the limit. *Neural Computation*, *10*(3), 521–527. https://doi.org/10.1162/089976698300017638.

Grill, R. J., Blesch, A., & Tuszynski, M. H. (1997). Robust growth of chronically injured spinal cord axons induced by grafts of genetically modified NGF-secreting cells. *Experimental Neurology*, *148*(2), 444–452. https://doi.org/10.1006/exnr.1997.6704.

Grill, R., Murai, K., Blesch, A., Gage, F. H., & Tuszynski, M. H. (1997). Cellular delivery of neurotrophin-3 promotes corticospinal axonal growth and partial functional recovery after spinal cord injury. *Journal of Neuroscience*, *17*(14), 5560–5572. https://doi.org/10.1523/JNEUROSCI.17-14-05560.1997.

Gundersen, R., & Barrett, J. (1979). Neuronal chemotaxis: Chick dorsal-root axons turn toward high concentrations of nerve growth factor. *Science (New York, N.Y.)*, *206*(4422), 1079–1080. https://doi.org/10.1126/science.493992.

Hauburger, A., Kliemannel, M., Madsen, P., Rudolph, R., & Schwarz, E. (2007). Oxidative folding of nerve growth factor can be mediated by the pro-peptide of neurotrophin-3. *FEBS Letters*, *581*(22), 4159–4164. https://doi.org/10.1016/j.febslet.2007.07.063.

Henriques, A., Pitzer, C., & Schneider, A. (2010). Neurotrophic growth factors for the treatment of amyotrophic lateral sclerosis: Where do we stand? *Frontiers in Neuroscience*, *4*, 32. https://doi.org/10.3389/fnins.2010.00032.

Hollis, E. R., 2nd, & Tuszynski, M. H. (2011). Neurotrophins: Potential therapeutic tools for the treatment of spinal cord injury. *Neurotherapeutics : The Journal of the American Society for Experimental NeuroTherapeutics*, *8*(4), 694–703. https://doi.org/10.1007/s13311-011-0074-9.

Houweling, D. A., Lankhorst, A. J., Gispen, W. H., Bär, P. R., & Joosten, E. A. (1998). Collagen containing neurotrophin-3 (NT-3) attracts regrowing injured corticospinal axons in the adult rat spinal cord and promotes partial functional recovery. *Experimental Neurology*, *153*(1), 49–59. https://doi.org/10.1006/exnr.1998.6867.

Johnson, P. J., Parker, S. R., & Sakiyama-Elbert, S. E. (2009). Controlled release of neurotrophin-3 from fibrin-based tissue engineering scaffolds enhances neural fiber sprouting following subacute spinal cord injury. *Biotechnology and Bioengineering*, *104*(6), 1207–1214. https://doi.org/10.1002/bit.22476.

Jones, L. L., Oudega, M., Bunge, M. B., & Tuszynski, M. H. (2001). Neurotrophic factors, cellular bridges and gene therapy for spinal cord injury. *The Journal of Physiology*, *533*(Pt 1), 83–89. https://doi.org/10.1111/j.1469-7793.2001.0083b.x.

Keefe, K. M., Sheikh, I. S., & Smith, G. M. (2017). Targeting neurotrophins to specific populations of neurons: NGF, BDNF, and NT-3 and their relevance for treatment of spinal cord injury. *International Journal of Molecular Sciences*, *18*(3). https://doi.org/10.3390/ijms18030548.

King, V. R., Bradbury, E. J., McMahon, S. B., & Priestley, J. V. (2000). Changes in truncated trkB and p75 receptor expression in the rat spinal cord following spinal cord hemisection and spinal cord hemisection plus neurotrophin treatment. *Experimental Neurology*, *165*(2), 327–341. https://doi.org/10.1006/exnr.2000.7480.

Kishino, A., Ishige, Y., Tatsuno, T., Nakayama, C., & Noguchi, H. (1997). BDNF prevents and reverses adult rat motor neuron degeneration and induces axonal outgrowth. *Experimental Neurology*, *144*(2), 273–286. https://doi.org/10.1006/exnr.1996.6367.

Kobayashi, N. R., Fan, D. P., Giehl, K. M., Bedard, A. M., Wiegand, S. J., & Tetzlaff, W. (1997). BDNF and NT-4/5 prevent atrophy of rat rubrospinal neurons after cervical axotomy, stimulate GAP-43 and Talpha1-tubulin mRNA expression, and promote axonal regeneration. *Journal of Neuroscience*, *17*(24), 9583–9595. https://doi.org/10.1523/JNEUROSCI.17-24-09583.1997.

Koda, M., Hashimoto, M., Murakami, M., Yoshinaga, K., Ikeda, O., Yamazaki, M., et al. (2004). Adenovirus vector-mediated in vivo gene transfer of brain-derived neurotrophic factor (BDNF) promotes rubrospinal axonal regeneration and functional recovery after complete transection of the adult rat spinal cord. *Journal of Neurotrauma*, *21*(3), 329–337. https://doi.org/10.1089/089771504322972112.

Kowiański, P., Lietzau, G., Czuba, E., Waśkow, M., Steliga, A., & Moryś, J. (2018). BDNF: A key factor with multipotent impact on brain signaling and synaptic plasticity. *Cellular and Molecular Neurobiology*, *38*(3), 579–593. https://doi.org/10.1007/s10571-017-0510-4.

Lee, T. T., Green, B. A., Dietrich, W. D., & Yezierski, R. P. (1999). Neuroprotective effects of basic fibroblast growth factor following spinal cord contusion injury in the rat. *Journal of Neurotrauma*, *16*(5), 347–356. https://doi.org/10.1089/neu.1999.16.347.

Lee, H. J., Ryu, J. S., & Vig, P. J. (2019). Current strategies for therapeutic drug delivery after traumatic CNS injury. *Therapeutic Delivery*, *10*(4), 251–263. https://doi.org/10.4155/tde-2019-0006.

Levi-Montalcini, R., & Hamburger, V. (1951). Selective growth stimulating effects of mouse sarcoma on the sensory and sympathetic nervous system of the chick embryo. *Journal of Experimental Zoology*, *116*(2), 321–361. https://doi.org/10.1002/jez.1401160206.

Liebl, D. J., Huang, W., Young, W., & Parada, L. F. (2001). Regulation of Trk receptors following contusion of the rat spinal cord. *Experimental Neurology*, *167*(1), 15–26. https://doi.org/10.1006/exnr.2000.7548.

Lin, J. C., Tsao, D., Barras, P., Bastarrachea, R. A., Boyd, B., Chou, J., et al. (2008). Appetite enhancement and weight gain by peripheral administration of TrkB agonists in non-human primates. *PLoS One*, *3*(4), e1900. https://doi.org/10.1371/journal.pone.0001900.

Lu, P., Jones, L. L., & Tuszynski, M. H. (2005). BDNF-expressing marrow stromal cells support extensive axonal growth at sites of spinal cord injury. *Experimental Neurology*, *191*(2), 344–360. https://doi.org/10.1016/j.expneurol.2004.09.018.

Lu, P., Yang, H., Jones, L. L., Filbin, M. T., & Tuszynski, M. H. (2004). Combinatorial therapy with neurotrophins and cAMP promotes axonal regeneration beyond sites of spinal cord injury. *Journal of Neuroscience*, *24*(28), 6402–6409. https://doi.org/10.1523/JNEUROSCI.1492-04.2004.

Madduri, S., & Gander, B. (2012). Growth factor delivery systems and repair strategies for damaged peripheral nerves. *Journal of Controlled Release*, *161*(2), 274–282. https://doi.org/10.1016/j.jconrel.2011.11.036.

Marshall, J., Szmydynger-Chodobska, J., Rioult-Pedotti, M. S., Lau, K., Chin, A. T., Kotla, S. K. R., et al. (2017). TrkB-enhancer facilitates functional recovery after traumatic brain injury. *Scientific Reports*, *7*(1), 10995. https://doi.org/10.1038/s41598-017-11316-8.

McCall, J., Weidner, N., & Blesch, A. (2012). Neurotrophic factors in combinatorial approaches for spinal cord regeneration. *Cell and Tissue Research*, *349*(1), 27–37. https://doi.org/10.1007/s00441-012-1388-6.

Meeker, R. B., & Williams, K. S. (2015). The p75 neurotrophin receptor: At the crossroad of neural repair and death. *Neural Regeneration Research*, *10*(5), 721–725. https://doi.org/10.4103/1673-5374.156967.

Menei, P., Montero-Menei, C., Whittemore, S. R., Bunge, R. P., & Bunge, M. B. (1998). Schwann cells genetically modified to secrete human BDNF promote enhanced axonal regrowth across transected adult rat spinal cord. *European Journal of Neuroscience*, *10*(2), 607–621. https://doi.org/10.1046/j.1460-9568.1998.00071.x.

Ming, G.-L., Lohof, A. M., & Zheng, J. Q. (1997). Acute morphogenic and chemotropic effects of neurotrophins on cultured embryonic Xenopus spinal neurons. *Journal of Neuroscience*, *17*(20), 7860–7871. https://doi.org/10.1523/JNEUROSCI.17-20-07860.1997.

Ming, G.-L., Song, H.-J., Berninger, B., Inagaki, N., Tessier-Lavigne, M., & Poo, M.-M. (1999). Phospholipase C-γ and phosphoinositide 3-kinase mediate cytoplasmic signaling in nerve growth cone guidance. *Neuron*, *23*(1), 139–148. https://doi.org/10.1016/S0896-6273(00)80760-6.

Mitra, S., Behbahani, H., & Eriksdotter, M. (2019). Innovative therapy for Alzheimer's disease-with focus on biodelivery of NGF. *Frontiers in Neuroscience*, *13*(38). https://doi.org/10.3389/fnins.2019.00038.

Nagahara, A. H., & Tuszynski, M. H. (2011). Potential therapeutic uses of BDNF in neurological and psychiatric disorders. *Nature Reviews Drug Discovery*, *10*(3), 209–219. https://doi.org/10.1038/nrd3366.

Nardone, R., Florea, C., Höller, Y., Brigo, F., Versace, V., Lochner, P., et al. (2017). Rodent, large animal and non-human primate models of spinal cord injury. *Zoology (Jena, Germany)*, *123*, 101–114. https://doi.org/10.1016/j.zool.2017.06.004.

Nguyen, L. H., Gao, M., Lin, J., Wu, W., Wang, J., & Chew, S. Y. (2017). Three-dimensional aligned nanofibers-hydrogel scaffold for controlled non-viral drug/gene delivery to direct axon regeneration in spinal cord injury treatment. *Scientific Reports*, *7*(1), 42212. https://doi.org/10.1038/srep42212.

Oudega, M., & Hagg, T. (1996). Nerve growth factor promotes regeneration of sensory axons into adult rat spinal cord. *Experimental Neurology*, *140*(2), 218–229. https://doi.org/10.1006/exnr.1996.0131.

Oudega, M., & Hagg, T. (1999). Neurotrophins promote regeneration of sensory axons in the adult rat spinal cord. *Brain Research*, *818*(2), 431–438. https://doi.org/10.1016/S0006-8993(98)01314-6.

Ploughman, M., Windle, V., MacLellan, C. L., White, N., Doré, J. J., & Corbett, D. (2009). Brain-derived neurotrophic factor contributes to recovery of skilled reaching after focal ischemia in rats. *Stroke*, *40*(4), 1490–1495. https://doi.org/10.1161/STROKEAHA.108.531806.

Ramekers, D., Versnel, H., Grolman, W., & Klis, S. F. L. (2012). Neurotrophins and their role in the cochlea. *Hearing Research*, *288*(1), 19–33. https://doi.org/10.1016/j.heares.2012.03.002.

Rodriguez-Tébar, A., Dechant, G., & Barde, Y. A. (1990). Binding of brain-derived neurotrophic factor to the nerve growth factor receptor. *Neuron*, *4*(4), 487–492. https://doi.org/10.1016/0896-6273(90)90107-q.

Rodríguez-Tébar, A., Dechant, G., Götz, R., & Barde, Y. A. (1992). Binding of neurotrophin-3 to its neuronal receptors and interactions with nerve growth factor and brain-derived neurotrophic factor. *EMBO Journal*, *11*(3), 917–922.

Sakuragi, S., Tominaga-Yoshino, K., & Ogura, A. (2013). Involvement of TrkB- and p75(NTR)-signaling pathways in two contrasting forms of long-lasting synaptic plasticity. *Scientific Reports*, *3*, 3185. https://doi.org/10.1038/srep03185.

Schmalbruch, H., & Rosenthal, A. (1995). Neurotrophin- 4/5 postpones the death of injured spinal motoneurones in newborn rats. *Brain Research*, *700*(1), 254–260. https://doi.org/10.1016/0006-8993(95)00982-V.

Schnell, L., Schneider, R., Kolbeck, R., Barde, Y.-A., & Schwab, M. E. (1994). Neurotrophin-3 enhances sprouting of corticospinal tract during development and after adult spinal cord lesion. *Nature*, *367*(6459), 170–173. https://doi.org/10.1038/367170a0.

Siegel, G. J., & Chauhan, N. B. (2000). Neurotrophic factors in Alzheimer's and Parkinson's disease brain. *Brain Research Reviews*, *33*(2), 199–227. https://doi.org/10.1016/S0165-0173(00)00030-8.

Stokols, S., Sakamoto, J., Breckon, C., Holt, T., Weiss, J., & Tuszynski, M. H. (2006). Templated agarose scaffolds support linear axonal regeneration. *Tissue Engineering*, *12*(10), 2777–2787. https://doi.org/10.1089/ten.2006.12.2777.

Stucky, C. L., Shin, J. B., & Lewin, G. R. (2002). Neurotrophin-4: A survival factor for adult sensory neurons. *Current Biology*, *12*(16), 1401–1404. https://doi.org/10.1016/s0960-9822(02)01072-2.

Sutter, A., Riopelle, R. J., Harris-Warrick, R. M., & Shooter, E. M. (1979). Nerve growth factor receptors. Characterization of two distinct classes of binding sites on chick embryo sensory ganglia cells. *Journal of Biological Chemistry*, *254*(13), 5972–5982.

Taylor, L., Jones, L., Tuszynski, M. H., & Blesch, A. (2006). Neurotrophin-3 gradients established by lentiviral gene delivery promote short-distance axonal bridging beyond cellular grafts in the injured spinal cord. *Journal of Neuroscience*, *26*(38), 9713–9721. https://doi.org/10.1523/jneurosci.0734-06.2006.

Tuszynski, M. H., Gabriel, K., Gage, F. H., Suhr, S., Meyer, S., & Rosetti, A. (1996). Nerve growth factor delivery by gene transfer induces differential outgrowth of sensory, motor, and noradrenergic neurites after adult spinal cord injury. *Experimental Neurology*, *137*(1), 157–173. https://doi.org/10.1006/exnr.1996.0016.

Tuszynski, M. H., Grill, R., Jones, L. L., Brant, A., Blesch, A., Löw, K., et al. (2003). NT-3 gene delivery elicits growth of chronically injured corticospinal axons and modestly improves functional deficits after chronic scar resection. *Experimental Neurology*, *181*(1), 47–56. https://doi.org/10.1016/S0014-4886(02)00055-9.

Tuszynski, M. H., Peterson, D. A., Ray, J., Baird, A., Nakahara, Y., & Gages, F. H. (1994). Fibroblasts genetically modified to produce nerve growth factor induce robust neuritic ingrowth after grafting to the spinal cord. *Experimental Neurology*, *126*(1), 1–14. https://doi.org/10.1006/exnr.1994.1037.

Weishaupt, N., Blesch, A., & Fouad, K. (2012). BDNF: The career of a multifaceted neurotrophin in spinal cord injury. *Experimental Neurology*, *238*(2), 254–264. https://doi.org/10.1016/j.expneurol.2012.09.001.

Weissmiller, A. M., & Wu, C. (2012). Current advances in using neurotrophic factors to treat neurodegenerative disorders. *Translational Neurodegeneration*, *1*(1), 14. https://doi.org/10.1186/2047-9158-1-14.

Widenfalk, J., Lundströmer, K., Jubran, M., Brené, S., & Olson, L. (2001). Neurotrophic factors and receptors in the immature and adult spinal cord after mechanical injury or kainic acid. *Journal of Neuroscience*, *21*(10), 3457–3475. https://doi.org/10.1523/JNEUROSCI.21-10-03457.2001.

Zhang, Y., Dijkhuizen, P. A., Anderson, P. N., Lieberman, A. R., & Verhaagen, J. (1998). NT-3 delivered by an adenoviral vector induces injured dorsal root axons to regenerate into the spinal cord of adult rats. *Journal of Neuroscience Research*, *54*(4), 554–562.

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Chapter 19

The neuroscience of transient receptor potential vanilloid type 4 (TRPV4) and spinal cord injury

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List of abbreviations

BSCB	blood–spinal cord barrier
CNS	central nervous system
CVOs	circumventricular organs
DRGs	dorsal root ganglia
ECs	endothelial cells
ECM	extracellular matrix
IL-1β	interleukin-1 beta
IP3R	inositol triphosphate receptors
mPOA	medial preoptic area
NVC	neurovascular coupling
PNS	peripheral nervous system
PVN	paraventricular nucleus
RVD	regulatory volume decrease.
SCI	spinal cord injury
TG	trigeminal ganglia
TJ	tight Junctions
TNF-α	tumor necrosis factor alpha
TRPV4	transient receptor potential vanilloid type 4
OVLT	organum vasculosum lamina terminalis
ZO-1	zona occludens

Introduction

Transient receptor potential vanilloid type 4 (TRPV4)

Transient receptor potential (TRP) cation channels form a superfamily of inimitable sensory proteins that play a substantial role in varied homeostatic functions. TRP channels are well established for their involvement in sensory transduction (Damann, Voets, & Nilius, 2008; Montell, Birnbaumer, & Flockerzi, 2002; Talavera, Nilius, & Voets, 2008), and are broadly divided into six subfamilies in mammals: TRPA (ankyrin), TRPC (canonical), TRPML (mucolipin), TRPM (melastatin), TRPP (polycystin), and TRPV (vanilloid) (Damann et al., 2008). TRPV4 channels belong to the TRPV class and are mainly expressed in mammalian tissues, including the PNS and the CNS (Montell et al., 2002). TRPV4 ion channels have six transmembrane alpha-helices (S1-S6) stretching across the lipid bilayer. Both NH_2 and COOH terminals are localized in the cytoplasm. The NH_2 terminus is a proline-rich region and plays a crucial role in mediating the effects of pacsin-3, a synaptic vesicular membrane trafficking protein that inhibits the basal expression of TRPV4. The COOH terminus region of TRPV4 maintains channel protein folding, maturation, and trafficking (Fig. 1). They are

Cellular, Molecular, Physiological, and Behavioral Aspects of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822427-4.00019-8

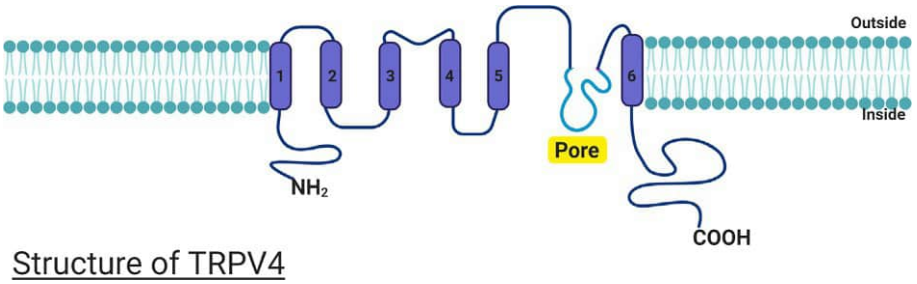

FIG. 1 TRPV4 Ion channels have six transmembrane alpha-helices (S1–S6) spread out across the lipid bilayer. Interestingly, both NH_2 and COOH terminals are contained in the cytoplasm. The proline-rich region (NH_2 terminus) plays a fundamental role in mediating the effects of pacsin-3, a synaptic vesicular membrane trafficking protein that inhibits the basal expression of TRPV4. COOH terminus region of TRPV4 maintains channel protein folding, maturation, and trafficking. The COOH region interacts with MAP-7. The pore that allows the cations is located between S5 and S6 domains.

permeable to many cations, with relatively high permeability to Ca^{2+} (5–10 times higher than the permeability to Na^+; $P_{Ca}/P_{Na} = 6$) (Kumar, Lee, Kim, Zeng, & Han, 2018; Plant & Strotmann, 2007; Watanabe et al., 2003). TRPV4 is nonspecific and is primarily recognized as a calcium-permeable non-selective cation channel, but its non-selective nature allows it to play a role as a polymodal cation channel permeable to other ions, notably Na^+. A comprehensive range of stimuli activates TRPV4, and it serves as an osmosensor and thermosensor (activated by innocuous warm temperatures in the range 27–35°C). It can also be activated directly or sensitized indirectly via intracellular signaling pathways (Kumar, Lee, et al., 2018; Liedtke et al., 2000; Plant & Strotmann, 2007; Strotmann, Harteneck, Nunnenmacher, Schultz, & Plant, 2000; Vennekens, Owsianik, & Nilius, 2008; Vriens et al., 2004; Wegierski, Lewandrowski, Muller, Sickmann, & Walz, 2009).

The expression of TRPV4 in the DRG cell bodies and the sensory nerve terminals projecting to laminae I and II of the spinal cord in the peripheral nociceptive neurons with cell bodies located in the TGs and DRGs allowing it to act as a sensor for noxious mechanical and osmotic stimuli (Alessandri-Haber et al., 2003). Interestingly, TRPV4 is transported distally toward peripheral nerve endings and act as an osmosensor, mechanosensor, and thermosensor. TRPV4-mediated Ca^{2+} oscillations in the endfeet arbitrate NVC (the connection between neurons and their vascular supply), suggesting that TRPV4 is crucial in controlling the brain's vascular tone and local perfusion (Dunn, Hill-Eubanks, Liedtke, & Nelson, 2013). Synaptic transmission, a process by which a neuron communicates to target cells across the synapse. Interestingly, astrocytes play an essential role in the regulation of synaptic transmission. These cell–cell communications in astroglia are finely tuned by intracellular Ca^{2+} responses elicited by extracellular signaling molecules and via activation of ion channels including TRPV4. TRPV4 is majorly found to be expressed in astrocytic membranes at the interface between the brain and extracerebral fluid spaces (Benfenati et al., 2007). It is obvious to predict that TRPV4 is a vital protein in controlling the astroglial osmosensation and plays a central role in brain-volume homeostasis (Benfenati et al., 2007). Not all astrocytes in the CNS express TRPV4; one of the studies reported that roughly 30% of astrocytes express TRPV4, signifying astrocytic subtypes' subsistence (Shibasaki, Ikenaka, Tamalu, Tominaga, & Ishizaki, 2014). Interestingly, astrocytes with TRPV4 expression ($TRPV4^+$ astrocytes) are exclusively accountable for instigating the excitatory gliotransmitter release that further augments the synaptic transmission, forms a core assembly of excitatory glia in the brain to augment the neuronal excitation efficiently (Shibasaki et al., 2014). Therefore, activation of TRPV4 plays an imperative role in the interaction between astrocytes and thereby improves neural activity (Shibasaki & Tominaga, 2007).

Spinal cord injury

Spinal cord injury (SCI) pathology is multifaceted, involving primary and secondary injury. The primary trauma causes tissue disruption, leading to secondary injury progression. The SCI pathology's significant events involve infiltration of neutrophils, the release of cytokines and chemokines leading to inflammation, followed by the death of ECs, neurons, and glial activation, glial, fibrotic scar formation, ECM remodeling, and cavitation (Kumar et al., 2020). SCI pathology also involves the loss of microcirculation, loss of structural organization, disruption of BSCB, endothelial cell, and vascular remodeling (Kumar, Ropper, Lee, & Han, 2017; Tator & Koyanagi, 1997). Vascular damage following SCI augments secondary damage, and vascular protection or maintaining vascular integrity through various ways has favorable effects (Kumar et al., 2017). Endothelial cells participate in all facets of vascular homeostasis; they play a wide variety of crucial roles in controlling vascular functions, including thrombosis, inflammation, or vascular wall remodeling. The death of endothelial cells disengages the vascular network, and ischemia results in apoptosis and cell death of CNS cells because they cannot survive without an adequate blood supply.

Inflammation is entrenched in SCI pathology and directly contributes to fibrosis scarring in part via altering numerous pathways. The continued presence of activated glial cells points toward a pro-inflammatory milieu concurrent with augmented neurotoxicity and weakens wound healing. The pathology of SCI is multifarious and diverse mechanisms might contribute to axonal conduction defects. Ion channels are an essential target that directly or indirectly contributes to sensory and motor functions. The role of several ion channels in regulating the pathology of SCI is established, and targeting TRP(s) seems fascinating to attenuate the SCI pathology (Gerzanich et al., 2009; Kumar et al., 2020; Shimizu et al., 2018).

TRPV4 and spinal cord injury

SCI is primarily caused by trauma, with the maximum incidence due to accidents or falls. There is a mechanical impact following the injury. It tends to change/excite the mechanosensor that can sense mechanical pressure and eventually increase the expression of ion channels and/or proteins, which can finally aggravate pathology. TRPV4 is an established mechanosensor, osmosensor, and thermosensor and plays a diverse role (Table 1). TRPV4 expression was increased during the inflammatory/acute phase and was correlated with injury severity at the epicenter after SCI (Fig. 2). After SCI, TRPV4 activation disrupted the EC organization, and the ECs were protected from SCI-induced damage in the TRPV4 absence (Kumar et al., 2020).

Similarly, TRPV4 deletion substantially impacted SCI-induced inflammatory cytokines and chemokine, BSCB integrity, the extent of scarring, and spontaneous locomotor recovery. Markedly, chemical inhibition with specific antagonists or deficiency of TRPV4 is propitious for endothelial factors, such as neurotrophins, angiopoietin, and BDNF, after SCI (Kumar et al., 2020). Notably, ECs detachment, which continues throughout the acute SCI phase (Koyanagi, Tator, & Lea, 1993), contributes to neuronal and glial cells' death (Casella, Marcillo, Bunge, & Wood, 2002). The SCI-induced expression of TGF-β/CD-68 was mitigated in TRPV4 KO mice signifying that increased TRPV4 levels contribute to the pathology and lessened SCI recovery (Kumar et al., 2020).

Interestingly, the injection of GSK, a TRPV4 agonist, brings about EC damage and scarring. Accordingly, the TRPV4 $^{-}/^{-}$ mice showed reduced reactive gliosis, decrease hyperalgesia toward heat, and quicker functional recovery after SCI than WT mice (Kumar et al., 2020). Activation of TRPV4 showed a differential effect in peripheral nerves, and CNS facilitated neurotrophic factor caused neuritogenesis in peripheral nerves (Jang et al., 2012), and induced neuronal apoptosis in the CNS (Jie et al., 2015). After SCI, axon regeneration necessitates synchronized neuronal homeostasis changes besides local cytoskeletal modifications necessary to promote growth cone formation. The neuron allows for proper mitochondrial trafficking, activation of transcription factors regulating pro-regenerative programs, and epigenetic modifications. Reduced scarring is seen in TRPV4 KO mice compared with that in WT mice after enhanced neuronal markers expression accompanied SCI. However, these increases were attenuated in TRPV4 KO mice, portentous that the enhanced TRPV4 expression in WT animals augmented the scarring (glial and fibrotic) process (Kumar et al., 2020).

After SCI, it leads to ischemia, which is well established to trigger several known and unknown pathways. Neutrophils arrive at the site of injury, and they start the release of chemokines and cytokines, which finally leads to disruption of ECs, TJs, and eventually affects BSCB integrity. TRPV4 is known to be expressed at astrocyte endfeet TRPV4 expression and is increased during the acute/inflammatory phase, which augments SCI's pathology by either contributing to the release of Ca^{2+} augmenting the pro-inflammatory cytokines or chemokines finally damage the ECs integrity (Fig. 3).

TRPV4, a non-selective cation channel expressed by astrocytes and neurons, is a critical factor of endothelial disruption and pathology after SCI. However, several mechanisms might be responsible for which these effects are observed in SCI's experimental model. (i) The upsurge in TRPV4 expression is induced by mechanical stimulation due to cell swelling, as TRPV4 also serves as a volume-sensitive mechanosensor (Nilius, Prenen, Wissenbach, Bödding, & Droogmans, 2001). TRPV4 is involved in mechanotransduction, and it functions as a mechanosensitive channel, and the traumatic injury eventually will cause mechanical stretch, thereby increasing the TRPV4 expression after SCI.

TABLE 1 Role of TRPV4 in different cells.

Astrocytes	Neurons	Microglia	Endothelial cells
• Control cell volume • Amplify NVC • Regulate Ca^{2+} release	• Regulates excitability • Apoptosis	• Increase M1 phenotypes • Promotes inflammation	• Activation damages ECs • Regulates signals controlling barrier property

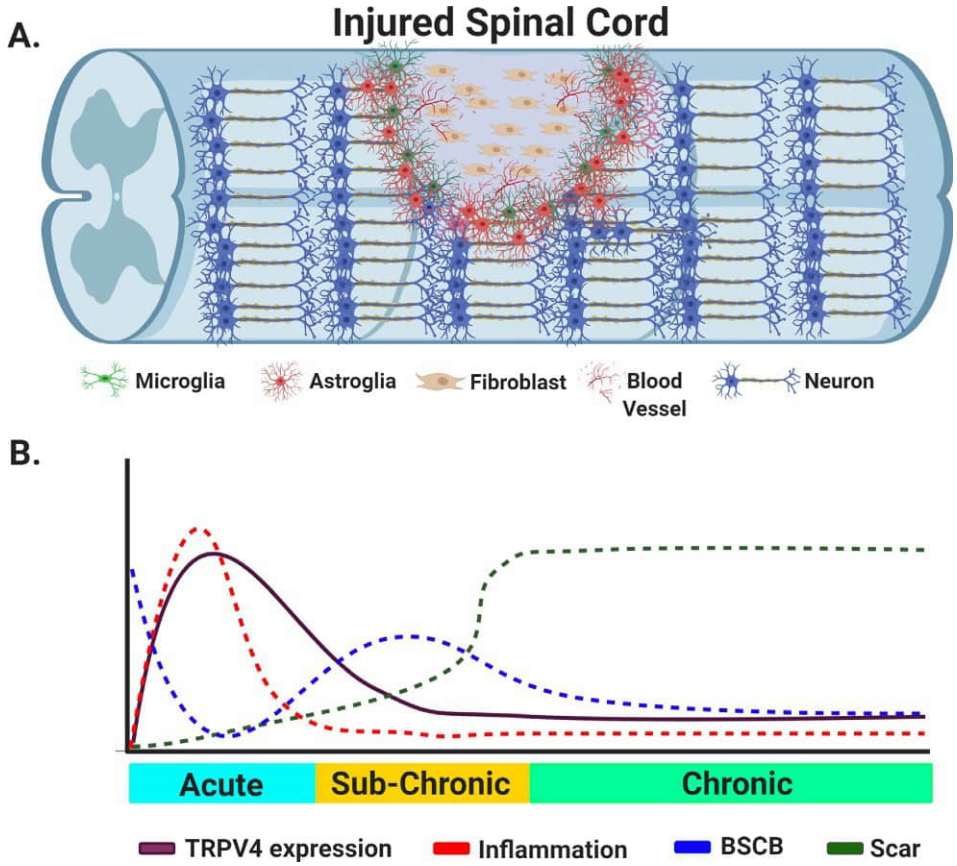

FIG. 2 TRPV4 expression in spinal cord injury pathology. TRPV4 expression is increased during the inflammatory phase. Both neuronal and non-neuronal cells express functional TRPV4, which is a response to a variety of stimuli. SCI leads to infiltration of neutrophils at the epicenter, followed by an increase in cytokines and chemokines. TRPV4 was reported to increase during the inflammatory phase, increasing secondary damage after spinal cord injury.

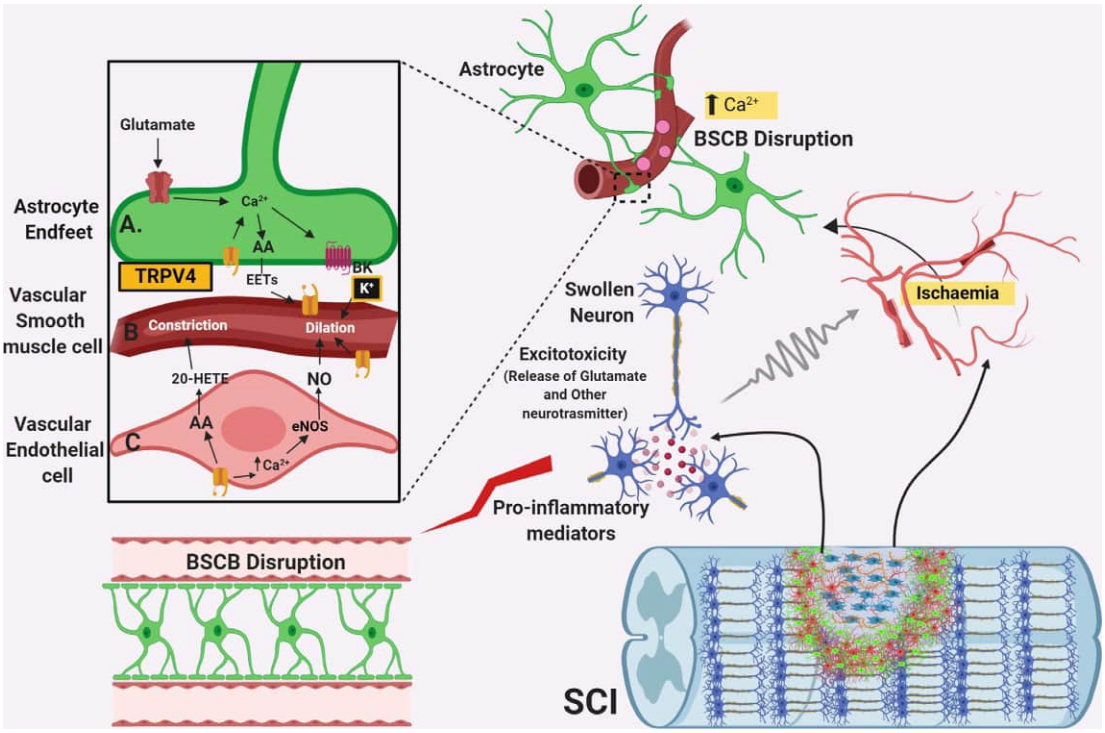

FIG. 3 Role of TRPV4 in the pathology of spinal cord injury (SCI). TRPV4 expression is upregulated after SCI. TRPV4 is expressed at the astrocyte end foot and endothelial cells. Increased expression of TRPV4 is linked with inflammation, endothelial damage, and blood–spinal cord barrier damage. SCI leads to ischemia, the release of pro-inflammatory mediators, and excitotoxicity, directly linked to endothelial damage and BSCB disruption. TRPV4 plays a crucial role in increasing calcium levels and promoting inflammation.

Reports indicate that an increase in TRPV4 activity disintegrated the blood-cerebrospinal fluid barrier (Narita et al., 2015). TRPV4 expression followed injury-dependent expression after mild, moderate, and severe SCI. Thus, a recent study indicates that escalating TRPV4 expression might be correlated with predicting CNS injury severity (Kumar et al., 2020).

The TJ proteins expression (occludin, ZO-1, and claudins) is reported to be downregulated after CNS injury, including SCI (Kumar et al., 2018), suggesting disturbances in the BSCB integrity. Pacsin-3, a synaptic vesicular membrane trafficking protein that impedes TRPV4 basal expression (D'hoedt et al., 2008), decreased after SCI [17], portentous that the SCI-induced upregulation of TRPV4 has functional relevance. Vascular ECs express TRPV4 in rodents (Watanabe et al., 2002) and humans (Sullivan, Francis, Pitts, Taylor, & Earley, 2012). Interestingly, TRPV4 presence has been confirmed in vascular smooth muscle cells (Senadheera et al., 2013) and in the astrocytic endfeet processes that wrap around blood vessels in the CNS (Benfenati et al., 2011). Activation of TRPV4 in the astrocytic endfeet contributes to NVC via regulating the Ca^{2+} entry (Dunn, Bonev, & Nelson, 2011). Neurovascular units include neurons, pericytes, and glia and are closely connected and functionally assembled with ECs in CNS. (Iadecola, 2004). Injection of specific TRPV4 agonists directly into the spinal cord and TRPV4 pharmacological activation and reduced the expression of TJ markers (ZO-1, ZO-2, and claudin-1). The TRPV4 agonist injection increases fibrosis and scarring, and it is enhanced in the presence of injury. The probable reason is in vivo application of GSK1016790A, a TRPV4 agonist, leading to the damage to ECs and basal lamina deposition, decreasing angiogenesis, and promoting cystic cavity formation, thereby enhancing EC damage after SCI. Interestingly, TRPV4 inhibition via RN-1734, a specific antagonist, attenuated inflammatory cascade, reduced free $[Ca^{2+}]_i$ levels, and preserved the BSCB (Kumar et al., 2020).

TJs proteins (Zona occludens, Claudins, and Occludins) are crucial for maintaining the integrity and preventing leakiness and disruption of these proteins that lead to BSCB instability and augmented permeability. TJs proteins' selective leakiness promotes the infiltration of inflammatory cytokines and chemokines, which are significant factors for secondary injury after SCI. Ion channels play a crucial role in maintaining the ECs integrity after SCI. After SCI, the secondary damage has been attributed to the augmented expression of sulfonylurea receptor 1-regulated $NC_{Ca\text{-}ATP}$ channels, such as Trpm4, by ECs (Gerzanich et al., 2009). Additionally, ECs express the TRPV4 receptor, which has also been associated with EC dysfunction and death during SCI-induced secondary damage (Kumar et al., 2020). TRPV4 KO mice ECs were better protected after SCI-induced damage, suggestive that SCI-induced TRPV4 activation might directly affect EC survival. A conceivable explanation is that TRPV4-mediated entry of Ca^{2+} into ECs regulates NO production and responds to inflammatory reaction/signals by changing the barrier properties (Tiruppathi et al., 2002) (Fig. 3). The absence of TRPV4 lessened SCI-induced inflammatory cascade, including the synthesis of chemokines and cytokines, in addition to enhanced EC integrity, reduced permeability, and reduced apoptosis (Kumar et al., 2020).

Spinal cord microvessels not only support neural parenchyma by bestowing adequate blood supply and oxygenation, but the CNS endothelium continuously secretes neurotrophins such as brain-derived neurotrophic factor (BDNF) and angiopoietins that are well established to support regenerating spinal cord tissue. The ECs permeability depends on several proteins that can directly or indirectly modulate the vascular permeability/inflammation. Angiopoietin-1 (ANG-1) is involved in maintaining vascular permeability, strengthening the endothelial associated molecules, and regulating the interendothelial adhesion. ANG-1 expression was decreased in the experimental model of SCI, and the reduction in ANG-1 was mitigated in TRPV4 KO mice (Kumar et al., 2020). The survival of EC depends on the continued presence and support of neurotrophins such as BDNF and NT-3, in addition to levels of NG-2, SMA, and vWF. Furthermore, TRPV4 KO mice preserved neurotrophins' levels and endorsed EC survival (Kumar et al., 2020).

TRPV4 role in non-injured conditions

CNS tissue responds to the different stressors by modulating the function of the protein or specific ion channels. Osmotic homeostasis also termed osmoregulation, is a vital physiological process, and the CNS serves as a central site for osmoregulation. The major areas controlling osmotic homeostasis are the OVLT, CVOs, mPOA of the hypothalamus, and the PVN. TRPV4 is osmotically activated and is articulated in the CVOs in the mammalian CNS (Liedtke & Friedman, 2003). The expression of TRPV4 is abundant in the astrocytic membranes unraveling the brain and extracellular liquid spaces, and therefore likely plays a critical role in brain-volume homeostasis (Benfenati et al., 2007). A crucial study observed the abnormalities in osmoregulation in TRPV4 null ($TRPV4^{-/-}$) mice suggesting that TRPV4 is essential for the typical response to osmotic pressure changes and serves as an osmosensor in the CNS (Liedtke & Friedman, 2003). TRPV4 expression is also reported in other neurosensory structures, including Merkel cells, inner-ear hair cells, and sensory neurons. $Trpv4^{-/-}$ mice showed diminished nociceptive responses to pressure (Liedtke & Friedman, 2003; Suzuki, Mizuno, Kodaira, & Imai, 2003). Knockdown or deletion of TRPV4 lessens nociceptive responses to hypotonic and mildly hypertonic stimuli (Alessandri-Haber et al., 2003) and in SCI's experimental model (Kumar et al., 2020). Thus, it's evident that TRPV4 functions to sense both osmotic and mechanical stimuli.

RVD is another process directly controlled by TRPV4 expression. RVD plays a crucial role in maintaining brain-volume homeostasis at the cellular and organ levels and prevents detrimental swelling in response to hypo-osmotic stress. Astrocytes-containing TRPV4/AQP4 complex plays a central role in maintaining RVD in the brain (Benfenati et al., 2011; Simard & Nedergaard, 2004).

Neurovascular coupling (NVC) is critical for neuronal survival and homeostasis. Astrocytes are considered an essential player in coordinating NVC (Koehler, Roman, & Harder, 2009). They perform this function in coordination with specific proteins/channels. Every astrocyte has no less than one process with endfeet surrounding a blood vessel (Simard, Arcuino, Takano, Liu, & Nedergaard, 2003). Interestingly, in contrast to astrocytes, neuronal processes are rarely in direct contact with intraparenchymal blood vessels; instead, they are indirectly connected. This anatomical association supports the hypothesis that astrocytes play a pivotal role in cerebral circulation's dynamic regulation (Paulson & Newman, 1987). TRPV4 channel presence has been well-known in astrocytes, and TRPV4 activation within the astrocytic endfeet contributes to NVC via Ca^{2+} entry (Dunn et al., 2011; Kumar et al., 2020).

Conversely, incubation of brain slices with HC067047, a selective TRPV4 antagonist, attenuates the Ca^{2+} oscillations (Dunn et al., 2011). These results suggest that TRPV4 selectively expressed at perivascular astrocytic endfeet regulates local cerebral blood flow and regulates the endfeet $[Ca^{2+}]_i$ to optimize NVC (Dunn et al., 2011; Dunn, Baylie, & Nelson, 2012). TRPV4 channels hasten Ca^{2+}-induced Ca^{2+} release from IP_3R in astrocytic endfeet and strengthen the NVC response (Dunn et al., 2013). As soon as the IP_3R-dependent Ca^{2+} wave reaches the astrocytic endfeet, the increase in endfeet $[Ca^{2+}]_i$ triggers Ca^{2+}-responsive pathways to liberate the vasoactive substances that commence the adjoining arteriole to dilate (Filosa et al., 2006; Straub & Nelson, 2007). The endfeet $[Ca^{2+}]_i$ is thus coupled to the vascular diameter and local perfusion, but there is a duality to this relationship: a medium increase in endfeet $[Ca^{2+}]_i$ dilates parenchymal arterioles, whereas high endfeet $[Ca^{2+}]_i$ constrict them (Girouard et al., 2010). This bidirectional vascular response suggests that endfoot intracellular Ca^{2+} concentration must be finely regulated to ensure adequate perfusion and maintain cerebral homeostasis. Similar to IP3Rs, TRPV4 channel activity is sensitive to modest $[Ca^{2+}]_i$ elevations and inhibited by high $[Ca^{2+}]_i$ (Strotmann, Schultz, & Plant, 2003).

Applications to other areas of neuroscience

TRPV4 expression exhibits age-related spinal cord changes and also shows alterations in cortical pyramidal neurons, the thalamus, and the cerebellum's basal nuclei during aging (Lee & Choe, 2014). Failure of neuronal TRPV4 expression in these brain regions may underlie some TRPV4-related pathological conditions. $TRPV4^{R269C}$, a TRPV4 mutant, expression in vivo causes neuronal dysfunction and axonal degeneration by increasing the intracellular Ca^{2+} through a CAMKII. Interestingly, TRPV4 antagonists may reverse the damage suggesting that inhibition of TRPV4 signaling may ameliorate TRPV4-linked neurodegenerative diseases (Woolums et al., 2020).

TRPV4 activates neuropeptide release from afferent nerves and stimulates neurogenic inflammation (Vergnolle et al., 2010). Interestingly, TRPV4 is also reported to be triggered by changes in osmolarity, causing increased release of pro-inflammatory cytokines (IL-1β and IL-6) in intervertebral discs (Walter et al., 2016). GSK2193874, a TRPV4 antagonist, attenuated the LPS-induced surge in pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6), signifying that blocking TRPV4 markedly decreases the production of cytokines in the development of sepsis (Dalsgaard, Sonkusare, Teuscher, Poynter, & Nelson, 2016). The role of TRPV4 in other areas in neuroscience is summarized in Table 2.

TABLE 2 TRPV4 roles/applications to other areas of neuroscience.

Disease	Role	Reference
Stroke	TRPV4 channels contribute to calcium influx into astrocytes and neurons and subsequent extracellular glutamate accumulation during PIDs	Rakers, Schmid, and Petzold (2017)
	Trpv4$^{-/-}$ mice showed reduced ischemia-induced lesion volume, water content, and Evans blue leakage and prevented TJs' loss compared to WT mice	Tanaka et al. (2020)
AD	TRPV4 expression in the brain of control mice, early-stage, and late-stage AD model mice significantly increased in the cerebral cortex, hippocampal formation, striatum, and thalamus of AD model mice compared with control mice. Interestingly, amyloid-β is reported to activate TRPV4 expression	Bai and Lipski (2014), Lee and Choe (2016)

TABLE 2 TRPV4 roles/applications to other areas of neuroscience—cont'd

Disease	Role	Reference
TBI	TBI causes augmented TRPV4 expression and then induced severe brain edema and neuronal damage by activating the MAPK cascade and Akt-related signaling pathway	Lu, Huang, Tsai, and Yang (2017)
MS	TRPV4 expression was increased in the mouse model of MS, and specific inhibition using a TRPV4 antagonist alleviated demyelination. Interestingly, TRPV4-antagonist inhibited glial activation and attenuated the production of TNF-α and IL-1β, suggesting that TRPV4 plays a role in CNS demyelination	Liu et al. (2018)
Leukodystrophy	Megalencephalic leukoencephalopathy with subcortical cysts (MLC), a rare leukodystrophy characterized by macrocephaly, subcortical fluid cysts, and myelin vacuolation. MLC1 gene is highly expressed in astrocytes, and it cooperates with the TRPV4	Lanciotti et al. (2012)
Migraine	TRPV4 activation within the meninges generates afferent nociceptive signaling that contributes to migraine headaches	Wei, Edelmayer, Yan, and Dussor (2011)
Hydrocephalus (an excessive accumulation of CSF)	TRPV4 antagonists inhibit the development of ventriculomegaly in a rodent model of communicating hydrocephalus, the Wpk rat (Tmem67$^{-/-}$)	Hochstetler et al. (2020)
Epilepsy	Activation of TRPV4 induces neuronal injury, enhances inflammatory response, and promotes the pro-inflammatory cytokines. TRPV4 activation with specific agonists causes microglia and astrocyte activation. It increases NLPR3 inflammasome and pro-inflammatory cytokines, whereas selective TRPV4 inhibition increases the number of surviving cells and attenuated the activated microglia and astrocyte	Wang et al. (2019)
	The frequencies of epileptic electroencephalogram in WT mice were significantly larger than those in Trpv4$^{-/-}$ mice in the experimental model of epilepsy. These results suggest that activation of TRPV4 contributes to the disease progression of epilepsy	(Shibasaki et al. (2020)
Amyotrophic lateral sclerosis	TRPV4 expression was evident in the cerebral cortex, hippocampal formation, thalamus, cerebellum, and spinal cord of symptomatic SOD1^{G93A} transgenic mice, an animal model of amyotrophic lateral sclerosis	Lee, Joo, Choe, and Cha (2012)

Mini-dictionary of terms

Spinal cord injury: A injury or damage to the spinal cord caused either by trauma or non-trauma. It can cause permanent or life-long disability.

TRPV4: A non-selective cationic channel that tunes the functions of diverse tissues.

Gliosis: Also known as glial scar in which reactive changes in the glial cells occur in response to damage to the CNS including SCI.

Fibrosis: Also known as fibrotic scarring, is a pathological process where connective tissue like fibroblasts replaces normal parenchymal leading to substantial tissue remodeling and the development of permanent scar. Fibrotic scar forms the core of the glial scar after SCI.

Blood–spinal cord barrier: Analogous to BBB, BSCB is formed by specialized small blood vessels that surround the spinal cord.

Endothelial cells: These are single cells layers that surround blood vessels and control the blood flow and nutritional exchange.

Tight junctions: These are the cells that seal the paracellular pathway. Thereby tightly regulates the transport and prevents leakage.

Neurovascular coupling: the relationship between local neural activity and resultant changes in cerebral blood flow.

Regulatory volume decrease: Cells can endure the changes in cell volume; specific proteins' expression tightly controls the mechanism to resist these changes. These proteins return cell volume to baseline following an osmolarity-induced swelling response. This volume recovery is termed RVD.

TRPV4 null mice: Transgenic mouse in which TRPV4 gene has been disrupted or deleted and there is no functional gene product. These are also known as knock-out mice.

Key facts about SCI

- SCI is a multifacet pathology mostly caused by traumatic and sometimes non-traumatic events.
- SCI is often associated with traumatic injury primarily caused by trauma/accidents, is synchronized with mechanical injury, shear stress, and osmolarity changes.
- The SCI involved a primary phase where inflammatory components predominate; whereas, the secondary phase involves scarring and secondary damages.
- During inflammatory phase, there is a release of chemokines, cytokines, and ECs damage which can cause BSCB disruption.
- During secondary phase, there is scarring where the core is made up of fibrotic tissues, and periphery is mostly formed by glial cells.

Key facts about TRPV4

- TRPV4 is a non-selective cationic channel whose activation is typically linked with the influx of Ca^{2+}. However, it also allows for the transport of other cations.
- TRPV4 acts as a thermosensor, mechanosensory, and osmosensor and is expressed in neuronal as well as non-neuronal cells. It controls physiological function, and TRPV4 activation is linked with pathological changes.
- TRPV4 expression is linked with CNS injuries pathology, including SCI, and linked with the injury's severity.
- Knockdown of TRPV4 lessens scarring (glial and fibrotic), and SCI-injured animals recovered faster than animals that had an expression of TRPV4.
- Targeting TRPV4 will be an excellent strategy to prevent endothelial damage, cell damage, and attenuate inflammation.

Summary points

- TRPV4, a non-selective cation channel, is commonly expressed in both excitable and non-excitable cells. After SCI, TRPV4 activation is correlated with the injury's severity at the epicenter at the time points that were reported to be crucial for repair/treatment. TRPV4 activation damages ECs that form the BSCB and thus contribute to scarring (glial and fibrotic).
- Crucially, TRPV4 inhibition/knockdown vetoed SCI-induced cell damage, inflammation, and scarring. Thus, the manipulation of TRPV4 signaling might lead to new therapeutic strategies or combinatorial therapies to protect ECs and augment repair after SCI. Subsequently, the maneuvering of TRPV4 signaling and downstream pathways might lead to new therapeutic approaches after CNS injuries, including SCI.

References

Alessandri-Haber, N., Yeh, J. J., Boyd, A. E., Parada, C. A., Chen, X., Reichling, D. B., et al. (2003). Hypotonicity induces TRPV4-mediated nociception in rat. *Neuron*, *39*(3), 497–511.

Bai, J.-Z., & Lipski, J. (2014). Involvement of TRPV4 channels in Aβ40-induced hippocampal cell death and astrocytic Ca2+ signalling. *Neurotoxicology*, *41*, 64–72.

Benfenati, V., Amiry-Moghaddam, M., Caprini, M., Mylonakou, M. N., Rapisarda, C., Ottersen, O. P., et al. (2007). Expression and functional characterization of transient receptor potential vanilloid-related channel 4 (TRPV4) in rat cortical astrocytes. *Neuroscience*, *148*(4), 876–892. https://doi.org/10.1016/j.neuroscience.2007.06.039.

Benfenati, V., Caprini, M., Dovizio, M., Mylonakou, M. N., Ferroni, S., Ottersen, O. P., et al. (2011). An aquaporin-4/transient receptor potential vanilloid 4 (AQP4/TRPV4) complex is essential for cell-volume control in astrocytes. *Proceedings of the National Academy of Sciences*, *108*(6), 2563–2568.

Casella, G. T., Marcillo, A., Bunge, M. B., & Wood, P. M. (2002). New vascular tissue rapidly replaces neural parenchyma and vessels destroyed by a contusion injury to the rat spinal cord. *Experimental Neurology*, *173*(1), 63–76.

Dalsgaard, T., Sonkusare, S. K., Teuscher, C., Poynter, M. E., & Nelson, M. T. (2016). Pharmacological inhibitors of TRPV4 channels reduce cytokine production, restore endothelial function and increase survival in septic mice. *Scientific Reports*, *6*, 33841. https://doi.org/10.1038/srep33841.

Damann, N., Voets, T., & Nilius, B. (2008). TRPs in our senses. *Current Biology*, *18*(18), R880–R889.

D'hoedt, D., Owsianik, G., Prenen, J., Cuajungco, M. P., Grimm, C., Heller, S., et al. (2008). Stimulus-specific modulation of the cation channel TRPV4 by PACSIN 3. *Journal of Biological Chemistry*, *283*(10), 6272–6280.

Dunn, K. M., Baylie, R. L., & Nelson, M. T. (2012). TRPV4 channels tune astrocytic endfoot Ca2+ to optimize neurovascular coupling. *The FASEB Journal*, *26*(Suppl. 1), 685.610.

Dunn, K. M., Bonev, A. D., & Nelson, M. T. (2011). Functional evidence of TRPV4-mediated Ca2+ signals in cortical astrocytes. *The FASEB Journal*, *25* (1 Supplement), 1024.1023.

Dunn, K. M., Hill-Eubanks, D. C., Liedtke, W. B., & Nelson, M. T. (2013). TRPV4 channels stimulate Ca2+−induced Ca2+ release in astrocytic endfeet and amplify neurovascular coupling responses. *Proceedings of the National Academy of Sciences*, *110*(15), 6157–6162.

Filosa, J. A., Bonev, A. D., Straub, S. V., Meredith, A. L., Wilkerson, M. K., Aldrich, R. W., et al. (2006). Local potassium signaling couples neuronal activity to vasodilation in the brain. *Nature Neuroscience*, *9*(11), 1397–1403. https://doi.org/10.1038/nn1779.

Gerzanich, V., Woo, S. K., Vennekens, R., Tsymbalyuk, O., Ivanova, S., Ivanov, A., et al. (2009). De novo expression of Trpm4 initiates secondary hemorrhage in spinal cord injury. *Nature Medicine*, *15*(2), 185.

Girouard, H., Bonev, A. D., Hannah, R. M., Meredith, A., Aldrich, R. W., & Nelson, M. T. (2010). Astrocytic endfoot Ca2+ and BK channels determine both arteriolar dilation and constriction. *Proceedings of the National Academy of Sciences of the United States of America*, *107*(8), 3811–3816. https://doi.org/10.1073/pnas.0914722107.

Hochstetler, A. E., Smith, H. M., Preston, D. C., Reed, M. M., Territo, P. R., Shim, J. W., et al. (2020). TRPV4 antagonists ameliorate ventriculomegaly in a rat model of hydrocephalus. *JCI Insight*, *5*(18), e137646.

Iadecola, C. (2004). Neurovascular regulation in the normal brain and in Alzheimer's disease. *Nature Reviews Neuroscience*, *5*(5), 347.

Jang, Y., Jung, J., Kim, H., Oh, J., Jeon, J. H., Jung, S., et al. (2012). Axonal neuropathy-associated TRPV4 regulates neurotrophic factor-derived axonal growth. *The Journal of Biological Chemistry*, *287*(8), 6014–6024. https://doi.org/10.1074/jbc.M111.316315.

Jie, P., Hong, Z., Tian, Y., Li, Y., Lin, L., Zhou, L., et al. (2015). Activation of transient receptor potential vanilloid 4 induces apoptosis in hippocampus through downregulating PI3K/Akt and upregulating p38 MAPK signaling pathways. *Cell Death & Disease*, *6*. https://doi.org/10.1038/cddis.2015.146, e1775.

Koehler, R. C., Roman, R. J., & Harder, D. R. (2009). Astrocytes and the regulation of cerebral blood flow. *Trends in Neurosciences*, *32*(3), 160–169.

Koyanagi, I., Tator, C. H., & Lea, P. J. (1993). Three-dimensional analysis of the vascular system in the rat spinal cord with scanning electron microscopy of vascular corrosion casts. Part 2: Acute spinal cord injury. *Neurosurgery*, *33*(2), 285–292.

Kumar, H., Choi, H., Jo, M.-J., Joshi, H. P., Muttigi, M., Bonanomi, D., et al. (2018). Neutrophil elastase inhibition effectively rescued angiopoietin-1 decrease and inhibits glial scar after spinal cord injury. *Acta Neuropathologica Communications*, *6*(1), 73.

Kumar, H., Lee, S.-H., Kim, K.-T., Zeng, X., & Han, I. (2018). TRPV4: A sensor for homeostasis and pathological events in the CNS. *Molecular Neurobiology*, *55*(11), 8695–8708.

Kumar, H., Lim, C. S., Choi, H., Joshi, H. P., Kim, K.-T., Kim, Y. H., et al. (2020). Elevated TRPV4 levels contribute to endothelial damage and scarring in experimental spinal cord injury. *Journal of Neuroscience*, *40*(9), 1943–1955.

Kumar, H., Ropper, A. E., Lee, S.-H., & Han, I. (2017). Propitious therapeutic modulators to prevent blood-spinal cord barrier disruption in spinal cord injury. *Molecular Neurobiology*, *54*(5), 3578–3590.

Lanciotti, A., Brignone, M. S., Molinari, P., Visentin, S., De Nuccio, C., Macchia, G., et al. (2012). Megalencephalic leukoencephalopathy with subcortical cysts protein 1 functionally cooperates with the TRPV4 cation channel to activate the response of astrocytes to osmotic stress: Dysregulation by pathological mutations. *Human Molecular Genetics*, *21*(10), 2166–2180.

Lee, J. C., & Choe, S. Y. (2014). Age-related changes in the distribution of transient receptor potential vanilloid 4 channel (TRPV4) in the central nervous system of rats. *Journal of Molecular Histology*, *45*(5), 497–505. https://doi.org/10.1007/s10735-014-9578-z.

Lee, J. C., & Choe, S. Y. (2016). Region-specific changes in the distribution of transient receptor potential vanilloid 4 channel (TRPV4) in the central nervous system of Alzheimer's disease model mice. *Genes & Genomics*, *38*(7), 629–637.

Lee, J. C., Joo, K. M., Choe, S. Y., & Cha, C. I. (2012). Region-specific changes in the immunoreactivity of TRPV4 expression in the central nervous system of SOD1 G93A transgenic mice as an in vivo model of amyotrophic lateral sclerosis. *Journal of Molecular Histology*, *43*(6), 625–631.

Liedtke, W., Choe, Y., Marti-Renom, M. A., Bell, A. M., Denis, C. S., Sali, A., et al. (2000). Vanilloid receptor-related osmotically activated channel (VR-OAC), a candidate vertebrate osmoreceptor. *Cell*, *103*(3), 525–535.

Liedtke, W., & Friedman, J. M. (2003). Abnormal osmotic regulation in trpv4 −/− mice. *Proceedings of the National Academy of Sciences of the United States of America*, *100*(23), 13698–13703. https://doi.org/10.1073/pnas.1735416100.

Liu, M., Liu, X., Wang, L., Wang, Y., Dong, F., Wu, J., et al. (2018). TRPV4 inhibition improved myelination and reduced glia reactivity and inflammation in a cuprizone-induced mouse model of demyelination. *Frontiers in Cellular Neuroscience*, *12*, 392.

Lu, K. T., Huang, T. C., Tsai, Y. H., & Yang, Y. L. (2017). Transient receptor potential vanilloid type 4 channels mediate Na-K-Cl-co-transporter-induced brain edema after traumatic brain injury. *Journal of Neurochemistry*, *140*(5), 718–727.

Montell, C., Birnbaumer, L., & Flockerzi, V. (2002). The TRP channels, a remarkably functional family. *Cell*, *108*(5), 595–598.

Narita, K., Sasamoto, S., Koizumi, S., Okazaki, S., Nakamura, H., Inoue, T., et al. (2015). TRPV4 regulates the integrity of the blood-cerebrospinal fluid barrier and modulates transepithelial protein transport. *The FASEB Journal*, *29*(6), 2247–2259.

Nilius, B., Prenen, J., Wissenbach, U., Bödding, M., & Droogmans, G. (2001). Differential activation of the volume-sensitive cation channel TRP12 (OTRPC4) and volume-regulated anion currents in HEK-293 cells. *Pflügers Archiv*, *443*(2), 227–233.

Paulson, O. B., & Newman, E. A. (1987). Does the release of potassium from astrocyte endfeet regulate cerebral blood flow? *Science*, *237*(4817), 896–898.

Plant, T. D., & Strotmann, R. (2007). Trpv4. *Handbook of Experimental Pharmacology*, (179), 189–205. https://doi.org/10.1007/978-3-540-34891-7_11.

Rakers, C., Schmid, M., & Petzold, G. C. (2017). TRPV4 channels contribute to calcium transients in astrocytes and neurons during peri-infarct depolarizations in a stroke model. *Glia*, *65*(9), 1550–1561.

Senadheera, S., Bertrand, P. P., Grayson, T. H., Leader, L., Murphy, T. V., & Sandow, S. L. (2013). Pregnancy-induced remodelling and enhanced endothelium-derived hyperpolarization-type vasodilator activity in rat uterine radial artery: Transient receptor potential vanilloid type 4 channels, caveolae and myoendothelial gap junctions. *Journal of Anatomy*, *223*(6), 677–686. https://doi.org/10.1111/joa.12127.

Shibasaki, K., Ikenaka, K., Tamalu, F., Tominaga, M., & Ishizaki, Y. (2014). A novel subtype of astrocytes expressing TRPV4 (transient receptor potential vanilloid 4) regulates neuronal excitability via release of gliotransmitters. *The Journal of Biological Chemistry*, *289*(21), 14470–14480. https://doi.org/10.1074/jbc.M114.557132.

Shibasaki, K., & Tominaga, M. (2007). Implication that TRPV4 activation induces the excitation of astrocytes. In *Paper presented at the Proceedings of Annual Meeting of the Physiological Society of Japan Proceedings of Annual Meeting of the Physiological Society of Japan.*

Shibasaki, K., Yamada, K., Miwa, H., Yanagawa, Y., Suzuki, M., Tominaga, M., et al. (2020). Temperature elevation in epileptogenic foci exacerbates epileptic discharge through TRPV4 activation. *Laboratory Investigation*, *100*(2), 274–284.

Shimizu, N., Wada, N., Shimizu, T., Suzuki, T., Takaoka, E.-I., Kanai, A. J., et al. (2018). Effects of nerve growth factor neutralization on TRP channel expression in laser-captured bladder afferent neurons in mice with spinal cord injury. *Neuroscience Letters*, *683*, 100–103.

Simard, M., Arcuino, G., Takano, T., Liu, Q. S., & Nedergaard, M. (2003). Signaling at the gliovascular interface. *The Journal of Neuroscience*, *23*(27), 9254–9262.

Simard, M., & Nedergaard, M. (2004). The neurobiology of glia in the context of water and ion homeostasis. *Neuroscience*, *129*(4), 877–896. https://doi.org/10.1016/j.neuroscience.2004.09.053.

Straub, S. V., & Nelson, M. T. (2007). Astrocytic calcium signaling: The information currency coupling neuronal activity to the cerebral microcirculation. *Trends in Cardiovascular Medicine*, *17*(6), 183–190. https://doi.org/10.1016/j.tcm.2007.05.001.

Strotmann, R., Harteneck, C., Nunnenmacher, K., Schultz, G., & Plant, T. D. (2000). OTRPC4, a nonselective cation channel that confers sensitivity to extracellular osmolarity. *Nature Cell Biology*, *2*(10), 695–702. https://doi.org/10.1038/35036318.

Strotmann, R., Schultz, G., & Plant, T. D. (2003). Ca2+−dependent potentiation of the nonselective cation channel TRPV4 is mediated by a C-terminal calmodulin binding site. *The Journal of Biological Chemistry*, *278*(29), 26541–26549. https://doi.org/10.1074/jbc.M302590200.

Sullivan, M. N., Francis, M., Pitts, N. L., Taylor, M. S., & Earley, S. (2012). Optical recording reveals novel properties of GSK1016790A-induced vanilloid transient receptor potential channel TRPV4 activity in primary human endothelial cells. *Molecular Pharmacology*, *82*(3), 464–472. https://doi.org/10.1124/mol.112.078584.

Suzuki, M., Mizuno, A., Kodaira, K., & Imai, M. (2003). Impaired pressure sensation in mice lacking TRPV4. *The Journal of Biological Chemistry*, *278*(25), 22664–22668. https://doi.org/10.1074/jbc.M302561200.

Talavera, K., Nilius, B., & Voets, T. (2008). Neuronal TRP channels: Thermometers, pathfinders and life-savers. *Trends in Neurosciences*, *31*(6), 287–295. https://doi.org/10.1016/j.tins.2008.03.002.

Tanaka, K., Matsumoto, S., Yamada, T., Yamasaki, R., Suzuki, M., Kido, M. A., et al. (2020). Reduced post-ischemic brain injury in transient receptor potential vanilloid 4 knockout mice. *Frontiers in Neuroscience*, *14*, 453.

Tator, C. H., & Koyanagi, I. (1997). Vascular mechanisms in the pathophysiology of human spinal cord injury. *Journal of Neurosurgery*, *86*(3), 483–492. https://doi.org/10.3171/jns.1997.86.3.0483.

Tiruppathi, C., Freichel, M., Vogel, S. M., Paria, B. C., Mehta, D., Flockerzi, V., et al. (2002). Impairment of store-operated Ca2+ entry in TRPC4 −/− mice interferes with increase in lung microvascular permeability. *Circulation Research*, *91*(1), 70–76.

Vennekens, R., Owsianik, G., & Nilius, B. (2008). Vanilloid transient receptor potential cation channels: An overview. *Current Pharmaceutical Design*, *14*(1), 18–31.

Vergnolle, N., Cenac, N., Altier, C., Cellars, L., Chapman, K., Zamponi, G., et al. (2010). A role for transient receptor potential vanilloid 4 in tonicity-induced neurogenic inflammation. *British Journal of Pharmacology*, *159*(5), 1161–1173.

Vriens, J., Watanabe, H., Janssens, A., Droogmans, G., Voets, T., & Nilius, B. (2004). Cell swelling, heat, and chemical agonists use distinct pathways for the activation of the cation channel TRPV4. *Proceedings of the National Academy of Sciences of the United States of America*, *101*(1), 396–401. https://doi.org/10.1073/pnas.0303329101.

Walter, B. A., Purmessur, D., Moon, A., Occhiogrosso, J., Laudier, D. M., Hecht, A. C., et al. (2016). Reduced tissue osmolarity increases TRPV4 expression and pro-inflammatory cytokines in intervertebral disc cells. *European Cells & Materials*, *32*, 123–136.

Wang, Z., Zhou, L., An, D., Xu, W., Wu, C., Sha, S., et al. (2019). TRPV4-induced inflammatory response is involved in neuronal death in pilocarpine model of temporal lobe epilepsy in mice. *Cell Death & Disease*, *10*(6), 1–10.

Watanabe, H., Vriens, J., Janssens, A., Wondergem, R., Droogmans, G., & Nilius, B. (2003). Modulation of TRPV4 gating by intra- and extracellular Ca2+. *Cell Calcium*, *33*(5–6), 489–495.

Watanabe, H., Vriens, J., Suh, S. H., Benham, C. D., Droogmans, G., & Nilius, B. (2002). Heat-evoked activation of TRPV4 channels in a HEK293 cell expression system and in native mouse aorta endothelial cells. *The Journal of Biological Chemistry*, *277*(49), 47044–47051. https://doi.org/10.1074/jbc.M208277200.

Wegierski, T., Lewandrowski, U., Muller, B., Sickmann, A., & Walz, G. (2009). Tyrosine phosphorylation modulates the activity of TRPV4 in response to defined stimuli. *The Journal of Biological Chemistry*, *284*(5), 2923–2933. https://doi.org/10.1074/jbc.M805357200.

Wei, X., Edelmayer, R. M., Yan, J., & Dussor, G. (2011). Activation of TRPV4 on dural afferents produces headache-related behavior in a preclinical rat model. *Cephalalgia*, *31*(16), 1595–1600.

Woolums, B. M., McCray, B. A., Sung, H., Tabuchi, M., Sullivan, J. M., Ruppell, K. T., et al. (2020). TRPV4 disrupts mitochondrial transport and causes axonal degeneration via a CaMKII-dependent elevation of intracellular ca 2+. *Nature Communications*, *11*(1), 1–17.

Chapter 20

Autoantibodies in spinal cord injury

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List of abbreviations

ALBU	albumin
ATPA	ATP synthase subunit alpha
CNS	central nervous system
CRMP2	collapsing response mediator protein-2
CSF	cerebrospinal fluid
ENOA	enolase alpha
GAPDH	glyceraldehyde 3-phosphate dehydrogenase
GFAP	glial fibrillary acidic protein
HBA	hemoglobin alpha
HBB	hemoglobin beta
IgG	immunoglobulin G
MBP	myelin basic protein
NFL	neurofilament light
NFM	neurofilament intermediate
NMDAR	*N*-methyl-D-aspartate receptors
PGK1	phosphoglycerate kinase 1
PPIA	peptidylprolyl isomerase A
SCI	spinal cord injury

Introduction

From a clinical perspective, immunodepression is the most obvious alteration of the immune system after spinal cord injury (SCI), exposed by the fact that infections are the leading cause of morbidity and mortality after SCI. However, the extent of alterations induced by SCI over the immune system is by far much more complex than just suffering from immunodepression. In fact, although it may seem paradoxical, patients with SCI also exhibit elevated levels of autoantibodies against both central nervous system and systemic antigens (Arevalo-Martin et al., 2018; Davies, Hayes, & Dekaban, 2007; Hayes et al., 2002; Hergenroeder et al., 2018; Hergenroeder, Moore, Schmitt, Redell, & Dash, 2016; Mizrachi et al., 1983; Palmers et al., 2016; Petrova, Ponomaryova, Alyoshkin, Eliseyev, & Yumashev, 1993; Taranova et al., 1992; Zajarías-Fainsod et al., 2012). While immunodepression is directly related to increased susceptibility to infections, the clinical consequences of elevated autoantibody levels are not that straightforward. The first study suggesting that autoantibodies could play a role in SCI pathology was that of Mizrachi and collaborators (Mizrachi et al., 1983), who described that patients with SCI exhibited higher blood serum levels of anti-MBP (myelin basic protein) and/or anti-GM1 ganglioside. In spite that the authors did not provide direct proof on the contribution of autoantibodies to pathology, they proposed that autoantibodies could be a factor impeding neural repair after SCI since GM1 ganglioside is involved in neuron maturation and serum from patients, enriched in anti-GM1 antibodies, inhibited neurite outgrowth in vitro. Later on, it was demonstrated that SCI increases the levels of IgM and IgG autoantibodies also in mice, and the injection of these IgG antibodies with unknown specificities into the spinal cord of intact mice induced necrotic inflammatory lesions and ipsilateral paralysis of hind limbs

Cellular, Molecular, Physiological, and Behavioral Aspects of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822427-4.00020-4

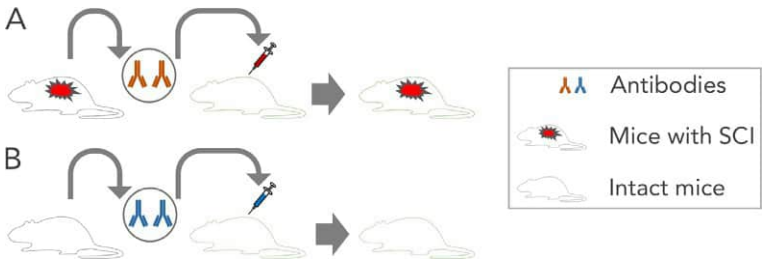

FIG. 1 Spinal cord injury induces pathogenic autoantibodies in mice. (A) Antibodies purified from mice with chronic SCI are pathogenic when injected into the spinal cord of intact mice, while (B) antibodies from intact mice do not elicit any pathogenic effect.

(Fig. 1) (Ankeny, Guan, & Popovich, 2009; Ankeny, Lucin, Sanders, McGaughy, & Popovich, 2006). But since the targets of these pathogenic antibodies in mice have not been identified, it remains still unknown which specific autoantibody or profile of autoantibodies was responsible for the pathological effects. Actually, it could happen that among the autoantibodies that increase in chronic SCI in mice some are pathogenic and some others are not. Accordingly, in a number of disorders, autoantibodies are increased but are not directly related to pathology. In these situations, in spite that autoantibodies are not potential therapeutic targets, they may be still useful for the clinical practice as diagnostic or prognostic biomarkers. Also, autoantibodies may provide further insights into the pathophysiological mechanisms that are taking place since they specifically point to the antigens against which the immune system is reacting. Whether autoantibodies are directly involved in the pathophysiology of human SCI or are just part of a secondary response to spinal cord damage is a question that remains open and constitutes a hot research topic in the field. Here we review the current knowledge about the origin, identities, and the known roles of autoantibodies that increase after human SCI.

Targets and possible origin of autoantibodies increased after SCI in humans

Currently, 24 different targets of autoantibodies that increase in peripheral blood after human SCI have been described (Table 1). Interestingly, at least 17 of these immunoglobulin G (IgG) autoantibodies are already elevated in the first hours/days after injury, before primary IgG responses to novel antigens may develop (Table 1) (Arevalo-Martin et al., 2018; Palmers et al., 2016). Such a rapid increase suggests that these autoantibodies are a part of pre-existing humoral immune responses, as occurs when the immune system is re-exposed to an antigen after an effective vaccination. Indeed, this is the case: the increased autoantibodies in the early stages after SCI are naturally occurring antibodies, i.e., antibodies naturally found in healthy subjects. The existence of naturally occurring autoantibodies (or natural autoantibodies) was reported almost 80 years ago (Kidd & Friedewald, 1942) and it has been a subject of research that challenges the classical view of autoantibodies as just effectors of an autoimmune disease (Cohen, 2007; Cohen & Cooke, 1986; Nataf, 2017). A hallmark of natural autoantibodies that is also observable in the autoantibodies increased in the early phases of SCI (Arevalo-Martin et al., 2018) is that they target altered or degraded proteins that arise under conditions of cellular stress or death (Fig. 2). Actually, many of the targets of the autoantibodies increased after injury are part of the SCI degradome, the group of proteins that are actively degraded by proteolytic enzymes activated after injury (Abou-El-Hassan et al., 2020). For this reason, natural autoantibodies have been suggested to participate in physiological responses to tissue damage, by pointing to cellular debris for their cleaning and, thus, promoting tissue healing (Fiskesund et al., 2010; Lutz, 2007; Schwartz-Albiez, Monteiro, Rodriguez, Binder, & Shoenfeld, 2009). Besides potentiating tissue repair, natural autoantibodies may be protective by counteracting pathological processes. For example, in patients who suffered from stroke, a neurological pathology shares some pathological mechanisms with SCI, the patients with natural anti-NMDAR (*N*-methyl-D-aspartate receptors) autoantibodies exhibit less expansion of the lesion area than the patients without these antibodies (provided that the blood-brain barrier was preserved before the insult) (Zerche et al., 2015). Suggesting that natural autoantibodies could also play a protective or repairing role after SCI, a commercial human intravenous IgG preparation—which is a pool of IgGs from thousands of healthy donors containing natural autoantibodies against antigens expressed by neurons, astrocytes, oligodendrocytes, and microglia—is therapeutic when administered immediately after SCI in mice (Brennan et al., 2016). Also, rats vaccinated with modified MBP after SCI present less neurological damage and a better functional recovery (Hauben et al., 2001). However, natural autoantibodies are proposed to be also the origin of pathogenic autoantibodies when the inflammatory response persists in time (Cohen, 2007; Cohen & Cooke, 1986; Nataf, 2017), as occurs in SCI. In this regard, as mentioned above, IgG antibodies from mice with chronic SCI (42 days

TABLE 1 Autoantibodies increased after human SCI.

Target	SCI stage[a]	References
AEBP1	Subacute	Palmers et al. (2016)
ALBU	Acute and subacute	Arevalo-Martin et al. (2018)
ATPA	Acute and subacute	Arevalo-Martin et al. (2018)
CAH2	Acute and subacute	Arevalo-Martin et al. (2018)
CRMP2	Subacute	Hergenroeder et al. (2018)
DHE3	Acute and subacute	Arevalo-Martin et al. (2018)
ENOA	Acute and subacute	Arevalo-Martin et al. (2018)
GalC	Chronic	Taranova et al. (1992)
GAPDH	Acute and subacute	Palmers et al. (2016), Arevalo-Martin et al. (2018)
GFAP	From acute to chronic	Hergenroeder et al. (2016), Arevalo-Martin et al. (2018), Hergenroeder et al. (2018)
GM1 ganglioside	From subacute to chronic	Mizrachi et al. (1983), Wang et al. (1995), Taranova et al. (1992), Hayes et al. (2002), Davies et al. (2007)
HBA	Acute and subacute	Arevalo-Martin et al. (2018)
HBB	Acute and subacute	Arevalo-Martin et al. (2018)
HSP7C	Acute and subacute	Arevalo-Martin et al. (2018)
IgG Fc	From subchronic to chronic	Petrova et al. (1993)
MBP	From acute to chronic	Mizrachi et al. (1983), Zajarías-Fainsod et al. (2012), Arevalo-Martin et al. (2018)
MYEOV2	Subacute	Palmers et al. (2016)
NFL	Acute and subacute	Arevalo-Martin et al. (2018)
NFM	Acute and subacute	Arevalo-Martin et al. (2018)
PEBP1	Acute and subacute	Arevalo-Martin et al. (2018)
PGK1	Acute and subacute	Arevalo-Martin et al. (2018)
PPIA	Acute and subacute	Arevalo-Martin et al. (2018)
PSMD4	Subacute	Palmers et al. (2016)
S100ß	Acute and subacute	Palmers et al. (2016)

AEBP1, adipocyte enhancer-binding protein 1; *ALBU*, albumin; *ATPA*, ATP synthase subunit alpha; *CAH2*, carbonic anhydrase 2; *CRMP2*, collapsing response mediator protein-2; *DHE3*, glutamate dehydrogenase 1; *ENOA*, enolase alpha; *GalC*, galactosylceramidase; *GAPDH*, glyceraldehyde 3-phosphate dehydrogenase; *GFAP*, glial fibrillary acidic protein; *GM1 ganglioside*, monosialotetrahexosylganglioside; *HBA*, hemoglobin subunit alpha; *HBB*, hemoglobin subunit beta; *HSP7C*, heat shock cognate 71 KDa protein; *IgG Fc*, constant fraction of immunoglobulin G; *MBP*, myelin basic protein; *MYEOV2*, myeloma-overexpressed gene 2; *NFL*, neurofilament light; *NFM*, neurofilament intermediate; *PEBP1*, phosphatidylethanolamine-binding protein 1; *PGK1*, phosphoglycerate kinase 1; *PPIA*, peptidylprolyl isomerase A; *PSMD4*, 26S proteasome non-ATPase regulatory subunit 4; *S100-ß*, protein S100-beta.
[a]*Stages: acute, from injury to 7 days after injury. Subacute, 2–6 weeks after injury. Subchronic, 3–6 months after injury. Chronic, more than 1 year after injury.*

after injury) are pathogenic when injected into the spinal cord of intact mice (Ankeny et al., 2009). Also, IgM natural autoantibodies against annexin IV and phospholipids have been shown to be produced by innate-like B1 cells in the peritoneum after SCI in mice and to be pathogenic (Narang et al., 2017).

The levels of autoantibodies after SCI are independent of lesion level and severity

Immunodepression following after SCI is more pronounced when the lesions occur at cervical or high thoracic spinal segments (above the 5th thoracic segment, T5) both in experimental models and in humans (Brommer et al., 2016; Lucin, Sanders, Jones, Malarkey, & Popovich, 2007; Lucin, Sanders, & Popovich, 2009). A detailed explanation about the pathogenic mechanisms underlying this can be found in the chapter "Infections and spinal cord injury: COVID-19 and beyond"

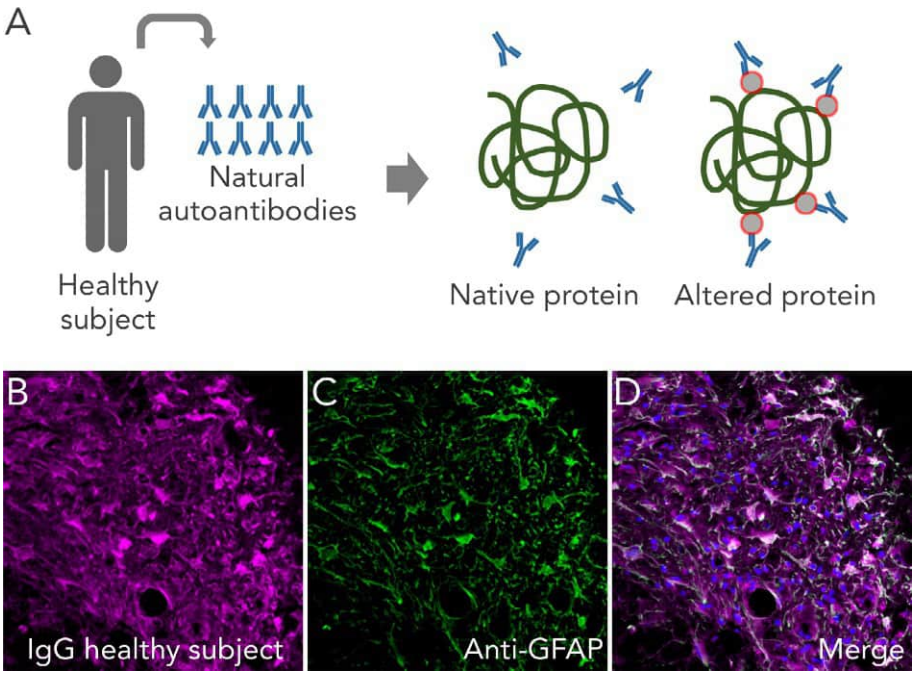

FIG. 2 Natural autoantibodies are preferentially directed against altered proteins. (A) Autoantibodies are normally present in healthy individuals. These naturally occurring autoantibodies (or natural autoantibodies) do not bind to native proteins but to proteins altered under stress conditions such as oxidative damage, inflammation, or cell death. (B) IgG antibodies from healthy human subjects bind to the damaged spinal cord of rats with SCI. (C, D) Among the targets of these natural autoantibodies are antigens expressed by astrocytes (GFAP-positive cells) surrounding the lesion site.

in this same book. Briefly, the spinal sympathetic preganglionic neurons located below the lesion level lose their inhibitory supraspinal descendent input, which results in their overactivation. As a consequence, there is an excessive release of norepinephrine in lymphoid organs, which binds to beta-2-adrenergic receptor on immune cells and drives immunosuppressive responses (Lucin et al., 2007). Since most of the sympathetic innervation of lymphoid organs arises from preganglionic neurons located below T5, lesions above this level result in a greater norepinephrine overflow of lymphoid organs than lesions that partially or totally preserve the normal sympathetic outflow to lymphoid organs. Therefore, it could be reasoned that autoantibody titers might be also affected by the lesion level and, thus, expected that titers should be lower in patients with cervical or high thoracic lesions. However, the autoantibody levels induced by SCI have not been found to be dependent on lesion level by five different studies (Table 2), either comparing patients with tetraplegia and those with paraplegia or comparing lesions above T5 and below T5 (Arevalo-Martin et al., 2018; Davies et al., 2007;

TABLE 2 Association of autoantibody levels with clinical and demographical variables.

Study	Severity (AIS grade)	Lesion level[a]	Gender	Age
Mizrachi et al. (1983)	–		–	–
Hayes et al. (2002)	–*	–		
Davies et al. (2007)		–		
Zajarías-Fainsod et al. (2012)	–*			
Palmers et al. (2016)		–		
Hergenroeder et al. (2018)	–	–		
Arevalo-Martin et al. (2018)	–	–	–	–

AIS, American Spinal Injury Association Impairment Scale.
–, no statistically significant association; +, statistically significant association; –*, differences between AIS grades, but not statistically significant.
[a]*Comparison between tetraplegia and paraplegia in all cases, and additionally above versus below 5th thoracic segment in the study by Arevalo-Martin et al. (2018).*

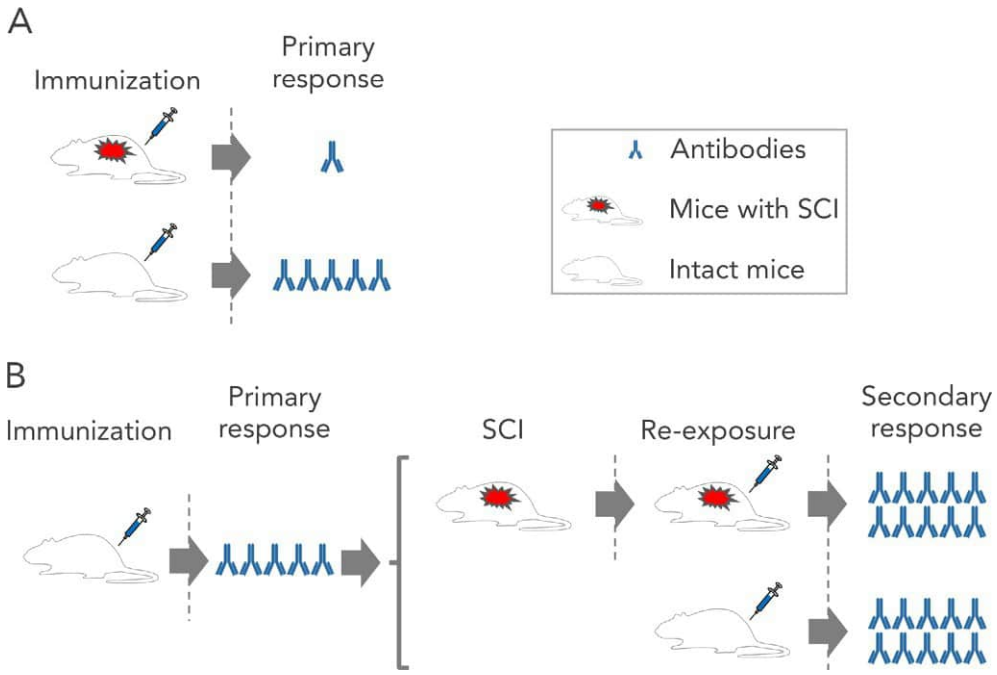

FIG. 3 Secondary antibody responses are preserved after SCI. (A) Primary antibody responses triggered by immunization against new antigens are impaired in mice with SCI. (B) However, the enhanced secondary antibody responses that are triggered after re-exposure to a previously encountered antigen are not different between mice with SCI and intact mice. Antibody levels are indicated by the number of them represented in the figure.

Hayes et al., 2002; Hergenroeder et al., 2018; Palmers et al., 2016). Therefore, the production of autoantibodies after SCI seems to be unsensitive to the main pathological mechanism driving immunodepression after SCI. Among the possible explanations, the B cell subpopulations that produce the autoantibodies elevated in SCI could lack beta-2-adrenergic receptors or these cells may not be reached by sympathetic terminals. Regardless of the molecular mechanism why autoantibodies increase in these otherwise immunodepressed patients, the fact that these antibodies have been identified as pre-existing natural autoantibodies agrees with previous reports demonstrating that SCI in mice preserves secondary humoral responses (increase of pre-existing antibodies) and only impairs primary humoral responses (Fig. 3) (Oropallo et al., 2012).

Also, five studies have reported that autoantibody levels are not associated with lesion severity measured by AIS grade (Table 2) (Arevalo-Martin et al., 2018; Hayes et al., 2002; Hergenroeder et al., 2018; Mizrachi et al., 1983; Zajarías-Fainsod et al., 2012). Among these, two reports have observed that the levels of autoantibodies are different depending on lesion severity, but the differences failed to reach statistical significance (Hayes et al., 2002; Zajarías-Fainsod et al., 2012).

Autoimmune diseases are more frequent in women than men. Although this could lead us to think that sex could make a difference in the autoantibody levels after SCI, these have not been found to be different when comparing by sex (Table 2) (Arevalo-Martin et al., 2018; Mizrachi et al., 1983).

Age is another factor affecting the development of autoimmune diseases, but the levels of autoantibodies after SCI do not vary depending on it (Table 2) (Arevalo-Martin et al., 2018; Mizrachi et al., 1983).

Therefore, data indicate that autoantibody levels rise up after SCI independently of lesion level, severity, gender, and age.

Autoantibodies increased after SCI target both CNS and peripheral antigens

Early studies on the specificities of autoantibodies increased after SCI was carried out by hypothesis-driven methodologies, specifically searching for autoantibodies directed against CNS antigens. With this approach, neurons (targeted by anti-GM1 ganglioside antibodies) and oligodendrocytes (targeted by anti-MBP and anti-GalC antibodies) were proposed as the CNS cellular objectives of a potential SCI-induced autoimmune response (Hayes et al., 2002; Mizrachi et al., 1983; Taranova et al., 1992). But the more recent use of hypothesis-free methodological approaches has expanded the list of autoantibody targets in the CNS to astrocytes (anti-GFAP antibodies) and to proteins that are expressed systemically or that are not considered to be expressed in the CNS (Arevalo-Martin et al., 2018; Hergenroeder et al., 2016; Palmers et al., 2016). Interestingly, this last group of autoantibodies is directed to proteins that seem to be related to secondary disorders occurring

after SCI, like anemia, metabolic alterations, or immune depression. For example, at the acute phase patients suffer from anemia and concomitantly exhibit elevated levels of autoantibodies against hemoglobin alpha (HBA) and beta (HBB) (Arevalo-Martin et al., 2018). Also, the metabolic rate is altered after SCI and patients show increased levels of antibodies against the metabolic enzymes glyceraldehyde 3-phosphate dehydrogenase (GAPDH), phosphoglycerate kinase 1 (PGK1), and enolase alpha (ENOA), as well as against the ATP synthase subunit alpha (ATPA) (Arevalo-Martin et al., 2018; Palmers et al., 2016). And the same applies to the antibody against anti-peptidylprolyl isomerase A (PPIA, also known as cyclophilin A), which targets the receptor for the immunosuppressor cyclosporine (PPIA) in patients who concomitantly suffer from immunodepression (Arevalo-Martin et al., 2018). Even if these antibodies do not play a pathogenic role, their increase could indicate that alterations in their target proteins are involved in the development of the systemic alterations after SCI, providing new research perspectives for these disorders.

Antibody levels elevate after their target antigens get exposed to the immune system or after normally exposed antigens are modified or degraded. Accordingly, among the autoantibody targets reported so far (Table 1) it has been observed that at least ENOA, neurofilament light (NFL), neurofilament intermediate (NFM), GFAP, and MBP elevate in the cerebrospinal fluid (CSF) and blood of patients with SCI, most probably as a consequence of cell damage (Ahadi et al., 2015; Hayakawa et al., 2012; Kuhle et al., 2015; Pouw et al., 2014; Wolf et al., 2014). However, it is no so evident why autoantibodies increase against targets that are not thought to be expressed by CNS cells, like HBA and HBB. A potential explanation is that anti-HBA and anti-HBB antibodies may increase after their antigens are released from erythrocytes accumulated in spinal cord hemorrhagic areas. But it should not be discarded that HBA and HBB have been described to be expressed also by neurons and to play a role in response to injury (Richter, Meurers, Zhu, Medvedeva, & Chesselet, 2009). Regardless of whether hemoglobins come from spinal cord bleeding or by endogenous production, their levels rise up in the CNS after SCI since HBB is detected in the CSF of patients with SCI as early as 1 day after injury (Sengupta et al., 2014). Similarly, antibodies against albumin (ALBU, Table 1), a protein mainly synthesized by the liver, increase after injury. Albumin is normally exposed to the immune system as a freely circulating protein in blood and as a normal constituent of CSF. Therefore, it seems that more likely anti-albumin antibodies could rise due to the modification or degradation of albumin rather than to changes in their blood levels. Accordingly, two of the three albumin isoforms targeted by anti-albumin antibodies exhibit a lower molecular weight than expected (Arevalo-Martin et al., 2018).

Summarizing, in spite that it seems evident to think that autoantibodies that increase after SCI must be triggered by damage to the spinal cord and must drive autoimmune responses against the CNS, it should not be discarded that autoantibody levels could be triggered by damage outside the CNS and could drive autoimmune responses outside the CNS.

Local versus systemic production of autoantibodies

One important question to solve for understanding how autoantibody responses take place after SCI is whether autoantibodies are produced locally, in the damaged spinal cord, or systemically. Supporting that intraspinal production may take place, B cells have been shown to accumulate in the spinal cord of mice with SCI, forming structures similar to lymphoid follicles (Ankeny et al., 2006, 2009). But in humans, a detailed histopathological analysis from the acute to chronic SCI failed to detect B cells infiltrating the spinal cord after SCI neither in injured areas nor in their surroundings (Fleming et al., 2006). In a more recent study, a pronounced B cell infiltration was found only in two cases from the 22 patients evaluated (Zrzavy et al., 2021). Nevertheless, even though if autoantibodies are produced majorly outside the CNS in human SCI, as data suggest, blood-brain barrier is damaged after SCI, so antibodies could rapidly enter into the injured spinal cord. Accordingly, antibodies binding to cell profiles reminiscent of glial cells and neurons are detected in the spinal cord of rats as soon as 1 day after injury (Arevalo-Martin et al., 2018).

Association of autoantibodies with neuropathic pain development

One of the most common secondary complications affecting patients with SCI is the development of neuropathic pain, caused among other factors by the inflammatory response in the peripheral and central nervous system. In fact, abrogating the inflammatory response in experimental models ameliorates neuropathic pain. Thus, since autoantibodies are specific biomarkers of the immune responses taking place, it is reasonable to think that some of the increased autoantibodies could serve as biomarkers of neuropathic pain. Accordingly, anti-GM1 ganglioside antibodies have been related to the development of neuropathic pain (Davies et al., 2007), since patients suffering from it exhibit higher levels of anti-GM1 antibodies than patients without it. However, this relationship is not statistically significant after adjusting for severity (measured as AIS grade) and paraplegia versus tetraplegia in multivariate linear regression models.

Also, the levels of anti-GFAP antibodies in the acute/subacute phase (at 16 ± 7 days after injury) have been shown to be significantly associated with the development of neuropathic pain (Hergenroeder et al., 2018). In fact, if instead of considering the raw anti-GFAP autoantibody levels, a titer of 1:128 is established as a threshold to classify patients among anti-GFAP-positive or -negative, the odds of developing neuropathic pain increase by almost eight times in anti-GFAP-positive patients (Hergenroeder et al., 2018). In addition, although anti-collapsing response mediator protein-2 (CRMP2) antibodies are not useful to predict neuropathic pain development on their own, they improve the predictive ability of anti-GFAP antibodies. The odds of developing neuropathic pain increases by 9.5 times in patients positive for anti-GFAP and/or anti-CRMP2 antibodies, remaining significant after adjusting for clinical and demographical variables. Whether anti-GFAP antibodies are involved in neuropathic pain pathophysiology or are just biomarkers is a question that remains unsolved.

Roles of the autoantibodies increased after SCI in other pathologies

In spite that there is a lack of a direct experimental demonstration about the pathogenic role of autoantibodies in human SCI, there is evidence for a pathogenic role of some of them in other neurological disorders. As commented earlier, anti-GM1 ganglioside antibodies were proposed to underlie the inhibition of neuritogenesis exerted by sera of patients with SCI on neuron cell cultures, but a direct evidence of anti-GM1 antibodies underlying this effect has not been provided (Mizrachi et al., 1983). However, anti-GM1 antibodies are known blockers of nerve currents and are associated with paralysis in Guillen-Barre syndrome, post-polio syndrome, and other neurological disorders, including amyotrophic lateral sclerosis (Illa et al., 1995; Takigawa et al., 1995; Yu & Usuki, 2014).

Recently, in 2016, a new meningoencephalomyelitis called Autoimmune Glial Fibrillary Acidic Protein Astrocytopathy was described (Fang et al., 2016). This pathology is characterized by high levels of pathogenic anti-GFAP autoantibodies and astrocyte damage (Kunchok, Zekeridou, & McKeon, 2019; Yang et al., 2019; Zhou, Yu, & Hong, 2021). Noteworthy, this pathological condition has been reported that may exhibit clinical characteristics of Brown-Sequard syndrome (Zhou et al., 2021).

After SCI, a progressive degradation of myelin is observed in the spinal cord of patients (Buss et al., 2004). Interestingly, anti-MBP antibodies from multiple sclerosis (MS) patients were shown to cleave MBP peptides and cause myelin damage (Ponomarenko et al., 2006a). Moreover, the hydrolytic activity of anti-MBP antibodies correlates with the Expanded Disability Status Scale (EDSS) used to quantify disability in MS patients (Ponomarenko et al., 2006b).

Also, anti-GalC antibodies open Ca^{2+} channels in oligodendrocytes that lead to cytoskeleton reorganization and contraction of myelin sheets (Dyer & Benjamins, 1990). In vivo, the implantation of a hybridoma secreting anti-GalC antibodies in the spinal cord dorsal column of early postnatal rats impairs myelination in the surroundings of the implant (Rosenbluth, Liu, Guo, & Schiff, 1994).

Overall, evidence support the notion that autoantibodies increasing after SCI may have a physiopathological role and constitute new therapeutic targets.

Applications to other areas of neuroscience

In this chapter, we have reviewed the current knowledge about the origin, specificities, and the potential physiopathological role of the autoantibodies that increases after spinal cord injury (SCI). Regarding their origin, we have discussed the data providing evidence that the increased autoantibodies are pre-existing natural antibodies. In other neurological diseases that share physiopathological mechanisms with SCI, like stroke, it has been previously reported that autoantibodies that are triggered after the insult are natural antibodies that depending on the previous state of the blood-brain barrier may act as a counteractive response or as a pathogenic factor (Zerche et al., 2015). Despite its clinical relevance, the idea of pre-existing antibodies in healthy subjects is still a controversial question (Ehrenreich, 2018). The observations performed in SCI may help to further support that the elevation of natural autoantibodies in neurological diseases is not anecdotic and should be taken into consideration for clinical studies.

Also, immunodepression and elevated levels of autoantibodies have been described to occur after stroke and in traumatic brain injuries (Javidi & Magnus, 2019). Both phenomena are classically considered to be mutually exclusive. However, the observations that after SCI pre-existing humoral immune responses are preserved and that increased autoantibodies are pre-existing natural antibodies may help to understand why immunodepression and elevated levels of autoantibodies also co-occur after stroke and traumatic head injuries.

Mini-dictionary of terms

AIS grade: One of the five categories included in the American Spinal Injury Association (ASIA) of severity of spinal cord injury based on the assessments following the International Standards for the Neurological Classification of Spinal Cord Injury (ISNCSCI). It includes four categories for patients with sensorimotor impairments, AIS A to AIS D, and an additional category, AIS E, for patients recovering sensorimotor function evaluated by ISNCSCI.

Autoantibodies: Antibodies recognizing self-antigens. May drive destructive immune responses against self-constituents.

Beta-2-adrenergic receptor: G protein-coupled receptor for norepinephrine. Expressed in multiple cell types, including leukocytes.

Galactosylceramidase (GalC): Enzyme that hydrolyzes the galactose ester bond from galactosylceramidase and other lipids in the cellular membrane. Expressed by oligodendrocytes in the central nervous system.

Glial fibrillary acidic protein (GFAP): Type III intermediate filament, constituent of astrocytes cytoskeleton.

GM1 ganglioside: Ganglioside involved in the normal development of central nervous system, in neural plasticity and neural repair. Its therapeutic potential has been tested in several neurological disorders, including spinal cord injury.

Immunodepression: Strong diminution of the immune responses. Clinically manifested as suffering from higher susceptibility to infections.

Myelin basic protein (MBP): A major protein component of myelin sheaths in the central and peripheral nervous system. Located in the myelin major dense lines, necessary for the correct packaging of myelin.

Neuropathic pain: Pain occurring after damage to the central or peripheral nervous systems that is unrelated to the existence of a nociceptive stimulus. Frequent among spinal cord injury patients and usually described as burning sensation and hypersensitive to touch.

Norepinephrine: Also called noradrenaline, is a neurotransmitter of the catecholamine family secreted by post-ganglionic sympathetic neurons. It may also act as a hormone.

Primary humoral responses: Antibody-mediated immune response occurring against an antigen when it is first encountered. After several steps and a period of time of 14–21 days, IgG-specific antibodies are generated.

Secondary humoral responses: Antibody-mediated immune response against an antigen previously recognized. These responses are much faster than primary responses since specific IgGs were already previously generated in the course of the first encounter with the antigen.

Key facts of autoantibodies

- Autoantibodies are antibodies that instead of being directed against external components (such as microorganisms) are directed to normal components of the body.
- Healthy individuals present autoantibodies called natural autoantibodies (shortening of naturally occurring autoantibodies).
- Natural autoantibodies play a role in the maintenance and repair of body tissues as well as in the control of immune reactions.
- Intravenous immunoglobulins are pools of antibodies extracted from thousands of healthy donors that are enriched in natural autoantibodies and are used as therapy for both autoimmune diseases and immunodepression.
- After persistent exposure to their molecular target, natural autoantibodies may give rise to pathogenic autoantibodies, i.e., autoantibodies that drive immune reactions against self-structures.
- Not all autoantibodies originate from natural autoantibodies. In this regard, a commonly proposed origin of autoantibodies are antibodies directed against microorganisms that cross-react with self-structures.
- Autoantibodies are active players in numerous autoimmune diseases, like multiple sclerosis, systemic lupus erythosus, or rheumatoid arthritis.

Summary points

- The levels of autoantibodies targeting 24 different antigens are increased in patients with spinal cord injury.
- The increased autoantibodies target both central nervous system specific antigens as well as systemic antigens.
- Autoantibody levels are independent of lesion level, severity, age, and gender.
- The increased autoantibodies have been shown to be, at least in the early phases, natural antibodies.

- IgG autoantibodies extracted from mice with chronic spinal cord injury (42 days after injury) elicit a necrotic inflammatory lesion when injected into the spinal cord of intact mice.
- Currently, there is not a direct demonstration of the physiopathological role of the autoantibodies that increase after human SCI. However, the levels of anti-GFAP antibodies are related (with statistical significance after adjusting for clinical and demographical variables) to the development of neuropathic pain in patients with spinal cord injury.
- Some of the autoantibodies elevated after spinal cord injury are known to be pathogenic in other neurological diseases.

References

Abou-El-Hassan, H., Bsat, S., Sukhon, F., Assaf, E. J., Mondello, S., Kobeissy, F., et al. (2020). Protein degradome of spinal cord injury: Biomarkers and potential therapeutic targets. *Molecular Neurobiology*, *57*, 2702–2726.

Ahadi, R., Khodagholi, F., Daneshi, A., Vafaei, A., Mafi, A. A., & Jorjani, M. (2015). Diagnostic value of serum levels of GFAP, pNF-H, and NSE compared with clinical findings in severity assessment of human traumatic spinal cord injury. *Spine*, *40*, E823–E830.

Ankeny, D. P., Guan, Z., & Popovich, P. G. (2009). B cells produce pathogenic antibodies and impair recovery after spinal cord injury in mice. *Journal of Clinical Investigation*, *119*, 2990–2999.

Ankeny, D. P., Lucin, K. M., Sanders, V. M., McGaughy, V. M., & Popovich, P. G. (2006). Spinal cord injury triggers systemic autoimmunity: Evidence for chronic B lymphocyte activation and lupus-like autoantibody synthesis. *Journal of Neurochemistry*, *99*, 1073–1087.

Arevalo-Martin, A., Grassner, L., Garcia-Ovejero, D., Paniagua-Torija, B., Barroso-Garcia, G., Arandilla, A. G., et al. (2018). Elevated autoantibodies in subacute human spinal cord injury are naturally occurring antibodies. *Frontiers in Immunology*, *9*, 2365.

Brennan, F. H., Kurniawan, N. D., Vukovic, J., Bartlett, P. F., Käsermann, F., Arumugam, T. V., et al. (2016). IVIg attenuates complement and improves spinal cord injury outcomes in mice. *Annals of Clinical and Translational Neurology*, *3*, 495–511.

Brommer, B., Engel, O., Kopp, M. A., Watzlawick, R., Müller, S., Prüss, H., et al. (2016). Spinal cord injury-induced immune deficiency syndrome enhances infection susceptibility dependent on lesion level. *Brain*, *139*, 692–707.

Buss, A., Brook, G. A., Kakulas, B., Martin, D., Franzen, R., Schoenen, J., et al. (2004). Gradual loss of myelin and formation of an astrocytic scar during Wallerian degeneration in the human spinal cord. *Brain*, *127*, 34–44.

Cohen, I. R. (2007). Biomarkers, self-antigens and the immunological homunculus. *Journal of Autoimmunity*, *29*, 246–249.

Cohen, I. R., & Cooke, A. (1986). Natural autoantibodies might prevent autoimmune disease. *Immunology Today*, *7*, 363–364.

Davies, A. L., Hayes, K. C., & Dekaban, G. A. (2007). Clinical correlates of elevated serum concentrations of cytokines and autoantibodies in patients with spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *88*, 1384–1393.

Dyer, C. A., & Benjamins, J. A. (1990). Glycolipids and transmembrane signaling: Antibodies to galactocerebroside cause an influx of calcium in oligodendrocytes. *Journal of Cell Biology*, *111*, 625–633.

Ehrenreich, H. (2018). Autoantibodies against N-methyl-d-aspartate receptor 1 in health and disease. *Current Opinion in Neurology*, *31*, 306–312.

Fang, B., McKeon, A., Hinson, S. R., Kryzer, T. J., Pittock, S. J., Aksamit, A. J., et al. (2016). Autoimmune glial fibrillary acidic protein astrocytopathy: A novel meningoencephalomyelitis. *JAMA Neurology*, *73*, 1297–1307.

Fiskesund, R., Stegmayr, B., Hallmans, G., Vikstrom, M., Weinehall, L., de Faire, U., et al. (2010). Low levels of antibodies against phosphorylcholine predict development of stroke in a population-based study from Northern Sweden. *Stroke*, *41*, 607–612.

Fleming, J. C., Norenberg, M. D., Ramsay, D. A., Dekaban, G. A., Marcillo, A. E., Saenz, A. D., et al. (2006). The cellular inflammatory response in human spinal cords after injury. *Brain*, *129*, 3249–3269.

Hauben, E., Agranov, E., Gothilf, A., Nero, U., Cohen, A., Smirnov, I., et al. (2001). Posttraumatic therapeutic vaccination with modified myelin self-antigen prevents complete paralysis while avoiding autoimmune disease. *Journal of Clinical Investigation*, *108*, 591–599.

Hayakawa, K., Okazaki, R., Ishii, K., Ueno, T., Izawa, N., Tanaka, Y., et al. (2012). Phosphorylated neurofilament subunit NF-H as a biomarker for evaluating the severity of spinal cord injury patients, a pilot study. *Spinal Cord*, *50*, 493–496.

Hayes, K. C., Hull, T. C. L., Delaney, G. A., Potter, P. J., Sequeira, K. A. J., Campbell, K., et al. (2002). Elevated serum titers of proinflammatory cytokines and CNS autoantibodies in patients with chronic spinal cord injury. *Journal of Neurotrauma*, *19*, 753–761.

Hergenroeder, G. W., Moore, A. N., Schmitt, K. M., Redell, J. B., & Dash, P. K. (2016). Identification of autoantibodies to glial fibrillary acidic protein in spinal cord injury patients. *Neuroreport*, *27*, 90–93.

Hergenroeder, G. W., Redell, J. B., Choi, H. A., Schmitt, L. H., Donovan, W., Francisco, G. E., et al. (2018). Increased levels of circulating GFAP and CRMP2 autoantibodies in the acute stage of spinal cord injury predict the subsequent development of neuropathic pain. *Journal of Neurotrauma*, *35*, 2530–2539.

Illa, I., Leon-Monzon, M., Agboatwalla, M., Ilyas, A., Latov, N., & Dalakas, M. C. (1995). Antiganglioside antibodies in patients with acute polio and post-polio syndrome. *Annals of the New York Academy of Sciences*, *753*, 374–377.

Javidi, E., & Magnus, T. (2019). Autoimmunity after ischemic stroke and brain injury. *Frontiers in Immunology*, *10*, 686.

Kidd, J. G., & Friedewald, W. F. (1942). A natural antibody that reacts in vitro with a sedimentable constituent of normal tissue cells : II. Specificity of the phenomenon: General discussion. *Journal of Experimental Medicine*, *76*, 557–578.

Kuhle, J., Gaiottino, J., Leppert, D., Petzold, A., Bestwick, J. P., Malaspina, A., et al. (2015). Serum neurofilament light chain is a biomarker of human spinal cord injury severity and outcome. *Journal of Neurology, Neurosurgery and Psychiatry*, *86*, 273–279.

Kunchok, A., Zekeridou, A., & McKeon, A. (2019). Autoimmune glial fibrillary acidic protein astrocytopathy. *Current Opinion in Neurology*, *32*, 452–458.

Lucin, K., Sanders, V., Jones, T., Malarkey, W., & Popovich, P. (2007). Impaired antibody synthesis after spinal cord injury is level dependent and is due to sympathetic nervous system dysregulation. *Experimental Neurology*, *207*, 75–84.

Lucin, K. M., Sanders, V. M., & Popovich, P. G. (2009). Stress hormones collaborate to induce lymphocyte apoptosis after high level spinal cord injury. *Journal of Neurochemistry*, *110*, 1409–1421.

Lutz, H. U. (2007). Homeostatic roles of naturally occurring antibodies: An overview. *Journal of Autoimmunity*, *29*(4), 287–294. https://doi.org/10.1016/j.jaut.2007.07.007.

Mizrachi, B. Y., Ohry, A., Aviel, A., Rozin, R., Brooks, M. E., & Schwartz, M. (1983). Systemic humoral factors participating in the course of spinal cord injury. *Paraplegia*, *21*, 287–293.

Narang, A., Qiao, F., Atkinson, C., Zhu, H., Yang, X., Kulik, L., et al. (2017). Natural IgM antibodies that bind neoepitopes exposed as a result of spinal cord injury, drive secondary injury by activating complement. *Journal of Neuroinflammation*, *14*, 120.

Nataf, S. (2017). Autoimmunity as a driving force of cognitive evolution. *Frontiers in Neuroscience*, *11*, 582.

Oropallo, M. A., Held, K. S., Goenka, R., Ahmad, S. A., O'Neill, P. J., Steward, O., et al. (2012). Chronic spinal cord injury impairs primary antibody responses but spares existing humoral immunity in mice. *Journal of Immunology*, *188*, 5257–5266.

Palmers, I., Ydens, E., Put, E., Depreitere, B., Bongers-Janssen, H., Pickkers, P., et al. (2016). Antibody profiling identifies novel antigenic targets in spinal cord injury patients. *Journal of Neuroinflammation*, *13*, 1–11.

Petrova, N. V., Ponomaryova, A. M., Alyoshkin, V. A., Eliseyev, A. T., & Yumashev, G. S. (1993). Serum rheumatoid factors in spinal cord injury patients. *Paraplegia*, *31*, 265–268.

Ponomarenko, N. A., Durova, O. M., Vorobiev, I. I., Belogurov, A. A., Kurkova, I. N., Petrenko, A. G., et al. (2006a). Autoantibodies to myelin basic protein catalyze site-specific degradation of their antigen. *Proceedings of the National Academy of Sciences of the United States of America*, *103*, 281–286.

Ponomarenko, N. A., Durova, O. M., Vorobiev, I. I., Belogurov, A. A., Telegin, G. B., Suchkov, S. V., et al. (2006b). Catalytic activity of autoantibodies toward myelin basic protein correlates with the scores on the multiple sclerosis expanded disability status scale. *Immunology Letters*, *103*, 45–50.

Pouw, M. H., Kwon, B. K., Verbeek, M. M., Vos, P. E., Van Kampen, A., Fisher, C. G., et al. (2014). Structural biomarkers in the cerebrospinal fluid within 24 h after a traumatic spinal cord injury: A descriptive analysis of 16 subjects. *Spinal Cord*, *52*, 428–433.

Richter, F., Meurers, B. H., Zhu, C., Medvedeva, V. P., & Chesselet, M. F. (2009). Neurons express hemoglobin α- and β-chains in rat and human brains. *Journal of Comparative Neurology*, *515*, 538–547.

Rosenbluth, J., Liu, Z., Guo, D., & Schiff, R. (1994). Inhibition of CNS myelin development in vivo by implantation of anti-GalC hybridoma cells. *Journal of Neurocytology*, *23*, 699–707.

Schwartz-Albiez, R., Monteiro, R. C., Rodriguez, M., Binder, C. J., & Shoenfeld, Y. (2009). Natural antibodies, intravenous immunoglobulin and their role in autoimmunity, cancer and inflammation. *Clinical and Experimental Immunology*, *158*, 43–50.

Sengupta, M. B., Basu, M., Iswarari, S., Mukhopadhyay, K. K., Sardar, K. P., Acharyya, B., et al. (2014). CSF proteomics of secondary phase spinal cord injury in human subjects: Perturbed molecular pathways post injury. *PLoS One*, *9*, e110885.

Takigawa, T., Yasuda, H., Kikkawa, R., Shigeta, Y., Saida, T., & Kitasato, H. (1995). Antibodies against GM1 ganglioside affect K+ and NA+ currents in isolated rat myelinated nerve fibers. *Annals of Neurology*, *37*, 436–442.

Taranova, N. P., Makarov, A. I., Amelina, O. A., Luchakova, O. S., Loboda, E. B., & Leikin, I. B. (1992). The production of autoantibodies to nerve tissue glycolipid antigens in patients with traumatic spinal cord injuries. *Zhurnal Voprosy Neĭrokhirurgii Imeni N. N. Burdenko*, *4-5*, 21–24.

Wang, R., Chen, J., Zhou, S., Li, C., Yuang, G., Xu, W., et al. (1995). Enzyme-linked immunoadsorbent assays for myelin basic protein and antibodies to myelin basic protein in serum and CSF of patients with diseases of the nervous system. *Hua Xi Yi Ke Da Xue Xue Bao*, *26*, 131–134.

Wolf, H., Krall, C., Pajenda, G., Leitgeb, J., Bukaty, A. J., Hajdu, S., et al. (2014). Alterations of the biomarker S-100B and NSE in patients with acute vertebral spine fractures. *Spine Journal*, *14*, 2918–2922.

Yang, X., Huang, Q., Yang, H., Liu, S., Chen, B., Liu, T., et al. (2019). Astrocytic damage in glial fibrillary acidic protein astrocytopathy during initial attack. *Multiple Sclerosis and Related Disorders*, *29*, 94–99.

Yu, R. K., & Usuki, S. (2014). Human anti-glycosphingolipids antibodies in Guillain-Barre syndrome. In Y. Shoenfeld, P. L. Meroni, & M. E. Gershwin (Eds.), *Autoantibodies* (3rd ed., pp. 581–594). Elsevier.

Zajarías-Fainsod, D., Carrillo-Ruiz, J., Mestre, H., Grijalva, I., Madrazo, I., & Ibarra, A. (2012). Autoreactivity against myelin basic protein in patients with chronic paraplegia. *European Spine Journal*, *21*, 964–970.

Zerche, M., Weissenborn, K., Ott, C., Dere, E., Asif, A. R., Worthmann, H., et al. (2015). Preexisting serum autoantibodies against the NMDAR subunit NR1 modulate evolution of lesion size in acute ischemic stroke. *Stroke*, *46*, 1180–1186.

Zhou, Z. H., Yu, Q. Y., & Hong, M. F. (2021). Autoimmune glial fibrillary acidic protein astrocytopathy with the detection of anti-GM3 and anti-GM4 IgG antibodies, masquerading as brown-sequared syndrome. *JAMA Neurology*, *78*, 115–116. Online ahead of print.

Zrzavy, T., Schwaiger, C., Wimmer, I., Berger, T., Bauer, J., Butovsky, O., et al. (2021). Acute and non-resolving inflammation associate with oxidative injury after human spinal cord injury. *Brain*, *144*, 144–161. awaa360.

Chapter 21

Calpain role in the pathophysiology of spasticity after spinal cord injury

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List of abbreviations

$[Cl^-]_i$	intracellular chloride concentration
AIS	axonal initial segment
Ca^{2+} PIC or I_{CaP}	calcium persistent inward current
$Ca_V1.3$	voltage-gated calcium channel 1.3
CPG	central pattern generator
E_{Cl}^-	chloride equilibrium potential
$GABA_A$	γ-aminobutyric acid type A receptor
KCC2	potassium-chloride cotransporter 2
Na^+PIC or I_{NaP}	sodium persistent inward current
$Na_V1.6$	voltage-gated sodium channel 1.6
PEST	proline, glutamic acid, serine, threonine
PICs	persistent inward currents
ROS	reactive oxygen species
SCI	spinal cord injury

Introduction

Spinal cord injury (SCI) is a major cause of permanent disability with physical and psychological secondary complications for patients (Table 1). Neurological damage after SCI occurs in two phases, referred to as primary and secondary injury, characterized by peculiar cellular and molecular modifications of the spinal microenvironment. The primary SCI is the direct result of the initial mechanical trauma that induces cell death within the lesion epicenter. It additionally causes anatomical disconnection with axon tracts along with the lesion undergoing *Wallerian degeneration* (Hill, Beattie, & Bresnahan, 2001). Vascularization is also disrupted and the reintroduction of oxygen to ischemic areas after surgical decompression of the spinal cord instigates *reperfusion injury* leading to oxidative damage and the release of reactive oxygen species (ROS) that further contribute to cell death and inflammation (Kalogeris, Baines, Krenz, & Korthuis, 2012).

The secondary SCI lasts until the *glial scar* appears and it dramatically expands the primary injury from the lesion epicenter into the adjacent spinal segments. It occurs due to a variety of concomitant factors, such as hemorrhage, ischemia, excitotoxicity, inflammation, that exacerbate neurological deficits and outcomes. The inflammatory response is supported by activated microglia and infiltrating immune cells that easily cross the disrupted blood-spinal cord barrier and massively release pro-inflammatory cytokines and chemo-attractant molecules. Inflammatory processes also contribute to ROS formation, which causes DNA oxidative stress, protein oxidation, and lipid peroxidation, further promoting cellular death (Hall, Wang, Bosken, & Singh, 2016; Liu et al., 2020). In turn, damaged cells release excitatory amino acids, such as glutamate and aspartate, which overexcite neighboring neurons and trigger a highly disruptive process named *excitotoxicity*. In addition, a loss of ionic homeostasis is established, with intracellular calcium concentration increasing and persisting high for long periods (Fan et al., 2018). Lastly, hypercalcemia triggers a series of destructive events, including mitochondrial dysfunction, cell death, ROS production, acidosis, activation of calcium-dependent enzymes like calpains.

Cellular, Molecular, Physiological, and Behavioral Aspects of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822427-4.00021-6

TABLE 1 Secondary conditions after spinal cord injury (SCI).

Physical conditions after SCI	Nonphysical conditions after SCI
Spinal shock	Sleep and circadian rhythm disorders
Spasticity	Depression
Autonomic dysreflexia	Anxiety
Orthostatic hypotension	Posttraumatic stress disorder
Bradycardia	
Thermal dysregulation	
Respiratory problems	
Bladder dysfunction	
Urinary tract infections	
Bowel dysfunction	
Sexual dysfunction	
Pregnancy complications	
Osteoporosis and osteoporotic limb fractures	
Joint and muscle pain	
Neuropathic pain (at and below level)	
Pressure ulcers	

Secondary conditions impact health and psychosocial well-being in individuals with SCI.

Hereinafter, we will focus on spasticity, one of the main pathophysiological consequences of SCI. We will present an overview of principal animal models for the study of this highly impairing condition. We will then extensively describe spinal changes taking place after SCI and leading to spasticity. This will be finally followed by a discussion of our recent studies on calpains, a family of calcium-activated proteases, as new therapeutic targets against spasticity.

Spasticity after spinal cord injury (SCI)

Spasticity is a pathological condition related to several neurological disorders inducing a primary and secondary injury of the motor system. The classical definition of spasticity states that it is a sensory-motor disorder characterized by heightened muscle tone (hypertonia) due to a velocity-dependent increase in tonic stretch reflexes (Lance, 1980). In other words, the faster a muscle stretch is performed, the higher the muscle resistance will be, showing the characteristic velocity-dependence of spasticity that results from abnormal spinal processing of proprioceptive input.

After SCI there is a 60–80% risk of developing spasticity one-year postinjury (Adams & Hicks, 2005), hence spasticity directly correlates with a significant economic burden. The time course of the disease is characterized by an initial period of flaccid muscle paralysis and a failure or depression of spinal reflexes below the level of the injury called *spinal shock* (Atkinson & Atkinson, 1996). Then, maladaptive mechanisms promoting generalized spinal hyperexcitability take place and typical clinical signs of spasticity appear, including pathological reflexes (or hyperreflexia), clonus (involuntary and rhythmic muscular contractions), spasms (involuntary contraction of a muscle or group of muscles), and hypertonia, that lead to muscle alterations and joint deformations.

There are several diagnostic tools for the measurement of spasticity, such as the Ashworth scale. However, clinical diagnosis is still operator-sensitive, lacks reliability, and does not provide detailed validation studies of such tools in the literature. This leads to erroneous management of spastic patients who likely undergo misclassification or delayed-treatment administration. The most adopted therapeutic strategy concerns the use of oral antispastic medications, which show limited effectiveness and various systemic side effects, especially in cases of severe and drug-resistant spasticity. Thus, systematic and in-depth investigations are required, by recurring to laboratory animal models.

Animal models of spasticity after SCI

Preclinical animal models of spasticity provide an essential tool to uncover pathological processes and to identify new and effective therapeutic strategies. Rodents are the most commonly used species in preliminary studies aimed at relating signs of sensory-motor dysfunction to network, cellular and molecular mechanisms (Sharif-Alhoseini et al., 2017). Rat models are relatively inexpensive, readily available having high reproductive rates, easy to handle and care, with a well-understood anatomy and pathology progress that mimics the human condition. Mice have the additional advantage of allowing for genetic manipulations and advanced optical techniques (e.g., optogenetics and calcium imaging) of identified neuron subpopulations, whereas the generation of transgenic models in rats is very limited.

Several rodent models have been developed in adult animals for the study of spasticity. Complete transection of the spinal cord is the most extensively used type of injury to induce spasticity, since it allows evoking long-lasting clinical symptoms closely resembling the human pathology, it is relatively easy to perform and very well reproducible. Our team has been investigating pathophysiological mechanisms of spasticity in a complete SCI model at a low thoracic level (T8-T9) in adult rats (Boulenguez et al., 2010; Brocard et al., 2016; Sadlaoud et al., 2020). This kind of injury causes complete paralysis of the hindlimbs, with animals using their forelimbs to move. As a result of the severe sensory-motor impairment, animals show co-contractions of antagonist muscles of the hindlimb that faithfully mimic clinical symptoms (Fig. 1A). Autonomic dysfunctions are also present and attentive caregiving is required, such as daily assisted bladder emptying, treatment of urinary infections and sores, etc. To preserve normal locomotor function and avoid autonomic signs, other groups opt for a sacral transection (S2 level) in adult rats, which evokes a spastic syndrome restricted to the tail muscles (Bennett et al., 1999). Importantly, the reduced diameter of the sacral spinal cord makes it viable for in vitro recordings of intracellular activities (Bennett, Li, & Siu, 2001), whereas big limitations are encountered in maintaining alive the lumbar spinal cord of adult animals ex vivo. To combine electrophysiology with genetic tools, the model of sacral SCI has recently been translated to adult mice (Bellardita, Marcantoni, Löw, & Kiehn, 2018), allowing to clarify mechanisms underlying muscle spasms after chronic SCI (Bellardita et al., 2017) and to identify potential therapeutic targets to prevent spasticity (Marcantoni et al., 2020).

Neonatal rodent models are also available for the study of spasticity. We have previously described a highly reproducible model where a complete transection is performed at T8-T9 spinal level in neonate rats at birth (Boulenguez et al., 2010; Brocard et al., 2016; Plantier et al., 2019). Interestingly, in neonates signs of spasticity emerge 4–5 days after SCI (Fig. 1B), with spinal hyperexcitability appearing already 48 h postinjury in the sublesional spinal cord (Plantier et al., 2019). On the contrary, adult animals undergo spinal shock during acute SCI and several weeks are necessary for spasticity to be firmly established (Bellardita et al., 2017; Bennett et al., 1999; Corleto et al., 2015). Therefore, the early appearance of

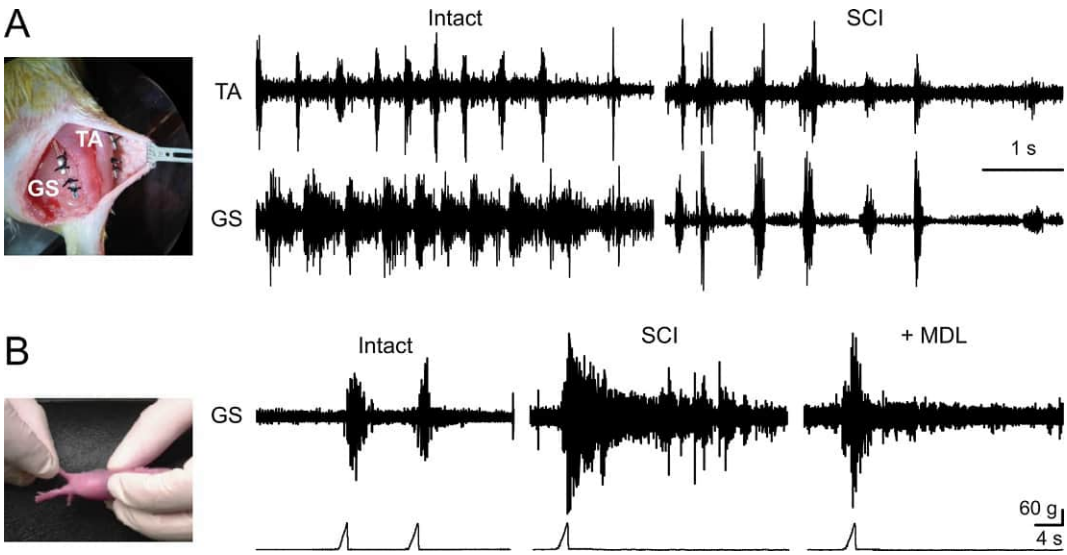

FIG. 1 Muscle spasms in animal models of spasticity after SCI. Electromyographic activity of hindlimb muscles recorded in adult rats (A), showing alternated contractions between antagonist muscles of the hindlimb in intact animals and co-contractions in paraplegic rats after SCI. In neonates (B), muscle activity was evoked by pressing the tail on a calibrated platform, and calpain inhibition with MDL28170 reduced huge muscle responses induced by the lesion. (*TA*, tibialis anterior; *GS*, gastrocnemius). *Panel (B): modified from Plantier, V., Sanchez-Brualla, I., Dingu, N., Brocard, C., Liabeuf, S., Gackière, F., et al. (2019) Calpain fosters the hyperexcitability of motoneurons after spinal cord injury and leads to spasticity*. eLife, *8, e51404*.

spasticity after SCI makes neonatal models very appealing, since they allow for collecting data in a quite shorter time. The greater viability for in vitro recordings and the almost unneeded postsurgical care should also be taken into account.

Network alterations contributing to spasticity after SCI

Animal models of spasticity allow shedding some light on the maladaptive plasticity of spinal networks. In in vitro spinal cords isolated at postnatal day 4/5 from SCI neonates, we observe a dramatic increase in spinal excitability, both in terms of spontaneous activity and evoked reflexes, strongly linked to spasticity (Fig. 2A–C; Plantier et al., 2019).

Spontaneous activities generally correspond to big bursts of uncorrelated tonic activity recorded as a network output from spinal ventral roots, collecting efferent fibers of α-motoneurons (Fig. 2B). Their origin is unclear since the spinal circuits responsible for their emergence are unknown. Sometimes spontaneous bursts appear as oscillatory rhythmic activities in lumbar ventral roots (Fig. 2B'). Given that the lumbar spinal nerves are responsible for muscle innervation of the hindlimbs, we assume that this oscillatory activity closely resembling *locomotor-like episodes* might likely arise from spinal networks belonging to the *central pattern generator* (CPG) for locomotion. This observation confirms a generalized hyperexcitability of the spinal cord, where circuits usually inactive like the CPG, that require pharmacological or electrical stimuli to be triggered, become spontaneously activated as a result of network plastic changes induced by the lesion. Furthermore, we can speculate that the clinical correlate of these big oscillatory bursts might be the rhythmic muscle contractions observed during clonus, whereas nonoscillatory bursts might correspond to involuntary muscle spasms. Indeed, the massive and prolonged activation of motoneuron pools is likely to induce a large release in acetylcholine at the neuromuscular junction promoting muscle fiber contraction compatible with spasticity symptoms.

Pathological mechanisms of exaggerated spinal reflexes are better understood and they relate to abnormal processing of proprioceptive input after SCI. Hyperexcitable reflex activities are characteristic in spasticity since several inhibitory pathways lose their regulatory role. Spastic reflexes typically arise as long responses lasting several seconds after stimulation and showing a huge polysynaptic component, referred to as *hyperreflexia* (Fig. 2C). Notably, long-lasting reflexes cannot be recorded during spinal shock in adult spinalized animals, neither as muscle spasms (Bennett, Sanelli, Cooke, Harvey, & Gorassini, 2004) nor as ventral spinal activities (Li, Harvey, Li, & Bennett, 2004), and at least a 2 -week period after SCI is required for their emergence. As previously remarked, neonates do not undergo areflexia, thus they present

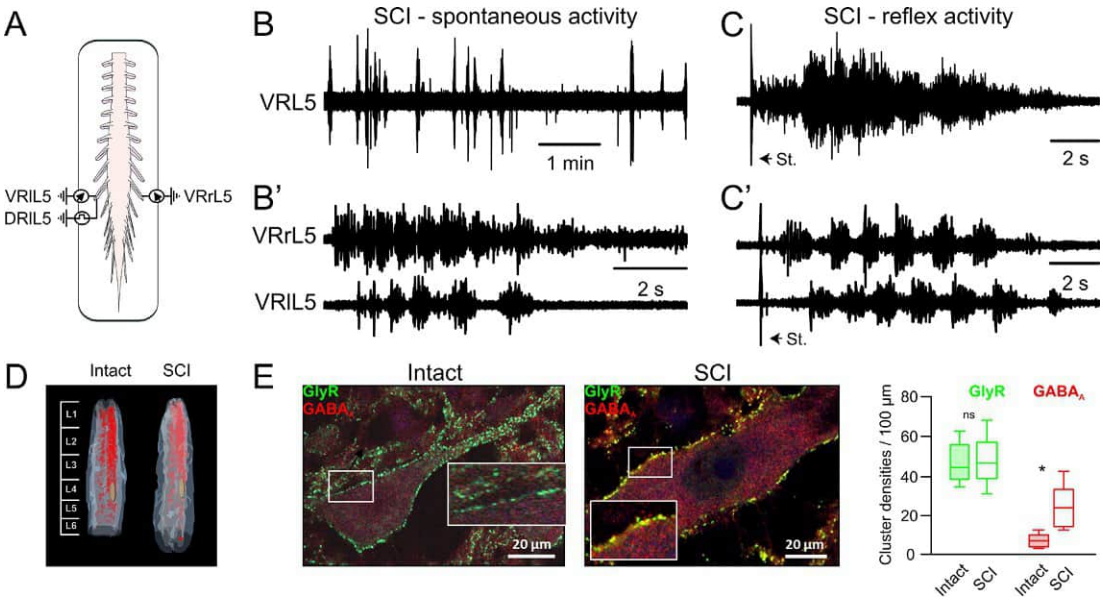

FIG. 2 Spinal network modifications related to spasticity after SCI. Ventral root recordings from isolated spinal cords in vitro (A), depicting exaggerated spontaneous (B) and evoked (C) spinal activities after SCI recorded at postnatal day 4/5. Sometimes activities arise as locomotor-like episodes (B'–C') suggesting activation of interneuronal networks of the locomotor CPG (VR/DR L5: ventral/dorsal root lumbar 5; r: right; l: left; St.: stimulation). Lumbar premotor interneurons show a trend of reduction after SCI (D). The expression of inhibitory receptors on motoneuron membranes is altered, with $GABA_A$ receptors being significantly enhanced postlesion (E). *Panel (D): modified from Khalki, L., Sadlaoud, K., Lerond, J., Coq, J.O., Brezun, J. M., Laurent, L., et al. (2018) Changes in innervation of lumbar motoneurons and organization of premotor network following training of transected adult rats.* Experimental Neurology, *299, 1–14.; Panel (E): modified from Bras, H, & Liabeuf, S. (2020) Differential effects of spinal cord transection on glycinergic and GABAergic synaptic signaling in sublesional lumbar motoneurons.* Journal of Chemical Neuroanatomy, *9, 101847.*

exaggerated reflexes as soon as 48 h postinjury (Plantier et al., 2019). Strikingly, a single electrical pulse is sufficient to trigger an episode of locomotor-like activity in spastic neonates after SCI (Fig. 2C'; Plantier et al., 2019), whereas trains of electrical stimuli at 1–10 Hz are usually required in control (Marchetti, Marco Beato, & Nistri, 2001). This further confirms the occurrence of maladaptive network changes in the sublesional spinal cord, involving not only motoneuron pools but also interneuron circuits of the locomotor CPG.

Cellular and molecular alterations contributing to spasticity after SCI

Spasticity is a condition related to increased central excitability where spinal reflexes are enhanced. The electrophysiological properties of motoneurons are closely involved in the emergence of hyperreflexia. Different pathophysiological mechanisms take place after SCI, responsible for an excitatory/inhibitory imbalance of spinal motoneurons. As a result, motoneuron intrinsic properties and synaptic transmission undergo maladaptive changes promoting an increased excitation (hyperexcitability) and a reduced inhibition (disinhibition) that allow for synaptic inputs to evoke exaggerated activity.

Long-lasting reflexes and muscle spasms are related to prolonged motoneuron firing in response to transient sensory transmission. Self-sustained firing is associated with the activation of persistent inward currents (PICs), which are slowly activating/inactivating voltage-sensitive conductances (Heckmann, Gorassini, & Bennett, 2005). PICs mediate *plateau potentials* in spinal motoneurons, consisting of a prolonged depolarization with self-sustained spiking triggered by a brief stimulation (Hounsgaard, Hultborn, Jespersen, & Kiehn, 1984). Therefore, plateau potentials are responsible for regulating spinal excitability by amplifying synaptic inputs and providing a sustained excitatory drive that allows motoneurons to fire even after stimulus termination, ultimately generating exaggerated and sustained reflex responses typical of spasticity.

Sublesional motoneurons exhibit large plateau potentials supported by an increase in PICs amplitude (Fig. 3C). PICs underlying the plateau are mediated by calcium (Ca^{2+}) currents through nifedipine-sensitive L-type Ca^{2+} channels ($Ca_v1.3$; Li & Bennett, 2003; Marcantoni et al., 2020) and sodium (Na^+) conductances through voltage-gated sodium channels $Na_v1.6$, densely expressed in the axonal initial segment (AIS) of lumbar motoneurons (Brocard et al., 2016). Ca^{2+}- and Na^+-dependent PICs are markedly depressed during acute SCI (spinal shock), but they spontaneously recover in motoneurons of chronic spinal rats some weeks after lesion, enabling huge plateaus, hyperreflexia, and muscle spasms (Bennett, Li, Harvey, & Gorassini, 2001; Bennett, Li, & Siu, 2001; Li & Bennett, 2003). The characteristic recovery of the chronic phase is concomitant with an increased expression of constitutively active serotonin receptors, which restore huge PICs in motoneurons by making them supersensitive to serotonin (Li, Murray, Harvey, Ballou, & Bennett, 2007; Murray et al., 2010). Interestingly, Ca^{2+}-PICs (or I_{CaP}) appear negligible in neonates, where Na^+-PICs (or I_{NaP}) seem to be the main component supporting exaggerated reflexes (Plantier et al., 2019). On the one hand, this is in line with delayed maturation of L-type Ca^{2+} channels peaking at the third postnatal week (Jiang et al., 1999). On the other hand, it fits with our previous work demonstrating that I_{NaP} is critical for driving plateau potentials in lumbar motoneurons during the perinatal period (Bouhadfane, Tazerart, Moqrich, Vinay, & Brocard, 2013).

Besides the aforementioned mechanisms of motoneuron hyperexcitability, processes underlying spinal disinhibition are of great relevance in the pathophysiology of spasticity (refer to schema in Fig. 4F). In mature neurons, a low intracellular chloride concentration ($[Cl^-]_i$) is maintained by the potassium-chloride cotransporter KCC2, which extrudes chloride anions hyperpolarizing the Cl^- *equilibrium potential* (E_{Cl}^-). When chloride-permeable γ-aminobutyric acid type A ($GABA_A$) and glycine receptors open, there is a net influx of Cl^- that induces neuron inhibition. The expression of KCC2 in motoneuron membranes of adult animals decreases in pathological conditions, including spasticity after SCI (Fig. 4A and B; Boulenguez et al., 2010; Bos et al., 2013). In neonates, GABA and glycine are not fully inhibitory, thus the physiological up-regulation of KCC2 contributes to the excitatory/inhibitory switch. On the contrary, after SCI the membrane expression of KCC2 in neonate motoneurons remains weak and promotes the early onset of spasticity typically observed in the perinatal period (Jean-Xavier, Pflieger, Liabeuf, & Vinay, 2006; Plantier et al., 2019). As a consequence, in both adult and neonate SCI models, the $[Cl^-]_i$ increases causing an efflux of Cl^- which depolarizes the E_{Cl}^-, thereby promoting spinal disinhibition (Fig. 4C–F). Besides KCC2 altered expression on motoneurons, inhibitory receptors are also affected in SCI adults, with $GABA_A$being long-term over-expressed on the plasma membrane (Fig. 2E; Sadlaoud et al., 2020). In lesioned neonates, the physiological up-regulation of glycine receptors is preserved in sublesional motoneurons, whereas the developmental down-regulation of $GABA_A$ does not take place (Sadlaoud et al., 2010). Inhibitory neurotransmission is also differentially influenced by the lesion, since presynaptic glycinergic inputs onto motoneurons show a similar density as in intact animals, whereas GABAergic boutons are increased (Khalki et al., 2018). This suggests an impairment of the GABAergic transmission and relative preservation of the glycinergic system in sublesional motoneurons (Bras & Liabeuf, 2020).

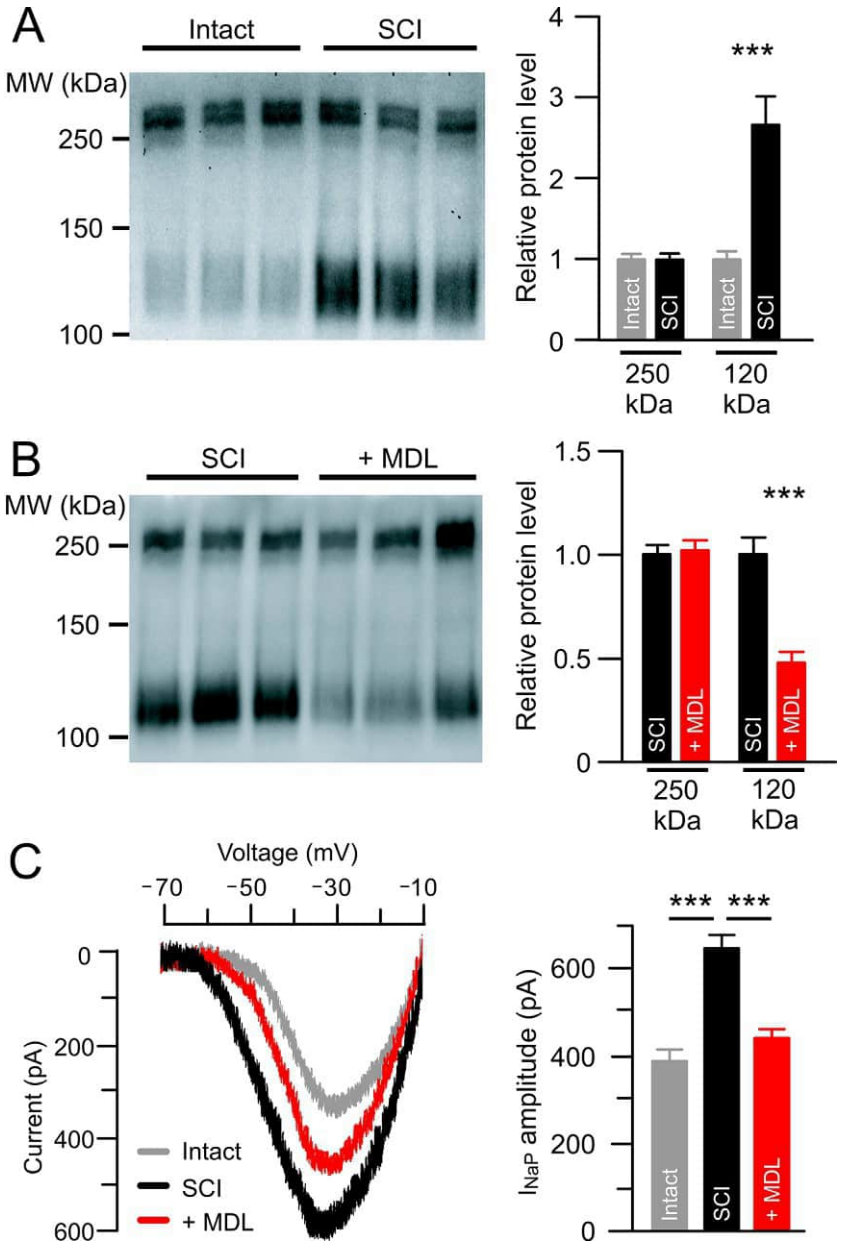

FIG. 3 $Na_v1.6$ channels as calpain targets after SCI. $Na_v1.6$ channels are cleaved after SCI, as confirmed by the appearance of a ~120 kDa band in Western blots (A). Calpains are responsible for channel cleavage, since MDL28170 reduces the amount of breakdown fragments (B). The amplitude of I_{NaP} is concomitantly increased after injury and recovers after MDL28170 application (C). *Modified from Brocard, C., Plantier, V., Boulenguez, P., Liabeuf, S., Bouhadfane, M., Viallat-Lieutaud, A., et al. (2016) Cleavage of Na(+) channels by calpain increases persistent Na(+) current and promotes spasticity after spinal cord injury*. Nature Medicine, *22, 404–411*.

Calpains and their role in spasticity after SCI

Calpains (*cal*cium-dependent proteases with pa*pain*-like activity) belong to a superfamily of cytoplasmic cysteine proteases activated by calcium. To date, 14 calpain members have been identified with both ubiquitous and tissue-specific localization (Sorimachi, Hata, & Ono, 2011). The best-characterized members are the μ- and m- calpains (or calpain 1 and 2), also referred to as "ubiquitous" or "conventional" as they are present in all mammalian tissues and cell types. Ubiquitous calpains differ in their in vitro calcium sensitivity, in the μM range for μ-calpain and in the mM range for m-calpain (Goll, Thompson, Li, Wei, & Cong, 2003). Calpains are mostly inactive in the cytosol and translocate to the membrane in response to increased intracellular calcium concentrations, where calcium-induced structural changes allow for their activation (Suzuki, Hata, Kawabata, & Sorimachi, 2004). Since calpains are involved in several pathophysiological processes, their activation is highly regulated by the endogenous peptidic inhibitor, calpastatin (Wendt, Thompson, & Goll, 2004). Calpains have a myriad of substrates and they need PEST (proline, glutamic acid, serine, and threonine) or PEST-like

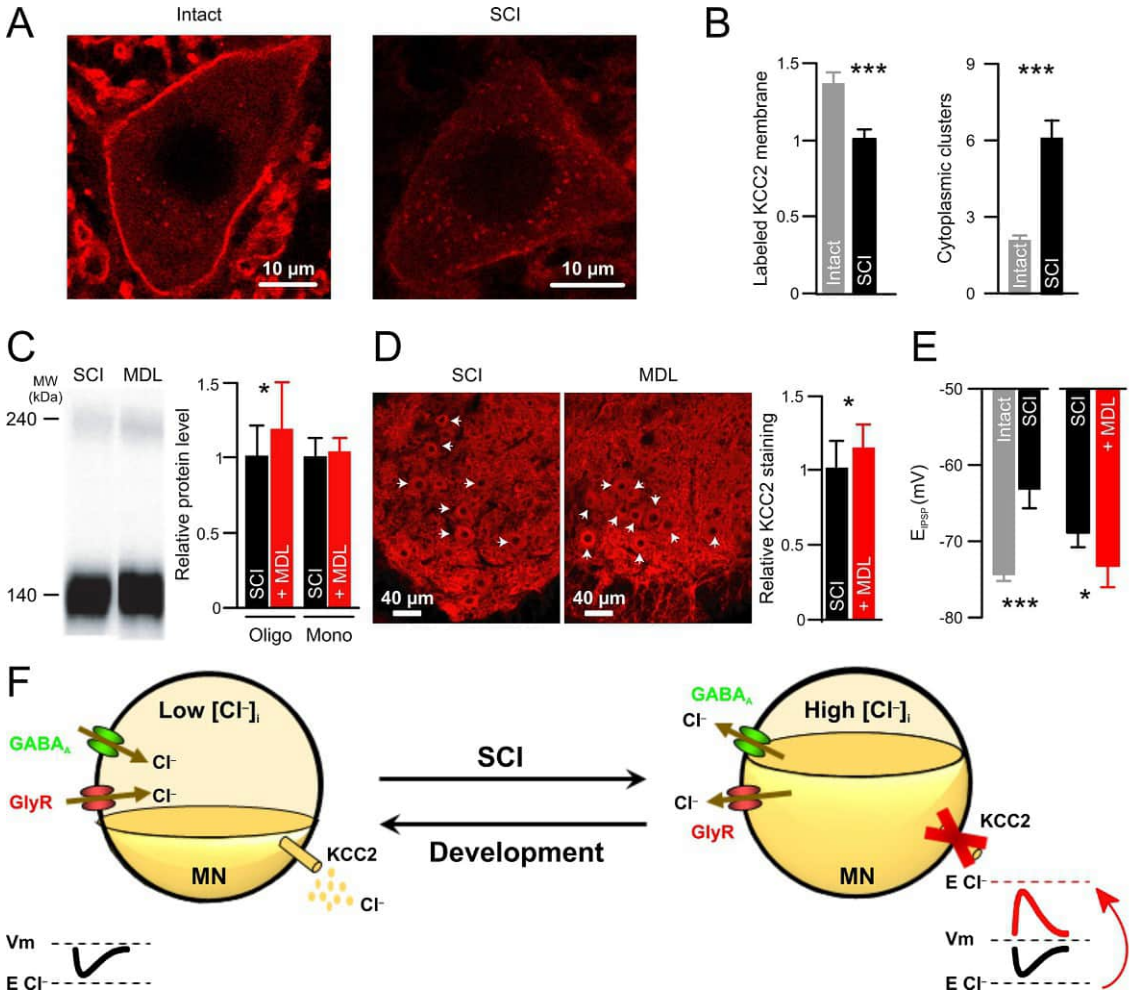

FIG. 4 KCC2 as calpain target after SCI. KCC2 is down-regulated at motoneuron membranes and internalized in the cytoplasm after SCI (A–B). MDL28170 recovers the functionally active oligomeric form of KCC2 on the plasma membrane (C–D). Note that the chloride equilibrium potential (E_{Cl}) affects the strength of synaptic inhibition, therefore we refer to it as E_{IPSP} (equilibrium potential of inhibitory postsynaptic potentials). E_{IPSP} undergoes a depolarizing shift after SCI and returns back to more hyperpolarized values when MDL28170 is applied (E). Summary schema showing that KCC2 down-regulation after SCI increases the intracellular Cl^- concentration and leads to spinal disinhibition (F). As pinpointed by the backward arrow in (F), the opposite condition takes place during development. *Panel (A–B): modified from Boulenguez, P., Liabeuf, S., Bos, R., Bras, H., Jean-Xavier, C., Brocard, C., et al. (2010) Down-regulation of the potassium-chloride cotransporter KCC2 contributes to spasticity after spinal cord injury.* Nature Medicine, *16, 302–307.; Panel (C–E): modified from Plantier, V., Sanchez-Brualla, I., Dingu, N., Brocard, C., Liabeuf, S., Gackière, F., et al. (2019) Calpain fosters the hyperexcitability of motoneurons after spinal cord injury and leads to spasticity.* eLife, *8, e51404*.

sequences for their recognition, although the existence of other restriction regions cannot be excluded (Tompa et al., 2004). Here we will address calpain expression and activity after SCI, followed by a discussion on identified and putative calpain targets related to spasticity, and final considerations on the role of calpain inhibition as an innovative antispastic treatment.

Calpain expression and activity after SCI

Excitotoxicity and intracellular hypercalcemia promote calpain activation and up-regulation during secondary SCI. The expression of ubiquitous calpains is increased at the lesion site and in the adjacent area during acute SCI, although it is still unclear whether this is due to either a selective rise in calpain 1/2 or both of them. We showed that calpain 1 (μ-calpain) is selectively enhanced in neonate rats (Plantier et al., 2019), whereas both calpains are augmented in adult rats acutely spinalized (Li, Hogan, & Banik, 1996). The pathophysiological meaning of this finding is not fully understood, although we speculate that higher intracellular calcium concentrations are required in the adult for calpain activation. Indeed, in adult animals calpains are posttranscriptionally regulated by many mechanisms, including calcium requirement, autoproteolytic cleavage, and the endogenous inhibitor calpastatin (Molinari & Carafoli, 1997). On the contrary, little is known about

calpain expression in chronic SCI, albeit a progressive decrease in calpastatin and a parallel increase in calpain levels have been reported (Wienecke, Westerdahl, Hultborn, Kiehn, & Ryge, 2010). However, which of the calpain isoforms is overexpressed during the chronic phase remains unclear and further investigation is required.

Calpain activity is generally determined by quantifying breakdown products of different protein targets. There are several substrates for calpains that are degraded in lesioned spinal cords. We showed that calpains cleave $Na_v1.6$ channels inducing the appearance of a lower molecular weight band of ~120 kDa in immunoblots from lumbar segments, in addition to the full-length band of ~250 kDa consistent with the native α-subunit of $Na_v1.6$ channels, both in adult (Brocard et al., 2016) and neonate (Plantier et al., 2019) spinal rats (Fig. 3A and B).

Identified and putative calpain targets involved in the pathophysiology of spasticity

Calpains contribute to spasticity by mediating the excitatory/inhibitory imbalance typically occurring in lumbar motoneurons after SCI. Calpain cleavage of several targets promotes hyperexcitability and disinhibition in lesioned spinal cords. Here, we will discuss the role of identified calpain substrates in spasticity and speculate on new potential targets that might impact on this pathological condition.

Several mechanisms of spinal hyperexcitability are supported by calpain-mediated proteolysis of ion channels and receptors. Our team demonstrated that calpains cleave $Na_v1.6$ channels, highly expressed in the AIS of lumbar motoneurons, by producing a breakdown product of ~120 kDa (Fig. 3A and B; Brocard et al., 2016; Plantier et al., 2019). We also pinpointed a direct relationship between the calpain-mediated cleavage of $Na_v1.6$ and the up-regulation of I_{NaP} (Fig. 3C). Although the exact mechanism remains to be defined, we hypothesize that calpain cleavage of the α-subunit of $Na_v1.6$ channels interferes with their inactivation process, thus increasing the amplitude of I_{NaP} and supporting motoneuron hyperexcitability and muscle spasms. Interestingly, the amount of full-length $Na_v1.6$ channels (~250 kDa) is unchanged at the plasma membrane after SCI, likely due to regulatory mechanisms for the expression of the native form supported by calpain-mediated proteolytic fragments (Onwuli et al., 2017).

Hyperexcitability can also be sustained by calcium-dependent cellular processes since calpains are typically activated by high intracellular calcium. It is well-established that glutamate receptors induce intracellular calcium overload leading to calpain activation (Doshi & Lynch, 2009). In turn, calpains directly target all of the major glutamate receptors, disrupting their function and leading to excitotoxicity. However, direct evidence linking calpain-mediated dysregulation of glutamatergic transmission to spasticity after SCI is still missing, although glutamate receptors seem to be good candidates. Similarly, L-type calcium channels also allow for calcium influx in neurons, contributing to calpain activation (Schön, Paquet-Durand, & Michalakis, 2016). They are catabolized by calpains at the C-terminus in the heart, skeletal muscle, and in some regions of the brain (Abele & Yang, 2012), albeit no data are currently available in the spinal cord.

A reduced or impaired inhibition also contributes to spasticity and we recently reported a role for calpains in motoneuron disinhibition. We demonstrated that the membrane down-regulation of KCC2 after SCI, previously reported by the team (Fig. 4A and B; Boulenguez et al., 2010; Bos et al., 2013), is actually due to calpain activation (Fig. 4C–E; Plantier et al., 2019). KCC2 is present on motoneuron membranes both in oligomeric and monomeric forms, with the oligomeric form having the highest sensitivity to calpains. We argue that KCC2 is cleaved at the C-terminus due to the presence of two predicted PEST sequences (Acton et al., 2012; Mercado, Broumand, Zandi-Nejad, Enck, & Mount, 2006). Given that phosphorylation regulates substrate vulnerability to calpains (Yamashita, Teramoto, & Kwak, 2016), calpain sensitivity of the oligomeric form might be due to an SCI-mediated dephosphorylation of serine 960 near the PEST motifs (Modol, Mancuso, Alé, Francos-Quijorna, & Navarro, 2014). Moreover, since KCC2 requires a functional C-domain to extrude Cl^- (Acton et al., 2012; Mercado et al., 2006), the depolarized E_{Cl}^- might be a direct consequence of calpain proteolysis.

Physiological and pharmacological inhibition of calpains and effects on spasticity

Calpains have a plethora of targets relevant to the pathophysiology of spasticity. Physiologically, calpains coexist with their endogenous inhibitor calpastatin in the cytosol and membrane (Kawasaki & Kawashima, 1996). Calpastatin has four inhibitory domains, each inhibiting one molecule of calpain with an inhibitory rate of 1:4 (Wendt et al., 2004). Interestingly, calpastatin protein and mRNA levels gradually increase in the central nervous system during development, showing a rapid rise at postnatal days 5–10 (Li, Bondada, Joshi, & Geddes, 2009). Therefore, a lower calpastatin expression might account for the earlier emergence of spasticity in neonates with respect to adult animals. Although calpastatin up-regulation has been promoted in many pathological conditions to counteract calpain activity, its therapeutic role in SCI must still be elucidated. On the one side, there are encouraging data showing some calpastatin-induced neuroprotection after SCI

(Yu et al., 2020). On the other side, there is clear evidence that the ratio calpain/calpastatin is increased after SCI, as a result of calpain-mediated degradation of calpastatin which disrupts its regulatory role and makes it unsuitable as a therapeutic agent for calpain inhibition (Ray, Hogan, & Banik, 2003).

A huge research effort has been focused on identifying effective therapeutic strategies to inhibit calpain activity in SCI. To date, several classes of pharmacological inhibitors are available. Between them, MDL28170 is a small aldehyde compound capable of penetrating the cell membrane by passive diffusion. We have demonstrated that the pharmacological use of MDL28170 is efficient in preventing both the cleavage of $Na_v1.6$ channels (Fig. 3B) and the down-regulation of KCC2 on the plasma membrane (Fig. 4C and D), thus restoring the excitatory/inhibitory equilibrium of motoneurons and protecting against spasticity (Fig. 3C, Fig. 4E; Brocard et al., 2016; Plantier et al., 2019).

The major issue with calpain inhibitors is their lack of specificity since they act also on other proteases. Moreover, they target both calpain 1 and 2 and no selective drug is currently available for either isoform. Given that calpains have important physiological roles that might be affected by systemic inhibition, local therapeutic strategies for calpain silencing are advisable. Next-generation treatments should allow for cell-specific manipulations, such as therapies selectively targeting motoneurons innervating spastic muscles, therefore avoiding systemic adverse effects related to oral drug administration. Lastly, choosing calpain as a possible hit would allow targeting the main upstream molecule accounting for multiple spinal mechanisms leading to spasticity, instead of singularly acting on downstream players (Fig. 5).

Applications to other areas of neuroscience

Increased calpain activation has been implicated not only in spinal cord injury (SCI) but also in a number of other neurological disorders including traumatic brain injury (Ray, Dixon, & Banik, 2002), cerebral ischemia (Sun, Zhao, & Xu, 2008), neurodegenerative diseases like Alzheimer's (Saito, 1993), Parkinson's (Mouatt-Prigent, 1996), Huntington's (Gafni & Ellerby, 2002) diseases and amyotrophic lateral sclerosis (Stifanese et al., 2014). Although the etiology underlying each disorder varies, the main pathologic mechanism converges on calcium homeostasis dysregulation leading to calpain activation and overexpression. Increased intracellular calcium is generally due to excitotoxicity, promoted by uncontrolled glutamate release and impaired re-uptake, ultimately resulting in augmented calcium influx through the hyperactivation of glutamate receptors. This cascade causes the pathologic activation of calpains that catalyze a myriad of substrates promoting neuronal death. Indeed, calpains induce apoptosis by activating caspases and cause necrosis by disrupting lysosomal membranes that release proteases, such as cathepsins. The production of calpain-mediated neurotoxic protein fragments is also a common feature in the pathophysiology of these neurological disorders. Interestingly, the deregulation of calpain activity represents a key cytotoxic event also in epilepsy, where calpain over-activation has been shown to down-regulate the potassium-chloride cotransporter KCC2 on the plasma membrane (Li et al., 2018), in addition to neurotoxicity and constitutive activation of glutamate receptors. Therefore, the search for effective and highly selective strategies to inhibit calpains has obvious applicability not only in the treatment of spasticity after SCI but also in a wide and heterogeneous range of neurological disorders where calpains seem to play a critical role.

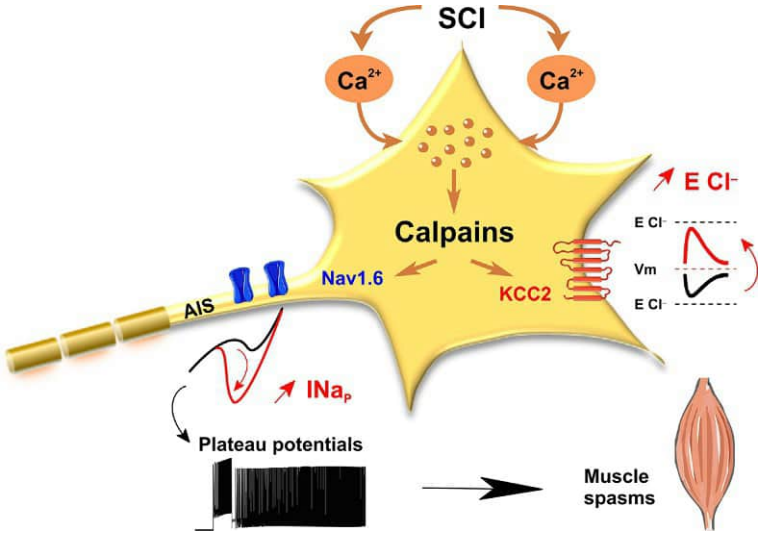

FIG. 5 Role of calpains in the pathophysiology of spasticity after SCI. The intracellular concentration of calcium increases after SCI inducing calpain activation. Calpains target several molecules, including $Na_v1.6$ channels (highly expressed at the axonal initial segment, AIS) and KCC2 that cause I_{NaP} up-regulation and a depolarizing shift of the E_{Cl}^-, respectively. As a result, an excitatory/inhibitory imbalance occurs in spinal motoneurons promoting plateau potentials and contributing to spasticity.

Mini-dictionary of terms

Wallerian degeneration: injury-induced program of axon degeneration consisting of deteriorating myelin ovoids and distal axon fragmentation, first described by Augustus Waller in 1850.

Reperfusion injury: cascade of events associated with the reestablishment of blood supply in ischemic tissues, which restores oxygenation, but also accelerates tissue necrosis through several mechanisms, such as the production of reactive oxygen species (ROS).

Glial scar: healing response supported by reactive astrogliosis and massive deposition of extracellular matrix at the injury site limiting functional repair after lesion.

Excitotoxicity: pathological process leading to neuronal death or damage arising from excessive or prolonged exposure to excitatory amino acids.

Spinal shock: temporary loss (areflexia) or depression (hyporeflexia) of spinal reflexes below the level of the injury occurring immediately after SCI.

Hyperreflexia: abnormal and exaggerated reflexes spontaneously appearing either at the end of the spinal shock phase in humans and in adult animals or few days postlesion in neonate animal models.

Central pattern generator (CPG): interneuron networks controlling rhythmicity and pattern formation in motor behaviors, such as locomotion, by providing the timing of motoneuron discharge and determining appropriate sequences of muscle contraction.

Locomotor-like episode: double alternation between flexor and extensor motor pools on the same side of the spinal cord and between left and right motor pools within the same spinal segment, which represents a hallmark of CPG activation in vitro.

Plateau potential: prolonged depolarization of the membrane potential supporting long-lasting discharges triggered by synaptic input or brief depolarizing pulse that activate persistent inward currents.

Equilibrium potential: membrane potential level where an ion is at the electrochemical equilibrium and there is no net flow of that ion across the membrane.

Key facts of "spinal hyperexcitability"

- It refers to molecular, cellular, and network modifications leading to an increased spinal excitation.
- We described a calpain-mediated mechanism involving the cleavage of voltage-gated sodium channels $Na_v1.6$ in SCI motoneurons.
- Calpain proteolysis likely affects the inactivation kinetics of $Na_v1.6$ channels.
- As a result, the sodium persistent inward current (I_{NaP}) is up-regulated and spinal motoneurons exhibit enhanced plateau potentials that contribute to exaggerated spinal activities and spasticity.
- The pharmacological inhibition of calpains prevents both the cleavage of $Na_v1.6$ channels and I_{NaP} up-regulation and protects from spasticity.

Key facts of "spinal disinhibition"

- It encloses spinal mechanisms causing a reduced or impaired inhibition.
- Calpains play a role by down-regulating the potassium-chloride cotransporter KCC2 on motoneuron membranes after SCI.
- The reduced expression of KCC2 causes an intracellular accumulation of chloride.
- When γ-aminobutyric acid type A ($GABA_A$) and glycine receptors open as a consequence of inhibitory neurotransmitter binding, chloride anions are extruded and there is a depolarizing shift of the chloride equilibrium potential (E_{Cl}^{-}).
- The reduced strength of the postsynaptic inhibition contributes to the onset of spasticity.
- The pharmacological blockage of calpains restores KCC2 on the plasma membrane recovering inhibitory transmission and preventing muscle spasms.

Summary points

- Spasticity is a pathological condition that develops in the majority of patients one year after SCI.
- Animal models for the study of spasticity after SCI represent an essential tool to uncover pathophysiological processes and to identify new therapeutic strategies.

- So far, several mechanisms responsible for an excitatory/inhibitory imbalance of spinal motoneurons have been related to spasticity after SCI.
- We reported that calpains have an upstream role in different spinal mechanisms leading to spasticity.
- On the one hand, calpains cleave voltage-gated sodium channels $Na_v1.6$ up-regulating the sodium persistent inward current (I_{NaP}); on the other hand, they down-regulate the potassium-chloride cotransporter KCC2 on motoneuron membranes depolarizing the chloride equilibrium potential ($E_{\overline{Cl}}$).
- These mechanisms synergize in generating exaggerated activities in spinal motoneurons, lastly contributing to spasticity.
- Other molecules might be targeted by calpains and impact the development of spasticity, therefore supporting the concept that calpain inhibition might be an effective antispastic treatment.
- Strategies for calpain inhibition can be adopted not only to prevent spasticity after SCI but also to counteract several neurological disorders where calpains are critically involved.

Acknowledgments

Our research was financed by a grant from Agence National de la Recherche Scientifique (CalpaSCI, ANR-16-16CE-0004) and from the French Institut pour la Recherche sur la Moelle épinière et l'Encéphale (IRME).

References

Abele, K., & Yang, J. (2012). Regulation of voltage-gated calcium channels by proteolysis. *Sheng Li Xue Bao*, *64*, 504–514.

Acton, B. A., Mahadevan, V., Mercado, A., Uvarov, P., Ding, Y., Pressey, J., et al. (2012). Hyperpolarizing GABAergic transmission requires the KCC2 C-terminal ISO domain. *The Journal of Neuroscience*, *32*, 8746–8751.

Adams, M. M., & Hicks, A. L. (2005). Spasticity after spinal cord injury. *Spinal Cord*, *43*, 577–586.

Atkinson, P. P., & Atkinson, J. L. (1996). Spinal shock. *Mayo Clinic Proceedings*, *71*, 384–389.

Bellardita, C., Caggiano, V., Leiras, R., Caldeira, V., Fuchs, A., Bouvier, J., et al. (2017). Spatiotemporal correlation of spinal network dynamics underlying spasms in chronic spinalized mice. *eLife*, *6*, e23011.

Bellardita, C., Marcantoni, M., Löw, P., & Kiehn, O. (2018). Sacral spinal cord transection and isolated sacral cord preparation to study chronic spinal cord injury in adult mice. *Bio-Protocol*, *8*, e2784.

Bennett, D. J., Gorassini, M., Fouad, K., Sanelli, L., Han, Y., & Cheng, J. (1999). Spasticity in rats with sacral spinal cord injury. *Journal of Neurotrauma*, *16*, 69–84.

Bennett, D. J., Li, Y., Harvey, P. J., & Gorassini, M. (2001). Evidence for plateaupotentials in tail motoneurons of awake chronic spinal rats with spasticity. *Journal of Neurophysiology*, *86*, 1972–1982.

Bennett, D. J., Li, Y., & Siu, M. (2001). Plateau potentials in sacrocaudal motoneurons of chronic spinal rats, recorded in vitro. *Journal of Neurophysiology*, *86*, 1955–1971.

Bennett, D. J., Sanelli, L., Cooke, C. L., Harvey, P. J., & Gorassini, M. A. (2004). Spastic long-lasting reflexes in the awake rat after sacral spinal cord injury. *Journal of Neurophysiology*, *91*, 2247–2258.

Bos, R., Sadlaoud, K., Boulenguez, P., Buttigieg, D., Liabeuf, S., Brocard, C., et al. (2013). Activationof 5-HT2A receptors upregulates the function of the neuronal K-Cl cotransporter KCC2. *PNAS*, *110*, 348–353.

Bouhadfane, M., Tazerart, S., Moqrich, A., Vinay, L., & Brocard, F. (2013). Sodium-mediated plateau potentials in lumbar motoneurons of neonatal rats. *The Journal of Neuroscience*, *33*, 15626–15641.

Boulenguez, P., Liabeuf, S., Bos, R., Bras, H., Jean-Xavier, C., Brocard, C., et al. (2010). Down-regulation of the potassium-chloride cotransporter KCC2 contributes to spasticity after spinal cord injury. *Nature Medicine*, *16*, 302–307.

Bras, H., & Liabeuf, S. (2020). Differential effects of spinal cord transection on glycinergic and GABAergic synaptic signaling in sub-lesional lumbar motoneurons. *Journal of Chemical Neuroanatomy*, *9*, 101847.

Brocard, C., Plantier, V., Boulenguez, P., Liabeuf, S., Bouhadfane, M., Viallat-Lieutaud, A., et al. (2016). Cleavage of Na(+) channels by calpain increases persistent Na(+) current and promotes spasticity after spinal cord injury. *Nature Medicine*, *22*, 404–411.

Corleto, J. A., Bravo-Hernández, M., Kamizato, K., Kakinohana, O., Santucci, C., Navarro, M. R., et al. (2015). Thoracic 9 spinal transection-induced model of muscle spasticity in the rat: A systematic electrophysiological and histopathological characterization. *PLoS One*, *10*, e0144642.

Doshi, S., & Lynch, D. R. (2009). Calpain and the glutamatergic synapse. *Frontiers in Bioscience (Scholar Edition)*, *1*, 466–476.

Fan, B., Wei, Z., Yao, X., Shi, G., Cheng, X., Zhou, X., et al. (2018). Microenvironment imbalance of spinal cord injury. *Cell Transplantation*, *27*, 853–866.

Gafni, J., & Ellerby, L. M. (2002). Calpain activation in Huntington's disease. *The Journal of Neuroscience*, *22*, 4842–4849.

Goll, D. E., Thompson, V. F., Li, H., Wei, W., & Cong, J. (2003). The calpain system. *Physiological Reviews*, *83*, 731–801.

Hall, E. D., Wang, J. A., Bosken, J. M., & Singh, I. N. (2016). Lipid peroxidation in brain or spinal cord mitochondria after injury. *Journal of Bioenergetics and Biomembranes*, *48*, 169–174.

Heckmann, C. J., Gorassini, M. A., & Bennett, D. J. (2005). Persistent inward currents in motoneuron dendrites: Implications for motor output. *Muscle & Nerve*, *31*, 135–156.

Hill, C. E., Beattie, M. S., & Bresnahan, J. C. (2001). Degeneration and sprouting of identified descending supraspinal axons after contusive spinal cord injury in the rat. *Experimental Neurology*, *171*, 153–169.

Hounsgaard, J., Hultborn, H., Jespersen, B., & Kiehn, O. (1984). Intrinsic membrane properties causing a bistable behaviour of alpha-motoneurones. *Experimental Brain Research*, *55*, 391–394.

Jean-Xavier, C., Pflieger, J. F., Liabeuf, S., & Vinay, L. (2006). Inhibitory postsynaptic potentials in lumbar motoneurons remain depolarizing after neonatal spinal cord transection in the rat. *Journal of Neurophysiology*, *96*, 2274–2281.

Jiang, Z., Rempel, J., Li, J., Sawchuk, M. A., Carlin, K. P., & Brownstone, R. M. (1999). Development of L-type calcium channels and a nifedipine-sensitive motor activity in the postnatal mouse spinal cord. *The European Journal of Neuroscience*, *11*, 3481–3487.

Kalogeris, T., Baines, C. P., Krenz, M., & Korthuis, R. J. (2012). Cell biology of ischemia/reperfusion injury. *International Review of Cell and Molecular Biology*, *298*, 229–317.

Kawasaki, H., & Kawashima, S. (1996). Regulation of the calpain-calpastatin system by membranes. *Molecular Membrane Biology*, *13*, 217–224.

Khalki, L., Sadlaoud, K., Lerond, J., Coq, J. O., Brezun, J. M., Laurent, L., et al. (2018). Changes in innervation of lumbar motoneurons and organization of premotor network following training of transected adult rats. *Experimental Neurology*, *299*, 1–14.

Lance, J. W. (1980). Symposium synopsis. In R. G. Feldman, R. R. Young, & W. P. Koella (Eds.), *Spasticity: Disordered motor control* (pp. 485–494).

Li, Y., & Bennett, D. J. (2003). Persistent sodium and calcium currents cause plateau potentials in motoneurons of chronic spinal rats. *Journal of Neurophysiology*, *90*, 857–869.

Li, Y., Bondada, V., Joshi, A., & Geddes, J. W. (2009). Calpain 1 and Calpastatin expression is developmentally regulated in rat brain. *Experimental Neurology*, *220*, 316–319.

Li, Y., Harvey, P. J., Li, X., & Bennett, D. J. (2004). Spastic long-lasting reflexes of the chronic spinal rat studied in vitro. *Journal of Neurophysiology*, *91*, 2236–2246.

Li, Z., Hogan, E. L., & Banik, N. L. (1996). Role of calpain in spinal cord injury: Increased calpain immunoreactivity in rat spinal cord after impact trauma. *Neurochemical Research*, *21*, 441–448.

Li, X., Murray, K., Harvey, P. J., Ballou, E. W., & Bennett, D. J. (2007). Serotonin facilitates a persistent calcium current in motoneurons of rats with and without chronic spinal cord injury. *Journal of Neurophysiology*, *97*, 1236–1246.

Liu, Z., Yao, X., Jiang, W., Li, W., Zhu, S., Liao, C., et al. (2020). Advanced oxidation protein products induce microglia-mediated neuroinflammation via MAPKs-NF-κB signaling pathway and pyroptosis after secondary spinal cord injury. *Journal of Neuroinflammation*, *17*, 90.

Marcantoni, M., Fuchs, A., Löw, P., Bartsch, D., Kiehn, O., & Bellardita, C. (2020). Early delivery and prolonged treatment with nimodipine prevents the development of spasticity after spinal cord injury in mice. *Science Translational Medicine*, *12*, eaay0167.

Marchetti, C., Marco Beato, M., & Nistri, A. (2001). Alternating rhythmic activity induced by dorsal root stimulation in the neonatal rat spinal cord in vitro. *The Journal of Physiology*, *530*, 105–112.

Mercado, A., Broumand, V., Zandi-Nejad, K., Enck, A. H., & Mount, D. B. (2006). A C-terminal domain in KCC2 confersconstitutive K+-Cl- cotransport. *The Journal of Biological Chemistry*, *281*, 1016–1026.

Modol, L., Mancuso, R., Alé, A., Francos-Quijorna, I., & Navarro, X. (2014). Differential effects on KCC2 expression andspasticity of ALS and traumatic injuries to motoneurons. *Frontiers in Cellular Neuroscience*, *8*, 7.

Molinari, M., & Carafoli, E. (1997). Calpain: A cytosolic proteinase active at the membranes. *The Journal of Membrane Biology*, *156*, 1–8.

Mouatt-Prigent, A. (1996). Increased m-calpain expression in the mesencephalon of patients with Parkinson's disease but not in other neurodegenerative disorders involving the mesencephalon: A role in nerve cell death? *Neuroscience*, *73*, 979–987.

Murray, K., Nakae, A., Stephens, M. J., Rank, M., D'Amico, J., Harvey, P. J., et al. (2010). Recovery of motoneuron and locomotor function after spinal cord injury depends on constitutive activity in 5-HT2C receptors. *Nature Medicine*, *16*, 694–700.

Onwuli, D. O., Yanez-Bisbe, L., Pinsach-Abuin, M. L., Tarradas, A., Brugada, R., Greenman, J., et al. (2017). Do sodium channel proteolytic fragments regulate sodium channel expression? *Channels*, *11*, 476–481.

Plantier, V., Sanchez-Brualla, I., Dingu, N., Brocard, C., Liabeuf, S., Gackière, F., et al. (2019). Calpain fosters the hyperexcitability of motoneurons after spinal cord injury and leads to spasticity. *eLife*, *8*, e51404.

Ray, S. K., Dixon, C. E., & Banik, N. L. (2002). Molecular mechanisms in the pathogenesis of traumatic brain injury. *Histology and Histopathology*, *17*, 1137–1152.

Ray, S. K., Hogan, E. L., & Banik, N. L. (2003). Calpain in the pathophysiology of spinal cord injury: Neuroprotection with calpain inhibitors. *Brain Research. Brain Research Reviews*, *42*, 169–185.

Sadlaoud, K., Khalki, L., Brocard, F., Vinay, L., Boulenguez, P., & Bras, H. (2020). Alteration of glycinergic receptor expression in lumbar spinal motoneurons is involved in the mechanisms underlying spasticity after spinal cord injury. *Journal of Chemical Neuroanatomy*, *106*, 101787.

Sadlaoud, K., Tazerart, S., Brocard, C., Jean-Xavier, C., Portalier, P., Brocard, F., et al. (2010). Differential plasticity of the GABAergic and glycinergic synaptic transmission to rat lumbar motoneurons after spinal cord injury. *The Journal of Neuroscience*, *30*, 3358–3369.

Saito, K. (1993). Widespread activation of calcium-activated neutral proteinase (calpain) in the brain in Alzheimer disease: A potential molecular basis for neuronal degeneration. *Proceedings of the National Academy of Sciences of the United States of America*, *90*, 2628–2632.

Schön, C., Paquet-Durand, F., & Michalakis, S. (2016). Cav1.4 L-type calcium channels contribute to Calpain activation in degenerating photoreceptors of rd1 mice. *PLoS One*, *11*, e0156974.

Sharif-Alhoseini, M., Khormali, M., Rezaei, M., Safdarian, M., Hajighadery, A., Khalatbari, M. M., et al. (2017). Animal models of spinal cord injury: A systematic review. *Spinal Cord*, *55*, 714–721.

Sorimachi, H., Hata, S., & Ono, Y. (2011). Calpain chronicle—An enzyme family under multidisciplinary characterization. *Proceedings of the Japan Academy. Series B, Physical and Biological Sciences*, *87*, 287–327.

Stifanese, R., Averna, M., De Tullio, R., Pedrazzi, M., Milanese, M., Bonifacino, T., et al. (2014). Role of calpain-1 in the early phase of experimental ALS. *Archives of Biochemistry and Biophysics*, *562*, 1–8.

Sun, M., Zhao, Y., & Xu, C. (2008). Cross-talk between calpain and caspase-3 in penumbra and core during focal cerebral ischemia-reperfusion. *Cellular and Molecular Neurobiology*, *28*, 71–85.

Suzuki, K., Hata, S., Kawabata, Y., & Sorimachi, H. (2004). Structure, activation, and biology of calpain. *Diabetes*, *53*(Suppl), 12–18.

Tompa, P., Buzder-Lantos, P., Tantos, A., Farkas, A., Szilágyi, A., Bánóczi, Z., et al. (2004). On the sequential determinants of calpain cleavage. *The Journal of Biological Chemistry*, *279*, 20775–20785.

Wendt, A., Thompson, V. F., & Goll, D. E. (2004). Interaction of calpastatin with calpain: A review. *Biological Chemistry*, *385*, 465–472.

Wienecke, J., Westerdahl, A. C., Hultborn, H., Kiehn, O., & Ryge, J. (2010). Global gene expression analysis of rodent motor neurons following spinal cord injury associates molecular mechanisms with development of postinjury spasticity. *Journal of Neurophysiology*, *103*, 761–778.

Yamashita, T., Teramoto, S., & Kwak, S. (2016). Phosphorylated TDP-43 becomes resistant to cleavage by calpain: A regulatory role for phosphorylation in TDP-43 pathology of ALS/FTLD. *Neuroscience Research*, *107*, 63–69.

Yu, C. G., Bondada, V., Joshi, A., Reneer, D. V., Telling, G. C., Saatman, K. E., et al. (2020). Calpastatin overexpression protects against excitotoxic hippocampal injury and traumatic spinal cord injury. *Journal of Neurotrauma*, *37*, 2268–2276.

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Chapter 22

Targeting mTOR signaling to promote autophagy for functional recovery after spinal cord injury

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List of abbreviations

Akt	Ak strain transforming or protein kinase B
AMPK	adenosine monophosphate-activated protein kinase
Bax	Bcl-2-associated protein X
GLP-1	glucagon-like peptide 1
LC3	microtubule-associated protein 1 light chain 3
mTOR	mechanistic target of rapamycin
p62/SQSTM1	sequestosome-1
p70S6K	the 70 kDa ribosomal protein S6 kinase
PI3KC3	phosphoinositide 3-kinase class 3 complex
PIKK	phosphatidylinositol 3-kinase-related kinase
SCI	spinal cord injury
VMNs	ventral motoeurons

Introduction

Spinal cord injury (SCI) is a devastating damage to the spinal cord causing significant impairments of the function of neurons distal to the site of injury (Drasites et al., 2020). SCI can lead to permanent debilitating neurological deficits, for example, paraplegia of the lower limbs, difficulties in breathing and respiratory insufficiency, altered sensation, and autonomous dysfunction of cardiovascular, gastrointestinal, respiratory, and urinary systems (Cheng, Liao, Liao, Chuang, & Shih, 2004; Galeiras Vázquez, Rascado Sedes, Mourelo Fariña, Montoto Marqués, & Ferreiro Velasco, 2013; Karlsson, 2006; Zompa, Cain, Everhart, Moyer, & Hulsebosch, 1997). SCI is a global problem with an annual incidence of 54 new cases per 1 million in the United States, with males affected more than females (Bracken, Freeman, & Hellenbrand, 1981; Jain et al., 2015). The etiology of SCI varies and it may occur due to internal and external causes that relate to patient's medical history, for example, primary or metastatic tumor of the spine or ischemic damage to the spinal cord manifesting a non-traumatic SCI, or most often, SCI occurs due to external causes due to severe physical trauma to the spine during traffic accidents on the road or in case of work-related injuries causing traumatic SCI (Ekong & Tator, 1985; Ge, Arul, & Mesfin, 2019; Lee, Cripps, Fitzharris, & Wing, 2014; Mauney et al., 1995). Traumatic SCI is the main focus of current research activities as it is more complex and more prevalent than non-traumatic SCI. From this point onward, we will use SCI only to refer to traumatic SCI. Current management of SCI varies based on the cause, location, duration, and severity of the trauma, and it is usually a combination of medical and surgical treatments that include immobilization, analgesia, and surgical intervention to decompress and stabilize the spine (Fehlings, Cadotte, & Fehlings, 2011).

The pathophysiology of SCI is complex and multifactorial, and it is characterized by immediate and late injuries to the neurons and surrounding tissue. Initial injury can lead to substantial neuronal loss, hemorrhage, and edema (Dumont et al., 2001; Nakamura & Okano, 2013). Following SCI initial damage, the neurons are exposed to further deleterious cascade of secondary damages, which cause further neuronal loss and demyelination leading to permanent neurological deficits

Cellular, Molecular, Physiological, and Behavioral Aspects of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822427-4.00022-8

(Dumont et al., 2001; Nakamura & Okano, 2013). Hence, early intervention for minimizing the secondary damages is crucial to preserve both integrity and function of the neurons and to promote functional recovery after SCI.

Macroautophagy is a highly conserved recycling mechanism within the cell and it can be further aggravated during stressful conditions, for example, cell injury, hypoxia, or nutritional deprivations (Kulkarni, Chen, & Maday, 2018; Li et al., 2021; Stacchiotti & Corsetti, 2020). Macroautophagy is well-regulated sequential events that aim to clear the cell from old or damaged organelles and/or other macromolecules by lysosomal degradation, and to recycle and reuse the cellular building blocks (Feng, He, Yao, & Klionsky, 2014; Nakatogawa, 2020; Xie, Nair, & Klionsky, 2008). Autophagy is characterized by development and function of three main autophagy machinery structures: phagophore, autophagosome, and autolysosome. Phagophore is a cup-shaped lipid-rich membrane that surrounds and engulfs a portion of the cytoplasm containing the damaged cellular components (Feng et al., 2014; Nakatogawa, 2020; Xie et al., 2008). Phagophore becomes elongated and its two ends are then fused to form a double-membrane large circular vesicle called autophagosome (Feng et al., 2014; Nakatogawa, 2020; Xie et al., 2008). Autophagosome is then fused with the lysosome to form the autolysosome, which contains various hydrolase enzymes that degrade the sequestered cellular organelles and other macromolecules (Feng et al., 2014; Nakatogawa, 2020; Xie et al., 2008).

Autophagy flux is the measure of the autophagy degradation activity, which requires well development of autophagosome, its fusion with lysosome, and efficient lysosomal degradation to prevent buildup of toxic materials within the cells (du Toit, Hofmeyr, Gniadek, & Loos, 2018; Klionsky et al., 2012). Molecular regulation of autophagy involves interactions among several proteins, which are critical for promoting autophagy flux with the development of autophagy machinery components including Beclin-1, LC3 (microtubule-associated protein 1 light chain 3), p62/SQSTM1 (sequestosome-1), and others. Beclin-1 is a part of phosphoinositide 3-kinase class 3 complex (PI3KC3), which regulates formation of autophagosome, degradation of caspases, and attenuation of apoptosis (Xie, Kang, & Tang, 2016). LC3 I and II are critical proteins for the formation and maturation of autophagosome (Brier et al., 2019; Giatromanolaki et al., 2011; Park, Huang, Wu, Foster, & Sinicrope, 2013). During autophagy, the soluble cytosolic protein LC3 I with the aid of Beclin-1 is coupled to phosphatidylethanolamine phospholipids for its conversion into the membrane-bound form LC3 II, which is one of the major constituents of the autophagosome membrane (Brier et al., 2019; Giatromanolaki et al., 2011; Park et al., 2013). p62 is a polyubiquitin-binding protein that can bind to both LC3 II and the misfolded and/or ubiquitylated proteins (Pankiv et al., 2007; Park et al., 2013; Rusten & Stenmark, 2010). During autophagy, LC3 II binds to p62 to promote autophagy flux and degradation in which autophagic cargo as well as p62 is degraded by the autolysosome (Pankiv et al., 2007; Park et al., 2013; Rusten & Stenmark, 2010).

The role of autophagy in SCI is still debatable; however, growing evidence suggests that autophagy flux is impaired after SCI and it negatively impacts locomotor functions and neuronal survival (Li, Du, Lu, & Lin, 2019; Wang, Jiang, et al., 2018; Zhang et al., 2017). Studies in rodent models showed activation of autophagy shortly after compression or contusion injury to the spinal cord; however, autophagy flux was impaired in these models coupled with increases in neuronal death and impaired locomotor function (Li, Du, et al., 2019; Wang, Jiang, et al., 2018; Zhang et al., 2017). Molecular analysis has shown downregulation of Beclin-1 expression, reduction in LC3 II/LC3 I ratio, upregulation of p62, and increase in neuronal apoptosis as assessed by activation of caspase-3 and/or pro-apoptotic Bax (Bcl-2-associated X) proteins (Li, Du, et al., 2019; Wang, Jiang, et al., 2018; Zhang et al., 2017). These results suggested that promoting autophagy flux could be a potential therapeutic option to alleviate secondary damages to the neurons and to limit neuronal death following SCI.

The mechanistic target of rapamycin (mTOR) is a serine-threonine protein kinase that belongs to phosphatidylinositol 3-kinase-related kinase (PIKK) family, which regulates various cellular processes in developing as well as in mature neurons, for example, regulations of cell growth, cell proliferation, cell death, protein translation, and autophagy (Perluigi, Di Domenico, & Butterfield, 2015). mTOR is a key regulator of autophagy and it can be activated via the sensor of energy such as the adenosine monophosphate-activated protein kinase (AMPK)-dependent or AMPK-independent pathways (Perluigi et al., 2015). Within the scope of SCI, in vivo and in vitro studies suggest that mTOR and its downstream regulator of protein synthesis, p70S6K (the 70 kDa ribosomal protein S6 kinase) is upregulated following the injury and it negatively impacts autophagy flux in the injured neurons and enhances their apoptosis. So, inhibition of mTOR signaling is an attractive therapeutic strategy for molecular alterations for the promotion of autophagy flux and inhibition of apoptosis in SCI (Fig. 1). In subsequent parts, we will describe current advances in targeting mTOR signaling pathway with natural, genetic, and pharmacological mTOR inhibitors to potentiate autophagy flux, preserve neurons, and accelerate functional recovery in SCI. All these results strongly imply a neuroprotective role of the mTOR inhibitors via enhancing autophagy flux.

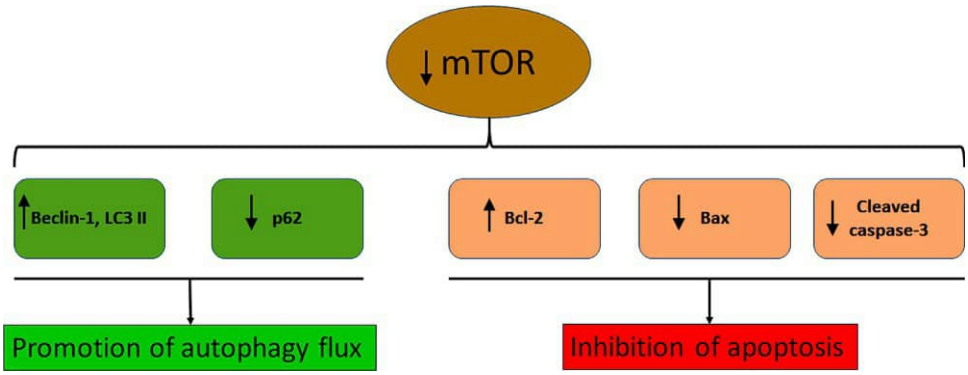

FIG. 1 Effect of mTOR inhibition on autophagy flux and apoptosis after SCI. Treatment with mTOR inhibitors promotes autophagy flux, which is characterized by increased conversion of LC3 I to LC3 II and decreasing the autophagy substrate p62. In contrast, mTOR inhibitors reduce apoptosis, which is marked by increasing anti-apoptotic protein Bcl-2, decreasing pro-apoptotic Bax protein, and preventing cleavage of pro-caspase-3 to caspase-3 in SCI.

Natural compounds for inhibition of mTOR signaling and promotion of autophagy flux and functional recovery after SCI

Studies show that various attempts have been made to inhibit mTOR signaling directly or indirectly in cell culture and animal models of SCI (Fig. 2). At first, we will describe the use of several natural compounds for inhibition of mTOR signaling to promote autophagy flux and enhance functional neuroprotection mostly in rodent models of SCI (Table 1).

Curcumin

It is a natural polyphenolic substance extracted from *Curcuma longa* plants and has been found to exert beneficial effects on neurological and non-neurological disorders via activation of autophagy (Fu et al., 2018; Kocaadam & Şanlier, 2017; Wang, Zhang, Teng, Zhang, & Li, 2014). Curcumin treatment has been shown to exert neuroprotective effects via activation of autophagy in rat SCI. Following contusion injury to spinal cord in rats, curcumin treatment potentiates autophagy, reduces neuronal apoptosis, and improves locomotor function via inhibition of protein kinase B or Akt /mTOR pathway (Li, Yao, et al., 2019).

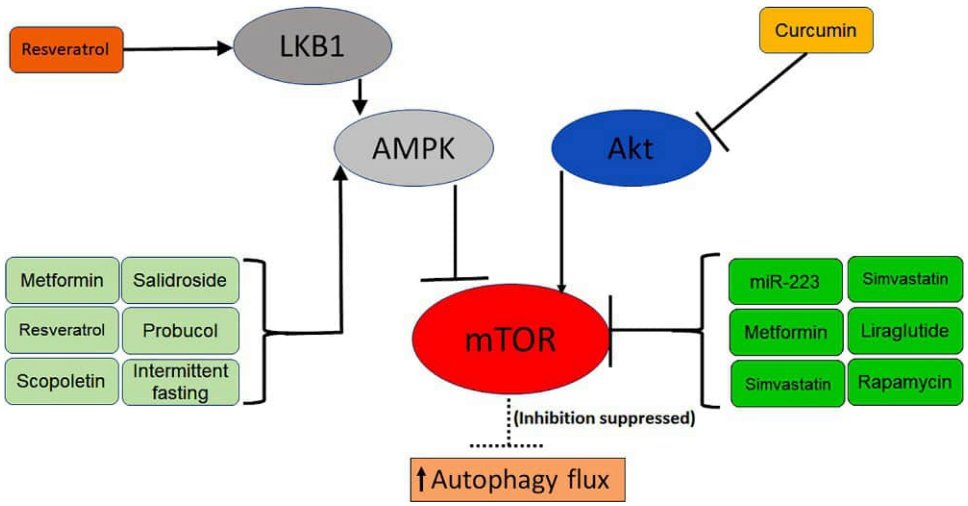

FIG. 2 Molecular mechanisms of mTOR inhibition using pharmacological and non-pharmacological approaches in SCI. Many mTOR inhibitors enhance autophagy flux via AMPK-dependent and AMPK-independent mechanisms in SCI.

TABLE 1 Effects of natural compounds on mTOR pathway and autophagy following SCI.

mTOR inhibitor	Class	SCI model	Effect on mTOR pathway	Effect on autophagy	Effect on SCI	References
Curcumin	Polyphenolic compound	Rat spinal cord contusion weight drop injury	Downregulates Akt/mTOR pathway	Enhances autophagy	Reduces neuronal apoptosis, improves functional recovery, preserves neurons, and enhances remyelination	Li, Yao, Li, Meng, and Sun (2019)
Resveratrol	Polyphenolic compound	Rat spinal cord contusion weight drop injury	Increases phosphorylation of AMPK and decreases phosphorylation of mTOR	Increases Beclin-1 and LC3 II/LC3 I ratio	Improves functional recovery following SCI	Wang, Jiang, et al. (2018)
Resveratrol	Polyphenolic compound	Rat spinal cord contusion weight drop injury	Increases expression of LKB1 and phosphorylation of AMPK and reduces phosphorylation of mTOR and p70S6K	Increases LC3 II/LC3 I ratio and decreases p62	Reduces neuronal apoptosis via decreasing activation of caspase-3 and Bax/Bcl-2 ratio, preserving motor neurons, and improving functional recovery	Meng et al. (2018)
Resveratrol	Polyphenolic compound	H_2O_2-treated-PC12 cells (in vitro oxidative injury)	Increases LKB1 expression and phosphorylation of AMPK and reduces phosphorylation of mTOR and p70S6K	Increases LC3 II/LC3 I ratio and decreases p62	Not available	Wang, Jiang, et al. (2018)
Salidroside	Phenolic glycoside	Rat spinal cord crush injury with vascular clip	Increases phosphorylation of AMPK and reduces phosphorylation of mTOR and p70S6K	Increases LC3 II expression and decreases p62 expression	Reduces neuronal apoptosis and motor neuron loss and promotes locomotor function	Wang, Wang, et al. (2018)
Scopoletin	Phytoalexin compound	Rat spinal cord damage by impounder impact	Increases phosphorylation of AMPK and reduces phosphorylation of mTOR	Promotes autophagy	Reduces neuronal apoptosis and improves functional recovery after SCI	Zhou et al. (2020)

Resveratrol

It is a plant-derived polyphenolic compound (3,5,4′-trihydroxy-*trans*-stilbene), which is found in the skin of red grapes and blueberries and it provides various health benefits due to its antioxidant, antitumor, and anti-inflammatory effects (Salehi et al., 2018). Resveratrol has been shown to promote autophagy flux and manifest neuroprotective roles on SCI both in vivo and in vitro. In rat model of SCI, resveratrol treatment enhances autophagy, reduces neuronal apoptosis, preserves motoneurons, and improves locomotor function (Meng et al., 2018; Wang, Jiang, et al., 2018). Resveratrol-mediated autophagy activation occurs via activation of AMPK/mTOR/p70S6K pathway (Meng et al., 2018; Wang, Jiang, et al., 2018). Similarly, resveratrol treatment of the H_2O_2-treated neuronal PC12 cells potentiated autophagy flux via AMPK/mTOR/p70S6K pathway (Wang, Jiang, et al., 2018).

Salidroside

Salidroside is a phenolic glycoside, which is extracted from *Rhodiola sachalinensis* plant, and it has antioxidant, anti-inflammatory, and neuroprotective roles (Han et al., 2015; Li & Chen, 2001; Tang et al., 2016). Salidroside treatment of SCI rats reduces neuroinflammation, enhances locomotor function, decreases spinal cord lesion and apoptosis, and reduces loss of ventral motoneurons (VMNs) (Wang, Wang, et al., 2018). Molecular analysis shows that salidroside promotes autophagy flux via AMPK/mTOR/p70S6K pathway (Wang, Wang, et al., 2018).

Scopoletin

It is a phytoalexin, which is extracted from many plants such as *Crossostephium chinensis* and *Sinomonium acutum*, possessing anti-inflammatory and antioxidant properties (Chang et al., 2012; Shaw, Chen, Hsu, Chen, & Tsai, 2003). Scopoletin treatment of SCI rats showed activation of autophagy, reduction of neuronal apoptosis, and enhancement of locomotor function. Induction of autophagy for neuroprotection is mediated via AMPK/mTOR pathway (Zhou et al., 2020).

Pharmacological inhibition of mTOR signaling for enhancing autophagy flux and functional recovery following SCI

Some investigators have used various pharmacological agents for inhibiting mTOR signaling so as to enhance autophagy flux and promote functional recovery in animal models of SCI (Table 2). Here, we will describe five pharmacological agents (rapamycin, metformin, liraglutide, simvastatin, and probucol) that have been shown to inhibit mTOR signaling in treating SCI in animals to achieve an increase in autophagy flux and improvements in neurological functions.

Rapamycin

It is a macrocyclic lactone compound extracted from *Streptomyces hygroscopicus* and it has both antifungal and antibiotic effects (Pallet, Beaune, Legendre, & Anglicheau, 2006). Rapamycin is a well-known compound for mTOR inhibition. Mice model of SCI treated with rapamycin shows inhibition of the mTOR downstream target, p70S6K phosphorylation, increase in autophagy, decrease in neuronal cell death, and improvement in locomotor function (Sekiguchi et al., 2012). Similarly, post-SCI rapamycin treatment of rats enhances autophagy via Akt/mTOR pathway, upregulates Beclin-1, and reduces neuronal apoptosis and loss in SCI (Li, Du, et al., 2019).

TABLE 2 Effects of pharmacological inhibition of mTOR signaling on autophagy in SCI.

mTOR inhibitor	Class	SCI model	Effect on mTOR pathway	Effect on autophagy	Effect on SCI	References
Rapamycin	Specific mTOR inhibitor	Mice	Decreases phosphorylation of p70S6K	Increases LC3 and Beclin-1 expression	Reduces neuronal death and improves locomotor function	Sekiguchi, Kanno, Ozawa, Yamaya, and Itoi (2012)
Rapamycin	Specific mTOR inhibitor	Rat compressive SCI with aneurysm clip	Decreases phosphorylation of mTOR and increases phosphorylation of Akt	Increases Beclin-1	Reduces neuronal apoptosis via increase in Bcl-2, decreases in Bax, mitochondrial cytochrome *c* release, and active caspase-3	Li, Du, et al. (2019)

Continued

TABLE 2 Effects of pharmacological inhibition of mTOR signaling on autophagy in SCI—cont'd

mTOR inhibitor	Class	SCI model	Effect on mTOR pathway	Effect on autophagy	Effect on SCI	References
Metformin	Oral anti-diabetes medicine	Rat	Increases phosphorylation of AMPK and inhibits phosphorylation of mTOR	Increases formation of autophagosome and expression of Beclin-1 and LC3 II and Beclin-1 expression while reduction of p62 and ubiquitinated proteins	Reduces neuronal apoptosis and improves functional recovery	Zhang et al. (2017)
Metformin	Oral diabetes medicine	Rat	Decreases phosphorylation of mTOR and p70S6K	Increases Beclin-1 and LC3 II expression	Preserves motor neurons and enhances their functions	Wang et al. (2016)
Metformin	Oral anti-diabetic drug	Rat	Decreases mTOR and p70S6K	Increases autophagy	Reduces apoptosis, increases number of the survived neurons, and improves locomotor function	Guo et al. (2018)
Liraglutide	Glucagon-like peptide 1 (GLP-1) analog	Rat spinal cord compression injury with vascular clamp	Reduces phosphorylation of mTOR and p62 expression	Increases formation of autophagosome, Beclin-1, and LC3 II/LC3 I ratio	Reduces motor neuron loss and improves locomotor function	Chen et al. (2017)
Simvastatin	3-Hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor	Rat spinal cord weight drop contusion injury	Reduces phosphorylation of mTOR and p70S6K	Increases Beclin-1 and LC3 IIB proteins	Inhibits apoptosis and enhances functional recovery	Gao et al. (2015)
Probucol	Anti-hyperlipidemic drug	Rat	Increases phosphorylation of AMPK and reduces phosphorylation of p70S6K	Increases Beclin-1 and LC3 IIB	Inhibits neural apoptosis and preserves motor neurons	Zhou et al. (2016)

Metformin

It is an oral biguanide commonly used to treat type 2 diabetes and it can potentiate autophagy via direct or indirect mTOR inhibition (Ling et al., 2017; Xiao et al., 2017). Metformin treatment of SCI rats potentiates autophagy, reduces neuronal death, decreases lesion size, and enhances functional recovery (Guo et al., 2018; Wang et al., 2016; Zhang et al., 2017). In these studies, metformin triggered autophagy via activation of AMPK/mTOR/p70S6K pathway or possibly via direct inhibition of mTOR. These results suggested that metformin could inhibit mTOR directly or indirectly via AMPK pathway.

Liraglutide

It is a glucagon-like peptide 1 (GLP-1) analog with anti-diabetic and anti-inflammatory properties (Hou et al., 2012). Liraglutide treatment of SCI rats enhances autophagy flux in neurons, reduces apoptosis, prevents neuronal loss, and enhances locomotor function. Liraglutide enhances autophagy flux via reduction of mTOR and p62 phosphorylation (Chen et al., 2017).

Simvastatin

It is a 3-hydroxy-3-methylglutaryl-coenzyme. As a reductase inhibitor, it has anti-hyperlipidemic properties and it is commonly used in the treatment of cardiovascular diseases (Li et al., 2020). Treatment of SCI in rats with simvastatin enhances autophagy, inhibits apoptosis, and improves functional recovery. Molecular analysis shows that the neuroprotective effects of simvastatin in SCI are regulated by activation of autophagy via inhibition of mTOR/p70S6K phosphorylation (Gao et al., 2015).

Probucol

It is an anti-hyperlipidemic drug with some anti-inflammatory and anti-diabetic effects (Mooranian et al., 2018). Treatment with probucol shows significant effects in increasing the number and function of motoneurons following SCI in rats. Treatment with probucol enhances autophagic activity and reduces induction of apoptosis via increasing phosphorylation of AMPK and decreasing phosphorylation of p70S6K (Zhou et al., 2016).

Genetic and non-genetic inhibitors of mTOR signaling to regulate autophagy in SCI

Some investigators have successfully used both genetic and non-genetic inhibitors for downregulating mTOR signaling for altering autophagy in the treatment of SCI in animals (Table 3). These approaches include miR-223 and intermittent fasting, which have beneficial effects in enhancing autophagy flux and locomotor function via inhibition of mTOR signaling pathways.

miR-223

It is a small non-coding single-stranded RNA that regulates gene expression in neurological and non-neuroglial diseases (Glasgow et al., 2013; Haneklaus, Gerlic, O'Neill, & Masters, 2013). Overexpression of miR-223 in lipopolysaccharide (LPS)-stimulated neuronal PC12 cells inhibits mTOR phosphorylation with downregulation of the histone demethylase protein RPH1, inhibits autophagy flux, blocks apoptosis, and improves cell viability. Results indicate that miR-223 reduces cell death and autophagy by targeting mTOR/RPH1 pathway in LPS-induced PC12 cells (Jia et al., 2017).

TABLE 3 Effects of genetic and non-genetic inhibition of mTOR on autophagy in SCI.

mTOR inhibitor	Class	SCI model	Effect on mTOR pathway	Effect on autophagy	Effect on SCI	References
miR-223 overexpression	Non-coding single-stranded RNA	LPS-stimulated PC12 cells	Inhibits phosphorylation of mTOR with downregulation of RPH1	Reduces Beclin-1 and LC3-II and increases p62	Inhibits neuronal apoptosis and enhances their survival	Jia, Niu, Li, and Zhang (2017)
Intermittent fasting	Dietary intervention	Rat	Increases phosphorylation of AMPK and decreases phosphorylation of mTOR	Increases Beclin-1 and LC3 II and decreases p62	Reduces neuronal apoptosis via decrease in Bax/Bcl-2 ratio and cleaved caspase-3	Yuan et al. (2021)

Intermittent fasting

It is a dietary intervention approach of short-term food restriction, which is known to promote autophagy in neurons (Alirezaei et al., 2010). Implementing intermittent fasting in rat model of SCI activates autophagy flux, reduces neuronal death, and increases survival and functional recovery following injury. This study found that intermittent fasting stimulated autophagy flux via inhibition of AMPK/mTOR pathway (Yuan et al., 2021).

Future directions

Impaired autophagy flux in SCI is a complex deregulated mechanism that is associated with increase in neuronal apoptosis and impaired functional recovery. Even though the role of autophagy in SCI could be protective or destructive (Ray, 2020), emerging evidence indicates that enhancing autophagy flux by inhibition of mTOR signaling has promising neuroprotective effects for functional recovery, particularly in severe contusion injury (Fig. 3). Although these studies have elucidated the role of AMPK-dependent or AMPK-independent mechanisms of mTOR inhibitors, further studies are required to understand more about the upstream molecular regulation of mTOR inhibition, the downstream target of mTOR that regulates autophagy flux, and how promotion of autophagy prevents apoptosis and neuronal loss in SCI. Further mechanistic studies are warranted to establish the precise role of autophagy in SCI.

Applications to other areas of neuroscience

So far recent studies strongly suggest that targeting mTOR signaling at an early phase of SCI can provide neuroprotective effects via promoting autophagy flux, reducing secondary damages, and improving functional recovery following SCI. In addition, mTOR signaling pathway is involved in deregulation of autophagy flux in other major neurodegenerative diseases including Alzheimer's disease and Parkinson's disease (Cai, Chen, He, Xiao, & Yan, 2015; Zhu et al., 2019). In Alzheimer's disease, deregulation of mTOR signaling and impairment of autophagy are found to be associated with increase in β-amyloid (Aβ) generation and deposition of amyloid precursor proteins (Cai et al., 2015). In Parkinson's disease, mTOR signaling is deregulated and it causes increase in accumulation of the aggregated harmful proteins such as α-synuclein, which is associated with autophagy impairment (Zhu et al., 2019). Similarly, combating mTOR signaling in these neurological diseases, with the use of pharmacological and non-pharmacological approaches, has shown to enhance autophagy flux via direct or indirect mTOR inhibition; however, it is still little known about the molecular regulation of upstream and downstream pathways to mTOR in these diseases. Although we have discussed the recent studies that highlight the role of mTOR inhibitors on locomotor recovery following SCI via natural, pharmacological, and genetic approaches, further studies will not only provide better understanding of the underlying mechanisms of the impaired autophagy flux in the pathogenesis of SCI but also will delineate the precise role of autophagy in other neurodegenerative diseases including Alzheimer's disease and Parkinson's disease, where deregulation of autophagy and mTOR signaling are well documented.

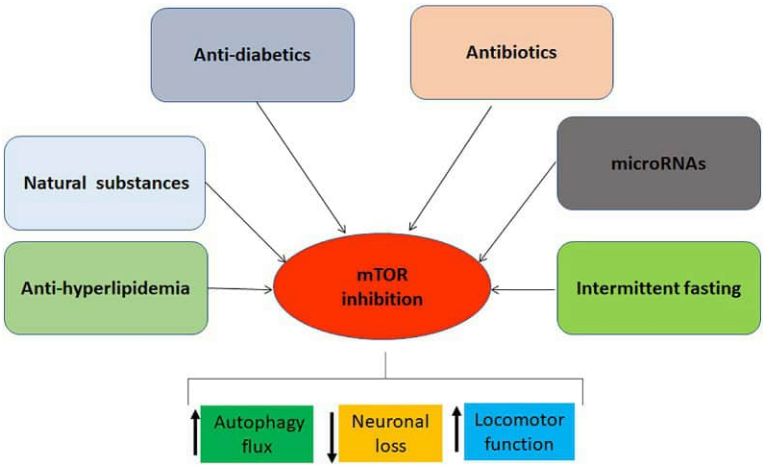

FIG. 3 Pharmacological and non-pharmacological inhibition of mTOR pathway in rodent model of SCI. Treatment with plant-derived natural substances, antibiotic drug, anti-diabetic drug, anti-hyperlipidemia drug, microRNAs, and intermittent fasting inhibits mTOR signaling, enhancing autophagy and functional recovery after SCI.

Mini-dictionary of terms

Traumatic spinal cord injury: it refers to direct physical injury to the spinal cord such as fracture of the spine during severe road traffic accident or falling from height.
Non-traumatic spinal cord injury: it refers to indirect injury to spinal cord that caused by progressive medical diseases, such as, in patients with vascular disease with poor circulation or abrupt impairment of blood supply to the spinal cord or in patients with chronic neurodegenerative diseases that involve the spinal cord.
Macroautophagy: it is a recycling process within the cell to clean the cytoplasm from the damaged or unused large molecules or organelles and reuse their degraded primary elements to maintain the function of the cell.

Key facts of targeting mTOR signaling in promotion of autophagy for functional recovery after SCI

- SCI is a serious neurodegenerative disorder, mostly traumatic in nature, and it frequently leads to long-life complications.
- Balance between autophagy and apoptosis is critical to minimize neuronal cell injury and improve functional recovery.
- Deregulation of macroautophagy, particularly autophagy flux, is evident shortly after SCI and it is associated with impairment of neuronal and neuroglial cell survival due to increase in apoptosis.
- Upregulation of mTOR has been reported in SCI and it is linked with the impaired autophagy flux.
- Therapeutic and natural inhibitions of mTOR signaling enhance autophagy flux and have shown promising beneficial effects on locomotor function following SCI.

Summary points

- Traumatic SCI is a deleterious global health problem with economic and medical burdens.
- Impairment of autophagy flux is one of the proposed secondary damaging mechanisms that is associated with poor functional recovery following SCI.
- Increase in mTOR signaling has been reported after SCI and it is thought to cause impairment in autophagy flux.
- Pharmacological and non-pharmacological inhibitions of mTOR signaling promote autophagy flux, increase neuronal cell survival, reduce apoptosis, and improve functional recovery following SCI.

Acknowledgments

The work was supported in part by the earlier R01 grants (CA-091460 and NS-057811) from the National Institutes of Health (Bethesda, MD, USA) and a current grant (SCIRF-2020-PD-01) from the State of South Carolina (Columbia, SC, USA).

References

Alirezaei, M., Kemball, C. C., Flynn, C. T., Wood, M. R., Whitton, J. L., & Kiosses, W. B. (2010). Short-term fasting induces profound neuronal autophagy. *Autophagy*, *6*(6), 702–710. https://doi.org/10.4161/auto.6.6.12376.

Bracken, M. B., Freeman, D. H., & Hellenbrand, K. (1981). Incidence of acute traumatic hospitalized spinal cord injury in the United States, 1970–1977. *American Journal of Epidemiology*, *113*(6), 615–622. https://doi.org/10.1093/oxfordjournals.aje.a113140.

Brier, L. W., Ge, L., Stjepanovic, G., Thelen, A. M., Hurley, J. H., & Schekman, R. (2019). Regulation of LC3 lipidation by the autophagy-specific class III phosphatidylinositol-3 kinase complex. *Molecular Biology of the Cell*, *30*(9), 1098–1107. https://doi.org/10.1091/mbc.E18-11-0743.

Cai, Z., Chen, G., He, W., Xiao, M., & Yan, L. J. (2015). Activation of mTOR: A culprit of Alzheimer's disease? *Neuropsychiatric Disease and Treatment*, *11*, 1015–1030. https://doi.org/10.2147/NDT.S75717.

Chang, T. N., Deng, J. S., Chang, Y. C., Lee, C. Y., Jung-Chun, L., Lee, M. M., … Huang, G. J. (2012). Ameliorative effects of scopoletin from *Cross-ostephium chinensis* against Inflammation pain and Its mechanisms in mice. *Evidence-Based Complementary and Alternative Medicine: eCAM*, *2012*, 595603. https://doi.org/10.1155/2012/595603.

Chen, J., Wang, Z., Mao, Y., Zheng, Z., Chen, Y., Khor, S., … Wang, X. (2017). Liraglutide activates autophagy via GLP-1R to improve functional recovery after spinal cord injury. *Oncotarget*, *8*(49), 85949–85968. https://doi.org/10.18632/oncotarget.20791.

Cheng, H., Liao, K. K., Liao, S. F., Chuang, T. Y., & Shih, Y. H. (2004). Spinal cord repair with acidic fibroblast growth factor as a treatment for a patient with chronic paraplegia. *Spine (Phila Pa 1976)*, *29*(14), E284–E288. https://doi.org/10.1097/01.brs.0000131217.61390.2c.

Drasites, K. P., Shams, R., Zaman, V., Matzelle, D., Shields, D. C., Garner, D. P., … Banik, N. L. (2020). Pathophysiology, biomarkers, and therapeutic modalities associated with skeletal muscle loss following spinal cord injury. *Brain Sciences*, *10*(12), 933. https://doi.org/10.3390/brainsci10120933.

du Toit, A., Hofmeyr, J. S., Gniadek, T. J., & Loos, B. (2018). Measuring autophagosome flux. *Autophagy*, *14*(6), 1060–1071. https://doi.org/10.1080/15548627.2018.1469590.

Dumont, R. J., Okonkwo, D. O., Verma, S., Hurlbert, R. J., Boulos, P. T., Ellegala, D. B., & Dumont, A. S. (2001). Acute spinal cord injury, part I: Pathophysiologic mechanisms. *Clinical Neuropharmacology*, *24*(5), 254–264. https://doi.org/10.1097/00002826-200109000-00002.

Ekong, C. E., & Tator, C. H. (1985). Spinal cord injury in the work force. *Canadian Journal of Surgery*, *28*(2), 165–167.

Fehlings, M. G., Cadotte, D. W., & Fehlings, L. N. (2011). A series of systematic reviews on the treatment of acute spinal cord injury: A foundation for best medical practice. *Journal of Neurotrauma*, *28*(8), 1329–1333. https://doi.org/10.1089/neu.2011.1955.

Feng, Y., He, D., Yao, Z., & Klionsky, D. J. (2014). The machinery of macroautophagy. *Cell Research*, *24*(1), 24–41. https://doi.org/10.1038/cr.2013.168.

Fu, H., Wang, C., Yang, D., Wei, Z., Xu, J., Hu, Z., … Cai, Q. (2018). Curcumin regulates proliferation, autophagy, and apoptosis in gastric cancer cells by affecting PI3K and P53 signaling. *Journal of Cellular Physiology*, *233*(6), 4634–4642. https://doi.org/10.1002/jcp.26190.

Galeiras Vázquez, R., Rascado Sedes, P., Mourelo Fariña, M., Montoto Marqués, A., & Ferreiro Velasco, M. E. (2013). Respiratory management in the patient with spinal cord injury. *BioMed Research International*, *2013*, 168757. https://doi.org/10.1155/2013/168757.

Gao, K., Wang, G., Wang, Y., Han, D., Bi, J., Yuan, Y., … Mei, X. (2015). Neuroprotective effect of simvastatin via inducing the autophagy on spinal cord injury in the rat model. *BioMed Research International*, *2015*, 260161. https://doi.org/10.1155/2015/260161.

Ge, L., Arul, K., & Mesfin, A. (2019). Spinal cord injury from spinal tumors: Prevalence, management, and outcomes. *World Neurosurgery*, *122*, e1551–e1556. https://doi.org/10.1016/j.wneu.2018.11.099.

Giatromanolaki, A., Koukourakis, M. I., Koutsopoulos, A., Chloropoulou, P., Liberis, V., & Sivridis, E. (2011). High beclin 1 expression defines a poor prognosis in endometrial adenocarcinomas. *Gynecologic Oncology*, *123*(1), 147–151. https://doi.org/10.1016/j.ygyno.2011.06.023.

Glasgow, S. M., Laug, D., Brawley, V. S., Zhang, Z., Corder, A., Yin, Z., Wong, S.T., … Deneen, B. (2013). The miR-223/nuclear factor I-A axis regulates glial precursor proliferation and tumorigenesis in the CNS. *The Journal of Neuroscience*, *33*(33), 13560–13568. https://doi.org/10.1523/JNEUROSCI.0321-13.2013.

Guo, Y., Wang, F., Li, H., Liang, H., Li, Y., Gao, Z., & He, X. (2018). Metformin protects against spinal cord injury by regulating autophagy via the mTOR signaling pathway. *Neurochemical Research*, *43*(5), 1111–1117. https://doi.org/10.1007/s11064-018-2525-8.

Han, J., Xiao, Q., Lin, Y. H., Zheng, Z. Z., He, Z. D., Hu, J., & Chen, L. D. (2015). Neuroprotective effects of salidroside on focal cerebral ischemia/reperfusion injury involve the nuclear erythroid 2-related factor 2 pathway. *Neural Regeneration Research*, *10*(12), 1989–1996. https://doi.org/10.4103/1673-5374.172317.

Haneklaus, M., Gerlic, M., O'Neill, L. A., & Masters, S. L. (2013). miR-223: Infection, inflammation and cancer. *Journal of Internal Medicine*, *274*(3), 215–226. https://doi.org/10.1111/joim.12099.

Hou, J., Manaenko, A., Hakon, J., Hansen-Schwartz, J., Tang, J., & Zhang, J. H. (2012). Liraglutide, a long-acting GLP-1 mimetic, and its metabolite attenuate inflammation after intracerebral hemorrhage. *Journal of Cerebral Blood Flow and Metabolism*, *32*(12), 2201–2210. https://doi.org/10.1038/jcbfm.2012.133.

Jain, N. B., Ayers, G. D., Peterson, E. N., Harris, M. B., Morse, L., O'Connor, K. C., & Garshick, E. (2015). Traumatic spinal cord injury in the United States, 1993–2012. *JAMA*, *313*(22), 2236–2243. https://doi.org/10.1001/jama.2015.6250.

Jia, D., Niu, Y., Li, D., & Zhang, Q. (2017). MicroRNA-223 alleviates lipopolysaccharide-induced PC-12 cells apoptosis and autophagy by targeting RPH1 in spinal cord injury. *International Journal of Clinical and Experimental Pathology*, *10*(9), 9223–9232.

Karlsson, A. K. (2006). Autonomic dysfunction in spinal cord injury: Clinical presentation of symptoms and signs. *Progress in Brain Research*, *152*, 1–8. https://doi.org/10.1016/S0079-6123(05)52034-X.

Klionsky, D. J., Abdalla, F. C., Abeliovich, H., Abraham, R. T., Acevedo-Arozena, A., Adeli, K., … Zuckerbraun, B. (2012). Guidelines for the use and interpretation of assays for monitoring autophagy. *Autophagy*, *8*(4), 445–544. https://doi.org/10.4161/auto.19496.

Kocaadam, B., & Şanlier, N. (2017). Curcumin, an active component of turmeric (*Curcuma longa*), and its effects on health. *Critical Reviews in Food Science and Nutrition*, *57*(13), 2889–2895. https://doi.org/10.1080/10408398.2015.1077195.

Kulkarni, A., Chen, J., & Maday, S. (2018). Neuronal autophagy and intercellular regulation of homeostasis in the brain. *Current Opinion in Neurobiology*, *51*, 29–36. https://doi.org/10.1016/j.conb.2018.02.008.

Lee, B. B., Cripps, R. A., Fitzharris, M., & Wing, P. C. (2014). The global map for traumatic spinal cord injury epidemiology: Update 2011, global incidence rate. *Spinal Cord*, *52*(2), 110–116. https://doi.org/10.1038/sc.2012.158.

Li, H. B., & Chen, F. (2001). Preparative isolation and purification of salidroside from the Chinese medicinal plant Rhodiola sachalinensis by high-speed counter-current chromatography. *Journal of Chromatography A*, *932*(1–2), 91–95. https://doi.org/10.1016/s0021-9673(01)01232-8.

Li, X. G., Du, J. H., Lu, Y., & Lin, X. J. (2019). Neuroprotective effects of rapamycin on spinal cord injury in rats by increasing autophagy and Akt signaling. *Neural Regeneration Research*, *14*(4), 721–727. https://doi.org/10.4103/1673-5374.247476.

Li, W., He, P., Huang, Y., Li, Y. F., Lu, J., Li, M., … Feng, D. (2021). Selective autophagy of intracellular organelles: recent research advances. *Theranostics*, *11*(1), 222–256. https://doi.org/10.7150/thno.49860.

Li, H., Rabearivony, A., Zhang, W., Chen, S., An, X., & Liu, C. (2020). Chronopharmacology of simvastatin on hyperlipidaemia in high-fat diet-fed obese mice. *Journal of Cellular and Molecular Medicine*, *24*(18), 11024–11029. https://doi.org/10.1111/jcmm.15709.

Li, W., Yao, S., Li, H., Meng, Z., & Sun, X. (2019). Curcumin promotes functional recovery and inhibits neuronal apoptosis after spinal cord injury through the modulation of autophagy. *Journal of Spinal Cord Medicine*, 1–9. https://doi.org/10.1080/10790268.2019.1616147.

Ling, S., Song, L., Fan, N., Feng, T., Liu, L., Yang, X., … Li, Y. (2017). Combination of metformin and sorafenib suppresses proliferation and induces autophagy of hepatocellular carcinoma via targeting the mTOR pathway. *International Journal of Oncology*, *50*(1), 297–309. https://doi.org/10.3892/ijo.2016.3799.

Mauney, M. C., Blackbourne, L. H., Langenburg, S. E., Buchanan, S. A., Kron, I. L., & Tribble, C. G. (1995). Prevention of spinal cord injury after repair of the thoracic or thoracoabdominal aorta. *Annals of Thoracic Surgery*, *59*(1), 245–252. https://doi.org/10.1016/0003-4975(94)00815-O.

Meng, H. Y., Shao, D. C., Li, H., Huang, X. D., Yang, G., Xu, B., & Niu, H. Y. (2018). Resveratrol improves neurological outcome and neuroinflammation following spinal cord injury through enhancing autophagy involving the AMPK/mTOR pathway. *Molecular Medicine Reports*, *18*(2), 2237–2244. https://doi.org/10.3892/mmr.2018.9194.

Mooranian, A., Negrulj, R., Takechi, R., Mamo, J., Al-Sallami, H., & Al-Salami, H. (2018). The biological effects of the hypolipidaemic drug probucol microcapsules fed daily for 4 weeks, to an insulin-resistant mouse model: Potential hypoglycaemic and anti-inflammatory effects. *Drug Delivery and Translational Research*, *8*(3), 543–551. https://doi.org/10.1007/s13346-017-0473-5.

Nakamura, M., & Okano, H. (2013). Cell transplantation therapies for spinal cord injury focusing on induced pluripotent stem cells. *Cell Research*, *23*(1), 70–80. https://doi.org/10.1038/cr.2012.171.

Nakatogawa, H. (2020). Mechanisms governing autophagosome biogenesis. *Nature Reviews. Molecular Cell Biology*, *21*(8), 439–458. https://doi.org/10.1038/s41580-020-0241-0.

Pallet, N., Beaune, P., Legendre, C., & Anglicheau, D. (2006). Rapamycine and mTOR inhibitors: From bench to bedside. *Annales de Biologie Clinique (Paris)*, *64*(2), 107–115.

Pankiv, S., Clausen, T. H., Lamark, T., Brech, A., Bruun, J. A., Outzen, H., … Johansen, T. (2007). p62/SQSTM1 binds directly to Atg8/LC3 to facilitate degradation of ubiquitinated protein aggregates by autophagy. *Journal of Biological Chemistry*, *282*(33), 24131–24145. https://doi.org/10.1074/jbc.M702824200.

Park, J. M., Huang, S., Wu, T. T., Foster, N. R., & Sinicrope, F. A. (2013). Prognostic impact of beclin 1, p62/sequestosome 1 and LC3 protein expression in colon carcinomas from patients receiving 5-fluorouracil as adjuvant chemotherapy. *Cancer Biology & Therapy*, *14*(2), 100–107. https://doi.org/10.4161/cbt.22954.

Perluigi, M., Di Domenico, F., & Butterfield, D. A. (2015). mTOR signaling in aging and neurodegeneration: At the crossroad between metabolism dysfunction and impairment of autophagy. *Neurobiology of Disease*, *84*, 39–49. https://doi.org/10.1016/j.nbd.2015.03.014.

Ray, S. K. (2020). Modulation of autophagy for neuroprotection and functional recovery in traumatic spinal cord injury. *Neural Regeneration Research*, *15*(9), 1601–1612. https://doi.org/10.4103/1673-5374.276322.

Rusten, T. E., & Stenmark, H. (2010). p62, an autophagy hero or culprit? *Nature Cell Biology*, *12*(3), 207–209. https://doi.org/10.1038/ncb0310-207.

Salehi, B., Mishra, A. P., Nigam, M., Sener, B., Kilic, M., Sharifi-Rad, M., … Sharifi-Rad, J. (2018). Resveratrol: a double-edged sword in health benefits. *Biomedicines*, *6*(3), 91. https://doi.org/10.3390/biomedicines6030091.

Sekiguchi, A., Kanno, H., Ozawa, H., Yamaya, S., & Itoi, E. (2012). Rapamycin promotes autophagy and reduces neural tissue damage and locomotor impairment after spinal cord injury in mice. *Journal of Neurotrauma*, *29*(5), 946–956. https://doi.org/10.1089/neu.2011.1919.

Shaw, C. Y., Chen, C. H., Hsu, C. C., Chen, C. C., & Tsai, Y. C. (2003). Antioxidant properties of scopoletin isolated from Sinomonium acutum. *Phytotherapy Research*, *17*(7), 823–825. https://doi.org/10.1002/ptr.1170.

Stacchiotti, A., & Corsetti, G. (2020). Natural compounds and autophagy: Allies against neurodegeneration. *Frontiers in Cell and Development Biology*, *8*, 555409. https://doi.org/10.3389/fcell.2020.555409.

Tang, H., Gao, L., Mao, J., He, H., Liu, J., Cai, X., … Wu, T. (2016). Salidroside protects against bleomycin-induced pulmonary fibrosis: activation of Nrf2-antioxidant signaling, and inhibition of NF-κB and TGF-β1/Smad-2/-3 pathways. *Cell Stress & Chaperones*, *21*(2), 239–249. https://doi.org/10.1007/s12192-015-0654-4.

Wang, P., Jiang, L., Zhou, N., Zhou, H., Liu, H., Zhao, W., … Hu, Z. (2018). Resveratrol ameliorates autophagic flux to promote functional recovery in rats after spinal cord injury. *Oncotarget*, *9*(9), 8427–8440. https://doi.org/10.18632/oncotarget.23877.

Wang, C., Liu, C., Gao, K., Zhao, H., Zhou, Z., Shen, Z., … Mei, X. (2016). Metformin preconditioning provide neuroprotection through enhancement of autophagy and suppression of inflammation and apoptosis after spinal cord injury. *Biochemical and Biophysical Research Communications*, *477*(4), 534–540. https://doi.org/10.1016/j.bbrc.2016.05.148.

Wang, C., Wang, Q., Lou, Y., Xu, J., Feng, Z., Chen, Y., … Zhang, X. (2018). Salidroside attenuates neuroinflammation and improves functional recovery after spinal cord injury through microglia polarization regulation. *Journal of Cellular and Molecular Medicine*, *22*(2), 1148–1166. https://doi.org/10.1111/jcmm.13368.

Wang, C., Zhang, X., Teng, Z., Zhang, T., & Li, Y. (2014). Downregulation of PI3K/Akt/mTOR signaling pathway in curcumin-induced autophagy in APP/PS1 double transgenic mice. *European Journal of Pharmacology*, *740*, 312–320. https://doi.org/10.1016/j.ejphar.2014.06.051.

Xiao, Z., Gaertner, S., Morresi-Hauf, A., Genzel, R., Duell, T., Ullrich, A., & Knyazev, P. G. (2017). Metformin triggers autophagy to attenuate drug-induced apoptosis in NSCLC cells, with minor effects on tumors of diabetic patients. *Neoplasia*, *19*(5), 385–395. https://doi.org/10.1016/j.neo.2017.02.011.

Xie, Y., Kang, R., & Tang, D. (2016). Role of the beclin 1 network in the cross-regulation between autophagy and apoptosis. In M. A. Hayat (Ed.), *Vol. 8. Autophagy: Cancer, other pathologies, inflammation, immunity, infection, and aging* (pp. 75–88). Academic Press.

Xie, Z., Nair, U., & Klionsky, D. J. (2008). Atg8 controls phagophore expansion during autophagosome formation. *Molecular Biology of the Cell*, *19*(8), 3290–3298. https://doi.org/10.1091/mbc.e07-12-1292.

Yuan, W., He, X., Morin, D., Barrière, G., Liu, X., Li, J., & Zhu, Y. (2021). Autophagy induction contributes to the neuroprotective impact of intermittent fasting on the acutely injured spinal cord. *Journal of Neurotrauma*, *38*(3), 373–384. https://doi.org/10.1089/neu.2020.7166.

Zhang, D., Xuan, J., Zheng, B. B., Zhou, Y. L., Lin, Y., Wu, Y. S., … Zhang, X. L. (2017). Metformin improves functional recovery after spinal cord injury via autophagy flux stimulation. *Molecular Neurobiology*, *54*(5), 3327–3341. https://doi.org/10.1007/s12035-016-9895-1.

Zhou, Z., Chen, S., Zhao, H., Wang, C., Gao, K., Guo, Y., … Mei, X. (2016). Probucol inhibits neural cell apoptosis via inhibition of mTOR signaling pathway after spinal cord injury. *Neuroscience*, *329*, 193–200. https://doi.org/10.1016/j.neuroscience.2016.05.019.

Zhou, R., Kan, S., Cai, S., Sun, R., Yuan, H., & Yu, B. (2020). Scopoletin activates adenosine monophosphate-activated protein kinase/mammalian target of rapamycin signaling pathway and improves functional recovery after spinal cord injury in rats. *Pharmacology*, *105*(5–6), 349–359. https://doi.org/10.1159/000503866.

Zhu, Z., Yang, C., Iyaswamy, A., Krishnamoorthi, S., Sreenivasmurthy, S. G., Liu, J., … Li, M. (2019). Balancing mTOR signaling and autophagy in the treatment of Parkinson's disease. *International Journal of Molecular Sciences*, *20*(3), 728. https://doi.org/10.3390/ijms20030728.

Zompa, E. A., Cain, L. D., Everhart, A. W., Moyer, M. P., & Hulsebosch, C. E. (1997). Transplant therapy: Recovery of function after spinal cord injury. *Journal of Neurotrauma*, *14*(8), 479–506. https://doi.org/10.1089/neu.1997.14.479.

Chapter 23

Tertiary damage: Hippocampal and brain changes after spinal cord injury

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Abbreviations

BDNF	brain-derived neurotrophic factor
BrdU	bromodeoxiuridine
CCL2	chemokine (C-C motif) ligand 2
CCL2R	chemokine (C-C motif) ligand 2 receptor
CCL3	chemokine (C-C motif) ligand 3
CCL21	chemokine (C-C motif) ligand 21
DCX	doublecortin
GFAP	glial fibrillary acidic protein
GFP	green fluorescent protein
HPA	hypothalamic-pituitary-adrenal
IL-1β	interleukin 1 beta
IL-6	interleukin 6
IL-18	interleukin 18
NO	nitric oxide
ROS	reactive oxygen species
TNFα	tumor necrosis factor-alpha

Introduction

Given the inability of the CNS to regenerate lost neurons and their connections, spinal cord injury (SCI) leads to permanent motor, sensory, and autonomic dysfunction. Mechanic SCI occurs when the spinal cord is severely bruised, compressed, lacerated, or severed as a result of the traumatic impact. The mechanic impact leads to primary damage which involves cellular death, extracellular matrix changes, edema formation, and blood-brain barrier breakdown. This primary damage drives to the well-known secondary damage characterized by microglia and astrocytes reactivity, periphery immune cell invasion, inflammation, and oxidative stress. These events result in neuron and oligodendrocyte death, which generate a loss of function (Ahuja et al., 2017).

In this chapter, a new concept in SCI research will be developed. Compelling evidence suggests that SCI spreads to the brain affecting rostral distal areas and producing progressive neurodegeneration and neuroinflammation (Table 1). This damage will be considered *Tertiary Damage*.

Traditionally SCI investigation was focused on pathophysiological changes in the spinal cord with efforts being made to recover sensorimotor function and relief neuropathic pain. Long-distal areas, such as the brain, have been ignored for many years. Fortunately, this scenario has changed in the last decades and the brain of spinal cord injured patients has been explored by magnetic resonance imaging (MRI), diffusion tensor imaging (DTI), and transcranial magnetic stimulation. In addition, animal models have revealed abnormalities in distal brain regions related to cognition and mood, which result in behavior impairment.

Cellular, Molecular, Physiological, and Behavioral Aspects of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822427-4.00023-X

TABLE 1 Effect of spinal cord injury on different brain regions.

	Neurons	Glial cells and neuroinflammation	References
Hippocampus	Neurogenesis reduction and NSCs inactivation Decrease of CA1 and granular neurons	Microglia and astrocyte activation CCL21, CCR2, CCL2 production	Felix et al. (2012) Jure, Pietranera, De Nicola, and Labombarda (2017) and Jure, De Nicola, Encinas, and Labombarda (2020) Wu, Stoica, et al. (2014) and Wu, Zhao, et al. (2014)
Thalamus	Neuronal reduction	Microglial activation CCL21, CCR2, CCL2 production	Li et al. (2020) Zhao, Waxman, and Hains (2007)
Sensorimotor cortex and pathways	Circuit reorganization, reduction of gray matter volume and corticoespinal tract atrophy	Myelin atrophy	Freund et al. (2013) Wrigley et al. (2009)
Other cortices	Neuronal reduction	Microglia activation	Wu, Stoica, et al. (2014) and Wu, Zhao, et al. (2014)
Whole brain studies		Production of pro-inflammatory cytokine mRNAs	Jure et al. (2020) Wu, Stoica, et al. (2014) and Wu, Zhao, et al. (2014)

Effects of spinal cord injury on neurons and glial cells in different brain regions during the chronic phase. *NSCs*, neural stem cells; *CA1*, pyramidal neurons.

Sensorimotor cortex and corticospinal tract alterations after SCI in humans

The sensorimotor cortex suffers deep plastic changes after SCI. An extensive circuit reorganization takes place as a consequence of cortical deafferentation. Neuroimaging and neurophysiological studies have shown changes in topographical maps of primary motor and sensory cortices which are related to the severity of the injury (Nardone et al., 2013). Although cortex circuit plasticity is involved in the sparse functional recovery, aberrant reorganization of the cerebral cortex also may have undesired consequences, such as phantom limb sensations or neuropathic pain. SCI drives not only to cortical reorganization but to the atrophy of the deafferentated sensorimotor cortex, corticospinal tract (CST), and to the spinal cord as well (Freund et al., 2013; Wrigley et al., 2009).

MRI studies using voxel-based morphometry have demonstrated that chronic lesion to the spinal cord reduces gray matter volume of the primary somatosensory and motor cortex as well as white matter volume of the CST. DTI measures the diffusion of water in tissues giving quantitative information on tissue microstructure. Alterations in DTI metrics reveal that the degeneration process includes microstructural changes related to myelin atrophy and axonal integrity of the CST and the subcortical area of the sensorimotor cortex (Freund et al., 2013; Wrigley et al., 2009). Anterograde and retrograde Wallerian degeneration spreads along white matter tracts producing axonal loss and demyelination. Notably, spinal cord atrophy, loss of CST integrity, and reduction of sensorimotor cortex volume are associated with poor clinical outcomes (Freund et al., 2013).

On the other hand, the survival of cortical axotomized motoneurons is a topic of debate and the information available comes from animal models. Few studies have described apoptotic neurons on Lamina V of the primary motor cortex. However, several reports have revealed that the number of upper-motoneurons persisted unchanged and no signs of apoptosis were observed after SCI (Brock et al., 2010; Lee et al., 2004). In spite of the discrepancy, both positions claim that large pyramidal motoneurons experience changes such as atrophy and shrinkage of the cell body. These changes are related to the atrophy of myelinated axons of the CST and may explain the reduction of cortical gray matter volume already mentioned.

Cognitive and emotional impairment after SCI

Humans

If little attention has been paid to regions of the brain related to motor and sensory functions, much less consideration has been given to those regions related to cognitive and emotional processes although cognitive impairment and emotional

dysfunction have been observed in patients after SCI. In this regard, a number of reports have identified cognitive deficits in humans long-term after SCI. All these studies included comorbid traumatic brain injury (TBI) in the exclusion criteria as TBI is a well-known factor to impair cognition. Using standardized neuropsychological tests, several reports have described impairments in executive functioning, span memory, concentration ability, memory function, attention, learning, and processing speed (Craig et al., 2015; Lazzaro, Tran, Wijesuriya, & Craig, 2013; Murray et al., 2007; Roth et al., 1989).

These findings were underestimated by the scientific community because 60% of spinal cord injured patients suffer from depression, anxiety, and neuropathic pain (Li et al., 2020). Certainly, all these conditions contribute to decreasing quality of life, reducing social participation, and affecting cognition (Craig et al., 2015). To make matters even worse, patients often take multiple medications and may also consume alcohol and drugs of abuse. SCI produces permanent disabilities in patients changing completely their lifestyle; thus, it is very complex to discern what the causes of their cognitive deficits are. Therefore, it is crucial to develop animal models to study whether there are biological changes in the brain after SCI that lead to cognitive changes and behavioral alterations.

Animal models

Faden's work is very significant because it demonstrates for the first time that SCI causes emotional and cognitive deficits in animals. In this regard, his group has revealed an interesting relationship between rodent cognition and chronic SCI employing well-establish cognitive tests (Wu, Stoica, et al., 2014; Wu, Zhao, et al., 2014). In their work, mice received a moderate contusion injury in the thoracic segment of the spinal cord to let animals perform cognitive tests which implied locomotion. Spatial learning and retention memory were evaluated in the chronic phase using the Morris water maze (MWM) (Wu, Zhao, et al., 2014). Results indicated that lesioned mice employed more time to locate the hidden platform during the acquisition phase and showed worse retention memory as they spent less time looking for the platform in the target quadrant during the probe test than sham mice (Wu, Zhao, et al., 2014). Using the Y-Maze spontaneous alternation test, Faden's group also demonstrated that lesioned mice displayed a reduction of spontaneous alternation, an indicative of dysfunctional spatial working memory. The authors also evaluated recognition memory using the Novel object recognition (NOR) test, which measures recognition memory based on rodent innate preference to explore novel objects. Lesioned mice spent less time exploring the novel object in the recognition phase than sham ones demonstrating that injured mice could not discriminate between the novel and the familiar object, an indicative of impaired recognition memory (Wu, Zhao, et al., 2014).

Contextual and emotional memory was also evaluated by the authors using the step-down fear-avoidance test. During the conditioning phase, the mouse is placed on a platform and it receives a small electric shock when it steps down. During the testing phase, the animal is returned to the platform and the latency to descend is registered. Faden's work shows that lesioned mice decreased latency in the testing phase demonstrating impaired memory of the aversive experience. Finally, the authors have explored depression-like behavior using the tail suspension and the sucrose preference test, neither of them related to locomotion. The tail suspension is based on the observation that mice develop an immobile posture when they are hung by their tail and suffer an inescapable hemodynamic stress. On the other hand, the sucrose preference test is an indicator of anhedonia based on the mouse's interest in seeking a sweet rewarding drink instead of plain water. A decrease in the preference of sucrose indicates depression-like behavior. Injured mice were found to increase immobility time in the tail suspension tests and to reduce sweet water consumption during the sucrose preference, indicating depression-like behavior (Wu, Zhao, et al., 2014).

These findings are very significant because they demonstrate that cognitive and mood deficits are not induced by lifestyle change, drugs of abuse, and polimedication. They are related to changes in brain structures such as the hippocampus involved in cognition and emotion and not in sensorimotor functions.

The effect of SCI on the hippocampus

Hippocampal neurons

The hippocampus has an impressive capacity for structural reorganization and adaptive plasticity since neuronal circuits undergo constant modifications in dendritic complexity and the number of synapses (Zemla & Basu, 2017).

Since cognitive and emotional impairment described in humans and rodents after SCI is related to hippocampal-dependent functions, one of the aims of our laboratory is to study the impact of SCI on this structure. To achieve this goal we have used a compression model of the spinal lesion in rodents (Jure et al., 2017, 2020). We have recently demonstrated that SCI increased hippocampal vulnerability in mice. The neural density of both the dorsal granular cell layer (GCL) and pyramidal cell layer 1 (CA1) declined in the chronic phase following SCI (Jure et al., 2020). The number of mature neurons

remained unchanged during the acute phase (Jure et al., 2020) even though BDNF production was down-regulated during the first-week post-injury (Fumagalli et al., 2009).

Faden's group has also shown that the number of total hippocampal neurons remained unchanged in the acute phase and decreased in the chronic phase (Wu, Stoica, et al., 2014; Wu, Zhao, et al., 2014). These results point out that hippocampal neurodegeneration after SCI is a long process that is verified in the chronic phase (at least 50 days after SCI in rodents). Moreover, they have shown that moderate and severe injury decreased the number of hippocampal neurons to the same extent, but mild injury preserved the neuronal population (Wu et al., 2016). These findings suggest that neuronal death is the result of an all-none response which is established after reaching a certain threshold.

Numerous reports describe that hippocampal dysfunction generates cognitive impairment in hippocampal-dependent learning such as retention and spatial memories (Ali, Badshah, Kim, & Kim, 2015; Belarbi et al., 2012; Li et al., 2016). In this regard, hippocampal failures are associated with low NOR and Y-Maze performances (Broadbent, Gaskin, Squire, & Clark, 2010; Cohen & Stackman Jr., 2015). In line with these findings, depressive-like behaviors are reported using the sucrose preference and the force swim test after hippocampal ischemia in mice (Luo et al., 2019). Therefore, cognitive and mood impairment described in patients and rodents could be explained through the neurodegeneration of hippocampal neurons.

It is important to clarify that although both cognition and emotional behavior involve the hippocampus, these functions also depend on other brain regions such as the amygdala, the hypothalamus as well as the prefrontal and perirhinal cortices (Spellman et al., 2015).

Neurogenesis

Neurogenesis during the acute phase

The subgranular zone (SGZ) of the dentate gyrus (DG) of the hippocampus is one of the brain regions where the generation of new neurons continues throughout life due to the persistence of a neural stem cell (NSC) population (Toda & Gage, 2018). Normally, NSCs are activated and produce highly proliferative transit-amplifying neural progenitors (ANPs). ANPs mostly die by apoptosis during the transition to immature neurons (Sierra et al., 2010). The surviving ANPs differentiate into DCX^+ immature neurons first and then become mature neurons that integrate into the hippocampal circuitry providing highly plastic properties and participating in the information processing (Toda & Gage, 2018) (Fig. 1).

The effect of SCI on neurogenesis during the acute phase is controversial. Our results, in accordance with Felix et al. (2012), have described a reduction in the number of DCX^+ cells during the first week after SCI (Fig. 2) (Felix et al., 2012; Jure et al., 2020). However, recent evidence has shown that neurogenesis increases after complete spinal cord transection 2 days post-injury but reaches control values after 3 months (Dehler et al., 2018). The use of different lesion models could explain the discrepancy in the results since transection lesions are usually characterized by a less rostral spread of secondary injury compared to the compression model used in our experiments (Beattie, Farooqui, & Bresnahan, 2000).

To further explore SCI effects on neurogenesis process, we have studied NSC and ANP activation in the neurogenic niche during the acute phase. Not only NSC and ANP differentiation but also their proliferation were unaltered in the acute

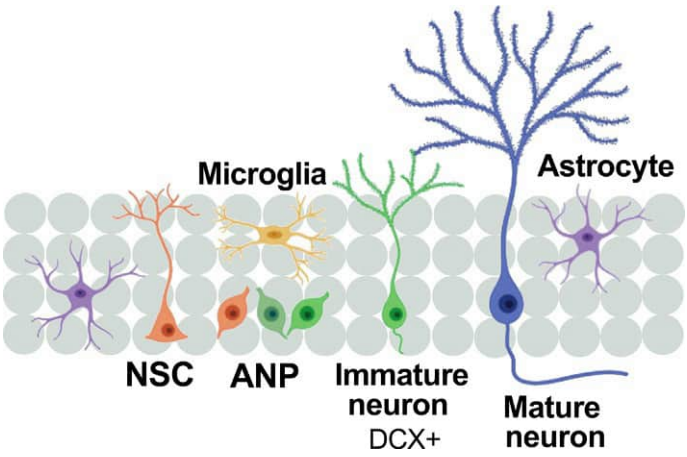

FIG. 1 Schematic summary of neurogenic process in the Subgranular zone. The scheme shows a neural stem cell (NSC) producing highly proliferative transit-amplifying neural progenitors (ANPs) which differentiate into immature DCX+ neurons. These cells become mature neurons that integrate into the hippocampal circuitry. *Image made with BioRender Create Illustration.*

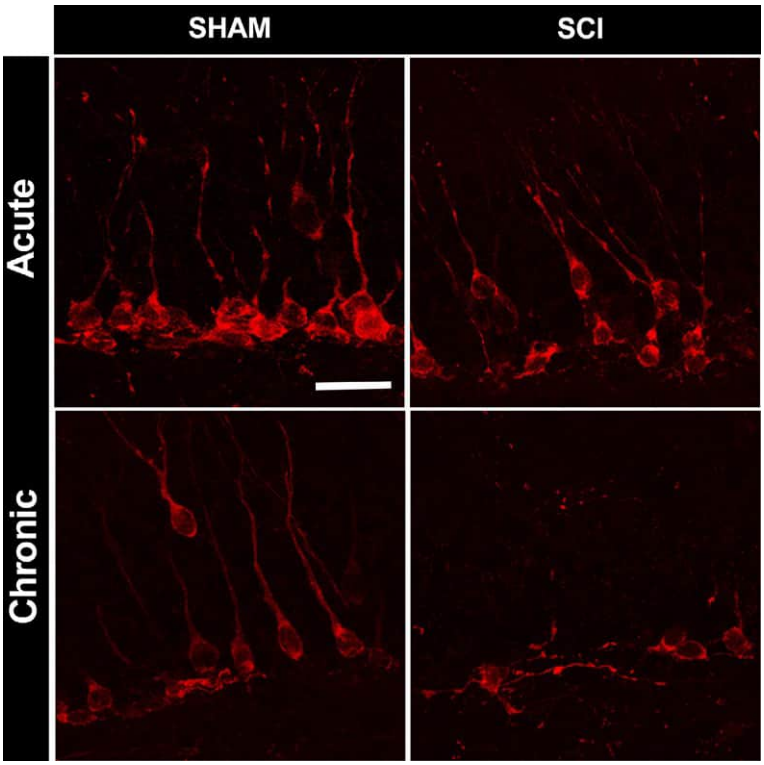

FIG. 2 Effect of spinal cord injury on neurogenesis during the acute and chronic phase. Immature neurons labeled with DCX at 7 and 50 days post-injury in spinal cord injured (SCI) and non-injured (sham) mice. The number of DCX+ cells decreases after injury in both phases. Scale bar: 30 μm. *Unpublished image*.

phase. Curiously, the number of total ANPs decreased while the number of NSCs remained unchanged after injury. Since NSC and ANP proliferation as well as the total number of NSCs were unaffected by SCI, the reduction of the ANP population could be due to ANP death. In accordance with this hypothesis the number of ANPs with abnormal nuclear morphology, an indicative of cellular death, increased in lesioned mice (Jure et al., 2020). These results were concurrent with the reduction of the number of DCX^+ cells aforementioned. Acute stress could explain the reduction of neurogenesis in the acute phase because glucocorticoids are well-known inhibitors of neurogenesis (Lucassen et al., 2015) and they are up-regulated during the first week after SCI (Popovich, Stuckman, Gienapp, & Whitacre, 2001).

Neurogenesis during the chronic phase

Long-term effects of SCI on neurogenesis are less controversial. In agreement with another group, we have described a reduction in the number of immature neurons (DCX^+ cells) in the SGZ after moderate and severe SCI during the chronic phase (Fig. 2) (Jure et al., 2017, 2020; Wu et al., 2016). Noteworthy, we have observed that in mildly injured rats neurogenesis remains unchanged, but in moderately and severely injured rats DCX^+ cells decreased in the same amount. Our data suggest that the down-regulation of neurogenesis could be an all-or-none response from a certain threshold (Jure et al., 2017). However, other authors have found that mild, moderate, and severe injuries decreased DCX^+ cells to the same extent and the reduction coincided with the expression of endoplasmic reticulum stress markers (Wu et al., 2016). In this regard, endoplasmic reticulum stress is related to newborn neurons´ death after traumatic brain injury (Hood et al., 2018).

We have also explored in detail the neurogenesis process long term after injury. In this regard, our results have shown that the number of total NSCs was unchanged, suggesting the survival of NSCs long term after SCI. However, dividing NSCs were down-regulated indicating their inactivation in the neurogenic niche (Jure et al., 2020). NSC quiescence is usually permanent and is related to neurodegenerative diseases, seizures, and aging (Martin-Suarez, Valero, Muro-Garcia, & Encinas, 2019; Sierra et al., 2015).

Regarding ANPs, we found a reduction in the number of both dividing and non-dividing precursor cells (Jure et al., 2020). This decrease could result from the inhibition of their proliferation and/or the reduction of NSC activation. Changes

in ANP proliferation are frequently transient and reversible such as those observed in exercise, deep brain stimulation, fluoxetine treatment, and acute stress (Lucassen et al., 2015; Sierra et al., 2014).

Any condition that provokes impairment of hippocampal neurogenesis is likely to have an impact on cognitive performance and emotional behavior. In fact, the inhibition of neurogenesis by irradiation, pharmacological, and genetical tools impairs spatial-related memory and learning, pattern separation, and responses to fear and stress (Bergami et al., 2008; Oomen, Bekinschtein, Kent, Saksida, & Bussey, 2014). Studies in mice which ablate adult-generated neurons have demonstrated that these neurons are crucial to form and endure spatial and contextual fear memories evaluated by MWM and fear conditioning test (Arruda-Carvalho, Sakaguchi, Akers, Josselyn, & Frankland, 2011). On the other hand, several reports have described that neurogenesis up-regulation alleviates anxiety and reduces depressive-like behavior assessed by the elevated plus maze, sucrose preference, and force swim tests (O'Leary & Cryan, 2014).

Based on these findings the reduction of neurogenesis induced by SCI could explain in part the cognitive and emotional deficits described previously in rodents (Wu, Stoica, et al., 2014; Wu, Zhao, et al., 2014).

Hippocampal neuroinflammation

Glial reaction during the acute phase

Microglial cells alongside astrocytes manage the inflammatory response in the CNS. Microglia and astrocytes are plastic cells that respond to several kinds of molecules generating a different spectrum of functional phenotypes (Tang & Le, 2016). Homeostasis recovery after injury depends on the fine-tuning polarization of microglia and astrocytes from pro-inflammatory towards anti-inflammatory phenotypes. Microglia are maintained in a surveillant state of activation through several inhibitory signaling between microglia and other cells (Frank, Fonken, Annis, Watkins, & Maier, 2018).

There is compelling evidence demonstrating that SCI induces microglial changes in rodents (Jure et al., 2017, 2020; Wu, Zhao, et al., 2014). In this regard, our group has described that the number of microglial cells increased during the acute phase in the hilus, molecular layer, and GCL + SGZ of the DG in mice (Fig. 3). However, mRNA levels of pro-inflammatory cytokines remained unaltered in the acute phase (Jure et al., 2020). In agreement with these results, Faden's group has shown an increase in the number of microglial cells concurrent with the up-regulation of mRNA expression of cycle genes (cyclin A1, A2, D1) (Wu, Stoica, et al., 2014). Moreover, they described that microglial cells change their

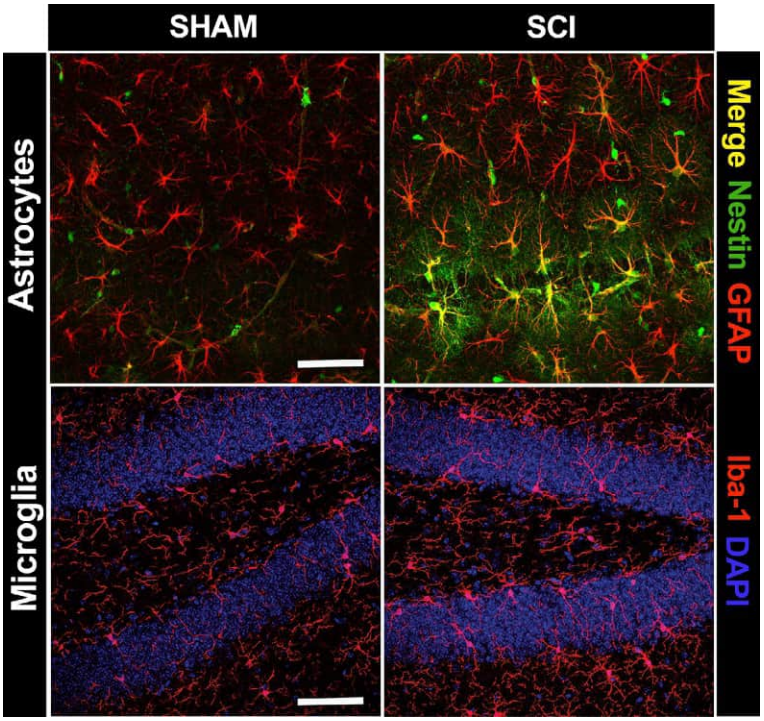

FIG. 3 Effect of spinal cord injury on glial cells during the acute phase. Immunohistochemistry for GFAP, Nestin, and Iba-1 in the dentate gyrus of spinal cord injured (SCI) and non-injured (sham) mice. Astrocytes are identified as GFAP+ cells while reactive astrocytes as GFAP+Nestin+ cells. Microglial cells are identified as iba-1+ cells. DAPI is a nuclear marker. The number of reactive astrocytes and microglial cells increases after SCI. Scale bar: 50 μm. *Unpublished image*.

morphology from ramified to hypertrophic and bushy, an indicative of microglia activation. However, coinciding with our results, mRNA levels of pro-inflammatory cytokines were experimented with no modifications 7 days post-injury (Felix et al., 2012; Wu, Stoica, et al., 2014).

Summarizing, during the acute phase microglial cells proliferate and acquire the morphology of an active cell although there is no production of pro-inflammatory cytokines. Thus, microglia remain in a primed state which has been characterized by a number of conditions such as infection, stress, and neurodegeneration (Frank et al., 2018). Furthermore, a hallmark of primed microglia is the fact that morphological changes are not followed by a pro-inflammatory profile.

Microglial priming occurs after acute stress and it is associated with the downregulation of CD200R (Frank et al., 2018). The increase of glucocorticoids after acute SCI could explain the prime of microglial cells. CD200:CD200R is a key signaling dyad that constrains microglial activation. CD200R is expressed only on myeloid cells while CD200 is widely distributed in neurons, oligodendrocytes, astrocytes, and endothelial cells. In this regard, we have demonstrated that the mRNA expression of CD200R was down-regulated after SCI, suggesting that the disruption of CD200:CD200R signaling could prime microglia to subsequent immune challenges (Jure et al., 2020). The disruption of CD200:CD200R signaling has also been involved in neuroinflammatory processes observed in aging, neuropathic pain, and Alzheimer's disease (Lyons et al., 2009). Regarding astrocytes, we have found that the number of activated astrocytes increased in the hilus, molecular layer, and GCL + SGZ during the acute phase (Fig. 3) (Jure et al., 2020).

Glial reaction during the chronic phase

The scenario definitely changes during the chronic phase. In agreement with Faden's results, we have shown that mRNA levels of pro-inflammatory cytokines such as IL-1β, TNFα, IL-18, and IL-6 were up-regulated. Furthermore, microglial cells presented an activated morphology displaying hypertrophic and bushy forms instead of the surveillant ramified phenotype. However, the number of total microglial cells decreased in the DG during the chronic phase (Jure et al., 2020; Wu, Stoica, et al., 2014). This can be explained because microglial cells die secondary to their activation in a process called activation-induced cell death (Arroyo et al., 2013). Microglial activation might be due to neuron release of chemokines after SCI. In this regard, some studies have shown that CA1, CA3, and hilar neurons increased the expression of CCL2, CCR2, CCL3, and CCL21 in the chronic phase (Li et al., 2020). The effects of CCL2 and CCL21 on microglial activation and the key role of these chemokines on neuron-glia communication are well-known (Zhang, Jiang, & Gao, 2017). On the other hand, astrocytes also play a critical role in regulating neuroinflammation, and the number of activated cells increases in the hilus, molecular layer, and SGZ + GCL after chronic SCI (Jure et al., 2020).

Neurogenic niches are modified by surrounding microenvironment and pathological conditions. Indeed, neuroinflammation has been extensively reported to impair hippocampal neurogenesis (Sierra et al., 2014). In fact, neurogenesis decreases with aging, chronic stress, and neurodegenerative diseases, all conditions where neuroinflammation is a common landmark. Indeed, pro-inflammatory cytokines such as IL-1β, TNFα reduce the proliferation and survival of NSCs and ANPs (Kuzumaki et al., 2010). Astrocytes also can contribute to neurogenesis regulation as they secrete pro-neurogenic factors in normal conditions. However, reactive astrocytes which chronically release IL-6 reduce proliferation, survival, and differentiation of newborn cells (Sierra et al., 2014). The recruitment of new neurons to hippocampal circuits associated with encoding spatial information is also decreased during chronic inflammation leading to cognitive impairment in rodents (Sierra et al., 2014).

Chronic neuroinflammation also generates hippocampal dysfunction altering synaptic plasticity, decreasing cognitive performance such as retention and spatial memories, and inducing depressive-like behavior (Belarbi et al., 2012). In this regard, treatment with anti-inflammatory drugs such as minocycline, cannabinoids, or TNFα inhibitors improves recognition memory evaluated by NOR and spatial memory assessed by the Y-maze (Ali et al., 2015; Belarbi et al., 2012; Li et al., 2016). In addition, anti-inflammatory drugs improve fear memory, reduce anhedonia measured by the sucrose preference test and decrease immobility time in the force swimming test (Troubat et al., 2021).

Neuroinflammation in the chronic phase could also be responsible for the death of hippocampal neurons since it is common to various neurological disorders such as epilepsy, degenerative diseases, and multiple sclerosis where several neurons are usually lost. In fact, pro-inflammatory microglia releases TNFα, NO and ROS, which produce neuronal death (Kaindl et al., 2012; Lull & Block, 2010).

Based on these results, chronical neuroinflammation and the activation of hippocampal glial cells could cause neurogenesis reduction and neurodegeneration, which lead to cognitive and emotional impairment in hippocampal-dependent behaviors after SCI.

SCI and other brain regions

A report from Faden and colleagues further supports that neuroinflammation and neurodegeneration could be a widespread phenomenon long term after SCI. Indeed, they have described the reduction in the number of cortical and thalamic neurons as well as changes in microglial morphology which display activated forms in those regions (Wu, Stoica, et al., 2014; Wu, Zhao, et al., 2014). The neurodegenerative process is supported by the progressive enlargement of the ventricles and the increase of cerebrospinal fluid volume (Li et al., 2020). Regarding neuroinflammation, several reports have described microglial activation in thalamic neurons and periaqueductal gray matter (Li et al., 2020). These results could involve the development of neuropathic pain since the thalamus is involved in sensory and pain processing. In line with these findings, human MRI studies have demonstrated that SCI generates a progressive reduction in gray matter volume in areas related to the processing of emotional information and the modulation of attentional states such as the anterior cingulate, insular, medial prefrontal, and temporal cortices (Nicotra, Critchley, Mathias, & Dolan, 2006; Wrigley et al., 2009). Moreover, neuronal activity is reduced in the anterior cingulate cortex during emotional processing according to a functional MRI study (Nicotra et al., 2006).

On the other hand, the gene expression of the whole brain after acute and subacute SCI was recently elucidated using transcriptome analysis. Genes belonging to the oxidative phosphorylation pathway were increased during the acute phase (3 h after injury). However, the enriched brain pathways associated with the subacute phase (14 days post-injury) were both the inflammatory response (cytokines and chemokine signaling) and endoplasmic reticulum stress-related pathways (Baek, Cho, & Kim, 2017). These findings relate the pathophysiology of SCI with widespread neuroinflammation and cellular stress in the brain.

Possible mechanisms underlying the tertiary damage

The mechanisms underlying how SCI drives acute and chronic brain changes remain unknown. However, some speculative mechanisms can be delineated. On the one hand, the retrograde and anterograde Wallerian degeneration spreads along white matter tracts from the spinal cord to rostral areas of the brain, producing axonal loss, demyelination, neuronal shrinkage, and even neuronal death. Chemokines such as CCL21, CCL2, CCL3, and the chemokine receptor CCR2 are not expressed in the healthy brain. However, after axonal damage or glutamate exposure, the synthesis of CCL21 and CCL2 is stimulated. Damaged neurons transport and release those chemokines at distant regions resulting in remote microglial activation. In this regard, dorsal horn neurons after injury release CCL21 to the thalamus through the spinothalamic tract (Zhao et al., 2007). The activated thalamic microglia induce the expression of CCL21 in thalamic neurons, which project to other areas of the brain such as the hippocampus, propagating microglial activation. Furthermore, the microglial activator CCL2 and its receptor CCR2 are chronically expressed in neurons after severe spinal contusion in the thalamus, hippocampus, and periaqueductal gray matter (Knerlich-Lukoschus et al., 2011). This evidence suggests that chemokines can be transported through axons to distant regions from the epicenter of the lesion. On the other hand, the systemic immune and neuroendocrine functions are markedly altered after SCI. In this regard, a systemic inflammatory response is developed during the acute phase. Pro-inflammatory cytokines such as TNFα, IL-1β, and IL-6 increased in serum while leukocyte infiltration into tissues is promoted. In this context, the systemic inflammation produced immediately after SCI could stimulate microglial activation and/or induce microglial priming in the brain (Campbell et al., 2005). In addition to the inflammatory response, SCI activates the HPA axis releasing glucocorticoids during the acute phase. The high levels of corticosterone described during the first week after SCI could prime microglia and model the brain producing long-term alterations since the hippocampus and cerebral cortex are vulnerable to glucocorticoids (Lucassen et al., 2015; Popovich et al., 2001). Therefore, systemic inflammatory reaction and glucocorticoid action could prime microglia to subsequent immune challenges such as neural and axonal degeneration that takes place long term after SCI. Finally, factors released by the spinal tissue could reach and affect the brain through the cerebral spinal fluid.

Applications to other areas of neuroscience

In this chapter, we have reviewed the effects of SCI on the brain, especially on the hippocampus. These findings support the hypothesis that tertiary damage really occurs after SCI. Indeed, the hippocampus and the thalamus are deeply and chronically altered as a consequence of the damage to the spinal cord. Alterations in these structures might lead to the generation of neuropathic pain as well as cognitive and mood disorders seen in rodents and even humans. It is time to consider SCI as a brain neurodegenerative disease and not only as an event circumscribed to the spinal cord. This approach is opening a new area in neurobiology since therapeutic strategies are focused on preventing secondary injury and ignore the encephalopathy

that develops at rostral sites. Future rehabilitation strategies should emphasize not only sensorimotor skills but also cognitive function and mood disorders. Understanding the mechanisms underlying hippocampal neurodegeneration further will help to develop new therapeutic strategies to treat spinal cord injured patients. For example, future therapies could include the inhibition of brain inflammatory response induced after SCI. On the other hand, cognitive and emotional impairment should be considered as a result of SCI and not as a consequence of lifestyle changes that occur after the disability. Brain neurodegeneration suggests that depressive and cognitive dysfunction might derive from a biological substrate. The study of brain pathology following SCI is a new exciting field of research whose development will provide valuable information for understanding the intimate interconnection among the spinal cord, the brain, and human behavior.

Mini-dictionary of terms

Primary damage: Damage to the spinal cord induced by mechanic impact.

Secondary damage: Cascade of cellular and molecular events that propagate the injury from the site of the mechanic impact to the rostrocaudal contiguous spinal segments.

Tertiary damage: Progressive neurodegeneration which affects distal parts of the brain after spinal cord injury.

Hippocampal neurogenesis: Production of newborn neurons from neural stem cells located in the subgranular zone of the dentate gyrus of the hippocampus.

Primed microglia: Activated microglia which does not release pro-inflammatory cytokines but produces an exaggerated response to future challenges.

Key facts of tertiary damage

- Tertiary Damage is a new concept in the field of Spinal cord injury (SCI).
- Tertiary Damage implies progressive neurodegeneration of distal parts of the brain after SCI.
- Axonal injury and microglial response are probably related to the development of Tertiary Damage.
- Tertiary Damage is associated with cognitive and emotional impairment described in animals and even humans after SCI.
- Tertiary Damage introduces new perspectives in rehabilitation and therapeutic strategies for spinal cord injured patients.

Summary points

- In this chapter, we propose the term tertiary damage to describe alterations suffered by distal parts of the brain after spinal cord injury (SCI).
- Traditionally, SCI investigation was focused on pathophysiological changes in the spinal cord with efforts being made to recover sensorimotor function and relieve neuropathic pain.
- Several studies have shown atrophy of the sensorimotor system (cortices and tracts).
- Although humans suffer from cognitive and emotional impairment, the study of brain areas related to these functions has been ignored for many years.
- Animal models have shown that SCI leads to cognitive deficits and depressive-like behavior which correlate with hippocampal neurodegeneration, neurogenesis reduction, and neuroinflammation.
- Neuroinflammation response and neurodegeneration after SCI reach other brain areas related to pain processing.
- The mechanisms underlying tertiary damage are unknown, but the release of chemokines at distance sites induced by axonal injury and the systemic response of the immune system and the stress axis could be involved.
- Finally, we discuss that rehabilitation and therapeutic strategies should include tertiary damage.

References

Ahuja, C. S., Wilson, J. R., Nori, S., Kotter, M. R. N., Druschel, C., Curt, A., et al. (2017). Traumatic spinal cord injury. *Nature Reviews. Disease Primers*, *3*, 17018.

Ali, T., Badshah, H., Kim, T. H., & Kim, M. O. (2015). Melatonin attenuates D-galactose-induced memory impairment, neuroinflammation and neurodegeneration via RAGE/NF-K B/JNK signaling pathway in aging mouse model. *Journal of Pineal Research*, *58*(1), 71–85.

Arroyo, D. S., Soria, J. A., Gaviglio, E. A., Garcia-Keller, C., Cancela, L. M., Rodriguez-Galan, M. C., et al. (2013). Toll-like receptor 2 ligands promote microglial cell death by inducing autophagy. *The FASEB Journal*, *27*(1), 299–312.

Arruda-Carvalho, M., Sakaguchi, M., Akers, K. G., Josselyn, S. A., & Frankland, P. W. (2011). Posttraining ablation of adult-generated neurons degrades previously acquired memories. *The Journal of Neuroscience*, *31*(42), 15113–15127.

Baek, A., Cho, S. R., & Kim, S. H. (2017). Elucidation of gene expression patterns in the brain after spinal cord injury. *Cell Transplantation*, *26*(7), 1286–1300.

Beattie, M. S., Farooqui, A. A., & Bresnahan, J. C. (2000). Review of current evidence for apoptosis after spinal cord injury. *Journal of Neurotrauma*, *17*(10), 915–925.

Belarbi, K., Jopson, T., Tweedie, D., Arellano, C., Luo, W., Greig, N. H., et al. (2012). TNF-alpha protein synthesis inhibitor restores neuronal function and reverses cognitive deficits induced by chronic neuroinflammation. *Journal of Neuroinflammation*, *9*, 23.

Bergami, M., Rimondini, R., Santi, S., Blum, R., Gotz, M., & Canossa, M. (2008). Deletion of TrkB in adult progenitors alters newborn neuron integration into hippocampal circuits and increases anxiety-like behavior. *Proceedings of the National Academy of Sciences of the United States of America*, *105*(40), 15570–15575.

Broadbent, N. J., Gaskin, S., Squire, L. R., & Clark, R. E. (2010). Object recognition memory and the rodent hippocampus. *Learning & Memory*, *17*(1), 5–11.

Brock, J. H., Rosenzweig, E. S., Blesch, A., Moseanko, R., Havton, L. A., Edgerton, V. R., et al. (2010). Local and remote growth factor effects after primate spinal cord injury. *The Journal of Neuroscience*, *30*(29), 9728–9737.

Campbell, S. J., Perry, V. H., Pitossi, F. J., Butchart, A. G., Chertoff, M., Waters, S., et al. (2005). Central nervous system injury triggers hepatic CC and CXC chemokine expression that is associated with leukocyte mobilization and recruitment to both the central nervous system and the liver. *The American Journal of Pathology*, *166*(5), 1487–1497.

Cohen, S. J., & Stackman, R. W., Jr. (2015). Assessing rodent hippocampal involvement in the novel object recognition task. A review. *Behavioural Brain Research*, *285*, 105–117.

Craig, A., Nicholson Perry, K., Guest, R., Tran, Y., Dezarnaulds, A., Hales, A., et al. (2015). Prospective study of the occurrence of psychological disorders and comorbidities after spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *96*(8), 1426–1434.

Dehler, S., Lou, W. P., Gao, L., Skabkin, M., Dallenbach, S., Neumann, A., et al. (2018). An immune-CNS axis activates remote hippocampal stem cells following spinal transection injury. *Frontiers in Molecular Neuroscience*, *11*, 443.

Felix, M. S., Popa, N., Djelloul, M., Boucraut, J., Gauthier, P., Bauer, S., et al. (2012). Alteration of forebrain neurogenesis after cervical spinal cord injury in the adult rat. *Frontiers in Neuroscience*, *6*, 45.

Frank, M. G., Fonken, L. K., Annis, J. L., Watkins, L. R., & Maier, S. F. (2018). Stress disinhibits microglia via down-regulation of CD200R: A mechanism of neuroinflammatory priming. *Brain, Behavior, and Immunity*, *69*, 62–73.

Freund, P., Weiskopf, N., Ashburner, J., Wolf, K., Sutter, R., Altmann, D. R., et al. (2013). MRI investigation of the sensorimotor cortex and the corticospinal tract after acute spinal cord injury: A prospective longitudinal study. *Lancet Neurology*, *12*(9), 873–881.

Fumagalli, F., Madaschi, L., Caffino, L., Marfia, G., Di Giulio, A. M., Racagni, G., et al. (2009). Acute spinal cord injury reduces brain derived neurotrohic factor expression in rat hippocampus. *Neuroscience*, *159*(3), 936–939.

Hood, K. N., Zhao, J., Redell, J. B., Hylin, M. J., Harris, B., Perez, A., et al. (2018). Endoplasmic reticulum stress contributes to the loss of newborn hippocampal neurons after traumatic brain injury. *The Journal of Neuroscience*, *38*(9), 2372–2384.

Jure, I., De Nicola, A. F., Encinas, J. M., & Labombarda, F. (2020). Spinal cord injury leads to hippocampal glial alterations and neural stem cell inactivation. *Cellular and Molecular Neurobiology*. https://doi.org/10.1007/s10571-020-00900-8. Online ahead of print.

Jure, I., Pietranera, L., De Nicola, A. F., & Labombarda, F. (2017). Spinal cord injury impairs neurogenesis and induces glial reactivity in the hippocampus. *Neurochemical Research*, *42*(8), 2178–2190.

Kaindl, A. M., Degos, V., Peineau, S., Gouadon, E., Chhor, V., Loron, G., et al. (2012). Activation of microglial N-methyl-D-aspartate receptors triggers inflammation and neuronal cell death in the developing and mature brain. *Annals of Neurology*, *72*(4), 536–549.

Knerlich-Lukoschus, F., Noack, M., von der Ropp-Brenner, B., Lucius, R., Mehdorn, H. M., & Held-Feindt, J. (2011). Spinal cord injuries induce changes in CB1 cannabinoid receptor and C-C chemokine expression in brain areas underlying circuitry of chronic pain conditions. *Journal of Neurotrauma*, *28*(4), 619–634.

Kuzumaki, N., Ikegami, D., Imai, S., Narita, M., Tamura, R., Yajima, M., et al. (2010). Enhanced IL-1beta production in response to the activation of hippocampal glial cells impairs neurogenesis in aged mice. *Synapse*, *64*(9), 721–728.

Lazzaro, I., Tran, Y., Wijesuriya, N., & Craig, A. (2013). Central correlates of impaired information processing in people with spinal cord injury. *Journal of Clinical Neurophysiology*, *30*(1), 59–65.

Lee, B. H., Lee, K. H., Kim, U. J., Yoon, D. H., Sohn, J. H., Choi, S. S., et al. (2004). Injury in the spinal cord may produce cell death in the brain. *Brain Research*, *1020*(1–2), 37–44.

Li, Y., Cao, T., Ritzel, R. M., He, J., Faden, A. I., & Wu, J. (2020). Dementia, depression, and associated brain inflammatory mechanisms after spinal cord injury. *Cell*, *9*(6).

Li, H. C., Xiao, J., Huang, Y. L., Li, L. J., Jiang, H., Huang, L. X., et al. (2016). Reduction in hypoxia-derived neuroinflammation and dysfunctional glutamate transporters by minocycline may restore hypoxia-injured cognition of neonatal rat. *Sheng Li Xue Bao*, *68*(2), 148–156.

Lucassen, P. J., Oomen, C. A., Naninck, E. F., Fitzsimons, C. P., van Dam, A. M., Czeh, B., et al. (2015). Regulation of adult neurogenesis and plasticity by (early) stress, glucocorticoids, and inflammation. *Cold Spring Harbor Perspectives in Biology*, *7*(9), a021303.

Lull, M. E., & Block, M. L. (2010). Microglial activation and chronic neurodegeneration. *Neurotherapeutics*, *7*(4), 354–365.

Luo, L., Li, C., Du, X., Shi, Q., Huang, Q., Xu, X., et al. (2019). Effect of aerobic exercise on BDNF/proBDNF expression in the ischemic hippocampus and depression recovery of rats after stroke. *Behavioural Brain Research*, *362*, 323–331.

Lyons, A., McQuillan, K., Deighan, B. F., O'Reilly, J. A., Downer, E. J., Murphy, A. C., et al. (2009). Decreased neuronal CD200 expression in IL-4-deficient mice results in increased neuroinflammation in response to lipopolysaccharide. *Brain, Behavior, and Immunity*, *23*(7), 1020–1027.

Martin-Suarez, S., Valero, J., Muro-Garcia, T., & Encinas, J. M. (2019). Phenotypical and functional heterogeneity of neural stem cells in the aged hippocampus. *Aging Cell*, *18*(4), e12958.

Murray, R. F., Asghari, A., Egorov, D. D., Rutkowski, S. B., Siddall, P. J., Soden, R. J., et al. (2007). Impact of spinal cord injury on self-perceived pre- and postmorbid cognitive, emotional and physical functioning. *Spinal Cord*, *45*(6), 429–436.

Nardone, R., Holler, Y., Brigo, F., Seidl, M., Christova, M., Bergmann, J., et al. (2013). Functional brain reorganization after spinal cord injury: Systematic review of animal and human studies. *Brain Research*, *1504*, 58–73.

Nicotra, A., Critchley, H. D., Mathias, C. J., & Dolan, R. J. (2006). Emotional and autonomic consequences of spinal cord injury explored using functional brain imaging. *Brain*, *129*(Pt. 3), 718–728.

O'Leary, O. F., & Cryan, J. F. (2014). A ventral view on antidepressant action: Roles for adult hippocampal neurogenesis along the dorsoventral axis. *Trends in Pharmacological Sciences*, *35*(12), 675–687.

Oomen, C. A., Bekinschtein, P., Kent, B. A., Saksida, L. M., & Bussey, T. J. (2014). Adult hippocampal neurogenesis and its role in cognition. *Wiley Interdisciplinary Reviews: Cognitive Science*, *5*(5), 573–587.

Popovich, P. G., Stuckman, S., Gienapp, I. E., & Whitacre, C. C. (2001). Alterations in immune cell phenotype and function after experimental spinal cord injury. *Journal of Neurotrauma*, *18*(9), 957–966.

Roth, E., Davidoff, G., Thomas, P., Doljanac, R., Dijkers, M., Berent, S., et al. (1989). A controlled study of neuropsychological deficits in acute spinal cord injury patients. *Paraplegia*, *27*(6), 480–489.

Sierra, A., Beccari, S., Diaz-Aparicio, I., Encinas, J. M., Comeau, S., & Tremblay, M. E. (2014). Surveillance, phagocytosis, and inflammation: How never-resting microglia influence adult hippocampal neurogenesis. *Neural Plasticity*, *2014*, 610343.

Sierra, A., Encinas, J. M., Deudero, J. J., Chancey, J. H., Enikolopov, G., Overstreet-Wadiche, L. S., et al. (2010). Microglia shape adult hippocampal neurogenesis through apoptosis-coupled phagocytosis. *Cell Stem Cell*, *7*(4), 483–495.

Sierra, A., Martin-Suarez, S., Valcarcel-Martin, R., Pascual-Brazo, J., Aelvoet, S. A., Abiega, O., et al. (2015). Neuronal hyperactivity accelerates depletion of neural stem cells and impairs hippocampal neurogenesis. *Cell Stem Cell*, *16*(5), 488–503.

Spellman, T., Rigotti, M., Ahmari, S. E., Fusi, S., Gogos, J. A., & Gordon, J. A. (2015). Hippocampal-prefrontal input supports spatial encoding in working memory. *Nature*, *522*(7556), 309–314.

Tang, Y., & Le, W. (2016). Differential roles of M1 and M2 microglia in neurodegenerative diseases. *Molecular Neurobiology*, *53*(2), 1181–1194.

Toda, T., & Gage, F. H. (2018). Review: Adult neurogenesis contributes to hippocampal plasticity. *Cell and Tissue Research*, *373*(3), 693–709.

Troubat, R., Barone, P., Leman, S., Desmidt, T., Cressant, A., Atanasova, B., et al. (2021). Neuroinflammation and depression: A review. *The European Journal of Neuroscience*, *53*(1), 151–171.

Wrigley, P. J., Gustin, S. M., Macey, P. M., Nash, P. G., Gandevia, S. C., Macefield, V. G., et al. (2009). Anatomical changes in human motor cortex and motor pathways following complete thoracic spinal cord injury. *Cerebral Cortex*, *19*(1), 224–232.

Wu, J., Stoica, B. A., Luo, T., Sabirzhanov, B., Zhao, Z., Guanciale, K., et al. (2014). Isolated spinal cord contusion in rats induces chronic brain neuroinflammation, neurodegeneration, and cognitive impairment. Involvement of cell cycle activation. *Cell Cycle*, *13*(15), 2446–2458.

Wu, J., Zhao, Z., Kumar, A., Lipinski, M. M., Loane, D. J., Stoica, B. A., et al. (2016). Endoplasmic reticulum stress and disrupted neurogenesis in the brain are associated with cognitive impairment and depressive-like behavior after spinal cord injury. *Journal of Neurotrauma*, *33*(21), 1919–1935.

Wu, J., Zhao, Z., Sabirzhanov, B., Stoica, B. A., Kumar, A., Luo, T., et al. (2014). Spinal cord injury causes brain inflammation associated with cognitive and affective changes: Role of cell cycle pathways. *The Journal of Neuroscience*, *34*(33), 10989–11006.

Zemla, R., & Basu, J. (2017). Hippocampal function in rodents. *Current Opinion in Neurobiology*, *43*, 187–197.

Zhang, Z. J., Jiang, B. C., & Gao, Y. J. (2017). Chemokines in neuron-glial cell interaction and pathogenesis of neuropathic pain. *Cellular and Molecular Life Sciences*, *74*(18), 3275–3291.

Zhao, P., Waxman, S. G., & Hains, B. C. (2007). Modulation of thalamic nociceptive processing after spinal cord injury through remote activation of thalamic microglia by cysteine cysteine chemokine ligand 21. *The Journal of Neuroscience*, *27*(33), 8893–8902.

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Section C

Physiological and metabolic effects

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Chapter 24

Hormonal events and spinal cord injury: A focus on vasopressin and natriuretic peptide

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Abbreviations

ABRT	activity-based recovery training
AD	autonomic dysreflexia
ANP	atrial natriuretic peptide
AQP2	aquaporin 2 channels
AVP	vasopressin
BNP	brain-derived natriuretic peptide
cAMP	cyclic adenosine monophosphate
CNP	C-type natriuretic peptide
CORT	corticosterone
NP	natriuretic peptide
NPRA	natriuretic peptide receptor-A
PVN	paraventricular nucleus
RAAS	renin aldosterone angiotensin system
SCI	spinal cord injury
SCN	suprachiasmatic nucleus
SON	supraoptic nucleus
V1R	vasopressin receptor 1
V2R	vasopressin receptor 2
V3R	vasopressin receptor 3

Introduction

Dysfunctions of the upper and lower urinary tracts that arise after spinal cord injury (SCI) include detrusor-sphincter dyssynergia, incontinence, polyuria, urinary retention, and loss of sensation. Bladder emptying methods include intermittent catheterization (self or by an attendant), indwelling catheters (transurethral or suprapubic), reflex triggering, straining, manual compression (Crede), and sacral anterior root stimulation. A poorly understood complication that develops after SCI which impacts the daily frequency of conducting these management techniques is polyuria, the overproduction and/or passage of urine, which has been documented in both human SCI and pre-clinical contusion models (Goh et al., 2017; Hubscher et al., 2016; Szollar, Dunn, Brandt, & Fincher, 1997; Ward & Hubscher, 2012). This excessive volume of urine requires more frequent catheterizations, increases the risk of bladder and urinary tract infections, and prompts the need for nightly awakenings for bladder emptying (nocturia) which is disruptive to sleep and receiving enough rest. Oftentimes, SCI individuals will limit their fluid intake to avoid nocturia, which introduces further and potentially more serious confounding issues such as dehydration, which exasperates bowel management through constipation, and autonomic dysreflexia, a life-threatening sudden increase in arterial blood pressure that is elicited by noxious (e.g., pain) and/or innocuous stimuli (e.g., bladder filling) from below the level of injury (Dolinak & Balraj, 2007; Wan & Krassioukov, 2014).

Cellular, Molecular, Physiological, and Behavioral Aspects of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822427-4.00024-1

The underlying mechanisms of polyuria/nocturia are unknown, but likely includes arginine vasopressin (AVP; also commonly referred to as anti-diuretic hormone), which regulates urine production and fluid homeostasis and has recently been shown to correlate with the incidence of SCI-induced polyuria (Denys et al., 2017; Montgomery & Hubscher, 2017). However, it remains undetermined what directly causes the decrease in AVP after SCI, as there are likely multiple factors contributing to polyuria (Fig. 1). These factors include the natriuretic peptides (NP), such as atrial natriuretic peptide (ANP), brain-derived natriuretic peptide (BNP), and C-type natriuretic peptide (CNP).

The focus of the current chapter review is upon SCI-induced changes in AVP and ANP as they play a major role in water/electrolyte balance. In addition, these neurohormones also impact the cardiovascular system. Substantial cardiovascular deficits present amongst the SCI population include orthostatic hypotension, bradycardia, daily fluctuations in blood pressure, and autonomic dysreflexia (Claydon, Steeves, & Krassioukov, 2006; Goh et al., 2017; Lindan, Joiner, Freehafer, & Hazel, 1980). Given these multiple functional roles of neurohormones, any imbalance is likely to impact the overall well-being of the SCI population. Additional hormones affected by SCI are listed in Table 1.

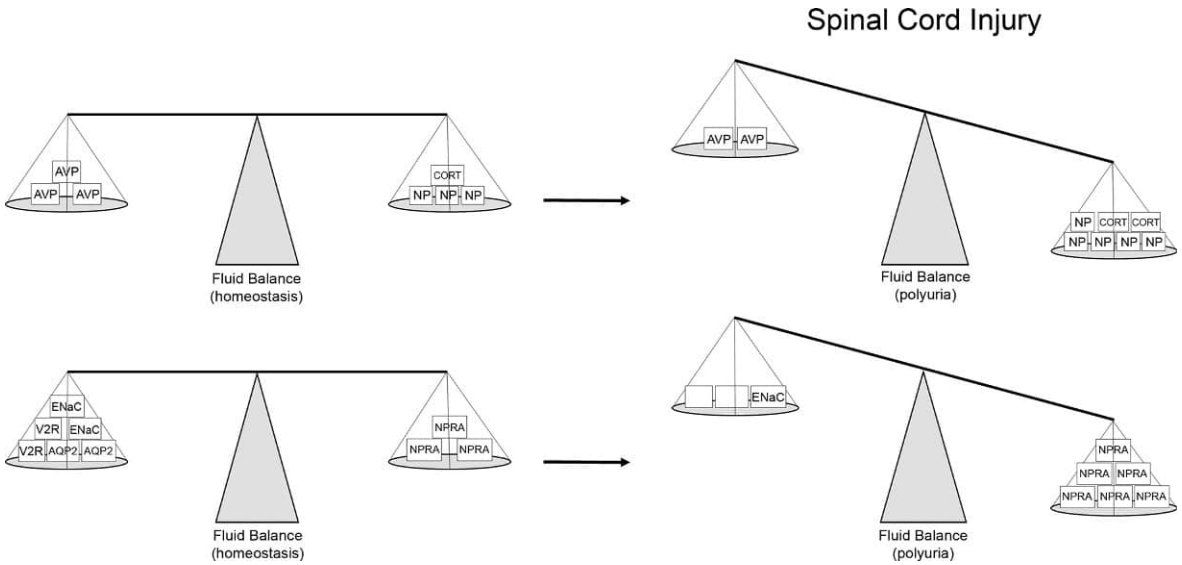

FIG. 1 Key hormone/receptors in fluid balance and how they are affected after SCI. Depiction of key hormones such as AVP, NPs, and CORT, along with paired receptors such as NPRA, V2R, AQP2, and ENaC, and how they contribute to fluid balance/homeostasis. In the non-injured state, these hormones and receptors work together to closely regulate fluid balance. After the injury, dysregulation occurs leading to an overproduction of water (polyuria/nocturia). Changes in the opposite direction would cause a decrease in urine production (oliguria).

TABLE 1 Hormone changes after SCI.

Major hormones affected by chronic spinal cord injury	
Adrenocorticotropic hormone (ACTH)	Increased
Atrial natriuretic peptide (ANP)	Increased
Cortisol	Increased
Human growth hormone	Decreased
Insulin-like growth factor (IGF-1)	Increased
Parathyroid hormone (PTH)	Decreased
Testosterone	Decreased
Vasopressin (AVP)	Decreased

This table outlines several important hormones that have been reported to be significantly altered after chronic spinal cord injury.
Note: Failure of SCI to alter the female menstrual cycle suggests no significant alteration in levels of 17 beta-estradiol and progesterone. Gonadal hormones have been examined therapeutically for their protective effects.

Function of vasopressin (AVP)

One of the bodies most important hormones required for the regulation of salt and water balance is AVP. The production of AVP takes place within neurons located in the supraoptic nucleus (SON), suprachiasmatic nucleus (SCN), and paraventricular nucleus (PVN) of the hypothalamus, regions of the brain limbic system having a central neuroendocrine function (Swanson & Eo Sawchenko, 1983; Van Leeuwen, Swaab, & De Raay, 1978). AVP is released from the posterior lobe of the pituitary in response to several different stimuli. First, under normal physiological circumstances, osmoreceptors located in the hypothalamus respond to an increase in blood osmolality (occurs with dehydration or a high sodium diet) (Cowley Jr, Skelton, Merrill, Quillen Jr, & Switzer, 1983; Kjeldsen et al., 1985) through physical shrinkage which triggers a signaling cascade to release AVP from the pituitary. Within the kidney, vasopressin 2 receptors (V2R) respond to elevated AVP circulating in the blood by increasing reabsorption of solute-free water back into the circulatory system through the opening of aquaporin 2 (AQP2) channels, which results in a decrease in urine volume. As many as 13 different types of aquaporins have been identified in mammals, of which at least seven are located within the kidney and function to transport water across membranes (Nielsen et al., 2002). However, AQP2 is the only kidney aquaporin known to be regulated by AVP.

There are three main AVP receptors; V1, V2, and V3. Each of these receptors has specific functions within different regions of the body. The V1 receptor (V1R) is mainly located in vascular smooth muscle and platelets, but can be found in brain, testis, superior cervical ganglion, liver, blood vessels, and kidney (Phillips et al., 1990). Functionally, the V1R is a G protein-coupled receptor and utilizes the activation of calcium influx, phospholipase A2, phospholipase C, and phospholipase D. The V1R functions mostly as a vasoconstrictor and in thrombosis, but has been shown to be associated with myocardial hypertrophy, glycogenolysis, and uterine contraction (Holmes, Landry, & Granton, 2003). V1Rs can also be found in the kidney where it also functions to promote vasoconstriction within the efferent arterioles, which reduces glomerular filtration rate.

The V2 receptor (V2R) is primarily located within the kidney and promotes a strong antidiuretic effect. As illustrated in Fig. 2, upon the binding of AVP to kidney V2 receptors, cAMP is activated which then triggers the fusion of AQP2 channels to the apical membrane of the collecting ducts (Harris, Zeidel, Jo, & Hammond, 1994). The increase in AQP2 channels promotes water reabsorption. For this reason, V2R is a target of pharmacological therapies to decrease urine production in cases like diabetes insipidus (Bichet et al., 1988) and SCI (Chancellor, Rivas, & Staas Jr, 1994; Zahariou, Karagiannis, Papaioannou, Stathi, & Michail, 2007). V2R is also located in vascular endothelium and smooth muscle cells and has vasodilation properties.

The V3 receptor (V3R) is also a G protein-coupled receptor but is far less distributed than either V1R or V2R. Less is known about V3R, but it is overexpressed in adrenocorticotropic hormone (ACTH)-secreting tumors. Additionally, its function is dependent on the concentration of AVP. One function of V3R is to promote ACTH release from the pituitary, but at other concentrations of AVP, V3R can increase DNA and cAMP synthesis, which is seen in tumor growth.

Function of natriuretic peptides (NP)

NPs include three structurally and functionally related hormone factors: ANP, BNP, and CNP, although there is evidence of a fourth, *Dendroaspis* natriuretic peptide (DNP, isolated from the green mamba snake). The primary function of NPs is to promote natriuresis (Potter, Yoder, Flora, Antos, & Dickey, 2009). Natriuretic peptide receptor A (NPRA) is the primary receptor for all three NPs. Although primarily found in the kidney as its function is to promote diuresis and natriuresis, NPRA is also located in lung, vasculature, heart, adrenal, adipose, and brain tissues (Goy et al., 2001; Lowe et al., 1989; Nagase, Katafuchi, Hirose, & Fujita, 1997). The ANP/NPRA interaction regulates blood pressure and therefore is essential for fluid balance homeostasis.

The release of both ANP and BNP is triggered by an increase in blood volume within the heart. While ANP is released primarily within the atria, BNP is released within the ventricles. Although ANP and BNP have a similar function, BNP has an estimated 10-fold lower affinity than ANP and therefore is considered a weaker diuretic. Clinically, serum ANP is used as a biomarker for cardiovascular disease, including myocardial infarction, stroke, coronary artery disease, and heart failure (Barbato et al., 2012; Sabatine et al., 2012; Wang et al., 2004). In clinical SCI research settings, ANP has been investigated as a therapeutic in ischemia/reperfusion injury (Nakayama et al., 2007), as well as for its role in exercise therapy (Yamamoto et al., 1999) and bladder distention (Yamamoto et al., 1999). Further work is necessary to elucidate the importance and extent to which the changes in these peptides after SCI affect urinary and cardiovascular health.

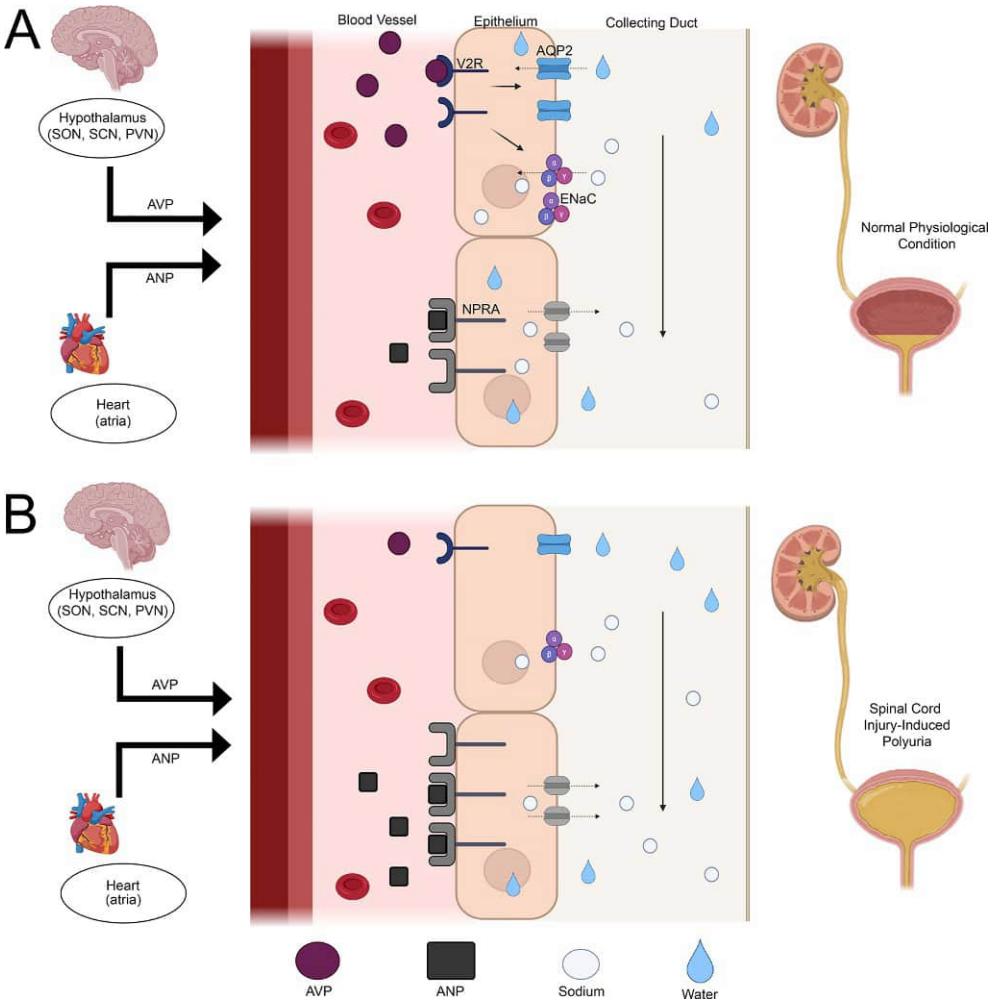

FIG. 2 Diagram of AVP/ANP and their receptors within the kidney under normal physiological conditions and after SCI. As part of normal physiological processes to maintain fluid homeostasis, AVP is released by the hypothalamus in response to conditions of hyperosmolality (A, upper portion). Once in the kidney, AVP binds to V2R, which triggers a response to open AQP2 channels to allow water flow from the kidney collecting duct back into the epithelium while ENaC allows for sodium to be reabsorbed. However, under conditions of elevated blood volume, ANP is released from the heart (A, lower portion) and upon binding to NPRA within the kidney, a cascade is triggered to permit salt and subsequently water excretions. As illustrated in B, there is a decrease in AVP, V2R, and ENaC as well as an increase in ANP and NPRA after SCI, which together contribute to the injury-induced occurrence of polyuria/nocturia. *Image created using Biorender.com.*

SCI-induced polyuria/nocturia

Nocturia is defined as the necessity to void one or more times at night, specifically while sleeping (Kerrebroeck et al., 2002). There are many potential causes of nocturia, including decreased bladder capacity, increase in fluid intake, and increased diuresis (Oelke et al., 2017). A common occurrence in the human SCI population is nocturnal polyuria or an excess of urine production/passage at night (Denys et al., 2017). This issue causes sleep disruptions, bladder overdistention, and an increased risk of acquiring lower urinary tract infections due to the necessity for additional intermittent catheterizations. Historically, SCI-induced polyuria was thought to be the effect of decreased vascular tone and pooling of fluid in the lower extremities, which upon fluid redistribution when supine at night-time causes "intravascular flooding" and subsequent diuresis (Krum, Louis, Brown, Jackman, & Howes, 1991; Williams et al., 1990). However, polyuria is present in animal SCI models (Gumbel, Montgomery, Yang, & Hubscher, 2020; Hubscher et al., 2016; Montgomery & Hubscher, 2017; Ward & Hubscher, 2012) which lack positional fluid redistribution, suggesting that other mechanisms are likely involved.

In chronic SCI patients, increased blood pressure at night versus day is associated with increased nighttime urine production (Goh et al., 2018). Further, nocturnal polyuria, SCI-induced or otherwise, can be caused by decreased AVP circulation, increased ANP, and cardiovascular insufficiency (Oelke, Adler, Marschall-Kehrel, Herrmann, & Berges,

2014). A study by Denys et al. revealed that SCI patients lacked circadian control of renal function (clearance of creatinine, free water, and solutes) (Denys et al., 2017). Together, these measured changes in circadian control of renal function, blood pressure, AVP, and ANP after SCI are all likely contributing to the mechanisms driving SCI-induced polyuria.

AVP after SCI

One potential factor that contributes to SCI-induced polyuria is a decrease in levels of AVP. Under normal conditions, humans exhibit an increase in circulating AVP at night which results in decreased sleep-time urine production and thus volume, thereby controlling the need for toileting. Clinically, children with nocturnal polyuria experience disruptions in the diurnal variation of AVP, specifically a decrease in circulating AVP, causing an abnormal increase in night-time urine production which may induce bed-wetting (Rittig, Knudsen, Norgaard, Pedersen, & Djurhuus, 1989). Similarly, the SCI population commonly experience disrupted diurnal variation of AVP (Kilinc, Akman, Levendoglu, & Özker, 1999; Szollar et al., 1997), leading to the need for bladder emptying one or more times a night. Additionally, individuals with SCI exhibit disrupted circadian control of renal creatinine clearance, water diuresis, and solute diuresis (Denys et al., 2017). This decrease in night-time AVP is likely a major contributor to SCI-induced polyuria/nocturia. Furthermore, persons with injuries above T6 tend to demonstrate an increase in nocturnal sodium excretion, which would suggest that the mechanisms behind SCI-induced polyuria include other factors such as ANP/BNP (Denys et al., 2017). However, polyuria has also been observed in individuals having varying severities and injury levels, trends consistent with metabolic cage results in the clinically relevant rat contusion model whereby polyuria was measured regardless of the extent of injury (Ward & Hubscher, 2012).

To further elucidate the potential mechanism of SCI-induced polyuria, pre-clinical experiments were conducted to investigate the changes in AVP and NPs in the rat SCI model. The reported data (Montgomery & Hubscher, 2017) are consistent with those described for the human SCI population. Beginning at 2-week post-SCI, male rats demonstrated a significant decrease in serum AVP (Montgomery & Hubscher, 2017), which continued at chronic time points as well (Gumbel et al., 2020). In addition to the sub-acute and chronic decrease in AVP, the key AVP receptor in the kidney, V2R, was significantly lower than uninjured surgical sham rats (Gumbel et al., 2020). This result is somewhat surprising as V2R is a G-coupled protein receptor and under normal physiological conditions, becomes desensitized to an abundance of its ligand (in this case, AVP), and inversely becomes sensitized under low levels of its ligand. Moreover, as illustrated in Fig. 2, protein levels of AQP2 channel and epithelial sodium channel (ENaC) within the kidney were also reduced along with V2R, further highlighting the importance of AVP in SCI-induced polyuria, as AQP2 channels are formed in response to the activation of V2R to promote water absorption, and ENaC functions to reabsorb sodium ions back into the bloodstream. Taken together, the changes in these receptor densities after SCI, as shown in Figs. 3 and 4, are in the direction expected to promote polyuria.

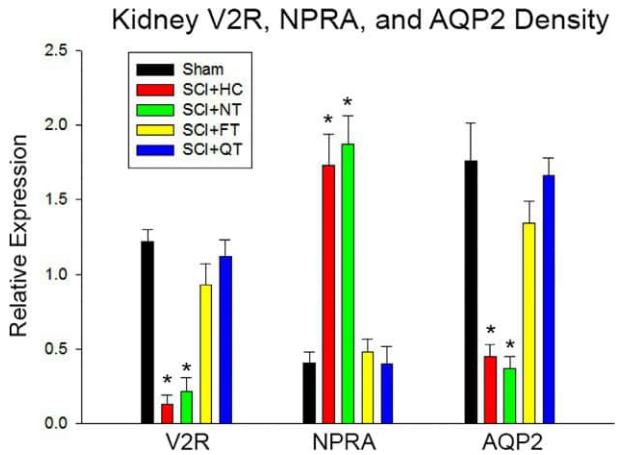

FIG. 3 Activity-based recovery training reverses several key fluid balance receptors in the kidney after SCI. After chronic SCI, V2R, NPRA, and AQP2 are significantly altered. Relative expression of proteins using Western blot reveals that V2R and AQP2 are significantly decreased while NPRA is significantly increased in groups of male Wistar rats that did not receive any therapeutic interventions (NT = non-trained; HC = home cage) after a moderate-severe contusion injury that yields approximately 11% white matter sparing at the T9 spinal level lesion epicenter. Animals that received ABRT involving quadrupedal or forelimb-only training (QT and FT, respectively) by stepping on a treadmill for 1 h a day, 7 days a week for 8 weeks beginning 2 weeks post-injury were found to have similar levels of these receptor/channel densities to surgical sham animals (spinal laminectomy but no contusion). Error bars: standard error of the mean.

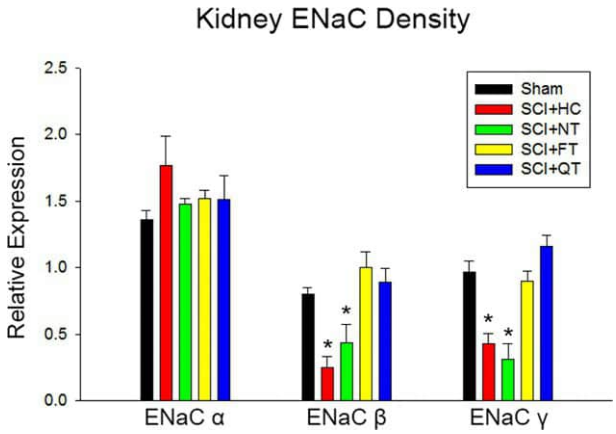

FIG. 4 Activity-based recovery training reverses ENaC β and γ sub-units deficit after SCI. After chronic SCI, both β and γ sub-units of ENaC are significantly decreased. However, after ABRT (SCI + FT and SCI + QT), the relative density of both β and γ sub-units was reversed to similar levels of surgical sham animals. Group abbreviations per Fig. 3. Error bars: standard error of the mean.

A significant increase in AVP has also been reported in female piglets 15 min after a cervical spinal transection, which is likely an acute response to cardiovascular changes to maintain homeostatic blood pressure (Zahra et al., 2010). This finding demonstrates that the hemodynamic changes seen after SCI are likely affecting the changes in AVP, as orthostatic hypotension is another common occurrence in the human SCI population (Claydon et al., 2006; Illman, Stiller, & Williams, 2000; Zerbe, Henry, & Robertson, 1983).

While desmopressin (a synthetic AVP analog) is used to suppress bedwetting in children (Glazener & Evans, 2002) and has yielded positive results in some cases of SCI-induced nocturnal polyuria (Chancellor et al., 1994; Zahariou, Karamouti, Karagiannis, & Papaioannou, 2008), its uses may be limited to those at lower risk of cardiovascular disease. Additionally, desmopressin only targets one of the several potential factors that lead to polyuria and leaves other pathways unchecked, such as ANP/NPRA.

ANP after SCI

Mechanisms driving the chronic decrease in AVP/V2R after SCI are unknown. Although blood osmolality is one driving force behind AVP release, non-osmotic stimuli such as NPs, glucocorticoids, and norepinephrine may control AVP levels and urine production (Dillingham & Anderson, 1986; Schrier, Berl, & Anderson, 1979). Of these stimuli, NPs (ANP/BNP) and corticosterone (CORT; primary glucocorticoid in rats) have been further investigated in the rat SCI model (see Fig. 1). While there is some evidence that SCI can induce changes in ANP in the clinical setting (Tajima et al., 1990), further preclinical and clinical experimental studies are necessary to further elucidate the impact of level and severity of the injury.

Changes in urinary ANP and CORT have been documented as early as two weeks after a moderate contusion injury in male rats, together with serum AVP (Montgomery & Hubscher, 2017). In a 2018 study of SCI rats with polyuria, both urinary ANP and CORT were significantly increased 2 weeks post- contusion, while surgical sham animals demonstrated no differences. Both ANP and CORT inhibit the function and release of AVP, therefore the significant changes in these hormones (increases in ANP and CORT and a decrease in AVP) are in the direction expected with respect to polyuria (Haack, Mohring, Mohring, Petri, & Hackenthal, 1977; Inoue, Nonoguchi, & Tomita, 2001). It is important to note that urinary BNP levels have not been shown to change after SCI. However, BNP is a weaker diuretic compared to ANP. It cannot be ruled out that plasma BNP changes occur after SCI, as its half-life is relatively short and potentially difficult to capture.

It has also been demonstrated that the significant changes in AVP and ANP continue chronically in SCI male rats (Gumbel et al., 2020). In a recent study, SCI animals having polyuria were randomized into one of two groups receiving different forms of activity-based recovery training (ABRT) on a treadmill or one of two groups having no therapeutic intervention (one group harnessed without any treadmill activity and one remaining in their home cage) (Gumbel et al., 2019). While all groups still demonstrated polyuria at the end of the study such that their 24-h urine volumes remained significantly increased from baseline pre-injury levels, the ABRT animals showed a significantly lower 24-h urine volume than the non-trained animals after the 8 weeks of daily 60-min training sessions. These findings were similar to those previously reported in animals (Hubscher et al., 2016; Ward et al., 2014) and human studies (Hubscher et al., 2018) demonstrating

multi-system benefits of locomotor training. In addition to changes in AVP, ANP, and corticosterone, relative expression densities of NPRA were found to be significantly increased in the non-trained animals, but not the ABRT animal groups (see Fig. 3). The inverse was found for V2R and AQP2 as their expression were significantly decreased in only the non-trained animal groups, while the ABRT animals were not significantly different from surgical sham animals. These findings, illustrated in Fig. 3, suggest that one potential mechanism behind the improvement in polyuria after exercise therapy is the regulation of key receptors within the kidney. Note that although high-intensity exercise induces an acute increase in AVP in able-bodied subjects (Convertino, Keil, Bernauer, & Greenleaf, 1981; Inder, Hellemans, Swanney, Prickett, & Donald, 1998) as well as ANP (Ohba et al., 2001), these effects may be short-lived and may differ under conditions such as SCI. More studies are needed to further elucidate underlying mechanisms.

Potential mechanisms causing changes in AVP and/or ANP after SCI

Although many variables lead to the release of AVP, two important physical changes include hypertonicity and/or hypovolemia, which are important because orthostatic hypotension is a common occurrence amongst the SCI population (Claydon et al., 2006). Another issue for the SCI population, specifically with higher-level injuries, is autonomic dysreflexia (AD), a sudden onset of hypertension (Krassioukov & Weaver, 1995). Repeated and frequent occurrences of AD may have an impact on AVP release and subsequent concentration of V2R in the kidney. Such changes in alpha-adrenergic receptors (receptors for epinephrine and norepinephrine) have already been linked to AD (Arnold, Feng, Delaney, & Teasell, 1995). AD has also been characterized following severe injuries in the rat model of SCI (Maiorov, Fehlings, & Krassioukov, 1998).

One potential mechanism behind the observed increase in NPRA after SCI in rodents (Gumbel et al., 2020) is an increase in glucocorticoids. An increase in glucocorticoids can increase the glomerular filtration rate (Haack et al., 1977), decrease the level of plasma AVP, upregulate NPRA within the kidney (Liu et al., 2011), and increase ANP release (Dananberg & Grekin, 1992). Corticosterone, the main glucocorticoid in rodents (equivalent to cortisol in humans), is elevated in both humans and rodents after SCI, which could relate to stress (Lucin, Sanders, Jones, Malarkey, & Popovich, 2007; Popovich, Stuckman, Gienapp, & Whitacre, 2001). It is also documented that glucocorticoids have the ability to alter immune activity, whereby a significant increase may lead to immunosuppression (Coutinho & Chapman, 2011; DePasquale-Jardieu & Fraker, 1979; Wiegers, Stec, Klinkert, & Reul, 2000). After SCI, specifically high-level injuries, elevated glucocorticoids are associated with a significant decrease in immune responses, which can lead to an increased risk of infections, including that of the bladder and kidney (Lucin, Sanders, & Popovich, 2009).

It is noteworthy that the renin aldosterone angiotensin system (RAAS) also regulates cardiovascular homeostasis (blood pressure and volume) in addition to fluid and electrolyte balance (urine concentration and excretion). RAAS is an additional factor that can affect both AVP and ANP, and therefore needs further investigation in its potential role in SCI-induced polyuria. While there are studies in the clinical setting that indicate there are acute changes in renin and aldosterone after SCI (Mathias et al., 1975; Wall et al., 1994), the focus of these studies relates to cardiovascular function.

Redistribution of body fluids in the SCI population at bedtime when shifting from a sitting to supine position produces cardiovascular fluctuations, which in turn affects the delicate hormone balance that controls homeostatic fluid balance (Viaene et al., 2019). This fluid redistribution is one potential mechanism of SCI-induced polyuria. Support comes from a study where the use of compression stockings was shown to reduce leg edema during the day and subsequent urine production during the night (Viaene et al., 2019). However, animal models with SCI-induced polyuria that do not undergo fluid redistribution suggest other mechanisms are likely involved, such as hormones previously identified with respect to fluid balance (see Fig. 1). As further research progresses, additional key hormones/receptors will be identified along with AVP and ANP, and their roles elucidated with respect to SCI-induced polyuria as well as cardiovascular health.

Applications to other areas of neuroscience

Several associations have been made between altered AVP function and several neurological disorders besides SCI, including autism, depression, bipolar, and schizophrenia (Iovino et al., 2018). For example, altered binding of AVP and V1R in the CNS has been linked to autism disorders, (Wassink et al., 2004) and elevated CSF levels of neurophysin II (hypothalamic carrier protein for AVP) were found in patients with schizophrenia (Linkowski, Geenen, Kerkhofs, Mendlewicz, & Legros, 1984). Also, in multiple sclerosis, an autoimmune disorder that affects the myelin sheaths of nerves within the CNS, urinary tract dysfunctions include polyuria/nocturia (Panicker, Fowler, & Kessler, 2015). The potential mechanisms behind multiple sclerosis-associated polyuria overlap with SCI-induced polyuria, such as disrupted AVP secretion and nocturnal hypertension (Peyronnet et al., 2019).

Other neurological involvements related to NPs have been shown for studies involving the olfactory bulb (Wildey & Glembotski, 1986), Purkinje fibers of the cerebellum (McKenzie, Juan, Thomas, Berman, & Klein, 2001), the retina (Spes et al., 2020), and development (Cao & Yang, 2008). There have also been studies indicating a potential neuroprotective role for NPs, likely through increasing cGMP levels (Cao & Yang, 2008; Fiscus, Alex, & Chew, 2001). Together, it is clear that both NPs and AVP are two critical entities that should be considered in other settings in addition to SCI.

Mini-dictionary of terms

Polyuria: Overproduction and passage of urine; greater than 2.5–3 L/ 24 h in adults.
Nocturia: When a person is woken up at night to use the bathroom to urinate one or more times a night.
Vasopressin (AVP): Also known as an antidiuretic hormone; functions to help re-absorb water into the bloodstream as well as vasoconstriction.
Natriuretic peptides (NPs): Group of peptides that function to promote natriuresis and subsequent water excretion.
Corticosterone: Produced in the cortex of the adrenal glands; the main glucocorticoid in many animal species, including rodents (instead of cortisol which is the primary glucocorticoid in humans).
Aquaporins: A group of channel proteins that function to allow water transport between cells.
Autonomic dysreflexia: A condition seen more commonly with high-level SCI where the body reacts to a stimulus such as a full bladder or distended bowel and triggers the sympathetic nervous system to increase blood pressure. Due to injury, the body is unable to control the response which can lead to life-threatening hypertension.
Diuretic: Either a drug (usually taken to lower high blood pressure) or natural hormone/peptide that causes an increase in urine and/or salt excretion.
Orthostatic hypotension: A decrease in blood pressure (20 mmHg for systolic and 10 mmHg for diastolic) caused by a sudden position change, such as standing up from sitting.
Activity-based recovery training: Types of rehabilitation such as treadmill walking with the assistance that use activity to restore neurological function.

Key facts of vasopressin and natriuretic peptide changes after SCI

Key facts of vasopressin after SCI

- AVP is made by magnocellular neurons in the supraoptic, suprachiasmatic, and paraventricular nuclei of the hypothalamus.
- AVP is used for the treatments of various medical conditions.
- Both pre-clinical and clinical SCI studies demonstrate a chronic decrease and disrupted levels of AVP post-SCI.
- The dysregulation of AVP after SCI likely plays a major role in SCI-induced polyuria/nocturia.
- Intense exercise is known to increase serum AVP levels.

Key facts of natriuretic peptides

- Natriuretic peptides include ANP, BNP, and CNP.
- ANP is released by cardiomyocytes located in the atria of the heart.
- BNP is released by cardiomyocytes located in the ventricles of the heart and has less effectiveness as ANP.
- Natriuretic peptides all function to promote natriuresis.
- ANP levels increase chronically post-SCI.

Summary points

This chapter focuses on AVP and NP changes after SCI, particularly with respect to polyuria/nocturia.

- Both AVP and NP affect cardiovascular and upper urinary tract-related functions.
- Although AVP and NP changes after SCI are important, changes in the density of their subsequent receptors in the kidney contribute to mechanisms underlying SCI-induced polyuria.
- Hormonal changes after SCI, including altered AVP and NP levels and their receptors, influence multiple physiological systems, with resulting deficits that impact both daily activities and quality of life.
- Numerous associations have been made between altered AVP/NP functions and several other neurological disorders.

References

Arnold, J. M. O., Feng, Q.-P., Delaney, G. A., & Teasell, R. W. (1995). Autonomic dysreflexia in tetraplegic patients: Evidence for α-adrenoceptor hyperresponsiveness. *Clinical Autonomic Research*, *5*, 267–270.

Barbato, E., Bartunek, J., Marchitti, S., Mangiacapra, F., Stanzione, R., Delrue, L., et al. (2012). NT-proANP circulating level is a prognostic marker in stable ischemic heart disease. *International Journal of Cardiology*, *155*, 311–312.

Bichet, D. G., Razi, M., Lonergan, M., Arthus, M.-F., Papukna, V., Kortas, C., et al. (1988). Hemodynamic and coagulation responses to 1-desamino [8-D-arginine] vasopressin in patients with congenital nephrogenic diabetes insipidus. *New England Journal of Medicine*, *318*, 881–887.

Cao, L.-H., & Yang, X.-L. (2008). Natriuretic peptides and their receptors in the central nervous system. *Progress in Neurobiology*, *84*, 234–248.

Chancellor, M. B., Rivas, D. A., & Staas, W. E., Jr. (1994). DDAVP in the urological management of the difficult neurogenic bladder in spinal cord injury: Preliminary report. *The Journal of the American Paraplegia Society*, *17*, 165–167.

Claydon, V. E., Steeves, J. D., & Krassioukov, A. (2006). Orthostatic hypotension following spinal cord injury: Understanding clinical pathophysiology. *Spinal Cord*, *44*, 341–351.

Convertino, V. A., Keil, L. C., Bernauer, E. M., & Greenleaf, J. E. (1981). Plasma volume, osmolality, vasopressin, and renin activity during graded exercise in man. *Journal of Applied Physiology*, *50*, 123–128.

Coutinho, A. E., & Chapman, K. E. (2011). The anti-inflammatory and immunosuppressive effects of glucocorticoids, recent developments and mechanistic insights. *Molecular and Cellular Endocrinology*, *335*, 2–13.

Cowley, A. W., Jr., Skelton, M. M., Merrill, D. C., Quillen, E. W., Jr., & Switzer, S. J. (1983). Influence of daily sodium intake on vasopressin secretion and drinking in dogs. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology*, *245*. R860–R872.

Dananberg, J. A. M. I. E., & Grekin, R. J. (1992). Corticoid regulation of atrial natriuretic factor secretion and gene expression. *American Journal of Physiology. Heart and Circulatory Physiology*, *263*. H1377–H1381.

Denys, M.-A., Viaene, A., Goessaert, A.-S., Van Haverbeke, F., Hoebeke, P., Raes, A., et al. (2017). Circadian rhythms in water and solute handling in adults with a spinal cord injury. *The Journal of Urology*, *197*, 445–451.

DePasquale-Jardieu, P., & Fraker, P. J. (1979). The role of corticosterone in the loss in immune function in the zinc-deficient A/J mouse. *The Journal of Nutrition*, *109*, 1847–1855.

Dillingham, M. A., & Anderson, R. J. (1986). Inhibition of vasopressin action by atrial natriuretic factor. *Science*, *231*, 1572–1573.

Dolinak, D., & Balraj, E. (2007). Autonomic dysreflexia and sudden death in people with traumatic spinal cord injury. *The American Journal of Forensic Medicine and Pathology*, *28*, 95–98.

Fiscus, R. R., Alex, W. K. T., & Chew, S. B. C. (2001). Natriuretic peptides inhibit apoptosis and prolong the survival of serum-deprived PC12 cells. *Neuroreport*, *12*, 185–189.

Glazener, C. M. A., & Evans, J. H. C. (2002). Desmopressin for nocturnal enuresis in children. *Cochrane Database of Systematic Reviews*, (3), CD002112.

Goh, M. Y., Millard, M. S., Wong, E. C. K., Berlowitz, D. J., Graco, M., Schembri, R. M., et al. (2018). Comparison of diurnal blood pressure and urine production between people with and without chronic spinal cord injury. *Spinal Cord*, *56*, 847–855.

Goh, M. Y., Millard, M. S., Wong, E. C. K., Brown, D. J., Frauman, A. G., & O'Callaghan, C. J. (2017). Diurnal blood pressure and urine production in acute spinal cord injury compared with controls. *Spinal Cord*, *55*, 39–46.

Goy, M. F., Oliver, P. M., Purdy, K. E., Knowles, J. W., Fox, J. E., Mohler, P. J., et al. (2001). Evidence for a novel natriuretic peptide receptor that prefers brain natriuretic peptide over atrial natriuretic peptide. *Biochemical Journal*, *358*, 379–387.

Gumbel, J. H., Montgomery, L. R., Yang, C. B., & Hubscher, C. H. (2020). Activity-based training reverses spinal cord injury-induced changes in kidney receptor densities and membrane proteins. *Journal of Neurotrauma*, *37*, 555–563.

Gumbel, J. H., Steadman, C. J., Hoey, R. F., Armstrong, J. E., Fell, J. D., Yang, C. B., et al. (2019). Activity-based training on a treadmill with spinal cord injured Wistar rats. *Journal of Visualized Experiments*, e58983.

Haack, D., Mohring, J., Mohring, B., Petri, M., & Hackenthal, E. (1977). Comparative study on development of corticosterone and DOCA hypertension in rats. *American Journal of Physiology. Renal Physiology*, *233*. F403–F411.

Harris, H. W., Zeidel, M. L., Jo, I., & Hammond, T. G. (1994). Characterization of purified endosomes containing the antidiuretic hormone-sensitive water channel from rat renal papilla. *Journal of Biological Chemistry*, *269*, 11993–12000.

Holmes, C. L., Landry, D. W., & Granton, J. T. (2003). Science review: Vasopressin and the cardiovascular system part 1–receptor physiology. *Critical Care*, *7*, 427.

Hubscher, C. H., Herrity, A. N., Williams, C. S., Montgomery, L. R., Willhite, A. M., Angeli, C. A., et al. (2018). Improvements in bladder, bowel and sexual outcomes following task-specific locomotor training in human spinal cord injury. *PLoS One*, *13*, e0190998.

Hubscher, C. H., Montgomery, L. R., Fell, J. D., Armstrong, J. E., Poudyal, P., Herrity, A. N., et al. (2016). Effects of exercise training on urinary tract function after spinal cord injury. *American Journal of Physiology. Renal Physiology*, *310*. F1258–F1268.

Illman, A., Stiller, K., & Williams, M. (2000). The prevalence of orthostatic hypotension during physiotherapy treatment in patients with an acute spinal cord injury. *Spinal Cord*, *38*, 741–747.

Inder, W. J., Hellemans, J., Swanney, M. P., Prickett, T. C. R., & Donald, R. A. (1998). Prolonged exercise increases peripheral plasma ACTH, CRH, and AVP in male athletes. *Journal of Applied Physiology*, *85*, 835–841.

Inoue, T., Nonoguchi, H., & Tomita, K. (2001). Physiological effects of vasopressin and atrial natriuretic peptide in the collecting duct. *Cardiovascular Research*, *51*, 470–480.

Iovino, M., Messana, T., De Pergola, G., Iovino, E., Dicuonzo, F., Guastamacchia, E., et al. (2018). The role of neurohypophyseal hormones vasopressin and oxytocin in neuropsychiatric disorders. *Endocrine, Metabolic & Immune Disorders Drug Targets*, *18*, 341–347.

Kerrebroeck, V., Philip, P. A., Chaikin, D., Donovan, J., Fonda, D., Jackson, S., et al. (2002). The standardisation of terminology in nocturia: Report from the standardisation sub-committee of the international continence society. *Neurourology and Urodynamics*, *21*, 179–183.

Kilinc, S., Akman, M. N., Levendoglu, F., & Özker, R. (1999). Diurnal variation of antidiuretic hormone and urinary output in spinal cord injury. *Spinal Cord*, *37*.

Kjeldsen, S. E., Os, I., Forsberg, G., Aakesson, I., Skjøtø, J., Frederichsen, P., et al. (1985). Dietary sodium intake increases vasopressin secretion in man. *Journal of Clinical Hypertension*, *1*, 123–131.

Krassioukov, A. V., & Weaver, L. C. (1995). Episodic hypertension due to autonomic dysreflexia in acute and chronic spinal cord-injured rats. *American Journal of Physiology. Heart and Circulatory Physiology*, *268*. H2077–H2083.

Krum, H., Louis, W. J., Brown, D. J., Jackman, G. P., & Howes, L. G. (1991). Diurnal blood pressure variation in quadriplegic chronic spinal cord injury patients. *Clinical Science*, *80*, 271–276.

Lindan, R., Joiner, E., Freehafer, A. A., & Hazel, C. (1980). Incidence and clinical features of autonomic dysreflexia in patients with spinal cord injury. *Spinal Cord*, *18*, 285–292.

Linkowski, P., Geenen, V., Kerkhofs, M., Mendlewicz, J., & Legros, J. J. (1984). Cerebrospinal fluid neurophysins in affective illness and in schizophrenia. *European Archives of Psychiatry and Neurological Sciences*, *234*, 162–165.

Liu, C., Chen, Y., Kang, Y., Ni, Z., Xiu, H., Guan, J., et al. (2011). Glucocorticoids improve renal responsiveness to atrial natriuretic peptide by up-regulating natriuretic peptide receptor-A expression in the renal inner medullary collecting duct in decompensated heart failure. *Journal of Pharmacology and Experimental Therapeutics*, *339*, 203–209.

Lowe, D. G., Chang, M.-S., Hellmiss, R., Chen, E., Sujay, S., Garbers, D. L., et al. (1989). Human atrial natriuretic peptide receptor defines a new paradigm for second messenger signal transduction. *The EMBO Journal*, *8*, 1377–1384.

Lucin, K. M., Sanders, V. M., Jones, T. B., Malarkey, W. B., & Popovich, P. G. (2007). Impaired antibody synthesis after spinal cord injury is level dependent and is due to sympathetic nervous system dysregulation. *Experimental Neurology*, *207*, 75–84.

Lucin, K. M., Sanders, V. M., & Popovich, P. G. (2009). Stress hormones collaborate to induce lymphocyte apoptosis after high level spinal cord injury. *Journal of Neurochemistry*, *110*, 1409–1421.

Maiorov, D. N., Fehlings, M. G., & Krassioukov, A. V. (1998). Relationship between severity of spinal cord injury and abnormalities in neurogenic cardiovascular control in conscious rats. *Journal of Neurotrauma*, *15*, 365–374.

Mathias, C. J., Christensen, N. J., Corbett, J. L., Frankel, H. L., Goodwins, T. J., & Peart, W. S. (1975). Plasma catecholamines, plasma renin activity and plasma aldosterone in tetraplegic man, horizontal and tilted. *Clinical Science and Molecular Medicine*, *49*, 291–299.

McKenzie, J. C., Juan, Y.-W., Thomas, C. R., Berman, N. E. J., & Klein, R. M. (2001). Atrial natriuretic peptide-like immunoreactivity in neurons and astrocytes of human cerebellum and inferior olivary complex. *The Journal of Histochemistry and Cytochemistry*, *49*, 1453–1467.

Montgomery, L. R., & Hubscher, C. H. (2017). Altered vasopressin and natriuretic peptide levels in a rat model of spinal cord injury: Implications for the development of polyuria. *American Journal of Physiology. Renal Physiology*, *314*, F58–F66.

Nagase, M., Katafuchi, T., Hirose, S., & Fujita, T. (1997). Tissue distribution and localization of natriuretic peptide receptor subtypes in stroke-prone spontaneously hypertensive rats. *Journal of Hypertension*, *15*, 1235–1243.

Nakayama, T., Harada, N., Asano, M., Nomura, N., Saito, T., Mishima, A., et al. (2007). Atrial natriuretic peptide reduces ischemia/reperfusion-induced spinal cord injury in rats by enhancing sensory neuron activation. *Journal of Pharmacology and Experimental Therapeutics*, *322*, 582–590.

Nielsen, S., Frøkiær, J., Marples, D., Kwon, T.-H., Agre, P., & Knepper, M. A. (2002). Aquaporins in the kidney: From molecules to medicine. *Physiological Reviews*, *82*, 205–244.

Oelke, M., Adler, E., Marschall-Kehrel, D., Herrmann, T. R. W., & Berges, R. (2014). *Nocturia: State of the art and critical analysis of current assessment and treatment strategies*. Springer.

Oelke, M., De Wachter, S., Drake, M. J., Giannantoni, A., Kirby, M., Orme, S., et al. (2017). A practical approach to the management of nocturia. *International Journal of Clinical Practice*, *71*, e13027.

Ohba, H., Takada, H., Musha, H., Nagashima, J., Mori, N., Awaya, T., et al. (2001). Effects of prolonged strenuous exercise on plasma levels of atrial natriuretic peptide and brain natriuretic peptide in healthy men. *American Heart Journal*, *141*, 751–758.

Panicker, J. N., Fowler, C. J., & Kessler, T. M. (2015). Lower urinary tract dysfunction in the neurological patient: Clinical assessment and management. *The Lancet Neurology*, *14*, 720–732.

Peyronnet, B., Krupp, L. B., Reynolds, W. S., Gamé, X., Amarenco, G., Cornu, J.-N., et al. (2019). Nocturia in patients with multiple sclerosis. *Reviews in Urology*, *21*, 63.

Phillips, P. A., Abrahams, J. M., Kelly, J. M., Mooser, V., Trinder, D., & Johnston, C. I. (1990). Localization of vasopressin binding sites in rat tissues using specific VI and V2 selective ligands. *Endocrinology*, *126*, 1478–1484.

Popovich, P. G., Stuckman, S., Gienapp, I. E., & Whitacre, C. C. (2001). Alterations in immune cell phenotype and function after experimental spinal cord injury. *Journal of Neurotrauma*, *18*, 957–966.

Potter, L. R., Yoder, A. R., Flora, D. R., Antos, L. K., & Dickey, D. M. (2009). Natriuretic peptides: their structures, receptors, physiologic functions and therapeutic applications. In *cGMP: Generators, effectors and therapeutic implications* Springer.

Rittig, S., Knudsen, U. B., Norgaard, J. P., Pedersen, E. B., & Djurhuus, J. C. (1989). Abnormal diurnal rhythm of plasma vasopressin and urinary output in patients with enuresis. *American Journal of Physiology. Renal Physiology*, *256*. F664–F671.

Sabatine, M. S., Morrow, D. A., de Lemos, J. A., Omland, T., Sloan, S., Jarolim, P., et al. (2012). Evaluation of multiple biomarkers of cardiovascular stress for risk prediction and guiding medical therapy in patients with stable coronary disease. *Circulation*, *125*, 233–240.

Schrier, R. W., Berl, T., & Anderson, R. J. (1979). Osmotic and nonosmotic control of vasopressin release. *American Journal of Physiology. Renal Physiology*, *236*. F321–F332.

Spes, Š., Katarina, S. H., Werner, F., Koch, F., Völker, K., Krebes, L., et al. (2020). Natriuretic peptides attenuate retinal pathological neovascularization via cyclic guanosine monophosphate signaling in pericytes and astrocytes. *Arteriosclerosis, Thrombosis, and Vascular Biology*, *40*, 159–174.

Swanson, L. W., & Eo Sawchenko, P. (1983). Hypothalamic integration: Organization of the paraventricular and supraoptic nuclei. *Annual Review of Neuroscience*, *6*, 269–324.

Szollar, S. M., Dunn, K. L., Brandt, S., & Fincher, J. (1997). Nocturnal polyuria and antidiuretic hormone levels in spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *78*, 455–458.

Tajima, F., Sagawa, S., Iwamoto, J., Miki, K., Freund, B. J., Claybaugh, J. R., et al. (1990). Cardiovascular, renal, and endocrine responses in male quadriplegics during head-out water immersion. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology*, *258*. R1424–R1430.

Van Leeuwen, F. W., Swaab, D. F., & De Raay, C. (1978). Immunoelectronmicroscopic localization of vasopressin in the rat suprachiasmatic nucleus. *Cell and Tissue Research*, *193*, 1–10.

Viaene, A., Roggeman, S., Goessaert, A.-. S., Kessler, T. M., Mehnert, U., Van Besien, V., et al. (2019). Conservative treatment for leg oedema and the effect on nocturnal polyuria in patients with spinal cord injury. *BJU International*, *123*, E43–E50.

Wall, B. M., Runyan, K. R., Williams, H. H., Bobal, M. A., Crofton, J. T., Share, L., et al. (1994). Characteristics of vasopressin release during controlled reduction in arterial pressure. *The Journal of Laboratory and Clinical Medicine*, *124*, 554–563.

Wan, D., & Krassioukov, A. V. (2014). Life-threatening outcomes associated with autonomic dysreflexia: A clinical review. *The Journal of Spinal Cord Medicine*, *37*, 2–10.

Wang, T. J., Larson, M. G., Levy, D., Benjamin, E. J., Leip, E. P., Omland, T., et al. (2004). Plasma natriuretic peptide levels and the risk of cardiovascular events and death. *New England Journal of Medicine*, *350*, 655–663.

Ward, P. J., Herrity, A. N., Smith, R. R., Willhite, A., Harrison, B. J., Petruska, J. C., et al. (2014). Novel multi-system functional gains via task specific training in spinal cord injured male rats. *Journal of Neurotrauma*, *31*, 819–833.

Ward, P. J., & Hubscher, C. H. (2012). Persistent polyuria in a rat spinal contusion model. *Journal of Neurotrauma*, *29*, 2490–2498.

Wassink, T. H., Piven, J., Vieland, V. J., Pietila, J., Goedken, R. J., Folstein, S. E., et al. (2004). Examination of AVPR1a as an autism susceptibility gene. *Molecular Psychiatry*, *9*, 968–972.

Wiegers, G. J., Stec, I. E. M., Klinkert, W. E. F., & Reul, J. M. H. M. (2000). Glucocorticoids regulate TCR-induced elevation of CD4: Functional implications. *The Journal of Immunology*, *164*, 6213–6220.

Wildey, G. M., & Glembotski, C. C. (1986). Cross-linking of atrial natriuretic peptide to binding sites in rat olfactory bulb membranes. *Journal of Neuroscience*, *6*, 3767–3776.

Williams, H. H., Wall, B. M., Horan, J. M., Presley, D. N., Crofton, J. T., Share, L., et al. (1990). Nonosmotic stimuli alter osmoregulation in patients with spinal cord injury. *The Journal of Clinical Endocrinology & Metabolism*, *71*, 1536–1543.

Yamamoto, M., Tajima, F., Okawa, H., Mizushima, T., Umezu, Y., & Ogata, H. (1999). Static exercise-induced increase in blood pressure in individuals with cervical spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *80*, 288–293.

Zahariou, A., Karagiannis, G., Papaioannou, P., Stathi, K., & Michail, X. (2007). The use of desmopressin in the management of nocturnal enuresis in patients with spinal cord injury. *Europa Medicophysica*, *43*, 333–338.

Zahariou, A., Karamouti, M., Karagiannis, G., & Papaioannou, P. (2008). Maximal bladder capacity is a positive predictor of response to desmopressin treatment in patients with MS and nocturia. *International Urology and Nephrology*, *40*, 65–69.

Zahra, M., Samdani, A., Piggott, K., Gonzalez-Brito, M., Solano, J., Santo, R. D. L., et al. (2010). Acute changes in systemic hemodynamics and serum vasopressin after complete cervical spinal cord injury in piglets. *Neurocritical Care*, *13*, 132–140.

Zerbe, R. L., Henry, D. P., & Robertson, G. L. (1983). Vasopressin response to orthostatic hypotension: Etiologic and clinical implications. *The American Journal of Medicine*, *74*, 265–271.

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Chapter 25

Linking sensorimotor plasticity, the motor cortex, and spinal cord injury

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Abbreviations

SCI	spinal cord injury
iSCI	incomplete spinal cord injury
TMS	transcranial magnetic stimulation
rTMS	repetitive transcranial magnetic stimulation
MRI	magnetic resonance imaging
fMRI	functional magnetic resonance imaging
M1	primary motor cortex
S1	primary somatosensory cortex
EEG	electroencephalography
CST	corticospinal tract
MEP	motor evoked potential
RMT	resting motor threshold
AMT	active motor threshold
CSP	cortical silent period
CMCT	central motor conduction time
SICI	short-interval intracortical inhibition
LICI	long-interval intracortical inhibition
SAI	short afferent inhibition
PAS	paired associative stimulation
CS	conditioning stimulus
TS	test stimulus
RC	recruitment curve
PSTHs	peristimulus time histograms
SVC	suppression of voluntary contraction
MVC	maximal voluntary contraction
VAC	volitional ankle control
MA	MEP-amplitudes with maximal stimulation
FE	facilitatory effects on MEP-amplitudes
APB	Abductor pollicis brevis
FCR	Flexor carpi radialis
BB	Biceps brachii
TA	Tibialis anterior

Sensorimotor plasticity after spinal cord injury

The treatment of spinal cord injury (SCI) is often frustrating and hopeless because of the remarkable morbidity and mortality, and restricted therapeutic options. SCI usually leads to loss of motor, sensory and autonomic functions below the

* In memoriam.

Cellular, Molecular, Physiological, and Behavioral Aspects of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822427-4.00025-3

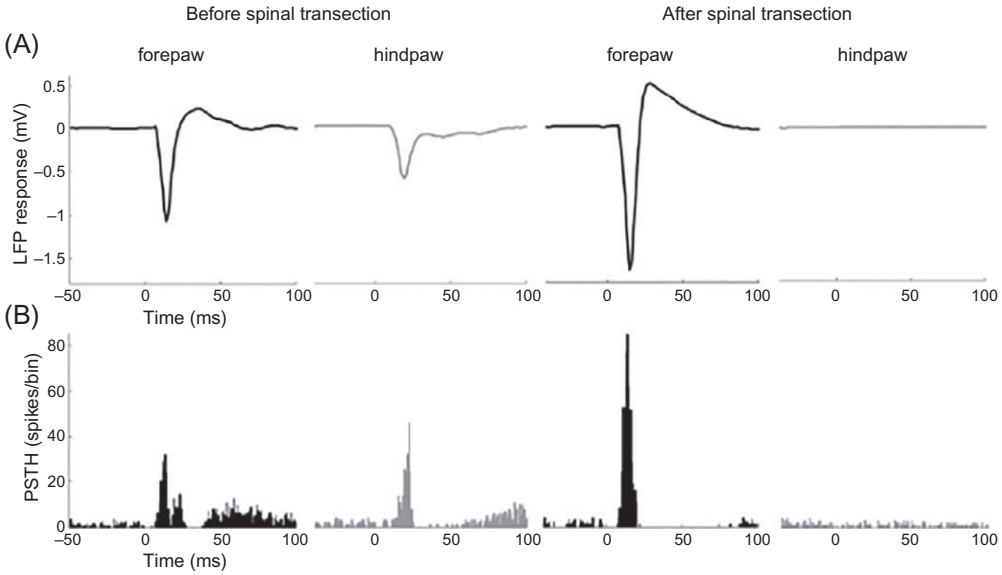

FIG. 1 (A) Responses in the forepaw cortex evoked by forepaw stimuli (*black*) and in the hindpaw cortex evoked by hindpaw stimuli (*gray*) before (*left*) and immediately after (*right*) complete thoracic spinal cord transection. (B) Peristimulus time histograms (PSTHs) represent multi-unit responses recorded from the same electrodes. Cortical responses and PSTHs were evaluated from 100 stimuli. Time 0 (*x*-axis) represents stimulus onset. The cortical responses are abolished by hindpaw stimuli, but enhanced by forepaw stimuli. *Reproduced with permission from Aguilar, J., Humanes-Valera, D., Alonso-Calvino, E., Yague, J.C., Moxon, K.A., Oliviero, A., et al. (2010). Spinal cord injury immediately changes the state of the brain.* Journal of Neuroscience, 30, *7528–7537.*

level of injury (Dietz & Curt, 2006), owing to the interruption of ascending and descending pathways (Freund et al., 2011; Jurkiewicz, Crawley, Verrier, Fehlings, & Mikulis, 2006; Wrigley et al., 2009).

Experimental electrophysiological studies have demonstrated extensive neuroplastic changes within the sensorimotor cortex after SCI. In anesthetized rats, an immediate functional reorganization has been observed in the primary somatosensory cortex (S1) following complete spinal transection (Aguilar et al., 2010) (Fig. 1). Cortical responses induced by somatosensory stimuli delivered below the level of the lesion are abolished, while those evoked by stimuli applied above the level of the lesion are enhanced. This increase could be explained by the unmasking of silent excitatory synapses, due to the elimination of inhibitory effects, similar to that typically reported after peripheral injuries in the thalamus (Faggin, Nguyen, & Nicolelis, 1997; Nicolelis, Lin, Woodward, & Chapin, 1993) and at the cortical level (Jacobs & Donoghue, 1991).

The augmented cortical responses following the deafferentation due to an SCI were found to be directly related to the slowdown of the cortical spontaneous activity, which becomes immediately overall slower and more silent, switching to a state of slow-wave activity. It has been hypothesized that the activity of brainstem structures and thalamic nuclei regulating cortical synchrony and arousal is directly affected by spinal transection, thus leading to these changes in cortical spontaneous activity (Aguilar & Castro-Alamancos, 2005). Accordingly, a slower cortical activity after SCI can also be detected in electroencephalography (EEG) recordings (Boord et al., 2008; Tran, Boord, Middleton, & Craig, 2004). This slow-wave activity probably plays an important role in shaping long-term cortical reorganization after deafferentation (Aton et al., 2009).

Functional imaging and electrophysiological studies have shown plasticity changes after SCI also in humans. It has been shown in EEG studies that changes of cortical motor activity to a posterior location occur after SCI (Green, Sora, Bialy, Ricamato, & Thatcher, 1998, 1999). This functional reorganization may result from a selective survival of axons arising in the somatosensory cortex and has also been found to have a significant relationship to prognosis in SCI patients with paraplegia.

Neuroimaging findings also suggest that SCI may lead to remarkable anatomical alterations in the human sensorimotor system. In particular, studies employing voxel-based morphometry of cortical volume have demonstrated a significant gray and white matter atrophy bilaterally in the S1. By contrast, some structural studies failed to find changes in gray matter volume in the primary motor cortex (M1) following SCI, whereas others have detected a significant decrease of gray matter volume also in M1 (Nardone et al., 2018). Cortical and subcortical mechanisms that underlie this functional reorganization of M1 and S1 are still incompletely understood.

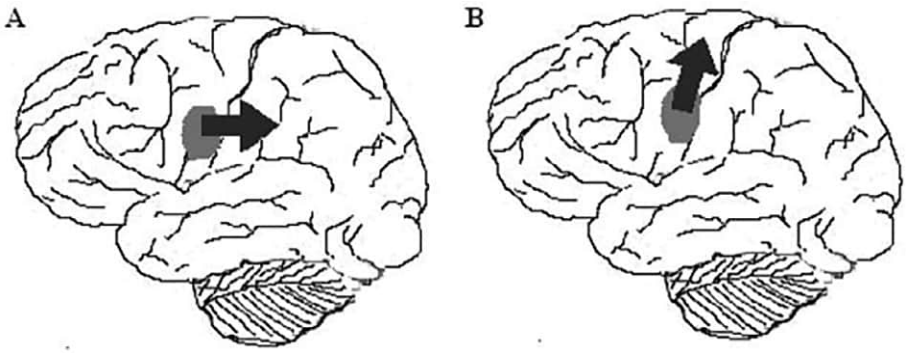

FIG. 2 (A) An upper limb motor task provokes a posterior shift of activation (represented by *shading*) toward the primary somatosensory cortex. (B) Activation of facial/upper limb movement is shifted in the direction of the deafferented upper/lower limb representation in para/tetraplegic subjects. *Reproduced with permission from Kokotilo, K.J., Eng, J.J., & Curt, A. (2009). Reorganization and preservation of motor control of the brain in spinal cord injury: A systematic review.* Journal of Neurotrauma, 26*, 2113–2126.*

A functional MRI (fMRI) study showed that in SCI patients the representation of the non-impaired upper limb muscles is changed, but a topographical reorganization in M1 was not found (Jurkiewicz, Mikuli, McIlroy, Fehlings, & Verrier, 2007). The reduction of subcortical white matter volume in M1 reported in some studies could be indicative of atrophy due to retrograde degeneration (Beaud et al., 2008; Hains, Black, & Waxman, 2003), but might also depend on the decreased cortical connectivity related to remodeling in dendritic spines or a reduction in angiogenesis (Hutton, Draganski, Ashburner, & Weiskopf, 2009). Transneuronal degeneration leads to reduced cellular activity, which can induce neuronal atrophy in the S1 (Fields, 2008).

Cortical atrophy (Jurkiewicz et al., 2006; Wrigley et al., 2009) and reorganization in the sensorimotor cortex (Kokotilo, Eng, & Curt, 2009) (Fig. 2) have been reported in other fMRI studies. In particular, during recovery following traumatic SCI (Jurkiewicz et al., 2007), or in subjects who undergo surgical decompression of cervical spinal stenosis (Duggal et al., 2010), a significantly increased volume of activation in M1 has been observed. The increase in cerebral activation during lower limb movement correlated with spinal cord atrophy and functional impairment (Lundell et al., 2011).

Although several studies demonstrating cortical reorganization after human SCI (Kokotilo et al., 2009), the role of output-deprived corticospinal neurons has still not been clarified and previous studies yielded contradictory results. Different fMRI studies revealed an expansion of task-related brain activation (Jurkiewicz et al., 2007), which correlated with atrophy of the lateral part of the cervical cord (Lundell et al., 2011), but also a reduced brain activation of subjects with SCI with persistent paralysis (Jurkiewicz, Mikuli, McIlroy, Fehlings, & Verrier, 2010). The observed expansion of the cortical M1 hand area into the output-deprived M1 leg area is thought to be related to rewiring of damaged hind limb neurons (Ghosh et al., 2010), driven by compensatory use of a less affected part of the body, similar to that observed following rehabilitative training after stroke (Nudo, Milliken, Jenkins, & Milliken, 1996) or overuse (Elbert, Pantev, Wienbruch, Rockstroh, & Taub, 1995).

Cortical and subcortical mechanisms that underlie this reorganization of M1 and S1 remain still matter of debate. Interestingly, in patients with low cervical SCI, movement of the impaired hand was found to be associated with increased blood oxygenation level dependent (BOLD) responses, not only in the expected M1 hand area but also in the expected location of the motor output-deprived M1 leg area. However, the pathophysiological basis of these fMRI findings is still not well understood and whether this cortical reorganization translates into functional gain is still unknown. It should be considered, that the interpretation of functional fMRI findings is limited to the nature of the BOLD signal, which reflects indirect neuronal activation that is mediated by both motor and sensory inputs. Instead, neurophysiological techniques, in particular the transcranial magnetic stimulation (TMS), may offer a reliable tool to characterize important neurophysiological and pathophysiological aspects of motor cortex involvement after SCI.

Functional evaluation of motor cortex

TMS mapping studies

An increased excitability of motor pathways projecting to muscles rostral to the level of a spinal transection has been reported (Topka, Cohen, Cole, & Hallett, 1991), thus suggesting that a functional reorganization may occur either within cortical motor representation areas or at the spinal cord level.

In two quadriplegic adults, an important functional reorganization of the motor cortical projection system has been observed in those cortical areas usually eliciting digit movements instead activate proximal muscles of upper limbs (Levy, Amassian, & Traad, 1990).

Four patients with traumatic cervical (C5–6) SCI showed an expanded cortical map of the preserved contralateral biceps brachii (BB) muscle as early as 6 days (Streletz et al., 1995).

These mapping studies were performed with conventional scalp reference points, and indicate increased excitability of corticospinal projections to non-paralyzed muscles above the spinal cord lesion. However, scalp mapping with TMS is limited by the variation in brain anatomy with regard to scalp topography in individual subjects. Freund and colleagues first used the navigated TMS to investigate the physiological properties of the corticospinal system in the same SCI patients, and demonstrated abnormalities in the topography and excitability of the corticomotor projections to a forearm muscle (Freund, Rothwell, Craggs, Thompson, & Bestmann, 2011). Stereotaxic TMS revealed that the location of the center of gravity of the forearm muscles was shifted posteriorly toward the region of the anatomically defined hand knob in the central sulcus. Changes in the corticospinal projections and within cortico-cortical connections of partially deprived corticospinal neurons innervating the hand neurons may therefore represent an underlying mechanism that drives cortical reorganization and represent an additional neuronal substrate contributing to muscle activation of the impaired upper limb.

Recently, in a patient with SCI resulting in a left-sided hemiparesis for 4 weeks, which by chance had a pre-lesional navigated TMS motor mapping 2 years before, the same examination could be repeated during the acute (after 1 day), subacute (after 10 days) and chronic (after 2 years) phase to trace the cortical reorganization following SCI (Dias Leao, Wiesinger, Ziemann, Tatagiba, & Naros, 2020). While MRI showed no abnormal findings, navigated TMS mapping revealed a posterior shift of the abductor pollicis brevis (APB) muscle representation from the anatomical hand knob toward the S1 in the acute in comparison to the pre-lesional phase. Also, a slight (6%) increase of resting motor threshold (RMT) to TMS was found. An incomplete reversal of the posterior shift, in parallel with a clinical improvement of motor function, occurred within 10 days. Long-term follow-up revealed complete restitution of navigated TMS cortical mapping and motor function. This case report study clearly demonstrated a rapid cortical reorganization within a few days after a transient spinal shock. These findings provide further evidence that a posterior shift of motor cortical representation occurs following SCI.

Single-pulse TMS

The RMT and the suppression of voluntary contraction (SVC) induced by TMS were both found to be higher in patients with cervical incomplete SCI (iSCI, motor level C3–C8) than in healthy control subjects, while the latency of MEPs, the latency of SVC, and SVC-MEP latency difference were increased (Davey et al., 1998). The authors concluded that the longer latency difference between MEPs and SVC may be related to a weak or absent early component of cortical inhibition in SCI patients.

In a subsequent study, the modulation of single motor unit discharges to TMS using peristimulus time histograms (PSTHs) was assessed (Smith et al., 2000). The authors aimed at improving the resolution of the excitatory and inhibitory responses previously observed in surface EMG recordings. The mean threshold for the excitatory peak (excitation) or inhibitory trough (inhibition) in the PSTHs, as well as the mean latencies of excitation and inhibition, were increased in the patients when compared with the control subjects. The latency difference (inhibition-excitation) was also significantly longer in patients than in healthy controls. The authors postulated that increased thresholds and latencies of excitation and inhibition might reflect altered corticospinal transmission in the spinal cord, while the relatively greater increase in the latency of inhibition compared with excitation could reflect a reduction of corticospinal output in response to TMS.

A long pathway, which presumably comprises interneuronal circuits within the motor cortex, is thought to be involved in producing this inhibition.

In another study of the same research group, electrophysiological evaluation of corticospinal function was performed using TMS and EMG recordings from thenar muscles in 21 patients with cervical iSCI (Smith et al., 2000). Both procedures were applied at different time points, from 19 to 384 days to 124–1109 days post-SCI. The group data were pooled into time epochs of 50 or 100 days post-injury for analysis. On the first assessment, the mean latency for MEPs and inhibition of voluntary EMG significantly differ from those of control values. The authors concluded that the decreased inhibition observed following SCI occurs within the first few days after the SCI.

Furthermore, to explore whether crossed facilitatory interactions in the corticospinal pathway are impaired in subjects with SCI, MEPs have been examined in a resting hand, arm, or foot muscle when the contralateral side remained at rest or performed 70% of maximal voluntary contraction (MVC) into index finger abduction, elbow flexion, and ankle dorsiflexion, respectively (Bunday, Oudega, & Perez, 2013). MEPs remained unchanged in muscles at and within 5 segments

below the injury during 70% of MVC compared to rest. Conversely, in muscles beyond 5 segments below the injury the size of MEPs increased similar to controls and in muscles distant (>15 segments) from the injury was even aberrantly high, twofold above controls.

A study that focused on plasticity processes of muscles cranial to the SCI level after complete SCI (Lotze, Laubis-Herrmann, & Topka, 2006) demonstrated different MEP recruitment curves (RC) of patients and control subjects. The APB muscle, which is supplied by motoneurons that are located more distinct from the cortical deafferented area than the BB muscle, showed decreased cortical excitability. Furthermore, other findings, such as the lack of relevant increase of MEP amplitudes with increasing stimulus intensities and prolonged cortical silent period (CSP) after SCI, point to reduced excitability of the cortical areas inferior-lateral to the deafferented area.

Since CSP reflect a long-lasting cortical inhibition mediated by $GABA_B$ most likely in the motor cortex (Ziemann et al., 2008), these results suggest an increase in excitability of cortical inhibitory circuits, which is indicative of reduced corticospinal excitability.

To further investigate the corticospinal excitability changes after SCI, the RC of the MEPs has been evaluated in five subjects with good recovery after traumatic cervical iSCI (Nardone et al., 2015). While RMT did not differ significantly between patients and controls, the slope of MEP RC was significantly increased in the patients. This abnormal finding suggests an adaptive response after SCI; the impaired ability of the motor cortex to generate proper voluntary movement may be compensated by increasing spinal excitability.

The easily performed measurement of MEP RC may thus provide a useful additional tool to improve the assessment and monitoring of motor cortical function in subjects with SCI.

Increasing our knowledge of the corticospinal excitability changes in the functional recovery after SCI may also support the development of effective therapeutic strategies.

Both MEP amplitude and latency were shown to have a relationship with the measures of volitional ankle control (VAC), such as tapping tasks, ankle strength, toe clearance during walking, and gait measures. In the studies that assessed VAC during tapping tasks, there was an association between maximal movement velocity and measures of CST transmission (Wirth, Van Hedel, & Curt, 2008a, 2008b, 2008c, 2008d). Two studies demonstrated an association between ankle strength with MEP latency (Wirth et al., 2008b) and MEP amplitude (Wirth et al., 2008c), while two others did not support a relationship between those measures (Labruyère, Zimmerli, & Van Hedel, 2013; Wirth et al., 2008d). The toe clearance during walking, which can be used to assess foot drop/toe drag, was measured in two MEP studies (Barthélemy et al., 2010; Barthélemy et al., 2013), which revealed that maximum toe elevation was associated with MEP amplitude and latency (Fig. 3).

A recent study aimed at establishing changes in corticospinal excitability with absent and partial body weight support; MEPs were reliably recorded at different sessions during stepping in healthy subjects (Knikou, Hajela, & Mummidisetty, 2013). The MEPs recorded from the tibialis anterior (TA) muscle were facilitated at heel contact and throughout the swing phase of the step cycle, while they progressively decrease during the stance phase. Conversely, the soleus MEPs were progressively increased at early-stance and depressed at the stance-to-swing transition as well as throughout the swing phase. These findings indicate that the strength of corticospinal drive will not be affected negatively during stepping under conditions of partial body loading.

Shimizu et al. first report three patients with cervical SCI who showed loss of the CSP after TMS. The absence of CSP was found in both the hand and foot muscles in two patients and in another one only in the foot muscle (Shimizu, Hino, Komori, & Hirai, 2000).

The active motor threshold (AMT) and the duration of CSP were increased in the SCI subjects (Freund, Rothwell, et al., 2011). There was also a negative association, as evaluated by multiple linear regression analysis between spinal cord atrophy and both, AMT and CSP duration. Increased AMT may reflect a reduced density of motoneurons and/or interneurons in low segments of the cervical cord that innervate the extensor digitorum communis muscle. Indeed, AMT differs from RMT in that provides a measure of corticospinal excitability with greater dependence on the spinal segmental level excitability (Hallett, 2000). Alternatively, the reduced density of surviving corticospinal neurons requires a higher intensity of TMS to recruit a given corticospinal output (Di Lazzaro et al., 2004).

The investigation of motor cortex excitability during fatiguing exercise may shed light on the role of exercise therapy in promoting brain reorganization and functional recovery in humans.

Therefore, the mechanisms of exercise-induced cortical plasticity have been evaluated in five patients with cervical iSCI (Nardone et al., 2013). The physiological lengthening of CSP during fatigue was not observed in the SCI patients. This reduced intracortical inhibition, probably secondary to decreased activity of the GABAergic inhibitory interneurons that modulate the corticomotoneuronal output, likely represents a "positive" neuroplastic response in an attempt to compensate for the loss of corticospinal axons.

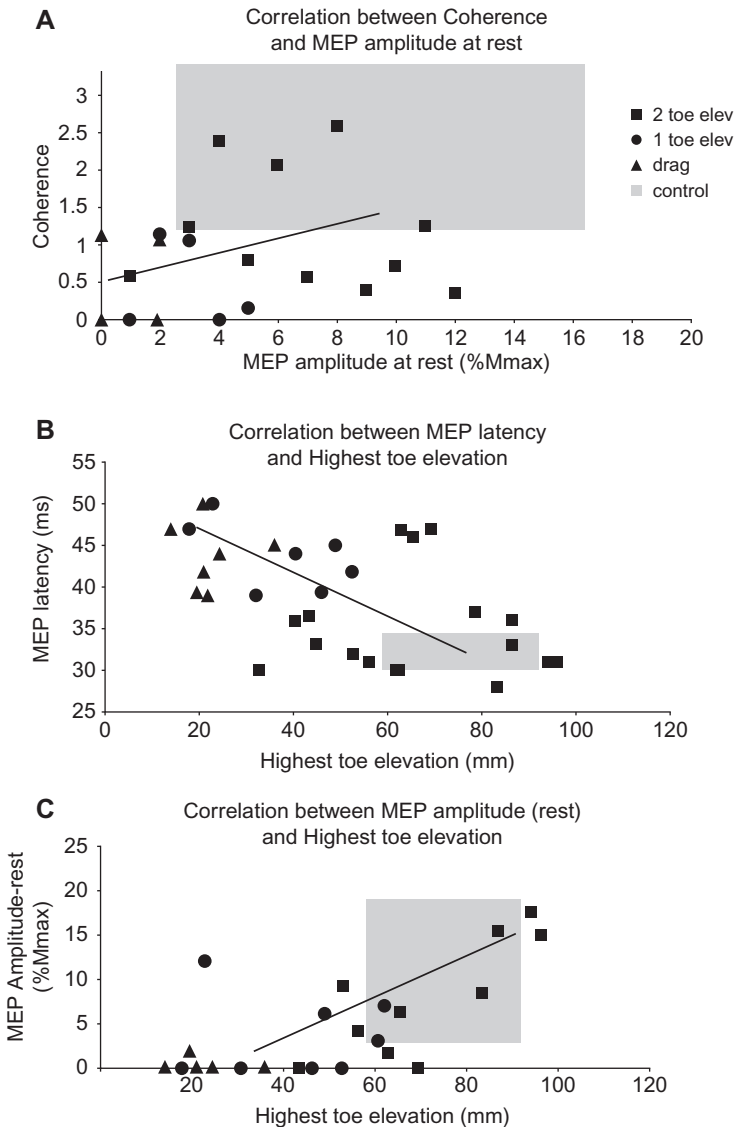

FIG. 3 Correlations between motor evoked potential (MEP), coherence, and kinematic measures. In (A) coherence is plotted against MEP amplitude assessed at rest. Each point represents a participant. In (B) MEP latency is correlated to the highest toe elevation and in (C) MEP amplitude at rest is correlated to the highest toe elevation (both legs of the participants were analyzed). *Reproduced with permission from Barthélemy, D., Willerslev-Olsen, M., Lundell, H., Conway, B.A., Knudsen, H., Biering-Sorensen, F., et al. (2010). Impaired transmission in the corticospinal tract and gait disability in spinal cord injured persons.* Journal of Neurophysiology, 104, *1167–1176.*

Paired-pulse TMS and paired associative stimulation

A paired-pulse TMS study revealed reduced excitability of inhibitory circuits as assessed in a single patient (Laubis-Herrmann, Dichgans, & Bilow, 2000). Two arm muscles distant to the SCI levels (T2–L3), the BB, and the APB muscles were studied in 13 patients. RMT, facilitatory effects on MEP-amplitudes (FE) with voluntary activation, MEP-amplitudes with maximal stimulation (MA), and MEP-RC were measured. Patients exhibited smaller MA from activated BB muscles, a tendency toward smaller FE and smaller RC-slopes. FE, MA, and RC-slopes tended to normalize.

Similarly, another TMS study in a single patient also showed reduced short-interval intracortical inhibition (SICI) (Saturno, Bonato, Miniussi, Di Lazzaro, & Callea, 2008). During posterior tibial nerve stimulation, the authors observed a contextual flexion of hand fingers contralateral to the stimulated lower limb, which suggests abnormal motor cortex excitability. TMS findings were consistent with reduced activity of motor cortex inhibitory circuits since SICI reflects mostly the $GABA_A$-mediated intracortical inhibitory interactions (Paulus et al., 2008). The authors postulated disinhibition of latent synapses within the motor cortex and the rewriting of a new motor cortical map.

Also in the study of Shimizu et al. (2000) paired-pulse TMS study in one SCI patient with pseudoathetotic hands showed reduced inhibition within the motor cortex.

Roy et al. compared SICI during a voluntary contraction in 16 patients with SCI and 14 control subjects, the latter group tested over a larger range of conditioning and test stimulus (CS and TS) intensities to best match the SCI patients data (Roy, Zewdie, & Gorassini, 2011). The main finding was that the average peak SICI in the TA muscle was typically 3–4 times lower in SCI subjects compared to controls. However, when matched for absolute TS intensity, in terms of maximum stimulator output, both U-shaped SICI RC were produced by similar CS intensities.

In another study, the effect of passive and active pedaling exercise on M1 leg area excitability in subjects with traumatic chronic cervical or thoracic SCI has been evaluated (Nardone et al., 2016). A significant effect of pedaling on SICI to paired TMS was found, thus a reduction of SICI, regardless of the experimental condition (active vs passive).

Mi and colleagues recorded long-interval intracortical inhibition (LICI), which reflects long-lasting cortical inhibitory mechanisms mediated by $GABA_B$ receptor transmission (Paulus et al., 2008), from the flexor carpi radialis (FCR) muscle during an isometric contraction equal to 15%–20% of MVC (Mi, Bailey, & Nelson, 2016). LICI was increased in the actively contracted FCR muscle in individuals with SCI compared with age-matched controls. These findings indicate that $GABA_B$ function mediating LICI is different in SCI vs controls. Increased LICI in SCI may be attributed to the medication baclofen or to changes in the neural mechanisms controlling contraction-related modulation of the LICI circuit.

More recently, the MEPs elicited by cortical and subcortical stimulation of corticospinal axons and SICI in the first dorsal interosseous muscle were examined in the preparatory phase of a reaction time task where individuals with chronic cervical iSCI and age-matched controls needed to suppress (NOGO) or initiate (GO) ballistic index finger isometric voluntary contractions (Federico & Perez, 2017) (Fig. 4).

MEPs remained unchanged compared to baseline in subjects with SCI but were suppressed in control subjects. During GO trials, MEPs amplitude increased to a similar extent in both groups but those elicited by subcortical stimulation

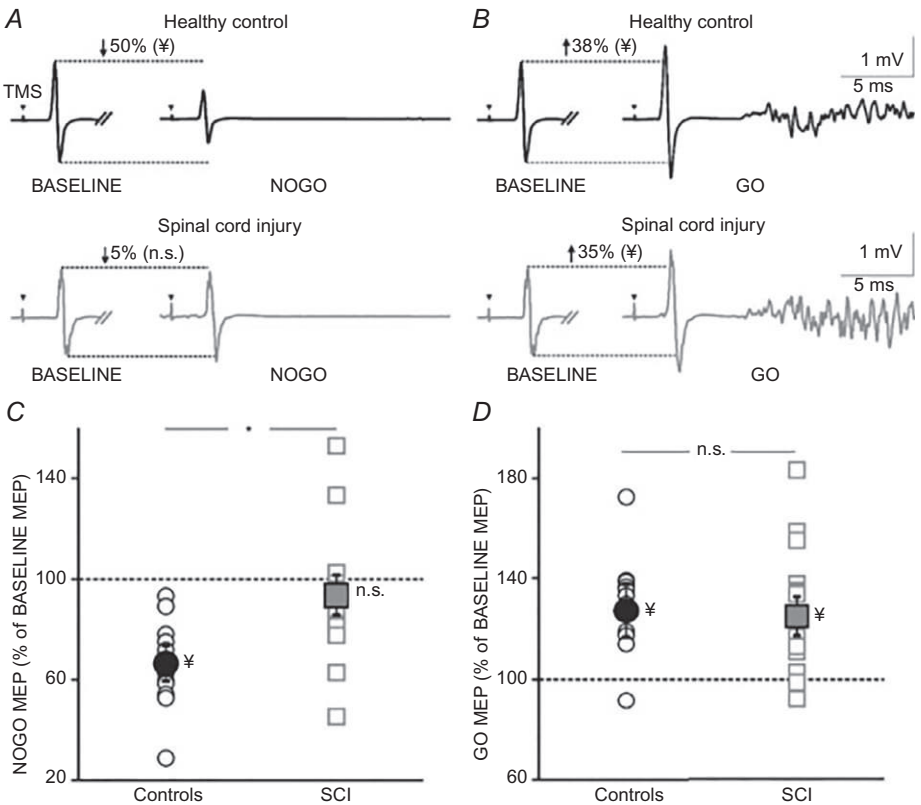

FIG. 4 (A and B) Raw traces of MEPs elicited by TMS in the first dorsal interosseous (FDI) muscle in representative control and SCI subject during NOGO (A) and GO (B) trials. Each waveform represents the average of 20 MEPs at baseline and during GO (control = *black*; SCI = *gray*) and NOGO (control = *black*; SCI = *gray*) trials. Amplitude scales are different for the SCI and control representative subjects to better show changes across the task. (C and D) Group data (controls, $n = 13$, *black circles*; SCI, $n = 18$, *gray squares*) show MEPs during NOGO (C) and GO (D). The *horizontal dotted line* shows the FDI MEP size at baseline. Data from individual subjects are shown in controls (*open circles*) and SCI subjects (*open squares*). Error bars indicate SEM. $^{*}P < 0.05$, comparison between groups; $^{¥}P < 0.05$, comparison between baseline and GO or NOGO trials. *Reproduced with permission from Federico, P., & Perez, M.A. (2017). Altered corticospinal function during movement preparation in humans with spinal cord injury*. Journal of Physiology, 595, *233–245*.

increased only in control subjects. The magnitude of SICI increased in control subjects but not in SCI patients during NOGO trials and decreased in both groups in GO trials.

Also, the investigation of the corticospinal I-waves, the so-called I-wave facilitation, revealed significant differences between SCI patients with normal and abnormal central motor conduction time (CMCT), and healthy controls (Nardone et al., 2015). SCI patients with normal CMCT showed increased I-wave facilitation, while those with prolonged CMCT showed lower I-wave facilitation compared to a control group.

Since the mechanisms responsible for the production of I-waves are mediated by GABA-related inhibition, these findings point to an increased motor cortical excitability in SCI patients with preserved corticospinal projections.

Another study examined short-latency afferent inhibition (SAI), which is thought to depend on the integrity of circuits linking sensory input and motor output (Sailer et al., 2003), in the FCR muscle in individuals SCI and uninjured controls (Bailey, Mi, & Nelson, 2015). The authors found that SAI was reduced in SCI in both the contracted and non-contracted muscles. MEP RC and RMT were decreased in SCI only in the active state and not the resting state. N20-P25 amplitude was similar between groups in both the resting and active states, even if sensory nerve action potentials were significantly reduced in SCI at rest. Reduced SAI in SCI can be attributed to neuroplasticity altering the intrinsic M1 circuitry mediating SAI and/or reduced afferent input traversing a direct thalamocortical route to M1.

The paired associative stimulation (PAS) protocol, which involves repeated pairs of electrical stimulation of a peripheral nerve (usually the median nerve) followed by TMS applied over the contralateral M1 hand area, can be considered a marker of motor cortical plasticity, and long-term plasticity-like mechanisms are thought to play a major role (Stefan, Kunesch, Benecke, Cohen, & Classen, 2002). PAS has been employed to determine whether the arrival of a corticospinal volley immediately prior to motoneuron discharge may enhance corticospinal transmission and voluntary motor control in patients with iSCI (Ellaway, Vásquez, & Craggs, 2014) (Fig. 5). A short period of paired-pulse stimulation, timed such that a corticospinal volley arrived 1–2 ms before the anti-dromic invasion of action potentials in motoneurons of the flexor digitorum longus muscle, resulted in an MEP facilitation lasting 30 min after PAS treatment.

Interestingly, the PAS protocol significantly enhanced corticospinal excitability in SCI patients with good motor recovery, while it was followed by a non-significant increase of MEP amplitude in the SCI patients with poor functional recovery (Versace et al., 2018).

Discussion

Neuroimaging and electrophysiological studies demonstrated that neuroplastic changes of large cortical networks occur after SCI and play a crucial role in the functional reorganization especially within the sensorimotor area. Besides the above reported TMS studies, increased EEG beta oscillations in the sensorimotor cortex in subjects with SCI may also be regarded as compensatory mechanisms activated to enhance neural plasticity (Simis, Uygur-Kucukseymen, Pacheco-Barrios, Mattistella, & Fregni, 2020).

SCI disrupts the pathways mediating efferent and afferent information flow between the spinal cord and the brain, resulting in dramatic cortical reorganization changes. Brain structures and functions react to missing or more often critically altered motor and sensory signals from peripheral nervous system. Indeed, in most subjects, some spared white matter still connects the caudal with the rostral spinal cord (Bunge, Puckett, Becerra, Marcillo, & Quencer, 1993), and part of surviving neurons remain receptive to synaptic input (Tseng & Prince, 1996; Hains et al., 2003).

A deeper understanding of the complex relationship between anatomical changes following SCI, sensorimotor reorganization, and upper limbs function is helpful for the identification of non-invasive biomarkers, which can quantify the impact of SCI upon the structural integrity, prognosis, and clinical trials for spinal cord repair. In turn, the investigation of the plastic changes which occur within the sensorimotor cortex after SCI could lead to a better understanding of the considerable complexity of the cortical reorganization, and may help to develop experimental and clinical models useful for managing that reorganization.

After SCI the functional recovery is often limited despite intensive efforts to improve the functional outcomes. Identification and better definition of the plasticity mechanisms in the adult human cortex after SCI is an important step toward the development of rationally founded treatment strategies in neurorehabilitation.

In particular, it would be desirable to find strategies for modulating the altered neural plasticity after SCI, not only in the spinal cord but also in higher-order structures, such as the sensorimotor cortex. The cortical reorganization induced by deafferentation may be functionally beneficial or maladaptive. Indeed, these plastic changes may contribute to the occurrence of secondary pathologic conditions, such as neuropathic pain, hyperalgesia, allodynia (Leemhuis, De Gennaro, & Pazzaglia, 2019). Since it is reasonable to expect that upregulation of SCI-induced cortical plasticity using non-invasive

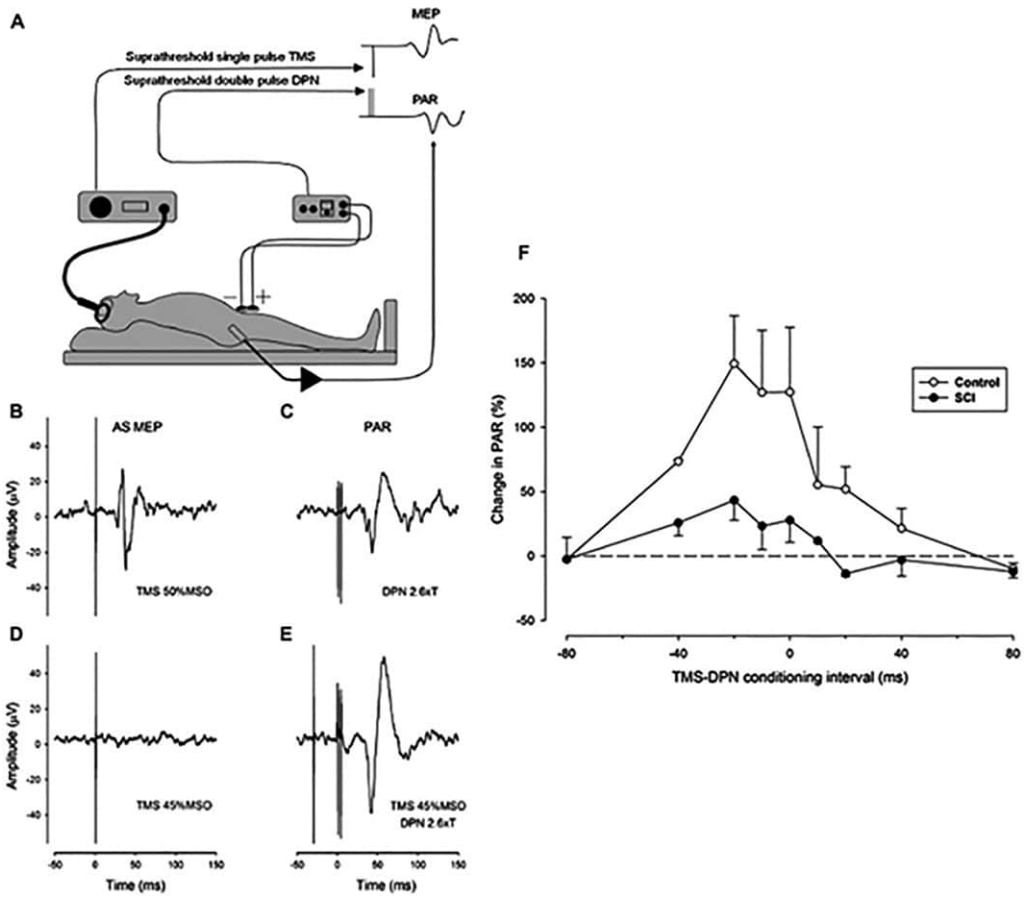

FIG. 5 Facilitation of the pudendal anal reflex (PAR) by single-pulse TMS. (A) Experimental set-up: dorsal penile nerve (DPN) stimulating electrodes, anal sphincter EMG recording electrode, and the TMS double cone coil. (*Insets*) Idealized PAR and anal sphincter MEP responses. (B–E) Anal sphincter EMG averaged ($n = 10$) evoked responses in a control subject. (B) MEP to cortical TMS at 50% of maximal stimulator output (MSO). (C) PAR response to stimulation of the DPN at 2.6 times sensory threshold (18 mA). (D) Lack of response to TMS at 45% MSO. (E) TMS at 45% MSO preceding DPN at 2.6 times sensory threshold by 30 ms. The DPN stimulus in E now evokes an increased PAR that is approximately double the peak-to-peak size of the unconditioned PAR in (C). (F) The degree of PAR facilitation of the PAR by TMS at different conditioning intervals. The graph shows the average percentage increase in the PAR for three control (*open symbols*) and three incomplete SCI (*closed symbols*) subjects. The *dashed horizontal line* indicates a level of zero facilitation. Facilitation is significantly greater for the control group (Wilcoxon signed-rank test $P = 0.008$). *Reproduced with permission from Ellaway, P.H, Vásquez, N., & Craggs, M. (2014). Induction of central nervous system plasticity by repetitive transcranial magnetic stimulation to promote sensorimotor recovery in incomplete spinal cord injury.* Frontiers in Integrative Neuroscience, 8, *42*.

brain stimulations could be an effective treatment method, it would be of interest to learn whether it is possible to purposely modulate the deafferentation-induced cerebral reorganization after SCI.

In fact, TMS can also be a useful tool for the functional assessment of the cortical reorganization following SCI, and rTMS could also play an important role as an intervention in SCI patients to enhance plasticity when used alone or in combination with other interventions to augment current pharmacotherapy and rehabilitation therapies for SCI rehabilitation.

Therefore, neural repair and neuroregeneration are critical goals and issues for rehabilitation in subjects with SCI, which also includes multi-modal neuromodulation techniques.

Magnetic/electrical modulation promotes neuroregeneration and neural repair by affecting signaling in the nervous system; namely, by exciting, inhibiting, or regulating neuronal and neural network activities to improve motor function and motor learning following SCI.

Interventions enhancing local plasticity such as rTMS or tDCS combined with robotic training also lead to an immediate increase in sensorimotor cortex activation, improvement in gait recovery, and a subsequent decrease in high-beta power on EEG.

If delivered repetitively, TMS can influence brain function and induce neuroplastic changes. Indeed, repetitive TMS (rTMS) can modulate cortical excitability, inducing lasting effects (Fitzgerald, Fountain, & Daskalakis, 2006; Lefaucheur

et al., 2020). Therefore, rTMS has evolved into a powerful neuroscientific tool allowing to interfere transiently with specific brain functions.

RTMS techniques are known to be able to modulate neural plasticity in the human cerebral cortex. The therapeutic approaches in subjects SCI are usually based on techniques aimed at enhancing cortical excitability, in particular HF rTMS. However, experimental studies have demonstrated that the deafferentation-induced plastic changes following SCI can be up-regulated by motor cortical LF rTMS stimulation.

Overall, examination of different rTMS protocols will provide a better understanding on modulation of deafferentiation-induced brain plasticity after SCI and a useful method in the neurorehabilitation of these patients.

Applications to other areas of neuroscience

In this chapter we have reviewed neuroimaging and, in particular, neurophysiological studies demonstrating that neuroplastic changes of large cortical networks occur after SCI and play a critical role in the functional reorganization, especially within the sensorimotor cortex.

The interconnections between sensorimotor plasticity and functional recovery have also been explored in subjects with other neurological diseases, in particular stroke and traumatic brain injury. Therefore, neural repair and neuroregeneration are critical goals and issues for rehabilitation in patients with various neurological diseases and possibly include multimodal neuromodulation techniques. Furthermore, transcranial magnetic stimulation and other techniques of non-invasive brain stimulation can influence brain function and induce neuroplastic changes in different pathological conditions.

Key facts

- The treatment of spinal cord injury (SCI) is often frustrating and hopeless.
- Experimental studies have demonstrated neuroplastic changes within the sensorimotor cortex after SCI.
- An immediate functional reorganization following complete spinal transection has been observed in the somatosensory cortex of rats.
- A slower cortical activity after SCI can also be detected in electroencephalography recordings.
- Neuroimaging studies suggest that SCI may lead to significant anatomical alterations in the human sensorimotor system.
- Cortical and subcortical mechanisms that underlie functional reorganization of sensory-motor cortex are still incompletely understood.

Mini-dictionary of terms

Transcranial magnetic stimulation: Non-invasive form of brain stimulation using a changing magnetic field.
Repetitive transcranial magnetic stimulation: Treatment that involves magnetic pulses delivered repetitively to target specific areas of the brain.
Sensorimotor cortex: **B**rain area that covers the primary sensory and motor areas of the brain.
Neuroplasticity: The ability of the brain to undergo changes involving cortical remapping.
Spinal cord injury: Damage to any part of the spinal cord that causes temporary or permanent loss of its functions.

Summary points

- Deafferentation due to spinal cord injury (SCI) alters the state of large cortical networks,
- Changes within the sensorimotor cortex play a critical role in the functional reorganization after SCI.
- Transcranial magnetic stimulation (TMS) has shown to be a reliable tool to measure the plastic changes that occur in the human brain.
- Repetitively TMS (repetitive TMS), can be used for modulation of plasticity also after an SCI.
- Understanding the relationship between anatomical changes, sensorimotor reorganization, and upper limbs function is helpful for the identification of non-invasive biomarkers.
- Understanding the cortical reorganization mechanisms may help to develop interventions to maximize rehabilitation strategies.

References

Aguilar, J. R., & Castro-Alamancos, M. A. (2005). Spatiotemporal gating of sensory inputs in thalamus during quiescent and activated states. *Journal of Neuroscience*, *25*, 10990–11002.

Aguilar, J., Humanes-Valera, D., Alonso-Calvino, E., Yague, J. C., Moxon, K. A., Oliviero, A., et al. (2010). Spinal cord injury immediately changes the state of the brain. *Journal of Neuroscience*, *30*, 7528–7537.

Aton, S. J., Seibt, J., Dumoulin, M., Jha, S. K., Steinmetz, N., Coleman, T., et al. (2009). Mechanisms of sleep-dependent consolidation of cortical plasticity. *Neuron*, *61*, 454–466.

Bailey, A. Z., Mi, Y. P., & Nelson, A. J. (2015). Short-latency afferent inhibition in chronic spinal cord injury. *Translational Neuroscience*, *6*, 235–243.

Barthélemy, D., Knudsen, H., Willerslev-Olsen, M., Lundell, H., Nielsen, J. B., & Biering-Sørensen, F. (2013). Functional implications of corticospinal tract impairment on gait after spinal cord injury. *Spinal Cord*, *51*, 852–856.

Barthélemy, D., Willerslev-Olsen, M., Lundell, H., Conway, B. A., Knudsen, H., Biering-Sorensen, F., et al. (2010). Impaired transmission in the corticospinal tract and gait disability in spinal cord injured persons. *Journal of Neurophysiology*, *104*, 1167–1176.

Beaud, E., Schmidlin, T., Wannier, P., Freund, P., Bloch, J., & Mir, A. (2008). Nogo-A antibody treatment does not prevent cell body shrinkage in the motor cortex in adult monkeys subjected to unilateral cervical cord lesion. *BMC Neuroscience*, *9*, 5.

Boord, P., Siddall, P. J., Tran, Y., Herbert, D., Middleton, J., & Craig, A. (2008). Electroencephalographic slowing and reduced reactivity in neuropathic pain following spinal cord injury. *Spinal Cord*, *46*, 118–123.

Bunday, L., Oudega, M., & Perez, M. A. (2013). Aberrant crossed corticospinal facilitation in muscles distant from a spinal cord injury. *PLoS One*, *8*, E76747.

Bunge, R. P., Puckett, W. R., Becerra, J. L., Marcillo, A., & Quencer, R. M. (1993). Observations on the pathology of human spinal cord injury. A review and classification of 22 new cases with details from a case of chronic cord compression with extensive focal demyelination. *Advances in Neurology*, *9*, 75–89.

Davey, N. J., Smith, H. C., Wells, E., Maskill, D. W., Savic, G., Ellaway, P. H., et al. (1998). Responses of thenar muscles to transcranial magnetic stimulation of the motor cortex in patients with incomplete spinal cord injury. *Journal of Neurology, Neurosurgery and Psychiatry*, *65*, 80–87.

Di Lazzaro, V., Oliviero, A., Pilato, F., Saturno, E., Dileone, M., Mazzone, P., et al. (2004). The physiological basis of transcranial motor cortex stimulation in conscious humans. *Clinical Neurophysiology*, *115*, 255–266.

Dias Leao, M. T., Wiesinger, L., Ziemann, U., Tatagiba, M., & Naros, G. (2020). Rapid motor cortical reorganization following subacute spinal cord dysfunction. *Brain Stimulation*, *13*, 783–785.

Dietz, V., & Curt, A. (2006). Neurological aspects of spinal-cord repair: Promises and challenges. *Lancet Neurology*, *5*, 688–694.

Duggal, N., Rabin, D., Bartha, R., Barry, L., Gati, J. S., Kowalczyk, I., et al. (2010). Brain reorganisation in patients with spinal cord compression evaluated using fMRI. *Neurology*, *74*, 1048–1054.

Elbert, T., Pantev, C., Wienbruch, C., Rockstroh, B., & Taub, E. (1995). Increased cortical representation of the fingers of the left hand in string players. *Science*, *270*, 305–307.

Ellaway, P. H., Vásquez, N., & Craggs, M. (2014). Induction of central nervous system plasticity by repetitive transcranial magnetic stimulation to promote sensorimotor recovery in incomplete spinal cord injury. *Frontiers in Integrative Neuroscience*, *8*, 42.

Faggin, B. M., Nguyen, K. T., & Nicolelis, M. A. (1997). Immediate and simultaneous sensory reorganisation at cortical and subcortical levels of the somatosensory system. *Proceedings of the National Academy of Sciences of the United States of America*, *94*, 9428–9433.

Federico, P., & Perez, M. A. (2017). Altered corticospinal function during movement preparation in humans with spinal cord injury. *Journal of Physiology*, *595*, 233–245.

Fields, R. D. (2008). White matter in learning, cognition and psychiatric disorders. *Trends in Neurosciences*, *31*, 361–370.

Fitzgerald, P. B., Fountain, S., & Daskalakis, Z. J. (2006). A comprehensive review of the effects of rTMS on motor cortical excitability and inhibition. *Clinical Neurophysiology*, *117*, 2584–2596.

Freund, P., Rothwell, J., Craggs, M., Thompson, A. J., & Bestmann, S. (2011). Corticomotor representation to a human forearm muscle changes following cervical spinal cord injury. *European Journal of Neuroscience*, *34*, 1839–1846.

Freund, P., Weiskopf, N., Ward, N. S., Hutton, C., Gall, A., Ciccarelli, O., et al. (2011). Disability, atrophy and cortical reorganization following spinal cord injury. *Brain*, *134*, 1610–1622.

Ghosh, A. F., Haiss, F., Sydekum, E., Schneider, R., Gullo, M., Wyss, M. T., et al. (2010). Rewiring of hindlimb corticospinal neurons after spinal cord injury. *Nature Neuroscience*, *13*, 97–104.

Green, J. B., Sora, E., Bialy, Y., Ricamato, A., & Thatcher, R. W. (1998). Cortical sensorimotor reorganization after spinal cord injury: An electroencephalographic study. *Neurology*, *50*, 1115–1121.

Green, J. B., Sora, E., Bialy, Y., Ricamato, A., & Thatcher, R. W. (1999). Cortical motor reorganization after paraplegia: An EEG study. *Neurology*, *53*, 736–743.

Hains, B. C., Black, J. A., & Waxman, S. C. (2003). Primary cortical motor neurons undergo apoptosis after axotomizing spinal cord injury. *The Journal of Comparative Neurology*, *462*, 328–341.

Hallett, M. (2000). Transcranial magnetic stimulation and the human brain. *Nature*, *406*, 147–150.

Hutton, C., Draganski, B., Ashburner, J., & Weiskopf, N. (2009). A comparison between voxel-based cortical thickness and voxel-based morphometry in normal aging. *NeuroImage*, *48*, 371–380.

Jacobs, K. M., & Donoghue, J. P. (1991). Reshaping the cortical motor map by unmasking latent intracortical connections. *Science*, *251*, 944–947.

Jurkiewicz, M. T., Crawley, A. P., Verrier, M. C., Fehlings, M. G., & Mikulis, D. J. (2006). Somatosensory cortical atrophy after spinal cord injury: A voxel-based morphometry study. *Neurology*, *66*, 62–764.

Jurkiewicz, M. T., Mikuli, D. J., McIlroy, W. E., Fehlings, M. G., & Verrier, M. C. (2007). Sensorimotor cortical plasticity during recovery following spinal cord injury: A longitudinal fMRI study. *Neurorehabilitation and Neural Repair*, *21*, 527–538.

Jurkiewicz, M. T., Mikuli, D. J., McIlroy, W. E., Fehlings, M. G., & Verrier, M. C. (2010). Sensorimotor cortical activation in patients with cervical spinal cord injury with persisting paralysis. *Neurorehabilitation and Neural Repair*, *24*, 136–140.

Knikou, M., Hajela, N., & Mummidisetty, C. K. (2013). Corticospinal excitability during walking in humans with absent and partial body weight support. *Clinical Neurophysiology*, *124*, 2431–2438.

Kokotilo, K. J., Eng, J. J., & Curt, A. (2009). Reorganization and preservation of motor control of the brain in spinal cord injury: A systematic review. *Journal of Neurotrauma*, *26*, 2113–2126.

Labruyère, R., Zimmerli, M., & Van Hedel, H. J. (2013). Slowed down: Response time deficits in well-recovered subjects with incomplete spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *94*, 2020–2026.

Laubis-Herrmann, U., Dichgans, J., & Bilow, H. (2000). Motor reorganization after spinal cord injury: Evidence of adaptive changes in remote muscles. *Restorative Neurology and Neuroscience*, *17*, 75–181.

Leemhuis, E., De Gennaro, L., & Pazzaglia, A. M. (2019). Disconnected body representation: Neuroplasticity following spinal cord injury. *Journal of Clinical Medicine*, *8*, 2144.

Lefaucheur, J. P., Aleman, A., Baeken, C., Benninger, D. H., Brunelin, J., Di Lazzaro, V., et al. (2020). Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014-2018). *Clinical Neurophysiology*, *131*, 474–528.

Levy, W. J., Amassian, V. E., & Traad, M. (1990). Focal magnetic coil stimulation reveals motor cortical system reorganized in humans after traumatic quadriplegia. *Brain Research*, *510*, 130–134.

Lotze, M., Laubis-Herrmann, U., & Topka, H. (2006). Combination of TMS and fMRI reveals a specific pattern of reorganization in M1 in patients after complete spinal cord injury. *Restorative Neurology and Neuroscience*, *24*, 97–107.

Lundell, H., Barthelemy, D., Skimminge, A., Dyrby, T. B., Biering-Sørensen, F., & Nielsen, J. B. (2011). Independent spinal cord atrophy measures correlate to motor and sensory deficits in individuals with spinal cord injury. *Spinal Cord*, *49*, 70–75.

Lundell, H., Christensen, M. S., Barthelemy, D., Willerslev-Olsen, M., Biering-Sørensen, F., & Nielsen, J. B. (2011). Cerebral activation is correlated to regional atrophy of the spinal cord and functional motor disability in spinal cord injured individuals. *NeuroImage*, *54*, 254–261.

Mi, Y. P., Bailey, A. Z., & Nelson, A. J. (2016). Short- and long-intracortical inhibition in incomplete spinal cord injury. *Canadian Journal of Neurological Sciences*, *43*, 183–191.

Nardone, R., Höller, Y., Bathke, A. C., Orioli, A., Schwenker, K., Frey, V., et al. (2015). Spinal cord injury affects I-wave facilitation in human motor cortex. *Brain Research Bulletin*, *116*, 93–97.

Nardone, R., Höller, Y., Brigo, F., Höller, P., Christova, M., Tezzon, F., et al. (2013). Fatigue-induced motor cortex excitability changes in subjects with spinal cord injury. *Brain Research Bulletin*, *99*, 9–12.

Nardone, R., Höller, Y., Sebastianelli, L., Versace, V., Saltuari, L., Brigo, F., et al. (2018). Cortical morphometric changes after spinal cord injury. *Brain Research Bulletin*, *137*, 107–119.

Nardone, R., Höller, Y., Thomschewski, A., Bathke, A. C., Ellis, A. R., Golaszewski, S. M., et al. (2015). Assessment of corticospinal excitability after traumatic spinal cord injury using MEP recruitment curves: A preliminary TMS study. *Spinal Cord*, *53*, 534–538.

Nardone, R., Langthaler, P. B., Bathke, A. C., Höller, Y., Brigo, F., Lochner, P., et al. (2016). Effects of passive pedaling exercise on the intracortical inhibition in subjects with spinal cord injury. *Brain Research Bulletin*, *124*, 144–149.

Nicolelis, M. A., Lin, R. C., Woodward, D. J., & Chapin, J. K. (1993). Induction of immediate spatiotemporal changes in thalamic networks by peripheral block of ascending cutaneous information. *Nature*, *361*, 533–536.

Nudo, R. J., Milliken, G. W., Jenkins, W. M., & Milliken, G. W. (1996). Use-dependent alterations of movement representations in primary motor cortex of adult squirrel monkeys. *Journal of Neuroscience*, *16*, 785–807.

Paulus, W., Classen, J., Cohen, L. G., Large, C. H., Di Lazzaro, V., Nitsche, M., et al. (2008). State of the art: Pharmacologic effects on cortical excitability measures tested by transcranial magnetic stimulation. *Brain Stimulation*, *1*, 151–163.

Roy, F. D., Zewdie, E. T., & Gorassini, M. A. (2011). Short-interval intracortical inhibition with incomplete spinal cord injury. *Clinical Neurophysiology*, *122*, 1387–1395.

Sailer, A., Molnar, G. F., Paradiso, G., Gunraj, C. A., Lang, A. E., & Chen, R. (2003). Short and long latency afferent inhibition in Parkinson's disease. *Brain*, *26*, 1883–1894.

Saturno, E., Bonato, C., Miniussi, C., Di Lazzaro, V., & Callea, L. (2008). Motor cortex changes in spinal cord injury: A TMS study. *Neurological Research*, *30*, 1084–1085.

Shimizu, T., Hino, T., Komori, T., & Hirai, S. (2000). Loss of the muscle silent period evoked by transcranial magnetic stimulation of the motor cortex in patients with cervical cord lesions. *Neuroscience Letters*, *286*, 199–202.

Simis, M., Uygur-Kucukseymen, E., Pacheco-Barrios, K., Mattistella, L. R., & Fregni, F. (2020). Beta-band oscillations as a biomarker of gait recovery in spinal cord injury patients: A quantitative electroencephalography analysis. *Clinical Neurophysiology*, *131*, 1806–1814.

Smith, H. C., Davey, N. J., Savic, G., Maskill, D. W., Ellaway, P. H., Jamous, M. A., et al. (2000). Modulation of single motor unit discharges using magnetic stimulation of the motor cortex in incomplete spinal cord injury. *Journal of Neurology, Neurosurgery, and Psychiatry*, *68*, 516–520.

Smith, H. C., Savic, G., Frankel, H. L., Ellaway, P. H., Maskill, D. W., Jamous, M. A., et al. (2000). Corticospinal function studied over time following incomplete spinal cord injury. *Spinal Cord*, *38*, 292–300.

Stefan, K., Kunesch, E., Benecke, R., Cohen, L. G., & Classen, J. (2002). Mechanisms of enhancement of human motor cortex excitability induced by interventional paired associative stimulation. *Journal of Physiology*, *543*, 699–708.

Streletz, L. J., Belevich, J. K., Jones, S. M., Bhushan, A., Shah, S. H., & Herbison, G. J. (1995). Transcranial magnetic stimulation: Cortical motor maps in acute spinal cord injury. *Brain Topography*, *7*, 245–250.

Topka, H., Cohen, L. G., Cole, R. A., & Hallett, M. (1991). Reorganization of corticospinal pathways following spinal cord injury. *Neurology*, *41*, 1276–1283.

Tran, Y., Boord, P., Middleton, J., & Craig, A. (2004). Levels of brain wave activity (8–13 Hz) in persons with spinal cord injury. *Spinal Cord*, *42*, 73–79.

Tseng, G. F., & Prince, D. A. (1996). Structural and functional alterations in rat corticospinal neurons after axotomy. *Journal of Neurophysiology*, *75*, 248–267.

Versace, V., Langthaler, P. B., Höller, Y., Frey, V. N., Brigo, F., Sebastianelli, L., et al. (2018). Abnormal cortical neuroplasticity induced by paired associative stimulation after traumatic spinal cord injury: A preliminary study. *Neuroscience Letters*, *664*, 167–171.

Wirth, B., Van Hedel, H. J. A., & Curt, A. (2008a). Ankle dexterity remains intact in patients with incomplete spinal cord injury in contrast to stroke patients. *Experimental Brain Research*, *191*, 353–361.

Wirth, B., Van Hedel, H. J. A., & Curt, A. (2008b). Ankle paresis in incomplete spinal cord injury: Relation to corticospinal conductivity and ambulatory capacity. *Journal of Clinical Neurophysiology*, *25*, 210–217.

Wirth, B., Van Hedel, H. J. A., & Curt, A. (2008c). Changes in corticospinal function and ankle motor control during recovery from incomplete spinal cord injury. *Journal of Neurotrauma*, *25*, 467–478.

Wirth, B., Van Hedel, H. J. A., & Curt, A. (2008d). Ankle dexterity is less impaired than muscle strength in incomplete spinal cord lesion. *Journal of Neurology*, *255*, 273–279.

Wrigley, P. J., Gustin, S. M., Macey, P. M., Nash, P. G., Gandevia, S. C., Macefiled, V. G., et al. (2009). Anatomical changes in human motor cortex and motor pathways following complete thoracic spinal cord injury. *Cerebral Cortex*, *19*, 224–232.

Ziemann, U., Paulus, W., Nitsche, M. A., Pascual-Leone, A., Byblow, W. D., Berardelli, A., et al. (2008). Consensus: Motor cortex plasticity protocols. *Brain Stimulation*, *1*, 164–182.

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Chapter 26

Bone loss at the knee after spinal cord injury: Radiographic imaging, fracture risk, and treatment

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Abbreviations

aBMD	areal bone mineral density
BMD	bone mineral density
BMC	bone mineral content
DXA	dual-energy X-ray absorptiometry
QCT	quantitative computed tomography
pQCT	peripheral quantitative computed tomography
SCI	spinal cord injury

Introduction

Severe bone loss at sub-lesional locations is a recognized sequela of spinal cord injury (SCI). Changes are often attributed to the loss of mechanical stimuli (disuse) following injury; however, the rate of bone loss after SCI is typically greater than other disuse scenarios, such as spaceflight (Edwards & Schnitzer, 2015), suggesting that bone loss is likely exacerbated by the unique neurological and hormonal environment resulting from SCI (Dolbow et al., 2011). The clinical consequence of bone loss after SCI is an increased risk of fracture, with studies reporting prevalence in up to 34% of individuals with SCI (Lala et al., 2014; Lazo et al., 2001). Bone loss is particularly severe around skeletal regions of the knee, where fractures commonly occur during routine activities with little-to-no external trauma (Lala et al., 2014). While many individuals with SCI are already non-ambulatory prior to fracture, these injuries are still associated with high rates of morbidity and mortality (Carbone et al., 2014).

Medical imaging provides powerful, non-invasive tools to quantify and understand bone loss after SCI. Indeed, a large number of studies, across different modalities, have been published. Both 2D areal (Zehnder et al., 2004) and 3D volumetric (Eser et al., 2004) modalities have been used to characterize bone loss at the knee after SCI. These studies reported losses in bone minerals up to 88% (Haider, Lobos, Simonian, Schnitzer, & Edwards, 2018), depending on the region and site measured. Cross-sectional studies have also demonstrated a quantitative link between the amount of bone loss and fracture risk (Lala et al., 2014; Lazo et al., 2001); however, options for treatment are less clear and there is no standard of care for managing bone loss after SCI. Pharmacological (Oleson, Marino, Formal, Modlesky, & Leiby, 2020) and non-pharmacological (Biering-Sørensen, Hansen, & Lee, 2009) interventions have been explored in the recent past, but treatment efficacy at the knee is not well established.

The remainder of this chapter will further expand on these issues related to bone loss and fracture risk at the knee following SCI. We will first provide a more detailed overview of medical imaging studies characterizing bone loss after SCI. This will be followed by a brief discussion of studies that have helped quantify the link between measured bone loss and clinical fracture risk. Finally, we will conclude with an overview of interventions for the attenuation/recovery of bone loss following SCI.

Cellular, Molecular, Physiological, and Behavioral Aspects of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822427-4.00026-5

Application to other areas of neuroscience

In this chapter, we review the phenomenon of bone loss after SCI and the clinical sequelae of skeletal fracture; however, the underlying mechanisms of bone loss after SCI are uncertain. Changes to the neurological environment, i.e., interruption of sensory and sympathetic nerve fibers in the lower limbs, have been implicated (Dolbow et al., 2011) but these pathways are not yet fully understood. This could be an important avenue for future research in neuroscience. Indeed, this work could help to better understand the multi-factorial nature of bone homeostasis and inform the development of new treatments for osteoporosis, perhaps even outside the context of SCI.

Other neurological conditions are also known to affect bone. For example, both stroke and cerebral palsy are associated with bone loss and elevated fracture risk, though there are important differences that distinguish bone loss from these conditions compared to SCI. The magnitude of bone loss is typically less severe than SCI, and there is greater involvement of sites proximal to the knee (hip, spine, ribs, and wrist); these suggest important differences in the underlying mechanisms of bone loss and fracture. However, the bone assessment techniques summarized here, i.e., different medical imaging modalities and subject-specific finite element (FE) modeling, are versatile and could be applied to sites most relevant for these diseases.

Bone loss at the knee after SCI

2D DXA imaging

DXA imaging allows for quantification of areal bone mineral density (aBMD) from 2D images of bone. As the name implies, two X-Ray energies are used, which allow this modality to isolate contributions from bone separate from soft tissue. DXA is the gold standard for the characterization of osteoporosis in non-disabled individuals, where scans are typically taken at the hip or spine; however, this modality can also be used to characterize bone loss at the knee. In the context of SCI, DXA measurements at the knee have been used in both cross-sectional and longitudinal studies (Table 1).

One of the earliest cross-sectional studies to examine bone loss at the knee in individuals with SCI reported that tibial BMC was, on average, only 50% of the value of age-matched controls (Biering-Sorensen et al., 1988), and this finding has been well supported by more recent studies (Garland et al., 1992, 2001; McPherson et al., 2014; Modlesky et al., 2004; Shields et al., 2005). Of course, cross-sectional studies comparing individuals with SCI to non-disabled controls at one time-point do not elucidate the time-course of bone loss; however, this phenomenon was explored by Zehnder, Risi, et al. (2004), who examined a large cross-section of 100 males with SCI 3–30 years post-injury, and identified a statistically significant relationship between time-since injury and decreasing aBMD z-score at the tibial diaphysis and epiphysis. Warden et al. (2002) longitudinally examined a group of 15 individuals over a 6-week period after SCI (30–180 days post-injury) and reported losses in tibial aBMD of -5.3% per week. A pair of studies over a longer duration (>1.5 years) have reported that bone loss is rapid soon after injury but eventually reaches a plateau, with steady-state measures that are 27–50% of the original baseline (Biering-Sørensen et al., 1990; Garland et al., 2004)—a finding that is consistent with cross-sectional literature.

Volumetric assessment of bone mineral and bone strength

DXA is a powerful clinical tool, but can only capture 2D areal projections of the bone, and potentially meaningful information may be lost. Bone is a complex three-dimensional structure, and cortical and trabecular compartments at different regions may have differing contributions to bone strength. As shown in Fig. 1, these regions can be assessed separately using quantitative computed tomography (QCT) or peripheral quantitative computed tomography (pQCT). In this section, we provide an overview of cross-sectional and longitudinal studies that used these volumetric imaging modalities in individuals with SCI (Table 2).

A number of large ($\geq$60 individuals) cross-sectional studies used regional QCT and pQCT imaging of the knee in individuals with varying injury durations (2 months to 50 years post-SCI) (Edwards et al., 2015; Eser et al., 2004; Haider et al., 2018). From these cross-sectional data, the authors were able to infer the temporal and spatial patterns of bone loss after SCI. Consistent with the DXA studies outlined above, these studies demonstrated that bone loss was most rapid immediately after injury and reached a plateau 2.6–7.6 years after injury, depending on the measure. After plateau, losses were most significant at the epiphysis, up to 88% relative to recently injured SCI controls (Haider et al., 2018); however, the magnitude of bone loss decreased progressively at more diaphyseal locations. Finally, these studies demonstrated that cortical bone is lost primarily via endocortical resorption, with little change to the periosteal surface or to cortical density over time. Smaller investigations also reported results consistent with these findings (Coupaud et al., 2009; Dudley-Javoroski & Shields, 2010; McCarthy et al., 2012; Rittweger et al., 2010). Longitudinal studies further elucidated the

TABLE 1 Summary of radiographic studies in individuals with spinal cord injury that include dual-energy X-ray absorptiometry measures of the knee.

Study design	Author (year)	Study sample	Knee region(s) of interest	Key findings at knee
Cross-sectional	Biering-Sorensen, Bohr, and Schaadt (1988)	26 SCI (duration = 6–25 years) vs ND reference group from literature	PT	Tibia BMC after SCI approximately 50% of values from ND reference group
	Garland, Adkins, Stewart, Ashford, and Vigil (2001)	31 SCI (duration = 5.7 ± 2.3 years) vs 17 ND controls	Whole knee	38%–47% lower knee aBMD in SCI compared to controls
	Garland, Adkins, and Stewart (2005)	18 SCI (duration = 3–43 years) vs 10 ND controls	DF and PT	aBMD at knee in SCI < 50% of controls
	Lala et al. (2014)	19 SCI with fracture vs 51 SCI with no fracture history (duration >2 years)	DF and PT	Lower aBMD associated with an elevated risk of fracture
	McPherson et al. (2014)	12 acute SCI (duration = 2.1 ± 0.7 months) vs 34 chronic SCI (duration = 196.9 ± 111.4 months)	Epiphysis and metaphysis of DF; Epiphysis of PT	50% lower aBMD in all three regions, in chronic SCI vs acute SCI
	Modlesky, Majumdar, Narasimhan, and Dudley (2004)	10 SCI (duration >2 years) vs 8 ND controls	PT	Tibia aBMD 43% lower in SCI; included HR-MRI, which identified deterioration of trabecular microstructure in SCI vs controls
	Shields et al. (2005)	11 SCI (duration >2 years) vs 11 ND controls	DF and PT	aBMD at both sites approx. 25% lower in SCI compared to controls
	Zehnder, Risi, et al. (2004)	100 SCI (duration 0.25–30 years)	PT epiphysis and diaphysis	Significant association between decreasing aBMD (*Z*-score) and time
Longitudinal	Biering-Sørensen, Bohr, and Schaadt (1990)	8 SCI assessed 1–54 months post-injury	PT	BMC at steady-state was 40%–50% of baseline. Steady-state reached approx. 2 years after injury
	Garland et al. (2004)	6 SCI assessed up to 523 days post-injury	DF and PT	aBMD loss of 27% and 32% at DF and PT, respectively
	Warden et al. (2002)	15 SCI assessed 30–180 days post-injury	PT	Progressive losses in aBMD over duration; average loss of 5.3% after 6 weeks
Mixed	Garland et al. (1992)	25 recent SCI (duration = 114 ± 8.6 days, reassessed at 16 months); 20 chronic SCI (duration >5 years); 10 ND controls	DF and PT	38% and 36% lower aBMD in chronic SCI vs controls, at DF and PT respectively. No difference between recent SCI at 16 months vs chronic SCI group

SCI, spinal cord injury; ND, non-disabled; DF, distal femur; PT, proximal tibia; aBMD, areal bone mineral density; BMC, bone mineral content; HR-MRI, high-resolution magnetic resonance imaging.
This table summarizes the literature where dual-energy absorptiometry was used to assess the knee in individuals with SCI. An overview of the study sample (including time since injury), the imaged regions of interest, and the key findings are provided.

time-course of bone loss after SCI. Studies within the first year of SCI (Coupaud et al., 2015; Edwards et al., 2013a; Frey-Rindova et al., 2000) demonstrate losses in bone mineral at the knee of up to 20%, relative to baseline, while longer studies (de Bruin et al., 2000; Dudley-Javoroski & Shields, 2012; Frotzler, Berger, Knecht, & Eser, 2008) have further demonstrated that bone loss is most rapid immediately after injury and reaches a plateau after approximately 2–8 years post-SCI.

A few studies have reported the changes to bone microarchitecture concomitant with bone loss. Using high-resolution magnetic resonance imaging, Modlesky et al. (2004) reported that individuals with SCI (>2 years post-SCI) demonstrated

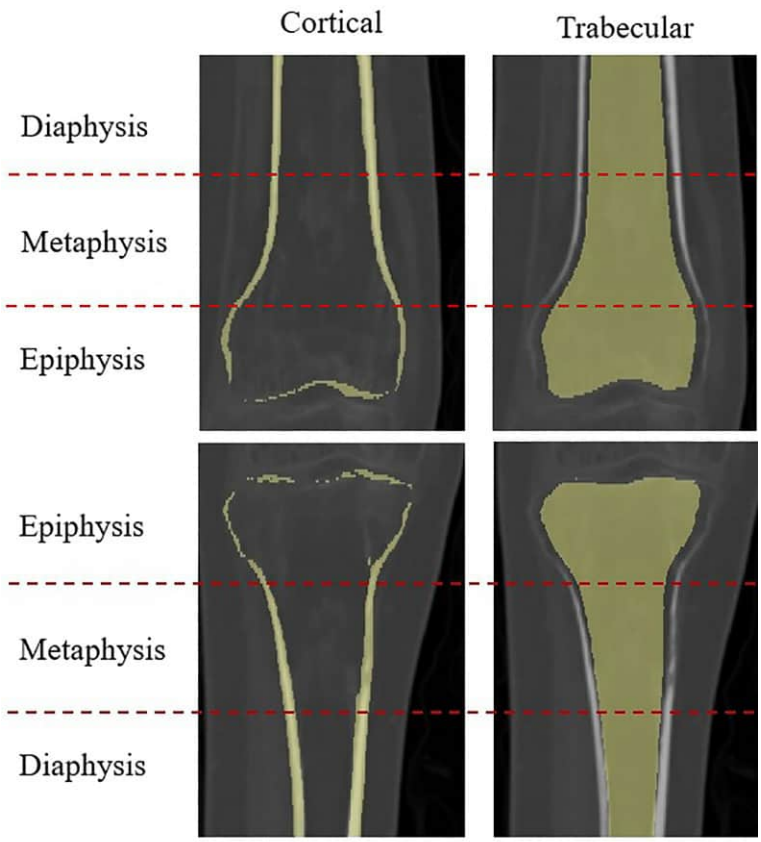

FIG. 1 Example of regional volumetric quantitative computed tomography analysis. This is an image of a frontal-plane slice from a three-dimensional computed tomography image of the knee. The distal femur (TOP) and proximal tibia (BOTTOM) were separated into epiphyseal, metaphysical, and diaphyseal regions. Cortical (LEFT) and trabecular (RIGHT) compartments were analyzed separately; this technique was used in a number of recent studies (Edwards, Schnitzer, & Troy, 2013a; Edwards, Simonian, Troy, & Schnitzer, 2015; Haider et al., 2018).

lower trabecular volume, lower trabecular number, and greater trabecular spacing (20%–44% reductions). A follow-up study by the same group (Slade et al., 2005) compared pre- and post-menopausal women with SCI against pre- and post-menopausal non-disabled women. Again, SCI was associated with 19%–26% lower trabecular number and 22%–33% reduced trabecular bone volume.

Changes in bone strength that occur as a result of bone loss after SCI have been estimated using finite element (FE) modeling, which are physics-based simulations derived from QCT imaging, and established relationships between bone density and local material properties. Tan et al. (2014) compared QCT and FE modeling data from individuals 0.12 to 37.5 years after SCI and confirmed a relationship between low bone mineral and low FE predicted stiffness. Another investigation (Edwards et al., 2013a, 2013b) looked at individuals <7 months post-SCI and used FE modeling to predict decreases in compressive stiffness of 1.3%–5.5%/month and 0.6%–5.9%/month across regions of the femur and tibia, respectively. Torsional stiffness also decreased by 1.3%–5.0%/month and 0.7%–5.2% at the femur and tibia, respectively. Moreover, losses in FE predicted stiffness and strength indices were approximately twice as large as losses in integral bone mineral, due to the highly non-linear relationship between bone mineral measures and the mechanical behavior of bone (Morgan, Bayraktar, & Keaveny, 2003). Furthermore, cross-sectional follow-up studies (Edwards et al., 2015; Haider et al., 2018) suggested that losses in stiffness accumulate to a total reduction of 40%–85% when bone loss plateaus. Torsional stiffness at the epiphysis of both the femur and tibia plateaued quickly, approximately 2 years post-SCI, suggesting that mechanically relevant changes occur rapidly. Again, losses in stiffness were greater than losses in bone mineral; at the tibial epiphysis, individuals with SCI had 33% of the integral BMC relative to the recently injured baseline, but only 16% of the torsional stiffness.

TABLE 2 Summary of radiographic studies that include volumetric assessment of the knee after spinal cord injury.

Study design	Author, year	Study sample	Modality	Knee region(s) of interest	Key findings at knee
Cross-sectional	Edwards et al. (2015)	60 SCI (duration = 0–50 years) vs 10 ND controls	QCT and FE	PT separated into three regions	Measures plateaued 2.1–2.7 years post-SCI, after which BMC, BMD, stiffness, and strength were 55%–69% lower than the reference group
	Coupaud, McLean, and Allan (2009)	47 SCI (duration = 0–42 years)	pQCT	DF and throughout length of tibia	Exponential decrease in BMD over time at both bones
	Eser et al. (2004)	89 SCI (duration = 0.2–50 years) vs 21 ND controls	pQCT	DF and PT; epiphysis and diaphysis	Total BMC lower by up to 60% at epiphysis and 35% at diaphysis; losses plateau after 3–8 years
	Haider et al. (2018)	101 SCI (duration = 0.2–50 years)	QCT and FE	DF and PT separated into three regions	Measures plateaued ≤3.6 years. After plateau, up to 88% lower stiffness and mineral measures compared to recently injured
	McCarthy, Bloomer, Gall, Keen, and Ferguson-Pell (2012)	8 acute SCI (duration <8 months); 9 chronic SCI (duration >48 months); 14 ND controls	pQCT	PT epiphysis and diaphysis + distal tibia epiphysis	Chronic SCI had significantly lower trabecular BMD at epiphyses and lower cross-section moment of inertia at PT diaphysis
	Rittweger, Goosey-Tolfrey, Cointry, and Ferretti (2010)	9 SCI (duration = 9–32 years) vs 9 ND controls	pQCT	Tibia, both ends + midshaft	47%–51% lower BMC at epiphysis. Differences more pronounced at epiphyses vs midshaft
	Tan et al. (2014)	27 SCI (duration = 0.1–38 years)	QCT and FE	DF	Reduced FE stiffness associated with BMD and years post-injury
	Modlesky et al. (2004)	10 SCI (duration = 2–20 years) vs 8 ND controls	HR-MRI	DF and PT	20%–27% lower bone volume and trabecular number, 33%–44% greater trabecular spacing
	Slade, Bickel, Modlesky, Majumdar, and Dudley (2005)	20 pre- and post-menopausal women with SCI vs 17 pre- and post-menopausal ND controls	HR-MRI	DF and PT	SCI had a greater effect than estrogen loss. SCI associated with 19%–26% fewer trabeculae and 22%–33% reduced trabecular volume
Longitudinal	de Bruin, Dietz, Dambacher, and Stüssi (2000)	12 SCI evaluated at 5 weeks and 2 years post-injury	pQCT	Tibia ankle and shaft	35% and 13% decrease in trabecular and cortical BMD
	Coupaud, McLean, Purcell, Fraser, and Allan (2015)	26 SCI (duration <5 weeks); baseline and 1-year follow-up	pQCT	DF and PT, shaft of both bones	BMC and BMD losses of 15%–20% at DF and PT, lower losses at more diaphyseal locations
	Edwards et al. (2013a); Edwards,	13 SCI (duration <4 months) follow-up after 3.5 months	QCT and FE	DF and PT, separated	Integral BMC losses of 0.4%–3.6%/month and BMD losses of 0.4%–3.4%/month at DF and PT.

Continued

TABLE 2 Summary of radiographic studies that include volumetric assessment of the knee after spinal cord injury—cont'd

Study design	Author, year	Study sample	Modality	Knee region(s) of interest	Key findings at knee
	Schnitzer, and Troy (2013b)			into three regions	FE predicted concomitant decreases in torsional and compressive stiffness
	Frey-Rindova, De Bruin, Stüssi, Dambacher, and Dietz (2000)	29 SCI evaluated at baseline, 6, 12, 24 months	pQCT	PT	Trabecular BMD reduced 5% and 15%, 6 and 12 months after injury; cortical BMD decreased 7% after 12 months after injury
	Frotzler et al. (2008)	39 SCI (duration = 0.9–34 years) follow-up at 15 and 30 months after baseline	pQCT	DF, PT, and midshaft of both bones	Differences over time were not significant; likely due to few individuals with injury duration <5 years
Mixed	Dudley-Javoroski and Shields (2012)	26 SCI scanned 0–5 years after SCI; 21 ND controls	pQCT	PT and tibia midshaft	BMD loss of 15%–35% in first year. Bone loss plateaued after 2–4 years, reaching BMD approx. 50% lower than controls
	Dudley-Javoroski and Shields (2010)	15 SCI received 1–3 scans 0.2–7 years post-injury; 10 ND controls	pQCT	DF metaphysis	Femur BMD losses 1.7%/month in first 2 years; bone loss appeared to plateau after 2 years. At end of study, BMD 40% lower than controls

SCI, spinal cord injury; ND, non-disabled; PT, proximal tibia; DF, distal femur; FE, finite element; (p)QCT, (peripheral) quantitative computed tomography; BMC, bone mineral content; BMD, bone mineral density; HR-MRI, high-resolution magnetic resonance imaging.
This table summarizes literature where volumetric imaging of the knee was used to assess bone minerals after spinal cord injury. The study sample, imaging modality, imaging region of interest, and key findings are reported.

Summary of bone loss after SCI—Temporal and spatial patterns

Radiographic studies of bone loss at the knee after SCI have demonstrated consistent results, and the temporal and spatial pattern of bone loss is clear. Losses occur most rapidly soon after injury, reaching a plateau 2–8 years after injury. Regionally, losses are most significant at the epiphysis of the distal femur and proximal tibia and become more attenuated at more diaphyseal sites; however, the relationship between bone mineral and bone mechanical properties is non-linear, and reductions in stiffness/strength may be twice as large as reductions in integral bone mineral measures.

Relationship between bone loss and fracture risk after SCI

In non-disabled individuals, a relationship between bone mineral measures and fracture risk is well established, and tools such as FRAX (Kanis et al., 2011) have been developed to estimate fracture risk based on BMD and other clinical risk factors. A similar tool does not exist for individuals with SCI; but a number of studies have quantified the relationship between bone loss and fracture risk in this context.

Lala et al. (2014), retrospectively assessed 70 individuals with SCI (19 fractured). After adjusting for motor completeness, logistic regression revealed that aBMD and pQCT measures at the knee were associated with a normalized odds ratio of 2.2–6.5 (the change in odds of fracture for a 1 standard deviation change in measure), with integral aBMD and trabecular BMD of the proximal tibia reported as the most sensitive measures. Another study (Lazo et al., 2001) identified a similar relationship between femoral neck aBMD and fracture risk, with a 2.2 and 2.8 increased odds of fracture per standard deviation decrease in *t*-score or *z*-score, respectively. Other radiographic studies have also reported statically

lower aBMD in fractured vs non-fractured individuals (Biering-Sorensen et al., 1988; Zehnder et al., 2004), consistent with logistic regression analyses. Finally, a cross-sectional study by Garland et al. (2005), suggested a knee aBMD fracture threshold of 0.78 g/cm^2.

Importantly, however, radiographic measures may provide an incomplete representation of bone fragility. Cadaveric studies suggest that 25%–43% of the measured variation in bone strength is not accounted for by simple measures of bone mineral (Edwards et al., 2013b), and this variation can be better explained using FE models of bone. With this in mind, a recent study examined FE models from 50 individuals with SCI (14 fractures) (Haider, Simonian, Schnitzer, & Edwards, 2020) and demonstrated that FE predicted tibial strength was a more sensitive predictor of fracture risk compared to DXA (spine, hip, and knee) or CT measures (knee). It is important to note that additional risk factors for fracture after SCI include age, sex, severity of injury, excessive alcohol consumption, and duration of injury (Craven, Robertson, McGillivray, & Adachi, 2009); however, it is unclear if these measures provide information independent from bone density or strength.

Interventions for bone loss after SCI

There is currently no standard of care for bone loss after SCI, and intervention strategies remain an area of active research. Both pharmacological and non-pharmacological interventions have been explored, with varying success. There is a large breadth of research, spanning decades, and this work has been reviewed in the past (Cirnigliaro et al., 2017; Dolbow et al., 2011). In this section, we summarize this body of work and highlight key studies that are recent or most impactful.

Non-pharmaceutical intervention

Functional electrical stimulation (FES) is a technique that has been studied extensively in individuals with SCI. In this technique, the nervous system is stimulated via electrodes, and the resulting action potential causes muscle contraction and limb motion (Ho et al., 2014). Hypothetically, this loading stimulus could slow or reverse the adaptive remodeling processes that resorb bone during disuse, and there is some evidence of this in the literature. One recent study used FES rowing excise in 4 individuals with an SCI duration of less than 2 years (Lambach et al., 2020). After 60 sessions (over 6–8 months), 2 individuals gained 6% and 8% trabecular BMD at the knee, while another 2 individuals demonstrated a decrease in the rate of bone loss. Benefits have also been observed in individuals with more chronic SCI. For example, Frotzler, Coupaud, et al. (2008) studied FES cycling in individuals >3.6 post-injury and reported increased trabecular and total BMD at the distal femur (14% and 7% increase, respectively) after 12 months. While these results are encouraging, it should be noted that a number of studies report no therapeutic effect of FES training on the bone (Eser et al., 2003; Shields & Dudley-Javoroski, 2007). It is unclear why results differ among studies, but differences in training volume or load intensity may play a role (Biering-Sørensen et al., 2009; Morse et al., 2019). Furthermore, there is evidence that the benefits of FES training fade soon after training is ceased or reduced (Chen et al., 2005).

A few studies have demonstrated beneficial effects of weight-bearing or walking exercise (without electrical stimulation) soon after SCI, but with varying results. One relatively large study examined 54 individuals with recent (1 < year) SCI and found that those who were able to ambulate demonstrated higher BMD at the leg compared to those who could not (Alekna, Tamulaitiene, Sinevicius, & Juocevicius, 2008). There have also been controlled experiments like that of de Bruin et al. (1999), where harness-assisted weight-bearing exercise was performed at different volumes with three groups of individuals. This study found that individuals who received the early intervention had little or no bone loss in the tibia after 25 weeks, compared to a marked reduction in individuals who were immobile. These encouraging examples are balanced by the fact that there are a number of studies which demonstrate no effects of weight-bearing or exercise on bone in individuals with recent SCI (Frey-Rindova et al., 2000; Giangregorio et al., 2005), but the reason for differences in the literature is not clear. Finally, weight-bearing activity appears to have little effect in individuals with injury duration >1 year (Biering-Sørensen et al., 2009).

Pharmaceutical intervention

A number of studies have examined pharmaceutical intervention using anti-resorptive drugs to slow or reverse bone loss soon after SCI. The anti-resorptives etidonrate (Pearson, Nance, Leslie, & Ludwig, 1997) and pamidronate (Nance et al., 1999) have been shown to attenuate lower limb aBMD loss over 12 months when administered to individuals with recent SCI (<6 weeks), though effects were strongest in individuals who regained the ability to ambulate. Other anti-resorptives have been shown to attenuate bone loss at the hip, but efficacy at the knee remains unclear. Gilchrist et al. (2007) detected

significant attenuation of aBMD loss at the hip after treatment with alendronate but did not examine the knee. Similarly, a number of studies have demonstrated the effects of zolendronate at the hip. In 2020, two separate studies (Goenka & Sethi, 2020; Oleson et al., 2020) reported that treatment was associated with attenuation of bone loss at the hip over 1 year, though benefits were not detected at the knee (Oleson et al., 2020) and older studies of this drug reported results consistent with these findings (Bubbear et al., 2011; Schnitzer et al., 2016; Shapiro et al., 2007). Finally, we note that recent investigations of the anti-resorptive denosumab have demonstrated promising early results. Gifre et al. (2016) treated 14 individuals (no control subjects) and found that denosumab was associated with statically significant increases to aBMD at the hip and spine (2%–8%), though the knee was not assessed. However, another recent study of denosumab (Cirnigliaro et al., 2020) demonstrated that treatment effectively maintained aBMD at the distal femur and attenuated losses at the tibia; however, pQCT measures did not demonstrate similarly robust significant effects, likely due to limited statistical power. Ultimately, these results are encouraging, but must be replicated before being put into practice. In particular, additional follow-up with a greater sample size and more robust volumetric imaging of the knee is needed.

A few studies have also examined treatment in individuals with a longer duration of SCI (>1 year). Alendronate has been used, but with mixed results. One study by Moran De Brito, Battistella, Saito, and Sakamoto (2005) reported no benefits to lower limb aBMD in individuals with SCI > 13 months. In contrast, Zehnder, Risi, et al. (2004) found that open-label alendronate effectively attenuated bone loss at the tibia; however, this study included individuals with a wide range of SCI durations (0.1–30 years prior to enrollment), and these results could be influenced by greater treatment effects in more recently injured individuals. A few other treatments have demonstrated statistically significant effects at the knee in individuals with longer SCI duration. For example, Bauman, Spungen, Morrison, Zhang, and Schwartz (2005) found that treatment with a vitamin D analog was associated with small, but statistically significant improvements to whole leg BMD after 24 months. Similarly, Morse et al. (2019) reported that FES exercise plus zolendronate was associated with improvement or mitigation of losses in bone geometric properties at the proximal tibia and distal femur, compared to FES exercise alone. Finally, Edwards et al. (2018) studied anabolic treatment with teriparatide. After 12 months, participants demonstrated treatment effect at the spine but not at the hip or the knee; however, after a 12-month open-label extension, individuals who received teriparatide for the entire 24 months demonstrated increased total hip aBMD (4%–7% compared to original baseline). Increases in QCT measures at the knee were demonstrated across all individuals receiving open-label drugs. Moreover, individuals who participated in a second extension with open-label alendronate (Haider et al., 2019) demonstrated that these benefits could be retained for at least 12 months after ceasing teriparatide. With that said, we note that all the studies discussed here demonstrated only modest improvements to the bone, and it is yet to be established whether differences are large enough to meaningfully influence fracture risk in this population.

Summary of interventions for bone loss after SCI

Non-pharmaceutical interventions to treat bone loss after SCI have been studied, with mixed results. There is some evidence that, at a sufficient training intensity and volume, FES exercise or assisted weight-bearing exercise (without FES) may help to attenuate bone loss at the knee in individuals with recent SCI (Biering-Sørensen et al., 2009), but the effects of treatment are likely to be lost after training is ended or reduced (Chen et al., 2005). A number of anti-resorptive drugs have been studied in individuals with recent SCI. In general, studies suggest that these drugs attenuate bone loss at the hip over the first 1–2 years after injury; however, efficacy at the knee in non-ambulatory individuals has not been established. Despite this limitation, these changes may still be clinically meaningful. Fractures at the hip can occur in this population, and these drugs may help reduce this risk. Moreover, a number of individuals will likely become ambulatory soon after SCI, and attenuation of bone loss at the spine and hip may help these individuals to rehabilitate quickly and safely. This may be particularly relevant in the future, as new or more effective treatments for SCI are introduced. Pharmaceutical intervention can also have statistically significant effects in individuals with a longer duration of SCI; however, we note that these studies typically report an attenuation of bone loss, with no large increases in bone mineral measures. It remains to be established if any treatments have a sufficiently large effect at the knee, to cause a meaningful reduction in clinical fracture risk.

There are a few important limitations in this body of work. We did not find any studies that evaluated recently injured individuals for a period greater than 2 years. In untreated individuals, fractures typically occur later than 2 years after injury (Gifre et al., 2014), highlighting the need to understand how treatment influences bone over these longer time periods. Furthermore, it is often unclear whether the magnitude of the treatment effect is sufficient to provide a clinically meaningful reduction in fracture risk. In the future, longitudinal follow-up with fracture surveillance may be warranted.

Summary and conclusions

There have been over two dozen radiographic studies of bone loss at the knee after SCI, across different modalities and study designs. Together, these studies unequivocally establish the fact that bone loss is rapid and severe. Furthermore, studies have also established a quantitative relationship between bone loss and fracture risk in this population, highlighting the potential benefit of preventing or reversing bone loss in these individuals; however, there is currently no standard of care for treatment of bone loss after SCI, and treatment options remain an area of active research. Anti-resorptive treatment can attenuate bone loss at the hip in individuals soon after SCI, but the efficacy of treatment and fracture risk reduction at the knee has not been well established in non-ambulatory individuals. Similarly, non-pharmaceutical intervention via FES exercise or assisted weight-bearing could plausibly help attenuate lower limb bone loss in individuals with recent SCI, but studies have yielded mixed results. In addition to exploring new types of treatment, we believe that more longitudinal investigation is needed to determine whether treatment effects can be retained over longer durations and provide clinically meaningful reductions in fracture risk.

Mini-dictionary terms

Cortical bone: Also called compact bone. This is low porosity (<15%) bone that is found on the outer shell of bones.
Diaphysis: The main body of long bones, located between the metaphysis (see definition below) of either end.
Dual-energy X-ray absorptiometry (DEXA): A 2D X-ray imaging technique, commonly used to obtain measurements of areal bone mineral density.
Finite element model: A computer representation of a system that simulates/predicts behavior by numerically solving the governing partial differential equations. In bone research, a finite element model can be used to predict the structural response (stiffness and strength) to the applied load.
Epiphysis: In long bones, this is the region above the growth plate, closest to the joint.
Quantitative computed tomography (QCT): An X-ray based imaging technique that combines information from multiple views (projections) around the object in order to build a 3D image. Commonly used to measure volumetric bone mineral density.
Metaphysis: In long bones, this region contains the growth plate and surrounding bone tissue that grows during development, to lengthen the bone.
Magnetic resonance imaging (MRI): A 3D imaging technique that identifies different materials/tissues by measuring the response to magnetic excitation.
Trabecular bone: Also called cancellous or spongy bone, a highly porous (>80%) bone that is found underneath the cortical layer, particularly at the ends of long bones. At the microstructure level, it is made of the rod (trabeculae) or plate-like structures.

Key facts

- The World Health Organization estimates that 250,000–500,000 individuals experience spinal cord injury each year. Thanks to modern medical practices, in-hospital mortality rates are <16% in Europe and America. Factors influencing long-term health, such as bone loss and fracture, are important concerns for the majority who survive.
- Clinical Dual-Energy Absorptiometry was first introduced in 1987, based on pioneering research by Dr. John Cameron in 1963 and Richard Mazess in 1981. Since then, it has become the gold standard for assessment of bone loss in non-disabled individuals and has seen substantial use in individuals with spinal cord injury.
- Bone strength is multi-factorial; the size, shape, and distribution of bone material can all influence bone fragility. However, these are not easily measured using dual-energy absorptiometry. Techniques like regional computed tomography analysis or finite element modeling are often used to better understand these factors.
- The modern finite element method was originally developed for the aerospace industry in the 1950s and 1960s. It was slowly adopted to other industries as digital computing became more accessible. Today, these techniques see widespread use in many fields, including bone research in individuals with spinal cord injury.
- Antiresorptive drugs are a mainstay of modern osteoporosis treatment in non-disabled individuals and are highly effective at reducing/reversing bone loss and reducing fracture risk in that population. However, spinal cord injury creates a unique mechanical and physiological environment that is challenging to bone health.

Summary points

- Bone loss is most rapid soon after spinal cord injury but plateaus 2–8 years after injury.
- After plateau, bone mineral is reduced by up to 88%. Losses are most severe at the epiphysis and become progressively less severe toward diaphyseal locations.
- Measures of bone mineral, and finite element predicted stiffness and strength, have been quantitatively linked to increased fracture risk.
- In recently injured (injury <1 year) individuals, pharmaceutical interventions have often demonstrated attenuation of bone loss at the hip, but efficacy at the knee in non-ambulatory individuals is not well established.
- Non-pharmaceutical intervention via functional electrical stimulation or assisted weight-bearing exercise may help attenuate bone loss after a recent spinal cord injury, but results have been mixed.

References

Alekna, V., Tamulaitiene, M., Sinevicius, T., & Juocevicius, A. (2008). Effect of weight-bearing activities on bone mineral density in spinal cord injured patients during the period of the first two years. *Spinal Cord*, *46*(11), 727–732. https://doi.org/10.1038/sc.2008.36.

Bauman, W. A., Spungen, A. M., Morrison, N., Zhang, R. L., & Schwartz, E. (2005). Effect of a vitamin D analog on leg bone mineral density in patients with chronic spinal cord injury. *Journal of Rehabilitation Research and Development*, *42*(5), 625–633. https://doi.org/10.1682/JRRD.2004.11.0145.

Biering-Sorensen, F., Bohr, H., & Schaadt, O. (1988). Bone mineral content of the lumbar spine and lower extremities years after spinal cord lesion. *Paraplegia*, *26*(5), 293–301. https://doi.org/10.1038/sc.1988.44.

Biering-Sørensen, F., Bohr, H. H., & Schaadt, O. P. (1990). Longitudinal study of bone mineral content in the lumbar spine, the forearm and the lower extremities after spinal cord injury. *European Journal of Clinical Investigation*, *20*(3), 330–335. https://doi.org/10.1111/j.1365-2362.1990.tb01865.x.

Biering-Sørensen, F., Hansen, B., & Lee, B. S. B. (2009). Non-pharmacological treatment and prevention of bone loss after spinal cord injury: A systematic review. *Spinal Cord*, *47*(7), 508–518. https://doi.org/10.1038/sc.2008.177.

Bubbear, J. S., Gall, A., Middleton, F. R. I., Ferguson-Pell, M., Swaminathan, R., & Keen, R. W. (2011). Early treatment with zoledronic acid prevents bone loss at the hip following acute spinal cord injury. *Osteoporosis International*, *22*(1), 271–279. https://doi.org/10.1007/s00198-010-1221-6.

Carbone, L. D., Chin, A. S., Burns, S. P., Svircev, J. N., Hoenig, H., Heggeness, M., et al. (2014). Mortality after lower extremity fractures in men with spinal cord injury. *Journal of Bone and Mineral Research*, *29*(2), 432–439. https://doi.org/10.1002/jbmr.2050.

Chen, S. C., Lai, C. H., Chan, W. P., Huang, M. H., Tsai, H. W., & Chen, J. J. J. (2005). Increases in bone mineral density after functional electrical stimulation cycling exercises in spinal cord injured patients. *Disability and Rehabilitation*, *27*(22), 1337–1341. https://doi.org/10.1080/09638280500164032.

Cirnigliaro, C. M., La Fountaine, M. F., Parrott, J. S., Kirshblum, S. C., McKenna, C., Sauer, S. J., et al. (2020). Administration of denosumab preserves bone mineral density at the knee in persons with subacute spinal cord injury: Findings from a randomized clinical trial. *JBMR Plus*, *4*(8). https://doi.org/10.1002/jbm4.10375.

Cirnigliaro, C. M., Myslinski, M. J., La Fountaine, M. F., Kirshblum, S. C., Forrest, G. F., & Bauman, W. A. (2017). Bone loss at the distal femur and proximal tibia in persons with spinal cord injury: Imaging approaches, risk of fracture, and potential treatment options. *Osteoporosis International*, *28*(3), 747–765. https://doi.org/10.1007/s00198-016-3798-x.

Coupaud, S., McLean, A. N., & Allan, D. B. (2009). Role of peripheral quantitative computed tomography in identifying disuse osteoporosis in paraplegia. *Skeletal Radiology*, *38*(10), 989–995. https://doi.org/10.1007/s00256-009-0674-1.

Coupaud, S., McLean, A. N., Purcell, M., Fraser, M. H., & Allan, D. B. (2015). Decreases in bone mineral density at cortical and trabecular sites in the tibia and femur during the first year of spinal cord injury. *Bone*, *74*, 69–75. https://doi.org/10.1016/j.bone.2015.01.005.

Craven, B. C., Robertson, L. A., McGillivray, C. F., & Adachi, J. D. (2009). Detection and treatment of sublesional osteoporosis among patients with chronic spinal cord injury: Proposed paradigms. *Topics in Spinal Cord Injury Rehabilitation*, *14*(4), 1–22. https://doi.org/10.1310/sci1404-1.

de Bruin, E. D., Dietz, V., Dambacher, M. A., & Stüssi, E. (2000). Longitudinal changes in bone in men with spinal cord injury. *Clinical Rehabilitation*, *14*(2), 145–152. https://doi.org/10.1191/026921500670532165.

de Bruin, E. D., Frey-Rindova, P., Herzog, R. E., Dietz, V., Dambacher, M. A., & Stüssi, E. (1999). Changes in tibia bending stiffness two years after spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *80*(February), 214–220.

Dolbow, D. R., Gorgey, A. S., Daniels, J. A., Adler, R. A., Moore, J. R., & Gater, D. R. (2011). The effects of spinal cord injury and exercise on bone mass: A literature review. *NeuroRehabilitation*, *29*(3), 261–269. https://doi.org/10.3233/NRE-2011-0702.

Dudley-Javoroski, S., & Shields, R. K. (2010). Longitudinal changes in femur bone mineral density after spinal cord injury: Effects of slice placement and peel method. *Osteoporosis International*, *21*(6), 985–995. https://doi.org/10.1007/s00198-009-1044-5.

Dudley-Javoroski, S., & Shields, R. K. (2012). Regional cortical and trabecular bone loss after spinal cord injury. *Journal of Rehabilitation Research and Development*, *49*(9), 1365–1376. https://doi.org/10.1682/jrrd.2011.12.0245.

Edwards, W. B., & Schnitzer, T. J. (2015). Bone imaging and fracture risk after spinal cord injury. *Current Osteoporosis Reports*, *13*(5), 310–317. https://doi.org/10.1007/s11914-015-0288-6.

Edwards, W. B., Schnitzer, T. J., & Troy, K. L. (2013a). Bone mineral and stiffness loss at the distal femur and proximal tibia in acute spinal cord injury. *Osteoporosis International*, *24*(9), 2461–2469. s00198-013-2557-5.

Edwards, W. B., Schnitzer, T. J., & Troy, K. L. (2013b). Torsional stiffness and strength of the proximal tibia are better predicted by finite element models than DXA or QCT. *Journal of Biomechanics*, *46*(10), 1655–1662. https://doi.org/10.1016/j.jbiomech.2013.04.016.

Edwards, W. B., Simonian, N., Haider, I. T., Anschel, A. S., Chen, D., Gordon, K. E., et al. (2018). Effects of teriparatide and vibration on bone mass and bone strength in people with bone loss and spinal cord injury: A randomized, controlled trial. *Journal of Bone and Mineral Research*, *33*(10), 1729–1740. Retrieved from http://doi.wiley.com/10.1002/jbmr.3525.

Edwards, W. B., Simonian, N., Troy, K. L., & Schnitzer, T. J. (2015). Reduction in torsional stiffness and strength at the proximal tibia as a function of time since spinal cord injury. *Journal of Bone and Mineral Research*, *30*(8), 1422–1430. https://doi.org/10.1002/jbmr.2474.

Eser, P., De Bruin, E. D., Telley, I., Lechner, H. E., Knecht, H., & Stüssi, E. (2003). Effect of electrical stimulation-induced cycling on bone mineral density in spinal cord-injured patients. *European Journal of Clinical Investigation*, *33*(5), 412–419. https://doi.org/10.1046/j.1365-2362.2003.01156.x.

Eser, P., Frotzler, A., Zehnder, Y., Wick, L., Knecht, H., Denoth, J., et al. (2004). Relationship between the duration of paralysis and bone structure: A pQCT study of spinal cord injured individuals. *Bone*, *34*(5), 869–880. https://doi.org/10.1016/j.bone.2004.01.001.

Frey-Rindova, P., De Bruin, E. D., Stüssi, E., Dambacher, M. A., & Dietz, V. (2000). Bone mineral density in upper and lower extremities during 12 months after spinal cord injury measured by peripheral quantitative computed tomography. *Spinal Cord*, *38*(1), 26–32. https://doi.org/10.1038/sj.sc.3100905.

Frotzler, A., Berger, M., Knecht, H., & Eser, P. (2008). Bone steady-state is established at reduced bone strength after spinal cord injury: A longitudinal study using peripheral quantitative computed tomography (pQCT). *Bone*, *43*(3), 549–555. https://doi.org/10.1016/j.bone.2008.05.006.

Frotzler, A., Coupaud, S., Perret, C., Kakebeeke, T. H., Hunt, K. J., de Donaldson, N. N., et al. (2008). High-volume FES-cycling partially reverses bone loss in people with chronic spinal cord injury. *Bone*, *43*(1), 169–176. https://doi.org/10.1016/j.bone.2008.03.004.

Garland, D. E., Adkins, R. H., Scott, M., Singh, H., Massih, M., & Stewart, C. (2004). Bone loss at the os calcis compared with bone loss at the knee in individuals with spinal cord injury. *Journal of Spinal Cord Medicine*, *27*(3), 207–211. https://doi.org/10.1080/10790268.2004.11753749.

Garland, D., Adkins, R., & Stewart, C. (2005). Fracture threshold and risk for osteoporosis and pathologic fractures in individuals with spinal cord injury. *Topics in Spinal Cord Injury Rehabilitation*, *11*(1), 61–69. https://doi.org/10.1310/G6TD-HPGC-XM3Q-7YJH.

Garland, D. E., Adkins, R. H., Stewart, C. A., Ashford, R., & Vigil, D. (2001). Regional osteoporosis in women who have a complete spinal cord injury. *Journal of Bone and Joint Surgery Series A*, *83*(8), 1195–1200. https://doi.org/10.2106/00004623-200108000-00009.

Garland, D. E., Stewart, C. A., Adkins, R. H., Hu, S. S., Rosen, C., Liotta, F. J., et al. (1992). Osteoporosis after spinal cord injury. *Journal of Orthopaedic Research*, *10*(3), 371–378. https://doi.org/10.1002/jor.1100100309.

Giangregorio, L. M., Hicks, A. L., Webber, C. E., Phillips, S. M., Craven, B. C., Bugaresti, J. M., et al. (2005). Body weight supported treadmill training in acute spinal cord injury: Impact on muscle and bone. *Spinal Cord*, *43*(11), 649–657. https://doi.org/10.1038/sj.sc.3101774.

Gifre, L., Vidal, J., Carrasco, J. L., Muxi, A., Portell, E., Monegal, A., et al. (2016). Denosumab increases sublesional bone mass in osteoporotic individuals with recent spinal cord injury. *Osteoporosis International*, *27*(1), 405–410. https://doi.org/10.1007/s00198-015-3333-5.

Gifre, L., Vidal, J., Carrasco, J., Portell, E., Puig, J., Monegal, A., et al. (2014). Incidence of skeletal fractures after traumatic spinal cord injury: A 10-year follow-up study. *Clinical Rehabilitation*, *28*(4), 361–369. https://doi.org/10.1177/0269215513501905.

Gilchrist, N. L., Frampton, C. M., Acland, R. H., Nicholls, M. G., March, R. L., Maguire, P., et al. (2007). Alendronate prevents bone loss in patients with acute spinal cord injury: A randomized, double-blind, placebo-controlled study. *Journal of Clinical Endocrinology and Metabolism*, *92*(4), 1385–1390. https://doi.org/10.1210/jc.2006-2013.

Goenka, S., & Sethi, S. (2020). Zoledronic acid attenuates early bone loss at forearm in patients with acute spinal cord injury. *The Indian Journal of Orthopaedics*, *54*(Suppl. 1), 127–133. https://doi.org/10.1007/s43465-020-00158-8.

Haider, I. T., Lobos, S. M., Simonian, N., Schnitzer, T. J., & Edwards, W. B. (2018). Bone fragility after spinal cord injury: reductions in stiffness and bone mineral at the distal femur and proximal tibia as a function of time. *Osteoporosis International*, *30*(8), 1422–1430. https://doi.org/10.1007/s00198-018-4733-0.

Haider, I. T., Simonian, N., Saini, A. S., Leung, F. M., Edwards, W. B., & Schnitzer, T. J. (2019). Open-label clinical trial of alendronate after teriparatide therapy in people with spinal cord injury and low bone mineral density. *Spinal Cord*. https://doi.org/10.1038/s41393-019-0303-3.

Haider, I. T., Simonian, N., Schnitzer, T. J., & Edwards, W. B. (2020). Stiffness and strength predictions from finite element models of the knee are associated with lower-limb fractures after spinal cord injury. *Annals of Biomedical Engineering*. https://doi.org/10.1007/s10439-020-02606-w.

Ho, C. H., Triolo, R. J., Elias, A. L., Kilgore, K. L., DiMarco, A. F., Bogie, K., et al. (2014). Functional electrical stimulation and spinal cord injury. *Physical Medicine and Rehabilitation Clinics of North America*, *25*(3), 631–654. ix https://doi.org/10.1016/j.pmr.2014.05.001.

Kanis, J. A., Hans, D., Cooper, C., Baim, S., Bilezikian, J. P., Binkley, N., et al. (2011). Interpretation and use of FRAX in clinical practice. *Osteoporosis International*, *22*(9), 2395–2411. https://doi.org/10.1007/s00198-011-1713-z.

Lala, D., Craven, B. C., Thabane, L., Papaioannou, A., Adachi, J. D., Popovic, M. R., et al. (2014). Exploring the determinants of fracture risk among individuals with spinal cord injury. *Osteoporosis International*, *25*(1), 177–185. https://doi.org/10.1007/s00198-013-2419-1.

Lambach, R. L., Stafford, N. E., Kolesar, J. A., Kiratli, B. J., Creasey, G. H., Gibbons, R. S., et al. (2020). Bone changes in the lower limbs from participation in an FES rowing exercise program implemented within two years after traumatic spinal cord injury. *Journal of Spinal Cord Medicine*, *43*(3), 306–314. https://doi.org/10.1080/10790268.2018.1544879.

Lazo, M. G., Shirazi, P., Sam, M., Giobbie-Hurder, A., Blacconiere, M. J., & Muppidi, M. (2001). Osteoporosis and risk of fracture in men with spinal cord injury. *Spinal Cord*, *39*(4), 208–214. https://doi.org/10.1038/sj.sc.3101139.

McCarthy, I. D., Bloomer, Z., Gall, A., Keen, R., & Ferguson-Pell, M. (2012). Changes in the structural and material properties of the tibia in patients with spinal cord injury. *Spinal Cord*, *50*(4), 333–337. https://doi.org/10.1038/sc.2011.143.

McPherson, J. G., Edwards, W. B., Prasad, A., Troy, K. L., Griffith, J. W., & Schnitzer, T. J. (2014). Dual energy X-ray absorptiometry of the knee in spinal cord injury: Methodology and correlation with quantitative computed tomography. *Spinal Cord*, *52*(11), 821–825. https://doi.org/10.1038/sc.2014.122.

Modlesky, C. M., Majumdar, S., Narasimhan, A., & Dudley, G. A. (2004). Trabecular bone microarchitecture is deteriorated in men with spinal cord injury. *Journal of Bone and Mineral Research*, *19*(1), 48–55. https://doi.org/10.1359/JBMR.0301208.

Moran De Brito, C. M., Battistella, L. R., Saito, E. T., & Sakamoto, H. (2005). Effect of alendronate on bone mineral density in spinal cord injury patients: A pilot study. *Spinal Cord*, *43*(6), 341–348. https://doi.org/10.1038/sj.sc.3101725.

Morgan, E. F., Bayraktar, H. H., & Keaveny, T. M. (2003). Trabecular bone modulus–density relationships depend on anatomic site. *Journal of Biomechanics*, *36*(7), 897–904. https://doi.org/10.1016/S0021-9290(03)00071-X.

Morse, L. R., Troy, K. L., Fang, Y., Nguyen, N., Battaglino, R., Goldstein, R. F., et al. (2019). Combination therapy with zoledronic acid and FES-row training mitigates bone loss in paralyzed legs: Results of a randomized comparative clinical trial. *JBMR Plus*, *3*(5). https://doi.org/10.1002/jbm4.10167, e10167.

Nance, P. W., Schryvers, O., Leslie, W., Ludwig, S., Krahn, J., & Uebelhart, D. (1999). Intravenous pamidronate attenuates bone density loss after acute spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *80*(3), 243–251. https://doi.org/10.1016/S0003-9993(99)90133-8.

Oleson, C. V., Marino, R. J., Formal, C. S., Modlesky, C. M., & Leiby, B. E. (2020). The effect of zoledronic acid on attenuation of bone loss at the hip and knee following acute traumatic spinal cord injury: A randomized-controlled study. *Spinal Cord*, *58*(8), 921–929. https://doi.org/10.1038/s41393-020-0431-9.

Pearson, E. G., Nance, P. W., Leslie, W. D., & Ludwig, S. (1997). Cyclical etidronate: Its effect on bone density in patients with acute spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *78*(3), 269–272. https://doi.org/10.1016/S0003-9993(97)90032-0.

Rittweger, J., Goosey-Tolfrey, V. L., Cointry, G., & Ferretti, J. L. (2010). Structural analysis of the human tibia in men with spinal cord injury by tomographic (pQCT) serial scans. *Bone*, *47*(3), 511–518. https://doi.org/10.1016/j.bone.2010.05.025.

Schnitzer, T. J., Kim, K., Marks, J., Yeasted, R., Simonian, N., & Chen, D. (2016). Zoledronic acid treatment after acute spinal cord injury: Results of a randomized, placebo-controlled pilot trial. *PM & R: The Journal of Injury, Function, and Rehabilitation*, *8*(9), 833–843. https://doi.org/10.1016/j.pmrj.2016.01.012.

Shapiro, J., Smith, B., Beck, T., Ballard, P., Dapthary, M., BrintzenhofeSzoc, K., et al. (2007). Treatment with zoledronic acid ameliorates negative geometric changes in the proximal femur following acute spinal cord injury. *Calcified Tissue International*, *80*(5), 316–322. https://doi.org/10.1007/s00223-007-9012-6.

Shields, R. K., & Dudley-Javoroski, S. (2007). Musculoskeletal adaptations in chronic spinal cord injury: Effects of long-term soleus electrical stimulation training. *Neurorehabilitation and Neural Repair*, *21*(2), 169–179. https://doi.org/10.1177/1545968306293447.

Shields, R. K., Schlechte, J., Dudley-Javoroski, S., Zwart, B. D., Clark, S. D., Grant, S. A., et al. (2005). Bone mineral density after spinal cord injury: A reliable method for knee measurement. *Archives of Physical Medicine and Rehabilitation*, *86*(10), 1969–1973. https://doi.org/10.1016/j.apmr.2005.06.001.

Slade, J. M., Bickel, C. S., Modlesky, C. M., Majumdar, S., & Dudley, G. A. (2005). Trabecular bone is more deteriorated in spinal cord injured versus estrogen-free postmenopausal women. *Osteoporosis International*, *16*(3), 263–272. https://doi.org/10.1007/s00198-004-1665-7.

Tan, C. O., Battaglino, R. A., Doherty, A. L., Gupta, R., Lazzari, A. A., Garshick, E., et al. (2014). Adiponectin is associated with bone strength and fracture history in paralyzed men with spinal cord injury. *Osteoporosis International*, *25*(11), 2599–2607. https://doi.org/10.1007/s00198-014-2786-2.

Warden, S. J., Bennell, K. L., Matthews, B., Brown, D. J., McMeeken, J. M., Wark, J. D., et al. (2002). Quantitative ultrasound assessment of acute bone loss following spinal cord injury: A longitudinal pilot study. *Osteoporosis International*, *13*(7), 586–592. https://doi.org/10.1007/s001980200077.

Zehnder, Y., Lüthi, M., Michel, D., Knecht, H., Perrelet, R., Neto, I., et al. (2004). Long-term changes in bone metabolism, bone mineral density, quantitative ultrasound parameters, and fracture incidence after spinal cord injury: A cross-sectional observational study in 100 paraplegic men. *Osteoporosis International*, *15*(3), 180–189. https://doi.org/10.1007/s00198-003-1529-6.

Zehnder, Y., Risi, S., Michel, D., Knecht, H., Perrelet, R., Kraenzlin, M., et al. (2004). Prevention of bone loss in paraplegics over 2 years with alendronate. *Journal of Bone and Mineral Research*, *19*(7), 1067–1074. https://doi.org/10.1359/JBMR.040313.

Chapter 27

Functional and morphological reorganization of the brain following spinal cord injury: Insights from MRI

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Abbreviations

SCI	spinal cord injury
MRI	magnetic resonance imaging
DTI	diffusion tensor imaging
fMRI	functional MRI
MRS	magnetic resonance spectroscopy
VBM	voxel-based morphometry
SBA	surface-based analysis
FA	fractional anisotropy
MD	mean diffusivity
BOLD	blood oxygen level-dependent signal
rsfMRI	resting state fMRI

Introduction

The spinal cord is a vital conduit for the flow of information to and from the brain. Any disruption in the integrity of the spinal cord secondary to injury would lead to an impaired information flow. Deprived of their normal sources of activation, neurons in the brain undergo re-organization, a phenomenon that has been implicated both in the ensuing recovery of function as well as the occurrence of maladaptive changes (Kaas et al., 2008). Despite significant ongoing research, the ability to restore normal function following spinal cord injury (SCI) is limited. The functional and morphological changes following SCI could play a major role in hastening or impeding recovery. A better understanding of these changes would pave the way for more effective therapeutic and rehabilitative strategies, thus translating into a better clinical outcome.

The use of imaging techniques facilitates an effective understanding of the brain changes secondary to SCI. Magnetic resonance imaging (MRI) is regarded as the modality of choice for the evaluation of the nervous system, thanks to its excellent spatial resolution, multi-planar imaging capability, multi-parametric approach, and the use of non-ionizing radiation. Beyond the information it provides in the routine clinical work-up of the extent of local damage produced in SCI, MRI can unravel the underlying brain changes which ensure secondary to cortical plasticity, through the use of novel techniques such as diffusion tensor imaging (DTI), brain morphometry, functional MRI (fMRI), MR spectroscopy (MRS), etc. (Table 1). This chapter provides a glimpse of the information that these techniques can provide in the assessment of the structural and functional brain changes secondary to SCI.

Brain morphometry

Morphometry is the study of the size and shape of the brain and its various structures. MRI has the inherent capability to produce high-resolution images of the anatomical structure of the brain, which are useful to assess various metrics such as

Cellular, Molecular, Physiological, and Behavioral Aspects of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822427-4.00027-7

TABLE 1 Advanced MR techniques for assessment of brain reorganization after SCI.

MR technique	Utility
Diffusion tensor imaging (DTI)	• High resolution imaging of fiber tracts in brain • Provides quantitative indices for assessment of microstructural integrity • Provides information on structural connectivity
Brain morphometry	• Quantification of anatomical features such as volume, surface area, curvature, cortical thickness, gyrification index • Provides information on subtle structural changes long before they are clinically apparent on conventional MR scanning
Functional MRI (fMRI)	• *Task-based fMRI*: Identification of brain regions which are functionally involved in a specific task performance • *Resting state fMRI*: Mapping of multiple functional neuronal networks in the absence of task performance • Provides information on the origin & organization of cognitive brain functioning in health and disease
MR spectroscopy (MRS)	• Quantitative measure of brain metabolites • Provides information on metabolic changes in the brain in various physiologic and pathologic states

the gray matter, white matter, and total brain volume, cortical surface area, cortical thickness, etc., through appropriate computational techniques. Two standard techniques in popular use at present in the study of intracranial changes post-SCI are voxel-based morphometry (VBM) and surface-based analysis (SBA). In VBM, one derives morphometric measures using a voxel-based volumetric approach, while SBA does so from geometric models of the cortical surface. These techniques have been used effectively in understanding several brain pathologies & processes such as aging, dementia, schizophrenia, multiple sclerosis, etc. (Mechelli, Price, Friston, & Ashburner, 2005) and show promise in the assessment of atrophic changes after SCI.

Diffusion tensor imaging (DTI)

DTI provides an excellent in vivo method of assessing the tissue microstructure, by measuring the diffusivity of water in multiple directions through brain tissue. Over and above the visualization of the white matter tracts in the brain, it provides useful quantitative indices to assess tissue integrity. These primarily include fractional anisotropy (FA) and mean diffusivity (MD). FA is a measure of the degree of directionality of water diffusion, while MD gives information on the overall diffusion. These indices are affected by cell size, shape, and integrity (Pierpaoli, Jezzard, Basser, Barnett, & Di Chiro, 1996) and get altered with cell degeneration as well as with disrupted tissue barriers, such as cell membranes and myelin sheaths (Basser, Pajevic, Pierpaoli, Duda, & Aldroubi, 2000). Other parameters such as axial diffusivity (AD) and radial diffusivity (RD), which report the extent of water diffusion along or across the axons, are thought to reflect the integrity of axons and myelin, respectively (Zhang et al., 2009).

Functional MRI (fMRI)

fMRI reflects blood oxygen level-dependent signal (BOLD) (Friston et al., 1995), which gets altered by hemodynamic changes secondary to neuronal activation and is thus an indirect marker of the same. fMRI is broadly of two types: task-based fMRI and resting state fMRI. Task-based fMRI is widely adopted to identify brain regions that are functionally involved in specific task performance (Logothetis, 2008). It is a commonly used tool both in clinical and cognitive neuroscience and is widely used in SCI research, but it relies heavily on patients' cognitive integrity and their cooperation in performing the task.

Resting state fMRI (rsfMRI) on the other hand, detects the spontaneous, temporally correlated changes in brain activity at rest, which occur in brain regions that are spatially distinct, but functionally related. As it entails performing the scan with the subject at rest, it is relatively free of compounding effects due to task difficulty, level of patient co-operation, practice and re-test, etc. The pattern of synchronous BOLD activity in different parts of the brain at rest, resembles the functional networks observed during the performance of cognitive tasks (Rigon, Duff, McAuley, Kramer, & Voss, 2016). rsfMRI has the ability to investigate several brain networks simultaneously such as the default mode network, frontoparietal network, central executive network, sensorimotor network, auditory network, visual network, etc. (Table 2).

TABLE 2 Brain neuronal networks commonly assessed on resting state functional MRI.

Resting state network	Main components	Salient function
Default mode network	Precuneus/posterior cingulate, lateral parietal, mesial prefrontal cortex	Active when individuals are focused on internal mental-state processes, e.g., interoception, autobiographical memory retrieval, etc.
Sensorimotor network	Precentral gyrus, post-central gyrus, supplementary motor area	Sensory and motor activity
Executive control network	Medial frontal gyrus, superior frontal gyrus, anterior cingulate cortex	Regulates the process of executive function, e.g., integration of sensory and motor information, working memory, etc.
Fronto-parietal network	Inferior frontal gyrus, medial frontal gyrus, precuneus, inferior parietal, angular gyrus	Co-ordinative control in a rapid, accurate, and flexible goal-driven manner
Visual network	*Medial visual*: Striate cortex and medial extra-striate eg. lingual gyrus *Lateral visual*: Occipital pole and occipito-temporal regions	Processing visual information
Auditory network	Superior temporal gyrus, Heschl's gyrus, insula, postcentral gyrus	Processing auditory information
Language network	Superior, middle, inferior frontal gyrus; superior and middle temporal gyrus, insula, angular gyrus, inferior parietal lobule	Language processing

MR spectroscopy

Magnetic resonance spectroscopy (MRS) provides a non-invasive assessment of various biochemical processes within the body. The key neurometabolites measured in the brain using MRS include *N*-acetylaspartate, choline, creatine, lactate, glutamate, glutamine, myoinositol, etc. (Bustillo, 2013). It is a widely used tool for the assessment of various brain pathologies such as tumors, infections, and degenerative processes. However, there are limited studies using MRS for assessing the brain changes secondary to SCI.

Structural reorganization—Insights from MRI

SCI leads to retrograde and anterograde degenerative processes within the spinal cord itself, leading to atrophy (Lundell et al., 2011). The disruption of tract integrity within the spinal cord secondary to injury (Fig. 1) has been elegantly demonstrated on DTI in previous studies (D'souza, Choudhary, Poonia, Kumar, & Khushu, 2017). These changes are however not limited to the spinal cord, but extend upwards into the brain.

In a cohort of 10 subjects with chronic SCI secondary to cervical injury, cord atrophy was seen to be accompanied by a decline in white matter volume in the brain using VBM, especially in the region of the cortico-spinal tract such as the pyramids and cerebral peduncles (Freund et al., 2011). These changes were observed to be accompanied by volumetric changes of gray matter in the denervated leg area of the primary motor (M1) and sensory cortex (S1). A correlation between the degree of cortical atrophy in the primary motor cortex and the extent of clinical impairment was noted in this study. Another study observed a similar correlation between the degree of volume loss in the somato-sensory cortex and the level of functional deficit (Jurkiewicz, Crawley, Verrier, Fehlings, & Mikulis, 2006).

A study performed at our center on a cohort of 30 cases of incomplete spinal cord injury analyzed surface-based measures (cortical thickness, cortical volume, and surface area) using the FreeSurfer 6.0 (Massachusetts General Hospital, Harvard Medical School) toolbox. The study revealed no significant volumetric changes at the early time point (namely within 15 days) post-injury, as compared to healthy, uninjured controls. However, on the follow-up study performed at approximately 6 months post-injury (range 5–8 months), there was a statistically significant decline in cortical surface area, thickness, and volume in the region of the bilateral pre- and post-central gyrus, paracingulate gyrus, the dorsolateral

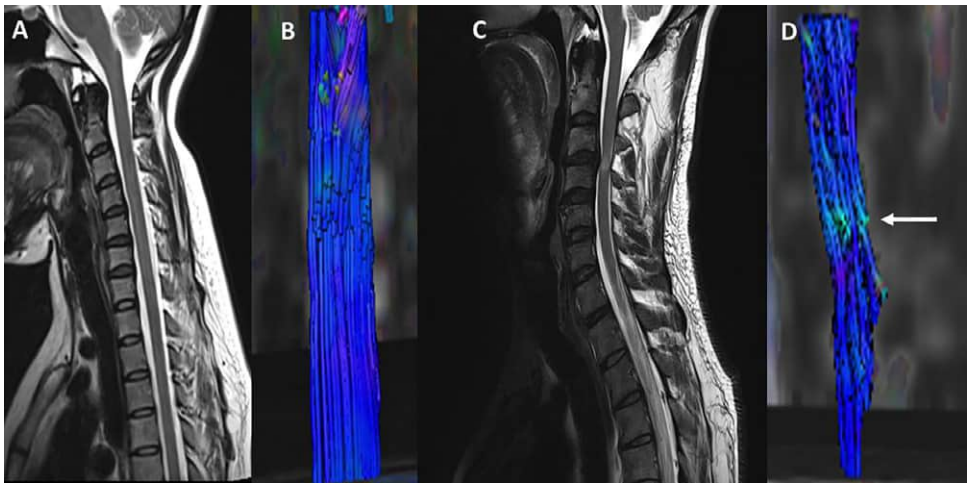

FIG. 1 Normal cervical cord on sagittal MRI (A) with normal tractography image on DTI (B). Sagittal MRI showing focal hyperintensity (*arrow*) in the cervical cord due to edema secondary to trauma (C) with corresponding tractography image (D) showing focal disruption (*arrow*).

pre-frontal and the orbitofrontal (also called the medial pre-frontal) cortex (Fig. 2). The pre- and post-central gyri represent the primary motor and sensory cortices, respectively. The dorsolateral pre-frontal cortex is involved in executive functions such as working memory, cognitive flexibility, planning, etc. The orbitofrontal cortex receives connections from the thalamus and limbic cortex and is thought to represent emotion and reward in decision making. Thus, the impairment of somatosensory input and motor output after SCI affects not just the sensory-motor cortices, but adjacent areas involved in higher-order cognitive function, emotion, etc. DTI studies performed using the tractography approach on the same cohort of incomplete SCI patients at the chronic time point, revealed a disruption in white matter integrity as evidenced by altered datametrics in the form of reduced FA and increased MD. The principal tracts to be involved were the bilateral corticospinal tracts (Fig. 3).

Over and above the observed changes within the sensorimotor systems, loss of gray matter volume has also been seen in the medial pre-frontal and anterior cingulate cortex in a cohort of patients with complete SCI, who sustained an injury to the thoracic cord (Wrigley, Gustin, et al., 2009). These areas play a crucial role in emotional processing. This study also revealed structural changes on whole-brain DTI analysis as evidenced by altered FA and MD in the above-mentioned areas and also in the superior cerebellar cortex. Additionally, structural abnormalities in the corticospinal and corticopontine tracts of the SCI subjects were observed on tractography. Most white matter pathways in the brain are oriented bilaterally. Although bilateral involvement is generally observed on DTI, it is usually asymmetrical (Freund et al., 2012). This

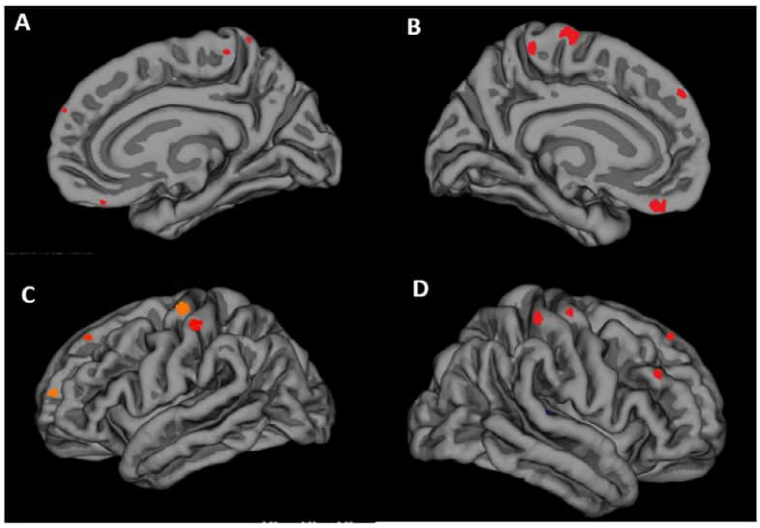

FIG. 2 Cortical regions showing decreased cortical thickness in SCI patients vs controls on surface-based morphometry (thresholded at $P < 0.05$). (A) and (B) Medial aspect of right and left cerebral hemispheres, respectively, with clusters of decreased cortical thickness in the pre- and post-central gyri and orbitofrontal cortex. (C) and (D) Lateral aspect of right and left cerebral hemispheres, respectively, with clusters of decreased cortical thickness in the pre- and post-central gyri and dorso-lateral pre-frontal cortex.

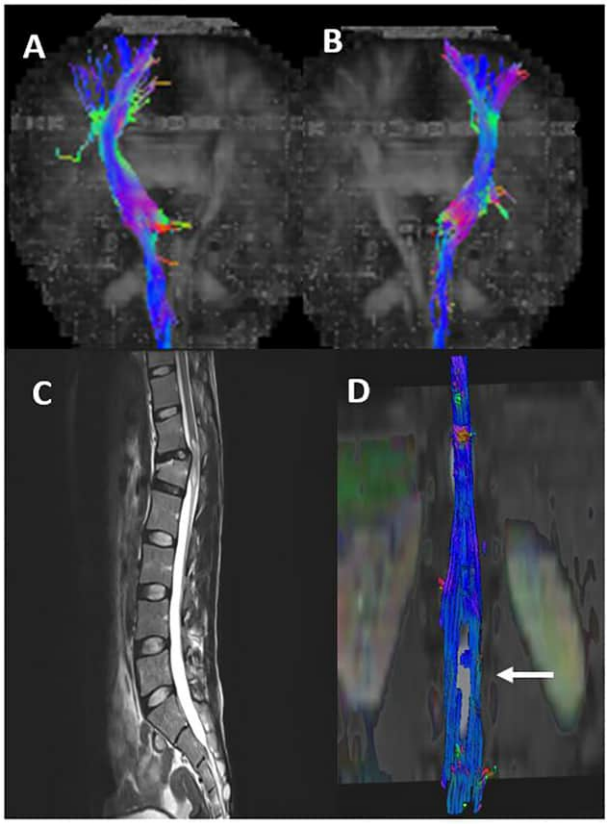

FIG. 3 Tractography images of right (A) and left (B) corticospinal tracts in a patient with dorsolumbar SCI secondary to a vertebral compression fracture as seen on sagittal MRI (C) with corresponding tractography image (D) showing the severed cord.

asymmetry could be partly owing to asymmetric use of bilateral limbs with compensatory overuse of the less-affected limb after SCI.

Changes in regional brain anatomy as determined on DTI, have also been linked to the phenomenon of persistent neuropathic pain after SCI. A study performed on 23 subjects with complete thoracic SCI (12 with neuropathic pain and 11 without) as well as 45 healthy controls, revealed an increase in MD on DTI in areas associated with nociceptive processing and the classic reward circuitry in patients experiencing neuropathic pain (Gustin, Wrigley, Siddall, & Henderson, 2010). These areas included the orbitofrontal, dorsolateral pre-frontal, and posterior parietal cortex as well as the nucleus accumbens. The degree of change in these areas was seen to correlate with the severity of pain.

Functional reorganization—Insights from MRI

Functional MRI (fMRI) studies

Evidence of functional reorganization of the brain was demonstrated using electrophysiological techniques several decades ago. Merzenich et al. used this technique to study the changes in the brain in monkeys post-amputation (Merzenich et al., 1983). They found that the S1 region which was originally innervated by inputs from the amputated digit was now invaded by neighboring S1 representations. Bruehlmeier et al. 18 observed similar changes in a cohort of complete thoracic SCI subjects, with a shift of the functional representation of upper limb digits into the deafferented cortex, originally receiving inputs from the lower limbs (Bruehlmeier et al., 1998). A task-based fMRI study on a cohort of complete thoracic SCI subjects, displayed functional re-organization in the M1 motor cortex, with a significant shift of the activated M1 maxima toward the deafferented cortex on performing tasks involving the spared upper limbs (Lotze, Laubis-Herrmann, Topka, Erb, & Grodd, 1999). A subsequent study observed that SCI patients displayed larger areas of M1 activation on performing tasks that involved muscle groups supplied proximal to the site of spinal injury (Cramer, Lastra, Lacourse, & Cohen, 2005). The degree of the shift was seen to increase with the time elapsed since the occurrence of injury, based on a study which made use of both fMRI and transcranial magnetic stimulation (Lotze, Laubis-Herrmann, & Topka, 2006).

Motor imagery (MI) is a popular technique, being employed in the rehabilitation of SCI patients with a view to the restoration of motor function. This cognitive approach involves imagining or mentally rehearsing movement representations. A study performed on 12 patients with chronic, complete SCI and 12 controls, utilized functional MRI during attempted, and during imagined, right foot movements to study the brain activation patterns (Cramer et al., 2005). It was observed that while many features of normal motor activation were preserved, there were several departures from normal as well. On attempted movement, the key areas to get activated in controls included the primary sensorimotor cortex, supplementary motor area, and cerebellum. Other areas which were activated included the left thalamus, right anterior cingulate, and left superior temporal gyrus. The authors observed a reduced volume of activation in several of these areas in patients with SCI. On imagined movement in controls, the activation pattern involved a cortical–subcortical motor network (involving the left mesial primary sensorimotor cortex, bilateral supplementary area, left basal ganglia, and right cerebellum), motor imitation areas (bilateral superior temporal gyrus and left ventral premotor cortex) as well as attention-related areas (bilateral inferior parietal lobule, left dorsolateral pre-frontal and left anterior cingulate cortex). Although SCI patients activated several of these areas, the volume of significant activation peaks was significantly smaller. Abnormal activation patterns were also observed in SCI subjects such as an increase in pallido–thalamocortical loop activity during attempted movement and abnormal processing in the primary sensorimotor cortex during imagined movement. Additionally, a change in task force level produced an altered modulation of the activation pattern in SCI patients as compared to controls. The authors concluded that while the fundamental aspects of motor system activation were largely intact in SCI patients, there were certain derangements in the activation patterns and their modulation with increasing task demands. This would need to be taken into consideration while planning rehabilitative strategies in SCI.

Another recent study undertaken in incomplete spinal cord injury patients to explore changes in the brain activation patterns during motor execution and motor imagery tasks found several nearly similar activation patterns in both patients and controls (Chen et al., 2016). The task here involved dorsi-plantar flexion of the right ankle. The motor imagery network was seen to be more preserved than the motor execution network in these patients, thus showing promise for the use of motor imagery in rehabilitative regimens. The neural mechanisms of motor imagery are quite similar to those that occur in the early stages of motor execution. Thus activating this network could help in rebuilding and strengthening neural connections. As compared to healthy controls, the incomplete spinal cord injury patients displayed greater activation than controls in the motor-related regions during the motor execution task and lesser activation in the parietal regions during both tasks. However, the cognitive-related regions (namely the left intraparietal lobule and supramarginal gyrus involved in motor attention and planning) showed decreased activation in SCI patients during both the motor execution and imagery tasks. Increased activation patterns in motor regions in SCI patients with complete cord injury as compared to healthy controls have also been observed in other studies (Alkadhi et al., 2005). The apparent differences in the level of activation between different studies could be due to variable study protocol including duration of injury, level of injury, and the specific activation task employed.

Resting-state fMRI studies

Task-based fMRI studies have an inherent limitation—the lack of standardized task protocols which can be uniformly applied to all subjects (Kokotilo, Eng, & Curt, 2009). Resting-state fMRI (rsfMRI) detects spontaneous low-frequency fluctuations in the blood oxygenation level-dependent (BOLD) contrast signal, while the patient is at rest. Hence it is a much more reproducible technique (Biswal, Yetkin, Haughton, & Hyde, 1995). As mentioned before, it has the added advantage of assessing multiple brain networks simultaneously. A rsfMRI study performed on 11 patients with complete cervical SCI in the chronic phase, revealed reorganization of the sensorimotor network with decreased functional connectivity in motor and sensory cortical regions when compared to controls (Oni-Orisan et al., 2016). Seed-based analysis was performed using motor and sensory regions of interest (ROI) in the bilateral pre- and post-central gyri, respectively. For both the motor ROIs, decreased connectivity was observed with bilateral primary motor and sensory regions as well as the interhemispheric region which serves as a connection between the primary motor and sensory areas. The sensory ROI in the left post-central gyrus revealed a similar pattern of decreased connectivity, while the ROI in the right post-central gyrus showed a significantly reduced connectivity only in the interhemispheric region. The authors conclude that a larger sample size would likely produce similar findings in the right-sided sensory ROI as well. Additionally, the left postcentral ROI demonstrated increased connectivity with the thalamus bilaterally. The increased thalamic connectivity may form the basis for the occurrence of neuropathic pain which is frequently observed in SCI subjects (Wrigley, Press, et al., 2009).

A study performed at our institution assessed the resting state networks on 30 incomplete SCI patients, at approximately 6 months post-injury using the independent component analysis and a dual regression approach. Decreased intra-network connectivity within the somatomotor network was observed in a cluster of regions principally involving the bilateral

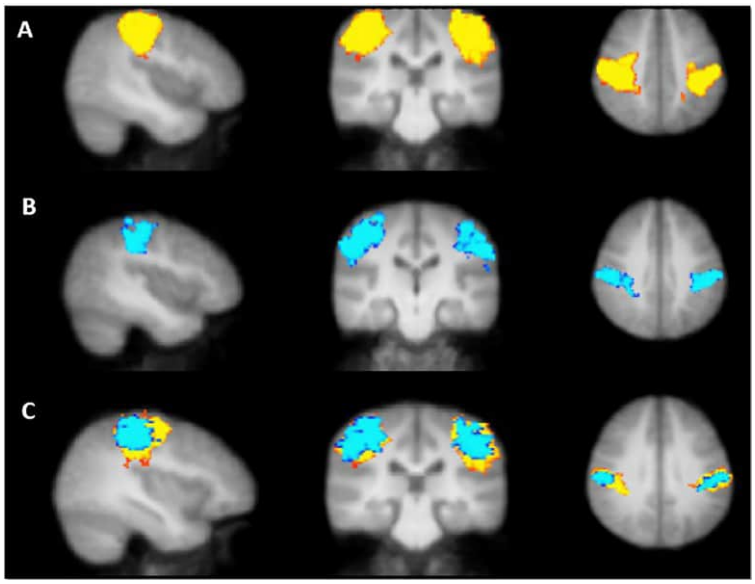

FIG. 4 Resting state fMRI map showing sagittal, coronal, and axial image of the somatomotor network in healthy control (A), SCI (B) and superimposition of healthy control on to SCI with evidence of decreased connectivity in SCI as compared to healthy controls.

pre- and post-central gyri (Fig. 4). There was also a significantly decreased temporal correlation in the default mode network in the region of the right superior frontal, bilateral anterior and posterior cingulate gyri, as compared to healthy controls. The default mode network, which is regarded as a key resting state network, supports internally directed mental activity. It also has an important influence on cognitive control through its interaction with several other brain networks. The diminished connectivity within the default mode network could have implications on cognitive task performance. A decline in motor output has been observed in acute SCI as well, in earlier studies (Hou et al., 2014). The study, performed on 25 patients with acute SCI and 25 healthy controls showed a decreased amplitude of low-frequency fluctuations in the bilateral primary sensorimotor cortex with an increase in the bilateral cerebellum and right orbitofrontal cortex. The study also revealed a decreased inter-hemispheric connectivity between the bilateral primary sensorimotor cortex, and increased intra-hemispheric connectivity within the motor network, including the primary sensorimotor cortex, premotor cortex, supplementary motor area, thalamus, and cerebellum.

Another group recently performed an assessment of resting state networks in a cohort of both complete and incomplete SCI patients (Hawasli et al., 2018). Seed-based analysis was performed on five networks: default-mode, dorsal-attention, salience, control, and somatomotor network. Decreased intra-network connectivity was observed within the somatomotor, default mode, and salience networks with a disrupted inter-network connectivity between the somato-motor and control networks. When the cohort of complete and incomplete SCI patients was analyzed separately with a group of age-matched controls, it was observed that the network connectivity changes were much more pronounced in the complete SCI group. It was also observed that connectivity changed with time: there was decreased connectivity between the primary motor and somatosensory cortex, decreased connectivity between the visual and the primary motor cortex, and increased connectivity between the visual and the sensory parietal cortex. The cerebellum is known to be anti-correlated with the primary motor and sensory cortices. However, this study demonstrated a disruption in this anti-correlation, with an increase in connectivity between the cerebellum and both primary motor and sensory cortices. This finding is corroborated by another recent study using a graph-theory of network efficiency, which found whole-brain connectivity changes, along with a disruption in the connectivity between the cerebellum and the cortex (Kaushal et al., 2017).

In another study on 19 patients with complete SCI (Karunakaran et al., 2020), a reorganization of thalamocortical connections has been observed with increased connectivity between the left pulvinar nucleus and the left inferior frontal gyrus and left inferior parietal lobule in the SCI group. Additionally, there was a decreased connectivity between the bilateral mediodorsal nucleus (of the thalamus) and right superior temporal gyrus and anterior cingulate cortex as well as the left ventrolateral thalamic nucleus and the left superior temporal gyrus. Disruptions in thalamic connectivity could have serious implications in sensory processing, as the thalamus is known to play an important role in multi-sensory integration and affective processing.

MR spectroscopy

This non-invasive technique allows brain chemistry to be studied by the in vivo measurements of specific metabolites such as *N*-acetylaspartate, choline. Creatine and phosphocreatine, etc., limited studies on SCI have been performed using MR spectroscopy. An MR spectroscopy of the thalamus was performed in SCI patients with paraplegia with and without neuropathic pain as compared to healthy controls (Puri et al., 1998). The study revealed that the concentration of *N*-acetyl aspartate was negatively correlated with pain intensity, thus pointing toward the fact that the presence of neuropathic pain after SCI is associated with biochemical changes in the thalamus. Another MRS study on patients with incomplete SCI observed an increased level of *N*-acetylaspartate, expressed relative to creatine in the motor cortex as compared to other cortical areas (Mirvis & Geisler, 1990). The authors interpreted the increase in *N*-acetylaspartate to be due to adaptive dendritic sprouting occurring in the reorganized brain secondary to injury.

Structural and functional reorganization—Insights from MRI

An integrated structural and functional assessment was performed by Freund et al. (2012) using a multi-modal MR protocol to study the relationship between spinal cord cross-sectional area, corticospinal tract integrity, and sensorimotor cortex reorganization in traumatic cervical SCI. The most significant finding of the study was that the reduction in corticospinal tract integrity (as assessed by DTI) was seen to be associated with changes in cortical motor function (as assessed by task-based fMRI). The tract integrity was assessed using an ROI approach at multiple levels—the pyramids, the internal capsule, the cerebral peduncle, and the hand area. The tract integrity in the region of the left pyramid was seen to predict increased task-related responses in the leg area of the primary motor cortex, while changes in the cerebral peduncle were predicted by reduced cord area. The increased task-related activation of the left primary motor cortex during right handgrip and its association with reduced FA in the left pyramid containing the corticospinal tract is suggestive of the fact that greater impairment engages additional neuronal resources to maximize motor output.

Another study which investigated reorganization of the primary somatosensory cortex in response to the loss of somatosensory drive from SCI, analyzed 20 subjects with complete thoracic SCI who underwent functional and structural MRI using fMRI and DTI, respectively (Henderson, Gustin, Macey, Wrigley, & Siddall, 2011). The cortical little finger representation (evoked by continuous brushing of the little finger at a pre-determined rate) was seen to move medially toward the deafferented lower body representation. A loss of gray matter volume was seen in the lower body representation, which however, was minimized as reorganization increased. Additionally, as the extent of reorganization increased, the fractional anisotropy decreased and the diffusion direction within the little finger representation was seen to be directed more medially (toward the region that would normally represent the leg) in SCI subjects. This phenomenon has been ascribed to the growth of new lateral connections as part of the re-organization process. The study elegantly demonstrates how the structural and functional changes go hand in hand and can be simultaneously demonstrated by optimizing the MR protocol.

Mechanisms underlying reorganization

Nearly 170 years ago, it was seen that subsequent to the injury of a peripheral nerve, axons lying distal to the injury undergo progressive degeneration, a phenomenon coined as Wallerian degeneration (Buss et al., 2004). Recent evidence suggests that retrograde and antegrade degeneration does indeed occur in the spinal cord of SCI subjects, with changes which extend further up into the brain. A decrease in both the size and numbers of corticospinal neurons as well as alterations in neuronal morphology and synaptic spine density have been reported (Ganchrow & Bernstein, 1985; Hains, Black, & Waxman, 2003; Tetzlaff et al., 1994). Although the use of immunohistochemical techniques provides an in-depth understanding of the morphological changes, it cannot be used in living humans. Electrophysiological studies have been used over the last few decades to glean information on cortical plasticity, post-SCI (Lacourse, Cohen, Lawrence, & Romero, 1999). Imaging studies which can non-invasively offer a high spatial resolution have shed further light on the structural and functional reorganization in the somatomotor cortex, extending into other parts of the brain (Mikulis et al., 2002).

What are the underlying mechanisms responsible for this well-established phenomenon of cortical re-organization that follows the loss of sensory drive and efferent output in SCI? The rapid unmasking of dormant synapses leading to facilitation or disinhibition of existing subthreshold inputs is believed to play a major role (Jacobs & Donoghue, 1991). In fact, investigators have reported that SI reorganization can occur in humans within hours of administering anesthesia, thus lending credence to the existence and unmasking of latent synapses (Björkman, Weibull, Rosén, Svensson, & Lundborg, 2009). With time, gradual mechanisms of subcortical rewiring (Ghosh et al., 2010) and lateral sprouting of dendrites (Henderson et al., 2011) enable the reinnervation of the cortex in SCI. Large cortical shifts that occur following massive sensory losses likely involve multiple mechanisms, which include the relatively rapid unmasking of already

existing synapses, but more importantly, the slower growth of new dendrites. Subcortical structures also play a major role in reorganization through the processes mentioned above. For instance, a study on complete SCI in humans demonstrated that the ventral thalamic area that would normally respond to inputs from the upper limb responded to inputs from the neck and occiput (Lenz et al., 1987). This may also influence pain perception following SCI. Finally, it is yet unclear whether the phenomenon of neurogenesis, which is seen to have a definite impact on reorganization in animal studies, has a role to play in the human brain.

Challenges related to MRI evaluation of SCI data

Although substantial research has been undertaken in recent years on the MR study of brain plasticity after SCI, it is marked by sizeable heterogeneity. To begin with, the inclusion criteria in different studies vary from only incomplete SCI (of varying degrees), to complete SCI to a combination of both. Likewise, some investigators restrict themselves to cervical or thoracic cord injury, while others include both. The time since injury is also highly variable, ranging from acute to chronic, with a duration of injury that may span several years. Most studies have a limited sample size. There is also variability in other demographic characteristics such as age and sex of the patients, handedness, etc.

Another reason for the limited reproducibility of findings could be the confounding role played by a multitude of therapeutic and rehabilitative strategies which some patients adopt assiduously, while others do not. In fact, this could account for the differential extent and pattern of volume loss assessed by morphometric studies as the volumetric changes are dynamic, have distinct temporal patterns and not only represent degeneration but also activity-induced changes. An inherent limitation in DTI is its limited ability in detecting crossing and sprouting fibers, as well as unsuitability in the detection of changes in small bundles and nerves due to limited resolution and noise. Thus, miniscule changes induced by dendritic sprouting, etc. have the potential to go undetected. The heterogeneity in post-processing algorithms used in different MR studies could add to the variability of findings. Finally, the issue of assessing the reorganization at the spinal cord level itself remains unaddressed in most studies.

The institution of large-scale, longitudinal, multi-centric studies with uniform selection criteria, study protocols, and data processing algorithms would help to resolve the apparent discrepancy in findings between different studies. This would facilitate the use of MRI as a physiological marker for a comprehensive assessment of brain connectivity changes after SCI, prognostication of functional outcome, and therapeutic monitoring and optimization.

Applications to other areas of neuroscience

In this chapter, we describe the role of MRI in the evaluation of structural and functional reorganization in the brain after spinal cord injury. MRI is a versatile non-invasive modality, which serves as an excellent tool for neuroimaging due to its high spatial resolution, soft tissue contrast, and capability to assess both structure and function. It is thus a useful technique to study brain plasticity in response to a variety of neuropathological conditions arising outside the brain, such as spinal cord injury, limb amputation, brachial plexus injury, etc. It has also been used extensively for studying reorganization in response to intracranial pathologies such as stroke, ischemia, traumatic brain injury, multiple sclerosis, etc. Brain reorganization has also been documented on MRI in physiological states as diverse as normal aging to situations like long-distance space flights. The use of MRI has the potential to serve as a biomarker for prognostication of pathological conditions, as well as guiding and monitoring therapeutic and rehabilitative interventions.

Mini-dictionary of terms

Complete spinal cord injury: Complete loss of sensation and motor function below the level of spinal cord injury.
Incomplete spinal cord injury: Incomplete loss of sensation and motor function below the level of spinal cord injury.
Functional MRI: An MRI technique that measures neuronal activity by detecting changes in blood flow.
Diffusion tensor imaging: An MRI technique that assesses the location, orientation, and integrity of white matter tracts.
Brain plasticity: The ability of the brain to reorganize its structural and functional connections in response to a variety of situations.

Key facts

- An injury to the spinal cord could lead to an impaired information flow to and from the brain.
- The brain thus undergoes reorganization, in response to the loss of sensory input and motor output.

- The phenomenon of cortical plasticity underlies the ensuing recovery of function as well as mal-adaptive changes such as neuropathic pain phenomena.
- MRI is an effective, non-invasive method to assess the level and extent of reorganization.
- Several MR tools such as diffusion tensor imaging, brain morphometry, functional MRI, and MR spectroscopy provide an in-depth understanding of the structural and functional changes in the brain secondary to SCI.
- MRI thus has a tremendous potential to serve as an imaging biomarker for brain reorganization after SCI.

Summary points

- SCI produces morphological and functional reorganization in the brain which can be detected on advanced MRI techniques.
- Diffusion tensor imaging shows alteration in the microstructural integrity of white matter tracts, principally the corticospinal tracts.
- Brain morphometry using voxel-based or surface-based analysis reveals a decline in volume in the somatomotor cortex, as well as remote parts of the brain.
- Functional reorganization with shift of cortical representation toward the deafferented cortex from adjacent areas of the brain is noted on fMRI.
- An alteration in connectivity measures of the neuronal networks is observed on resting state fMRI.
- Perturbations in structure and function progress with time and are modified by rehabilitative interventions.
- Assessment of brain reorganization on MRI is a promising method to predict functional recovery and guide effective therapy in SCI patients.

References

Alkadhi, H., Brugger, P., Boendermaker, S. H., Crelier, G., Curt, A., Hepp-Reymond, M. C., et al. (2005). What disconnection tells about motor imagery: Evidence from paraplegic patients. *Cerebral Cortex*, *15*(2), 131–140. https://doi.org/10.1093/cercor/bhh116.

Basser, P. J., Pajevic, S., Pierpaoli, C., Duda, J., & Aldroubi, A. (2000). In vivo fiber tractography using DT-MRI data. *Magnetic Resonance in Medicine*, *44*(4), 625–632. https://doi.org/10.1002/1522-2594(200010)44:4<625::aid-mrm17>3.0.co;2-o.

Biswal, B., Yetkin, F. Z., Haughton, V. M., & Hyde, J. S. (1995). Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magnetic Resonance in Medicine*, *34*(4), 537–541. https://doi.org/10.1002/mrm.1910340409.

Björkman, A., Weibull, A., Rosén, B., Svensson, J., & Lundborg, G. (2009). Rapid cortical reorganisation and improved sensitivity of the hand following cutaneous anaesthesia of the forearm. *The European Journal of Neuroscience*, *29*(4), 837–844. https://doi.org/10.1111/j.1460-9568.2009.06629.x.

Bruehlmeier, M., Dietz, V., Leenders, K. L., Roelcke, U., Missimer, J., & Curt, A. (1998). How does the human brain deal with a spinal cord injury? *The European Journal of Neuroscience*, *10*(12), 3918–3922. https://doi.org/10.1046/j.1460-9568.1998.00454.x.

Buss, A., Brook, G. A., Kakulas, B., Martin, D., Franzen, R., Schoenen, J., et al. (2004). Gradual loss of myelin and formation of an astrocytic scar during Wallerian degeneration in the human spinal cord. *Brain: A Journal of Neurology*, *127*(Pt 1), 34–44. https://doi.org/10.1093/brain/awh001.

Bustillo, J. R. (2013). Use of proton magnetic resonance spectroscopy in the treatment of psychiatric disorders: A critical update. *Dialogues in Clinical Neuroscience*, *15*(3), 329–337. https://doi.org/10.31887/DCNS.2013.15.3/jbustillo.

Chen, X., Wan, L., Qin, W., Zheng, W., Qi, Z., Chen, N., et al. (2016). Functional preservation and reorganization of brain during motor imagery in patients with incomplete spinal cord injury: A pilot fMRI study. *Frontiers in Human Neuroscience*, *10*, 46. https://doi.org/10.3389/fnhum.2016.00046.

Cramer, S. C., Lastra, L., Lacourse, M. G., & Cohen, M. J. (2005). Brain motor system function after chronic, complete spinal cord injury. *Brain: A Journal of Neurology*, *128*(Pt 12), 2941–2950. https://doi.org/10.1093/brain/awh648.

D'souza, M. M., Choudhary, A., Poonia, M., Kumar, P., & Khushu, S. (2017). Diffusion tensor MR imaging in spinal cord injury. *Injury*, *48*(4), 880–884. https://doi.org/10.1016/j.injury.2017.02.016.

Freund, P., Weiskopf, N., Ward, N. S., Hutton, C., Gall, A., Ciccarelli, O., et al. (2011). Disability, atrophy and cortical reorganization following spinal cord injury. *Brain: A Journal of Neurology*, *134*(Pt 6), 1610–1622. https://doi.org/10.1093/brain/awr093.

Freund, P., Wheeler-Kingshott, C. A., Nagy, Z., Gorgoraptis, N., Weiskopf, N., Friston, K., et al. (2012). Axonal integrity predicts cortical reorganisation following cervical injury. *Journal of Neurology, Neurosurgery, and Psychiatry*, *83*(6), 629–637. https://doi.org/10.1136/jnnp-2011-301875.

Friston, K. J., Holmes, A. P., Worsley, K. J., Poline, J. B., Frith, C. D., & Frackowiak, R. S. J. (1995). Statistical parametric maps in functional imaging: A general linear approach. *Human Brain Mapping*, *2*, 189–210.

Ganchrow, D., & Bernstein, J. J. (1985). Thoracic dorsal funicular lesions affect the Bouton patterns on, and diameters of, layer VB pyramidal cell somata in rat hindlimb cortex. *Journal of Neuroscience Research*, *14*(1), 71–81. https://doi.org/10.1002/jnr.490140107.

Ghosh, A., Haiss, F., Sydekum, E., Schneider, R., Gullo, M., Wyss, M. T., et al. (2010). Rewiring of hindlimb corticospinal neurons after spinal cord injury. *Nature Neuroscience*, *13*(1), 97–104. https://doi.org/10.1038/nn.2448.

Gustin, S. M., Wrigley, P. J., Siddall, P. J., & Henderson, L. A. (2010). Brain anatomy changes associated with persistent neuropathic pain following spinal cord injury. *Cerebral Cortex*, *20*(6), 1409–1419. https://doi.org/10.1093/cercor/bhp205.

Hains, B. C., Black, J. A., & Waxman, S. G. (2003). Primary cortical motor neurons undergo apoptosis after axotomizing spinal cord injury. *The Journal of Comparative Neurology*, *462*(3), 328–341. https://doi.org/10.1002/cne.10733.

Hawasli, A. H., Rutlin, J., Roland, J. L., Murphy, R., Song, S. K., Leuthardt, E. C., et al. (2018). Spinal cord injury disrupts resting-state networks in the human brain. *Journal of Neurotrauma*, *35*(6), 864–873. https://doi.org/10.1089/neu.2017.5212.

Henderson, L. A., Gustin, S. M., Macey, P. M., Wrigley, P. J., & Siddall, P. J. (2011). Functional reorganization of the brain in humans following spinal cord injury: Evidence for underlying changes in cortical anatomy. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *31*(7), 2630–2637. https://doi.org/10.1523/JNEUROSCI.2717-10.2011.

Hou, J. M., Sun, T. S., Xiang, Z. M., Zhang, J. Z., Zhang, Z. C., Zhao, M., et al. (2014). Alterations of resting-state regional and network-level neural function after acute spinal cord injury. *Neuroscience*, *277*, 446–454. https://doi.org/10.1016/j.neuroscience.2014.07.045.

Jacobs, K. M., & Donoghue, J. P. (1991). Reshaping the cortical motor map by unmasking latent intracortical connections. *Science (New York, N.Y.)*, *251* (4996), 944–947. https://doi.org/10.1126/science.2000496.

Jurkiewicz, M. T., Crawley, A. P., Verrier, M. C., Fehlings, M. G., & Mikulis, D. J. (2006). Somatosensory cortical atrophy after spinal cord injury: A voxel-based morphometry study. *Neurology*, *66*(5), 762–764. https://doi.org/10.1212/01.wnl.0000201276.28141.40.

Kaas, J. H., Qi, H. X., Burish, M. J., Gharbawie, O. A., Onifer, S. M., & Massey, J. M. (2008). Cortical and subcortical plasticity in the brains of humans, primates, and rats after damage to sensory afferents in the dorsal columns of the spinal cord. *Experimental Neurology*, *209*(2), 407–416. https://doi.org/10.1016/j.expneurol.2007.06.014.

Karunakaran, K. D., Yuan, R., He, J., Zhao, J., Cui, J. L., Zang, Y. F., et al. (2020). Resting-state functional connectivity of the thalamus in complete spinal cord injury. *Neurorehabilitation and Neural Repair*, *34*(2), 122–133.

Kaushal, M., Oni-Orisan, A., Chen, G., Li, W., Leschke, J., Ward, B. D., et al. (2017). Evaluation of whole-brain resting-state functional connectivity in spinal cord injury: A large-scale network analysis using network-based statistic. *Journal of Neurotrauma*, *34*, 1278–1282.

Kokotilo, K. J., Eng, J. J., & Curt, A. (2009). Reorganization and preservation of motor control of the brain in spinal cord injury: A systematic review. *Journal of Neurotrauma*, *26*(11), 2113–2126. https://doi.org/10.1089/neu.2008.0688.

Lacourse, M. G., Cohen, M. J., Lawrence, K. E., & Romero, D. H. (1999). Cortical potentials during imagined movements in individuals with chronic spinal cord injuries. *Behavioural Brain Research*, *104*(1–2), 73–88. https://doi.org/10.1016/s0166-4328(99)00052-2.

Lenz, F. A., Tasker, R. R., Dostrovsky, J. O., Kwan, H. C., Gorecki, J., Hirayama, T., et al. (1987). Abnormal single-unit activity recorded in the somatosensory thalamus of a quadriplegic patient with central pain. *Pain*, *31*(2), 225–236. https://doi.org/10.1016/0304-3959(87)90038-8.

Logothetis, N. K. (2008). What we can do and what we cannot do with fMRI. *Nature*, *453*(7197), 869–878. https://doi.org/10.1038/nature06976.

Lotze, M., Laubis-Herrmann, U., & Topka, H. (2006). Combination of TMS and fMRI reveals a specific pattern of reorganization in M1 in patients after complete spinal cord injury. *Restorative Neurology and Neuroscience*, *24*(2), 97–107.

Lotze, M., Laubis-Herrmann, U., Topka, H., Erb, M., & Grodd, W. (1999). Reorganization in the primary motor cortex after spinal cord injury—A functional magnetic resonance (fMRI) study. *Restorative Neurology and Neuroscience*, *14*(2–3), 183–187.

Lundell, H., Barthelemy, D., Skimminge, A., Dyrby, T. B., Biering-Sørensen, F., & Nielsen, J. B. (2011). Independent spinal cord atrophy measures correlate to motor and sensory deficits in individuals with spinal cord injury. *Spinal Cord*, *49*(1), 70–75. https://doi.org/10.1038/sc.2010.87.

Mechelli, A., Price, C., Friston, K., & Ashburner, J. (2005). Voxel-based morphometry of the human brain: Methods and applications. *Current Medical Imaging Reviews*, *1*.

Merzenich, M. M., Kaas, J. H., Wall, J., Nelson, R. J., Sur, M., & Felleman, D. (1983). Topographic reorganization of somatosensory cortical areas 3b and 1 in adult monkeys following restricted deafferentation. *Neuroscience*, *8*(1), 33–55. https://doi.org/10.1016/0306-4522(83)90024-6.

Mikulis, D. J., Jurkiewicz, M. T., McIlroy, W. E., Staines, W. R., Rickards, L., Kalsi-Ryan, S., et al. (2002). Adaptation in the motor cortex following cervical spinal cord injury. *Neurology*, *58*(5), 794–801. https://doi.org/10.1212/wnl.58.5.794.

Mirvis, S. E., & Geisler, F. H. (1990). Intraoperative sonography of cervical spinal cord injury: Results in 30 patients. *American Journal of Neuroradiology*, *11*(4), 755–761.

Oni-Orisan, A., Kaushal, M., Li, W., Leschke, J., Ward, B. D., Vedantam, A., et al. (2016). Alterations in cortical sensorimotor connectivity following complete cervical spinal cord injury: A prospective resting-state fMRI study. *PLoS One*, *11*(3). https://doi.org/10.1371/journal.pone.0150351, e0150351.

Pierpaoli, C., Jezzard, P., Basser, P. J., Barnett, A., & Di Chiro, G. (1996). Diffusion tensor MR imaging of the human brain. *Radiology*, *201*(3), 637–648. https://doi.org/10.1148/radiology.201.3.8939209.

Puri, B. K., Smith, H. C., Cox, I. J., Sargentoni, J., Savic, G., Maskill, D. W., et al. (1998). The human motor cortex after incomplete spinal cord injury: An investigation using proton magnetic resonance spectroscopy. *Journal of Neurology, Neurosurgery, and Psychiatry*, *65*(5), 748–754. https://doi.org/10.1136/jnnp.65.5.748.

Rigon, A., Duff, M. C., McAuley, E., Kramer, A. F., & Voss, M. W. (2016). Is traumatic brain injury associated with reduced inter-hemispheric functional connectivity? A study of large-scale resting state networks following traumatic brain injury. *Journal of Neurotrauma*, *33*(11), 977–989. https://doi.org/10.1089/neu.2014.3847.

Tetzlaff, W., Kobayashi, N. R., Giehl, K. M., Tsui, B. J., Cassar, S. L., & Bedard, A. M. (1994). Response of rubrospinal and corticospinal neurons to injury and neurotrophins. *Progress in Brain Research*, *103*, 271–286. https://doi.org/10.1016/s0079-6123(08)61142-5.

Wrigley, P. J., Gustin, S. M., Macey, P. M., Nash, P. G., Gandevia, S. C., Macefield, V. G., et al. (2009). Anatomical changes in human motor cortex and motor pathways following complete thoracic spinal cord injury. *Cerebral Cortex*, *19*(1), 224–232. https://doi.org/10.1093/cercor/bhn072.

Wrigley, P. J., Press, S. R., Gustin, S. M., Macefield, V. G., Gandevia, S. C., Cousins, M. J., et al. (2009). Neuropathic pain and primary somatosensory cortex reorganization following spinal cord injury. *Pain*, *141*(1–2), 52–59. https://doi.org/10.1016/j.pain.2008.10.007.

Zhang, J., Jones, M., DeBoy, C. A., Reich, D. S., Farrell, J. A., Hoffman, P. N., et al. (2009). Diffusion tensor magnetic resonance imaging of Wallerian degeneration in rat spinal cord after dorsal root axotomy. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *29*(10), 3160–3171. https://doi.org/10.1523/JNEUROSCI.3941-08.2009.

Chapter 28

Cardiometabolic changes and upper exercise as an augmentative strategy in spinal cord injury

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List of abbreviations

AB	able-bodied
ACE	arm crank ergometry
ACSM	American College of Sports Medicine
AIS	American Spinal Injury Association Impairment Scale
ANS	autonomic nervous system
BMR	basal metabolic rate
CMS	cardiometabolic syndrome
CRP	C-reactive protein
CVD	cardiovascular disease
FES	functional electrical stimulation
FFM	fat-free mass
FM	fat mass
GH	human growth hormone
HDL	high density
HOMA-IR	homeostatic model for assessing insulin resistance
IGF	insulin like growth factor
IMF	intramuscular fat
LDL	low-density lipoprotein
LOI	level of injury
OGTT	oral glucose tolerance testing
ROS	reactive oxygen species
SCI	spinal cord injury
VLDL	very low density lipoprotein
WHO	World Health Organization

Introduction

Spinal cord injury (SCI) is traditionally thought about in terms of obvious outward characteristics including paralysis, functional deficits, and loss of sensation. These deficits can grossly be categorized as somatic nervous system dysfunction. In addition to the aforementioned impairment and disabilities, individuals with SCI have less outwardly recognizable autonomic nervous system (ANS) dysfunction related to their injury (Krassioukov et al., 2012). ANS dysfunction leads to a myriad of initially sub-clinical states including neurogenic obesity (Farkas & Gater, 2018b) and neurogenic inflammation (Bloom, Herman, & Spungen, 2020) in addition to the more typically discussed neurogenic bowl, neurogenic bladder, and autonomic dysreflexia. To further complicate ANS dysfunction, level of injury (LOI) and completeness of injury (ISNSCI impairment scale) are correlated to the severity of ANS dysfunction (Bauman, Adkins, Spungen, & Waters, 1999; Bauman & Spungen, 1994; Schilero et al., 2014; Schmid et al., 2000).

Cellular, Molecular, Physiological, and Behavioral Aspects of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822427-4.00028-9

Changes in neuropeptides after SCI lead to cardiovascular alterations including hypotension, decreased cardiac output, and decreased resting heart rate (Krassioukov & Claydon, 1990) as well as metabolic derangements including increased LDL, increased triglycerides, and decreased HDL (Gorgey et al., 2014). The broncho-pulmonary system is also significantly impacted by autonomic dysfunction resulting in obstructive lung disease caused by parasympathetic-induced bronchoconstriction and airway inflammation (Schilero et al., 2014; Schilero, Grimm, Bauman, Lenner, & Lesser, 2005) in addition to restrictive lung disease caused by chest wall paralysis (Schilero et al., 2014; Stone & Keltz, 1963).

Cardiovascular disease (CVD) is now the primary cause of death for individuals with SCI greater than 1 year after the initial injury (Bauman & Spungen, 2008; Garshick et al., 2005; Myers, Lee, & Kiratli, 2007). The combination of neurogenic obesity, neurogenic inflammation, cardiovascular alterations, broncho-pulmonary dysfunction, paralysis, barriers to exercise, and poor exercise tolerance due to sympathetic blunting ultimately promote a sedentary lifestyle that pleiotropically promotes cardiometabolic syndrome and increases morbidity and mortality (Farkas & Gater, 2018b; Gater & Farkas, 2017; Gorgey et al., 2014; Gorgey, Dolbow, Dolbow, Khalil, & Gater, 2015; Gorgey, Mather, Poarch, & Gater, 2011).

There is excellent evidence that exercise and increasing daily physical activity is effective in warding off comorbidities in the able-bodied (AB) population (Booth, Roberts, & Laye, 2012). There are also well-defined guidelines for exercise in the AB population (Piercy et al., 2018). Nearly three in four individuals with SCI are interested in being involved in an exercise program (Scelza, Kalpakjian, Zemper, & Tate, 2005) yet only one in four individuals participate in moderate physical activity on a regular basis (Mat Rosly et al., 2018). Unfortunately, individuals with SCI face unique barriers to exercise including functional, physiological, economic, and architectural considerations (Gorgey, 2014; Scelza et al., 2005). Recently, a multinational committee assessed SCI and physical activity with the goal of creating an exercise recommendation and ultimately disseminated a document to all major SCI and exercise organizations suggesting 30 min of moderate to vigorous activity 3 days per week (Martin Ginis, Jetha, MacK, & Hetz, 2010).

Application to other areas of neuroscience

The utility of exercise does not stop at reversing the detrimental effects cardiometabolic changes can have on the SCI patient. Exercise has a profound impact on neuroplasticity, the brain's ability to reprogram and create new neural connections in response to injury and disease. Specifically, in relation to SCI, neuroplasticity allows lost or impaired motor/sensory functions to be restored, via mechanisms of axonal sprouting and neural circuit reconstruction (Liu, Yang, Jiang, Wang, & Yang, 2012). Similarly, exercise in the post-stroke population has demonstrated positive results in promoting neuroplasticity for motor recovery (Mang, Campbell, Ross, & Boyd, 2013). Furthermore, activity and exercise have been linked in decreasing fatigue and depression in the SCI population. A meta-analysis examining physical activity and SCI patient self-report of well-being revealed a statistically significant positive relationship between physical activity and reported well-being (Martin Ginis et al., 2010). Exercise and physical activity has also been studied in regards to pain; in a study of SCI patients undergoing a 9-month exercise program, there was a reduction in pain and reported improvement in quality of life (Hicks et al., 2003). Exercise has also been linked to halting the development of neuropathic pain (Detloff, Smith, Quiros Molina, Ganzer, & Houlé, 2014), a common etiology of pain for the SCI population.

Main narrative text

Role of inflammation

The vast role of inflammation, local and systemic, acute and chronic has been widely explored within the general population. At its most fundamental level, inflammation is the biological response of our immune system to foreign materials, tissue damage, or toxic exposures (Chen et al., 2018). This response usually matches the degree of injury and result in healthy repair. Alternatively, this response may be disproportionate to the original injury, either in duration or intensity, at which point the inflammatory process can become harmful to the body. Chronically elevated levels of inflammation are associated with many comorbid conditions including metabolic syndrome and cardiovascular disease (Tracey, 2007). Inflammatory markers have been investigated more in recent years to better understand the mechanisms by which inflammation drives some of the physiologic and pathologic changes in patients following SCI.

The cytokine theory of disease established a direct connection between the immune system and the aforementioned inflammatory cascades (Tracey, 2007). Cytokines are small proteins locally produced at the site of tissue damage by immune cells (macrophages, T cells, B cells, natural killer cells). Interleukins (IL), tumor necrosis factors (TNF),

colony-stimulating factors (CSF), and chemokines are all examples of inflammatory cytokines (Tracey, 2007). In addition, adipokines, a subset of cytokines, are pro-inflammatory mediators secreted by adipocytes (fat cells) (Farkas & Gater, 2018a). Adipokines provide a connection between body fat and inflammation.

Within minutes of a traumatic SCI, pro-inflammatory cytokines at the site of the injury promote activation of peripheral leukocytes and lymphocytes and migration (Burnside & Bradbury, 2014). Inflammation around the cord itself increases the permeability of the blood-spinal cord barrier for up to 8 weeks, allowing for toxins and larger molecules to pass (Schwab, Zhang, Kopp, Brommer, & Popovich, 2014). This places patients at high risk for infection and further damage to the cord.

Astrocytes are glial cells of the brain and spinal cord that support the endothelial cells of the blood-brain barrier. They also play a key role in the acute phase of SCI. Astrocytes release reactive oxygen species (ROS) and increase fibrin deposition and scarring at the site of the injury (Burnside & Bradbury, 2014). This limits axonal regeneration and neural plasticity, further worsening the secondary damage following SCI (Burnside & Bradbury, 2014).

Intraspinal macrophage concentration begins to rise within 1 h of SCI, peaks approximately 5–10 days after injury, and may stay elevated for several months (Fleming et al., 2006). Similarly, intraspinal concentrations of neutrophils rise within hours, and CD4 and CD8 T cells are elevated within weeks of injury (Fleming et al., 2006). This increase in immune cells is mirrored by an increase in inflammatory biomarkers (Kwon et al., 2010). Specifically, concentrations of IL-6, IL-8, IL-16, MCP-1, and IP-10 showed a proportionate increase to the severity of the injury (degree of completeness) and thus have the greatest elevation in American Spinal Injury Association Scale (AIS) A patients (Kwon et al., 2010).

This inflammatory response is the target of many therapeutic interventions in the acute phase following SCI. One of the most widely utilized and polarizing treatments for neural protection is glucocorticoids (Genovese et al., 2009). This has been extensively studied and large sample size has been unable to match the functional benefit to the theoretical, though it remains in favor with many surgeons (Wing, 2008).

In addition to the acute changes at the level of the injury, many chronic inflammatory changes are of particular concern in individuals with SCI as systemic inflammation directly impairs functional recovery (Arnold & Hagg, 2011). Systemic inflammation inversely correlates with mobility status, so higher levels of injury are associated with greater levels of inflammation (Schwab et al., 2014). This is in part because physical activity is a natural anti-inflammatory and individuals with lower levels of injury can be more active. In addition, individuals with a higher level of injury can activate fewer large muscle groups. Large muscle use promotes breakdown during activity and repair following. This energy expenditure reduces the amount of adipose tissue deposition, which is a potent producer of inflammatory mediators (Farkas & Gater, 2018a).

Individuals with SCI have increased adipose deposition compared to the able-bodied individuals with similar activity levels (Farkas & Gater, 2018a). This increases the systemic plasma concentration of adipokines which directly contributes to the rapid progression of metabolic disease and obesity (Farkas, Gorgey, Dolbow, Berg, & Gater, 2018). The level of injury does not change the distribution of new adipose tissue deposition but does impact the overall level of adipokines such that higher levels result in greater pro-inflammatory adipokine levels (Farkas et al., 2018). Following SCI, patients gain an average of 10 kg in the first 2 years following injury (Farkas & Gater, 2018a). In addition, 40%–60% of SCI patients will develop obesity (Shojaei, Alavinia, & Craven, 2017).

Catecholamines also play a key role in the modulation of the inflammatory process and help maintain homeostasis. Catecholamines (dopamine, epinephrine, and norepinephrine) are hormones produced and secreted by the adrenal medulla, which is innervated by T5–9 (Garstang & Miller-Smith, 2007). Injury at or above the T6 level results in decreased circulating plasma concentrations of catecholamines and IL-6 in response to strenuous activity suggesting that sympathetic tone plays a key role in the cytokine inflammatory response to exercise (Paulson, Goosey-Tolfrey, Lenton, Leicht, & Bishop, 2013), which is unfortunately blunted in patients with SCI at or above the T6 level (Bernstein, Damron, Schonberg, & Shapiro, 2009). Higher injuries cause a greater reduction in catecholamine production and sympathetic tone, which directly blunts the anti-inflammatory response (Paulson et al., 2013; Steinberg et al., 2000). In chronic stages, this may contribute to chronically elevated levels of inflammation.

Cardiometabolic changes

Cardiovascular disease

Individuals with spinal cord injuries are at uniquely high risk for the development of cardiovascular disease given the increased prevalence of risk factors and cardiometabolic changes following SCI including greater incidence of obesity, lipid disorders, cardiometabolic syndrome, and diabetes as compared to the AB population. These changes are due to the inflammatory response previously discussed, decrease energy expenditure due to paralysis, and hormonal changes after

SCI (Myers et al., 2007). A decrease in physical activity coupled with decreased anabolic hormone production leads to changes in body composition of muscles predisposing individuals with SCI to pre-mature aging and cardiovascular disease (CVD) (Gorgey et al., 2014). A study of 545 SCI subjects found that the risk of developing CVD was related to the level and extent of injury, finding a 44% increased rate of CVD in those with complete injuries (Groah, Weitzenkamp, Sett, Soni, & Savic, 2001).

Body composition

Following SCI, several structural changes to muscle tissue have been observed, including skeletal muscle atrophy, decreased lean mass, increase in intramuscular fat (IMF), and decrease in fat-free muscle (FFM) (Gorgey et al., 2014). In the first 6 months following SCI, cross-sectional area (CSA) of paralyzed muscles decreased 45%–80% compared to age and weight-matched AB controls (Castro, Apple Jr, Hillegass, & Dudley, 1999). Spungen et al. (2003) examined body composition in chronic SCI and found a significantly lower total body and regional lean mass and also higher fat mass, especially with advancing age Furthermore, in a study of six incomplete SCI patients matched with six controls, there was a threefold higher rate of IMF in the SCI group as well as a notable 26% increase in IMF after 3 months from the initial measurement in the SCI group (Gorgey & Dudley, 2007). A decrease in FFM in combination with decreased sympathetic output results in SCI individuals having a loss of metabolically active muscle mass and reduced basal metabolic rate (BMR) by as much as 14%–27% compared to AB controls (Buchholz & Pencharz, 2004).

Following SCI there are decreased levels of testosterone, human growth hormone (GH), and insulin growth factors (IGF) all of which lead to decreased cellular repair capacity and promote the loss of lean muscle mass and strength (Gorgey et al., 2014). In addition, a study found that individuals 45 years old or younger with SCI had significantly lower mean plasma IGF-I levels when compared to controls (Bauman et al., 1994). Individuals with SCI have decreased total and free testosterone and these values further decline with increasing duration of injury (Tsitouras, Zhong, Spungen, & Bauman, 1995). Consequently, with decreased anabolic hormones there is a resulting increased body FM and decreased FFM that also contributes to an increase in CVD risk for the SCI population (Gorgey et al., 2014). A summary of body composition changes can be found in Table 1.

Lipid disorders

The SCI population is predisposed to dyslipidemia (Schmid et al., 2000). A group of 100 tetraplegic and paraplegic SCI veterans were found to have 16% higher rates of diabetes, carbohydrate disorders at a younger age, decreased high-density lipoprotein (HDL) cholesterol levels, a direct correlation between peak plasma insulin and serum triglyceride (TG), and an inverse correlation between serum TG and HDL cholesterol (Bauman & Spungen, 1994). Lipid derangements post-SCI appear to be level dependent with tetraplegic individuals having worse dyslipidemia (Schmid et al., 2000), further contributing to this populations' increased risk of CVD (Myers et al., 2007).

Cardiometabolic syndrome

Those with SCI are also at high risk for the development of cardiometabolic syndrome (CMS). CMS occurs at a rate of 22.9% in the general US population whereas this increases to a rate of 50% in those with SCI (Beltrán-Sánchez, Harhay, Harhay, & McElligott, 2013; Dyson-Hudson & Nash, 2009). CMS is defined as having three or more of the following: abdominal (central) obesity, hypertension, insulin resistance, and dyslipidemia, all of which are at increased prevalence after SCI (Myers et al., 2007). The prevalence of obesity in the SCI population ranges from 40% to 66% across studies (Shojaei et al., 2017). The SCI population has a high occurrence of sarcopenic obesity (decrease muscle mass in combination with increased fat mass) as well as insulin resistance, further contributing to CMS (Pelletier, Miyatani, Giangregorio, & Craven, 2016). Insulin resistance is

TABLE 1 Body composition changes after SCI.

Increase	Decrease
Intramuscular fat	Fat-free muscle
Total body fat mass	Skeletal muscle
Percent fat per unit body mass index	Bone mass

Summary of changes after SCI as they relate to body composition.

TABLE 2 Hormonal and metabolic changes after SCI.

Increase	Decrease
Serum triglyceride	Total and free testosterone
Very low-density lipoprotein	Human growth hormone
Low-density lipoprotein	Insulin growth factors
Total cholesterol	High-density lipoprotein
Insulin resistance	Bone density

Summary of hormonal and metabolic changes after SCI.

significantly increased after SCI (Bauman et al., 1999; Gorgey et al., 2014) and can be further broken down into hepatic and peripheral insulin sensitivity. Hepatic insulin sensitivity is most commonly measured by fasting insulin concentration and the homeostatic model for assessing insulin resistance (HOMA-IR) while peripheral insulin sensitivity is most commonly measured by assessing insulin and glucose levels to create an "area under the curve" and oral glucose tolerance testing (OGTT) (Wallace, Levy, & Matthews, 2004). A summary of hormonal and metabolic changes can be found in Table 2.

Peripheral vascular regulation

After SCI there is known dysregulation of the autonomic nervous system, stemming from the loss of supraspinal control over the descending sympathetic pathways, leading to the decreased sympathetic output below the level of injury in conjunction with unopposed vagal parasympathetic outflow (Grigorean et al., 2009). The impaired sympathetic response results in low heart rate, low blood pressure, orthostatic hypotension, lack of adaptability, and loss of diurnal fluctuation of blood pressure (Grigorean et al., 2009). Due to the reduced sympathetic response, during exercise those with SCI lack the ability to maintain cardiac output have reduced heart rate variability, and decreased cardiac contractility further contributing to exercise intolerance and deconditioning (Myers et al., 2007; Teasell, Arnold, Krassioukov, & Delaney, 2000).

Role of exercise as a mitigating treatment

The World Health Organization (WHO) recommends at least 150 min per week of moderate-intensity aerobic activity or 75 min per week of vigorous-intensity aerobic activity), plus muscle-strengthening activities twice per week to reduced morbidity and mortality for the general population across a range of medical conditions (WHO, 2010). Physical activity has been shown to improve physical fitness and cardiometabolic health outcomes in people with chronic SCI (Hicks et al., 2011; Myers et al., 2007). Unfortunately, the WHO guidelines were not developed with specific attention to people with SCI, including exercise capacity and feasibility, upper-body over-use injuries (Requejo et al., 2008), skin breakdown (Groah, Schladen, Pineda, & Hsieh, 2015), autonomic dysreflexia (Eldahan & Rabchevsky, 2018), over-heating (Griggs, Price, & Goosey-Tolfrey, 2014), and bone mineral density (Dolbow et al., 2011).

A number of organizations, including the American College of Sports Medicine (ACSM) and SCI Action Canada, have provided recommendations for cardiorespiratory training in SCI (Evans et al., 2015; Ginis et al., 2011). There are differences in the prescribed exercise frequency, intensity, and duration, and resultant cardiometabolic health outcomes but there are clear areas of agreement: (1) aerobic exercise is necessary to maintain or improve cardiorespiratory fitness, (2) moderate to vigorous-intensity exercise is required to induce the metabolic demand necessary for a positive training effect, (3) the duration of aerobic exercise should be a minimum of 20–30 min per session at a frequency of at least 2–3 times per week. A wide variety of exercise intervention strategies have been applied to people with SCI. These interventions include arm-based exercises such as arm crank ergometry (ACE), functional electrical stimulation (FES)-augmented training (Figs. 1 and 2), and robotic-assisted activity training.

Arm-based exercise where the patient initiates and carries through movement has included ACE (Figs. 3 and 4), upper extremity resistance training, wheelchair propulsion, swimming, and circuit resistance training, among others (Nash, Jacobs, Mendez, & Goldberg, 2001; Verellen, Vanlandewijck, Andrews, & Wheeler, 2007). It is more difficult for people with higher-level SCI to participate in volitional exercise owing to functional capacity and increased requirements of staff and equipment. Still, a recent study found that 10 weeks of 30 min per day, 3 days per week ACE at 70% VO_{2Peak} in high

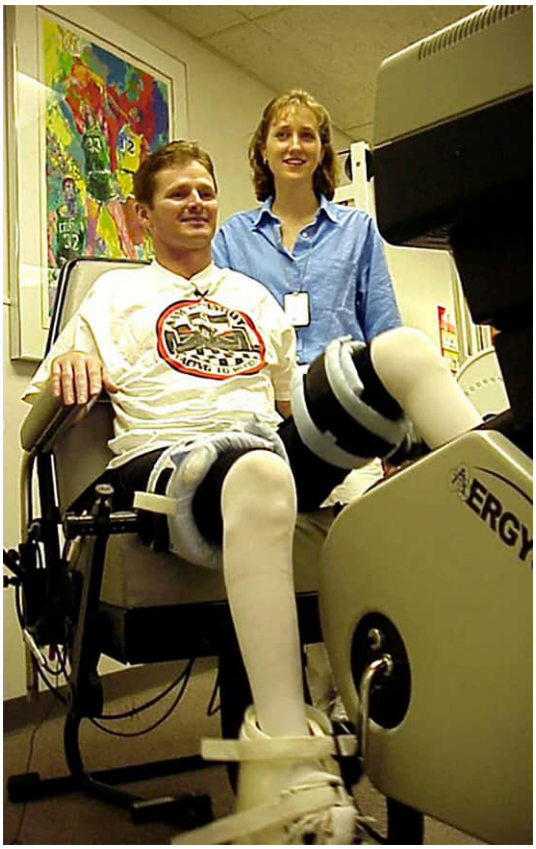

FIG. 1 FES cycling machine. *Permission to use granted from John W. McDonald, MD PhD, International Center for Spinal Cord Injury, Kennedy Krieger Institute. This is an example of an FES cycling machine set up with a patient using it.*

FIG. 2 FES cycling machine. Another example of an FES cycling machine without a patient.

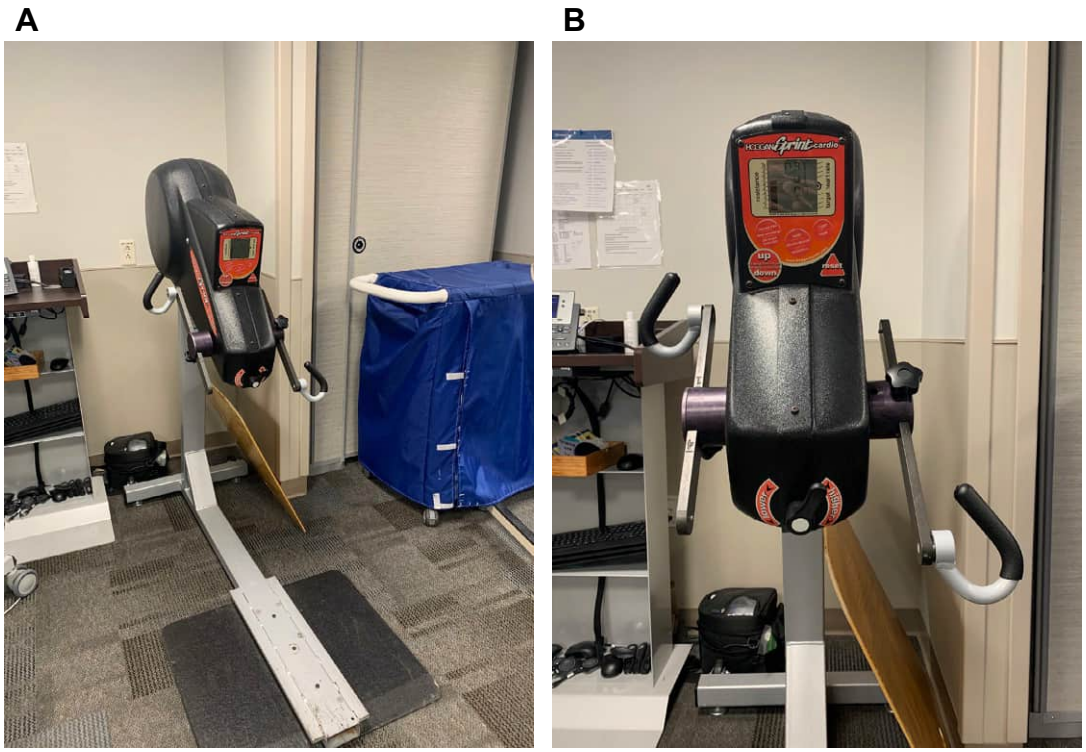

FIG. 3 ACE cycling machine, compact. ACE cycling machine at an appropriate height for wheelchair use.

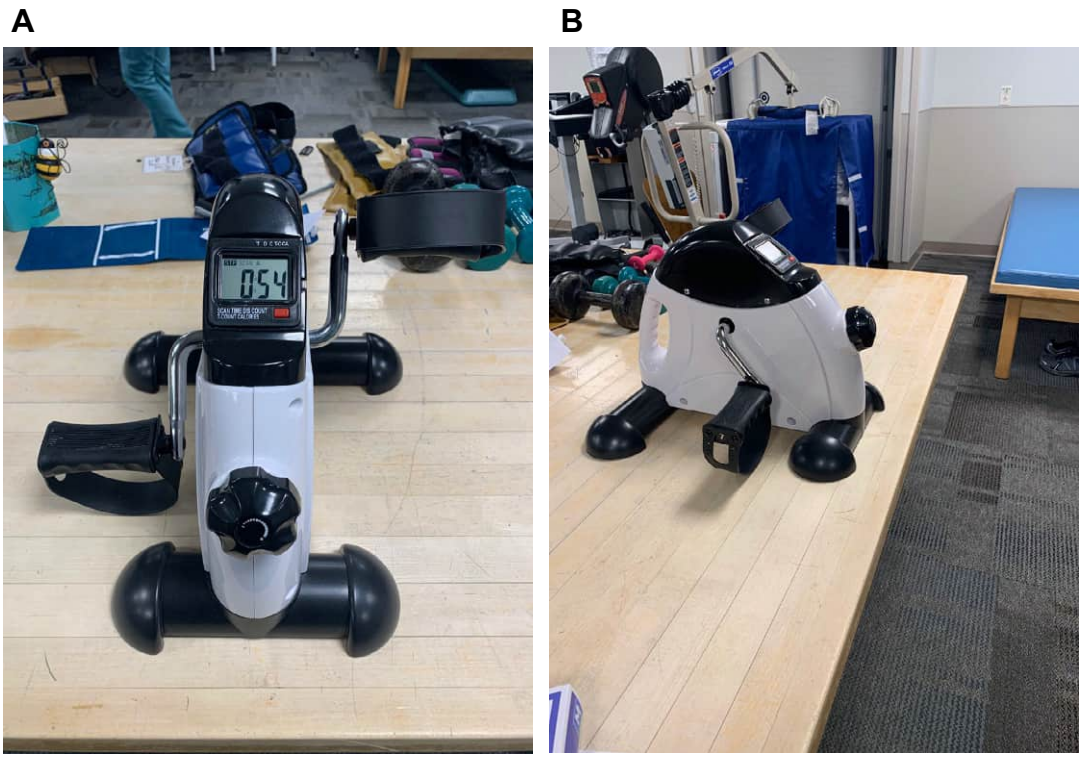

FIG. 4 ACE cycling machine. ACE cycling machine at table height that is portable.

motor complete SCI improves aerobic capacity, community mobility, and metabolic profiles independent of changes in body composition (Bresnahan, Farkas, Clasey, Yates, & Gater, 2019). A recent metaanalysis of 65 studies evaluating upper extremity aerobic exercise training at >75% maximum heart rate or equivalent VO_{2peak} found upper extremity training to be sufficient for improving endurance, waist circumference, and hepatic insulin sensitivity but insufficient for improving fasting glucose, lipid profiles, or resting blood pressure (Farrow et al., 2020). Upper extremity aerobic activity has been shown to improve hepatic insulin resistance but not peripheral insulin resistance (Bresnahan et al., 2019). Glucose intolerance after SCI is at least 70% due to the accumulation of IMF (Elder, Apple, Bickel, Meyer, & Dudley, 2004) and it is well established that upper extremity training alone also does not change body composition (Bresnahan et al., 2019; Farrow et al., 2020; Gorgey et al., 2014). The addition of FES to the lower extremities is beneficial for decreasing IMF (Gorgey, Mather, Cupp, & Gater, 2012) and there is an active trial ongoing to evaluate the potential benefit on insulin resistance as a function of changes in body composition (Gorgey et al., 2019).

Mini-dictionary of terms

Cardiovascular disease: A systemic group of disorders affecting the heart and blood vessels including coronary artery disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis, and pulmonary embolism. Cardiovascular disease is the primary cause of death after 1-year post-injury in paraplegic individuals and probably the most common cause of death in tetraplegic individuals greater than 1-year post-injury.

Metabolic syndrome or cardiometabolic syndrome (CMS): A cluster of conditions that together increase the risk of heart attack and stroke. Metabolic syndrome is defined as having at least three of the following five metabolic risk factors: waistline of 35 in. or more for women or 40 or more inches for men, triglyceride level of 150 mg/dL or higher, HDL level of less than 50 mg/dL for women or less than 40 mg/dL for men, blood pressure of 130/85 or higher, and/or a fasting blood sugar of 100 mg/dL or higher.

Functional electrical stimulation (FES): The use of small electrical pulses applied over muscle groups in meaningful synchrony to cause muscle contractions and ultimately cause joints to move in a functionally meaningful manner for the sake of exercising paralyzed muscles and increasing aerobic capacity. FES can be coupled with cycling machines (Figs. 1 and 2) or rowing machines.

Arm-Crank ergometry (ACE): An arm crank or also known as arm cycle device that can be used as a reliable mode of upper extremity exercise to assess physiologic changes (Figs. 3 and 4).

VO_{2max}: The maximum rate of oxygen consumption during exercise, which can provide a quantitative surrogate for car diovascular endurance fitness. Measured in L/min.

Body mass index (BMI): Body mass divided by the square of the body height, expressed in kg/m^2. BMI is a standardized method for evaluating obesity.

Fat mass (FM): Total body mass composed of just fat.

Fat-free mass (FFM): Total body mass composed of internal organs, bone, muscle, water, and connective tissue.

Intramuscular fat (IMF): Fat stored inside muscle fibers in lipid droplets. Excess accumulation of IMF is associated with poor physical fitness, insulin resistance, and type 2 diabetes.

Basal metabolic rate (BMR) or resting energy expenditure (REE): Number of calories used by the body at rest throughout the day.

Total energy expenditure (TEE): Total number of calories used by the body throughout the day due to physical activity in addition to resting energy expenditure.

Key facts: Cardiometabolic changes and exercise in SCI

- Cardiometabolic syndrome occurs in more than 50% of those with SCI.
- Dyslipidemia occurs in a level-dependent fashion in individual with SCI with higher level lesions causing a more dyslipidemic state.
- After SCI there is a cascade of changes in body composition including a decrease in fat-free mass, significant skeletal muscle atrophy, increase in intramuscular fat accumulations and up to 25% decrease in basal metabolic rate.
- There is a level-dependent increase in adipokines and inflammatory markers (CRP, TNF-a, TLRs, IL-6, IL-10, and others) after SCI that contributes to a neurogenic pro-inflammatory state that likely influences the aforementioned cardiometabolic changes.

- Exercise, especially aerobic exercise activating lower extremity paralyzed muscle groups, can help reverse changes in body composition, improve aerobic fitness, improve cardiometabolic profiles, decrease neurogenic inflammation, and improve community mobility.
- Upper extremity exercise alone may not result in robust changes in body composition but can still improve fitness, alter cardiometabolic profiles, and improve community mobility.

Summary points

- Cardiometabolic syndrome is the number one long-term risk factor for death after SCI
- There are four distinct phases of neuroinflammatory response after SCI.
  1. Mechanical trauma leading to disruption of spinal vasculature and the blood-spinal cord barrier.
  2. Secondary injury increases inflammation, promotes cellular apoptosis.
  3. Glial scar formation by activated astrocytes.
  4. Spinal cord remodeling and structural tissue reorganization.
- Individuals with SCI are much less active than their able-bodied peers.
- Individuals with SCI express interest in using exercise as an augmentative strategy to combat cardiometabolic changes but have many physical barriers to accessible exercise programs.
- Exercise after SCI can help reverse changes in body composition, improve cardiometabolic profiles, decrease neurogenic inflammation, and improve community mobility.

References

Arnold, S. A., & Hagg, T. (2011). Anti-inflammatory treatments during the chronic phase of spinal cord injury improve locomotor function in adult mice. *Journal of Neurotrauma*, *28*(9), 1995–2002. https://doi.org/10.1089/neu.2011.1888.

Bauman, W. A., Adkins, R. H., Spungen, A. M., & Waters, R. L. (1999). The effect of residual neurological deficit on oral glucose tolerance in persons with chronic spinal cord injury. *Spinal Cord*, *37*(11), 765–771. https://doi.org/10.1038/sj.sc.3100893.

Bauman, W. A., & Spungen, A. M. (1994). Disorders of carbohydrate and lipid metabolism in veterans with paraplegia or quadriplegia: A model of premature aging. *Metabolism*, *43*(6), 749–756. https://doi.org/10.1016/0026-0495(94)90126-0.

Bauman, W. A., & Spungen, A. M. (2008). Coronary heart disease in individuals with spinal cord injury: Assessment of risk factors. *Spinal Cord*, *46*, 466–476. https://doi.org/10.1038/sj.sc.3102161.

Bauman, W., Spungen, A., Flanagan, S., Zhong, Y.-G., Alexander, L., & Tsitouras, P. (1994). Blunted growth hormone response to intravenous arginine in subjects with a spinal cord injury. *Hormone and Metabolic Research*, *26*(03), 152–156. https://doi.org/10.1055/s-2007-1000798.

Beltrán-Sánchez, H., Harhay, M. O., Harhay, M. M., & McElligott, S. (2013). Prevalence and trends of metabolic syndrome in the adult US population, 1999–2010. *Journal of the American College of Cardiology*, *62*(8), 697–703. https://doi.org/10.1016/j.jacc.2013.05.064.

Bernstein, I. M., Damron, D., Schonberg, A. L., & Shapiro, R. (2009). The relationship of plasma volume, sympathetic tone, and proinflammatory cytokines in young healthy nonpregnant women. *Reproductive Sciences*, *16*(10), 980–985. https://doi.org/10.1177/1933719109338876.

Bloom, O., Herman, P. E., & Spungen, A. M. (2020). Systemic inflammation in traumatic spinal cord injury. *Experimental Neurology*, *325*(2020), 1–11. https://doi.org/10.1016/j.expneurol.2019.113143.

Booth, F. W., Roberts, C. K., & Laye, M. J. (2012). Lack of exercise is a major cause of chronic diseases. *Comprehensive Physiology*, *2*(2), 1143–1211. https://doi.org/10.1002/cphy.c110025.

Bresnahan, J. J., Farkas, G. J., Clasey, J. L., Yates, J. W., & Gater, D. R. (2019). Arm crank ergometry improves cardiovascular disease risk factors and community mobility independent of body composition in high motor complete spinal cord injury. *Journal of Spinal Cord Medicine*, *42*(3), 272–280. https://doi.org/10.1080/10790268.2017.1412562.

Buchholz, A., & Pencharz, P. (2004). Energy expenditure in chronic spinal cord injury. *Current Opinion in Clinical Nutrition and Metabolic Care*, *7*(6), 635–639.

Burnside, E. R., & Bradbury, E. J. (2014). Review: Manipulating the extracellular matrix and its role in brain and spinal cord plasticity and repair. *Neuropathology and Applied Neurobiology*, *40*(1), 26–59. https://doi.org/10.1111/nan.12114.

Castro, M. J., Apple, D. F., Jr., Hillegass, E. A., & Dudley, G. A. (1999). Influence of complete spinal cord injury on skeletal muscle cross-sectional area within the first 6 months of injury. *European Journal of Applied Physiology and Occupational Physiology*, *80*(4), 373–378. https://doi.org/10.1007/s004210050606.

Chen, L., Deng, H., Cui, H., Fang, J., Zuo, Z., Deng, J., et al. (2018, January 23). Inflammatory responses and inflammation-associated diseases in organs. *Oncotarget*. https://doi.org/10.18632/oncotarget.23208.

Detloff, M. R., Smith, E. J., Quiros Molina, D., Ganzer, P. D., & Houlé, J. D. (2014). Acute exercise prevents the development of neuropathic pain and the sprouting of non-peptidergic (GDNF- and artemin-responsive) c-fibers after spinal cord injury. *Experimental Neurology*, *255*, 38–48. https://doi.org/10.1016/j.expneurol.2014.02.013.

Dolbow, D. R., Gorgey, A. S., Daniels, J. A., Adler, R. A., Moore, J. R., & Gater, D. R. (2011). The effects of spinal cord injury and exercise on bone mass: A literature review. *Neuropsychological Rehabilitation*. https://doi.org/10.3233/NRE-2011-0702. article, Netherlands.

Dyson-Hudson, T., & Nash, M. (2009). Guideline-driven assessment of cardiovascular disease and related risks after spinal cord injury. *Topics in Spinal Cord Injury Rehabilitation*, *14*(3), 32–45. https://doi.org/10.1310/sci1403-32.

Eldahan, K. C., & Rabchevsky, A. G. (2018). Autonomic dysreflexia after spinal cord injury: Systemic pathophysiology and methods of management. *Autonomic Neuroscience: Basic & Clinical*. https://doi.org/10.1016/j.autneu.2017.05.002.

Elder, C. P., Apple, D. F., Bickel, C. S., Meyer, R. A., & Dudley, G. A. (2004). Intramuscular fat and glucose tolerance after spinal cord injury—A cross-sectional study. *Spinal Cord*, *42*(12), 711–716. https://doi.org/10.1038/sj.sc.3101652.

Evans, N., Wingo, B., Sasso, E., Hicks, A., Gorgey, A. S., & Harness, E. (2015). Exercise recommendations and considerations for persons with spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *96*(9), 1749–1750. https://doi.org/10.1016/j.apmr.2015.02.005.

Farkas, G. J., & Gater, D. R. (2018a). Neurogenic obesity and systemic inflammation following spinal cord injury: A review. *The Journal of Spinal Cord Medicine*, *41*(4), 378–387. https://doi.org/10.1080/10790268.2017.1357104.

Farkas, G. J., & Gater, D. R. (2018, July 4). Neurogenic obesity and systemic inflammation following spinal cord injury: A review. *Journal of Spinal Cord Medicine*. https://doi.org/10.1080/10790268.2017.1357104. Taylor and Francis Ltd.

Farkas, G. J., Gorgey, A. S., Dolbow, D. R., Berg, A. S., & Gater, D. R. (2018). The influence of level of spinal cord injury on adipose tissue and its relationship to inflammatory adipokines and cardiometabolic profiles. *The Journal of Spinal Cord Medicine*, *41*(4), 407–415. https://doi.org/10.1080/10790268.2017.1357918.

Farrow, M., Nightingale, T. E., Maher, J., Mckay, C. D., Thompson, D., & Bilzon, J. L. J. (2020). Effect of exercise on Cardiometabolic risk factors in adults with chronic spinal cord injury: A systematic review. *Archives of Physical Medicine and Rehabilitation*, *S0003-9993*, 30283–30285. https://doi.org/10.1016/j.apmr.2020.04.020.

Fleming, J. C., Norenberg, M. D., Ramsay, D. A., Dekaban, G. A., Marcillo, A. E., Saenz, A. D., et al. (2006). The cellular inflammatory response in human spinal cords after injury. *Brain*, *129*(12), 3249–3269. https://doi.org/10.1093/brain/awl296.

Garshick, E., Kelley, A., Cohen, S. A., Garrison, A., Tun, C. G., Gagnon, D., et al. (2005). A prospective assessment of mortality in chronic spinal cord injury. *Spinal Cord*, *43*(7), 408–416. https://doi.org/10.1038/sj.sc.3101729.

Garstang, S. V., & Miller-Smith, S. A. (2007). Autonomic nervous system dysfunction after spinal cord injury. *Physical Medicine and Rehabilitation Clinics of North America*, *18*(2), 275–296. https://doi.org/10.1016/j.pmr.2007.02.003.

Gater, D. R., & Farkas, G. J. (2017). Alterations in body composition after SCI and the mitigating role of exercise. In J. A. Taylor, & L. Morse (Eds.), *The physiology of exercise in spinal cord injury* (pp. 175–199). New York, NY: Springer Healthcare LLC.

Genovese, T., Esposito, E., Mazzon, E., Crisafulli, C., Paterniti, I., Di Paola, R., et al. (2009). PPAR-α modulate the anti-inflammatory effect of glucocorticoids in the secondary damage in experimental spinal cord trauma. *Pharmacological Research*, *59*(5), 338–350. https://doi.org/10.1016/j.phrs.2009.01.018.

Ginis, K., Martin, A., Hicks, A. L., Latimer, A. E., Warburton, D. E. R., Bourne, C., et al. (2011). The development of evidence-informed physical activity guidelines for adults with spinal cord injury. *Spinal Cord*. https://doi.org/10.1038/sc.2011.63. article, England.

Gorgey, A. S. (2014). Exercise awareness and barriers after spinal cord injury. *World Journal of Orthopaedics*, *5*(3), 158–162. https://doi.org/10.5312/wjo.v5.i3.158.

Gorgey, A. S., Dolbow, D. R., Dolbow, J. D., Khalil, R. K., Castillo, C., & Gater, D. R. (2014). Effects of spinal cord injury on body composition and metabolic profile—Part I. *The Journal of Spinal Cord Medicine*, *37*(q), 693–702. https://doi.org/10.1179/2045772314Y.0000000245.

Gorgey, A. S., Dolbow, D. R., Dolbow, J. D., Khalil, R. K., & Gater, D. R. (2015). The effects of electrical stimulation on body composition and metabolic profile after spinal cord injury—Part II. *The Journal of Spinal Cord Medicine*, *38*(1), 23–37. https://doi.org/10.1179/2045772314Y.0000000244.

Gorgey, A. S., & Dudley, G. A. (2007). Skeletal muscle atrophy and increased intramuscular fat after incomplete spinal cord injury. *Spinal Cord*, *45*(4), 304–309. https://doi.org/10.1038/sj.sc.3101968.

Gorgey, A. S., Khalil, R. E., Davis, J. C., Carter, W., Gill, R., Rivers, J., et al. (2019). Skeletal muscle hypertrophy and attenuation of cardio-metabolic risk factors (SHARC) using functional electrical stimulation-lower extremity cycling in persons with spinal cord injury: Study protocol for a randomized clinical trial. *Trials*, *20*(1). https://doi.org/10.1186/s13063-019-3560-8.

Gorgey, A. S., Mather, K. J., Cupp, H. R., & Gater, D. R. (2012). Effects of resistance training on adiposity and metabolism after spinal cord injury. *Medicine and Science in Sports and Exercise*, *44*(1), 165–174. https://doi.org/10.1249/MSS.0b013e31822672aa.

Gorgey, A. S., Mather, K. J., Poarch, H. J., & Gater, D. R. (2011). Influence of motor complete spinal cord injury on visceral and subcutaneous adipose tissue measured by multi-axial magnetic resonance imaging. *The Journal of Spinal Cord Medicine*, *34*(1), 99–109. https://doi.org/10.1179/107902610X12911165975106.

Griggs, K. E., Price, M. J., & Goosey-Tolfrey, V. L. (2014). Cooling athletes with a spinal cord injury. *Sports Medicine*. https://doi.org/10.1007/s40279-014-0241-3.

Grigorean, V., Sandu, A., Popescu, M., Lacobini, M., Stoian, R., Neascu, C., et al. (2009). Cardiac dysfunctions following spinal cord injury. *Journal of Medicine and Life*, *2*(2), 133–145.

Groah, S. L., Schladen, M., Pineda, C. G., & Hsieh, C. H. J. (2015). Prevention of pressure ulcers among people with spinal cord injury: A systematic review. *PM & R: The Journal of Injury, Function, and Rehabilitation*, *7*(6), 613–636. https://doi.org/10.1016/j.pmrj.2014.11.014.

Groah, S. L., Weitzenkamp, D., Sett, P., Soni, B., & Savic, G. (2001). The relationship between neurological level of injury and symptomatic cardiovascular disease risk in the aging spinal injured. *Spinal Cord*, *39*. Retrieved from www.nature.com/sc.

Hicks, A. L., Martin, K. A., Ditor, D. S., Latimer, A. E., Craven, C., Bugaresti, J., et al. (2003). Long-term exercise training in persons with spinal cord injury: Effects on strength, arm ergometry performance and psychological well-being. *Spinal Cord*, *41*(1), 34–43. https://doi.org/10.1038/sj.sc.3101389.

Hicks, A. L., Martin Ginis, K. A., Pelletier, C. A., Ditor, D. S., Foulon, B., & Wolfe, D. L. (2011). The effects of exercise training on physical capacity, strength, body composition and functional performance among adults with spinal cord injury: A systematic review. *Spinal Cord*, *49*(11), 1103–1127. https://doi.org/10.1038/sc.2011.62.

Krassioukov, A., Biering-Sørensen, F., Donovan, W., Kennelly, M., Kirshblum, S., Krogh, K., et al. (2012). International standards to document remaining autonomic function after spinal cord injury. *Journal of Spinal Cord Medicine*, *35*(4), 201–210. https://doi.org/10.1179/1079026812Z.00000000053.

Krassioukov, A., & Claydon, V. E. (1990). The clinical problems in cardiovascular control following spinal cord injury: An overview. *Progress in Brain Research*, *152*. https://doi.org/10.1016/S0079-6123(05)52014-4.

Kwon, B. K., Stammers, A. M. T., Belanger, L. M., Bernardo, A., Chan, D., Bishop, C. M., et al. (2010). Cerebrospinal fluid inflammatory cytokines and biomarkers of injury severity in acute human spinal cord injury. *Journal of Neurotrauma*, *27*(4), 669–682. https://doi.org/10.1089/neu.2009.1080.

Liu, J., Yang, X., Jiang, L., Wang, C., & Yang, M. (2012). Neural plasticity after spinal cord injury. *Neural Regeneration Research*, *7*(5), 386–391. https://doi.org/10.3969/j.issn.1673-5374.2012.05.010.

Mang, C. S., Campbell, K. L., Ross, C. J. D., & Boyd, L. A. (2013). Perspective promoting neuroplasticity for motor rehabilitation after stroke: Brain-derived neurotrophic factor. *Physical Therapy*, *93*(12), 1707–1716.

Martin Ginis, K. A., Jetha, A., MacK, D. E., & Hetz, S. (2010). Physical activity and subjective well-being among people with spinal cord injury: A meta-analysis. *Spinal Cord*, *48*(1), 65–72. https://doi.org/10.1038/sc.2009.87.

Mat Rosly, M., Halaki, M., Hasnan, N., Mat Rosly, H., Davis, G. M., & Husain, R. (2018). Leisure time physical activity participation in individuals with spinal cord injury in Malaysia: Barriers to exercise. *Spinal Cord*, *56*(8), 806–818. https://doi.org/10.1038/s41393-018-0068-0.

Myers, J., Lee, M., & Kiratli, J. (2007). Cardiovascular disease in spinal cord injury: An overview of prevalence, risk, evaluation, and management. *American Journal of Physical Medicine & Rehabilitation*, *86*(2), 142–152. https://doi.org/10.1097/PHM.0b013e31802f0247.

Nash, M. S., Jacobs, P. L., Mendez, A. J., & Goldberg, R. B. (2001). Circuit resistance training improves the atherogenic lipid profiles of persons with chronic paraplegia. *Journal of Spinal Cord Medicine*, *24*(1), 2–9. https://doi.org/10.1080/10790268.2001.11753548.

Paulson, T. A., Goosey-Tolfrey, V. L., Lenton, J. P., Leicht, C. A., & Bishop, N. C. (2013). Spinal cord injury level and the circulating cytokine response to strenuous exercise. *Medicine & Science in Sports & Exercise*, *45*(9), 1649–1655. https://doi.org/10.1249/MSS.0b013e31828f9bbb.

Pelletier, C. A., Miyatani, M., Giangregorio, L., & Craven, B. C. (2016). Sarcopenic obesity in adults with spinal cord injury: A cross-sectional study. *Archives of Physical Medicine and Rehabilitation*, *97*(11), 1931–1937. https://doi.org/10.1016/j.apmr.2016.04.026.

Piercy, K. L., Troiano, R. P., Ballard, R. M., Carlson, S. A., Fulton, J. E., Galuska, D. A., et al. (2018). The physical activity guidelines for Americans. *Journal of the American Medical Association*, *320*(19), 2020–2028. https://doi.org/10.1001/jama.2018.14854.

Requejo, P. S., Mulroy, S. J., Haubert, L. L., Newsam, C. J., Gronley, J. A. K., & Perry, J. (2008). Evidence-based strategies to preserve shoulder function in manual wheelchair users with spinal cord injury. *Topics in Spinal Cord Injury Rehabilitation*. https://doi.org/10.1310/sci1304-86.

Scelza, W. M., Kalpakjian, C. Z., Zemper, E. D., & Tate, D. G. (2005). Perceived barriers to exercise in people with spinal cord injury. *American Journal of Physical Medicine and Rehabilitation*, *84*(8), 576–583. https://doi.org/10.1097/01.phm.0000171172.96290.67.

Schilero, G. J., Grimm, D. R., Bauman, W. A., Lenner, R., & Lesser, M. (2005). Assessment of airway caliber and bronchodilator responsiveness in subjects with spinal cord injury. *Chest*, *127*(1), 149–155. https://doi.org/10.1378/chest.127.1.149.

Schilero, G. J., Radulovic, M., Wecht, J. M., Spungen, A. M., Bauman, W. A., & Lesser, M. (2014). A center's experience: Pulmonary function in spinal cord injury. *Lung*, *192*, 339–346. https://doi.org/10.1007/s00408-014-9575-8.

Schmid, A., Halle, M., Stutzle, C., Konig, D., Baumstark, M. W., Storch, M. J., et al. (2000). Lipoproteins and free plasma catecholamines in spinal cord injured men with different injury levels. *Clinical Physiology*, *20*(4), 304–310. https://doi.org/10.1046/j.1365-2281.2000.00263.x.

Schwab, J. M., Zhang, Y., Kopp, M. A., Brommer, B., & Popovich, P. G. (2014). The paradox of chronic neuroinflammation, systemic immune suppression, autoimmunity after traumatic chronic spinal cord injury. *Experimental Neurology*, *258*, 121–129. https://doi.org/10.1016/j.expneurol.2014.04.023.

Shojaei, M. H., Alavinia, S. M., & Craven, B. C. (2017). Management of obesity after spinal cord injury: A systematic review. *The Journal of Spinal Cord Medicine*, *40*(6), 783–794. https://doi.org/10.1080/10790268.2017.1370207.

Spungen, A. M., Adkins, R. H., Stewart, C. A., Wang, J., Pierson, R. N., Waters, R. L., et al. (2003). Factors influencing body composition in persons with spinal cord injury: A cross-sectional study. *Journal of Applied Physiology*, *95*(6), 2398–2407. https://doi.org/10.1152/japplphysiol.00729.2002.

Steinberg, L. L., Lauro, F. A. A., Sposito, M. M. M., Tufik, S., Mello, M. T., Naffah-Mazzacoratti, M. G., et al. (2000). Catecholamine response to exercise in individuals with different levels of paraplegia. *Brazilian Journal of Medical and Biological Research*, *33*(8), 913–918. https://doi.org/10.1590/S0100-879X2000000800007.

Stone, D. J., & Keltz, H. (1963). The effect of respiratory muscle dysfunction on pulmonary function. Studies in patients with spinal cord injuries. *American Review of Respiratory Diseases*, *88*(5), 621–629.

Teasell, R. W., Arnold, J. M. O., Krassioukov, A., & Delaney, G. A. (2000). Cardiovascular consequences of loss of supraspinal control of the sympathetic nervous system after spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *81*(4), 506–516. https://doi.org/10.1053/mr.2000.3848.

Tracey, K. J. (2007). Physiology and immunology of the cholinergic antiinflammatory pathway. *Journal of Clinical Investigation*, *117*(2), 289–296. https://doi.org/10.1172/JCI30555.

Tsitouras, P., Zhong, Y.-G., Spungen, A., & Bauman, W. (1995). Serum testosterone and growth hormone insulin-like growth factor-I in adults with spinal cord injury. *Hormone and Metabolic Research*, *27*(06), 287–292. https://doi.org/10.1055/s-2007-979961.

Verellen, J., Vanlandewijck, Y., Andrews, B., & Wheeler, G. D. (2007). Cardiorespiratory responses during arm ergometry, functional electrical stimulation cycling, and two hybrid exercise conditions in spinal cord injured. *Disability and Rehabilitation. Assistive Technology*, *2*(2), 127–132. Article https://doi.org/10.1080/09638280600765712.

Wallace, T. M., Levy, J. C., & Matthews, D. R. (2004). Use and abuse of HOMA modeling. *Diabetes Care*. https://doi.org/10.2337/diacare.27.6.1487.

WHO. (2010). *Global recommendations on physical activity for health* (p. 60). Geneva: World Health Organization. Retrieved from http://medcontent.metapress.com/index/A65RM03P4874243N.pdf%5Cnhttp://scholar.google.com/scholar?hl=en&btnG=Search&q=intitle:Global+Recomendations+on+physical+activity+for+health#0.

Wing, P. C. (2008). Early acute management in adults with spinal cord injury: A clinical practice guideline for health-care providers. Who should read it? *The Journal of Spinal Cord Medicine*, *31*(4), 360. https://doi.org/10.1080/10790268.2008.11760737.

Chapter 29

Electrophysiological outcome measures in spinal cord injury: A new narrative

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List of abbreviations

ALS	amyotrophic lateral sclerosis
CHEPs	contact heat evoked potentials
CMAP	compound muscle action potential
EP	electrophysiological
EMG	electromyography
GABA	gamma-aminobutyric acid
HD	high density
H-reflex	Hoffman reflex
ITB	intrathecal baclofen
MEPs	motor evoked potentials
MUAP	motor unit action potential
MUNE	motor unit number estimation
MVC	maximum voluntary contraction
NCS	nerve conduction studies
PAD	post-activation depression
rMT	at resting motor thresholds
SCI	spinal cord injury
SP	silent period
SSEPs	somatosensory evoked potentials
SSR	sympathetic skin response
TMS	transcranial magnetic stimulation

Introduction

The assessment of residual sensory, motor, and autonomic function after spinal cord injury (SCI) is frequently measured by electrophysiological (EP) measures in clinical and research settings over the last 2 decades (Hubli et al., 2019; Korupolu, Stampas, Singh, Zhou, & Francisco, 2019). EP measures can detect subtle changes in the nervous system and improve prognostication and assessment of neuro-recovery after spinal cord injury (SCI) (Curt & Dietz, 1999; Curt, Rodic, Schurch, & Dietz, 1997; Hupp et al., 2018; Iseli, Cavigelli, Dietz, & Curt, 1999; Korupolu et al., 2019). EP measures can also evaluate the effects of an intervention on neurophysiology and provide valuable mechanistic data to guide future treatments. Electrophysiological assessments can complement clinical evaluations, such as the International Standards for Neurological Classification of SCI (ISNCSCI), and other standard clinical evaluations after SCI (Curt et al., 1997; Curt & Dietz, 1999; Hupp et al., 2018; Iseli et al., 1999; Korupolu et al., 2019; Xie & Boakye, 2008). The combination of EP measures used in conjunction with standard clinical evaluations can provide qualitative and quantitative information that can guide rehabilitation treatments and improve functional outcomes prediction. With the growing usage of EP measures in SCI research studies, there is a need to standardize the measurement and reporting methods of EP measures. Due to the lack of standard guidelines, there is significant variation in reporting of EP measures. Standardization of reporting of EP

Cellular, Molecular, Physiological, and Behavioral Aspects of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822427-4.00029-0

measures in SCI clinical trials could provide better comparative data, which will benefit our field by improving our understanding of these measures in relation to neurologic recovery.

In addition, the sample size in SCI clinical trials in which EP measures were reported is small and lacks justification (Korupolu et al., 2019), limiting our ability to assess an intervention's efficacy. If studies consistently reported the EP measures in a standardized fashion, it would allow us to compare or perform a meta-analysis of studies, providing valuable information for the scientific community.

This chapter will discuss commonly reported EP outcome measures in SCI clinical trials, the clinical and research application of these measures (Table 1), current methods of measurement, and reporting. Electromyography (EMG), motor evoked potentials (MEPs), somatosensory evoked potentials (SSEPs), and H-reflex are typical EP outcome measures in SCI clinical trials. Other infrequently reported electrophysiological measures include reflex EMG activity, nerve conduction studies (NCS), silent period, contact heat evoked potentials (CHEPs), and sympathetic skin response (SSR) (Korupolu et al., 2019). EP outcomes were frequently used in interventions studying neuromodulation, stem cells, and gait training to assess neuro recovery (Korupolu et al., 2019). Infrequently, some studies utilized EP outcome measures to detect changes in response to medications, diet, and hypoxia.

Electromyography (EMG)

EMG is an electrodiagnostic tool to record muscles' electrical activity for evaluating neuromuscular disorders. Clinically, it can be measured with a needle or surface electrode to record spontaneous, insertional, and voluntary muscle activity. The needle electrodes measure spontaneous and insertional activity from target muscles, which is then analyzed to report the electrical activity duration, initial deflection of the waveform, amplitude, rate, and rhythm of the firing of electrical potentials. The motor unit action potential (MUAP) is an electrical potential produced by voluntary muscle activity. The MUAP

TABLE 1 Commonly used electrophysiological measures in people with spinal cord injury.

Type	Units of measure	Clinical and research application
Somatosensory evoked potentials	Latency, amplitude	To assess ascending sensory pathways.
Motor evoked potentials	Latency, amplitude	To assess descending motor pathways.
Contact heat evoked potentials	Latency, amplitude	To study small fiber peripheral neuropathy.
Cortical silent period	Duration and latency	To assess corticospinal excitability.
Cutaneous silent period	Duration and latency	To assess spinal motor neuron activity.
Electromyography (EMG)	EMG area, frequency, recruitment, peak amplitude, mean amplitude, motor unit number estimation	To study the pathophysiology of motor neurons and muscles. To assess motor recovery or improvement. To assess progression or improvement of neuromuscular disorders.
Nerve conduction studies	Latency, amplitude, conduction velocities	To assess peripheral nerve disorders.
H reflex	Latency, amplitude	To assess abnormalities of proximal segments of peripheral nerves. To evaluate malfunction of intrathecal baclofen delivery system. To evaluate spinal excitability.
Sympathetic skin response	Waveform, frequency of occurrence, latency, amplitude	To assess the sympathetic sudomotor function.

Describes commonly used electrophysiological measures, units of measures, and application of these measures in clinical and research.

waveform and motor unit firing pattern obtained help to differentiate between a peripheral nerve or muscle pathology. MUAP size in amplitude, number of phases, and frequency of firing are often analyzed clinically.

Characterization of abnormal insertional and spontaneous EMG activity helps differentiate between muscle fiber or nerve pathology. Long duration and large amplitude polyphasic potentials suggest reinnervation from collateral sprouting. Even after maximal muscle contraction, the firing of a few MUAPS suggests reduced recruitment and is commonly seen in nerve disorders. In contrast, the firing of many MUAPS, even with a mild muscle contraction, suggests a muscle disorder and known as early recruitment. EMG signals obtained during gait or upper extremity motion studies help analyze and evaluate abnormal muscle activation patterns in clinical settings. However, it is challenging to interpret EMG activity in people with chronic SCI due to atrophy of muscles and baseline abnormal activity below the spinal cord injury level, thus limiting its application to diagnose peripheral nerve and muscle disorders in people with SCI (Kirshblum, Lim, Garstang, & Millis, 2001).

Research application

In the majority of clinical trials, EMG signals/activity are acquired from surface electrodes placed directly on the skin (Chhabra et al., 2016; Gorassini, Norton, Nevett-Duchcherer, Roy, & Yang, 2009; Houldin, Luttin, & Lam, 2011; Kawashima, Nozaki, Abe, & Nakazawa, 2008; Lam, Wirz, Lunenburger, & Dietz, 2008; Lima et al., 2010; Mazzoleni et al., 2011; Trumbower, Hayes, Mitchell, Wolf, & Stahl, 2017). EMG activity obtained via surface electrodes is frequently reported as mean EMG amplitude, sometimes as peak EMG amplitude, and few times as the presence or absence of any EMG activity pre-post-intervention. Other infrequent methods of reporting EMG results include EMG area, median frequency, and recruitment.

In some studies, improvement in EMG activity was associated with improved motor strength and locomotion (Gorassini et al., 2009; Mazzoleni et al., 2011; Trumbower et al., 2017). In a systematic review, EMG activity was reported as the most commonly used EP measures in SCI clinical trials (Korupolu et al., 2019). More recently, newer EMG techniques such as high density (HD) surface EMG have emerged, which provides motor unit number estimation (MUNE) (Bromberg, 2004) and have been used to detect a change in motor innervation zones (Afsharipour, Sandhu, Rasool, Suresh, & Rymer, 2016).

Reflex EMG activity

Reflex EMG activity is applied in clinical trials as an outcome measure to study the effects of various interventions on reflex excitability. In these studies, researchers recorded reflex EMG activity to quantify spasticity before and after the application of an intervention (D'Amico, Li, Bennett, & Gorassini, 2013; Khan, Patrick, Roy, Gorassini, & Yang, 2016; Kumru et al., 2010). Reflex EMG activity is measured from target muscles using surface electrodes in response to cutaneous stimulation. Clinicians and researchers have used different terms to report this reflex activity. For example, in three studies (D'Amico et al., 2013; Khan et al., 2016; Zewdie, Roy, Yang, & Gorassini, 2015), reflex EMG activity was reported as a **cutaneous muscular reflex which** is evoked by electrical stimulation of the tibial nerve behind the medial malleolus or median arch of the foot (D'Amico et al., 2013; Khan et al., 2016; Zewdie et al., 2015). In another two studies, it was reported as **withdrawal reflex activity**, or flexion reflex, which is evoked by electrical stimulation of the medial arch of the foot (Kumru et al., 2010; Theiss, Hornby, Rymer, & Schmit, 2011), and sometimes by stimulation of the sural nerve (Hajela, Mummidisetty, Smith, & Knikou, 2013), to produce tibialis anterior EMG activity. The **T-reflex, or T-wave**, is recorded from the soleus muscle after tapping the Achilles tendon (Kumru et al., 2010; Murillo et al., 2011). Regardless of the terminology, reflex EMG activity is consistently reported as mean EMG amplitude. Reduction in reflex EMG activity was associated with decreased spasticity and improved walking (D'Amico et al., 2013; Khan et al., 2016; Zewdie et al., 2015).

Overall EMG activity provides an objective outcome measure in SCI clinical trials to study motor output to assess motor recovery and reflex excitability to assess spasticity, providing mechanistic data. It is essential to understand the mechanism to develop interventions with a specific target to maximize recovery. EMG can be measured non-invasively with minimal discomfort, and it can be localized to target a particular muscle, which makes it an excellent outcome tool. For example, We cannot quantify each muscle involved in elbow flexion (Biceps, brachialis, brachioradialis) separately via standard clinical exam, whereas we can study each muscle separately using EMG.

Evoked potentials

Evoked potentials are the evoked responses generated by the nervous system in response to various external stimuli. Evoked potentials are recorded as electrical signals from target areas to assess ascending sensory or descending motor pathways' integrity (Fig. 1). The most frequently reported evoked potentials in SCI clinical trials are motor evoked potentials (MEPs)

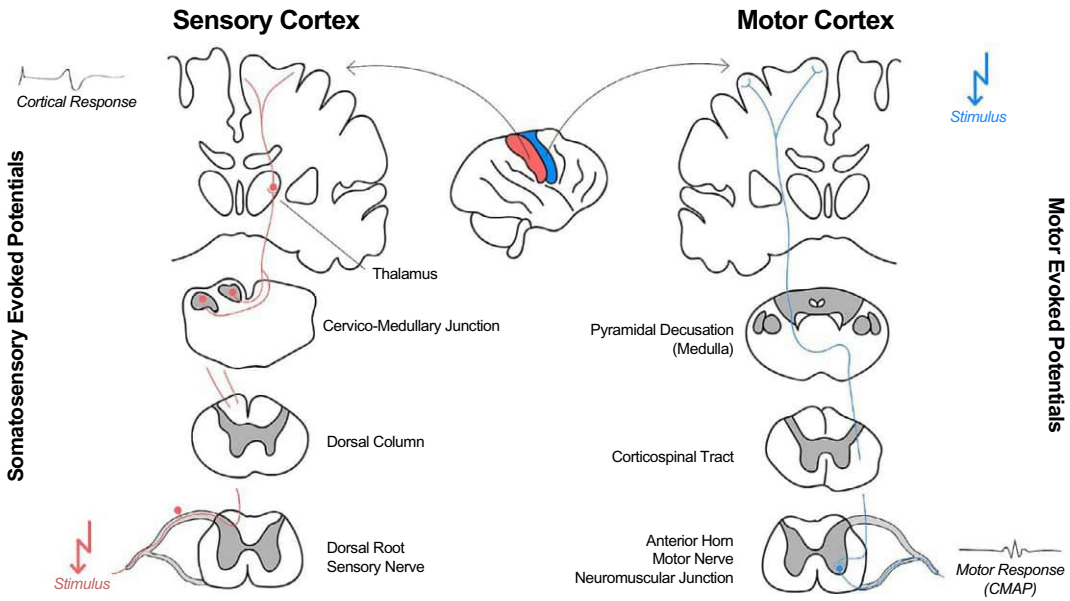

FIG. 1 Pathways of somatosensory and motor evoked potentials. *Courtesy of Maier, S., Goebel, U., Krause, S., Benk, C., Schick, M. A., Buerkle, H., et al. (2018). Principles of transcranial motor evoked potentials and somatosensory evoked potentials.* PLoS One. *Figure. https://doi.org/10.1371/journal.pone.0205410.g001. (An email was sent to PLOS to obtain permission. Permission was granted per their policy to use with acknowledgment.)*

followed by Somatosensory Evoked Potentials (SSEPs) (Korupolu et al., 2019). Contact heat evoked potentials (CHEPs) are infrequently used to study neuropathic pain (Kumru et al., 2012, 2013). We will discuss these evoked potentials in detail below.

Somatosensory evoked potentials (SSEPs)

SSEPs assess the ascending somatosensory conduction pathway integrity, from peripheral nerves to the spinal cord (posterior columns) to the contralateral sensory cortex (Caizhong et al., 2014). An SSEP is recorded from the scalp (over sensory cortex area), spine, and extremities following the electrical stimulation of mixed or sensory nerves with surface electrodes (Fig. 1). Commonly, SSEPs are recorded with stimulation of the median nerve at the wrist for upper extremities and the posterior tibial nerve at the ankle for lower extremities, clinically for diagnostic purposes and in research studies as outcome measures. An electrical stimulus to these nerves activates large myelinated fibers of mixed nerve, action potential travels up toward dorsal root ganglia to the ipsilateral dorsal columns of the spinal cord, then pass synapses in dorsal nuclei at the cervico-medullary junction and ascend toward sensory cortex via medial lemniscus. Clinically latencies of SSEPs are studied to assess abnormalities in ascending sensory pathways and for localization of lesions through ascending sensory pathways. SSEP latencies provide information on the speed of conduction of electrical potentials. For example, prolonged latency suggests abnormal conduction. SSEPs also help predict functional prognosis after SCI (Curt & Dietz, 1999; Iseli et al., 1999). In addition, the presence of tibial and pudendal SSEPs after acute SCI has been shown to predict bladder function recovery (Curt et al., 1997). Other routinely used function of SSEP is to monitor the integrity of the spinal cord during spine surgeries (Pajewski, Arlet, & Phillips, 2007).

Research application

In addition to obtaining SSEPs from the median nerve and tibial nerve; infrequently, SSEPs are obtained from the ulnar nerve and para-vertebral area in SCI clinical trials as an outcome measure. Para-vertebral SSEPs are obtained to report changes in sensory neurologic levels, pre-post intervention. Reporting of SSEPs in clinical trials is inconsistent. Researchers often reported the presence or absence of SSEPs pre-post intervention in most studies; some reported latencies, and others reported amplitudes and latencies (Adel, Hamdy, Afifi, & Mahmoud, 2009; Chhabra et al., 2016; Cristante et al., 2009; Frolov & Bryukhovetskiy, 2012; Grijalva et al., 2010; Lima et al., 2010; Mackay-Sim et al., 2008).

In one study, investigators suggested that recovery of SSEPs could indicate the formation of new synapses or remyelination following stem cell intervention (Cristante et al., 2009). In another stem cell study, an increase in SSEPs amplitudes

was considered to indicate enlargement of the amount of the conducting axons. An improvement in latency was considered an indication of remyelination of upper sensory pathways (Frolov & Bryukhovetskiy, 2012).

It is quite challenging to obtain lower extremity SSEPs in people with SCI using surface electrodes in our experience. The presence of ankle edema and body habitus limits stimulation and recording over the spine in many cases. Furthermore, the lower extremity homunculus is located medially and not easily accessible to record SSEPs with surface electrodes. We experienced difficulty obtaining reproducible SSEPs above the injury site after stimulation of mixed nerves from the lower extremities below the injury site, even in people with incomplete SCI, because of these challenges. It is important to note that SSEPs provide information regarding the dorsal columns' connectivity with the sensory cortex.

Motor evoked potentials (MEPs)

Muscle action potentials elicited by stimulation of the motor cortex or spinal cord are known as motor evoked potentials (Fig. 1). MEPs are recorded over target muscles via surface electrodes and are commonly elicited by transcranial or transspinal stimulation, either electrical or magnetic. On stimulation of the motor cortex, an electrical signal travels from upper motor neurons located in the motor cortex to the corticospinal tract. It crosses to the contralateral side at the medulla oblongata level. It descends through alpha motor neurons to peripheral nerves resulting in muscle activation. Clinically, MEPs elicited by transcranial electrical stimulation (invasive and non-invasive) can monitor the integrity of the upper motor neuron pathways (motor cortex and corticospinal tract). Monitoring of MEPs is a reliable technique to assess spinal cord ischemia and injury during thoracoabdominal aortic aneurysm repair and spinal surgeries (Pajewski et al., 2007).

Clinical application of MEPs to assess upper motor neuron pathways is currently limited due to the need for expensive equipment, special skills, and training to measure MEPs.

Research application

Non-invasive methods of eliciting MEPs have become popular as an outcome measure in SCI clinical trials to assess neurologic motor recovery following an intervention (Beekhuizen & Field-Fote, 2008; Bolliger et al., 2018; Chhabra et al., 2009, 2016; El-Kheir et al., 2014; Frolov & Bryukhovetskiy, 2012; Gomes-Osman & Field-Fote, 2015a, 2015b; Hoffman & Field-Fote, 2010; Hur et al., 2016; Jette, Cote, Meziane, & Mercier, 2013; Korupolu et al., 2019; Kuppuswamy et al., 2011; Mackay-Sim et al., 2008; Murray et al., 2015; Oh et al., 2016; Shin et al., 2015; Tabakow et al., 2013; Vaquero et al., 2016, 2017; Zewdie et al., 2015; Zhao et al., 2017). MEPs can be non-invasively produced by electrical or magnetic stimulation of the motor cortex or spinal cord (Rossini et al., 2015). However, the use of high voltage electrical stimulation required to elicit MEPs is limited in clinical trials due to local discomfort at the stimulation site (Rossini et al., 2015). In the last two decades, the development of transcranial magnetic stimulation (TMS) to elicit MEPs has become popular as an outcome measure in SCI research studies (Beekhuizen & Field-Fote, 2008; Bolliger et al., 2018; Chhabra et al., 2009, 2016; El-Kheir et al., 2014; Frolov & Bryukhovetskiy, 2012; Gomes-Osman & Field-Fote, 2015a, 2015b; Hoffman & Field-Fote, 2010; Hur et al., 2016; Jette et al., 2013; Korupolu et al., 2019; Kuppuswamy et al., 2011; Mackay-Sim et al., 2008; Murray et al., 2015; Oh et al., 2016; Shin et al., 2015; Tabakow et al., 2013; Vaquero et al., 2017, 2016; Zewdie et al., 2015; Zhao et al., 2017). Magnetic coils or cortical stimulators can be of a different shape to target different areas of the motor cortex. After mapping the cortical region of interest, the devices are held over the target area to stimulate the motor cortex or spinal cord to record the MEPS over the target muscles (Fig. 2). Researchers map the motor cortex to identify the optimal location for obtaining MEPs by obtaining MEPs at resting motor thresholds (rMT). Cortical motor mapping indicates the location and strength of the cortical representation of a given muscle. The rMT is the lowest stimulator intensity required to produce MEPs with an amplitude of at least 50 μV. However, the amplitude size required to determine rMT vary. rMT is a measure of neuronal membrane excitability (Bunday & Perez, 2012; Chen, 2000; Ziemann, Chen, Cohen, & Hallett, 1998). It is reproducible across sessions and is thus extensively used in longitudinal studies (Mills & Nithi, 1997). MEPs can be elicited at various intensities above the resting motor threshold to obtain a recruitment curve. Various methods of collecting MEPs are reported in the current literature. Several researchers obtained MEPs in resting-state at various intensities ranging from 1.1 to 1.4 times resting motor threshold (Beekhuizen & Field-Fote, 2008; Gomes-Osman & Field-Fote, 2015a; Hoffman & Field-Fote, 2010; Jette et al., 2013; Kuppuswamy et al., 2011; Murray et al., 2015; Shin et al., 2015; Stetkarova & Kofler, 2013). Most commonly in SCI clinical trials, MEPs are obtained from the upper limbs, followed by lower limbs, likely due to the challenge in accessing the lower extremity homunculus. There are inconsistencies in methods and reporting of MEPs as an outcome measure in SCI clinic trials (Beekhuizen & Field-Fote, 2008; Chhabra et al., 2009, 2016; El-Kheir et al., 2014; Frolov & Bryukhovetskiy, 2012; Gomes-Osman & Field-Fote, 2015a, 2015b; Hoffman & Field-Fote, 2010; Hur et al., 2016; Korupolu et al., 2019; Kuppuswamy et al., 2011; Mackay-Sim et al., 2008; Murray et al., 2015; Oh et al., 2016; Shin et al., 2015;

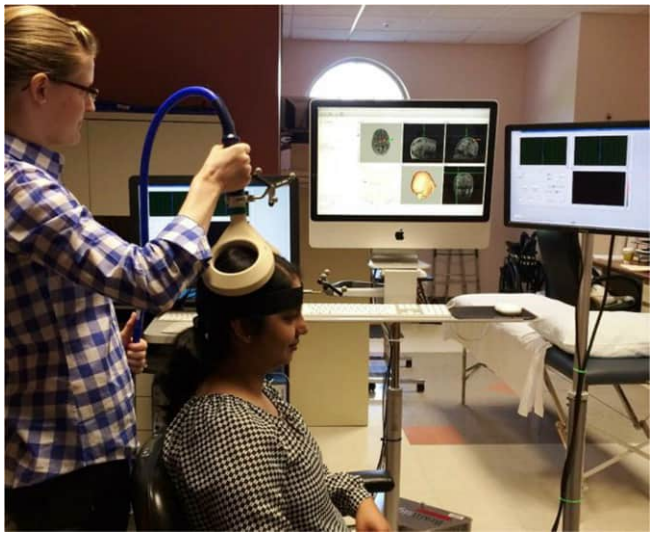

FIG. 2 Transmagenstic stimulation to elicit motor evoked potential. Mapping of the motor cortex to obtain motor evoked potentials using double cone trans magnetic coil for lower extremities.

Tabakow et al., 2013; Vaquero et al., 2016, 2017; Zewdie et al., 2015; Zhao et al., 2017). In a recently published systematic review, some studies reported MEP amplitudes obtained at resting state or during voluntary contraction of a muscle. Other MEP measures reported were MEP latencies, cortical motor map, and recruitment curve.

MEP latencies provide information on conduction in descending motor pathways. A change in latency suggests changes in the myelination, regeneration, and a change in connectivity of the corticospinal tract over time (Xie & Boakye, 2008). Investigators found an association between improvement in MEP amplitudes and improved muscle movement (Wirth, Van Hedel, & Curt, 2008). An increase in the cortical map's spatial volume has been associated with neuroplasticity (Hallett, 2001; Hoffman & Field-Fote, 2010; Sawaki et al., 2008; Wittenberg et al., 2003). The recruitment curve indicates the relationship between stimulus intensity and motor output. An increase in the recruitment curve slope is an indicator of increased neuroplasticity (Chen, 2000; Kaelin-Lang et al., 2002; Thomas & Gorassini, 2005). Investigators reported the presence and absence of MEPs pre-post intervention in few studies. Few researchers collected active MEPs obtained at various percentages of maximum voluntary contraction (MVC), which ranged from 10% to 70% of MVC (Gomes-Osman & Field-Fote, 2015a; Nardone et al., 2017). Definition of active MEPs and stimulator intensities to produce active MEPs also differed in each study (Beekhuizen & Field-Fote, 2008; Gomes-Osman & Field-Fote, 2015b; Mendonca et al., 2014; Nardone et al., 2017; Tabakow et al., 2013). Currently, there is lack of a standard method of collecting and reporting MEPs in SCI clinical trials which is essential to assess the validity of MEPs as an outcome tool to assess motor pathways (Caizhong et al., 2014; Korupolu et al., 2019).

Contact heat evoked potentials (CHEPs)

CHEPs have been used to study small fiber peripheral neuropathy (Kumru et al., 2012, 2013). CHEPs are obtained noninvasively by applying a heat stimulus of 32–51 °C over the skin, and the resulting evoked potentials are recorded over the sensory cortex. CHEPs amplitudes and latencies are utilized to detect small fiber pathologies in people with neuropathic pain. CHEPs are infrequently used to study the effects of an intervention on neuropathic pain in people with SCI (Kumru et al., 2013). CHEPs are not used routinely in the clinical diagnosis of peripheral neuropathy.

H-reflex

The Hoffman reflex (H-reflex) is named after Paul Hoffman, who originally described it in 1910 (Palmieri, Ingersoll, & Hoffman, 2004). It is an electrically induced reflex that bypasses the muscle spindle in contrast to mechanically induced stretch reflex (Knikou & Taglianetti, 2006; Palmieri et al., 2004). It is a compound muscle action potential elicited by low-threshold electrical stimulation of afferent fibers in the mixed nerve with subsequent monosynaptic excitation of alpha motoneurons (Knikou & Taglianetti, 2006; Palmieri et al., 2004). Subsequently, the stimulus is transmitted down the alpha motor neuron axon to the motor end plates and collected using surface electrodes (Burke, 2016; Knikou & Taglianetti, 2006;

Palmieri et al., 2004). H-reflex latencies help diagnose abnormalities in the peripheral nervous system's proximal segments, such as the plexus and nerve roots. Prolonged latencies suggest abnormal nerve conduction. It is commonly elicited by selectively stimulating the Ia fibers of the posterior tibial or median nerve and recorded over the soleus and flexor carpi radialis muscle, respectively (Fig. 3). Clinically, H-reflex latencies are used to study sensory radiculopathy. The H-reflex amplitude helps assess spasticity and study the malfunction of intrathecal baclofen pump delivery systems. A decrease in H-reflex amplitude was seen after intrathecal baclofen (ITB) therapy suggesting a reduction in spasticity (Stokic & Yablon, 2012; Stokic, Yablon, Hayes, Vesovic-Potic, & Olivier, 2006).

Research application

In SCI clinical trials, the H-reflex is used as an outcome measure to assess changes in spinal excitability in response to an intervention. It is necessary to normalize the H-reflex value to obtain between-subject comparisons. Different methods have been advocated to normalize the H-reflex between subjects for comparisons. The most common method of reporting the H-reflex is the ratio of maximum H-reflex to maximum compound muscle action potential (CMAP) amplitude, known as Hmax/Mmax. The M-wave is a CMAP produced by direct supra-maximal stimulation of motor axons. Changes in the ratio of the maximal H-reflex amplitude and maximal M-wave amplitude (Hmax/Mmax) provide a rough estimate of modulation in spinal excitability (D'Amico, Li, Bennett, & Gorassini, 2013; Khan, Patrick, Roy, Gorassini, & Yang, 2016). Higher Hmax/Mmax ratio suggests increased spinal excitability. Other alternatives used for normalization include soleus H-reflex conditioned by peroneal nerve stimulation and plantar stimulation,(Knikou & Mummidisetty, 2014; Piazza et al., 2018) H-reflex obtained at stimulation intensities adjusted with reference to Mmax (Chang et al., 2012, 2013; D'Amico et al., 2013; Knikou & Mummidisetty, 2014), and H-reflex collected at an intensity to evoke 50% of H-max (Piazza et al., 2018). Some researchers reported H-reflex post-activation depression (PAD) at various frequencies by comparing H-reflex amplitudes pre and post-intervention (Chang et al., 2012, 2013; Knikou & Mummidisetty, 2014; Piazza et al., 2018). The H-reflex can be depressed if the interstimulus gap is less than 10 s; this phenomenon is known as post-activation depression. PAD is decreased in people with upper motor neuron disorders, suggesting an increase in spinal excitability or hyperreflexia. A positive association has been found between decreased PAD and the severity of spasticity. Therefore, changes in PAD have been evaluated in clinical trials assessing interventions for spasticity (Adams & Hicks, 2011; Kumru et al., 2010; Murillo et al., 2011; Stetkarova & Kofler, 2013).

The H-reflex is a useful outcome measure to assess spasticity objectively following SCI. However, there are many complexities involved with its collection. In our experience, joint contractures and severe spasticity limit the proper positioning of a person with SCI, which is essentially required to record H-reflex reliably. Anti-spasticity medications alter H-reflex. It is essential to consider the concomitant usage (dosing and timing) of these medications during participation in a research study if H-reflex is recorded as an outcome tool.

Nerve conduction studies (NCS)

NCS provide information on the conduction properties of peripheral nerves and aid in diagnosing peripheral nerve disorders (Mallik & Weir, 2005). Sensory NCS are performed with electrical stimulation of sensory or mixed nerves at a proximal location, and sensory action potentials are recorded over sensory nerves distally. Latencies of sensory nerves of right and

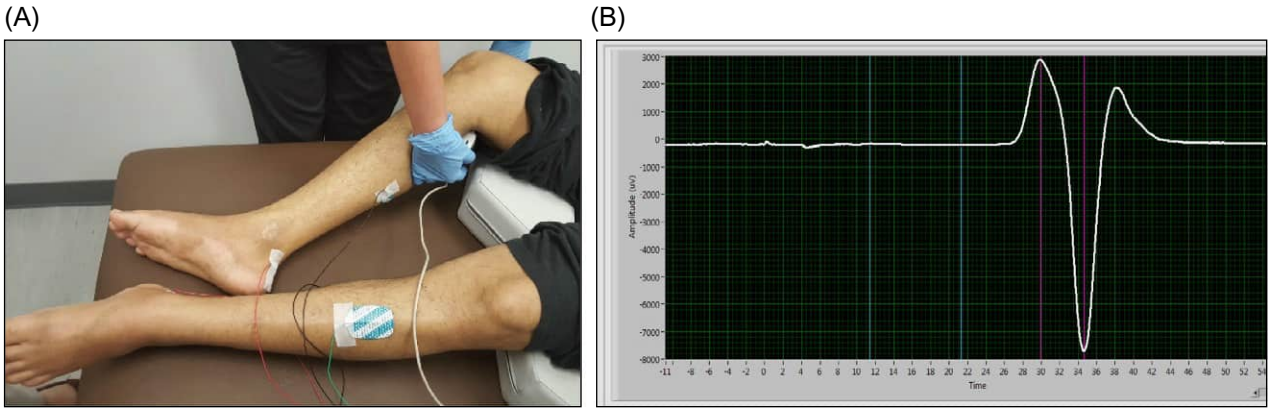

FIG. 3 (A) H reflex from a person with a spinal cord injury. (B) H wave.

left upper extremities are compared to study conduction abnormalities. Motor NCS are performed with electrical stimulation of motor or mixed nerve proximally, and CMAPs are collected via surface electrodes placed over a target muscle. CMAP amplitude and latencies are studied to study abnormalities in conduction. However, the usefulness of NCS in chronic SCI is limited due to muscle atrophy. There were no changes in sural, tibial and peroneal nerve latencies in a study of people with chronic complete cervical SCI, but amplitudes were diminished (Kirshblum et al., 2001). Due to changes in NCS after SCI, routine clinical application of NCS is limited in the diagnosis of peripheral nerve disorders in people with chronic SCI.

Research application

In SCI clinical trials, sensory and motor NCS were obtained from various peripheral nerves as an outcome measure. Conduction velocities were compared in some studies (Allison, Gabriel, Klentrou, Josse, & Ditor, 2017; Hur et al., 2016; Tabakow et al., 2013; Vaquero et al., 2017), and CMAP amplitudes were compared in a few other studies (Allison et al., 2017; Tabakow et al., 2013). CMAP amplitude is dependent on stimulation of the number of axons of a nerve band on the area of muscle fibers served by these axons. For these reasons, serial measurement of CMAP can be a useful tool to assess neuro recovery after acute SCI. Especially to study the recovery of muscles innervated by segments at and around the level of SCI.

F-wave is a low amplitude late response and is elicited by supramaximal electrical stimulation of a mixed or a motor nerve resulting in anti-dromic stimulation of alpha motor neurons (Mallik & Weir, 2005). F-waves may not appear after each stimulus and are inherently variable in shape, latency, and amplitude. F-waves are obtained for the diagnostic evaluation of proximal peripheral nerve lesions in the clinical setting. Infrequently, it is also used as an outcome measure in SCI clinical trials (Murray et al., 2015). F-waves were captured as an outcome measure in a study to investigate the effects of anodal transcranial direct current stimulation on spinal excitability (Murray et al., 2015).

Silent period (SP)

Cortical SP refers to the suppression of EMG activity following a suprathreshold transcranial magnetic stimulation during the contralateral target muscle's voluntary contraction (Poston, Kukke, Paine, Francis, & Hallett, 2012). Current evidence suggests that intracortical inhibition resulting in suppression of muscle activity is Gamma-aminobutyric acid (GABA) receptor-mediated (McDonnell, Orekhov, & Ziemann, 2006). As a result, cortical SPs are mainly used in research studies to assess GABA-mediated pathways. In SCI clinical trials, cortical SPs are studied to evaluate changes in corticospinal excitability in response to baclofen and repetitive trans magnetic stimulation (rTMS) (Kuppuswamy et al., 2011; Stetkarova & Kofler, 2013). In these studies, cortical SP was obtained at various TMS and maximal voluntary contraction intensities. In one study, there was no difference in duration and latency of cortical SP after five sessions of rTMS (Kuppuswamy et al., 2011). Cortical SP latency and duration increased progressively up to 3 h following the ITB dose administration in another study suggesting increased GABA mediated activity (Stetkarova & Kofler, 2013). This finding confirms the usefulness of this tool to study GABA-mediated interventions.

Cutaneous SP is a brief transient period with a loss of voluntary EMG activity following noxious cutaneous nerve stimulation. It is considered a spinal inhibitory reflex produced due to afferent sensory stimulation of small diameter, slow conducting A-delta fibers. Afferent stimulation of A-delta fibers results in suppression of spinal motor neuron activity (Kofler, Frohlich, & Saltuari, 2003; Kofler, Kronenberg, Brenneis, Felber, & Saltuari, 2003). Results of a study following intrathecal baclofen bolus dose suggest that GABA B receptor-mediated interventions do not modulate cutaneous SP reflex pathways (Stetkarova & Kofler, 2013). There was no change in cutaneous SP latency, end latency, and duration following the ITB bolus in this study. The mechanism of cutaneous SP is not known at this time.

Sympathetic skin response (SSR)

Sympathetic skin response (SSR) is a non-invasive measure to assess sympathetic sudomotor function. SSR is generated by efferent small unmyelinated fibers of sweat glands and elicited by stimulation of afferent large myelinated fibers (Vetrugno, Liguori, Cortelli, & Montagna, 2003). SSR is usually collected over the palms and soles after electrical stimulation of the contralateral median and tibial nerves, respectively (Vetrugno et al., 2003). However, SSR can be evoked by various stimuli, including deep breathing, intense emotion, cough, and loud noise (Vetrugno et al., 2003). Latency and amplitudes are compared to normative data to determine abnormality if present. Though SSR is a simple technique, it may be difficult to reproduce and obtain consistently. To our knowledge, the routine clinical use of SSR is not performed in people with SCI.

Research application

To our knowledge, SSR has been used in one SCI clinic trial to investigate the function of the sympathetic system (Kuppuswamy et al., 2011). In this study, SSR was obtained from surface electrodes from the hand's palmar and dorsal surface. SSR was elicited by applying magnetic stimulation to the back of the neck at 65% of maximum stimulator output. The waveform, frequency of occurrence, latency, and amplitude of SSR potentials were collected. However, researchers were able to collect SSR in less than 50% of the subjects. The inability to collect this measure consistently limits its usage as an outcome measure in SCI clinical trials at this time.

Discussion

EP outcome measures are valuable prognostic and diagnostic tools for the quantification of neuromuscular dysfunction after SCI. In SCI clinical trials, EP tools have been used to evaluate neuromodulation of sensory, motor, and autonomic function in response to an intervention. The EP outcome measures provide objective evaluation and eliminate biases of subjective evaluation. However, current evidence suggests a lack of consistency in collecting and reporting EP outcome measures. As a result of this heterogeneity, it is challenging to compare and replicate these studies. The development of standardized methods of collection and reporting of EP outcome measures is critically important to overcome these challenges. A limiting factor for routine incorporation of EP measures in clinical and research settings is the need for expensive equipment, lengthy testing, a standardized environment, and special training to perform these tests.

In summary, this chapter provides information on commonly used EP measures that can complement the clinical assessments and provide objective changes in neurophysiology after SCI. Clinical and functional outcomes cannot be applied during acute phases of injury due to altered mentation, sedation, and inability to follow commands, limiting their application to assess longitudinal recovery from acute to chronic SCI stages. Conversely, EP measures can be applied acutely, even in patients unable to follow commands, providing necessary objective measures. Thus, EP measures can be useful tools in assessing neuromuscular changes throughout the spectrum of recovery after SCI. However, before widespread application for clinical and research purposes, it is essential to validate methods and standardize reporting of these measures.

As our understanding of EP measures in the setting of SCI improves, the application of these measures in SCI research will continue to grow.

Applications to other areas of neuroscience

EP measures are widely used to diagnose and monitor disease progression and recovery of neuromuscular disorders such as neuropathy, amyotrophic lateral sclerosis (ALS), and myopathies. Abnormal EMG findings can assist in differentiating pathologies of lower motor neurons from a muscle disorder. Furthermore, EMG and nerve conduction studies can assist in localizing the site of the lesion. High-density surface EMG and motor unit number estimation are emerging non-invasive techniques for diagnosing and monitoring of amyotrophic lateral sclerosis (ALS) (Bromberg, 2004). MEPs and SEEPs are used extensively to diagnose multiple sclerosis and evaluate prognosis after stroke. MEPs and SSEPs are also recorded during spine and brain surgeries for intra-operative monitoring (Azad et al., 2018; Park, Park, Park, & Lee, 2017). CHEPs are obtained to detect changes in conduction in small fibers, which results in neuropathic pain in various neurological disorders (Madsen, Finnerup, & Baumgartner, 2014). H-reflex and F-waves help diagnose the peripheral nervous system's proximal segments, including plexus and nerve roots (Jerath & Kimura, 2019). Sympathetic skin response has been studied to assess autonomic dysfunction of neurological disorders including multiple sclerosis, Parkinson's disease, and ALS (Vetrugno et al., 2003).

Key facts of electrophysiological measures

- EP measures are useful tools to assess residual function after SCI for objective prognostication. In research studies, EP measures are widely used to assess changes in conduction, connectivity, and regeneration across the injury site.
- Commonly used EP measures in SCI clinical trials include EMG, SSEPs, MEPs, and H-reflex.
- There are no standard guidelines for the collection and reporting of EP measures in SCI clinical trials.

Summary points

- Electrophysiological measures help prognosticate, assess residual function after spinal cord injury, and evaluate pain and spasticity.
- Electrophysiological measures are widely used to evaluate response to intervention in SCI clinical trials.
- Electrophysiological measures are increasingly utilized due to their ability to provide objective measurements and detect subtle changes with quantitative data on neural function.
- Frequently reported electrophysiological outcomes in clinical trials of people with SCI include: electromyography activity, motor-evoked potentials, somatosensory evoked potentials, and H-reflex.
- There is heterogeneity in the methods of measurement and the reporting of EP outcome data that warrant the standardization of electrophysiological measures in SCI clinical trials.

References

Adams, M. M., & Hicks, A. L. (2011). Comparison of the effects of body-weight-supported treadmill training and tilt-table standing on spasticity in individuals with chronic spinal cord injury. *The Journal of Spinal Cord Medicine*, *34*(5), 488–494. https://doi.org/10.1179/2045772311Y.0000000028.

Adel, N. G. H., Hamdy, S., Afifi, L., & Mahmoud, H. (2009). Stem cell therapy in chronic spinal cord injuries. *Egyptian Journal of Neurology, Psychiatry and Neurosurgery*, *46*(2), 467–478.

Afsharipour, B., Sandhu, M. S., Rasool, G., Suresh, N. L., & Rymer, W. Z. (2016). Using surface electromyography to detect changes in innervation zones pattern after human cervical spinal cord injury. *Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, *2016*, 3757–3760. https://doi.org/10.1109/EMBC.2016.7591545.

Allison, D. J., Gabriel, D. A., Klentrou, P., Josse, A. R., & Ditor, D. S. (2017). The influence of chronic inflammation on peripheral motor nerve conduction following spinal cord injury: A randomized clinical trial. *Topics in Spinal Cord Injury Rehabilitation*, *23*(4), 377–385. https://doi.org/10.1310/sci16-00045.

Azad, T. D., Pendharkar, A. V., Nguyen, V., Pan, J., Connolly, I. D., Veeravagu, A., … Grant, G. A. (2018). Diagnostic utility of intraoperative neurophysiological monitoring for intramedullary spinal cord tumors: Systematic review and meta-analysis. *Clinical Spine Surgery*, *31*(3), 112–119. https://doi.org/10.1097/BSD.0000000000000558.

Beekhuizen, K. S., & Field-Fote, E. C. (2008). Sensory stimulation augments the effects of massed practice training in persons with tetraplegia. *Archives of Physical Medicine and Rehabilitation*, *89*(4), 602–608. https://doi.org/10.1016/j.apmr.2007.11.021.

Bolliger, M., Blight, A. R., Field-Fote, E. C., Musselman, K., Rossignol, S., Barthelemy, D., … Steeves, J. (2018). Lower extremity outcome measures: Considerations for clinical trials in spinal cord injury. *Spinal Cord*, *56*(7), 628–642. https://doi.org/10.1038/s41393-018-0097-8.

Bromberg, M. B. (2004). Motor unit number estimation: New techniques and new uses. *Supplements to Clinical Neurophysiology*, *57*, 120–136. https://doi.org/10.1016/s1567-424x(09)70350-2.

Bunday, K. L., & Perez, M. A. (2012). Impaired crossed facilitation of the corticospinal pathway after cervical spinal cord injury. *Journal of Neurophysiology*, *107*(10), 2901–2911. https://doi.org/10.1152/jn.00850.2011.

Burke, D. (2016). Clinical uses of H reflexes of upper and lower limb muscles. *Clinical Neurophysiology Practice*, *1*, 9–17. https://doi.org/10.1016/j.cnp.2016.02.003.

Caizhong, X., Chunlei, S., Beibei, L., Zhiqing, D., Qinneng, D., & Tong, W. (2014). The application of somatosensory evoked potentials in spinal cord injury rehabilitation. *NeuroRehabilitation*, *35*(4), 835–840. https://doi.org/10.3233/NRE-141158.

Chang, Y. J., Liang, J. N., Hsu, M. J., Lien, H. Y., Fang, C. Y., & Lin, C. H. (2013). Effects of continuous passive motion on reversing the adapted spinal circuit in humans with chronic spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *94*(5), 822–828. https://doi.org/10.1016/j.apmr.2012.11.035.

Chang, S. H., Tseng, S. C., McHenry, C. L., Littmann, A. E., Suneja, M., & Shields, R. K. (2012). Limb segment vibration modulates spinal reflex excitability and muscle mRNA expression after spinal cord injury. *Clinical Neurophysiology*, *123*(3), 558–568. https://doi.org/10.1016/j.clinph.2011.08.001.

Chen, R. (2000). Studies of human motor physiology with transcranial magnetic stimulation. *Muscle & Nerve. Supplement*, *9*, S26–S32.

Chhabra, H. S., Lima, C., Sachdeva, S., Mittal, A., Nigam, V., Chaturvedi, D., … Khan, T. A. H. (2009). Autologous mucosal transplant in chronic spinal cord injury: An Indian pilot study. *Spinal Cord*, *47*(12), 887–895. https://doi.org/10.1038/sc.2009.54.

Chhabra, H. S., Sarda, K., Arora, M., Sharawat, R., Singh, V., Nanda, A., … Tandon, V. (2016). Autologous bone marrow cell transplantation in acute spinal cord injury—An Indian pilot study. *Spinal Cord*, *54*(1), 57–64. https://doi.org/10.1038/sc.2015.134.

Cristante, A. F., Barros-Filho, T. E., Tatsui, N., Mendrone, A., Caldas, J. G., Camargo, A., … Marcon, R. M. (2009). Stem cells in the treatment of chronic spinal cord injury: Evaluation of somatosensitive evoked potentials in 39 patients. *Spinal Cord*, *47*(10), 733–738. https://doi.org/10.1038/sc.2009.24.

Curt, A., & Dietz, V. (1999). Electrophysiological recordings in patients with spinal cord injury: Significance for predicting outcome. *Spinal Cord*, *37*(3), 157–165. https://doi.org/10.1038/sj.sc.3100809.

Curt, A., Rodic, B., Schurch, B., & Dietz, V. (1997). Recovery of bladder function in patients with acute spinal cord injury: Significance of ASIA scores and somatosensory evoked potentials. *Spinal Cord*, *35*(6), 368–373. https://doi.org/10.1038/sj.sc.3100423.

D'Amico, J. M., Li, Y., Bennett, D. J., & Gorassini, M. A. (2013). Reduction of spinal sensory transmission by facilitation of 5-HT1B/D receptors in noninjured and spinal cord-injured humans. *Journal of Neurophysiology*, *109*(6), 1485–1493. https://doi.org/10.1152/jn.00822.2012.

El-Kheir, W. A., Gabr, H., Awad, M. R., Ghannam, O., Barakat, Y., Farghali, H. A., … Sabaawy, H. E. (2014). Autologous bone marrow-derived cell therapy combined with physical therapy induces functional improvement in chronic spinal cord injury patients. *Cell Transplantation*, *23*(6), 729–745. https://doi.org/10.3727/096368913X664540.

Frolov, A. A., & Bryukhovetskiy, A. S. (2012). Effects of hematopoietic autologous stem cell transplantation to the chronically injured human spinal cord evaluated by motor and somatosensory evoked potentials methods. *Cell Transplantation*, *21*(Suppl. 1), S49–S55. https://doi.org/10.3727/096368912X633761.

Gomes-Osman, J., & Field-Fote, E. C. (2015a). Cortical vs. afferent stimulation as an adjunct to functional task practice training: A randomized, comparative pilot study in people with cervical spinal cord injury. *Clinical Rehabilitation*, *29*(8), 771–782. https://doi.org/10.1177/0269215514556087.

Gomes-Osman, J., & Field-Fote, E. C. (2015b). Improvements in hand function in adults with chronic tetraplegia following a multiday 10-Hz repetitive transcranial magnetic stimulation intervention combined with repetitive task practice. *Journal of Neurologic Physical Therapy*, *39*(1), 23–30. https://doi.org/10.1097/NPT.0000000000000062.

Gorassini, M. A., Norton, J. A., Nevett-Duchcherer, J., Roy, F. D., & Yang, J. F. (2009). Changes in locomotor muscle activity after treadmill training in subjects with incomplete spinal cord injury. *Journal of Neurophysiology*, *101*(2), 969–979. https://doi.org/10.1152/jn.91131.2008.

Grijalva, I., Garcia-Perez, A., Diaz, J., Aguilar, S., Mino, D., Santiago-Rodriguez, E., … Madrazo, I. (2010). High doses of 4-aminopyridine improve functionality in chronic complete spinal cord injury patients with MRI evidence of cord continuity. *Archives of Medical Research*, *41*(7), 567–575. https://doi.org/10.1016/j.arcmed.2010.10.001.

Hajela, N., Mummidisetty, C. K., Smith, A. C., & Knikou, M. (2013). Corticospinal reorganization after locomotor training in a person with motor incomplete paraplegia. *BioMed Research International*, *2013*, 516427. https://doi.org/10.1155/2013/516427.

Hallett, M. (2001). Functional reorganization after lesions of the human brain: Studies with transcranial magnetic stimulation. *Revue Neurologique (Paris)*, *157*(8–9 Pt 1), 822–826. 829&population=N&View=abstract.

Hoffman, L. R., & Field-Fote, E. C. (2010). Functional and corticomotor changes in individuals with tetraplegia following unimanual or bimanual massed practice training with somatosensory stimulation: A pilot study. *Journal of Neurologic Physical Therapy*, *34*(4), 193–201. https://doi.org/10.1097/NPT.0b013e3181fbe692.

Houldin, A., Luttin, K., & Lam, T. (2011). Locomotor adaptations and aftereffects to resistance during walking in individuals with spinal cord injury. *Journal of Neurophysiology*, *106*(1), 247–258. https://doi.org/10.1152/jn.00753.2010.

Hubli, M., Kramer, J. L. K., Jutzeler, C. R., Rosner, J., Furlan, J. C., Tansey, K. E., & Schubert, M. (2019). Application of electrophysiological measures in spinal cord injury clinical trials: A narrative review. *Spinal Cord*, *57*(11), 909–923. https://doi.org/10.1038/s41393-019-0331-z.

Hupp, M., Pavese, C., Bachmann, L. M., Koller, R., Schubert, M., & EMSCI Study Group. (2018). Electrophysiological multimodal assessments improve outcome prediction in traumatic cervical spinal cord injury. *Journal of Neurotrauma*, *35*(24), 2916–2923. https://doi.org/10.1089/neu.2017.5576.

Hur, J. W., Cho, T. H., Park, D. H., Lee, J. B., Park, J. Y., & Chung, Y. G. (2016). Intrathecal transplantation of autologous adipose-derived mesenchymal stem cells for treating spinal cord injury: A human trial. *The Journal of Spinal Cord Medicine*, *39*(6), 655–664. https://doi.org/10.1179/2045772315Y.0000000048.

Iseli, E., Cavigelli, A., Dietz, V., & Curt, A. (1999). Prognosis and recovery in ischaemic and traumatic spinal cord injury: Clinical and electrophysiological evaluation. *Journal of Neurology, Neurosurgery, and Psychiatry*, *67*(5), 567–571. https://doi.org/10.1136/jnnp.67.5.567.

Jerath, N., & Kimura, J. (2019). F wave, a wave, H reflex, and blink reflex. *Handbook of Clinical Neurology*, *160*, 225–239. https://doi.org/10.1016/B978-0-444-64032-1.00015-1.

Jette, F., Cote, I., Meziane, H. B., & Mercier, C. (2013). Effect of single-session repetitive transcranial magnetic stimulation applied over the hand versus leg motor area on pain after spinal cord injury. *Neurorehabilitation and Neural Repair*, *27*(7), 636–643. https://doi.org/10.1177/1545968313484810.

Kaelin-Lang, A., Luft, A. R., Sawaki, L., Burstein, A. H., Sohn, Y. H., & Cohen, L. G. (2002). Modulation of human corticomotor excitability by somatosensory input. *The Journal of Physiology*, *540*(Pt 2), 623–633.

Kawashima, N., Nozaki, D., Abe, M. O., & Nakazawa, K. (2008). Shaping appropriate locomotive motor output through interlimb neural pathway within spinal cord in humans. *Journal of Neurophysiology*, *99*(6), 2946–2955. https://doi.org/10.1152/jn.00020.2008.

Khan, A. S., Patrick, S. K., Roy, F. D., Gorassini, M. A., & Yang, J. F. (2016). Training-specific neural plasticity in spinal reflexes after incomplete spinal cord injury. *Neural Plasticity*, *2016*, 6718763. https://doi.org/10.1155/2016/6718763.

Kirshblum, S., Lim, S., Garstang, S., & Millis, S. (2001). Electrodiagnostic changes of the lower limbs in subjects with chronic complete cervical spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *82*(5), 604–607. https://doi.org/10.1053/apmr.2001.22348.

Knikou, M., & Mummidisetty, C. K. (2014). Locomotor training improves premotoneuronal control after chronic spinal cord injury. *Journal of Neurophysiology*, *111*(11), 2264–2275. https://doi.org/10.1152/jn.00871.2013.

Knikou, M., & Taglianetti, C. (2006). On the methods employed to record and measure the human soleus H-reflex. *Somatosensory & Motor Research*, *23*(1–2), 55–62. https://doi.org/10.1080/08990220600702715.

Kofler, M., Frohlich, K., & Saltuari, L. (2003). Preserved cutaneous silent periods in severe entrapment neuropathies. *Muscle & Nerve*, *28*(6), 711–714. https://doi.org/10.1002/mus.10595.

Kofler, M., Kronenberg, M. F., Brenneis, C., Felber, A., & Saltuari, L. (2003). Cutaneous silent periods in intramedullary spinal cord lesions. *Journal of the Neurological Sciences*, *216*(1), 67–79. https://doi.org/10.1016/s0022-510x(03)00211-9.

Korupolu, R., Stampas, A., Singh, M., Zhou, P., & Francisco, G. (2019). Electrophysiological outcome measures in spinal cord injury clinical trials: A systematic review. *Topics in Spinal Cord Injury Rehabilitation*, *25*(4), 340–354. https://doi.org/10.1310/sci2504-340.

Kumru, H., Murillo, N., Samso, J. V., Valls-Sole, J., Edwards, D., Pelayo, R., … Pascual-Leone, A. (2010). Reduction of spasticity with repetitive transcranial magnetic stimulation in patients with spinal cord injury. *Neurorehabilitation and Neural Repair*, *24*(5), 435–441. https://doi.org/10.1177/1545968309356095.

Kumru, H., Soler, D., Vidal, J., Navarro, X., Tormos, J. M., Pascual-Leone, A., & Valls-Sole, J. (2013). The effects of transcranial direct current stimulation with visual illusion in neuropathic pain due to spinal cord injury: An evoked potentials and quantitative thermal testing study. *European Journal of Pain*, *17*(1), 55–66. https://doi.org/10.1002/j.1532-2149.2012.00167.x.

Kumru, H., Soler, D., Vidal, J., Tormos, J. M., Pascual-Leone, A., & Valls-Sole, J. (2012). Evoked potentials and quantitative thermal testing in spinal cord injury patients with chronic neuropathic pain. *Clinical Neurophysiology*, *123*(3), 598–604. https://doi.org/10.1016/j.clinph.2011.07.038.

Kuppuswamy, A., Balasubramaniam, A. V., Maksimovic, R., Mathias, C. J., Gall, A., Craggs, M. D., & Ellaway, P. H. (2011). Action of 5 Hz repetitive transcranial magnetic stimulation on sensory, motor and autonomic function in human spinal cord injury. *Clinical Neurophysiology*, *122*(12), 2452–2461. https://doi.org/10.1016/j.clinph.2011.04.022.

Lam, T., Wirz, M., Lunenburger, L., & Dietz, V. (2008). Swing phase resistance enhances flexor muscle activity during treadmill locomotion in incomplete spinal cord injury. *Neurorehabilitation and Neural Repair*, *22*(5), 438–446. https://doi.org/10.1177/1545968308315595.

Lima, C., Escada, P., Pratas-Vital, J., Branco, C., Arcangeli, C. A., Lazzeri, G., … Peduzzi, J. D. (2010). Olfactory mucosal autografts and rehabilitation for chronic traumatic spinal cord injury. *Neurorehabilitation and Neural Repair*, *24*(1), 10–22. https://doi.org/10.1177/1545968309347685.

Mackay-Sim, A., Feron, F., Cochrane, J., Bassingthwaighte, L., Bayliss, C., Davies, W., … Geraghty, T. (2008). Autologous olfactory ensheathing cell transplantation in human paraplegia: A 3-year clinical trial. *Brain*, *131*(Pt 9), 2376–2386. https://doi.org/10.1093/brain/awn173.

Madsen, C. S., Finnerup, N. B., & Baumgartner, U. (2014). Assessment of small fibers using evoked potentials. *Scandinavian Journal of Pain*, *5*(2), 111–118. https://doi.org/10.1016/j.sjpain.2013.11.007.

Mallik, A., & Weir, A. I. (2005). Nerve conduction studies: Essentials and pitfalls in practice. *Journal of Neurology, Neurosurgery, and Psychiatry*, *76* (Suppl. 2), ii23–31. https://doi.org/10.1136/jnnp.2005.069138.

Mazzoleni, S., Boldrini, E., Laschi, C., Carrozza, M. C., Stampacchia, G., & Rossi, B. (2011). Changes on EMG activation in healthy subjects and incomplete SCI patients following a robot-assisted locomotor training. *IEEE International Conference on Rehabilitation Robotics*, *2011*, 5975467. https://doi.org/10.1109/ICORR.2011.5975467.

McDonnell, M. N., Orekhov, Y., & Ziemann, U. (2006). The role of GABA(B) receptors in intracortical inhibition in the human motor cortex. *Experimental Brain Research*, *173*(1), 86–93. https://doi.org/10.1007/s00221-006-0365-2.

Mendonca, M. V., Larocca, T. F., de Freitas Souza, B. S., Villarreal, C. F., Silva, L. F., Matos, A. C., … dos Santos, R. R. (2014). Safety and neurological assessments after autologous transplantation of bone marrow mesenchymal stem cells in subjects with chronic spinal cord injury. *Stem Cell Research & Therapy*, *5*(6), 126. https://doi.org/10.1186/scrt516.

Mills, K. R., & Nithi, K. A. (1997). Corticomotor threshold to magnetic stimulation: Normal values and repeatability. *Muscle & Nerve*, *20*(5), 570–576. https://doi.org/10.1002/(SICI)1097-4598(199705)20:5<570::AID-MUS5>3.0.CO;2-6 (pii).

Murillo, N., Kumru, H., Vidal-Samso, J., Benito, J., Medina, J., Navarro, X., & Valls-Sole, J. (2011). Decrease of spasticity with muscle vibration in patients with spinal cord injury. *Clinical Neurophysiology*, *122*(6), 1183–1189. https://doi.org/10.1016/j.clinph.2010.11.012.

Murray, L. M., Edwards, D. J., Ruffini, G., Labar, D., Stampas, A., Pascual-Leone, A., & Cortes, M. (2015). Intensity dependent effects of transcranial direct current stimulation on corticospinal excitability in chronic spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *96*(Suppl. 4), S114–S121. https://doi.org/10.1016/j.apmr.2014.11.004.

Nardone, R., Langthaler, P. B., Orioli, A., Holler, P., Holler, Y., Frey, V. N., … Trinka, E. (2017). Effects of intermittent theta burst stimulation on spasticity after spinal cord injury. *Restorative Neurology and Neuroscience*, *35*(3), 287–294. https://doi.org/10.3233/RNN-160701.

Oh, S. K., Choi, K. H., Yoo, J. Y., Kim, D. Y., Kim, S. J., & Jeon, S. R. (2016). A phase III clinical trial showing limited efficacy of autologous mesenchymal stem cell therapy for spinal cord injury. *Neurosurgery*, *78*(3), 436–447. discussion 447 https://doi.org/10.1227/NEU.0000000000001056.

Pajewski, T. N., Arlet, V., & Phillips, L. H. (2007). Current approach on spinal cord monitoring: The point of view of the neurologist, the anesthesiologist and the spine surgeon. *European Spine Journal*, *16*(Suppl. 2), S115–S129. https://doi.org/10.1007/s00586-007-0419-6.

Palmieri, R. M., Ingersoll, C. D., & Hoffman, M. A. (2004). The Hoffmann reflex: Methodologic considerations and applications for use in sports medicine and athletic training research. *Journal of Athletic Training*, *39*(3), 268–277.

Park, T., Park, J., Park, Y. G., & Lee, J. (2017). Intraoperative neurophysiological monitoring for spinal cord tumor surgery: Comparison of motor and somatosensory evoked potentials according to tumor types. *Annals of Rehabilitation Medicine*, *41*(4), 610–620. https://doi.org/10.5535/arm.2017.41.4.610.

Piazza, S., Torricelli, D., Gomez-Soriano, J., Serrano-Munoz, D., Avila-Martin, G., Galan-Arriero, I., … Taylor, J. (2018). Assessing sensorimotor excitability after spinal cord injury: A reflex testing method based on cycling with afferent stimulation. *Medical & Biological Engineering & Computing*, *56*(8), 1425–1434. https://doi.org/10.1007/s11517-018-1787-2.

Poston, B., Kukke, S. N., Paine, R. W., Francis, S., & Hallett, M. (2012). Cortical silent period duration and its implications for surround inhibition of a hand muscle. *The European Journal of Neuroscience*, *36*(7), 2964–2971. https://doi.org/10.1111/j.1460-9568.2012.08212.x.

Rossini, P. M., Burke, D., Chen, R., Cohen, L. G., Daskalakis, Z., Di Iorio, R., … Ziemann, U. (2015). Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: Basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. committee. *Clinical Neurophysiology*, *126*(6), 1071–1107. https://doi.org/10.1016/j.clinph.2015.02.001.

Sawaki, L., Butler, A. J., Leng, X., Wassenaar, P. A., Mohammad, Y. M., Blanton, S., … Wittenberg, G. F. (2008). Constraint-induced movement therapy results in increased motor map area in subjects 3 to 9 months after stroke. *Neurorehabilitation and Neural Repair*, *22*(5), 505–513. Doi:22/5/505 [pii] https://doi.org/10.1177/1545968308317531.

Shin, J. C., Kim, K. N., Yoo, J., Kim, I. S., Yun, S., Lee, H., … Park, K. I. (2015). Clinical trial of human fetal brain-derived neural stem/progenitor Cell transplantation in patients with traumatic cervical spinal cord injury. *Neural Plasticity*, *2015*, 630932. https://doi.org/10.1155/2015/630932.

Stetkarova, I., & Kofler, M. (2013). Differential effect of baclofen on cortical and spinal inhibitory circuits. *Clinical Neurophysiology*, *124*(2), 339–345. https://doi.org/10.1016/j.clinph.2012.07.005.

Stokic, D. S., & Yablon, S. A. (2012). Effect of concentration and mode of intrathecal baclofen administration on soleus H-reflex in patients with muscle hypertonia. *Clinical Neurophysiology*, *123*(11), 2200–2204. https://doi.org/10.1016/j.clinph.2012.04.007.

Stokic, D. S., Yablon, S. A., Hayes, A., Vesovic-Potic, V., & Olivier, J. (2006). Dose-response relationship between the H-reflex and continuous intrathecal baclofen administration for management of spasticity. *Clinical Neurophysiology*, *117*(6), 1283–1289. https://doi.org/10.1016/j.clinph.2006.02.018.

Tabakow, P., Jarmundowicz, W., Czapiga, B., Fortuna, W., Miedzybrodzki, R., Czyz, M., … Raisman, G. (2013). Transplantation of autologous olfactory ensheathing cells in complete human spinal cord injury. *Cell Transplantation*, *22*(9), 1591–1612. https://doi.org/10.3727/096368912X663532.

Theiss, R. D., Hornby, T. G., Rymer, W. Z., & Schmit, B. D. (2011). Riluzole decreases flexion withdrawal reflex but not voluntary ankle torque in human chronic spinal cord injury. *Journal of Neurophysiology*, *105*(6), 2781–2790. https://doi.org/10.1152/jn.00570.2010.

Thomas, S. L., & Gorassini, M. A. (2005). Increases in corticospinal tract function by treadmill training after incomplete spinal cord injury. *Journal of Neurophysiology*, *94*(4), 2844–2855. doi:00532.2005 [pii] https://doi.org/10.1152/jn.00532.2005.

Trumbower, R. D., Hayes, H. B., Mitchell, G. S., Wolf, S. L., & Stahl, V. A. (2017). Effects of acute intermittent hypoxia on hand use after spinal cord trauma: A preliminary study. *Neurology*, *89*(18), 1904–1907. https://doi.org/10.1212/WNL.0000000000004596.

Vaquero, J., Zurita, M., Rico, M. A., Bonilla, C., Aguayo, C., Fernandez, C., … Neurological Cell Therapy Group. (2017). Repeated subarachnoid administrations of autologous mesenchymal stromal cells supported in autologous plasma improve quality of life in patients suffering incomplete spinal cord injury. *Cytotherapy*, *19*(3), 349–359. https://doi.org/10.1016/j.jcyt.2016.12.002.

Vaquero, J., Zurita, M., Rico, M. A., Bonilla, C., Aguayo, C., Montilla, J., … Neurological Cell Therapy Group. (2016). An approach to personalized cell therapy in chronic complete paraplegia: The Puerta de Hierro phase I/II clinical trial. *Cytotherapy*, *18*(8), 1025–1036. https://doi.org/10.1016/j.jcyt.2016.05.003.

Vetrugno, R., Liguori, R., Cortelli, P., & Montagna, P. (2003). Sympathetic skin response: Basic mechanisms and clinical applications. *Clinical Autonomic Research*, *13*(4), 256–270. https://doi.org/10.1007/s10286-003-0107-5.

Wirth, B., Van Hedel, H. J., & Curt, A. (2008). Changes in corticospinal function and ankle motor control during recovery from incomplete spinal cord injury. *Journal of Neurotrauma*, *25*(5), 467–478. https://doi.org/10.1089/neu.2007.0472.

Wittenberg, G. F., Chen, R., Ishii, K., Bushara, K. O., Eckloff, S., Croarkin, E., … Cohen, L. G. (2003). Constraint-induced therapy in stroke: Magnetic-stimulation motor maps and cerebral activation. *Neurorehabilitation and Neural Repair*, *17*(1), 48–57.

Xie, J., & Boakye, M. (2008). Electrophysiological outcomes after spinal cord injury. *Neurosurgical Focus*, *25*(5). https://doi.org/10.3171/FOC.2008.25.11.E11, E11.

Zewdie, E. T., Roy, F. D., Yang, J. F., & Gorassini, M. A. (2015). Facilitation of descending excitatory and spinal inhibitory networks from training of endurance and precision walking in participants with incomplete spinal cord injury. *Progress in Brain Research*, *218*, 127–155. https://doi.org/10.1016/bs.pbr.2014.12.005.

Zhao, Y., Tang, F., Xiao, Z., Han, G., Wang, N., Yin, N., … Dai, J. (2017). Clinical study of NeuroRegen scaffold combined with human mesenchymal stem cells for the repair of chronic complete spinal cord injury. *Cell Transplantation*, *26*(5), 891–900. https://doi.org/10.3727/096368917X695038.

Ziemann, U., Chen, R., Cohen, L. G., & Hallett, M. (1998). Dextromethorphan decreases the excitability of the human motor cortex. *Neurology*, *51*, 1320–1324.

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Chapter 30

Features and physiology of spinal stretch reflexes in people with chronic spinal cord injury

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List of abbreviations

A-P GRF	anterior-posterior ground reaction force
CP	cerebral palsy
CNS	central nervous system
EMG	electromyography
LLR	(spinal) long latency reflex
MLR	(spinal) medium latency reflex
SCI	spinal cord injury
SE	standard error (of mean)
SLR	(spinal) short latency reflex
TA	tibialis anterior

Introduction

The activity of spinal reflex pathways is task- and phase-dependently modulated in normal motor control (Duysens, Bastiaanse, Smits-Engelsman, & Dietz, 2004; Stein & Capaday, 1988; Zehr & Stein, 1999). During locomotion, different sensory afferents and associated spinal pathways contribute to the generation of locomotor muscle activity (Grey, Nielsen, Mazzaro, & Sinkjaer, 2007; Mazzaro, Grey, do Nascimento, & Sinkjaer, 2006; Mazzaro, Grey, & Sinkjaer, 2005; Sinkjaer, Andersen, & Larsen, 1996). After spinal cord injury (SCI) disrupts the activity of supraspinal and propriospinal pathways, spinal reflexes are often altered (Crone, Johnsen, Biering-Sorensen, & Nielsen, 2003; Hiersemenzel, Curt, & Dietz, 2000; Stein, Yang, Belanger, & Pearson, 1993; Thompson, Estabrooks, Chong, & Stein, 2009; Yang et al., 1991). Abnormal neuronal behaviors and reflex behaviors during static motor tasks or isolated joint motion in individuals with SCI (Gorassini, Knash, Harvey, Bennett, & Yang, 2004; Hornby, Kahn, Wu, & Schmit, 2006; Hultborn, 2003; Li, Gorassini, & Bennett, 2004) have led to our fields' general assumption that spinal reflex abnormalities contribute to movement disorders (Dietz & Sinkjaer, 2007; Nielsen, Crone, & Hultborn, 2007). A typical example is spasticity, which is commonly characterized by a velocity-dependent increase in tonic stretch reflexes with exaggerated tendon jerks (Lance, 1980). Spasticity, which is reported to affect 65%–78% of people after SCI (Adams & Hicks, 2005; Maynard, Karunas, & Waring, 1990; Skold, Levi, & Seiger, 1999) is negatively associated with quality of life after SCI (Westerkam, Saunders, & Krause, 2011). While different symptoms are likely reported as spasticity in clinical practice, including the hyperexcitability of tonic (e.g., hypertonia) and phasic (e.g., clonus) stretch reflexes (Adams & Hicks, 2005), spastic movement disorders are often viewed as problems of hyperactivity in spinal stretch reflex pathways. However, an increasing body of findings in stroke, multiple sclerosis, and cerebral palsy (CP) questions this view (see opinion paper by Nielsen, Christensen, Farmer, & Lorentzen, 2020).

This chapter reviews and discusses functions and contributions of spinal stretch reflex pathways in normal locomotion, characteristics of stretch reflexes in different task conditions (e.g., in resting and actively contracting muscles) in people after SCI, and their potential implications in spastic movement disorders post-SCI.

Cellular, Molecular, Physiological, and Behavioral Aspects of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822427-4.00030-7

Spinal stretch reflexes

An abrupt stretch of a muscle elicits stretch reflexes in that muscle. In an actively contracting lower extremity muscle, three components of stretch reflexes can be observed (Fig. 1): spinal short-latency reflex (SLR, also known as M1, mainly Ia muscle spindle afferent origin), spinal medium-latency reflex (MLR, also known as M2, presumably mainly spindle afferent II mediated), and long-latency reflex (LLR, also known as M3, suggested to be transcortical or subcortical) (Af Klint, Mazzaro, Nielsen, Sinkjaer, & Grey, 2010; Corna, Grasso, Nardone, & Schieppati, 1995; Schieppati & Nardone, 1997; Sinkjaer, Andersen, Nielsen, & Hansen, 1999). Normally, SLR is the most dominant and persistent among the three components. In order to investigate Ia excitation of homonymous motoneurons, the Hoffmann (or H-) reflex is frequently used as a convenient substitute to eliciting SLR, as these responses share the same pathways (Henneman & Mendell, 1980; Mendell & Henneman, 1971). However, SLR and H-reflex do not necessarily respond to modulatory input in the same way (Sinkjaer et al., 1996). The H-reflex is an electrically-elicited spinal reflex that arises mainly from synchronous axonal excitation of large Ia (and some Ib/II) afferents, whereas the stretch reflexes elicited by rapid joint rotation arise from less synchronous activation of Ia and II afferents and reflect γ-motoneuron mediated fusimotor control (Henneman & Mendell, 1980; Magladery, Porter, Park, & Teasdall, 1951). Ib afferents arising from Golgi tendon organ also fire in response to muscle stretch, and depending on the motor task, also excite motoneurons via interneurons (Donelan & Pearson, 2004; Duysens, Clarac, & Cruse, 2000; Gossard, Brownstone, Barajon, & Hultborn, 1994; Jankowska & Edgley, 2010; Jankowska & McCrea, 1983; Nichols, 2018; Schafer, Dadfar, Hartel, Haupts, & Fischer, 1999; Vincent et al., 2017). Thus, investigation of stretch reflexes with mechanical perturbation provides important information for understanding normal and impaired motor control; it is not readily substituted by the H-reflex studies.

Function of the soleus stretch reflex pathways in intact human locomotion

During locomotion, stretch and load receptor afferents (i.e., Ia, II, and Ib) fire in a phasic manner, in accord with joint rotations that change the muscle length and loading/unloading (i.e., stance/swing), and contribute to the excitation of plantarflexor motoneurons through reflex pathways (Donelan & Pearson, 2004; Gossard et al., 1994; Mayer et al., 2018). To understand how different sensory afferent pathways contribute to soleus activity during the stance phase of locomotion, Sinkjaer and his colleagues applied fast and slow dorsiflexion or plantarflexion perturbations while participants walked on a treadmill (Grey et al., 2007; Mazzaro et al., 2005, 2006; Sinkjaer, Andersen, Ladouceur, Christensen, & Nielsen, 2000). During the stance phase, when the naturally occurring dorsiflexion is blocked or plantarflexion is imposed, the ankle plantarflexors become unloaded and the afferent firing would decrease. This unloading manipulation results in a significant reduction of soleus activity (Sinkjaer et al., 2000). Since this unloading response is unaffected by an ischemic block of Ia afferent or block of the common peroneal nerve that causes reciprocal inhibition of the plantarflexors, feedback from spindle afferent II and/or load receptor afferent Ib from the plantarflexors would be the major contributors to naturally occurring (i.e., undisturbed) soleus activity in the mid-stance phase (Sinkjaer et al., 2000). When additional dorsiflexion is imposed during the same (mid-stance) phase, it elicits spinal stretch reflexes (Mazzaro et al., 2005). A picture that emerged through those studies was that Ia, II, and Ib contribute differently to the stance phase soleus activity; that is,

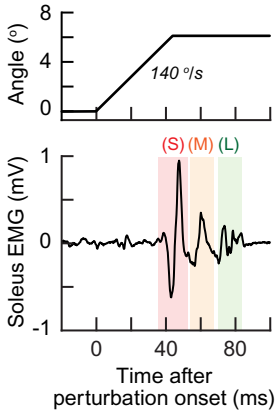

FIG. 1 Soleus stretch reflexes. An example of the soleus short (SLR), medium (MLR), and long (LLR) latency stretch reflexes elicited by 6° of ankle dorsiflexion at 140°/s during standing in an individual with no known neurological injuries.

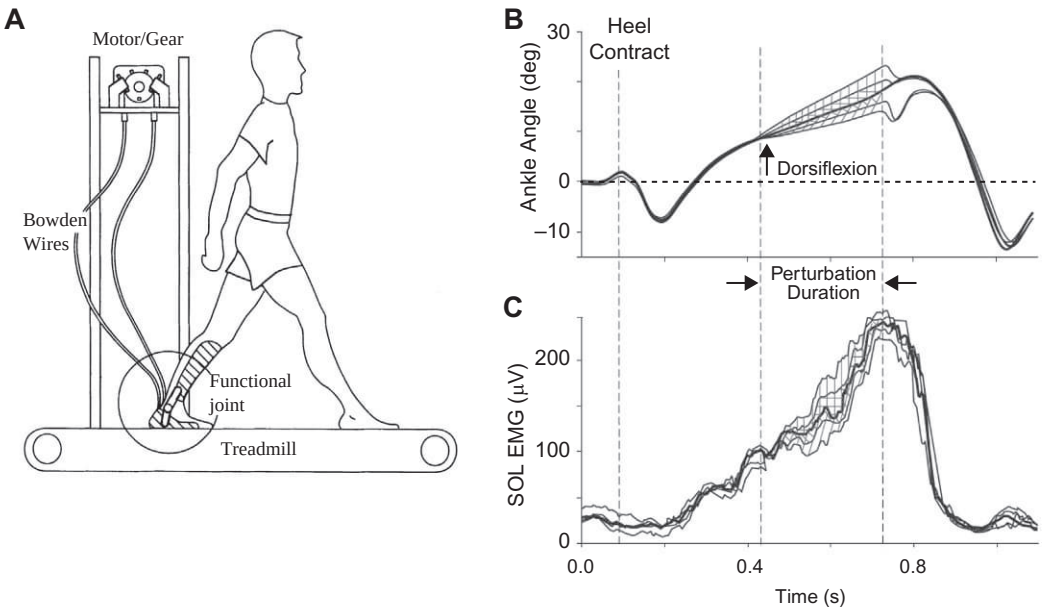

FIG. 2 Proprioceptive afferent input contributes to the soleus EMG activity during walking. Slow and small ankle joint rotation perturbations (enhancement or reduction of dorsiflexion) that manipulate the activity of stretch and load receptor afferents change the soleus EMG activity during the stance phase of walking (Mazzaro et al., 2005). (A) Experimental setup. The participant wears a motorized mechanical joint, which can impose precisely timed and controlled (both in amount and speed) ankle joint rotation at any part of the gait cycle (Sinkjaer et al., 1996). (B) A thick line indicates ankle joint angle during non-perturbed steps and thin lines indicate dorsiflexion enhancement and reduction perturbations (±2° at ±6°/s and ± 5° at ±16°/s). During the stance phase of non-perturbed steps, ≅10° of dorsiflexion occurred at 33°/s. (C) Rectified and filtered soleus EMG during perturbed and non-perturbed steps that correspond to (B). *(Modified from Mazzaro, N., Grey, M. J., & Sinkjaer, T. (2005). Contribution of afferent feedback to the soleus muscle activity during human locomotion.* Journal of Neurophysiology, 93*(1), 167–177. https://doi.org/10.1152/jn.00283.2004).*

SLR originated from Ia excitation is present when rapid perturbation triggers a corrective reaction, whereas feedback from Ib and/or II afferents likely contribute to the soleus activation in unperturbed steps (Sinkjaer et al., 2000). In line with locomotor-related Ib excitation found in cats (Donelan & Pearson, 2004; Gossard et al., 1994), the contribution of force-sensitive afferent pathways to the ongoing soleus activation in unperturbed steps has been repeatedly confirmed in humans during more natural-like walking conditions (Af Klint et al., 2010; Grey et al., 2007; Mazzaro et al., 2005, 2006) (Fig. 2). These studies show that Ia-mediated stretch reflex pathways are accessible on a moment-to-moment basis when there is a need to increase the muscle activity in response to small or large perturbation, but the primary pathways that generate the normal, undisturbed stance phase soleus activation during locomotion are likely not Ia but load sensitive afferents mediated pathways (Grey et al., 2007).

Features of spinal stretch reflexes in people with SCI

Spinal reflexes change after SCI (Crone et al., 2003; Hiersemenzel et al., 2000; Stein et al., 1993; Thompson et al., 2009; Yang et al., 1991). In the soleus muscle of people with chronic incomplete SCI, task-dependent modulation of the H-reflex becomes absent or diminished (Boorman, Lee, Becker, & Windhorst, 1996; Thompson et al., 2009); Ib inhibition becomes absent (Morita et al., 2006); reciprocal inhibition between the soleus and tibialis anterior becomes abnormal (Ashby & Wiens, 1989; Boorman et al., 1996; Boorman, Hulliger, Lee, Tako, & Tanaka, 1991; Crone et al., 2003; Thompson et al., 2009; Xia & Rymer, 2005); and recurrent inhibition may increase (Shefner, Berman, Sarkarati, & Young, 1992). Changes of neuronal (i.e., motoneurons and interneurons) behaviors in the spinal cord (Gorassini et al., 2004; Hultborn, 2003; Li et al., 2004) would also likely be part of these reflex abnormalities. If and how these abnormal reflex characteristics, which are often defined in non-dynamic postures and tasks, affect control and execution of dynamic motion, such as locomotion, are yet to be fully understood.

When SCI results in affecting the behaviors of different spinal pathways, what happens to the spinal stretch reflexes? In spastic individuals with chronic SCI, the soleus stretch reflex excitability is elevated during sitting or lying in supine (Mirbagheri, Barbeau, Ladouceur, & Kearney, 2001; Nakazawa, Kawashima, & Akai, 2006); and repeated ankle joint rotations facilitate the soleus reflexes and reflex-induced plantarflexion torque velocity-dependently (Hornby et al., 2006).

Unlike the observations in people with spastic hemiparesis due to stroke, in whom the reflexes are hyperexcitable at rest or in passive conditions but near normal during active muscle contractions (e.g., Berger, Horstmann, & Dietz, 1988; Sinkjaer & Magnussen, 1994), in spastic individuals with SCI, the stretch reflex gain and reflex stiffness do not decrease with muscle activation (rather, they remain high) (Mirbagheri et al., 2001). Similarly, abnormal modulation and large soleus reflexes during voluntary muscle contraction have also been found with the H-reflex in people with chronic SCI (Kim, Corcos, & Hornby, 2015; Taylor, Ashby, & Verrier, 1984; Thompson et al., 2009). Do these observations made in static postures and tasks account for stretch reflex behaviors that impair locomotion in people with SCI?

Soleus stretch reflexes during locomotion in people with chronic incomplete SCI

In people with chronic incomplete SCI, clonus and abnormal modulation of the locomotor soleus H-reflex activity are frequently present (Barbeau, Ladouceur, Mirbagheri, & Kearney, 2002; Corcos, Gottlieb, Penn, Myklebust, & Agarwal, 1986; Fung & Barbeau, 1989, 1994; Hidler & Rymer, 1999; Knikou, Angeli, Ferreira, & Harkema, 2009; Stein et al., 1993; Yang et al., 1991). A recent study showed that the SLR, MLR, and H-reflex are abnormally modulated during walking in individuals with chronic incomplete SCI (Thompson, Mrachacz-Kersting, Sinkjaer, & Andersen, 2019). During the swing phase, the SLR and H-reflex were suppressed in individuals without injuries but not in an individual with SCI (Fig. 3), suggesting reduced inhibition of Ia excitatory pathways in this phase in individuals with SCI. MLR was modulated similarly to SLR; in individuals with SCI, MLR amplitudes were very large in the mid-late swing phase (Fig. 3). Such exaggerated MLR could be due to reduced inhibition of group II afferents, increased oligo or polysynaptic Ia excitation, and/or increased excitation of other afferents (e.g., actions of excitatory and inhibitory interneurons that receive input from Ib afferents could also affect MLR modulation (Jankowska & Edgley, 2010; Schafer et al., 1999). Unique firing behaviors of Ia, II, and Ib afferents (Donelan & Pearson, 2004; Henneman & Mendell, 1980), together with altered modulation of their interneuron excitability, may also partly explain abnormal soleus EMG burst or large MLR activity in the late-swing phase of locomotion in people with SCI.

It is noteworthy that, in addition to abnormal modulation of locomotor stretch reflexes, a normal positive correlation between locomotor EMG and reflex excitability (Stein & Capaday, 1988) was rare in individuals with SCI (Thompson et al., 2019). This suggests that, while useful in characterizing the pathways altered by SCI, the reflex abnormalities measured in selected passive states, during isolated joint movements, and/or during static motor tasks may not explain how they impact locomotion after SCI. Hence, the question arises; does the hyperexcitability of stretch reflex pathways impair locomotion in people with incomplete SCI?

Stretch reflexes in spastic gait after SCI

Normally, the soleus stretch reflexes are phase-dependently modulated during walking, in accord with soleus motoneuron excitability level (expressed indirectly through the EMG activity), which is high in the mid-stance phase and little-to-none in the swing phase (Sinkjaer et al., 1996, 1999). In individuals with SCI, soleus EMG is often unsuppressed during the swing phase but reduced in the mid-stance phase (e.g., Fig. 3); at the same time, the stretch reflexes are unsuppressed or often larger in the mid-late swing phase. These observations support a possibility that inadequately hyperactive soleus elevating the reflex excitability and/or unsuppressed reflex pathways contributing to the reduced soleus suppression in the swing phase. Interestingly, and in consistently with observations in hemiplegic stroke and CP (Dietz & Sinkjaer, 2007, 2012), the soleus stretch reflexes are not hyperactive in mid-stance, during which group II and Ib afferents can positively contribute to the generation of locomotor EMG and Ia afferent input can further increase the EMG burst (see above). That is, the stretch reflex pathways are hyperactive and powerful when their activation is meaningless (e.g., during the swing), whereas they are "near" normal when the muscle is functionally active (i.e., during stance).

A clear example of not-suppressed stretch reflex pathways negatively affecting movements is clonus, which is triggered or produced by hyperexcitable stretch reflexes (Corcos et al., 1986; Latash, Penn, Corcos, & Gottlieb, 1989; Rossi, Mazzocchio, & Scarpini, 1990; however, see also Beres-Jones, Johnson, & Harkema, 2003). On the contrary to a common conception, elicitation of stretch reflexes requires only a degree or two of joint rotation (Stein & Kearney, 1995). In spastic individuals, small joint displacement such as repositioning a foot in the wheelchair (Wallace, Ross, & Thomas, 2012) or a foot's ground contact can induce clonus (Fig. 4). Clonus triggered by ground contact, which is a small joint motion perturbation, often continues into the stance phase, exaggerates breaking force, and reduces forward propulsion (Turns, Neptune, & Kautz, 2007). Furthermore, clonic bursts are often followed by more clonic bursts and/or a smaller fused push-off burst in the mid-late stance phase (Fig. 4), which would result in the ineffective generation of propulsive force

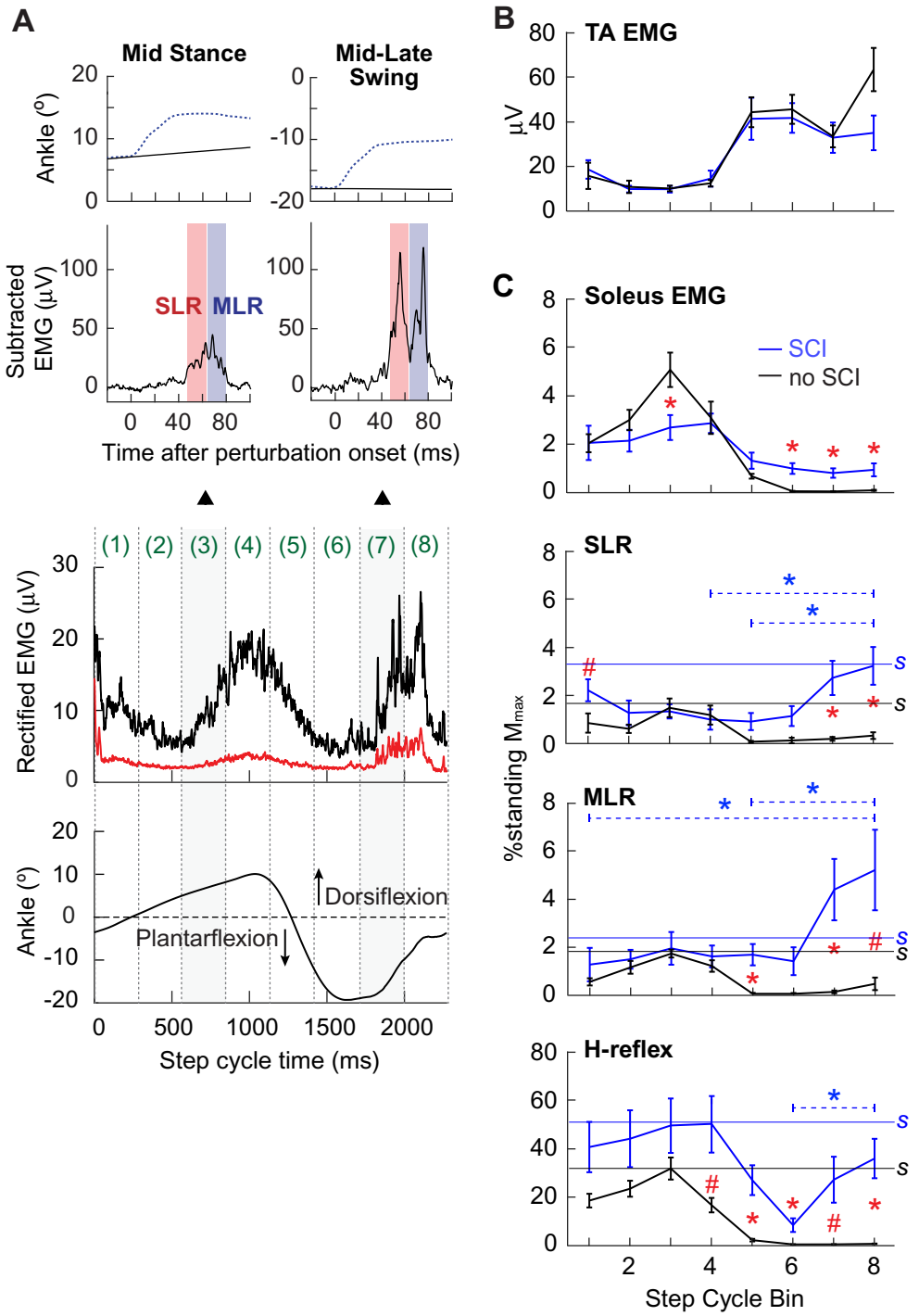

FIG. 3 Soleus stretch reflexes during walking in people with chronic incomplete SCI. (A) Soleus stretch reflexes elicited by 6° dorsiflexion perturbation at 250°/s in mid-stance and mid-late swing, soleus, and tibialis anterior (TA) EMG, and ankle joint motion in individuals with chronic incomplete SCI. The top panel shows the average ankle joint motion around the time of perturbation in unperturbed steps (solid line) and perturbed steps (dotted line). The second panel shows the averaged [perturbed − unperturbed] EMG response. 10–15 responses were averaged together. The third panel shows locomotor EMG activity in the soleus (black) and TA (red). The fourth panel shows the average ankle joint motion of unperturbed steps. For the third and fourth panels, >50 unperturbed steps were averaged together. (B) Locomotor TA EMG (mean ± SE) in individuals with chronic incomplete SCI ($N = 9$, blue) and individuals without injuries ($N = 9$, black). In general, bins 1–4 correspond to the stance phase, bin 5 to the stance-swing transition, and bins 6–8 to the swing phase. (C) Locomotor soleus EMG and reflexes in the same individuals with B. All values are normalized to the standing maximum M-wave (M_{max}) value. For reflexes, ≥10 responses were averaged together for each individual's each bin. Horizontal lines labeled with "S" indicate the average reflex sizes during standing. Statistical differences between the groups and between the bins (SCI group only) by Student *t*-test with Bonferroni correction are indicated with * ($\alpha = 0.05$) and # ($\alpha = 0.1$). *(Modified from Thompson, A. K., Estabrooks, K. L., Chong, S., & Stein, R. B. (2009). Spinal reflexes in ankle flexor and extensor muscles after chronic central nervous system lesions and functional electrical stimulation.* Neurorehabilitation and Neural Repair, *23(2), 133–142. https://doi.org/10.1177/1545968308321067).*

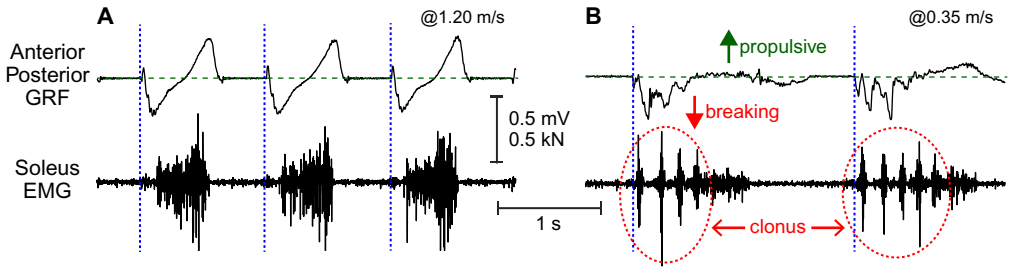

FIG. 4 Anterior-posterior (A-P) ground reaction force (GRF) and soleus EMG during walking. Positive A-P GRF represents propulsion and the positive area under the curve is the propulsive impulse; inversely, negative A-P GRF represents breaking and the negative area under the curve is the breaking impulse (Bowden et al., 2006). (A) In an individual with no injuries, after ground contact (indicated by vertical dotted lines), soleus EMG activity increases gradually through mid-late stance while the A-P GRF transitions smoothly from breaking to propulsion. (B) In a spastic individual, clonus triggered by ground contact and ineffective push-off burst are accompanied by exaggerating breaking force and little-to-no propulsive force.

(Turns et al., 2007) and reduction of gait speed (Bowden, Balasubramanian, Neptune, & Kautz, 2006). Thus, clonus impairs locomotion in people with incomplete SCI.

Do hyperexcitable stretch reflexes contribute to spastic gait in people with SCI? Among several spinal and supraspinal pathways possibly involved in spastic movement disorders (Burke, Wissel, & Donnan, 2013; Dietz & Sinkjaer, 2007; Hultborn, 2003; Nielsen et al., 2007), current opinions on post-stroke spastic gait are dismissive of hyperexcitable stretch reflexes (Dietz & Sinkjaer, 2015; Nielsen et al., 2020). In people with spastic hemiparesis due to stroke, stretch reflexes are hyperexcitable at rest or in passive conditions but near normal or even suppressed during active muscle contractions (Berger et al., 1988; Sinkjaer & Magnussen, 1994), and anti-spastic medication aiming to reduce hyperreflexia and hypertonus is not necessarily helpful (Dietz & Sinkjaer, 2012). Thus, the role of hyperexcitable stretch reflexes in impaired locomotion post-stroke is not immediately clear. Since the stretch reflex gain and stiffness in active versus passive conditions (Mirbagheri et al., 2001) and the effects of anti-spastic medicine such as baclofen and tizanidine (Hornby et al., 2006; Mirbagheri, Chen, & Rymer, 2010) seem to differ between spastic SCI and hemiparetic stroke, the origin of reflex hyperexcitability may be different, and further investigation would be essential in evaluating the role of hyperexcitable stretch reflexes in post-SCI spastic gait.

Consideration of CNS plasticity in addressing the reflex hyperexcitability in chronic SCI

Abnormal reflex behaviors observed in chronic, impaired movements do not necessarily mean that such reflex behaviors are the primary causes of impairments; they may be the results of (non-functional) CNS plasticity, adaptation to or compensation for other problems caused by injuries or disease. Thus, while impaired use of sensory afferent input or abnormally functioning spinal pathways may pose or exacerbate movement disorders, simply removing or disabling them may not solve the problem. This might be the case in treating post-stroke hemiparetic gait (Dietz & Sinkjaer, 2007, 2015; Nielsen et al., 2020) with pharmacological interventions that aim to tame stretch reflex hyperexcitability.

In people with incomplete SCI, as summarized above, behaviors of multiple spinal pathways including stretch reflex pathways become abnormal. When the spinal cord is in such states, feedback from certain afferents (e.g., muscle spindle afferents) and their associated reflexes (e.g., stretch reflexes) would be, not only useless but also detrimental in the execution of the motor function (e.g., Figs. 3 and 4). A rather simple CNS strategy to deal with this problem would be to circumvent it by avoiding activation of problem-causing afferents and their pathways. As a result, the muscles and limb with hyperreflexia would be engaged less, leading to a cascade of other complications, such as disuse atrophy, step and postural asymmetry, and other muscular mechanical changes (Dietz & Sinkjaer, 2007, 2012, 2015). To prevent such maladaptive problems, one might opt for surgical (Smyth & Peacock, 2000) or pharmacological approaches (Dario & Tomei, 2004; Sheean, 2006; Ward, 2008). However, suppressing the transmission of spinal pathways or eliminating afferent feedback does not normalize the excitability of a specific pathway in a targeted manner, and necessitates compensation and adaptation to pharmacologically or surgically induced changes (some of which are irreversible). In fact, in spastic stroke, the problem may well be that the afferent integration is too suppressed during walking (Mazzaro, Nielsen, Grey, & Sinkjaer, 2007). Functioning abnormally or being unusable does not mean that stretch reflex pathways should be uniformly suppressed or eliminated for good. Instead, making these pathways more usable by restoring their excitability modulation may help to attain better functional recovery. Indeed, in an individual with spastic hyperreflexia due to chronic incomplete SCI, when the soleus H-reflex excitability was reduced through operant down-conditioning, their locomotor EMG activity

improved in the conditioned soleus and other lower and upper leg muscles, and walking speed increased significantly (Thompson, Pomerantz, & Wolpaw, 2013; Thompson & Wolpaw, 2019). Interestingly but not surprisingly, decreasing the H-reflex excitability did not decrease but increased soleus activity in the mid-late stance phase (Fig. 5 in Thompson et al., 2013), likely contributed to increased walking speed in those individuals with SCI. These observations are in line with the above argument. An emerging picture is this: when the Ia excitatory pathway is not usable (because its excitability is too high and cannot be readily modulated) and its inappropriate activation hinders movement execution, the associated spinal circuitry (and thereby the associated muscles) would become less used as if it is to avoid activating the "annoying" Ia pathway. When the Ia excitatory pathway becomes modulable and thus usable (e.g., through operant conditioning; Thompson & Wolpaw, 2015; Wolpaw, 2018), it becomes unnecessary to avoid engaging that leg/muscle; this would allow the associated circuitry, including other pathways (e.g., group II and Ib pathways) to become functionally viable, enabling them to contribute to locomotor muscle activation. Regardless of whether or not hyperexcitable stretch or Ia reflex pathways are the causes of spastic gait, they are often part of it in people with SCI (Thompson et al., 2019), and their excitability reduction is accompanied by gait function improvement (Thompson et al., 2013; Thompson & Wolpaw, 2019). Stretch reflex stiffness and intrinsic muscle stiffness also decrease along with gait improvements resulting from long-term functional electrical stimulation assisted walking (Mirbagheri, Ladouceur, Barbeau, & Kearney, 2002) and robotic-assisted step training (Mirbagheri, Kindig, & Niu, 2015) in spastic individuals with chronic incomplete SCI.

Conclusion

Recently, the validity of hyperexcitable stretch reflexes as a cause of spastic hemiparetic gait disorders has been questioned (Dietz & Sinkjaer, 2007; Nielsen et al., 2020). So, we considered the following questions in spastic individuals with SCI. Do the soleus stretch reflexes become abnormal after SCI? Do the stretch reflexes behave abnormally during locomotion, and if so, do the abnormal reflexes contribute to their gait disorders?

The currently available data from spastic individuals with chronic SCI indicate that the stretch reflex gain and reflex stiffness are high (Mirbagheri et al., 2001); the soleus H-reflex is also large during voluntary muscle contraction (Kim et al., 2015; Taylor et al., 1984; Thompson et al., 2009). During walking, the soleus stretch reflexes (SLR, MLR) are near normal in the mid-late stance phase but are facilitated in the swing phase (Thompson et al., 2019). Unsuppressed stretch reflexes in mid-late swing through early stance trigger clonus, which very likely negatively affect locomotion in chronic SCI.

It would be important to remind ourselves that abnormal reflex behaviors observed during chronically impaired locomotion do not necessarily mean that they are the causes of impairments. Hyperexcitable stretch or Ia reflex pathways may be the partial causes of spastic gait or the products of compensatory or adaptive plasticity to chronic SCI; regardless of this, they are often part of post-SCI spastic gait (Thompson et al., 2019). When one considers these issues, simply removing or disabling stretch reflex pathways seems far from an optimal solution. Instead, making these pathways more usable by restoring their excitability modulation through neurobehavioral training (e.g., locomotor training and reflex operant conditioning) could be a better solution for enhancing functional recovery after SCI.

Applications to other areas of neuroscience

After SCI, many spinal reflexes become abnormal. Supported by abnormal reflex behaviors observed in muscles at rest or during static motor tasks, there has been a general assumption that abnormal spinal reflexes, especially hyperactive spinal stretch reflexes, contribute to spastic movement disorders in individuals with SCI. However, the cumulative evidence in other CNS populations such as stroke, multiple sclerosis, and cerebral palsy questions this view.

The findings in SCI suggest a negative impact of stretch reflex hyperexcitability on post-SCI spastic gait in the swing and swing-stance transition phases, whereas in the mid-late stance phase (where the plantarflexors are active) the behavior is near normal, as seen in stroke and CP individuals. This suggests that some parts of underlying neural mechanisms of hyperreflexia and spasticity are alike, whereas some other parts may differ between SCI and other CNS impaired populations. These differences and how they can help to guide the restoration of walking need to be carefully investigated in the future.

Regardless of the etiology of spastic movement disorders, when examining abnormal reflex behaviors, one must be careful not to presume a causal relationship between a malfunctioning reflex and motor impairments. In the case of SCI, the hyperexcitability of stretch reflex pathways may be a cause or a result of (i.e., adaptation to) chronically impaired movement. In another CNS population, another kind of reflex abnormality may be more prominent. Neurobehavioral training approach, such as reflex operant conditioning, may therefore become a useful tool for improving the excitability and behavior of a specific reflex pathway that is a part of an individual's motor deficits, so as to enhance motor function recovery in each and every individual.

Mini-dictionary of terms

- Stretch reflex. A fast spinal reflex originated from multiple sensory afferents. Stretch of the nerve endings in the muscle spindle excites group Ia and II afferents, which in turn excites α-motoneurons in the spinal cord. The gain of this reflex is affected by γ-motoneuron mediated fusimotor control. Muscle stretch (muscle tension change) also excites group Ib Golgi tendon organ afferents.
- Hoffmann (or H-) reflex. An artificially elicited spinal reflex, commonly viewed as an electrical analog of the spinal short-latency stretch reflex. With electrical stimulation of a mixed nerve (e.g., tibial nerve), group Ia (and some II) afferent axons and group Ib Golgi tendon organ afferent axons are excited electrically.
- Clonus. An involuntary, reflexive, rhythmic, cyclic muscle activation. While its mechanisms are not completely understood, it is generally accompanied by hyperreflexia due to CNS lesions.
- Spasticity. A condition that is commonly characterized by a velocity-dependent increase in tonic stretch reflexes with exaggerated tendon jerks.
- Dorsiflexion. Upward flexion of the foot. Upward rotation of the ankle joint.
- Plantarflexion. Downward flexion of the foot. Downward rotation of the ankle joint.
- Soleus. A muscle in the lower calf, situated below the gastrocnemius muscles. Its action is plantarflexion. It is innervated by the tibial nerve.
- Motoneuron (or α-motoneuron). Part of a pool of large neurons located in the anterior/ventral portion of the spinal cord. Motoneurons innervate extrafusal muscle fibers of skeletal muscle, and their excitation produces muscle contraction. α-motoneurons are distinct from γ motoneurons, which innervate intrafusal muscle fibers of muscle spindles.
- Interneuron. A neuron that transmits signals between other neurons.
- Hemiparesis. A unilateral paresis (a weakness of one side of the body). An inability to move one side of the body. Hemiparesis is often caused by stroke or other brain conditions and injuries. Its most severe form is called hemiplegia, which is complete paralysis of half of the body.

Key facts of spinal reflexes

- Although they are involuntary responses to stimuli applied to the periphery, spinal reflexes are posture and task-dependently modulated.
- Excitability of spinal reflexes is phase-dependently modulated during dynamic motion such as locomotion.
- In humans, specific patterns of reflex behaviors are acquired use- and activity-dependently in early childhood and maintained throughout life.
- Aging affects the excitability and behaviors of spinal reflexes.
- Spinal reflexes are affected by injuries and diseases. Some of the reflex changes caused by injuries and/or diseases can be reversed through various treatments and interventions.

Summary points

- In spastic individuals with chronic SCI, the stretch reflex gain and reflex stiffness are high at rest and do not decrease with muscle activation.
- In the mid-late stance phase of walking, the stretch reflex behavior is near normal, as seen in post-stroke and CP individuals.
- Hyperexcitable stretch reflexes in mid-late swing through swing-stance transition trigger clonus and negatively affect locomotion in people with chronic SCI.
- This suggests that some of the underlying neural mechanisms of hyperreflexia and spasticity are alike whereas some other mechanisms may differ between SCI and other CNS impaired populations.
- Different from pharmacologically or surgically disabling a reflex pathway, changing a reflex through operant conditioning can change the reflex behavior in a desirable direction and induce CNS multi-site plasticity in the brain and the spinal cord.
- Changing an abnormal reflex behavior through neurobehavioral training (e.g., locomotor training and reflex conditioning) could provide a new means to enhance motor function recovery in people with SCI.

Funding acknowledgments

The presented work was supported in part by the National Institutes of Health [NS069551 and NS114279 to AKT, U44 NS114420 (Clements, Thompson, Wolpaw), P41-EB018783 (Wolpaw), P2C HD086844 (Kautz), U54-GM104941 (Binder-MacLeod)]; the South Carolina Spinal Cord Injury Research Fund (AKT); the New York State Spinal Cord Injury Research Trust Fund (AKT and Wolpaw); and Juhl Memorial Scholarship Denmark (TS).

References

Adams, M. M., & Hicks, A. L. (2005). Spasticity after spinal cord injury. *Spinal Cord*, *43*(10), 577–586. https://doi.org/10.1038/sj.sc.3101757.

Af Klint, R., Mazzaro, N., Nielsen, J. B., Sinkjaer, T., & Grey, M. J. (2010). Load rather than length sensitive feedback contributes to soleus muscle activity during human treadmill walking. *Journal of Neurophysiology*, *103*(5), 2747–2756. https://doi.org/10.1152/jn.00547.2009.

Ashby, P., & Wiens, M. (1989). Reciprocal inhibition following lesions of the spinal cord in man. *Journal of Physiology*, *414*, 145–157.

Barbeau, H., Ladouceur, M., Mirbagheri, M. M., & Kearney, R. E. (2002). The effect of locomotor training combined with functional electrical stimulation in chronic spinal cord injured subjects: Walking and reflex studies. *Brain Research. Brain Research Reviews*, *40*(1–3), 274–291.

Beres-Jones, J. A., Johnson, T. D., & Harkema, S. J. (2003). Clonus after human spinal cord injury cannot be attributed solely to recurrent muscle-tendon stretch. *Experimental Brain Research*, *149*(2), 222–236. https://doi.org/10.1007/s00221-002-1349-5.

Berger, W., Horstmann, G. A., & Dietz, V. (1988). Spastic paresis: Impaired spinal reflexes and intact motor programs. *Journal of Neurology, Neurosurgery and Psychiatry*, *51*(4), 568–571.

Boorman, G., Hulliger, M., Lee, R. G., Tako, K., & Tanaka, R. (1991). Reciprocal Ia inhibition in patients with spinal spasticity. *Neuroscience Letters*, *127*(1), 57–60.

Boorman, G. I., Lee, R. G., Becker, W. J., & Windhorst, U. R. (1996). Impaired "natural reciprocal inhibition" in patients with spasticity due to incomplete spinal cord injury. *Electroencephalography and Clinical Neurophysiology*, *101*(2), 84–92.

Bowden, M. G., Balasubramanian, C. K., Neptune, R. R., & Kautz, S. A. (2006). Anterior-posterior ground reaction forces as a measure of paretic leg contribution in hemiparetic walking. *Stroke*, *37*(3), 872–876. https://doi.org/10.1161/01.STR.0000204063.75779.8d.

Burke, D., Wissel, J., & Donnan, G. A. (2013). Pathophysiology of spasticity in stroke. *Neurology*, *80*(3 Suppl. 2), S20–S26. https://doi.org/10.1212/WNL.0b013e31827624a7.

Corcos, D. M., Gottlieb, G. L., Penn, R. D., Myklebust, B., & Agarwal, G. C. (1986). Movement deficits caused by hyperexcitable stretch reflexes in spastic humans. *Brain*, *109*(Pt. 5), 1043–1058.

Corna, S., Grasso, M., Nardone, A., & Schieppati, M. (1995). Selective depression of medium-latency leg and foot muscle responses to stretch by an alpha 2-agonist in humans. *The Journal of Physiology*, *484*(Pt. 3), 803–809.

Crone, C., Johnsen, L. L., Biering-Sorensen, F., & Nielsen, J. B. (2003). Appearance of reciprocal facilitation of ankle extensors from ankle flexors in patients with stroke or spinal cord injury. *Brain*, *126*(Pt. 2), 495–507.

Dario, A., & Tomei, G. (2004). A benefit-risk assessment of baclofen in severe spinal spasticity. *Drug Safety*, *27*(11), 799–818.

Dietz, V., & Sinkjaer, T. (2007). Spastic movement disorder: Impaired reflex function and altered muscle mechanics. *Lancet Neurology*, *6*(8), 725–733. https://doi.org/10.1016/S1474-4422(07)70193-X.

Dietz, V., & Sinkjaer, T. (2012). Spasticity. *Handbook of Clinical Neurology*, *109*, 197–211. https://doi.org/10.1016/B978-0-444-52137-8.00012-7.

Dietz, V., & Sinkjaer, T. (2015). Secondary changes after damage of the central nervous system: Significance of spastic muscle tone in rehabilitation. In V. Dietz, & N. Ward (Eds.), *Oxford textbook of neurorehabilitation* Oxford University Press.

Donelan, J. M., & Pearson, K. G. (2004). Contribution of force feedback to ankle extensor activity in decerebrate walking cats. *Journal of Neurophysiology*, *92*(4), 2093–2104.

Duysens, J., Bastiaanse, C. M., Smits-Engelsman, B. C., & Dietz, V. (2004). Gait acts as a gate for reflexes from the foot. *Canadian Journal of Physiology and Pharmacology*, *82*(8–9), 715–722.

Duysens, J., Clarac, F., & Cruse, H. (2000). Load-regulating mechanisms in gait and posture: Comparative aspects. *Physiological Reviews*, *80*(1), 83–133.

Fung, J., & Barbeau, H. (1989). A dynamic EMG profile index to quantify muscular activation disorder in spastic paretic gait. *Electroencephalography and Clinical Neurophysiology*, *73*(3), 233–244.

Fung, J., & Barbeau, H. (1994). Effects of conditioning cutaneomuscular stimulation on the soleus h-reflex in normal and spastic paretic subjects during walking and standing. *Journal of Neurophysiology*, *72*(5), 2090–2104.

Gorassini, M. A., Knash, M. E., Harvey, P. J., Bennett, D. J., & Yang, J. F. (2004). Role of motoneurons in the generation of muscle spasms after spinal cord injury. *Brain*, *127*(Pt. 10), 2247–2258. https://doi.org/10.1093/brain/awh243.

Gossard, J. P., Brownstone, R. M., Barajon, I., & Hultborn, H. (1994). Transmission in a locomotor-related group ib pathway from hindlimb extensor muscles in the cat. *Experimental Brain Research*, *98*(2), 213–228. https://doi.org/10.1007/BF00228410.

Grey, M. J., Nielsen, J. B., Mazzaro, N., & Sinkjaer, T. (2007). Positive force feedback in human walking. *The Journal of Physiology*, *581*(Pt. 1), 99–105. https://doi.org/10.1113/jphysiol.2007.130088.

Henneman, E., & Mendell, L. M. (1980). Functional organization of motoneuron pool and its inputs. In *Handbook of physiology: Section 1: The nervous system volume ii, part 1 &2: Motor control* (pp. 423–507). American Physiological Society. https://doi.org/10.1002/cphy.cp010211.

Hidler, J. M., & Rymer, W. Z. (1999). A simulation study of reflex instability in spasticity: Origins of clonus. *IEEE Transactions on Rehabilitation Engineering*, *7*(3), 327–340.

Hiersemenzel, L. P., Curt, A., & Dietz, V. (2000). From spinal shock to spasticity: Neuronal adaptations to a spinal cord injury. *Neurology*, *54*(8), 1574–1582.

Hornby, T. G., Kahn, J. H., Wu, M., & Schmit, B. D. (2006). Temporal facilitation of spastic stretch reflexes following human spinal cord injury. *The Journal of Physiology*, *571*(Pt 3), 593–604. https://doi.org/10.1113/jphysiol.2005.102046.

Hultborn, H. (2003). Changes in neuronal properties and spinal reflexes during development of spasticity following spinal cord lesions and stroke: Studies in animal models and patients. *Journal of Rehabilitation Medicine*, (41 Suppl), 46–55.

Jankowska, E., & Edgley, S. A. (2010). Functional subdivision of feline spinal interneurons in reflex pathways from group ib and ii muscle afferents; an update. *The European Journal of Neuroscience*, *32*(6), 881–893. https://doi.org/10.1111/j.1460-9568.2010.07354.x.

Jankowska, E., & McCrea, D. A. (1983). Shared reflex pathways from ib tendon organ afferents and ia muscle spindle afferents in the cat. *The Journal of Physiology*, *338*, 99–111. https://doi.org/10.1113/jphysiol.1983.sp014663.

Kim, H. E., Corcos, D. M., & Hornby, T. G. (2015). Increased spinal reflex excitability is associated with enhanced central activation during voluntary lengthening contractions in human spinal cord injury. *Journal of Neurophysiology*, *114*(1), 427–439. https://doi.org/10.1152/jn.01074.2014.

Knikou, M., Angeli, C. A., Ferreira, C. K., & Harkema, S. J. (2009). Soleus h-reflex modulation during body weight support treadmill walking in spinal cord intact and injured subjects. *Experimental Brain Research*, *193*(3), 397–407. https://doi.org/10.1007/s00221-008-1636-x.

Lance, J. W. (1980). The control of muscle tone, reflexes, and movement: Robert wartenberg lecture. *Neurology*, *30*(12), 1303–1313.

Latash, M. L., Penn, R. D., Corcos, D. M., & Gottlieb, G. L. (1989). Short-term effects of intrathecal baclofen in spasticity. *Experimental Neurology*, *103*(2), 165–172.

Li, Y., Gorassini, M. A., & Bennett, D. J. (2004). Role of persistent sodium and calcium currents in motoneuron firing and spasticity in chronic spinal rats. *Journal of Neurophysiology*, *91*(2), 767–783.

Magladery, J. W., Porter, W. E., Park, A. M., & Teasdall, R. D. (1951). Electrophysiological studies of nerve and reflex activity in normal man. Iv. The two-neurone reflex and identification of certain action potentials from spinal roots and cord. *Bulletin of the Johns Hopkins Hospital*, *88*(6), 499–519.

Mayer, W. P., Murray, A. J., Brenner-Morton, S., Jessell, T. M., Tourtellotte, W. G., & Akay, T. (2018). Role of muscle spindle feedback in regulating muscle activity strength during walking at different speed in mice. *Journal of Neurophysiology*, *120*(5), 2484–2497. https://doi.org/10.1152/jn.00250.2018.

Maynard, F. M., Karunas, R. S., & Waring, W. P., 3rd. (1990). Epidemiology of spasticity following traumatic spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *71*(8), 566–569.

Mazzaro, N., Grey, M. J., do Nascimento, O. F., & Sinkjaer, T. (2006). Afferent-mediated modulation of the soleus muscle activity during the stance phase of human walking. *Experimental Brain Research*, *173*(4), 713–723. https://doi.org/10.1007/s00221-006-0451-5.

Mazzaro, N., Grey, M. J., & Sinkjaer, T. (2005). Contribution of afferent feedback to the soleus muscle activity during human locomotion. *Journal of Neurophysiology*, *93*(1), 167–177. https://doi.org/10.1152/jn.00283.2004.

Mazzaro, N., Nielsen, J. F., Grey, M. J., & Sinkjaer, T. (2007). Decreased contribution from afferent feedback to the soleus muscle during walking in patients with spastic stroke. *Journal of Stroke and Cerebrovascular Diseases*, *16*(4), 135–144. https://doi.org/10.1016/j.jstrokecerebrovasdis.2007.01.003.

Mendell, L. M., & Henneman, E. (1971). Terminals of single ia fibers: Location, density, and distribution within a pool of 300 homonymous motoneurons. *Journal of Neurophysiology*, *34*(1), 171–187.

Mirbagheri, M. M., Barbeau, H., Ladouceur, M., & Kearney, R. E. (2001). Intrinsic and reflex stiffness in normal and spastic, spinal cord injured subjects. *Experimental Brain Research*, *141*(4), 446–459.

Mirbagheri, M. M., Chen, D., & Rymer, W. Z. (2010). Quantification of the effects of an alpha-2 adrenergic agonist on reflex properties in spinal cord injury using a system identification technique. *Journal of Neuroengineering and Rehabilitation*, *7*, 29. https://doi.org/10.1186/1743-0003-7-29.

Mirbagheri, M. M., Kindig, M. W., & Niu, X. (2015). Effects of robotic-locomotor training on stretch reflex function and muscular properties in individuals with spinal cord injury. *Clinical Neurophysiology*, *126*(5), 997–1006. https://doi.org/10.1016/j.clinph.2014.09.010.

Mirbagheri, M. M., Ladouceur, M., Barbeau, H., & Kearney, R. E. (2002). The effects of long-term fes-assisted walking on intrinsic and reflex dynamic stiffness in spastic spinal-cord-injured subjects. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, *10*(4), 280–289.

Morita, H., Shindo, M., Momoi, H., Yanagawa, S., Ikeda, S., & Yanagisawa, N. (2006). Lack of modulation of ib inhibition during antagonist contraction in spasticity. *Neurology*, *67*(1), 52–56. https://doi.org/10.1212/01.wnl.0000223399.59212.f4.

Nakazawa, K., Kawashima, N., & Akai, M. (2006). Enhanced stretch reflex excitability of the soleus muscle in persons with incomplete rather than complete chronic spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *87*(1), 71–75. https://doi.org/10.1016/j.apmr.2005.08.122.

Nichols, T. R. (2018). Distributed force feedback in the spinal cord and the regulation of limb mechanics. *Journal of Neurophysiology*, *119*(3), 1186–1200. https://doi.org/10.1152/jn.00216.2017.

Nielsen, J. B., Christensen, M. S., Farmer, S. F., & Lorentzen, J. (2020). Spastic movement disorder: Should we forget hyperexcitable stretch reflexes and start talking about inappropriate prediction of sensory consequences of movement? *Experimental Brain Research*, *238*(7–8), 1627–1636. https://doi.org/10.1007/s00221-020-05792-0.

Nielsen, J. B., Crone, C., & Hultborn, H. (2007). The spinal pathophysiology of spasticity—From a basic science point of view. *Acta Physiologica (Oxford, England)*, *189*(2), 171–180.

Rossi, A., Mazzocchio, R., & Scarpini, C. (1990). Clonus in man: A rhythmic oscillation maintained by a reflex mechanism. *Electroencephalography and Clinical Neurophysiology*, *75*(2), 56–63.

Schafer, S. S., Dadfar, F., Hartel, J., Haupts, S., & Fischer, M. (1999). The period of latency before a muscle receptor generates an action potential as a response to a muscle stretch. *Brain Research*, *843*(1–2), 36–47.

Schieppati, M., & Nardone, A. (1997). Medium-latency stretch reflexes of foot and leg muscles analysed by cooling the lower limb in standing humans. *The Journal of Physiology*, *503*(Pt. 3), 691–698.

Sheean, G. (2006). Botulinum toxin treatment of adult spasticity: A benefit-risk assessment. *Drug Safety*, *29*(1), 31–48.

Shefner, J. M., Berman, S. A., Sarkarati, M., & Young, R. R. (1992). Recurrent inhibition is increased in patients with spinal cord injury. *Neurology*, *42*(11), 2162–2168.

Sinkjaer, T., Andersen, J. B., Ladouceur, M., Christensen, L. O., & Nielsen, J. B. (2000). Major role for sensory feedback in soleus EMG activity in the stance phase of walking in man. *Journal of Physiology*, *523*(Pt. 3), 817–827.

Sinkjaer, T., Andersen, J. B., & Larsen, B. (1996). Soleus stretch reflex modulation during gait in humans. *Journal of Neurophysiology*, *76*(2), 1112–1120.

Sinkjaer, T., Andersen, J. B., Nielsen, J. F., & Hansen, H. J. (1999). Soleus long-latency stretch reflexes during walking in healthy and spastic humans. *Clinical Neurophysiology*, *110*(5), 951–959.

Sinkjaer, T., & Magnussen, I. (1994). Passive, intrinsic and reflex-mediated stiffness in the ankle extensors of hemiparetic patients. *Brain*, *117*(Pt. 2), 355–363. https://doi.org/10.1093/brain/117.2.355.

Skold, C., Levi, R., & Seiger, A. (1999). Spasticity after traumatic spinal cord injury: Nature, severity, and location. *Archives of Physical Medicine and Rehabilitation*, *80*(12), 1548–1557.

Smyth, M. D., & Peacock, W. J. (2000). The surgical treatment of spasticity. *Muscle and Nerve*, *23*(2), 153–163.

Stein, R. B., & Capaday, C. (1988). The modulation of human reflexes during functional motor tasks. *Trends in Neurosciences*, *11*(7), 328–332.

Stein, R. B., & Kearney, R. E. (1995). Nonlinear behavior of muscle reflexes at the human ankle joint. *Journal of Neurophysiology*, *73*(1), 65–72.

Stein, R. B., Yang, J. F., Belanger, M., & Pearson, K. G. (1993). Modification of reflexes in normal and abnormal movements. *Progress in Brain Research*, *97*, 189–196.

Taylor, S., Ashby, P., & Verrier, M. (1984). Neurophysiological changes following traumatic spinal lesions in man. *Journal of Neurology, Neurosurgery, and Psychiatry*, *47*(10), 1102–1108.

Thompson, A. K., Estabrooks, K. L., Chong, S., & Stein, R. B. (2009). Spinal reflexes in ankle flexor and extensor muscles after chronic central nervous system lesions and functional electrical stimulation. *Neurorehabilitation and Neural Repair*, *23*(2), 133–142. https://doi.org/10.1177/1545968308321067.

Thompson, A. K., Mrachacz-Kersting, N., Sinkjaer, T., & Andersen, J. B. (2019). Modulation of soleus stretch reflexes during walking in people with chronic incomplete spinal cord injury. *Experimental Brain Research*, *237*(10), 2461–2479. https://doi.org/10.1007/s00221-019-05603-1.

Thompson, A. K., Pomerantz, F. R., & Wolpaw, J. R. (2013). Operant conditioning of a spinal reflex can improve locomotion after spinal cord injury in humans. *The Journal of Neuroscience*, *33*(6), 2365–2375. https://doi.org/10.1523/JNEUROSCI.3968-12.2013.

Thompson, A. K., & Wolpaw, J. R. (2015). Restoring walking after spinal cord injury: Operant conditioning of spinal reflexes can help. *The Neuroscientist*, *21*(2), 203–215. https://doi.org/10.1177/1073858414527541.

Thompson, A. K., & Wolpaw, J. R. (2019). H-reflex conditioning during locomotion in people with spinal cord injury. *The Journal of Physiology*. https://doi.org/10.1113/JP278173.

Turns, L. J., Neptune, R. R., & Kautz, S. A. (2007). Relationships between muscle activity and anteroposterior ground reaction forces in hemiparetic walking. *Archives of Physical Medicine and Rehabilitation*, *88*(9), 1127–1135. https://doi.org/10.1016/j.apmr.2007.05.027.

Vincent, J. A., Gabriel, H. M., Deardorff, A. S., Nardelli, P., Fyffe, R. E. W., Burkholder, T., et al. (2017). Muscle proprioceptors in adult rat: Mechanosensory signaling and synapse distribution in spinal cord. *Journal of Neurophysiology*, *118*(5), 2687–2701. https://doi.org/10.1152/jn.00497.2017.

Wallace, D. M., Ross, B. H., & Thomas, C. K. (2012). Characteristics of lower extremity clonus after human cervical spinal cord injury. *Journal of Neurotrauma*, *29*(5), 915–924. https://doi.org/10.1089/neu.2010.1549.

Ward, A. B. (2008). Spasticity treatment with botulinum toxins. *Journal of Neural Transmission*, *115*(4), 607–616. https://doi.org/10.1007/s00702-007-0833-2.

Westerkam, D., Saunders, L. L., & Krause, J. S. (2011). Association of spasticity and life satisfaction after spinal cord injury. *Spinal Cord*, *49*(9), 990–994. https://doi.org/10.1038/sc.2011.49.

Wolpaw, J. R. (2018). The negotiated equilibrium model of spinal cord function. *The Journal of Physiology*, *596*(16), 3469–3491. https://doi.org/10.1113/JP275532.

Xia, R., & Rymer, W. Z. (2005). Reflex reciprocal facilitation of antagonist muscles in spinal cord injury. *Spinal Cord*, *43*(1), 14–21. https://doi.org/10.1038/sj.sc.3101656.

Yang, J. F., Fung, J., Edamura, M., Blunt, R., Stein, R. B., & Barbeau, H. (1991). H-reflex modulation during walking in spastic paretic subjects. *Canadian Journal of Neurological Sciences*, *18*(4), 443–452.

Zehr, E. P., & Stein, R. B. (1999). What functions do reflexes serve during human locomotion? *Progress in Neurobiology*, *58*(2), 185–205.

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Chapter 31

Metabolic syndrome in spinal cord injury: Impact on health

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List of abbreviations

ATP	adenosine triphosphate
BMI	body mass index
CRP	C-reactive protein
CVD	cardiovascular disease
eNOS	endothelial nitric oxide synthase
ET-1	endothelin-1
FFM	fat-free mass
FPG	fasting plasma glucose
GH	growth hormone
GLUT	glucose transporter
HDL	high-density lipoprotein
IDF	International Diabetes Federation
IFG	impaired fasting glucose
IGT	impaired glucose tolerance
IGF-1	insulin-like growth factor-1
IL-6	interleukin-6
IMF	intramuscular fat
IR	insulin resistance
IRS	insulin receptor substrate
LDL	low-density lipoprotein
LH	luteinizing hormone
LTPA	leisure time physical activity
MAPK	mitogen activated protein kinase
MetS	metabolic syndrome
NAFLD	non-alcoholic fatty liver disease
NCEP:ATPIII	National Cholesterol Education Program/third Adult Treatment Panel
NEFA	non-esterified fatty acid
NO	nitric oxide
OCN	osteocalcin
PI3K	phosphatidylinositol 3-kinase
SAT	subcutaneous adipose tissue
SCI	spinal cord injury
SERCA	sarco(endo)plasmic reticulum calcium-ATP-ase
SHBG	sex hormone-binding globulin
T2DM	type 2 diabetes mellitus
TNF-α	tumor-necrosis factor-α
VAT	visceral adipose tissue
VLDL	very low-density lipoprotein
WC	waist circumference
WHO	World Health Organization
WHR	waist-to-hip ratio

Cellular, Molecular, Physiological, and Behavioral Aspects of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822427-4.00031-9

Introduction

In the last decades, advances in healthcare and clinical management of the acute post-injury phase resulted in an obvious improvement in the life expectancy of people with spinal cord injury (SCI). In chronic SCI (lasting more than 1 year), clinical concerns closely related to neurological damage largely overlap with those from different fields of medicine with a substantial impact on quality of life, morbidity, and mortality. This chapter outlines the pathophysiology and diagnostic challenges of metabolic syndrome (MetS) in people with SCI, where the cluster of clinical and metabolic factors underlying the MetS definition, together with the systemic inflammation associated with visceral obesity, results in cardiovascular health deterioration. Emerging correlates of MetS, including androgen deficiency and hypovitaminosis D, will be also described, as they are highly prevalent in chronic SCI and establish complex multi-directional relationships with visceral obesity.

Changes in body composition after spinal cord injury

In people with SCI, the lack of neurotrophic influences of motor nerve projections results in a dramatic and early muscle wasting below the level of the lesion up to sarcopenia (Gorgey et al., 2014). Skeletal muscle adaptive molecular responses to denervation would occur within just a few days after SCI with upregulation of genes involved in the proteolytic ubiquitin-proteasome pathway, leading to degradation of contractile proteins (Urso et al., 2007). In keeping with findings from animal models, where muscle atrophy can be demonstrated within the first few months following spinal cord transection (Roy, Baldwin, & Edgerton, 1991), Castro, Apple Jr, Hillegass, and Dudley (1999) reported that in patients with complete cervical/thoracic SCI, the average cross-sectional area in lower extremity muscles, as assessed by magnetic resonance, was up to 80% smaller than that of age- and weight-matched able-bodied controls 24 weeks post-injury. Muscle atrophy does not spare individuals with incomplete SCI, exhibiting an approximately 30% smaller average cross-sectional area in affected muscles of lower extremities with respect to controls (Shah et al., 2006).

Biopsy data showed qualitative other than quantitative muscle changes in the early time period after SCI with an increased ratio between fast- (type II) and slow- (type I) twitch fibers and a decrease in the proportion of fibers with the slow isoform (type 2) of sarco(endo)plasmic reticulum calcium- adenosine triphosphate (ATP)-ase (SERCA2), which transports calcium from the cytosol into the sarcoplasmic reticulum (Talmadge, Castro, Apple Jr, & Dudley, 2002). These shifts make the skeletal muscle more fatigable. In fact, while slow-twitch muscle fibers are aerobic fatigue-resistant fibers supporting endurance physical activity, the anaerobic fast-twitch fibers provide more powerful forces, but for a shorter time and fatigue quickly. Moreover, the fast SERCA isoform (SERCA1), which is prevalent in muscle from people with SCI, is more susceptible to repeated contraction-relaxation cycles, resulting in lower calcium uptake by the sarcoplasmic reticulum between contractions. Poorer intracellular calcium stores and, hence, lower calcium release from sarcoplasmic reticulum during contraction would result in decreased myofilament activation and force output.

The loss of muscle trophism and performance ability underlies a substantial decrease in overall energy expenditure, by as much as 54% (Gorgey et al., 2014). Energy expenditure is the combination of basal metabolic rate, thermic effect of food digestion, and thermic effect of physical activity, with the former accounting for 60%–70% of the total (Gater Jr., 2007). The major contribution to the basal metabolic rate is provided by the fat-free mass (FFM), 85% of which is accounted for by the skeletal muscle (Gater Jr., 2007). Therefore, a loss in skeletal muscle mass significantly affects both physical activity-related energy expenditure and basal metabolic rate, with obvious reflections on total daily energy expenditure. On this basis, in people with SCI, body energy balance is overwhelmed since energy intake easily exceeds energy expenditure thus leading to fat mass increase. When compared to waist circumference (WC)-matched able-bodied individuals, people with SCI exhibit greater volumes of visceral adipose tissue (VAT). Indeed, in this population, for every centimeter increase in WC and for every unit increase in body mass index (BMI), VAT increases by 30% and 20%, respectively (Cirnigliaro et al., 2015), resulting in a high ratio of VAT to subcutaneous adipose tissue (SAT), which represents a well-known risk factor for insulin resistance (IR) and endocrine-metabolic disorders.

Insulin resistance in spinal cord injury: Pathophysiology and clinical features

As visceral body fat is highly sensitive to lipolytic stimuli, its accumulation is accompanied by an increased generation of non-esterified fatty acids (NEFA), which are released in the blood circulation and deposited into muscle and liver cells. This could explain the very high prevalence of non-alcoholic fatty liver disease (NAFLD) (Barbonetti, Caterina Vassallo, et al., 2016) as well as the accumulation of intramuscular fat (IMF) (Elder, Apple, Bickel, Meyer, & Dudley, 2004), peculiar to people with SCI. The presence of NEFA in such ectopic sites triggers serine phosphorylations of the insulin receptors, thus negatively affecting the downstream signaling cascade of insulin receptor substrates (IRSs) and phosphatidylinositol 3-kinase (PI3K) (Gallagher, LeRoith, & Karnieli, 2008).

In skeletal muscle, impaired insulin signaling results in inhibited translocation of glucose transporters-4 (GLUT-4) to the cell membrane with decreased glucose entrance into the cell and, hence, post-prandial hyperglycemia (Gallagher et al., 2008). In individuals with SCI, these events can be amplified by physical inactivity which contributes to decreasing insulin sensitivity in skeletal muscle. Accordingly, a high prevalence of diabetes has been reported in SCI (Cragg, Noonan, Krassioukov, & Borisoff, 2013), where IMF accumulation and muscle atrophy would account for 70% of glucose intolerance (Elder et al., 2004). In the liver, NEFA accumulation and IR negatively affect both glucose and lipid metabolism: higher rates of gluconeogenesis result in fasting hyperglycemia; meanwhile, an increased generation of very low-density (VLDL) and low-density (LDL) lipoproteins is accompanied by a slowed synthesis of apolipoprotein A, with a consequent decrease in high-density lipoproteins (HDL) (Kolovou, Anagnostopoulou, & Cokkinos, 2005). These pathogenic processes underpin the unfavorable lipid profile peculiar to people with SCI exhibiting low HDL, high triglycerides, and high LDL (Gater Jr., 2007).

An additional mechanism by which adipose tissue contributes to IR involves the adipocyte release of proinflammatory cytokines, such as interleukin-6 (IL-6) and tumor-necrosis factor-α (TNF-α), which interfere with insulin signaling (Farkas & Gater, 2018). IL-6 and TNF-α also account for low-grade vascular inflammation by promoting the hepatic synthesis of acute-phase reactants, including C-reactive protein (CRP) (Farkas & Gater, 2018). Accordingly, when compared to matched able-bodied controls, individuals with SCI exhibit higher circulating CRP levels (Liang, Mojtahedi, Chen, & Braunschweig, 2008), which are positively associated with both WC and percentage of body fat (Gibson et al., 2008) and negatively associated with HDL (Liang et al., 2008).

Complex pathogenetic mechanisms also underlie the relationship of visceral obesity with hypertension. Fat-derived proinflammatory cytokines non only induce a systemic vascular inflammation but also promote the hepatic synthesis of angiotensinogen, thus activating the renin-angiotensin-aldosterone system (Engeli, Negrel, & Sharma, 2000). Moreover, VAT secretes leptin, a hormone which reaches high circulating concentrations in individuals with SCI (Wang et al., 2005) and affects blood pressure control by stimulating the sympathetic nervous system activity (Wofford & Hall, 2004). An additional mechanism reflects an imbalance in the biosynthesis of vasodilator and vasoconstrictor molecules. Indeed, at the cellular level, the vascular response to insulin reflects a balance between PI3K-dependent insulin signaling pathways that regulate the endothelial generation of the vasodilator nitric oxide (NO) by the endothelial NO synthase (eNOS), and mitogen activated protein kinase (MAPK)-dependent pathways regulating the secretion of the vasoconstrictor endothelin-1 (ET-1). Endothelial IR is typically characterized by a defective PI3K-NO pathway accompanied by an intact or enhanced MAPK-ET-1 pathway: the net effect is a vasoconstriction that increases peripheral vascular resistance and, hence, diastolic blood pressure (Muniyappa & Sowers, 2013).

Diagnostic challenges of metabolic syndrome in people with spinal cord injury

The constellation of central obesity and its correlates, including IR, glycemic dysregulation, hypertension, and dyslipidemia has been referred to as "metabolic syndrome" (MetS), a cluster of clinical and metabolic factors that increase the risk of stroke and cardiovascular disease (CVD) (Zafar, Khaliq, Ahmad, Manzoor, & Lone, 2018).

Over the past decade, different diagnostic criteria for MetS have been proposed (Table 1). The first definition by the World Health Organization (WHO), focusing on insulin resistance as the key element for the diagnosis (Alberti & Zimmet, 1998), was followed by the recommendations from the National Cholesterol Education Program/third Adult Treatment Panel (NCEP:ATP III), where no single factor was required for establishing the diagnosis, but instead, central obesity, dyslipidemia, hypertension, and impaired fasting glucose (IFG)/T2DM were placed on the same level (NCEP:ATP III, 2002). The subsequent definition by the International Diabetes Federation (IDF) emphasized abdominal obesity as a prerequisite for the MetS diagnosis, while maintaining unchanged the remainder of the NCEP:ATP III criteria (Ford, 2005).

Unfortunately, all these definitions that are widely used in the able-bodied general population result to be inappropriate in people with SCI, where the diagnosis of obesity is challenged by the deep changes in body composition. According to the WHO criteria, overweight and obesity are defined as BMI values $\geq$25 kg/m^2 and $\geq$ 30 kg/m^2, respectively (WHO, 1995). As lean tissue, fat tissue, and bone mass together contribute to the body weight, for the same BMI value, people with SCI exhibit a higher percentage of body fat than able-bodied individuals, due to the muscle wasting below the level of the lesion: this means that, in this population, the use of traditional BMI cut-off points grossly underestimates the diagnosis of overweight and obesity (Jones, Legge, & Goulding, 2003). Indeed, bioelectrical impedance analyses showed that, in adults with chronic SCI, a BMI of 22–25 kg/m^2 translates to >30% body fat (Nash et al., 2019), which is well above the accepted threshold for obesity of 22% body fat in the in able-bodied population. Accordingly, the recent guidelines for identification and management of cardiometabolic risk after SCI (Nash et al., 2019), recommended a BMI $\geq$22 kg/m^2 as the best cutoff point when used as a surrogate marker for obesity in this population. It has been also suggested that WC could represent a better measure of obesity than is BMI in this population (Ravensbergen, Lear, & Claydon, 2014). However, no specific WC

TABLE 1 Main definitions of metabolic syndrome.

WHO, 1998	NCEP:ATP III, 2001	IDF, 2006
IGT or IFG or T2DM and/or IR[a] plus any 2 or more of the following:	Any three or more of the following:	WC ≥94 cm for men and ≥ 80 cm for women[b] plus any 2 or more of the following
• BMI >30 Kg/m^2 or WHR >0.90 for men and > 0.85 for women	• WC ≥102 cm for men and ≥ 88 cm for women	
• Blood pressure ≥ 140/90 mmHg	• Blood pressure ≥ 130/85 mmHg	• Blood pressure ≥ 130/85 mmHg or on treatment
• Triglycerides ≥150 mg/dL or on treatment • HDL <35 mg/dL for men and < 39 mg/dL for women • Urinary albumin excretion rate ≥ 20 μg/min or urine albumin/creatine ratio ≥ 30 mg/g	• Triglycerides ≥150 mg/dL or on treatment • HDL <40 mg/dL for men and < 50 mg/dL for women • FPG ≥100 mg/dL or on treatment for T2DM	• Triglycerides ≥150 mg/dL or on treatment • HDL <40 mg/dL for men and < 50 mg/dL for women • FPG ≥100 mg/dL or on treatment for T2DM

Abbreviations: BMI, body mass index; FPG, fasting plasma glucose; HDL, high-density lipoprotein; IDF, International Diabetes Federation; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IR, insulin resistance; NCEP:ATPIII, National Cholesterol Education Program/third Adult Treatment Panel; T2DM, type 2 diabetes mellitus; WC, waist circumference; WHO, World Health Organization; WHR, waist-to-hip ratio.
[a]*As assessed by the euglycemic hyperinsulinemic clamp method.*
[b]*The WC criterion can be assumed if BMI ≥30 kg/m^2.*

cut-off points have been validated so far in large series of individuals with SCI, where WC may be expanded due to the abdominal muscle paralysis, leading to a substantial overestimate of central obesity.

An equally thorny issue is the diagnosis of hypertension which can be confounded by the SCI-related neurogenic derangement of blood pressure control. On this basis, traditional models for the assessment of cardiovascular risk appear to be largely unsuitable in people with SCI (Barton et al., 2020).

In this scenario, inconsistent results produced by studies investigating the prevalence of MetS in people with SCI not only reflect differences in clinical characteristics of the study populations, but also the use of different criteria that have to deal with the complexity of MetS diagnosis in SCI. In clinically different small series from different countries, the prevalence of MetS largely varied from 3.6% to 19.0% according to WHO definition, from 12.3% to 43.0% when using NCEP: ATP III definition and from 19.3% to 31.0% when the IDF criteria were adopted (Yahiro, Wingo, Kunwor, Parton, & Ellis, 2020). Recently, among 473 veterans with SCI, aged 56.0 ± 13.1 years, where IDF criteria were modified by the inclusion of a BMI ≥22 Kg/m^2 as an SCI-appropriate surrogate marker of obesity, the prevalence of MetS reached 57%, with high prevalence rates of single components of MetS: 76.7% with BMI ≥22 kg/m^2, 55.1% with hypertension, 49.7% with T2DM and 69.7% with dyslipidemia (Gater Jr., Farkas, Berg, & Castillo, 2019). This highly prevalent clustering of vascular/metabolic risk factors, together with physical inactivity, proatherogenic systemic inflammation, and impaired autonomic cardiovascular control, largely accounts for the unfavorable cardiovascular and cardiometabolic profile of people with chronic SCI.

Cardiovascular reflections of metabolic syndrome in spinal cord injury

While most of the research dealing with the relationship between SCI and CVD has documented higher prevalence rates of cardiovascular risk factors, only a few studies have specifically assessed CVD prevalence and risk estimates. In a British multi-centric study on medical records from 545 individuals with long-lasting SCI (Groah, Weitzenkamp, Sett, Soni, & Savic, 2001), the age-adjusted rates of all CVD ranged from 21.2 to 35.2 per 1000 SCI person-years, according to the level of the lesion. The risk increased with both advancing age and the severity of SCI: tetraplegic state conferred an excess 16% risk of all CVD and a fivefold risk of cerebrovascular when compared with paraplegia; meanwhile more complete SCI resulted in an excess 44% all CVD risk. More recently, in a large 4-year follow-up cohort study on 2806 SCI individuals from Taiwan's National Health Insurance Research Database (Wu et al., 2012), the incidence rate of hospitalized stroke (5.96 per 1000 person-years) was approximately 3 times higher than that in 28,060 able-bodied controls (2.04 per 1000 person-years). Finally, a cross-sectional analysis of a representative sample of more than 60,000 individuals from the Canadian Community Health Survey (Cragg, Noonan, Dvorak, et al., 2013) revealed a significant and independent association of SCI with both self-reported heart disease (OR: 2.72, 95% CI: 1.94–3.82) and stroke (OR: 3.72, 95% CI:

2.22–6.23), after adjustment for age and gender. These findings are in line with mortality data. In recent years, major advances in life support treatments and medical care resulted in a substantial improvement in life expectancy in this population. While a larger number of patients survive now the acute post-injury stage, for long-term SCI, morbidity, and mortality from cardiovascular diseases have become increasingly meaningful, also as a result of better clinical management of renal and pulmonary comorbidities, the primary causes of SCI-related mortality in the previous decades. In a 70-year retrospective analysis on more than 5000 individuals who were injured between 1943 and 2010 and survived first-year post-injury (Savic et al., 2017), mortality rates showed improvement over time for most cases, and, interestingly, among the leading causes of mortality, cardiovascular and cerebrovascular diseases (26.7% of all certified causes) were second only to respiratory disorders (29.3%) and followed by cancer (13.9%), urogenital complications (11.5%), digestive causes (5.3%) and suicide (4.5%).

As a further threat to metabolic and cardiovascular health, a decline in anabolic hormones has been also reported following SCI. Indeed, chronic SCI has been postulated to accelerate age-related hormonal changes that can contribute to maintaining the deterioration in body composition (Gorgey et al., 2014). These abnormalities not only include a possible decrease in circulating levels of growth hormone (GH)/insulin-like growth factor-1 (IGF-1), likely due to the drastic drop in daily physical activity (Bauman et al., 1994), but also androgen deficiency, which represents an emerging concern in SCI male population.

Pathophysiology of androgen deficiency in men with chronic spinal cord injury

A decline in circulating testosterone levels in men following SCI has been repeatedly reported in the last decades (Barbonetti et al., 2014, 2019; Barbonetti, Sperandio, et al., 2016; Barbonetti, Caterina Vassallo, et al., 2016; Bauman, Fountaine, & Spungen, 2014; Clark et al., 2008; D'Andrea, Castellini, et al., 2020; Kostovski, Iversen, Birkeland, Torjesen, & Hjeltnes, 2008; Schopp et al., 2006). The very high proportion of men with biochemical androgen deficiency during the acute post-injury stage, reaching 83% (Schopp et al., 2006), can reflect the impact of severe physical distress and systemic illness on testosterone secretion. Nevertheless, when compared to age-matched able-bodied controls, also men with chronic SCI tend to exhibit higher prevalence rates of low testosterone (Bauman et al., 2014; Kostovski et al., 2008).

The pathophysiology of androgen deficiency in this population, albeit not yet fully elucidated, seems to be highly complex and multi-factorial. The aforementioned low-grade systemic inflammation related to obesity is exacerbated by recurrent urinary and respiratory infections, as well as by the presence of severe pressure sores in many patients. The resultant increase in the levels of proinflammatory cytokines can lower testosterone levels by suppressing the pituitary secretion of luteinizing hormone (LH). Moreover, adipocytes express aromatase activity accounting for higher levels of estrogens which exert a well-known inhibitory effect on LH secretion in males (Giagulli, Kaufman, & Vermeulen, 1994), thus promoting a "non-hypergonadotropic" form of androgenic deficiency peculiar to men with chronic SCI (Barbonetti et al., 2014, 2019; Barbonetti, Caterina Vassallo, et al., 2016; Bauman et al., 2014; Kostovski et al., 2008) (Fig. 1). Estrogens also increase the circulating concentrations of sex hormone-binding globulin (SHBG), resulting in lower free testosterone levels (Fig. 1). Androgen deficiency, in turn, would make obesity worse, as testosterone drives the pluripotent stem cell commitment into myogenic rather than adipogenic lineage (Bhasin et al., 2003), thus establishing a vicious cycle (Fig. 2).

A possible additional physiopathological factor is osteocalcin (OCN), the key mediator of the so-called "bone–testis axis." OCN is a non-collagenous protein synthesized by osteoblasts that, after carboxylation of glutamic residues, is deposited on the extracellular matrix of the bone (Neve, Corrado, & Cantatore, 2013). As bone resorption is accompanied by OCN released from the bone matrix into the blood circulation, serum levels of OCN represent a sensitive marker of both bone formation and turnover (Neve et al., 2013). Interestingly, experimental data from the mouse model indicate that the circulating undercarboxylated fraction of OCN can exert extra-skeletal endocrine effects, leading to an increase in insulin secretion and insulin sensitivity, a decrease of visceral fat (Lee et al., 2007), and, notably, an increase of testosterone biosynthesis via the Gprc6a receptor of Leydig cells (Oury et al., 2011) (Fig. 3). However, in large population-based studies, the positive association between OCN and testosterone levels remains controversial, likely due to the preeminent role of a well-functioning hypothalamus–pituitary axis in stimulating testosterone biosynthesis. Following SCI, although circulating levels of bone remodeling markers, including OCN, are usually high during the acute post-injury stage, they undergo a substantial decrease during the chronic phase (Sabour et al., 2014). Interestingly, we recently demonstrated a significant positive association of OCN with both total and calculated free testosterone in a series of men with chronic SCI. This suggests that, in this population, the association would be unmasked by the blunted pituitary LH response (Barbonetti et al., 2019).

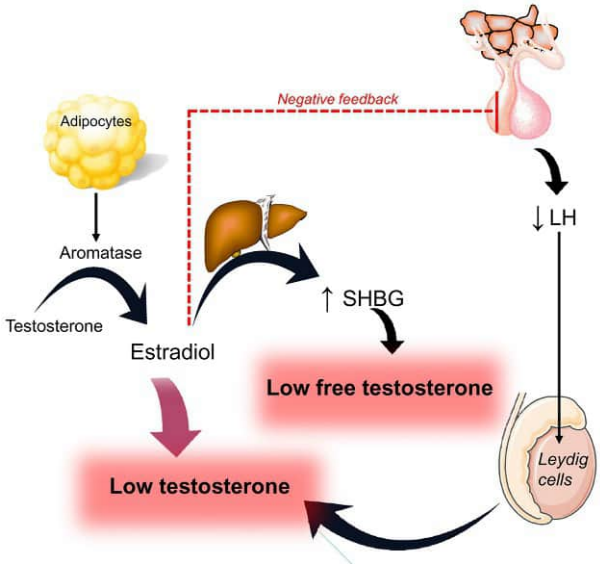

FIG. 1 Aromatase activity of adipocytes converts testosterone into estrogens: the levels of estrogens increases, while testosterone decreases. High levels of estrogens exert an inhibitory effect on luteinizing hormone (LH) secretion, leading to a "non-hypergonadotropic" form of androgenic deficiency. Estrogens also increase the circulating concentrations of sex hormone-binding globulin (SHBG), which binds to testosterone, resulting in lower free testosterone levels.

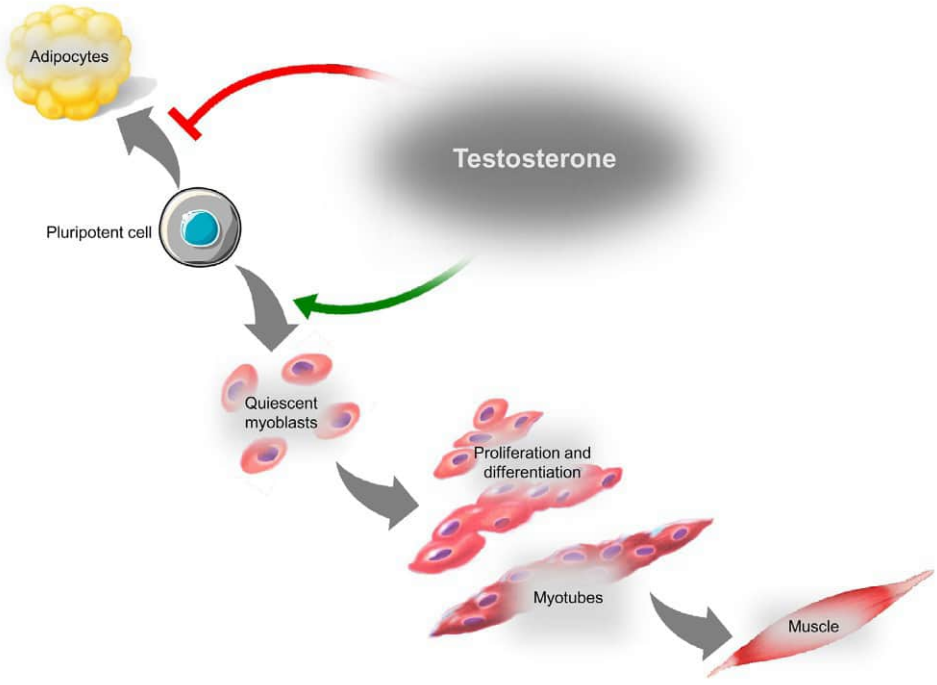

FIG. 2 Testosterone drives the pluripotent stem cell commitment into myogenic rather than adipogenic lineage.

Correlates of androgen deficiency in chronic spinal cord injury

Whether the SCI-related biochemical androgen deficiency can translate into clinical hypogonadism still remains an unsolved matter. The diagnosis of "androgen deficiency" as a biochemical and clinical syndrome requires the demonstration of unequivocally low testosterone levels as well as characteristic symptoms and signs (Bhasin et al., 2010), with sexual symptoms (poor morning erection, decreased libido, and erectile dysfunction) displaying a significant syndromic association with low testosterone in aging men (Wu et al., 2010) (Fig. 4). Unfortunately, in men with SCI, not only sexual

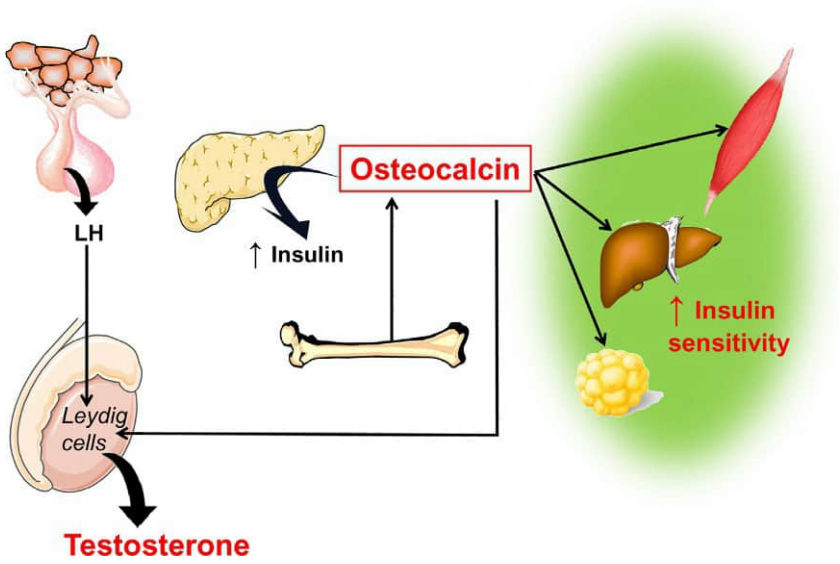

FIG. 3 Circulating undercarboxylated fraction of osteocalcin, released during bone resorption, exerts extra-skeletal endocrine effects on the pancreas, skeletal muscle, liver, and adipocytes, resulting in increased insulin secretion and sensitivity. Osteocalcin also promotes testosterone biosynthesis by acting on Leydig cells.

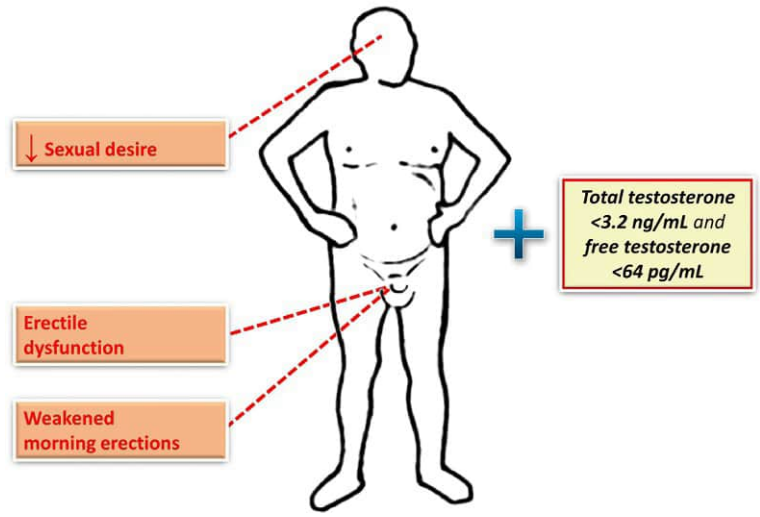

FIG. 4 Hypogonadism is a biochemical and clinical syndrome, where unequivocally low testosterone levels are associated with characteristic symptoms and signs. In aging men, sexual symptoms (poor morning erection, decreased libido, and erectile dysfunction) exhibit a significant syndromic association with low testosterone levels.

symptoms but also many other clinical features which can suggest a diagnosis of hypogonadism (e.g., body composition changes, anemia, osteoporosis, and depression) could represent direct or indirect reflections of neurological injury and disability (Fig. 5). In a series of men with chronic SCI, modifiable lifestyle-related risk factors, such as high BMI and poor leisure-time physical activity (LTPA), as well as a decreased sexual desire were found to be significant and independent predictors of low testosterone (Barbonetti et al., 2014). Notably, due to the very high prevalence of androgen deficiency, chronic SCI could represent an attractive clinical model to explore emerging correlates of low testosterone; among these, hypovitaminosis D deserves to be mentioned.

Leydig cells express the CYP2R1 gene, which encodes 25-hydroxylase, the enzyme involved in the first step of the cholecalciferol activation process (Blomberg Jensen et al., 2010). Therefore, it has been hypothesized that Leydig cell dysfunctions could result in both low testosterone and 25(OH)D deficiency (Foresta et al., 2011). Actually, in a recent meta-analysis of 18 case-control studies, hypovitaminosis D was associated with a slight decrease in serum testosterone levels, although the pooled estimate was burdened with a large heterogeneity between the included studies (D'Andrea et al., 2021).

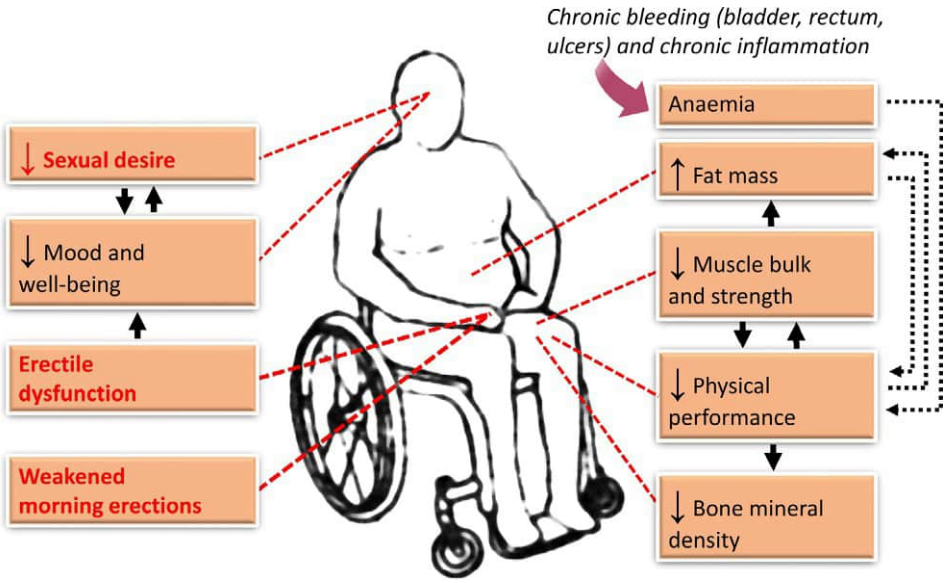

FIG. 5 In spinal cord-injured men, not only sexual symptoms (highlighted in red) but also many other clinical features suggesting a diagnosis of hypogonadism (e.g., body composition changes, anemia, osteoporosis, and depression) could represent direct or indirect reflections of neurological injury and disability.

Notably, at a sub-group analysis according to health-related characteristics of the study populations, a significant positive association between testosterone and vitamin D only arose from studies enrolling patients with clinical frailty (D'Andrea et al., 2021). Indeed, a combination of obesity, inadequate diet, and poor sunlight exposure could contribute to vitamin D deficiency in frail individuals. In particular, obesity, a recognized risk factor for androgen deficiency, is also associated with hypovitaminosis D, as the sequestration in fat mass decreases the bioavailability of the lipophilic 25(OH)D in blood circulation. Therefore, both androgen deficiency and hypovitaminosis D might represent markers of poor health conditions, sharing common pathogenetic mechanisms. In this light, it is not surprising that the strongest association was demonstrated in men with chronic SCI, who exhibit a very high prevalence of comorbidity-related risk factors predisposing to both low testosterone and vitamin D deficiency (Barbonetti, Sperandio, et al., 2016).

Hypovitaminosis D plays a key role in the weakening of bone mineral density in this population; however, vitamin D is now regarded as a pleiotropic hormone and the ubiquitous distribution of its receptor provides biological plausibility to a wide spectrum of systemic effects on a variety of target tissues, including nervous system (Eyles, Smith, Kinobe, Hewison, & McGrath, 2005) and skeletal muscle (Bischoff et al., 2001). Intriguingly, in people with chronic SCI, we demonstrated that lower vitamin D exhibits an independent association with both depression (Barbonetti et al., 2017) and poorer physical function (Barbonetti, Vassallo, Felzani, Francavilla, & Francavilla, 2016) and predicts the physical function worsening over time (Barbonetti et al., 2018). Obviously, the demonstration of direct causal links could be produced only by intervention studies assessing the effects of vitamin D supplementation.

Applications to other areas of neuroscience

In this chapter, we have reviewed the pathogenetic mechanisms underlying metabolic syndrome (MetS), the diagnostic challenges, and its reflections on cardiovascular and endocrine/metabolic health in people with spinal cord injury (SCI).

Although chronic SCI represents a unique clinical model to study the effects of an increased fat mass to lean mass ratio, to a lesser extent, the loss of muscle mass and physical inactivity represent hallmarks for many other neurological disorders. Indeed, increasing evidence indicates that in neurodegenerative diseases the pathophysiological links with MetS could be bidirectional: on one hand, muscle hypotrophy/weakening and physical disability lower energy expenditure, thus promoting adiposity accumulation; on the other hand, MetS is associated with systemic inflammation (Farkas & Gater, 2018) which is thought to induce a breakdown of the blood–brain barrier (Van Dyken & Lacoste, 2018). A higher permeability of the blood–brain-barrier could predispose to infiltration of immune cells and neuroinflammation (Van Dyken & Lacoste, 2018) which is involved in the pathogenesis of several neurological disorders. Intriguingly, the relationship of obesity and diabetes with Alzheimer's disease has been well documented (Nguyen, Killcross, & Jenkins, 2014;

Pugazhenthi, Qin, & Reddy, 2017) and it has been reported that the presence of obesity during adolescence is associated with a higher odd for developing multiple sclerosis later on (Hedström, Olsson, & Alfredsson, 2012, 2016). It has been suggested that the infiltration of immune cells, accompanied by the generation of inflammatory cytokines and reactive oxygen species, would decrease the threshold for autoimmune activation and stimulation of myelin-reactive cells (Van Dyken & Lacoste, 2018). Further studies are warranted to assess whether these pathophysiological events could also occur in people with chronic SCI.

Mini-dictionary of terms

Androgen deficiency: biochemical and clinical syndrome characterized by unequivocally low testosterone levels as well as symptoms and signs of hypogonadism.

Energy expenditure: the sum of basal metabolic rate, thermic effect of food digestion, and thermic effect of physical activity.

Erectile dysfunction: sexual dysfunction characterized by recurrent inability to achieve or maintain an adequate penis erection.

Fat-free mass (FFM): the total amount of lean (nonfat) components of the body, consisting of bone, muscle, and organs.

Impaired fasting glucose (IFG): fasting glucose levels between 100 and 125 mg per dL (5.6 to 6.9 mmol per L).

Insulin resistance: metabolic disorder in which the biological effect produced by a known concentration of insulin is lower than expected due to poor responsiveness of cells to the hormone action.

Leisure-time physical activity (LTPA): physical activities that individuals choose to do in free time independently of rehabilitation (walking/wheeling, playing sport).

Non-alcoholic fatty liver disease (NAFLD): liver phenotype of metabolic syndrome in which an excess of fat builds up in the liver with no obvious causes such as alcohol abuse.

Sarcopenia: extensive loss of muscle mass, strength, and function, strongly correlated with a physical disability.

Visceral obesity: excess of fat deposition in the abdominal viscera and omentum tissue.

Key facts of metabolic syndrome in spinal cord injury: Impact on health

- Metabolic syndrome (MetS) is a cluster of clinical and metabolic factors that increases the risk of developing cardiovascular and metabolic diseases, highly prevalent in people with chronic spinal cord injury (SCI).
- MetS features include visceral obesity, insulin resistance, hyperglycemia, hypertension, and dyslipidemia.
- In people with SCI, the use of the traditional cut-off point of body mass index (BMI) for obesity ($\geq$30 kg/m^2) grossly underestimates the diagnosis due to the muscle wasting below the level of the lesion: the same value of BMI reflects higher percentages of body fat than able-bodied individuals.
- In people with SCI the measure of waist circumference could overestimate visceral obesity due to abdominal muscle paralysis.
- Multi-factorial pathogenetic mechanisms, largely related to visceral obesity and MetS, could account for an accelerated age-dependent decline in testosterone levels peculiar to men with chronic SCI.
- Androgen deficiency is a biochemical and clinical syndrome where unequivocally low testosterone levels are associated with symptoms and signs of hypogonadism.
- In men with SCI, clinical features suggestive of hypogonadism could represent a reflection of neurological damage and disability, thus challenging the diagnosis of clinical hypogonadism.

Summary points

- Following spinal cord injury (SCI), a dramatic and early muscle wasting occurs below the level of the lesion
- This underlies a substantial decrease in overall energy expenditure which is easily overwhelmed by energy intake, thus leading to a fat mass increase
- Accumulation of visceral fat mass promotes insulin resistance, the key element of metabolic syndrome (MetS) which increases the risk of developing cardiometabolic diseases
- All definitions, that are widely accepted in the general able-bodied population, result to be inappropriate in people with SCI, where the diagnosis of obesity is challenged by the changes in body composition.
- The deranged metabolic profile of chronic SCI also includes a decline in testosterone levels that can further contribute to the deterioration in body composition.

- Due to the very high prevalence of androgen deficiency, chronic SCI could represent an attractive clinical model to study hypogonadism and the emerging correlates of low testosterone.

References

Alberti, K. G., & Zimmet, P. Z. (1998). Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabetic Medicine*, *15*, 539–553.

Barbonetti, A., Caterina Vassallo, M. R., Cotugno, M., Felzani, G., Francavilla, S., & Francavilla, F. (2016). Low testosterone and non-alcoholic fatty liver disease: Evidence for their independent association in men with chronic spinal cord injury. *The Journal of Spinal Cord Medicine*, *39*, 443–449.

Barbonetti, A., Cavallo, F., D'Andrea, S., Muselli, M., Felzani, G., Francavilla, S., et al. (2017). Lower vitamin D levels are associated with depression in people with chronic spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *98*, 940–946.

Barbonetti, A., D'Andrea, S., Martorella, A., Felzani, G., Francavilla, S., & Francavilla, F. (2018). Low vitamin D levels are independent predictors of 1-year worsening in physical function in people with chronic spinal cord injury: A longitudinal study. *Spinal Cord*, *56*, 494–501.

Barbonetti, A., D'Andrea, S., Samavat, J., Martorella, A., Felzani, G., Francavilla, S., et al. (2019). Can the positive association of osteocalcin with testosterone be unmasked when the preeminent hypothalamic-pituitary regulation of testosterone production is impaired? The model of spinal cord injury. *Journal of Endocrinological Investigation*, *42*, 167–173.

Barbonetti, A., Sperandio, A., Micillo, A., D'Andrea, S., Pacca, F., Felzani, G., et al. (2016). Independent Association of Vitamin D with Physical Function in people with chronic spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *97*, 726–732.

Barbonetti, A., Vassallo, M. R., Felzani, G., Francavilla, S., & Francavilla, F. (2016). Association between 25(OH)-vitamin D and testosterone levels: Evidence from men with chronic spinal cord injury. *The Journal of Spinal Cord Medicine*, *39*, 246–252.

Barbonetti, A., Vassallo, M. R., Pacca, F., Cavallo, F., Costanzo, M., Felzani, G., et al. (2014). Correlates of low testosterone in men with chronic spinal cord injury. *Andrology*, *2*, 721–728.

Barton, T. J., Low, D. A., Bakker, E. A., Janssen, T., de Groot, S., van der Woude, L., et al. (2020). Traditional cardiovascular risk factors strongly underestimate the 5-year occurrence of cardiovascular morbidity and mortality in spinal cord injured individuals. *Archives of Physical Medicine and Rehabilitation*, *S0003-9993*(20), 30529–3.

Bauman, W. A., Fountaine, M. F., & Spungen, A. M. (2014). Age-related prevalence of low testosterone in men with spinal cord injury. *The Journal of Spinal Cord Medicine*, *37*, 32–39.

Bauman, W. A., Spungen, A. M., Flanagan, S., Zhong, Y. G., Alexander, L. R., & Tsitouras, P. D. (1994). Blunted growth hormone response to intravenous arginine in subjects with a spinal cord injury. *Hormone and Metabolic Research*, *26*, 152–156.

Bhasin, S., Cunningham, G. R., Hayes, F. J., Matsumoto, A. M., Snyder, P. J., Swerdloff, R. S., et al. (2010). Testosterone therapy in men with androgen deficiency syndromes: An Endocrine Society clinical practice guideline. *The Journal of Clinical Endocrinology and Metabolism*, *95*, 2536–2559.

Bhasin, S., Taylor, W. E., Singh, R., Artaza, J., Sinha-Hikim, I., Jasuja, R., et al. (2003). The mechanisms of androgen effects on body composition: Mesenchymal pluripotent cell as the target of androgen action. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *58*, M1103–M1110.

Bischoff, H. A., Borchers, M., Gudat, F., Duermueller, U., Theiler, R., Stähelin, H. B., et al. (2001). In situ detection of 1,25-dihydroxyvitamin D3 receptor in human skeletal muscle tissue. *The Histochemical Journal*, *33*, 19–24.

Blomberg Jensen, M., Nielsen, J. E., Jørgensen, A., Rajpert-De Meyts, E., Kristensen, D. M., Jørgensen, N., et al. (2010). Vitamin D receptor and vitamin D metabolizing enzymes are expressed in the human male reproductive tract. *Human Reproduction*, *25*, 1303–1311.

Castro, M. J., Apple, D. F., Jr., Hillegass, E. A., & Dudley, G. A. (1999). Influence of complete spinal cord injury on skeletal muscle cross-sectional area within the first 6 months of injury. *European Journal of Applied Physiology and Occupational Physiology*, *80*, 373–378.

Cirnigliaro, C. M., LaFountaine, M. F., Dengel, D. R., Bosch, T. A., Emmons, R. R., Kirshblum, S. C., et al. (2015). Visceral adiposity in persons with chronic spinal cord injury determined by dual energy X-ray absorptiometry. *Obesity (Silver Spring)*, *23*, 1811–1817.

Clark, M. J., Schopp, L. H., Mazurek, M. O., Zaniletti, I., Lammy, A. B., Martin, T. A., et al. (2008). Testosterone levels among men with spinal cord injury. *American Journal of Physical Medicine & Rehabilitation*, *87*, 758–767.

Cragg, J. J., Noonan, V. K., Dvorak, M., Krassioukov, A., Mancini, G. B., & Borisoff, J. F. (2013). Spinal cord injury and type 2 diabetes: Results from a population health survey. *Neurology*, *81*, 1864–1868.

Cragg, J. J., Noonan, V. K., Krassioukov, A., & Borisoff, J. (2013). Cardiovascular disease and spinal cord injury: Results from a national population health survey. *Neurology*, *81*, 723–728.

D'Andrea, S., Castellini, C., Minaldi, E., Totaro, M., Felzani, G., Francavilla, S., et al. (2020). Testosterone, level of the lesion and age are independently associated with prostate volume in men with chronic spinal cord injury. *Journal of Endocrinological Investigation*, *43*, 1599–1606.

D'Andrea, S., Martorella, A., Coccia, F., Castellini, C., Minaldi, E., Totaro, M., et al. (2021). Relationship of vitamin D status with testosterone levels: A systematic review and meta-analysis. *Endocrine*, *72*, 49–61.

Elder, C. P., Apple, D. F., Bickel, C. S., Meyer, R. A., & Dudley, G. A. (2004). Intramuscular fat and glucose tolerance after spinal cord injury—A cross-sectional study. *Spinal Cord*, *42*, 711–716.

Engeli, S., Negrel, R., & Sharma, A. M. (2000). Physiology and pathophysiology of the adipose tissue renin-angiotensin system. *Hypertension*, *35*, 1270–1277.

Eyles, D. W., Smith, S., Kinobe, R., Hewison, M., & McGrath, J. J. (2005). Distribution of the vitamin D receptor and 1 alpha-hydroxylase in human brain. *Journal of Chemical Neuroanatomy*, *29*, 21–30.

Farkas, G. J., & Gater, D. R. (2018). Neurogenic obesity and systemic inflammation following spinal cord injury: A review. *The Journal of Spinal Cord Medicine*, *41*, 378–387.

Ford, E. S. (2005). Prevalence of the metabolic syndrome defined by the international diabetes federation among adults in the U.S. *Diabetes Care*, *28*, 2745–2749.

Foresta, C., Strapazzon, G., De Toni, L., Perilli, L., Di Mambro, A., Muciaccia, B., et al. (2011). Bone mineral density and testicular failure: Evidence for a role of vitamin D 25-hydroxylase in human testis. *The Journal of Clinical Endocrinology and Metabolism*, *96*, E646–E652.

Gallagher, E. J., LeRoith, D., & Karnieli, E. (2008). The metabolic syndrome—From insulin resistance to obesity and diabetes. *Endocrinology and Metabolism Clinics of North America*, *37*(559–79), vii.

Gater, D. R., Jr. (2007). Obesity after spinal cord injury. *Physical Medicine and Rehabilitation Clinics of North America*, *18*, 333–vii.

Gater, D. R., Jr., Farkas, G. J., Berg, A. S., & Castillo, C. (2019). Prevalence of metabolic syndrome in veterans with spinal cord injury. *The Journal of Spinal Cord Medicine*, *42*, 86–93.

Giagulli, V. A., Kaufman, J. M., & Vermeulen, A. (1994). Pathogenesis of the decreased androgen levels in obese men. *The Journal of Clinical Endocrinology and Metabolism*, *79*, 997–1000.

Gibson, A. E., Buchholz, A. C., Martin Ginis, K. A., & SHAPE-SCI Research Group. (2008). C-reactive protein in adults with chronic spinal cord injury: Increased chronic inflammation in tetraplegia vs paraplegia. *Spinal Cord*, *46*, 616–621.

Gorgey, A. S., Dolbow, D. R., Dolbow, J. D., Khalil, R. K., Castillo, C., & Gater, D. R. (2014). Effects of spinal cord injury on body composition and metabolic profile—Part I. *The Journal of Spinal Cord Medicine*, *37*, 693–702.

Groah, S. L., Weitzenkamp, D., Sett, P., Soni, B., & Savic, G. (2001). The relationship between neurological level of injury and symptomatic cardiovascular disease risk in the aging spinal injured. *Spinal Cord*, *39*, 310–317.

Hedström, A. K., Olsson, T., & Alfredsson, L. (2012). High body mass index before age 20 is associated with increased risk for multiple sclerosis in both men and women. *Multiple Sclerosis Journal*, *18*, 1334–1336.

Hedström, A., Olsson, T., & Alfredsson, L. (2016). Body mass index during adolescence, rather than childhood, is critical in determining MS risk. *Multiple Sclerosis Journal*, *22*, 878–883.

Jones, L. M., Legge, M., & Goulding, A. (2003). Healthy body mass index values often underestimate body fat in men with spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *84*, 1068–1071.

Kolovou, G. D., Anagnostopoulou, K. K., & Cokkinos, D. V. (2005). Pathophysiology of dyslipidaemia in the metabolic syndrome. *Postgraduate Medical Journal*, *81*, 358–366.

Kostovski, E., Iversen, P. O., Birkeland, K., Torjesen, P. A., & Hjeltnes, N. (2008). Decreased levels of testosterone and gonadotrophins in men with long-standing tetraplegia. *Spinal Cord*, *46*, 559–564.

Lee, N. K., Sowa, H., Hinoi, E., Ferron, M., Ahn, J. D., Confavreux, C., et al. (2007). Endocrine regulation of energy metabolism by the skeleton. *Cell*, *130*, 456–469.

Liang, H., Mojtahedi, M. C., Chen, D., & Braunschweig, C. L. (2008). Elevated C-reactive protein associated with decreased high-density lipoprotein cholesterol in men with spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *89*, 36–41.

Muniyappa, R., & Sowers, J. R. (2013). Role of insulin resistance in endothelial dysfunction. *Reviews in Endocrine & Metabolic Disorders*, *14*, 5–12.

Nash, M. S., Groah, S. L., Gater, D. R., Dyson-Hudson, T. A., Lieberman, J. A., Myers, J., et al. (2019). Identification and Management of Cardiometabolic Risk after spinal cord injury. *The Journal of Spinal Cord Medicine*, *42*, 643–677.

National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). (2002). Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III) final report. *Circulation*, *106*, 3143–3421.

Neve, A., Corrado, A., & Cantatore, F. P. (2013). Osteocalcin: Skeletal and extra-skeletal effects. *Journal of Cellular Physiology*, *228*, 1149–1153.

Nguyen, J. C. D., Killcross, A. S., & Jenkins, T. A. (2014). Obesity and cognitive decline: Role of inflammation and vascular changes. *Frontiers in Neuroscience*, *8*, 375.

Oury, F., Sumara, G., Sumara, O., Ferron, M., Chang, H., Smith, C. E., et al. (2011). Endocrine regulation of male fertility by the skeleton. *Cell*, *144*, 796–809.

Pugazhenthi, S., Qin, L., & Reddy, P. H. (2017). Common neurodegenerative pathways in obesity, diabetes, and Alzheimer's disease. *Biochimica et Biophysica Acta*, *1863*, 1037–1045.

Ravensbergen, H., Lear, S., & Claydon, V. (2014). Waist circumference is the best index for obesity-related cardiovascular disease risk in individuals with spinal cord injury. *Journal of Neurotrauma*, *31*, 292–300.

Roy, R. R., Baldwin, K. M., & Edgerton, V. R. (1991). The plasticity of skeletal muscle: Effects of neuromuscular activity. *Exercise and Sport Sciences Reviews*, *19*, 269–312.

Sabour, H., Norouzi Javidan, A., Latifi, S., Larijani, B., Shidfar, F., Vafa, M. R., et al. (2014). Bone biomarkers in patients with chronic traumatic spinal cord injury. *The Spine Journal*, *14*, 1132–1138.

Savic, G., DeVivo, M. J., Frankel, H. L., Jamous, M. A., Soni, B. M., & Charlifue, S. (2017). Causes of death after traumatic spinal cord injury-a 70-year British study. *Spinal Cord*, *55*, 891–897.

Schopp, L. H., Clark, M., Mazurek, M. O., Hagglund, K. J., Acuff, M. E., Sherman, A. K., et al. (2006). Testosterone levels among men with spinal cord injury admitted to inpatient rehabilitation. *American Journal of Physical Medicine & Rehabilitation*, *85*, 678–684.

Shah, P. K., Stevens, J. E., Gregory, C. M., Pathare, N. C., Jayaraman, A., Bickel, S. C., et al. (2006). Lower-extremity muscle cross-sectional area after incomplete spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *87*, 772–778.

Talmadge, R. J., Castro, M. J., Apple, D. F., Jr., & Dudley, G. A. (2002). Phenotypic adaptations in human muscle fibers 6 and 24 wk after spinal cord injury. *Journal of Applied Physiology*, *92*, 147–154.

Urso, M. L., Chen, Y. W., Scrimgeour, A. G., Lee, P. C., Lee, K. F., & Clarkson, P. M. (2007). Alterations in mRNA expression and protein products following spinal cord injury in humans. *The Journal of Physiology*, *579*, 877–892.

Van Dyken, P., & Lacoste, B. (2018). Impact of metabolic syndrome on neuroinflammation and the blood-brain barrier. *Frontiers in Neuroscience*, *12*, 930.

Wang, Y. H., Huang, T. S., Liang, H. W., Su, T. C., Chen, S. Y., & Wang, T. D. (2005). Fasting serum levels of adiponectin, ghrelin, and leptin in men with spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *86*, 1964–1968.

Wofford, M. R., & Hall, J. E. (2004). Pathophysiology and treatment of obesity hypertension. *Current Pharmaceutical Design*, *10*, 3621–3637.

World Health Organization. (1995). Physical status: the use and interpretation of anthropometry. In *Report of a WHO Expert Committee. WHO technical report series 854*. Geneva, Switzerland: WHO Press.

Wu, J. C., Chen, Y. C., Liu, L., Chen, T. J., Huang, W. C., Cheng, H., et al. (2012). Increased risk of stroke after spinal cord injury: A nationwide 4-year follow-up cohort study. *Neurology*, *78*, 1051–1057.

Wu, F. C., Tajar, A., Beynon, J. M., Pye, S. R., Silman, A. J., Finn, J. D., et al. (2010). Identification of late-onset hypogonadism in middle-aged and elderly men. *The New England Journal of Medicine*, *363*, 123–135.

Yahiro, A. M., Wingo, B. C., Kunwor, S., Parton, J., & Ellis, A. C. (2020). Classification of obesity, cardiometabolic risk, and metabolic syndrome in adults with spinal cord injury. *The Journal of Spinal Cord Medicine*, *43*, 485–496.

Zafar, U., Khaliq, S., Ahmad, H. U., Manzoor, S., & Lone, K. P. (2018). Metabolic syndrome: An update on diagnostic criteria, pathogenesis, and genetic links. *Hormones (Athens, Greece)*, *17*, 299–313.

Chapter 32

Body composition and spinal cord injury

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List of abbreviations

2-C	two-compartment model
3-C	three-compartment model
4-C	four-compartment model
AIS	ASIA impairment scale
ALS	amyotrophic lateral sclerosis
BIA	bioelectrical impedance analysis
BIS	bioimpedance spectroscopy
BMI	body mass index
CSA	cross-sectional area
DXA	dual X-ray absorptiometry
EXF	extracellular fluid
FFM	fat-free mass
FM	fat mass
ICF	intracellular fluid
IMF	intramuscular fat
LTM	lean tissue mass
MRI	magnetic resonance imaging
MS	multiple sclerosis
PD	Parkinson's disease
SCI	spinal cord injury
WHO	World Health Organization

Introduction

Adverse body composition changes, including gains in fat mass and losses in lean muscle mass, occur following spinal cord injury (SCI) due to multiple factors including the metabolic response to trauma, secondary complications such as urinary tract infections and pressure injuries, and their associated inflammatory cascades. Inactivation of skeletal muscle caused by paralysis, immobility, and the subsequent reduced loading and decrease in habitual physical activity also contribute to these changes (Gorgey et al., 2014). There is also evidence that decreased production of sex hormones due to acute stress from trauma, hypothalamic-pituitary axis dysfunction, and certain medications and related side effects can all impact body composition (Bryce, 2010). Loss of muscle mass in the early period following traumatic SCI has equivalent consequences to those described in the general population including higher acute care mortality, adverse events, and postoperative complications (Banaszek et al., 2019). In the longer term, ongoing muscle wasting results in decreased muscular strength, power, and endurance, increased fatigue, and reduced levels of physical function. Furthermore, muscle wasting leads to a reduced resting energy expenditure that predisposes individuals with SCI to weight gain, other co-morbid complications and chronic diseases such as diabetes and cardiovascular disease (Gorgey et al., 2014), and an increased risk for falls and fragility fractures (Galea, 2012).

In this section, we review the effects of traumatic SCI on body composition (muscle and fat). We also provide an overview of the available methods for assessing body composition and the considerations for use in individuals with SCI.

Cellular, Molecular, Physiological, and Behavioral Aspects of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822427-4.00032-0

Body composition

Assessment of body composition is important in clinical practice as it provides information on nutritional status and health risk at a single time point and when measured longitudinally, is a surrogate measure of the adequacy of nutrition and/or exercise interventions (Teigen, Kuchnia, Mourtzakis, & Earthman, 2017). Body composition is commonly described in terms of the number of physiologically functional compartments assessed using atomic, molecular, cellular, or tissue models (Siervo & Jebb, 2010), which are largely determined by the technology available to measure these compartments rather than based on anatomical measurements as these are not readily practicable. Fig. 1 presents commonly used models representing physiologically functional compartments along with the percentage contribution of each compartment to total body mass. Models variously subdivide body mass into two, three, four, or more compartments. In the simplest two-compartment model (2-C), body mass is divided into fat-free mass (FFM) and fat mass (FM), in the three-compartment (3-C) model lean tissue mass, fat, and bone and in the four-compartment (4-C) model water, fat, protein and bone.

Body composition changes following traumatic spinal cord injury

Body composition changes substantially during the first year following spinal cord injury (SCI) and persists in individuals with long-standing SCI. The most rapid muscle wasting occurs in the first 3 months following injury but gradual muscle loss continues for up to 12 months post-injury (Castro, Apple Jr, Hillegass, & Dudley, 1999; Gorgey & Dudley, 2007; Singh, Rohilla, Saini, & Kaur, 2014). The extent of muscle wasting varies across the different regions of the body and according to the level and severity of injury (Singh et al., 2014). For instance, a 12-month longitudinal study following acute SCI (within 3 days post-injury) using dual-energy X-ray absorptiometry (DXA) observed a 20% loss of leg lean tissue mass (LTM) in individuals with tetraplegia and paraplegia (Singh et al., 2014). As shown in Fig. 2, differences were observed in the magnitude of loss in the arms and trunk, where individuals with tetraplegia lost 12% more LTM and gained 6% more fat in the arms than those with paraplegia (Singh et al., 2014). Similarly, people with motor complete injuries were reported to lose 4% to 6% more LTM in the trunk and legs and gain 8% more fat mass in the legs compared to those with incomplete injuries who had an 8% decrease in leg fat mass (Singh et al., 2014). These alterations in body composition are persistent, with cross-sectional studies using DXA reporting that individuals with long-standing (>1 year) SCI have 3–11 kg lower total body LTM and 9%–12% higher total body fat and trunk fat mass than controls (Beck, Lamb, Atkinson, Wuermser, & Amin, 2014; Buchholz, McGillivray, & Pencharz, 2003; Maggioni et al., 2003; Spungen et al., 2003). In addition, there are marked variations in segmental body composition changes between tetraplegia and paraplegia and complete and incomplete categories of SCI (Spungen et al., 2003). The temporal nature of body composition, time since injury, the severity of the injury

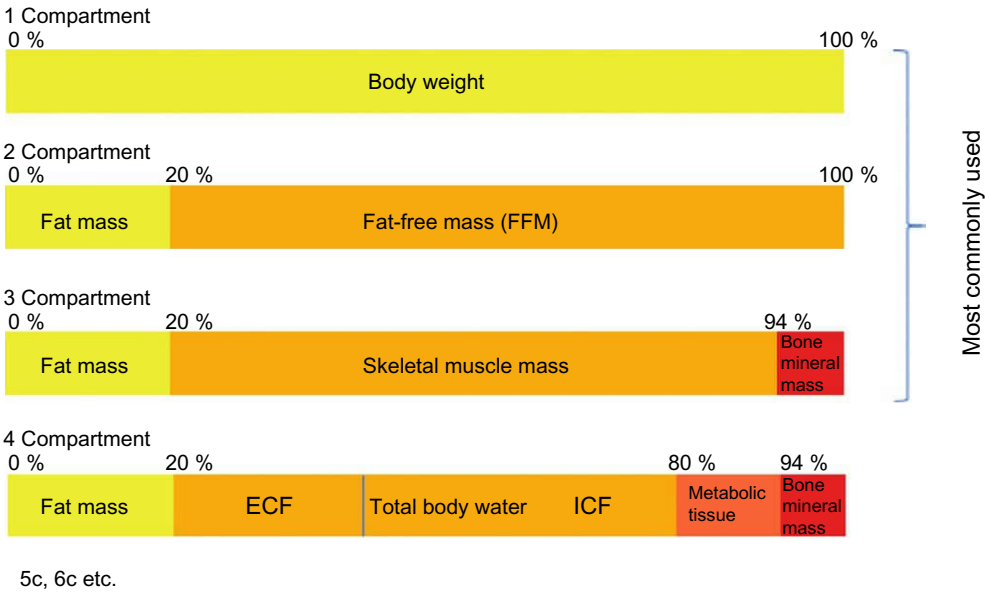

FIG. 1 Models of body composition. 1-C = one-compartment model; 2-C = two-compartment model, e.g., as measured by bioelectrical impedance analysis (BIA); 3-C = three-compartment model, e.g., as measured by dual-energy X-ray absorptiometry (DXA); 4-C = four-compartment model, e.g., as measured by isotope dilution (TBW) combined with DXA (BMC) and air-displacement plethysmography (body volume and density); *ECF*, extracellular fluid; *ICF*, intracellular fluid, measured by tracer dilution or bioimpedance spectroscopy.

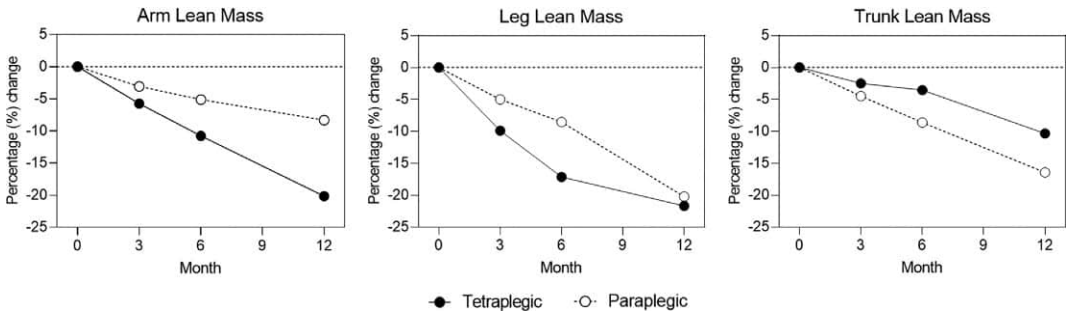

FIG. 2 Longitudinal changes in regional lean body mass in tetraplegia and paraplegia in 12 months following acute SCI. Body composition changes during the 12 months following spinal cord injury are show for arms, legs and trunk of people with tetraplegia and paraplegia. *Arm-T*, mean both arms tetraplegia (g); *arm-P*, mean both arms paraplegia (g); *trunk-T*, mean trunk tetraplegia (g); *trunk -P*, mean trunk paraplegia (g); *leg-T*, mean both legs tetraplegia (g); *leg-P*, mean both legs paraplegia (g). *(Modified from Singh, R., Rohilla, R. K., Saini, G., & Kaur, K. (2014). Longitudinal study of body composition in spinal cord injury patients.* Indian Journal of Orthopaedics, *48(2), 168.)*

and segmental changes, along with normal age-related changes, all need to be considered when assessing the nutritional status of individuals with SCI.

Studies using more advanced imaging techniques such as quantitative computed tomography (QCT) and magnetic resonance imaging (MRI) to quantify changes in muscle cross-sectional area (CSA) have likewise reported marked and heterogeneous muscle losses according to the severity of injury (Castro et al., 1999; Gorgey & Dudley, 2007; Modlesky et al., 2004). For instance, a study in six people with incomplete SCI using MRI found that mid-thigh skeletal muscle CSA was 33% smaller and intramuscular fat CSA 126% greater than able-bodied controls at 6 weeks after injury (Fig. 3). In a 3-month follow-up, thigh skeletal muscle CSA did not change significantly whereas intramuscular fat increased by a further 26% (Gorgey & Dudley, 2007). A study using thigh skeletal muscle biopsy described a dramatic 22% decrease in average muscle fiber CSA from 6 to 11 weeks post-injury, with a more gradual decline (10%) from 11 to 24 weeks. At week 24, average muscle fiber CSA in individuals with complete SCI was a third the size of age and weight-matched able-bodied controls (Castro et al., 1999). These changes in skeletal muscle morphology in SCI patients are also persistent. A study using MRI and DXA in eight individuals followed ≥2 years following SCI found a 17% lower mid-thigh skeletal muscle mass and two times higher mid-thigh percentage fat (34%) in individuals with complete SCI than controls (Modlesky et al., 2004). Another study using peripheral quantitative computed tomography (pQCT) found tibial midshaft muscle CSA was 33% smaller in men with paraplegia of ~6 years duration compared with age-matched able-bodied men (Dionyssiotis et al., 2019). Clinically these losses in muscle are important as low muscle mass has been associated with significantly more adverse events (including post-operatively) and in-hospital mortality in acute SCI patients (Banaszek et al., 2019); however, the impact of low muscle mass on morbidity and mortality in people with long-term SCI has not been investigated.

In summary, there is a dramatic loss of muscle below the level of the lesion in the first 6–12 weeks following acute spinal cord injury that differs regionally according to the level and severity of the injury and persists long term. Generally, higher level and complete injuries result in greater muscle wasting than lower level and incomplete injuries. This loss in muscle mass may have implications for morbidity and mortality and has a profound effect on the energy needs of individuals with SCI that are described in another chapter.

Sarcopenia and SCI

Sarcopenia is a term historically used to describe low skeletal muscle mass, but in more recent years it has evolved to include a combination of low muscle mass, low muscle strength, and/or impaired physical function (Cruz-Jentoft et al., 2019). While there is currently no international consensus on the diagnostic criteria for sarcopenia, there is considerable evidence that sarcopenia is associated with an increased risk for many chronic diseases, including cardiac and respiratory diseases, insulin resistance and type 2 diabetes, impaired cognition, and dementia, falls and fractures and premature mortality (Pacifico et al., 2020). Sarcopenia is also associated with a reduced ability to perform activities of daily living, impaired mobility, loss of independence, higher levels of disability and increases the risk of hospitalization, healthcare costs, and mortality (Cruz-Jentoft et al., 2019). Individuals with SCI are at increased risk of secondary (disease-related) sarcopenia due to neurological impairment, immobility, and disability (Cruz-Jentoft et al., 2019); however, there is an absence of research on the assessment and impacts of sarcopenia in SCI, and whether the same sarcopenia criteria used in able body individuals are appropriate for people with SCI. Two studies in individuals with chronic SCI report a prevalence of sarcopenia defined as low muscle mass only of 57%–97% (Dionyssiotis et al., 2019; Pelletier, Miyatani,

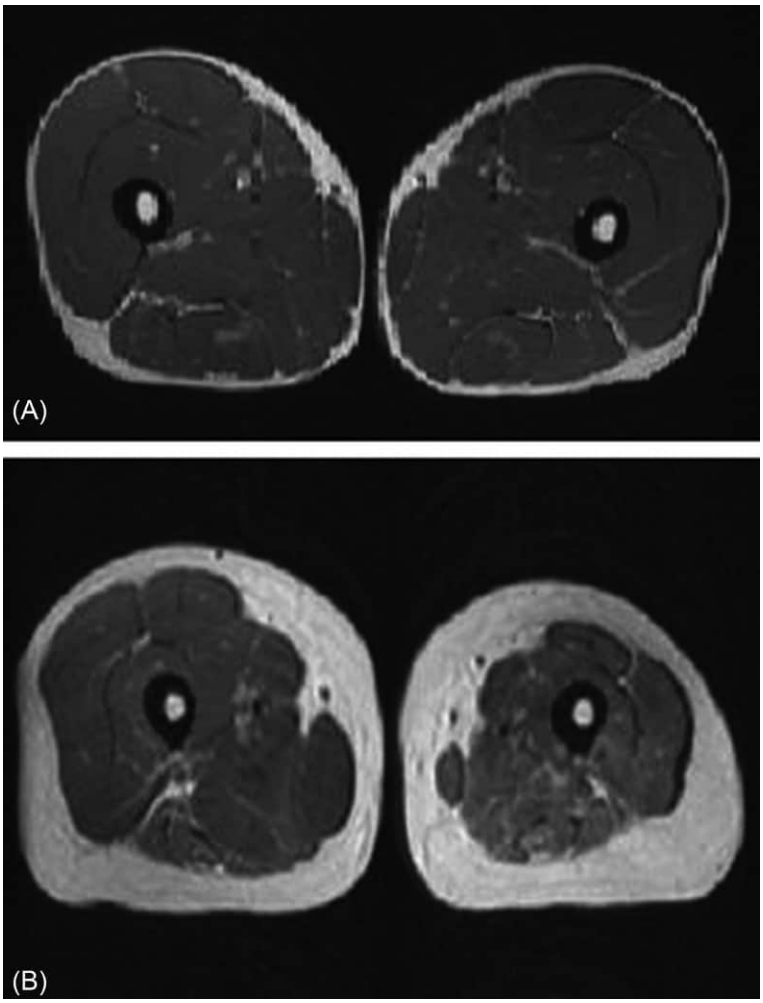

FIG. 3 Comparison of MRI muscle cross-sectional area, subcutaneous and intramuscular fat at the mid-thigh in able-bodied control versus an incomplete SCI patient 6 weeks following injury. The mid-thigh of an able-bodied individual (A) and a person with incomplete SCI 6 weeks following injury (B) are shown. Note that the mid-thigh muscle of the person with incomplete SCI is a third smaller than the able-bodied person with a marked increase in subcutaneous and intramuscular fat *(white regions). (From Gorgey, A., & Dudley, G. (2007). Skeletal muscle atrophy and increased intramuscular fat after incomplete spinal cord injury*. Spinal Cord, 45*(4), 304, with permission obtained from the Publishers.)*

Giangregorio, & Craven, 2016). In these studies, sarcopenia was diagnosed using a DXA-derived appendicular lean mass index (ALMI), calculated from appendicular lean tissue mass (kg) divided by height $(m)^2$ using cut-points of $\leq$7.26 kg/m^2 for men and $\leq$ 5.50 kg/m^2 for women, which were based on the criteria (cut-points) defined for able-bodied populations (Cruz-Jentoft et al., 2019). Another study that used total psoas muscle CSA derived from QCT to diagnose sarcopenia reported significantly more adverse events, post-operative adverse events, and in-hospital mortality in sarcopenic SCI patients (Banaszek et al., 2019). Collectively, these findings highlight that low muscle mass is highly prevalent following SCI, but sarcopenia is not well studied nor defined in this population. Despite this, there is strong evidence to support the routine assessment of muscle mass in people with SCI, and whether the inclusion of muscle strength and/or function provides further clinically important information requires further investigation.

Another condition that might be of relevance to SCI is sarcopenic obesity, which is characterized by the coexistence of sarcopenia and excess fat mass (Pelletier et al., 2016). There is some evidence that sarcopenic obesity is more strongly linked to metabolic-related diseases such as insulin resistance, metabolic syndrome, dyslipidemia, inflammation, hypertension, and diabetes than either obesity or sarcopenia alone (Roh & Choi, 2020). Although not well studied in SCI, one study in 136 people with chronic SCI (>15 years post-injury) reported a prevalence of sarcopenic obesity of 42% using percentage body fat $\geq$25% for men and $\geq$ 35% for women with the ALMI cut-offs mentioned previously (Pelletier et al., 2016). No reports have described the impact of sarcopenic obesity on metabolic risk or mortality in SCI.

In summary, preserving skeletal muscle mass and reducing fat mass are important goals to avoid secondary comorbidities following SCI. Monitoring changes in body composition is critical to inform and monitor outcomes of diet and/or exercise interventions. The following section summarizes the technical and practical considerations when choosing a method for assessing body composition in individuals with SCI.

Body composition assessment

Bedside and field methods

A variety of field and bedside methods are available to measure body composition, but there are a number of practical considerations specific to using and interpreting these methods in people with SCI, as outlined in Table 1.

TABLE 1 Bedside and field body composition assessment methods, strengths, limitations, and considerations for use in individuals with SCI.

Method	Strengths	Limitations	Considerations for use in individuals with SCI
Anthropometry	Fast Non-invasive Minimal equipment High mobility		
Weight		Does not distinguish between changes in muscle and fat	Choice of chair, hoist, platform depends on mobility and balance Aim for a consistent method Ensure legs are not touching any surfaces Subtract the weight of wheelchair and any accessories or sling attachment 5%–10% weight loss ≤6 months or 10%–20% weight loss ≥6 months not appropriate for malnutrition diagnosis in acute SCI Use SCI adjusted healthy weight range for chronic SCI
Height		Requires ability to stand and balance or accessibility to a bed	Measure supine length for people unable to stand
BMI		Does not distinguish between components of weight or their distribution	Unclear which cut-off to use for acute SCI Proposed SCI-specific BMI cut-off >22 kg/m^2 for chronic SCI
Waist circumference		Proposed methods for SCI require accessibility to a bed	Proposed SCI-specific waist circumference cut-offs 1. ≥ 94 cm measured supine at the narrowest part of the waist after normal expiration 2. ≥ 96 cm measured supine at the midpoint between the top of the iliac crest and the lower margin of the last palpable rib in the mid-axillary line after several consecutive natural breaths OR measurement at the lowest rib after normal expiration Use consistent method
Skinfolds and circumferences		Require meticulous site location and standardized measurement techniques Not sensitive enough to detect small changes	Underestimate percentage body fat in SCI Poor mobility and sitting balance limits assessment of suprailiac and subscapular sites Excess weight and obesity limit assessment of triceps and subscapular skinfolds Lack of SCI population-specific equations and normative values Use of skinfold measurements discouraged in SCI Thigh and calf circumferences and sagittal and transverse abdominal diameters may be used in SCI population-specific energy requirement prediction equation

Continued

TABLE 1 Bedside and field body composition assessment methods, strengths, limitations, and considerations for use in individuals with SCI—cont'd

Method	Strengths	Limitations	Considerations for use in individuals with SCI
Other methods			
Bioimpedance	Portable Affordable Precision 2.7%–4.0% Performed easily at bedside Minimal training required Promptly repeatable Estimates muscle mass ICF and ECF can be differentiated with BIS and MF-BIA	Validity affected by assumptions including body geometry, constant hydration, body resistivity and is influenced by sex, age, ethnicity Precision and accuracy influenced by fever, fluid, and electrolyte disturbances Differences between devices and software SF-BIA and MF-BIA rely on proprietorial, undisclosed prediction equations to estimate whole-body and segmental body composition	BIS validated in acute and chronic SCI SCI population-specific FFM prediction equation exists BIS can be used in chronic SCI to predict FFM and LTM of the body regions BIS may have utility to assess and monitor the presence of edema from extracellular fluid to intracellular fluid volume ratios
Ultrasound	Portable Affordable Performed easily at bedside Promptly repeatable Ability to differentiate between muscle and subcutaneous adipose tissue Can measure muscle quality and support diagnosis of sarcopenia	Lack of consensus on an appropriate protocol Longitudinal measures influenced by inconsistent technique and protocol Single site measurement assumed to represent whole-body composition	Not widely used in SCI Moderate correlation between DXA and ultrasound for android region, percent fat in SCI Research needed to validate prediction equations for use in SCI Lack of SCI-specific protocol and cut-off points

Portable body composition assessment methods that can be used at the bedside or in the community and factors to consider for use in people with spinal cord injury are described. *SCI*, spinal cord injury; *BMI*, body mass index; *MF-BIA*, multi-frequency bioimpedance; *SF-BIA*, single-frequency bioimpedance; *ICF*, intracellular fluid; *ECF*, extracellular fluid; *BIS*, bioimpedance spectroscopy; *FFM*, fat free mass; *LTM*, lean tissue mass; *DXA*, dual-energy X-ray absorptiometry. Modified from for SCI Affuso, O., Pradhan, L., Zhang, C., Gao, S., Wiener, H. W., Gower, B., … Allison, D. B. (2018). A method for measuring human body composition using digital images. *PLoS One, 13*(11), e0206430. doi:10.1371/journal.pone.0206430; Borga, M., West, J., Bell, J. D., Harvey, N. C., Romu, T., Heymsfield, S. B., & Leinhard, O. D. (2018). Advanced body composition assessment: From body mass index to body composition profiling. *Journal of Investigative Medicine: The Official Publication of the American Federation for Clinical Research, 66*, 887–895; Cirnigliaro, C. M., La Fountaine, M. F., Emmons, R., Kirshblum, S. C., Asselin, P., Spungen, A. M., & Bauman, W. A. (2013). Prediction of limb lean tissue mass from bioimpedance spectroscopy in persons with chronic spinal cord injury. *Journal of Spinal Cord Medicine, 36*(5), 443–453. doi:10.1179/2045772313Y.0000000108; Clasey, J. L., & Gater Jr, D. R. (2005). A comparison of hydrostatic weighing and air displacement plethysmography in adults with spinal cord injury. *Archives of Physical Medicine and Rehabilitation, 86*(11), 2106–2113. doi:10.1016/j.apmr.2005.06.013; Desneves, K. J., Panisset, M. G., Galea, M. P., Kiss, N., Daly, R. M., & Ward, L. C. (2020). Comparison of segmental lean tissue mass in individuals with spinal cord injury measured by dual energy X-ray absorptiometry and predicted by bioimpedance spectroscopy. *Spinal Cord*, 1–8. doi:10.1038/s41393-020-00568-3; Academy of Nutrition and Dietetics (2009). Spinal Cord Injury (SCI) evidence-based nutrition practice guideline; Evidence analysis library. Retrieved October 2018, https://www.andeal.org/topic.cfm?menu=5292; Dionyssiotis, Y., Skarantavos, G., Petropoulou, K., Galanos, A., Rapidi, C.-A., & Lyritis, G. P. (2019). Application of current sarcopenia definitions in spinal cord injury. *Journal of Musculoskeletal & Neuronal Interactions, 19*(1), 21; Edwards, L. A., Bugaresti, J. M., & Buchholz, A. C. (2008). Visceral adipose tissue and the ratio of visceral to subcutaneous adipose tissue are greater in adults with than in those without spinal cord injury, despite matching waist circumferences. *American Journal of Clinical Nutrition, 87*(3), 600–607; Fosbol, M. O., & Zerahn, B. (2015). Contemporary methods of body composition measurement. *Clinical Physiology and Functional Imaging, 2*, 81. doi:10.1111/cpf.12152; Fraser, C., Iruthayarajah, J., McIntyre, A., Serrato, J., Benton, B., & Teasell, R. W. (2016). Nutrition issues following spinal cord injury. Version 6.0.; Garshick, E., Ashba, J., Tun, G. C., Lieberman, L. S., & Brown, R. (1997). Assessment of stature in spinal cord injury. *The Journal of Spinal Cord Medicine, 20*(1), 36–42; Kocina, P., & Heyward, V. (1997). Validation of a bioimpedance equation for estimating fat-free mass of spinal cord injured adults 319. *Medicine & Science in Sports & Exercise, 29*(5), 55; Kyle, U. G., Bosaeus, I., De Lorenzo, A. D., Deurenberg, P., Elia, M., Gómez, J. M., … Pirlich, M. (2004). Bioelectrical impedance analysis—Part I: Review of principles and methods. *Clinical Nutrition, 23*(5), 1226–1243; Lee, S. Y., & Gallagher, D. (2008). Assessment methods in human body composition. *Current Opinion in Clinical Nutrition and Metabolic Care, 11*(5), 566; Maggioni, M., Bertoli, S., Testolin, G., Merati, G., Margonato, V., & Veicsteinas, A. (2003). Body composition assessment in spinal cord injury subjects. *Acta Diabetologica, 40*(Suppl. 1), S183–S186. doi:10.1007/s00592-003-0061-7; Modlesky, C. M., Bickel, C. S., Slade, J. M., Cureton, K. J., Dudley, G. A., & Meyer, R. A. (2004). Assessment of skeletal muscle mass in men with spinal cord injury using dual-energy X-ray absorptiometry and magnetic resonance imaging. *Journal of Applied Physiology, 96*(2), 561–565. doi:10.1152/japplphysiol.00207.2003; Panisset, M. G., Desneves, K., Ward, L. C., Rafferty, J., Rodi, H., Roff, G., … Galea, M. P. (2018). Bedside quantification of fat-free mass in acute spinal cord injury using bioelectrical impedance analysis: A psychometric study. *Spinal Cord, 56*(4), 355; Siervo, M., & Jebb, S. A. (2010). Body composition assessment: Theory into practice: Introduction of multicompartment models. *IEEE Engineering in Medicine and Biology Magazine, 29*(1), 48–59; Silveira, S., Ledoux, T., Robinson-Whelen, S., Stough, R., & Nosek, M. (2017). Methods for classifying obesity in spinal cord injury: A review. *Spinal Cord, 55*(9), 812; Teigen, L. M., Kuchnia, A. J., Mourtzakis, M., & Earthman, C. P. (2017). The use of technology for estimating body composition: Strengths and weaknesses of common modalities in a clinical setting. *Nutrition in Clinical Practice, 32*(1), 20–29.

Anthropometry

Anthropometry, the external measurement of body proportions and size (e.g., weight, height, waist circumference, skinfold thickness, and mid-arm muscle and calf circumferences), provides body composition information based on the one or two-compartment models and/or an assessment of health risk (Gibson, 2005). A brief overview of these methods specific to SCI is provided below.

Weight and height

Percentage weight loss is frequently used as an indicator of malnutrition risk (Cederholm et al., 2019). However, it is common to see a weight loss of 5–10 kg following traumatic SCI (Cox et al., 1985) and it is difficult to distinguish between unavoidable weight loss due to denervation and avoidable weight loss due to inadequate energy intake. Consequently, the usual phenotypic criteria of 5%–10% weight loss within 6 months or 10%–20% loss of weight over greater than 6 months (Cederholm et al., 2019) are not appropriate for the diagnosis of malnutrition in acute SCI. However, weight should be routinely monitored following SCI.

Height may be assessed by measuring supine length, heel to crown between metal bookends, using a rigid tape measure (Garshick, Ashba, Tun, Lieberman, & Brown, 1997). However, standards for healthy body weight for height have not been established or validated in SCI. Guidelines recommend adjusting the Metropolitan Life Insurance tables for individuals of an equivalent height and weight by 10%–15% or 7–9 kg and 5%–10% or 5–7 kg lower than the table weight for tetraplegia and paraplegia respectively (Academy of Nutrition and Dietetics, 2009). However, this recommendation is based on consensus (Academy of Nutrition and Dietetics, 2009) and does not account for relative changes in lean muscle and fat mass.

Body mass index

Body mass index (BMI) is a weight for height indicator that does not distinguish between the individual components of weight or body composition. BMI ranges associated with the risk of developing chronic diseases provided by WHO are based on data for able-bodied individuals but individuals with SCI within the normal BMI range (<25) often have lower LTM, higher total fat mass, and percentage body fat than equivalent abled-bodied individuals (Silveira, Ledoux, Robinson-Whelen, Stough, & Nosek, 2017). Hence, a lower SCI-specific BMI cut-off (>22 kg/m^2) to identify obesity and estimate cardiometabolic health risk has been proposed and validated in individuals with chronic SCI (Silveira et al., 2017). However, it is unclear whether WHO criteria or chronic SCI-specific BMI cut-offs should be used in acute SCI.

Waist circumference

Waist circumference is a predictor of intra-abdominal fat and has been associated with an increased risk for a range of cardiometabolic-related diseases (Gandy, 2014). A 26% higher mean total abdominal tissue, 58% greater mean visceral adipose tissue and a 48% greater ratio of visceral adipose tissue to subcutaneous adipose tissue has been reported in individuals with SCI compared with controls (Edwards, Bugaresti, & Buchholz, 2008). Consequently, lower SCI-specific waist circumference cut-offs ($\geq$94 cm and $\geq$ 96 cm) have been proposed to identify health risks compared to non-disabled individuals. However, various studies have used different waist circumference measurement sites and proposed a range of alternative cut-offs (Edwards et al., 2008; Ravensbergen, Lear, & Claydon, 2014). In summary, there is no consensus with regard to the specific assessment or cut-points to define a waist circumstance threshold that is associated with increased health risks in SCI populations (Silveira et al., 2017). One of the challenges for this cohort is that it is not always practical within the clinical setting to obtain a supine measurement. However, if measuring waist circumference to define disease risk or monitor changes over time, it is important to use an SCI-specific cut-off value and a consistent method for assessment.

Skinfolds and circumferences

Changes in body fat provide an indirect estimate of alterations in energy balance. Total body fat or percentage body fat can be estimated using one or more skinfold thickness measurements at indicator sites for subcutaneous adipose tissue, with or without limb circumference measurements in empirical regression equations (Gibson, 2005). The combination of skinfold thickness at the triceps, biceps, mid-thigh and calf with circumference of the same limb enables calculation of limb adipose area which is more accurate than a single skinfold (Gibson, 2005). Generally, the measurement of skinfolds at multiple sites

such as triceps, biceps, subscapular, and suprailiac provides a more accurate estimate of total body fat content than a single site (Gibson, 2005). Likewise, estimates of total body muscle mass and subsequently protein nutritional status can be predicted from mid-upper arm muscle circumference and area as both are correlated with measures of total muscle mass. However, these methods have a number of limitations including requiring highly standardized protocols and measurement techniques due to substantial intra- and interobserver variability, they are not sufficiently sensitive to detect small changes, have low accuracy and precision in obese people with measurements influenced by hydration (Fosbol & Zerahn, 2015). It is also important to be aware of the population in which predictive algorithms were developed and that data are compared to appropriate reference norms (Fosbol & Zerahn, 2015), which are not available for the SCI population.

For individuals with SCI, practical difficulties such as poor mobility and sitting balance may limit assessment of some skinfold measures (e.g., suprailiac and subscapular) and excess weight and obesity limit assessment at other sites (e.g., triceps, subscapular, and mid-thigh skinfolds) (Desport et al., 2000). Additionally, mid-upper arm muscle circumference may be disproportionate to total muscle mass in manual wheelchair users. Studies have reported that anthropometric methods using multiple skinfolds with or without circumferences underestimate the percentage body fat in people with SCI (Maggioni et al., 2003; Spungen, Bauman, Wang, & Pierson, 1995). There is also a lack of SCI population-specific equations for estimation of percentage body fat and SCI-specific normative values (Maggioni et al., 2003); consequently, guidelines discourage the use of skinfold measurements to assess body composition in persons with SCI due to the various limitations and inaccuracy (Academy of Nutrition and Dietetics, 2009).

Bioelectrical impedance

Bioelectrical impedance analysis (bioimpedance, BIA) is a non-invasive, portable, inexpensive bedside method that provides measures of total body water, FFM, FM, and body fat percentage (Kyle et al., 2004) using a 2-C model. There are three types of bioimpedance devices; single frequency (SFBIA), multi-frequency (MFBIA), and bioimpedance spectroscopy (BIS). SFBIA and MFBIA devices are generally limited by their reliance on proprietary undisclosed prediction equations to estimate whole-body and segmental body composition, which may not be suitable to use in individuals with SCI. In contrast, BIS data predicts body composition (ECF, ICF, FFM, LTM, and FM) from impedance measures using fundamental model-based equations/algorithms developed against the reference method deuterium dilution (Teigen et al., 2017). The overall reproducibility/precision of BIS is 2.7%–4.0% (Kyle et al., 2004). BIS is a promising tool that has been validated for the assessment of body composition in individuals with acute (Panisset et al., 2018) and chronic SCI when a population-specific prediction equation is used (Kocina & Heyward, 1997). BIS has also been used in chronic SCI (Cirnigliaro et al., 2013) and more recently acute SCI to predict FFM and LTM of the body regions and may have utility to assess and monitor the presence of edema from the extracellular fluid to intracellular fluid volume ratios to monitor fluid shifts and distribution (Desneves et al., 2020). To minimize the variability due to hydration it is important to perform impedance measurements under standardized euhydration conditions. The Academy of Nutrition and Dietetics Spinal Cord Injury Evidence-Based Nutrition Practice Guidelines recommend using bioimpedance to assess body composition (Academy of Nutrition and Dietetics, 2009) in SCI; however, SCI-specific population normative values for interpretation of whole and regional body composition measures are lacking. Despite the lack of population-specific reference data, it is appropriate to use bioimpedance to measure body composition changes over time in people with SCI; however, precision must be taken into consideration when interpreting results.

Ultrasound

Ultrasound can also assess regional distribution of body fat, quantify abdominal subcutaneous fat and intra-abdominal diameter and be used in severely obese subjects (Rashmi & Snekhalatha, 2019). Ultrasound has the advantage of being non-invasive, portable and can be used in real time at the bedside (Teigen et al., 2017). However, it currently has limited value in monitoring longitudinal muscle changes due to the lack of consensus on standardized measurement protocols for assessing muscle mass, primarily site selection and the amount of force or muscle compression to apply (Teigen et al., 2017). It is also assumed that measurements obtained at a single site are representative of whole-body composition (Teigen et al., 2017). To date, ultrasound has not been widely used to assess body composition in SCI, though one study in individuals with chronic SCI found a moderate correlation between DXA and ultrasound for the android region, percent fat (Emmons et al., 2011). Further research is needed to determine the utility of ultrasound in people with SCI.

Laboratory and research methods

More advanced body composition assessment tools, which are often less readily available as they are limited to a hospital or research setting, including emerging technologies used to assess body composition based on the two, three, or four-compartment models, and the strengths, limitations, and considerations for use in individuals with SCI, are summarized in Table 2.

TABLE 2 Laboratory and research body composition assessment methods, strengths, limitations and considerations for use in individuals with SCI.

Method	Strengths	Limitations	Considerations for use in individuals with SCI
Isotope dilution	Gold standard for determination of TBW Reference measure for validation of other methods Excellent precision, 1%–2% for TBW and ECW Medium-high safety Medium-high mobility	Limited to research Medium-high cost Medium-highly complex methodology Assumes fat-free mass hydration is stable	Feasible to collect urine samples with bladder management
Air-displacement plethysmography	Based on 2C-model Non-invasive Safe Fast No radiation exposure No need for sedation Precision for FM ~ 1.7%–4.5%	Limited to research and clinical Affected by variations in bone mineral content and hydration	Measurement of thoracic gas volume problematic in SCI above T3 due to paralysis of intercostal and abdominal muscles Population-specific predicted thoracic gas volume equation is lacking Inbuilt scale device inaccessible for wheelchair users
Dual-energy X-ray absorptiometry	Gold standard measure of bone density Based on 3-C model Used to validate other body composition estimating devices and equations High precision 0.8%–2.7% whole-body FM, 0.4%–1.3% whole-body LTM Useful for sarcopenia diagnosis Provides whole-body and regional data Widely available	Medium cost Low dose radiation Low mobility Medium-high methodology Scanners have weight and size limitations Doesn't differentiate between organ versus skeletal muscle lean tissue	Physical height of DXA scanning beds limit accessibility for SCI Challenges positioning individuals with SCI, especially those with spasticity Presence of metal implants is a source of error Evidence-based SCI guidelines suggest assessing and monitoring body composition using DXA Validity in SCI may be compromised due to altered hydration
MRI	Gold standard for body composition measurement at tissue level High accuracy and reproducibility Excellent precision, ~1.2%–2% error Measures whole-body and regional adipose tissue and skeletal muscle Used for sarcopenia diagnosis	High cost Time-consuming image analysis Patient positioning important to minimize error Limited availability Claustrophobic persons cannot be scanned Scanners cannot accommodate very large people (BMI > 40 kg/m^2) Only available when performed as part of routine care	Accessibility of scanning bed for individuals with SCI Challenges positioning individuals with SCI, especially those with spasticity

Continued

TABLE 2 Laboratory and research body composition assessment methods, strengths, limitations and considerations for use in individuals with SCI—cont'd

Method	Strengths	Limitations	Considerations for use in individuals with SCI
CT	Gold standard for body composition measurement at tissue level Provide reference measures of body composition Excellent precision ~2% Able to differentiate skeletal muscle, adipose and organ tissue Prognostic tool to establish muscle quantity and outcomes Mid-thigh muscle area is a good predictor of whole-body skeletal muscle and sensitive to change Can be used when diagnosing sarcopenia	High cost Only available when requested for medical treatment purposes High dose of radiation Assumes single slice measure is representative of whole-body composition Repeatability limited by patient positioning Density measures influenced by physiological variability e.g., edema. Differences in devices/software Not advised for serial measurements in longitudinal studies	Accessibility of scanning bed for individuals with SCI Challenges positioning individuals with SCI, especially those with spasticity Total psoas muscle CSA on lumbar CT used to predict early post-injury mortality and adverse events
Peripheral computed tomography	Minimum radiation exposure Precision for limb muscle area < 5%, low for intramuscular adipose tissue (3%–42%)	Medium cost Limited to appendicular sites (arms and legs) Scans easily influenced by movement artifacts Single slice assessment at a given site	Contractures may limit knee and ankle range of motion Spasms may create movement artifacts
Computerized digital image analysis	Novel approach. Simple Portable Relatively inexpensive Reduced bias as requires little human input during photography and processing	Early stages of development. Unclear if generalizable to very lean or very obese individuals, all race-ethnic groups	Requires subject to stand motionless with arms and legs abducted Applicability for people unable to stand for photographs is unknown Further research is required to create norms for mobility status

Sophisticated body composition assessment methods that are usually used in research laboratories and factors to consider for use in people with spinal cord injury are described. *TBW*, total body water; *ECW*, extracellular water; *FM*, fat mass; *LTM*, lean tissue mass; *2C-model*, 2 compartment model; *3-C model*, 3 compartment model; *SCI*, spinal cord injury; *DXA*, dual-energy X-ray absorptiometry; *MRI*, magnetic resonance imaging; *CT*, computed tomography; *CSA*, cross-sectional area.

Modified from for SCI Affuso, O., Pradhan, L., Zhang, C., Gao, S., Wiener, H. W., Gower, B., … Allison, D. B. (2018). A method for measuring human body composition using digital images. *PLoS One, 13*(11), e0206430. doi:10.1371/journal.pone.0206430; Borga, M., West, J., Bell, J. D., Harvey, N. C., Romu, T., Heymsfield, S. B., & Leinhard, O. D. (2018). Advanced body composition assessment: From body mass index to body composition profiling. *Journal of Investigative Medicine: The Official Publication of the American Federation for Clinical Research 66*, 887–895; Cirnigliaro, C. M., La Fountaine, M. F., Emmons, R., Kirshblum, S. C., Asselin, P., Spungen, A. M., & Bauman, W. A. (2013). Prediction of limb lean tissue mass from bioimpedance spectroscopy in persons with chronic spinal cord injury. *Journal of Spinal Cord Medicine, 36*(5), 443–453. doi:10.1179/2045772313Y.0000000108; Clasey, J. L., & Gater Jr, D. R. (2005). A comparison of hydrostatic weighing and air displacement plethysmography in adults with spinal cord injury. *Archives of Physical Medicine and Rehabilitation, 86*(11), 2106–2113. doi:10.1016/j.apmr.2005.06.013; Cruz-Jentoft, A. J., Bahat, G., Bauer, J., Boirie, Y., Bruyère, O., Cederholm, T., … Writing Group for the European Working Group on Sarcopenia in Older People 2 (EWGSOP2), and the Extended Group for EWGSOP2. (2019). Sarcopenia: Revised European consensus on definition and diagnosis. *Age and Ageing, 48*, 16–31. doi:10.1093/ageing/afy169; Academy of Nutrition and Dietetics, (2009). Spinal Cord Injury (SCI) evidence-based nutrition practice guideline; Evidence analysis library. Retrieved October 2018 https://www.andeal.org/topic.cfm?menu=5292; Dionyssiotis, Y., Skarantavos, G., Petropoulou, K., Galanos, A., Rapidi, C.-A., & Lyritis, G. P. (2019). Application of current sarcopenia definitions in spinal cord injury. *Journal of Musculoskeletal & Neuronal Interactions, 19*(1), 21; Erlandson, M., Lorbergs, A., Mathur, S., & Cheung, A. (2016). Muscle analysis using pQCT, DXA and MRI. *European Journal of Radiology, 85*(8), 1505–1511.; Fosbol, M. O., & Zerahn, B. (2015). Contemporary methods of body composition measurement. *Clinical Physiology and Functional Imaging, 2*, 81. doi:10.1111/cpf.12152; Fraser, C., Iruthayarajah, J., McIntyre, A., Serrato, J., Benton, B., & Teasell, R. W. (2016). Nutrition issues following spinal cord injury. Version 6.0.; Lee, S. Y., & Gallagher, D. (2008). Assessment methods in human body composition. *Current Opinion in Clinical Nutrition and Metabolic Care, 11*(5), 566; Mitsiopoulos, N., Baumgartner, R., Heymsfield, S., Lyons, W., Gallagher, D., & Ross, R. (1998). Cadaver validation of skeletal muscle measurement by magnetic resonance imaging and computerized tomography. *Journal of Applied Physiology, 85*(1), 115–122; Modlesky, C. M., Bickel, C. S., Slade, J. M., Cureton, K. J., Dudley, G. A., & Meyer, R. A. (2004). Assessment of skeletal muscle mass in men with spinal cord injury using dual-energy X-ray absorptiometry and magnetic resonance imaging. *Journal of Applied Physiology, 96*(2), 561–565. doi:10.1152/japplphysiol.00207.2003; Siervo, M., & Jebb, S. A. (2010). Body composition assessment: Theory into practice: Introduction of multicompartment models. *IEEE Engineering in Medicine and Biology Magazine, 29*(1), 48–59; Teigen, L. M., Kuchnia, A. J., Mourtzakis, M., & Earthman, C. P. (2017). The use of technology for estimating body composition: Strengths and weaknesses of common modalities in a clinical setting. *Nutrition in Clinical Practice, 32*(1), 20–29.

Tracer dilution

Tracer dilution is a common method to assess body composition based on the principle that all the body water is present in the FFM (body fat contains no water), and the assumption that 73.2% of the FFM is composed of water (Fosbol & Zerahn, 2015). To assess TBW a dose of tracer-labeled water (either deuterium and/or oxygen-18) is ingested after collection of a baseline urine sample to determine background isotope enrichment of body water (Siervo & Jebb, 2010). Urine samples are collected again after an equilibration period of 2–3 h following the given dose of tracer-labeled water (Siervo & Jebb, 2010). Isotope dilution methods are based on the assumption that the tracer only distributes in the body pool which consists of plasma, interstitial and intracellular fluids, is equally distributed in this pool, that equilibration occurs rapidly and the tracer is not metabolized during the equilibration time. Since water is found exclusively within FFM, the amount of FFM can be determined from TBW using an assumed hydration constant for FFM of 0.732, which represents 73.2% water in adults (Siervo & Jebb, 2010). FM is then derived by subtracting FFM from total body weight. This technique is considered the reference method for TBW and has a precision of 1%–2% for TBW (Siervo & Jebb, 2010) but is expensive due to the high cost of isotopes and analytical procedures but is a feasible approach in SCI as tracer administration and urine sampling can be undertaken in the home.

Air-displacement plethysmograph

Air-displacement plethysmograph (ADP) is based on the two-compartment model and measures the volume of air displaced by the body inside an enclosed chamber to provide an estimate of total body volume (Siervo & Jebb, 2010). Body density is then calculated by the ratio between volume and mass (weight). Using known densities of FFM and FM estimated from chemical analysis of cadavers and derived formulas, percentage body fat is calculated (Siervo & Jebb, 2010). Precision for FM is 1.7%–4.5% (Siervo & Jebb, 2010). Given that the density of FFM is known to vary between different groups (e.g., children, older adults, obese, blacks), a limitation of this technique is that FFM is assumed to have a constant density (Fields, Goran, & McCrory, 2002). In addition, the use of ADP is limited to research settings and there are practical difficulties associated with measuring lung volumes which must be accounted for when estimating total body volume in individuals with SCI above T3 due to paralysis of intercostal and abdominal muscles (Clasey & Gater Jr, 2005). For SCI populations, measuring weight and access into the measurement chamber are also limitations that may hinder its use clinically (Clasey & Gater Jr, 2005).

Imaging techniques

Dual-energy X-ray absorptiometry

Dual-energy X-ray absorptiometry (DXA) is a two-dimensional X-ray imaging procedure based on the 3-C model that differentiates the body into bone mineral, fat mass, and non-fat (lean) mass (Erlandson, Lorbergs, Mathur, & Cheung, 2016). This method is based on the attenuation characteristics of different tissues in the body exposed to two X-rays of high and low energy, which allow bone attenuation to be separated from soft tissue attenuation (Erlandson et al., 2016). As a result, DXA can provide estimates of total body and regional (arms, legs, trunk) fat mass, percent body fat, lean tissue mass, and bone mineral mass [bone mineral content (BMC, g) and bone mineral density (BMD, g/cm^2)] (Teigen et al., 2017). DXA is considered the gold standard for the diagnosis of osteoporosis (Lee & Gallagher, 2008) and has been used for defining low total and ALM which is part of the sarcopenia criteria (Teigen et al., 2017). The precision of DXA estimates of whole-body FM and lean tissue mass in sequential measurements range from 0.8%–2.7% and 0.4%–1.3% respectively and the precision of regional, particularly trunk fat mass are poorer than whole-body measures (Fosbol & Zerahn, 2015). While the majority of body composition studies in the SCI population have utilized DXA and its' use is recommended in The Academy of Nutrition and Dietetics Spinal Cord Injury Evidence-Based Nutrition Practice Guidelines (Academy of Nutrition and Dietetics, 2009) physical access to the scanning bed and difficulty positioning people with SCI limit its' routine use.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) is highly precise, ~1.2%–2% (Mitsiopoulos et al., 1998), well suited for serial measurements (Erlandson et al., 2016), and able to provide detailed three-dimensional images of the body, and thus can be used to determine the quantity and distribution of adipose tissue (visceral, subcutaneous and intermuscular) and skeletal muscle (muscle cross-sectional area) at any site in the body (Siervo & Jebb, 2010). However, there are a number of limitations. It is

time consuming and costly, requires highly trained personnel, is not appropriate for people with implants (e.g., pacemakers), is claustrophobic for some people (Fosbol & Zerahn, 2015), is difficult to access and maintain a prolonged supine position for people with impaired mobility such as SCI (Erlandson et al., 2016) and movement artifacts may arise from spasms and contractures.

Computed tomography

Computed tomography (CT) estimates total and regional adipose tissue (visceral, subcutaneous, and intermuscular), skeletal muscle, and bone (Borga et al., 2018) and is also highly precise ~2% (Mitsiopoulos et al., 1998). CT is considered a reference measure of body composition but due to high cost and radiation when used for whole-body composition, usage is limited to diagnostic purposes (Fosbol & Zerahn, 2015). CT measures at specific sites such as L3 and mid-thigh regions obtained are correlated with DXA whole-body FFM and skeletal muscle mass and have been suggested as alternatives to whole-body measurements for detecting low muscle mass (Cruz-Jentoft et al., 2019); however, this has not been investigated in people with SCI. The psoas muscle CSA measured using CT has also been proposed as an alternative tool to predict muscle quantity (Cruz-Jentoft et al., 2019) and has been used in one study as a measure of sarcopenia in individuals with acute traumatic SCI (Banaszek et al., 2019). While newer CT machines have lower radiation doses, accessibility for individuals with disabilities such as SCI remains problematic and spasms may create movement artifacts. Furthermore, the use of CT measures at specific sites to predict whole-body muscle mass warrants further investigation in people with SCI.

Peripheral quantitative computer tomography

Peripheral quantitative computed tomography (pQCT) is a newer imaging tool that uses similar technology to CT and produces a three-dimensional cross-sectional image of the tissue structure (BMD, BMC, muscle, and fat CSA) of a limb (Erlandson et al., 2016). pQCT has a lower radiation exposure, a shorter scan time, and the equipment is cheaper than a whole-body CT scanner, with precision for limb muscle area of <5% (Erlandson et al., 2016). The main limitations of pQCT are that it is largely used as a research tool, precision is low for intramuscular adipose tissue (3%–42%), accuracy is lower than MRI, scanning is limited to a single slice at appendicular sites (arms and legs), and a gold standard protocol for image analysis is lacking (Erlandson et al., 2016). Furthermore, movement artifacts, e.g., spasms and contractures may limit application in people with SCI.

Novel technique

Computerized digital image analysis

This novel approach is under development but entails deriving body shape and volume from back and side photographic images of the body while standing motionless with arms and legs abducted (Affuso et al., 2018). Percentage body fat predicted from computer algorithm using support vector regression models correlates moderately well with DXA (Affuso et al., 2018). This method has not been used in people with impaired mobility, such as SCI.

Summary of body composition assessment methods

In summary, it is currently recommended that weight, BMI, waist circumference, and body composition are routinely monitored following SCI. Choice of a body composition method will be dependent on a range of factors as outlined in the following section.

Choosing a body composition method for use in SCI

When selecting a method(s) to quantify body composition in individuals with SCI, a number of factors should be taken into consideration, including the:

- compositional variable to be quantified
- validity and precision of the method
- ease of use
- cost
- safety and convenience for the individual undergoing measurement

- measurement frequency, i.e., single point in time or longitudinal
- existence of population-specific prediction equations and reference measures or cut-off values developed and cross-validated for use in SCI
- accessibility to equipment for people with impaired mobility

When selecting a body composition technique, it is critical to use population-specific prediction equations and reference measures or cut-off values developed and cross-validated for use in SCI when available or to be aware of the limitations of using those developed in non-disabled people.

Applications to other areas of neuroscience

In this chapter, we reviewed the effects of traumatic spinal cord injury on body composition. We also provided an overview of the methods for assessing body composition and the considerations for use in individuals with spinal cord injury. Heterogeneous alterations in body composition are also seen in other neurological disorders and there are numerous etiological factors that are disease genotype and phenotype specific. These include whether the disease is neurodegenerative, stage of the disease, inflammatory abnormalities, endocrine, metabolic and motor disorders, and decreased physical activity (Çekici & Acar Tek, 2020).

Neurological diseases show a variety of impacts on body composition. A high prevalence of sarcopenia and segmental body composition changes similar to spinal cord injury have been described following stroke and in men with Multiple Sclerosis (Wingo, Young, & Motl, 2018). Whereas, asymmetrical disease effects, i.e., greater muscle wasting on the affected side of the body are seen in amyotrophic lateral sclerosis (Desport et al., 2003) and stroke, with a greater decline in lean mass of limbs on the hemiplegic side (Chang, Wu, Huang, & Han, 2020). Analogous to spinal cord injury, level of impairment impacts body composition in persons with relapsing-remitting multiple sclerosis; whole body, regional fat mass, and percentage body fat are higher in those with moderate compared with mild disability (Pilutti & Motl, 2019). In contrast, progressive weight loss composed of decreases in fat mass, percentage body fat, trunk, and peripheral fat mass with the maintenance of fat-free mass has been described in Parkinson's disease (Tan et al., 2018; Yong et al., 2020). However, the reason for the maintenance of fat-free mass is unclear (Tan et al., 2018; Yong et al., 2020). Differences in body composition between neurological disease subtypes have also been reported in Parkinson's disease (Femat-Roldán et al., 2020) and subgroups of Spinocerebellar ataxias (Leite et al., 2020). The diverse changes in the whole body and segmental body composition seen in spinal cord injury are reflected in other neurological diseases.

Considerations for body composition assessment in spinal cord injury described in Tables 1 and 2 are also applicable to other neurological conditions. For example, use of skinfold and bioimpedance prediction equations generated in normal-able bodied adults are inaccurate compared with dual-energy X-ray absorptiometry and oxygen-18 for prediction of percentage body fat in adults with cerebral palsy (Hildreth, Johnson, Goran, & Contompasis, 1997) and not valid in patients with amyotrophic lateral sclerosis (Desport et al., 2003). Difficulties accessing suprailiac, abdomen, mid-thigh, and subscapular skinfolds in wheelchair-bound subjects have also been reported (Hildreth et al., 1997). A population-specific bioimpedance equation has been validated (Desport et al., 2003) and recommended in guidelines for amyotrophic lateral sclerosis (Burgos et al., 2018). Analogous to spinal cord injury, the conventional BMI cut-off for classifying obesity underestimates the true adiposity in multiple sclerosis compared with dual-energy X-ray absorptiometry (Pilutti & Motl, 2016). In summary, when selecting a body composition technique it is critical to use population-specific prediction equations and reference measures or cut-off values developed and cross-validated for use in the specific neurological condition when available or to be aware of the limitations of using those developed in able-bodied people.

Key facts

Muscle wasting and increases in body fat, particularly around the waist occur following SCI.
Muscle wasting is more dramatic in severe SCI, such as tetraplegia and complete injuries.
Muscle wasting and body fat increases are greater in tetraplegia than paraplegia.
People with tetraplegia lose more muscle and gain more fat in the arms than those with paraplegia.
Increased body fat around the waist increases the risk of health problems such as heart disease and diabetes in people with SCI.
It is unclear whether low muscle mass increases health risk and early death in people with SCI.
Standards that define a healthy body weight normalised for height/ supine length have not been established.

Recommended waist circumference standards that define an increased health risk are lower than that for the healthy population, however the optimal cut point is not established.
Physical access to anthropometric and sophisticated body composition techniques may be limited by impaired mobility and sitting balance.
Bioelectrical impedance analysis shows promise as an accurate and practical tool to measure body composition.
Equations that estimate percentage body fat using skinfold thickness and fat and muscle using bioimpedance developed in healthy populations are inaccurate in SCI.
Population-specific bioimpedance equations developed in spinal cord-injured people estimate body composition more accurately.
SCI-specific reference ranges and cut-offs for muscle and fat have not been defined.

Mini-dictionary of terms

Lean tissue mass: Sum of all soft tissue minus bone mineral content and excluding fat mass, e.g., measured using dual-energy X-ray absorptiometry.
Fat-free mass: Lean tissue mass plus bone mineral content, e.g., measured using bioimpedance or deuterium dilution.
Fat mass: Bodyweight minus fat-free mass.
Extracellular fluid: Fluid contained outside of body cells, including interstitial fluid, lymph, vascular fluid.
Intracellular fluid: Fluid contained within the body cells.
Total body water: Water content of the body, composed of extracellular fluid plus intra-cellular fluid.
Sarcopenia: Low muscle mass, combined with reduced strength and functional impairment.

Summary points

This chapter focuses on the alterations that occur to body composition and body composition assessment methods suitable for use in clinical practice following spinal cord injury.

- Muscle wasting occurs below the level of the injury and body fat increases.
- Alterations in body composition are more dramatic in people with more severe injuries such as tetraplegia and complete injuries.
- Muscle wasting and gains in body fat are associated with poor health outcomes and increased risk of cardiovascular disease and diabetes.
- Anthropometric methods used routinely to measure and monitor body composition in non-disabled people are not appropriate or convenient to use in people with SCI.
- Reference "norms" to classify health risks in non-disabled people are not appropriate to use in people with SCI.
- Anthropometry may be suitable to monitor changes over time in an individual with SCI if a consistent method is used.
- Bioimpedance is a valid and convenient tool to measure body composition in people with SCI when population-specific equations are used.
- Imaging methods such as MRI, CT, and DXA are not easily accessible for people with SCI but are important for diagnostic purposes.

References

Academy of Nutrition and Dietetics. (2009). *Spinal cord injury (SCI) evidence-based nutrition practice guideline*. *Evidence analysis library*. Retrieved October 2018 https://www.andeal.org/topic.cfm?menu=5292.

Affuso, O., Pradhan, L., Zhang, C., Gao, S., Wiener, H. W., Gower, B., … Allison, D. B. (2018). A method for measuring human body composition using digital images. *PLoS One*, *13*(11), e0206430. https://doi.org/10.1371/journal.pone.0206430.

Banaszek, D., Inglis, T., Ailon, T., Charest-Morin, R., Dea, N., Fisher, C. G., … Street, J. (2019). P153. Sarcopenia, independent of age, predicts mortality and acute care adverse events in patients with traumatic spinal cord injury. *The Spine Journal*, *19*(9), S229.

Beck, L. A., Lamb, J. L., Atkinson, E. J., Wuermser, L. A., & Amin, S. (2014). Body composition of women and men with complete motor paraplegia. *Journal of Spinal Cord Medicine*, *37*(4), 359–365. https://doi.org/10.1179/2045772313Y.0000000151.

Borga, M., West, J., Bell, J. D., Harvey, N. C., Romu, T., Heymsfield, S. B., & Leinhard, O. D. (2018). Advanced body composition assessment: From body mass index to body composition profiling. *Journal of Investigative Medicine: The Official Publication of the American Federation for Clinical Research*, *66*, 887–895.

Bryce, T. N. (2010). *Spinal cord injury*. New York: Demos Medical.

Buchholz, A. C., McGillivray, C. F., & Pencharz, P. B. (2003). Differences in resting metabolic rate between paraplegic and able-bodied subjects are explained by differences in body composition. *American Journal of Clinical Nutrition*, *77*(2), 371–378.

Burgos, R., Bretón, I., Cereda, E., Desport, J. C., Dziewas, R., Genton, L., … Bischoff, S. C. (2018). ESPEN guideline clinical nutrition in neurology. *Clinical Nutrition*, *37*(1), 354–396. https://doi.org/10.1016/j.clnu.2017.09.003.

Castro, M. J., Apple, D. F., Jr., Hillegass, E. A., & Dudley, G. A. (1999). Influence of complete spinal cord injury on skeletal muscle cross-sectional area within the first 6 months of injury. *European Journal of Applied Physiology and Occupational Physiology*, *80*(4), 373–378.

Cederholm, T., Jensen, G., Correia, M., Gonzalez, M., Fukushima, R., Higashiguchi, T., … Coats, A. (2019). GLIM criteria for the diagnosis of malnutrition—A consensus report from the global clinical nutrition community. *Journal of Cachexia, Sarcopenia and Muscle*, *10*(1), 207–217.

Çekici, H., & Acar Tek, N. (2020). Determining energy requirement and evaluating energy expenditure in neurological diseases. *Nutritional Neuroscience*, *23*(7), 543–553.

Chang, K., Wu, W., Huang, K., & Han, D. (2020). Segmental body composition transitions in stroke patients: Trunks are different from extremities and strokes are as important as hemiparesis. *Clinical Nutrition*, *39*(6), 1968–1973.

Cirnigliaro, C. M., La Fountaine, M. F., Emmons, R., Kirshblum, S. C., Asselin, P., Spungen, A. M., & Bauman, W. A. (2013). Prediction of limb lean tissue mass from bioimpedance spectroscopy in persons with chronic spinal cord injury. *Journal of Spinal Cord Medicine*, *36*(5), 443–453. https://doi.org/10.1179/2045772313Y.0000000108.

Clasey, J. L., & Gater, D. R., Jr. (2005). A comparison of hydrostatic weighing and air displacement plethysmography in adults with spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *86*(11), 2106–2113. https://doi.org/10.1016/j.apmr.2005.06.013.

Cox, S., Weiss, S. M., Posuniak, E. A., Worthington, P., Prioleau, M., & Heffley, G. (1985). Energy expenditure after spinal cord injury: An evaluation of stable rehabilitating patients. *The Journal of Trauma*, *25*(5), 419–423.

Cruz-Jentoft, A. J., Bahat, G., Bauer, J., Boirie, Y., Bruyère, O., Cederholm, T., … Writing Group for the European Working Group on Sarcopenia in Older People 2 (EWGSOP2), and the Extended Group for EWGSOP2. (2019). Sarcopenia: Revised European consensus on definition and diagnosis. *Age and Ageing*, *48*, 16–31. https://doi.org/10.1093/ageing/afy169.

Desneves, K. J., Panisset, M. G., Galea, M. P., Kiss, N., Daly, R. M., & Ward, L. C. (2020). Comparison of segmental lean tissue mass in individuals with spinal cord injury measured by dual energy X-ray absorptiometry and predicted by bioimpedance spectroscopy. *Spinal Cord*, 1–8. https://doi.org/10.1038/s41393-020-00568-3.

Desport, J. C., Preux, P. M., Bouteloup-Demange, C., Clavelou, P., Beaufrere, B., Bonnet, C., & Couratier, P. P. (2003). Validation of bioelectrical impedance analysis in patients with amyotrophic lateral sclerosis. *The American Journal of Clinical Nutrition*, *77*(5), 1179.

Desport, J. C., Preux, P. M., Guinvarc'h, S., Salle, J. Y., Daviet, J. C., Dudognon, P., … Ritz, P. (2000). Total body water and percentage fat mass measurements using bioelectrical impedance analysis and anthropometry in spinal cord-injured patients. *Clinical Nutrition*, *19*(3), 185–190. https://doi.org/10.1054/clnu.1999.0122.

Dionyssiotis, Y., Skarantavos, G., Petropoulou, K., Galanos, A., Rapidi, C.-A., & Lyritis, G. P. (2019). Application of current sarcopenia definitions in spinal cord injury. *Journal of Musculoskeletal & Neuronal Interactions*, *19*(1), 21.

Edwards, L. A., Bugaresti, J. M., & Buchholz, A. C. (2008). Visceral adipose tissue and the ratio of visceral to subcutaneous adipose tissue are greater in adults with than in those without spinal cord injury, despite matching waist circumferences. *American Journal of Clinical Nutrition*, *87*(3), 600–607.

Emmons, R. R., Garber, C. E., Cirnigliaro, C. M., Kirshblum, S. C., Spungen, A. M., & Bauman, W. A. (2011). Assessment of measures for abdominal adiposity in persons with spinal cord injury. *Ultrasound in Medicine and Biology*, *37*(5), 734–741.

Erlandson, M., Lorbergs, A., Mathur, S., & Cheung, A. (2016). Muscle analysis using pQCT, DXA and MRI. *European Journal of Radiology*, *85*(8), 1505–1511.

Femat-Roldán, G., Gaitán Palau, M. A., Castilla-Cortázar, I., Elizondo Ochoa, G., Moreno, N. G., Martín-Estal, I., & Jiménez Yarza, M. (2020). Altered body composition and increased resting metabolic rate associated with the postural instability/gait difficulty Parkinson's disease subtype. *Parkinson's Disease*, 1–9. https://doi.org/10.1155/2020/8060259. 20420080.

Fields, D. A., Goran, M. I., & McCrory, M. A. (2002). Body-composition assessment via air-displacement plethysmography in adults and children: A review. *American Journal of Clinical Nutrition*, *75*(3), 453–467. https://doi.org/10.1093/ajcn/75.3.453.

Fosbol, M. O., & Zerahn, B. (2015). Contemporary methods of body composition measurement. *Clinical Physiology and Functional Imaging*, *2*, 81. https://doi.org/10.1111/cpf.12152.

Galea, M. P. (2012). Spinal cord injury and physical activity: Preservation of the body. *Spinal Cord*, *50*(5), 344–351. https://doi.org/10.1038/sc.2011.149.

Gandy, J. (2014). *Manual of dietetic practice*. Hoboken, United Kingdom: John Wiley & Sons, Incorporated.

Garshick, E., Ashba, J., Tun, G. C., Lieberman, L. S., & Brown, R. (1997). Assessment of stature in spinal cord injury. *The Journal of Spinal Cord Medicine*, *20*(1), 36–42.

Gibson, R. S. (2005). *Principles of nutritional assessment*. USA: Oxford University Press.

Gorgey, A. S., Dolbow, J. D., Khalil, R. K., Dolbow, D. R., Castillo, C., & Gater, D. R. (2014). Effects of spinal cord injury on body composition and metabolic profile—Part I. *Journal of Spinal Cord Medicine*, *37*(6), 693–702.

Gorgey, A., & Dudley, G. (2007). Skeletal muscle atrophy and increased intramuscular fat after incomplete spinal cord injury. *Spinal Cord*, *45*(4), 304.

Hildreth, H. G., Johnson, R. K., Goran, M. I., & Contompasis, S. H. (1997). Body composition in adults with cerebral palsy by dual-energy X-ray absorptiometry, bioelectrical impedance analysis, and skinfold anthropometry compared with the 18O isotope-dilution technique. *The American Journal of Clinical Nutrition*, *66*(6), 1436–1442.

Kocina, P., & Heyward, V. (1997). Validation of a bioimpedance equation for estimating fat-free mass of spinal cord injured adults 319. *Medicine & Science in Sports & Exercise*, *29*(5), 55.

Kyle, U. G., Bosaeus, I., De Lorenzo, A. D., Deurenberg, P., Elia, M., Gómez, J. M., … Pirlich, M. (2004). Bioelectrical impedance analysis—Part I: Review of principles and methods. *Clinical Nutrition*, *23*(5), 1226–1243.

Lee, S. Y., & Gallagher, D. (2008). Assessment methods in human body composition. *Current Opinion in Clinical Nutrition and Metabolic Care*, *11*(5), 566.

Leite, C. D. M. B. A., Schieferdecker, M. E. M., Frehner, C., Munhoz, R. P., Ashizawa, T., & Teive, H. A. G. (2020). Body composition in spinocerebellar ataxia type 3 and 10 patients: Comparative study with control group. *Nutritional Neuroscience*, *23*(1), 49–54.

Maggioni, M., Bertoli, S., Testolin, G., Merati, G., Margonato, V., & Veicsteinas, A. (2003). Body composition assessment in spinal cord injury subjects. *Acta Diabetologica*, *40*(Suppl. 1), S183–S186. https://doi.org/10.1007/s00592-003-0061-7.

Mitsiopoulos, N., Baumgartner, R., Heymsfield, S., Lyons, W., Gallagher, D., & Ross, R. (1998). Cadaver validation of skeletal muscle measurement by magnetic resonance imaging and computerized tomography. *Journal of Applied Physiology*, *85*(1), 115–122.

Modlesky, C. M., Bickel, C. S., Slade, J. M., Cureton, K. J., Dudley, G. A., & Meyer, R. A. (2004). Assessment of skeletal muscle mass in men with spinal cord injury using dual-energy X-ray absorptiometry and magnetic resonance imaging. *Journal of Applied Physiology*, *96*(2), 561–565. https://doi.org/10.1152/japplphysiol.00207.2003.

Pacifico, J., Geerlings, M. A. J., Reijnierse, E. M., Phassouliotis, C., Lim, W. K., & Maier, A. B. (2020). Prevalence of sarcopenia as a comorbid disease: A systematic review and meta-analysis. *Experimental Gerontology*, *131*. https://doi.org/10.1016/j.exger.2019.110801.

Panisset, M. G., Desneves, K., Ward, L. C., Rafferty, J., Rodi, H., Roff, G., … Galea, M. P. (2018). Bedside quantification of fat-free mass in acute spinal cord injury using bioelectrical impedance analysis: A psychometric study. *Spinal Cord*, *56*(4), 355.

Pelletier, C. A., Miyatani, M., Giangregorio, L., & Craven, B. C. (2016). Original research: Sarcopenic obesity in adults with spinal cord injury: A cross-sectional study. *Archives of Physical Medicine and Rehabilitation*, *97*, 1931–1937. https://doi.org/10.1016/j.apmr.2016.04.026.

Pilutti, L. A., & Motl, R. W. (2016). Body mass index underestimates adiposity in persons with multiple sclerosis. *Archives of Physical Medicine and Rehabilitation*, *97*(3), 405–412.

Pilutti, L. A., & Motl, R. W. (2019). Body composition and disability in people with multiple sclerosis: A dual-energy X-ray absorptiometry study. *Multiple Sclerosis and Related Disorders*, *29*, 41–47. https://doi.org/10.1016/j.msard.2019.01.009.

Rashmi, R., & Snekhalatha, U. (2019). Evaluation of body composition parameters using various diagnostic methods: A meta analysis study. *Obesity Medicine*, *16*. https://doi.org/10.1016/j.obmed.2019.100150.

Ravensbergen, H. J. C., Lear, S. A., & Claydon, V. E. (2014). Waist circumference is the best index for obesity-related cardiovascular disease risk in individuals with spinal cord injury. *Journal of Neurotrauma*, *31*(3), 292–300. https://doi.org/10.1089/neu.2013.3042.

Roh, E., & Choi, K. M. (2020). Health consequences of sarcopenic obesity: A narrative review. *Frontiers in Endocrinology*, *11*, 332.

Siervo, M., & Jebb, S. A. (2010). Body composition assessment: Theory into practice: Introduction of multicompartment models. *IEEE Engineering in Medicine and Biology Magazine*, *29*(1), 48–59.

Silveira, S., Ledoux, T., Robinson-Whelen, S., Stough, R., & Nosek, M. (2017). Methods for classifying obesity in spinal cord injury: A review. *Spinal Cord*, *55*(9), 812.

Singh, R., Rohilla, R. K., Saini, G., & Kaur, K. (2014). Longitudinal study of body composition in spinal cord injury patients. *Indian Journal of Orthopaedics*, *48*(2), 168.

Spungen, A. M., Adkins, R. H., Stewart, C. A., Wang, J., Pierson, R. N., Jr., Waters, R. L., & Bauman, W. A. (2003). Factors influencing body composition in persons with spinal cord injury: A cross-sectional study. *Journal of Applied Physiology*, *95*(6), 2398.

Spungen, A. M., Bauman, W. A., Wang, J., & Pierson, R. N. (1995). Measurement of body fat in individuals with tetraplegia: A comparison of eight clinical methods. *Spinal Cord*, *33*(7), 402.

Tan, A. H., Hew, Y. C., Lim, S.-Y., Ramli, N. M., Kamaruzzaman, S. B., Tan, M. P., … Lang, A. E. (2018). Altered body composition, sarcopenia, frailty, and their clinico-biological correlates, in Parkinson's disease. *Parkinsonism & Related Disorders*, *56*, 58–64. https://doi.org/10.1016/j.parkreldis.2018.06.020.

Teigen, L. M., Kuchnia, A. J., Mourtzakis, M., & Earthman, C. P. (2017). The use of technology for estimating body composition: Strengths and weaknesses of common modalities in a clinical setting. *Nutrition in Clinical Practice*, *32*(1), 20–29.

Wingo, B. C., Young, H.-J., & Motl, R. W. (2018). Body composition differences between adults with multiple sclerosis and BMI-matched controls without MS. *Disability and Health Journal*, *11*(2), 243–248. https://doi.org/10.1016/j.dhjo.2017.10.003.

Yong, V. W., Tan, Y. J., Ng, Y.-D., Choo, X. Y., Sugumaran, K., Chinna, K., … Tan, A. H. (2020). Progressive and accelerated weight and body fat loss in Parkinson's disease: A three-year prospective longitudinal study. *Parkinsonism & Related Disorders*, *77*, 28–35. https://doi.org/10.1016/j.parkreldis.2020.06.015.

Chapter 33

Energy requirements and spinal cord injury

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List of abbreviations

BMR	basal metabolic rate
DLW	doubly labeled water
FFM	fat free mass
IC	indirect calorimetry
PAEE	physical activity energy expenditure
REE	resting energy expenditure
RMR	resting metabolic rate
SCI	spinal cord injury
TEE	total energy expenditure
TEF	thermic effect of food

Introduction

Muscle wasting following spinal cord injury (SCI) leads to a decreased resting energy expenditure, which combined with reduced levels of physical activity pre-disposes individuals with SCI to weight gain, other co-morbid complications, and chronic diseases such as diabetes and cardiovascular disease (Gorgey et al., 2014). It is important to assess and monitor the energy needs of people with SCI to prescribe diet and exercise interventions that preserve muscle mass and prevent positive energy balance, weight gain, and adiposity. In this section, we review the effects of traumatic SCI on energy expenditure. We also provide an overview of the available methods for assessing energy requirements and considerations for use in individuals with SCI.

Energy expenditure

Total energy expenditure (TEE) is the energy used by an individual over a 24-h period and comprises basal metabolic rate (BMR), the thermic effect of food (TEF), and physical activity-related energy expenditure (PAEE) (Gandy, 2014). Each of these terms is defined in the mini-dictionary. BMR is often substituted in the scientific literature with resting metabolic rate (RMR) and resting energy expenditure (REE). BMR is the largest element of TEE, comprising 60%–75% of TEE in a healthy person (Nevin, Steenson, Vivanti, & Hickman, 2016) and is influenced by age, gender, body weight, and body composition. Fat free mass (FFM) is the greatest predictor of RMR in non-disabled and SCI people and explains 70% of the variation in RMR (Buchholz & Pencharz, 2004). The second largest and most variable component is PAEE, which is usually only 25%–30% of TEE (Buchholz & Pencharz, 2004), whereas the third component, the TEF generally accounts for 5%–10% TEE (Buchholz & Pencharz, 2004).

Energy expenditure following SCI

It has been suggested that the energy needs of individuals with SCI vary over time (Nevin et al., 2016). During the acute phase of injury energy requirements are thought to be raised due to neurogenic shock (Nevin et al., 2016), surgical

Cellular, Molecular, Physiological, and Behavioral Aspects of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822427-4.00033-2

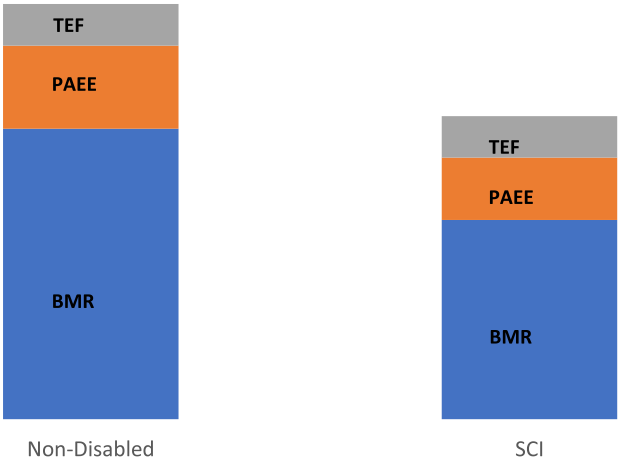

FIG. 1 Total energy expenditure in non-disabled and SCI. Comparison of components of total energy expenditure in non-disabled people and people with long-term spinal cord injury; *BMR*, basal metabolic rate; *TEF*, thermic effect of food; *PAEE*, physical activity energy expenditure. Note that total energy expenditure is lower in SCI due to a reduction in BMR and PAEE (Buchholz & Pencharz, 2004; Gorgey et al., 2014; Nevin et al., 2016).

intervention, and medical complications (Long, Schaffel, Geiger, Schiller, & Blakemore, 1979). However, a systematic review of studies investigating measured and predicted energy needs found no evidence of this theorized hypermetabolism in the acute phase (<1-month post-injury) (Nevin et al., 2016). It is plausible that reductions in PAEE due to paralysis and immobility may neutralize any stress-induced increases in BMR in the early stages following injury (Gandy, 2014). In contrast, it is well documented that individuals with chronic SCI have a reduced RMR, indicative of hypometabolism, with cross-sectional studies in SCI patients ≥1.5 years post-injury reporting an RMR 14%–27% less than non-injured controls (Buchholz & Pencharz, 2004). This reduced RMR is attributed to lower FFM and decreased sympathetic nervous system activity (Buchholz & Pencharz, 2004). Injury severity also affects energy expenditure in chronic SCI, with a ∼19% lower BMR observed in individuals with tetraplegia compared with paraplegia (Farkas, Gorgey, Dolbow, Berg, & Gater, 2019). Physical activity levels have also been reported to be 39% lower in tetraplegia than paraplegia (Kyriakides et al., 2019) and 18% lower in persons with complete compared with incomplete SCI (Buchholz & Pencharz, 2004). However, no changes to the TEF have been reported in people with SCI (Gorgey et al., 2014). In summary, it is difficult to draw any conclusions about the energy needs in the acute phase post-injury due to a lack of studies. However, it is well documented that individuals with chronic SCI have a reduced RMR that is directly related to loss of FFM and injury severity. This reduced RMR combined with declines in PAEE contributes to positive energy balance which likely explains fat mass gains and the increased risk for multiple co-morbidities in people with SCI. These differences in RMR and PAEE in non-disabled and long-term SCI are illustrated in Fig. 1.

Methods for determining energy requirements

It is important to accurately assess the energy needs of people with SCI for two reasons:

(1) To preserve lean (muscle) mass.
(2) To prevent positive energy balance that contributes to weight and fat gain.

The following section details methods available and considerations when choosing a method for predicting energy expenditure in people with SCI.

Doubly labeled water

The reference method for the determination of total energy expenditure (TEE) is isotope dilution using two stable isotopes, deuterium (^2H_2O) and ^{18}O-labeled water ($^2H_2^{18}O$, or oxygen-18) (DeLany, 1997). After ingestion, doubly-labeled water (DLW) rapidly reaches equilibrium with total body water (TBW) and enters the metabolic pool. Deuterium is eliminated as water, and oxygen-18 is eliminated both as water and carbon dioxide. Isotope ratio mass spectroscopy analysis is used to determine the elimination rates of the isotopes in urine. The difference between the rates of disappearance of the two isotopes permits calculation of the CO_2 produced and using respiratory equations, the total energy expended. This method is

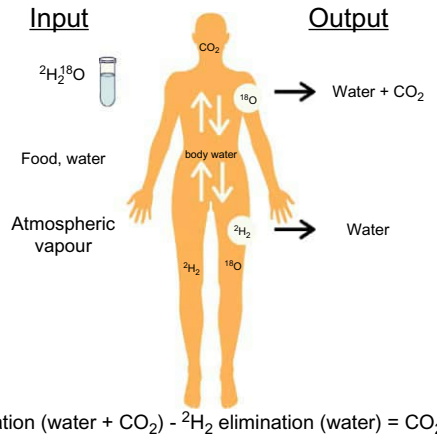

FIG. 2 Doubly labeled water method. After ingestion, doubly-labeled water (DLW-$^{2}H_2^{18}O$) rapidly reaches equilibrium with total body water (TBW) and enters the metabolic pool. Deuterium ($^{2}H_2$) is eliminated as water, and oxygen-18 (^{18}O) is eliminated both as water (H_2O) and carbon dioxide (CO_2). The difference between the rates of disappearance of the two isotopes permits calculation of the CO_2 produced and using respiratory equations, the total energy expended (DeLany, 1997).

illustrated in Fig. 2. An additional advantage of the DLW technique is that it concomitantly allows calculation of body composition from dilution of either tracer (usually deuterium).

Indirect calorimetry

Indirect calorimetry (IC) is considered the gold standard for assessing BMR and REE/RMR (Gandy, 2014; Nevin et al., 2016) and is recommended for use in critically ill adults (McClave et al., 2016) and people with SCI (Academy of Nutrition and Dietetics, 2009). IC involves the measurement of oxygen consumption and CO_2 production. Energy expenditure is then calculated using a respiratory equation, the modified Weir equation (Haugen, Chan, & Li, 2007) shown in Table 1. Both doubly-labeled water and indirect calorimetry methods are typically limited to a research setting due to cost, practical considerations, and availability (Gandy, 2014; Nevin et al., 2016).

TABLE 1 Common energy prediction equations developed in non-disabled populations.

Source	Age range	Equation
Schofield (1985) (MJ/d)	18–30	Males BMR = (0.063 × W) + 2.896 Females BMR = (0.062 × W) + 2.036
	30–60	Males BMR = (0.048 × W) + 3.653 Females BMR = (0.034 × W) +3.538
	>60	Males BMR = (0.049 × W) + 2.459 Females BMR = (0.038 × W) + 2.755
Henry (2005) (MJ/d)	18–30	Males BMR = (0.0669 × W) + 2.28 Females BMR = (0.0546 × W) + 2.33
	30–60	Males BMR = (0.0592 × W) + 2.48 Females BMR = (0.0407 × W) + 2.90
	60+	Males BMR = (0.0563 × W) + 2.15 Females BMR = (0.0424 × W) + 2.38
Harris and Benedict (1918) (kJ/d)		Males BMR = 278 + (57.5 × W) + (20.9 × H)−(28.3 × A) Females BMR = 2741 + (40 × W) + (7.7 × H)−(19.6 × A)
Weir (kcal/d) (Haugen et al., 2007)		[(VO_2 (L/min)×3.941) + (VCO_2 (L/min)×1.11)]×1440

Common equations used to predict energy needs in non-disabled populations and the modified Weir equation used to predict resting energy expenditure (REE) from oxygen consumption and carbon dioxide production. *W*, weight in kg; *A*, age in years; *H*, height in cm (Harris & Benedict, 1918; Haugen et al., 2007; Henry, 2005; Schofield, 1985).

Predictive equations

In clinical practice, published predictive equations incorporating a combination of age, weight, or sex are commonly used to estimate REE when IC is unavailable. The most commonly used predictive equations are shown in Table 1. The Harris and Benedict (1918), Schofield (1985), and Henry (2005) equations were derived from able-bodied populations. These are adjusted by multiplying REE by activity and/or stress factors to predict the total energy expenditure of an individual, their use is subjective and has received much criticism due to their inaccuracy (Reeves & Capra, 2003). Another more convenient, commonly used method is to calculate energy requirements based simply on energy values per kilogram of body weight, e.g., 25 kcal/kg, with adjustments for certain conditions, such as hypermetabolism or malabsorption that are not based on scientific evidence (Reeves & Capra, 2003). This method also doesn't take into consideration age, gender, metabolic state, or body composition, all factors known to affect energy expenditure (Gandy, 2014).

A less utilized method in clinical practice is to calculate energy requirements based on published prediction equations that incorporate body composition measurements (Cunningham, 1991). Recently SCI-specific equations that include body composition measures (FFM, FM, and/or circumferences) have emerged for use in chronic SCI (Chun, Shin, & Kim, 2017; Kocina & Heyward, 1997; Nightingale & Gorgey, 2018). These are summarized in Table 2. The accuracy and validity of predictive equations for use in the various phases following SCI is discussed in the next section.

Predictive equations validated in SCI

Energy prediction equations and activity factors developed in non-disabled people are inaccurate when used in SCI (Nevin et al., 2016). Guidelines suggest using Harris-Benedict with an injury factor of 1.2 and an activity factor of 1.1 if the SCI patient is in the acute phase, and that individuals with long term paraplegia and tetraplegia have their energy needs to be estimated using 22.7 and 27.9 kcal/kg, respectively (Academy of Nutrition and Dietetics, 2009). However, a systematic review found that energy prediction equations including age, weight, or sex developed in non-disabled populations are inaccurate in SCI, overestimating energy requirements by up to 90% (Nevin et al., 2016). The simple kcal/kg method also shows the poor predictive value (Desneves et al., 2019; Ramirez et al., 2018; Sedlock & Laventure, 1990), as do prediction equations developed in non-disabled people that include FFM (Chun et al., 2017; Nightingale & Gorgey, 2018; Sedlock & Laventure, 1990). Compounding this, the use of the able-bodied physical activity correction factor of 1.2 when applied to Harris and Benedict (1918), Schofield (1985), and Henry (2005) equations has been found to inaccurately estimate TEE in people with acute SCI (Desneves et al., 2019) and an SCI-specific correction factor of 1.15 has been suggested (Farkas et al., 2019). However, the reliability and validity of this recommendation have not been tested (Farkas et al., 2019). The use of equations and activity factors developed in non-disabled people and the kcal/kg method are inaccurate and not recommended for predicting energy needs in people with SCI.

Contemporary research has focused on the development and validation of SCI-specific regression equations utilizing FFM with or without anthropometric measurements to predict BMR in chronic SCI (Andersen, Sweet, Reid, Sydney, & Plourde, 2018; Buchholz et al., 2003; Chun et al., 2017; Nightingale & Gorgey, 2018). The Buchholz et al. (2003) RMR prediction equation developed in men and women with paraplegia that includes FFM has been cross-validated in people with acute and chronic SCI. A study in people with acute SCI (<2 months post-injury) found that the Buchholz et al., RMR equation multiplied by a combined stress and activity factor of 1.3 was the most accurate estimate of TDEE compared with

TABLE 2 SCI-specific energy prediction equations.

Source	Equation
Buchholz, McGillivray, and Pencharz (2003) (kJ/d)	RMR =10,682–1238(ln age)−521(sex)−24(H) + 87(FFM)
Chun et al. (2017) (kcal/d)	BMR = 24.5 × FFM + 244.4
Nightingale and Gorgey (2018) (kcal/day)	BMR = 23.469 × FFM + 294.330 BMR = 23.995 × FFM + 6.189 × SAD +6.384 × TAD–6.948 × TC + 275.211 BMR = 19.789 × FFM + 5.156 × W + 8.090 × H − 15.301 × C BMR = 13.202 × H + 11.329 × W − 16.729 × TAD − 1185.445

Equations used to predict energy needs developed specifically for use in people with spinal cord injury are listed; *W*, weight in kg; *H*, height in cm; *A*, age in years; FFM in kg; *SAD*, sagittal abdominal diameter in cm; *TAD*, transverse abdominal diameter in cm; *TC*, thigh circumference in cm; *C*, calf circumference in cm (Buchholz et al., 2003; Chun et al., 2017; Nightingale & Gorgey, 2018).

DLW, whereas a study in individuals with chronic SCI found that predicted RMR was not significantly different to measured RMR using IC. Others have reported a non-significant difference (bias minus 84 kJ/day) between predicted and measured BMR using the Chun et al. (2017), a population-specific equation that also includes FFM. A newer SCI-specific BMR equation incorporating FFM, weight, height, and calf circumference as predictor variables has not been cross-validated with a larger, independent group of males and females with SCI (Nightingale & Gorgey, 2018). These equations need the input of FFM which requires access to equipment such as bioimpedance. While FFM predicted from bioimpedance spectroscopy using the SCI-population specific Kocina and Heyward FFM equation (Kocina & Heyward, 1997) is comparable to FFM calculated from DLW (Desneves et al., 2019) it is unclear whether it is practical and feasible to use bioimpedance spectroscopy to obtain FFM for use in energy prediction equations in clinical practice.

In summary, prediction equations and activity factors derived from non-disabled populations have not been successfully validated in SCI patients (Nevin et al., 2016) but there is mounting evidence that population-specific prediction equations based on body composition measures and SCI-specific activity factors are more accurate when predicting energy requirements in both acute and chronic SCI.

Choosing an energy requirement method for use in SCI

In the absence of indirect calorimetry, it is preferable to use an SCI population-specific energy prediction equation and an activity factor. However, clinical judgment should be used when choosing any energy prediction method and when interpreting requirement calculations. Calculations should only be used as a starting point and SCI patients should be reviewed regularly and requirements recalculated in alignment with substantial alterations in clinical condition, physical activity levels, and treatment goals.

Applications to other areas of neuroscience

In this chapter, we have reviewed the effects of traumatic spinal cord injury on energy requirements. We also provided an overview of the available methods for assessing energy requirements and the considerations for use in individuals with spinal cord injury. Heterogeneous alterations in energy expenditure are also seen in other neurological disorders and there are numerous etiological factors that are disease genotype and phenotype-specific. These include whether the disease is neurodegenerative, stage of the disease, inflammatory abnormalities, endocrine, metabolic, motor disorders, and decreased physical activity (Çekici & Acar Tek, 2020).

The effect of neurological disease on energy expenditure is diverse. Hypometabolism has been reported in some neurological diseases, whereas increased total energy expenditure due to increased physical activity resulting from motor disorders including tremor, rigidity, dystonia, dyskinesia, and chorea has been reported in others. Further details can be found in the review: Determining energy requirement and evaluating energy expenditure in neurological disease (Çekici & Acar Tek, 2020).

Indirect calorimetry is the ideal method for determining energy requirements in healthy individuals, spinal cord injury, and some other neurological diseases. In addition to the usual considerations such as availability, cost, and need for trained personnel, it is difficult to use indirect calorimetry in patients with excessive movement such as Huntington's disease due to severe chorea movements and in children with Cerebral palsy because it is hard to determine oxygen levels as a result of breathing difficulties (Çekici & Acar Tek, 2020). Since each neurological disease has different impacts on energy expenditure due to varying etiologies, it is recommended that resting energy expenditure and total energy expenditure are measured on an individual basis if possible or that neurological disease-specific equations and activity adjustment factors are used to predict energy requirements (Çekici & Acar Tek, 2020).

Mini-dictionary of terms

Basal metabolic rate: The energy an individual needs to maintain body functions at rest. Basal metabolic rate is measured using indirect calorimetry and following a strict protocol; including mental and physical rest, following a 12 h fast, at 27–29°C, with no vigorous physical activity or stimulants within the previous 24 h, calibration of gases and establishment of steady-state.

Resting energy expenditure or resting metabolic rate: A measurement is taken using indirect calorimetry when any criteria for basal metabolic rate are not met.

Thermic effect of food: The energy used digesting, absorbing, and transporting nutrients within the body.

Physical activity energy expenditure: Energy used for incidental or planned movement above rest.

Total energy expenditure: The energy used by an individual consisting of basal metabolic rate, thermic effect of food, and physical activity.
Hypermetabolism: A basal metabolic rate higher than predicted for healthy individuals of the same age and weight due to injury or illness.
Hypometabolism: A basal metabolic rate below that predicted for healthy, non-injured individuals.

Key facts of energy metabolism

- It is unclear if energy needs are elevated immediately following spinal cord injury.
- People with long-term spinal cord injury have lower energy needs than non-disabled people due to muscle loss, reduced metabolism, and lower physical activity levels.
- Energy needs are lower in people with more severe injuries.
- It is recommended that indirect calorimetry is used to measure energy needs when available because energy prediction equations developed in healthy people are inaccurate when used in people with spinal cord injury.
- Energy prediction equations developed in spinal cord injury that include body composition measures are more accurate to use in people with spinal cord injury.
- A spinal cord injury-specific activity correction factor of 1.15 has been suggested but the reliability and validity have not been tested.

Summary points

This chapter focuses on the alterations that occur to energy requirements following spinal cord injury:

- The total energy expenditure of people with long-term spinal cord injury is lower than non-disabled people due to a reduced basal metabolic rate and lower levels of physical activity. These predispose people with spinal cord injury to positive energy balance and weight gain.
- It is important to assess energy needs accurately to preserve muscle and prevent weight and fat gain.
- Clinical guidelines recommend using indirect calorimetry to assess energy needs in people with spinal cord injury, however, this method is not usually available in clinical practice.
- Energy prediction equations are often used in clinical practice but equations developed in nondisabled people are inaccurate when used in people with spinal cord injury.
- Spinal cord injury-population-specific equations to predict energy needs incorporating body composition measures have been developed and validated for use in people with spinal cord injury.
- Bioimpedance can be used to predict fat-free mass for use in these equations.
- It is preferable to use a spinal cord injury-specific activity factor. Although the reliability and validity have not been tested.
- Clinical judgment should be used when choosing any energy prediction method and when interpreting requirement calculations.
- Calculations should be used as a starting point and spinal cord injury patients should be reviewed regularly and requirements recalculated in alignment with substantial alterations in clinical condition, physical activity levels, and treatment goals.

References

Academy of Nutrition and Dietetics. (2009). *Spinal cord injury (SCI) evidence-based nutrition practice guideline. Evidence analysis library*. Retrieved October 2018 https://www.andeal.org/topic.cfm?menu=5292.

Andersen, R. E., Sweet, S. N., Reid, R. E. R., Sydney, F., & Plourde, H. (2018). Accuracy of two generic prediction equations and one population-specific equation for resting energy expenditure in individuals with spinal cord injury. *Canadian Journal of Dietetic Practice and Research: A Publication of Dietitians of Canada*, *79*, 1–6. https://doi.org/10.3148/cjdpr-2018-021.

Buchholz, A. C., McGillivray, C. F., & Pencharz, P. B. (2003). Differences in resting metabolic rate between paraplegic and able-bodied subjects are explained by differences in body composition. *American Journal of Clinical Nutrition*, *77*(2), 371–378.

Buchholz, A. C., & Pencharz, P. B. (2004). Energy expenditure in chronic spinal cord injury. *Current Opinion in Clinical Nutrition and Metabolic Care*, *7*(6), 635–639.

Çekici, H., & Acar Tek, N. (2020). Determining energy requirement and evaluating energy expenditure in neurological diseases. *Nutritional Neuroscience*, *23*(7), 543–553.

Chun, S. M., Shin, H. I., & Kim, H. R. (2017). Estimating the Basal metabolic rate from fat free mass in individuals with motor complete spinal cord injury. *Spinal Cord*, *55*(9), 844–847.

Cunningham, J. J. (1991). Body composition as a determinant of energy expenditure: A synthetic review and a proposed general prediction equation. *The American Journal of Clinical Nutrition*, *54*(6), 963–969.

DeLany, J. P. (1997). *Doubly labeled water for energy expenditure in emerging technologies for nutrition research: Potential for Assessing Military Performance Capability Committee on Military Nutrition Research, Institute of Medicine (Chapter 12, pp. 281)*. National Academies Press, ISBN:0-309-55338-5.

Desneves, K. J., Panisset, M. G., Rafferty, J., Rodi, H., Ward, L. C., Nunn, A., & Galea, M. P. (2019). Comparison of estimated energy requirements using predictive equations with total energy expenditure measured by the doubly labelled water method in acute spinal cord injury. *Spinal Cord*, *57*(7), 562–570.

Farkas, G. J., Gorgey, A. S., Dolbow, D. R., Berg, A. S., & Gater, D. R. (2019). Caloric intake relative to total daily energy expenditure using a spinal cord injury—Specific correction factor. *American Journal of Physical Medicine & Rehabilitation*, *98*(11), 947–952.

Gandy, J. (2014). *Manual of dietetic practice*. Hoboken, United Kingdom: John Wiley & Sons.

Gorgey, A. S., Dolbow, J. D., Khalil, R. K., Dolbow, D. R., Castillo, C., & Gater, D. R. (2014). Effects of spinal cord injury on body composition and metabolic profile—Part I. *Journal of Spinal Cord Medicine*, *37*(6), 693–702.

Harris, J. A., & Benedict, F. G. (1918). A biometric study of human basal metabolism. *Proceedings of the National Academy of Sciences*, *4*(12), 370–373.

Haugen, H. A., Chan, L. N., & Li, F. (2007). Indirect calorimetry: A practical guide for clinicians. *Nutrition in Clinical Practice*, *22*(4), 377–388.

Henry, C. (2005). Basal metabolic rate studies in humans: Measurement and development of new equations. *Public Health Nutrition*, *8*(7a), 1133–1152.

Kocina, P., & Heyward, V. (1997). Validation of a bioimpedance equation for estimating fat-free mass of spinal cord injured adults 319. *Medicine & Science in Sports & Exercise*, *29*(5), 55.

Kyriakides, A., Poulikakos, D., Galata, A., Konstantinou, D., Panagiotopoulos, E., & Chroni, E. (2019). The effect of level of injury and physical activity on heart rate variability following spinal cord injury. *Journal of Spinal Cord Medicine*, *42*(2), 212–219. https://doi.org/10.1080/10790268.2017.1383709.

Long, C. L., Schaffel, N., Geiger, J. W., Schiller, W. R., & Blakemore, W. S. (1979). Metabolic response to injury and illness: Estimation of energy and protein needs from indirect calorimetry and nitrogen balance. *Journal of Parenteral and Enteral Nutrition*, *3*(6), 452–456.

McClave, S. A., Taylor, B. E., Martindale, R. G., Warren, M. M., Johnson, D. R., Braunschweig, C., … Cresci, G. A. (2016). Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (ASPEN). *Journal of Parenteral and Enteral Nutrition*, *40*(2), 159–211.

Nevin, A. N., Steenson, J., Vivanti, A., & Hickman, I. J. (2016). Investigation of measured and predicted resting energy needs in adults after spinal cord injury: A systematic review. *Spinal Cord*, *54*(4), 248.

Nightingale, T. E., & Gorgey, A. S. (2018). Predicting Basal metabolic rate in men with motor complete spinal cord injury. *Medicine and Science in Sports and Exercise*, *50*(6), 1305–1312.

Ramirez, C. L., Pelekhaty, S., Massetti, J. M., Galvagno, S., Harmon, L., Botwinick, I., … Stein, D. M. (2018). Validation of predictive equations to assess energy expenditure in acute spinal cord injury. *Journal of Trauma and Acute Care Surgery*, *85*(5), 984–991.

Reeves, M. M., & Capra, S. (2003). Predicting energy requirements in the clinical setting: Are current methods evidence based? *Nutrition Reviews*, *61*(4), 143–151.

Schofield, W. (1985). Predicting basal metabolic rate, new standards and review of previous work. *Human Nutrition. Clinical Nutrition*, *39*, 5–41.

Sedlock, D. A., & Laventure, S. J. (1990). Body composition and resting energy expenditure in long term spinal cord injury. *Spinal Cord*, *28*(7), 448.

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Chapter 34

Virtual walking and spinal cord injury neuropathic pain

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List of abbreviations

2D	two-dimensional
3D	three-dimensional
fMRI	functional magnetic resonance imaging
HMD	head-mount display
SCI	spinal cord injury
tDCS	transcranial direct current stimulation
VR	virtual reality

Introduction

An unfortunate reality for many with spinal cord injury (SCI) is the number of secondary complications that can arise beyond the immediate physical impairments from their injury such as sensorimotor disruptions (Kirshblum & Lin, 2019; Richardson, Richards, & Boyer, 2008; see Table 1). Persistent pain is a common secondary complication following spinal cord injury (SCI), affecting over two-thirds of individuals with SCI (Bonica, 1991). Chronic pain following SCI is not a unitary phenomenon, as there are multiple subtypes of SCI-related pain with various underlying pathophysiological mechanisms. Individuals who are many years post-SCI may experience chronic musculoskeletal pain from prolonged manual wheelchair use (Siddall & Loeser, 2001), while neuropathic forms of pain may develop soon after the SCI (Siddall, McClelland, Rutkowski, & Cousins, 2003; Siddall, Taylor, McClelland, Rutkowski, & Cousins, 1999). Unlike musculoskeletal forms of post-SCI pain, SCI-related neuropathic pain is often described as burning or "electric" and is typically experienced at or below the level of injury in areas with sensory disturbance (Bryce et al., 2007, 2012).

SCI-related neuropathic pain affects more than half of those with SCI (Burke, Fullen, Stokes, & Lennon, 2017) and for many, it persists in its course (Finnerup, 2013; Siddall, 2009) or even worsens with time (Jensen, Kuehn, Amtmann, & Cardenas, 2007). Thus, it is not surprising that SCI-related neuropathic pain is associated with disruptions in several life activities and an overall decline in quality of life (Burke, Lennon, & Fullen, 2018). Finding more effective forms of treatment for SCI-related neuropathic pain has become increasingly important given these negative psychosocial effects as well as the shortcomings of currently available pharmacological agents (Cardenas & Jensen, 2006; Teasell et al., 2010). Recent evidence suggests virtual walking as a potentially viable non-pharmacological alternative or at least an effective adjunctive treatment for SCI-related neuropathic pain. The mechanisms underlying this treatment approach draw upon conceptualizing SCI-related neuropathic pain as a result of central nervous system changes that arise from the SCI.

This chapter will begin by discussing SCI-related forms of neuropathic pain and the theoretical concepts of its development and maintenance that may underlie the efficacy of virtual reality (VR) walking therapies. We will define VR and identify the components of VR with therapeutic utility. Lastly, this chapter will describe the evidence to date on the use of VR walking or other VR protocols to treat SCI-related pain as well as future directions for further validating the clinical utility for this form of therapy for SCI-related neuropathic pain.

Cellular, Molecular, Physiological, and Behavioral Aspects of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822427-4.00034-4

TABLE 1 Common secondary complications that can arise following spinal cord injury (SCI).

Autonomic dysreflexia
Bowel and bladder dysfunction (including urinary tract infection)
Cardiovascular dysfunction
Muscle spasticity below the level of injury
Pain
Pressure sores
Pulmonary/respiratory complications
Sexual dysfunction

Based on Richardson, E. J., Richards, J. S., & Boyer, B. A. (2008). Spinal cord injury. In B. A. Boyer & M. I. Paharia (Eds.), *Comprehensive handbook of clinical health psychology*. Hoboken, NJ: Wiley; Kirshblum, S., & Lin, V. W. (Eds). (2019). *Spinal cord medicine*. New York: Demos Medical Publishing.

SCI-related neuropathic pain as a deafferentation pain

Adding to the clinical complexity of SCI-related neuropathic pain is that it can present in different forms that may be associated with different symptoms and outcomes (Finnerup, Johannesen, Fuglsang-Frederiksen, et al., 2003; Jordan & Richardson, 2016; Richardson & Redden, 2014). *At-level* neuropathic pain is often experienced as a "band-like" pain within three dermatomes of the level of injury (Bryce et al., 2012) and likely involves peripheral mechanisms to some degree, such as nerve root damage (Siddall & Loeser, 2001). In contrast, changes within the central nervous system are believed to primarily mediate *below-level* neuropathic pain, which occurs in regions well below the level of injury (Siddall, Taylor, & Cousins, 1997). Such centrally mediated pain is associated with an altered spinothalamic function that can be measured by evoked sensitivity thresholds (Bowsher, 1996). The severity of below-level SCI-related neuropathic pain among those with SCI is related to the degree of *at-level* neuronal hyperexcitability, and likely hyperexcitability at supraspinal levels as well (Finnerup et al., 2003). In rodent models of SCI (not specific to SCI-related *pain*), neuronal hyperexcitability was found specifically within the somatosensory cortex (Yague, Foffani, & Aguilar, 2011). In humans, functional magnetic resonance imaging (fMRI) has revealed functional reorganization in the sensorimotor cortices following SCI, with the most notable changes occurring among those with below-level SCI-related neuropathic pain (Wrigley, Press, Gustin, et al., 2009; see Fig. 1). Anatomically, there are also differences in several brain regions among those with below-level SCI-related neuropathic pain, including the posterior parietal cortices, the nucleus accumbens, and the prefrontal cortex, as well as regions known to be associated with pain processing, such as the thalamus (Gustin, Wrigley, Siddall, & Henderson, 2010). Differences in resting blood flow within regions of the cerebellum and prefrontal cortex in those with SCI-related neuropathic pain have also been observed, potentially relating to the affective-motivational and cognitive-evaluative aspects of the pain experience (Richardson, Deutsch, Deshpande, & Richards, 2020).

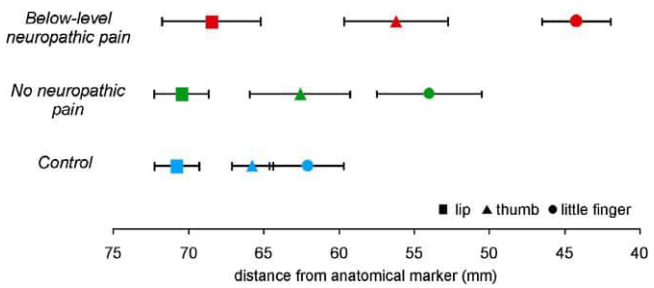

FIG. 1 Reorganization of the primary somatosensory cortex was found by Wrigley et al. (2009). Individuals with SCI, with and without pain, received tactile stimulation to the lip, thumb, and little finger. These researchers measured the distance between the point of maximum activation and a common point: the intersection of the longitudinal and central sulcus. Compared to able-bodied subjects, those with SCI showed encroachment of somatosensory cortical activation formerly representing the legs, with those who had SCI-related neuropathic pain showing the greatest shift. *(Data from Wrigley, P. J., Press, S. R., Gustin, S. M., et al. (2009). Neuropathic pain and primary somatosensory cortex reorganization following spinal cord injury.* Pain, 141, *52–59, with permission.)*

These findings, particularly the functional reorganization that occurs in somatosensory cortices among those with SCI-related neuropathic pain (Wrigley et al., 2009) parallel other deafferentation pain syndromes such as phantom limb pain. Phantom limb pain can also persist many years following amputation (Ephraim, Wegener, MacKenzie, Dillingham, & Pezzin, 2005) and has been conceptualized as a product of neuroplastic changes that occur as a result of deafferentation. Specifically, somatosensory neurons that formerly processed sensory information from the deafferented limb may subsequently become responsive to sensory input from nearby regions of the body represented on the homunculus (Ramachandran & Hirstein, 1998).

While such models often focus on changes specific to the somatosensory cortex, it is important to note that multiple forms of sensory input (vision, proprioception, and touch, for example) together with motor output are involved in creating an overall body percept (Tsakiris, 2017). Deafferentation and the loss of sensory input may disrupt this system (e.g., descending motor messages without the congruent sensory or proprioceptive feedback) and create the sensation of pain (Flor, Nikolajsen, & Jensen, 2006; Harris, 1999).

Mirror therapy: A precursor to virtual walking

Disrupted equilibrium between sensory/afferent and motor/efferent feedback (understood to underpin central pain) is highlighted by reductions in phantom pain observed when a person is given the visual illusion that the amputated limb has returned and is moving (Chan et al., 2007; Ramachandran & Altschuler, 2009). Mirror box therapy, or simply *mirror therapy*, has also shown benefit with other centrally mediated pain conditions, such as complex regional pain syndrome (Sayegh et al., 2013)—a pain syndrome that is also characterized by changes in bodily percepts (Moseley, 2005). Interestingly, mirror therapy may recalibrate the dysfunctional cortical reorganization accompanying phantom limb pain. Foell, Bekrater-Bodmann, Diers, and Flor (2014) found reorganization in the somatosensory cortex of the hemisphere that previously processed the amputated limb, but following mirror therapy, the functional organization in the somatosensory cortices of both hemispheres became more similar, suggesting a reversal of the cortical changes associated with amputation. However, it is important to consider that maladaptive cortical reorganization may not be a cause of pain, but rather a consequence or a correlate. Behavioral and psychological factors, including catastrophic appraisals of pain, also appear to contribute to the development of phantom pain following amputation (Andoh, Milde, Tsao, & Flor, 2018; Richardson, Glenn, Horgan, & Nurmikko, 2007).

What is VR?

Visual stimulation has now extended from the use of mirrors to virtual reality (VR), which offers a broader array of sensory stimulation. There has not been a singular definition of VR, as the technology with which to deliver VR has rapidly evolved in recent years and continues to do so (Trost, France, Anam, & Shum, 2020). Nonetheless, the goal of VR has remained the same: to simulate an altered experience by some degree of sensory stimulation (Chi, Chau, Yeo, & Ta, 2019; Mallari, Spaeth, Goh, & Boyd, 2019). VR therapies can be deconstructed into several components, including *VR Configuration Factors*, *User Experiential Factors*, and *Pain Targets* (Trost et al., 2020). VR Configuration Factors mostly apply to the technology itself and how real-time data, such as the user's location in space and their movement is incorporated and transposed into a virtual environment that is experienced by the user (Trost et al., 2020). Configuration of the VR, in turn, influences key User Experiential Factors of *interactivity* (the degree to which the user can manipulate the virtual environment), *immersion* and *presence* (the degree to which the user feels present and absorbed in the virtual environment), and *embodiment* (the degree to which the user feels a virtual body to be their own) (Burdea & Coifett, 2003; Matamala-Gomez et al., 2019; Trost et al., 2020). It is suggested that user experiential factors be considered as a continuum of degree rather than a dichotomy (e.g., a VR experience can vary in degree of immersion) as this will depend on the VR equipment used as well as individual factors, such as one's susceptibility to being "absorbed" into the virtual environment (Baños et al., 1999; Richardson et al., 2020). Nonetheless, it is these experiential factors that ultimately mediate changes in one's pain experience, whether that is via the cognitive, emotional, behavioral, or sensory aspects of pain (Trost et al., 2020).

There are also two primary pain targets for using VR to treat pain: (1) distraction, or shifting one's attention from pain, and (2) promoting central nervous system plasticity (Austin & Siddall, 2019; Gupta, Scott, & Dukewich, 2018). Generally, VR therapies for acute and procedural pain have focused on distraction as a primary target, whereas neuroplasticity is a primary target for chronic forms of pain (Trost et al., 2020).

Considering the above components, VR therapy targeting SCI-related neuropathic pain has focused on configuration factors that aid in creating the simulated experience of lower leg movement, such as walking, to reduce the intensity of below and at-level pain (Donati, Shokur, Morya, et al., 2016; Jordan and Richardson, 2016; Moseley, 2007; Özkul,

Kılınç, Yıldırım, Topçuoğlu, & Akyüz, 2015; Richardson et al., 2019; Soler et al., 2010; Soler, Moriña, Kumru, Vidal, & Navarro, 2021; Sumitani et al., 2008; Villiger et al., 2013). The targeted mechanism by which pain is reduced by VR walking or leg movement is functional central nervous system reorganization, by potentially reversing the maladaptive plasticity that is believed to underpin the pain (Austin & Siddall, 2019; Eick & Richardson, 2015; Wrigley et al., 2009). There is some evidence that these forms of therapy activate functionally reorganized cortical regions. In one small pilot study by Eick and Richardson (2015), individuals with SCI (though not necessarily with neuropathic pain) were provided a non-immersive illusion of walking as well as wheeling while undergoing functional magnetic resonance imaging (fMRI). Greater activation was observed in the somatosensory cortex, whereas abled-bodied individuals showed little to no activation in this region (Eick & Richardson, 2015; see Fig. 2).

Non- or partially-immersive virtual walking in SCI

Much of the research on virtual walking to treat SCI-related neuropathic pain has been done using non- or partially immersive modalities, such as having the individual seated in front of 2D or 3D screens to view walking imagery (Austin & Siddall, 2019). This likely reflects the time in which the studies were conducted, as study design and implementation of published results may not have kept pace with the rapidly evolving VR technology, such as cost-effective commercially available VR setups, smaller and more compact equipment, and ease of use with various computer interfaces.

A pilot trial by Sumitani et al. (2008) using mirror therapy in a small mixed sample of individuals with incomplete SCI, peripheral nerve injury, or amputation, resulted in a reduction in pain intensity. Using this paradigm, participants viewed the reflection of an unaffected limb, which resulted in a significant reduction of pain in the affected limb or phantom. However, Moseley (2007) was one of the first to create a full analog to mirror therapy to treat SCI-related neuropathic pain. In this original method, a mirror was used to reflect the participant's upper torso; this mirror was placed above a screen that projected a video of an actor's legs (waist down) walking (see Fig. 3). Thus, individuals observed their upper body coordinated with the video of walking legs. Participants experienced a significant (65%) reduction in pain lasting approximately 30 min following treatment. Soler et al. (2010) replicated Moseley's (2007) method in participants with SCI-related neuropathic pain but complemented this paradigm with transcranial direct current stimulation (tDCS) over the primary motor cortex. Illusory walking alone significantly reduced levels of neuropathic pain, but the pain-reducing benefits were enhanced when the motor cortex was simultaneously stimulated. When considering subtypes of SCI-related neuropathic pain, these studies in combination suggest that those with at-level (Moseley, 2007) and below-level (Soler et al., 2010) experienced pain reduction from virtual walking.

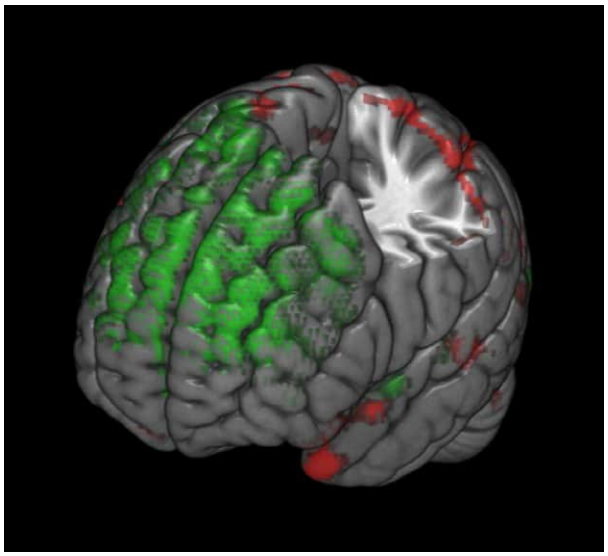

FIG. 2 fMRI cortical activation during virtual walking (non-immersive) among individuals with and without SCI from Eick and Richardson (2015). fMRI brain activity during illusory walking when controlling for brain activation during illusory wheeling. Significant activation was observed in the bilateral somatosensory cortex, right paracentral lobule, and to a lesser degree, medial motor areas among those with SCI *(red)*. Individuals without SCI *(green)* had greater activation in frontal and premotor regions. *(From Eick, J., & Richardson, E. J. (2015). Cortical activation during visual illusory walking in persons with spinal cord injury: A pilot study.* Archives of Physical Medicine and Rehabilitation, 96*, 750–753, with permission.)*

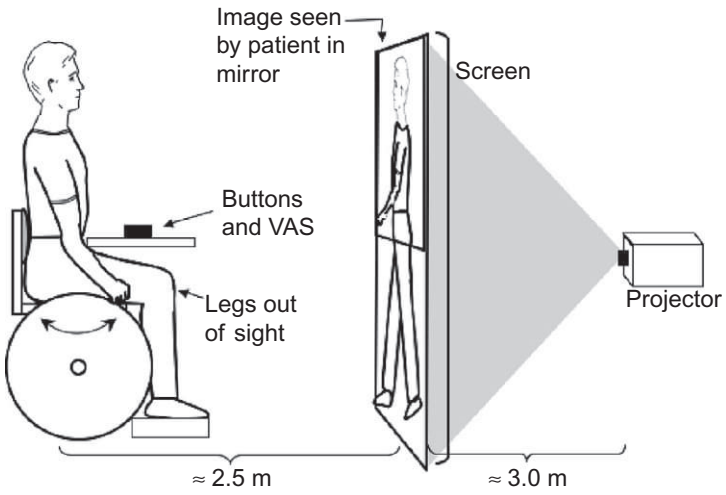

FIG. 3 Virtual walking setup from Moseley (2007). A mirror was used to reflect the participant's upper body and a screen, projecting legs of an actor walking, was placed below the mirror to provide the illusion that the individual's body was walking. Participants' upper body movements were synchronized with the actor's gait. Participants rated pain using a visual analog scale (VAS) by pressing right and left buttons. *(From Moseley, G. L. (2007). Using visual illusion to reduce at-level neuropathic pain in paraplegia.* Pain, 130, *294–298. https://doi.org/10.1016/j.pain.2007.01.007, with permission.)*

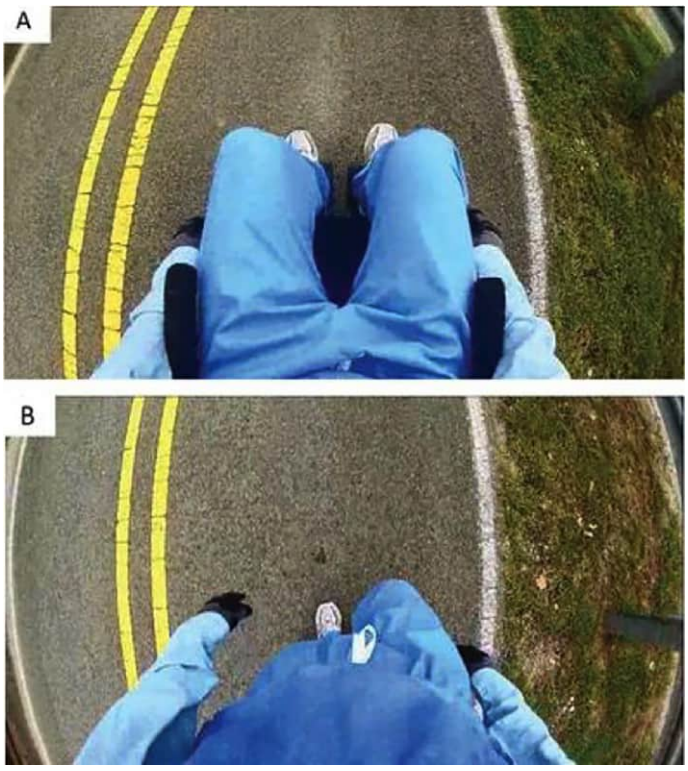

FIG. 4 First-person view in a partially immersive virtual walking protocol by Richardson et al. (2019). (A) is the first-person view of the virtual wheeling condition, and (B) is the virtual walking condition. Video was of an actor walking and was recorded using a stereoscopic (3D) camera, hence the "fish-eye" effect of the 2D image above. *(From Richardson, E. J., McKinley, E. C., Fazlur Rahman, A. K. M., Klebine, P., Redden, D. T., & Richards, J. S. (2019). Effects of virtual walking on spinal cord injury-related neuropathic pain: A randomized, controlled trial.* Rehabilitation Psychology, 64*(1), 13–24. https://doi.org/10.1037/rep0000246, with permission.)*

More recently, we examined the efficacy of a partially immersive virtual walking paradigm to treat SCI-related neuropathic pain in a randomized controlled trial (Richardson et al., 2019). Unlike the studies above, this trial used virtual reality technology as it is understood today. Expanding on the illusory walking paradigm used by Moseley (2007) and Soler et al. (2010), participants with SCI-related neuropathic pain were randomized to watch a 20-min stereoscopic 3D video of a first-person view of an actor's legs walking (walking condition) or seated in a manual wheelchair while propelling down the same path (wheeling condition). Video stills of both conditions are shown in Fig. 4. After one session, participants' levels of pain declined in both the walking and wheeling conditions; however, there was a significant pre- to

post-treatment reduction in SCI-pain irrespective of subtype of pain (musculoskeletal, neuropathic, or mixed forms of pain) in the walking condition, but not the wheeling condition. When considering SCI-related neuropathic pain specifically, the walking condition resulted in a significant reduction in the pain unpleasantness rating of their neuropathic pain, but not the intensity of it. Further, SCI-related neuropathic pain that was experienced as "cold," "deep" or associated with increased skin sensitivity was significantly reduced following virtual walking. Quantitative sensory testing to examine at-level neuronal hyperexcitability (evoked sensitivity within 3 dermatomes of their neurologic level of injury) was performed in a subset of participants in this study (Jordan and Richardson, 2016). Declines in SCI-related neuropathic pain were greatest in the virtual walking conditioning, regardless of whether the pain was at or below the level of injury. While it was not statistically significant, there was a trend for the relationship between increased at-level evoked sensitivity and less favorable below-level SCI-related neuropathic pain outcomes after virtual walking treatment (Jordan and Richardson, 2016). Soler et al. (2021) have since replicated their virtual walking and tDCS paradigm, and while they again found a reduction in SCI-related neuropathic pain with the combined treatment, there were no differences with respect to different sensory profiles of SCI-related neuropathic pain. Taken together, these results suggest that the mechanisms potentially underlying subtypes of SCI-related neuropathic pain are not entirely clear. At- and below-level forms of neuropathic pain may have different initial precipitating mechanisms, but both may eventually be maintained by supraspinal changes (Meacham, Shepherd, Mohapatra, & Haroutounian, 2017).

Though the existing studies are sparse and comprised of small sample sizes, non-immersive virtual walking therapies appear to offer some benefit for both at and below-level SCI-related neuropathic pain (Austin & Siddall, 2019; Chi et al., 2019). The larger controlled trial (Richardson et al., 2019), which was not included in Austin and Siddall's (2019) or Chi et al.'s (2019) review, suggest that non-immersive virtual walking paradigms may be effective with only certain aspects of SCI-related neuropathic pain, such as specific sensory-discriminative aspects or the affective-motivational component of this form of pain (Richardson et al., 2019). However, this trial only examined one session of virtual walking, and it is, therefore, unclear if there is a dose-dependent effect on neuropathic pain and whether pain intensity would be significantly reduced with additional sessions. One small, randomized trial of 24 patients found that a single exposure to non-immersive virtual walking that did not use a first-person view significantly reduced pain but the effect did not last after 2 weeks (Özkul et al., 2015). Studies that implemented repeated virtual walking or limb movement sessions across time showed the largest reductions in SCI-related neuropathic pain (Austin & Siddall, 2019).

Immersion, embodiment, and interactivity

As noted, immersion, interactivity, presence, and embodiment are key experiential indices of virtual reality experience (Trost et al., 2020). The illusory or virtual walking interventions described above to a large degree include the passive (non-interactive) observation that incorporates elements of the participant's body via reflection (Moseley, 2007; Soler et al., 2010) or a first-person view (Richardson et al., 2019) to create the illusion of walking outside a fully immersive context. Emerging applications of modern virtual technologies to illusory walking allow us to examine the potential utility of additional experiential factors. For instance, Villiger et al. (2013) were among the first to integrate *interactivity*, albeit in a non-immersive context. Specifically, Villiger et al. (2013) used a virtual reality-augmented paradigm in a sample of 14 participants with incomplete SCI who also had some motor sparing. In this paradigm, participant's real legs and feet were mapped in real-time to 3D virtual lower limb displayed, in the first-person perspective, on a 2D monitor (see Fig. 5). Participants were required to engage in various tasks that incorporated elements of gaming, such as mastering various levels of difficulty or earning point values for completing specific tasks. VR sessions were 45-min in duration, and sessions were repeated 16–20 times within 4 weeks. Of the 9 participants who experienced SCI-related pain (at- or below-level), 6 experienced clinically meaningful reductions in pain, which persisted 12–16 weeks later (Villiger et al., 2013). This suggests that including goal-directed, gaming-like tasks may increase user interactivity, which in turn improves effectiveness. Volitional interactive use similarly serves as a key component in exergaming to improve physical functioning among those with a physical disability (Mat Rosly, Mat Rosly, Davis Oam, Husain, & Hasnan, 2017).

Although not strictly a virtual reality intervention, an investigation by Pozeg et al. (2017) focused on the effects of illusory embodiment. These researchers examined the effects of inducing a virtual leg illusion or full-body illusion using an HMD in a sample of 20 individuals (11 of whom had at or below-level neuropathic pain). Rather than creating illusory movement, using the HMD, these researchers allowed participants to view a stationary dummy to which tactile stimulation was provided. Using an embodiment paradigm traditionally applied in rubber hand/body research (Christ & Reiner, 2014), participants received visuotactile stimulation to their actual back as well as dummy legs, which were observed from a first-person perspective on the HMD. To create a full-body illusion, Pozeg et al. (2017) had the participants view, in real-time, video of their own back receiving tactile stimulation through the HMD as they were experiencing it. For both conditions,

FIG. 5 First-person view VR lower limb movement protocol by Villiger et al. (2013). Incorporation of participant movement in a virtual environment among individuals with incomplete SCI using movement sensors fitted to participants' feet. Goal-directed and motivated interaction with the virtual environment was also used. *(From Villiger, M., Bohli, D., Kiper, D., Pyk, P., Spillmann, J., Meilick, B., et al. (2013). Virtual reality-augmented neurorehabilitation improves motor function and reduces neuropathic pain in patients with incomplete spinal cord injury.* Neurorehabilitation and Neural Repair, 27*(8), 675–683. https://doi.org/10.1177/1545968313490999, with permission.)*

tactile and visual stimulation occurred synchronously or asynchronously. Synchronous visuotactile stimulation in either illusory condition created a sense of embodiment, and even without movement, this appeared to offer at least modest relief with SCI-neuropathic pain following a single exposure (Pozeg et al., 2017).

To date, participants in non-immersive VR environments have not been fully disconnected from stimuli within the real world, such as surrounding vision or sound (Chi et al., 2019). Conversely, more immersive virtual reality methods may reduce or attempt to eliminate stimuli from the real world by integrating full visual and tactile stimulation or by allowing the participant to have motor control of the virtual environment (Trost et al., 2020). Greater immersion increases the potency of virtual walking to where single interventions may become more clinically effective (Austin & Siddall, 2019). Perhaps one of the more striking studies to date that addressed immersion and multiple experiential factors is that of Donati et al. (2016). These researchers investigated the potential for locomotion recovery in 8 individuals with paraplegia using brain-machine interface-based gait neurorehabilitation over 12 months. Their intervention made use of a fully immersive virtual environment using an HMD, brain-controlled 3D avatar, and robotic gain training, as well as the integration of visual and tactile feedback. The participants in the study described pain experienced below the level of their injury, and while the pain was not a primary outcome of this study, participants demonstrated improved ability to localize their pain and reported a decrease in day-to-day pain intensity outside of sessions (Donati et al., 2016). Functional changes (assessed by electroencephalography) in leg representation areas of the primary sensorimotor cortices following the intervention were also observed (Donati et al., 2016).

A recent study by Trost and colleagues (Anam et al., 2019) is of particular note, as it is the first study to leverage the interactive, immersive, and embodiment characteristics of a portable virtual reality interface to provide individuals with SCI-related neuropathic pain volitional control over their virtual legs. Participants' virtual ambulation within a 360-degree virtual environment was self-guided by hand-held controllers; participants moved their arms using gestures analogous to natural gait which translated into leg movement in the virtual world (see Fig. 6). Participants matched their avatar to personal characteristics and viewed their virtual arms and legs from a first-person perspective through an HMD. The "VRWalk" intervention incorporated exploratory gaming elements to promote interactivity and motivation. The study included 18 individuals with complete paraplegia, who completed twice daily 5-min VR sessions in their own homes for a total of 20 sessions. Participants reported strong enjoyment and embodiment effects ("I felt like the legs were my own") following the intervention. The investigators observed statistically and clinically significant decrement in neuropathic pain intensity ratings from prior to following individual sessions, as well as the full intervention. Similar improvements in mood and affect were also observed. Improved pain ratings persisted at 2 weeks and 1 month following intervention. The results of this study tentatively support the value of strong immersion/presence, embodiment, and

FIG. 6 The VRWalk intervention described in Anam et al. (2019). Participants were immersed in a virtual scene via HMD with a 360-degree, first-person view. Arm movements to simulate walking and motion sensing controllers generated a virtual gait for the avatar. *(Unpublished image by the author (Trost).)*

motivation in SCI neuropathic pain intervention, and perhaps most significantly, suggest the acceptability and generalizability of a self-guided VR intervention to home use.

Applications to other areas of neuroscience

Just over a third of existing studies examining the application of VR for pain have been done on those with chronic pain, and within that category only approximately 8% have been conducted on individuals experiencing SCI-related chronic pain (Trost et al., 2020). Clearly, there is a need for more rigorously controlled and comparative studies, and there remains much to be understood regarding the most effective VR configurations, their dose, and which user experiential factors are most potent in producing an analgesic effect. However, there is reason to believe that VR applications that incorporate interactive, goal-directed walking rather than passive visual input have a greater potential of targeting neuroplastic changes that may underlie deafferented neuropathic pain (Foell et al., 2014). For example, individuals with upper limb amputation showed significantly increased activation in the primary motor and somatosensory cortices performing a movement task with the intact hand that displayed the phantom moving within a virtual space (Andoh et al., 2020). Tasks with functional value or volitional interactive use versus simply imagining a movement are also associated with increased activity in the primary somatosensory cortex (Raffin, Mattout, Reilly, & Giraux, 2012). As suggested by more recent studies, the use of multisensory integration (e.g., sound, haptic, and visual stimuli) can increase the user's sense of embodiment of the virtual legs or body, thus increasing the pain-alleviating effects of VR (Matamala-Gomez et al., 2019).

It is also important to note that the experience of pain, regardless of its underlying mechanism, is best understood as having physiological, cognitive, social, and emotional components (Melzack, 1999). While much of the work focuses on the central nervous system changes associated with SCI-related neuropathic pain, individuals with SCI may also experience pain-related fear-conditioned from interoceptive, proprioceptive, or external stimuli (Vlaeyen & Linton, 2012). Thus, VR configurations may combine immersion, interactivity, and gaming in a virtual environment that exposes that individual to feared movements, positions, or contexts or distracts from negative pain-related cognitions (Freitas & Spadoni, 2019). Such an application may work through enhancing activity within the brain's reward circuit, which tends to override pain processing (Becker, Gandhi, Pomares, Wager, & Schweinhardt, 2017). Specifically, Becker et al. (2017) observed that PFC was involved in inhibiting other cortical regions that were involved in establishing the relative threat value of pain.

Thus, experiencing a reward, or even the expectation of reward, may diminish the drive to avoid pain to continue pursuit of the desired reward.

In a related vein, individuals with SCI may face several environmental barriers that interfere with social participation (Tsai et al., 2017), yet greater positive social interaction is associated with better functioning among individuals with physical disabilities (Jensen, Moore, Bockow, Ehde, & Engel, 2011) and lower risk for developing phantom pain following amputation (Hanley et al., 2004). Interpersonal interactions may reduce pain similarly through the brain's reward pathway, via dopamine systems (Younger, Aron, Parke, Chatterjee, & Mackey, 2010). Thus, VR configurations that incorporate gaming environments with social elements may best target the social and affective components of the pain experience for those with SCI.

With the increasing availability of commercially available VR computer interfaces and hardware in recent years, it is expected that relevant lines of research will broaden to encompass identifying the VR configuration and user experiential factors that are the strongest mediators of cortical reorganization in SCI-related neuropathic pain. Moreover, user experiential factors associated with VR walking modalities can be altered to address cognitive, emotional, and social factors in order to comprehensively target a wider range of pain outcomes in those with SCI-related pain.

Mini-dictionary of terms

Autonomic dysreflexia: Bouts of abrupt increases in blood pressure due to disruptions in autonomic pathways.
Avatar: A representation of one's body, in part or whole, in a virtual environment.
Deafferentation: The state in which afferent neural fibers no longer transmit information to receiving regions, typically discussed as disrupted peripheral input to the brain.
Exergaming: The use of gaming or other motivating tasks in exercise.
Functional reorganization: Changes in neural activity in certain regions of the brain due to changes in input, environmental stimulation, or behavior of the organism.
Interoceptive: A type of stimulus that comes from within the body.
Neuropathic pain: Pain arising from peripheral or central nervous system damage.
Mirror therapy: A therapeutic modality that provides the visual illusion, through the use of mirrors, that an area of the body is intact and functioning normally.
Supraspinal: Regions of the central nervous system above the spinal cord.
Virtual reality: A general modality that alters one's perception of the environment, themselves, or both in various degrees.

Key facts of virtual walking and spinal cord injury neuropathic pain

Key facts of SCI neuropathic pain

- Neuropathic pain following SCI is persistent and often refractory to currently available treatments.
- SCI-related neuropathic pain is associated with interference in life activities and a decline in quality of life.
- SCI-related neuropathic pain is associated with functional cortical reorganization, particularly in somatosensory regions.
- These neurological changes have led to conceptualizing SCI-related neuropathic pain as a deafferentation pain, similar to phantom limb phenomena.
- Several lines of research have examined ways to adapt visual stimulation forms of therapy used for a phantom limb to spinal cord injury.

Key facts of VR use for SCI neuropathic pain

- Virtual reality (VR) is a modality that alters an individual's sensory experience as it pertains to the sense of self or one's environment.
- VR can vary in degrees of immersiveness, presence, interactivity, and embodiment.
- VR that simulates walking has shown promise with reducing levels of neuropathic pain in SCI.
- VR that creates embodiment or simulates other types of lower limb movement is also associated with reduced pain.
- VR modalities that incorporate multisensory input and goal-directed activity, such as gaming, may increase treatment effect.
- VR may also target other biopsychosocial aspects of SCI-related pain.

Summary points

- SCI-related neuropathic pain is difficult to treat with traditional pharmacological therapies.
- It is experienced at or below the neurological level of injury.
- SCI-related neuropathic pain is associated with maladaptive neuroplastic changes in supraspinal regions of the central nervous system.
- It can be described as a deafferentation pain, similar to post-amputation phantom limb pain.
- Visual illusory modalities incorporating movement of the lower extremities to treat phantom limb pain have been extended to SCI-related neuropathic pain.
- Less immersive virtual walking treatments have shown some benefits in reducing pain.
- Using currently available technology to create more immersive, multisensory virtual reality (VR) walking modalities will likely offer greater benefit.

References

Anam, M., Sizemore, K., Mansour, H., Seward, J., Mitchell, L., Shum, C., et al. (2019). Virtual reality walking for neuropathic pain in spinal cord injury: Preliminary efficacy findings. *The Journal of Pain*, *20*(4, Suppl), S51.

Andoh, J., Milde, C., Diers, M., Bekrater-Bodmann, R., Trojan, J., Fuchs, X., et al. (2020). Assessment of cortical reorganization and preserved function in phantom limb pain: A methodological perspective. *Scientific Reports*, *10*, 11504.

Andoh, J., Milde, C., Tsao, J. W., & Flor, H. (2018). Cortical plasticity as a basis of phantom limb pain: Fact or fiction? *Neuroscience*, *387*, 85–91. https://doi.org/10.1016/j.neuroscience.2017.11.015.

Austin, P. D., & Siddall, P. J. (2019). Virtual reality for the treatment of neuropathic pain in people with spinal cord injuries: A scoping review. *The Journal of Spinal Cord Medicine*. https://doi.org/10.1080/10790268.2019.1575554.

Baños, R., Botella, C., García-Palacios, A., Villa, H., Perpiñá, C., & Gallardo, M. (1999). Psychological variables and reality judgment in virtual environments: The roles of absorption and dissociation. *Cyberpsychology & Behavior*, *2*, 143–148. https://doi.org/10.1089/cpb.1999.2.143.

Becker, S., Gandhi, W., Pomares, F., Wager, T. D., & Schweinhardt, P. (2017). Orbitofrontal cortex mediates pain inhibition by monetary reward. *Social Cognitive and Affective Neuroscience*, *12*, 651–661. https://doi.org/10.1093/scan/nsw173.

Bonica, J. J. (1991). Introduction: Semantic, epidemiologic, and educational issues. In K. L. Casey (Ed.), *Pain and central nervous system disease: The central pain syndromes* (pp. 13–29). New York, NY: Raven Press.

Bowsher, D. (1996). Central pain: Clinical and physiological characteristics. *Journal of Neurology, Neurosurgery, and Psychiatry*, *61*, 62Y9.

Bryce, T. N., Biering-Sørensen, F., Finnerup, N. B., Cardenas, D. D., Defrin, R., Lundeberg, T., et al. (2012). International spinal cord injury pain classification: Part I. Background and description. *Spinal Cord*, *50*, 413–417.

Bryce, T. N., Budh, C. N., Cardenas, D. D., Dijkers, M., Felix, E. R., Finnerup, N. B., et al. (2007). Pain after spinal cord injury: An evidence-based review for clinical practice and research. *Journal of Spinal Cord Medicine*, *30*, 421–440.

Burdea, G. C., & Coifett, P. (2003). *Virtual reality technology* (2nd ed.). Hoboken, NJ: John Wiley & Sons. Available from https://www.wiley.com/en-us/Virtual+Reality+Technology%2C+2nd+Edition-p-9780471360896 (Accessed 21 January 2020).

Burke, D., Fullen, B. M., Stokes, D., & Lennon, O. (2017). Neuropathic pain prevalence following spinal cord injury: A systematic review and meta-analysis. *European Journal of Pain*, *21*(1), 29–44. https://doi.org/10.1002/ejp.905.

Burke, D., Lennon, O., & Fullen, B. M. (2018). Quality of life after spinal cord injury: The impact of pain. *European Journal of Pain*, *22*(9), 1662–1672. https://doi.org/10.1002/ejp.1248.

Cardenas, D. D., & Jensen, M. P. (2006). Treatments for chronic pain in persons with spinal cord injury: A survey study. *Journal of Spinal Cord Medicine*, *29*, 109–117.

Chan, B. L., Witt, R., Charrow, A. P., Magee, A., Howard, R., Pasquina, P. F., et al. (2007). Mirror therapy for phantom limb pain. *New England Journal of Medicine*, *357*, 2206–2207.

Chi, B., Chau, B., Yeo, E., & Ta, P. (2019). Virtual reality for spinal cord injury-associated neuropathic pain: Systematic review. *Annals of Physical Medicine & Rehabilitation*, *62*, 49–57. https://doi.org/10.1016/j.rehab.2018.09.006.

Christ, O., & Reiner, M. (2014). Perspectives and possible applications of the rubber hand and virtual hand illusion in non-invasive rehabilitation: Technological improvements and their consequences. *Neuroscience and Biobehavioral Reviews*, *44*, 33–44.

Donati, A., Shokur, S., Morya, E., et al. (2016). Long-term training with a brain-machine interface-based gait protocol induces partial neurological recovery in paraplegic patients. *Scientific Reports*, *6*, 30383. https://doi.org/10.1038/srep30383.

Eick, J., & Richardson, E. J. (2015). Cortical activation during visual illusory walking in persons with spinal cord injury: A pilot study. *Archives of Physical Medicine and Rehabilitation*, *96*, 750–753.

Ephraim, P. L., Wegener, S. T., MacKenzie, E. J., Dillingham, T. R., & Pezzin, L. E. (2005). Phantom pain, residual limb pain, and back pain in amputees: Results of a national survey. *Archives of Physical Medicine and Rehabilitation*, *86*, 1910–1919. https://doi.org/10.1016/j.apmr.2005.03.031.

Finnerup, N. B. (2013). Pain in patients with spinal cord injury. *Pain*, *154*(Suppl. 1), S71–S76.

Finnerup, N. B., Johannesen, I. L., Fuglsang-Frederiksen, A., et al. (2003). Sensory function in spinal cord injury patients with and without central pain. *Brain*, *126*, 57Y70.

Flor, H., Nikolajsen, L., & Jensen, T. S. (2006). Phantom limb pain: A case of maladaptive CNS plasticity? *Nature Reviews Neuroscience*, *7*, 873–881. https://doi.org/10.1038/nrn1991.

Foell, J., Bekrater-Bodmann, R., Diers, M., & Flor, H. (2014). Mirror therapy for phantom limb pain: Brain changes and the role of body representation. *European Journal of Pain*, *18*, 729–739. https://doi.org/10.1002/j.1532-2149.2013.00433.x.

Freitas, D. M., & Spadoni, V. S. (2019). Is virtual reality useful for pain management in patients who undergo medical procedures? *Einstein (Sao Paulo)*, *17* (2), eMD4837. https://doi.org/10.31744/einstein_journal/2019MD4837.

Gupta, A., Scott, K., & Dukewich, M. (2018). Innovative technology using virtual reality in the treatment of pain: Does it reduce pain via distraction, or is there more to it? *Pain Medicine*, *19*(1), 151–159.

Gustin, S. M., Wrigley, P. J., Siddall, P. J., & Henderson, L. A. (2010). Brain anatomy changes associated with persistent neuropathic pain following spinal cord injury. *Cerebral Cortex*, *20*, 1409–1419.

Hanley, M. A., Jensen, M. P., Ehde, D. M., Hoffman, A. J., Patterson, D. R., & Robinson, L. R. (2004). Psychosocial predictors of long-term adjustment to lower-limb amputation and phantom limb pain. *Disability and Rehabilitation*, *26*, 882–893.

Harris, A. J. (1999). Cortical origin of pathological pain. *Lancet*, *354*, 1464–1466.

Jensen, M. P., Kuehn, C. M., Amtmann, D., & Cardenas, D. D. (2007). Symptom burden in persons with spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *88*, 638–645.

Jensen, M. P., Moore, M. R., Bockow, T. B., Ehde, D. M., & Engel, J. M. (2011). Psychosocial factors and adjustment to chronic pain in persons with physical disabilities: A systematic review. *Archives of Physical Medicine and Rehabilitation*, *92*, 146–160.

Jordan, M., & Richardson, E. J. (2016). Effects of virtual walking treatment on spinal cord injury-related neuropathic pain: Pilot results and trends related to location of pain and at-level neuronal hypersensitivity. *American Journal of Physical Medicine & Rehabilitation*, *95*(5), 390–396. https://doi.org/10.1097/PHM.0000000000000417.

Kirshblum, S., & Lin, V. W. (Eds.). (2019). *Spinal cord medicine*. New York: Demos Medical Publishing.

Mallari, B., Spaeth, E. K., Goh, H., & Boyd, B. S. (2019). Virtual reality as an analgesic for acute and chronic pain in adults: A systematic review and meta-analysis. *Journal of Pain Research*, *12*, 2053–2085.

Mat Rosly, M., Mat Rosly, H., Davis Oam, G. M., Husain, R., & Hasnan, N. (2017). Exergaming for individuals with neurological disability: A systematic review. *Disability and Rehabilitation*, *39*(8), 727–735. https://doi.org/10.3109/09638288.2016.1161086.

Matamala-Gomez, M., Donegan, T., Bottiroli, S., Sandrini, G., Sanchez-Vives, M. V., & Tassorelli, C. (2019). Immersive virtual reality and virtual embodiment for pain relief. *Frontiers in Human Neuroscience*, *13*, 279. https://doi.org/10.3389/fnhum.2019.00279.

Meacham, K., Shepherd, A., Mohapatra, D. P., & Haroutounian, S. (2017). Neuropathic pain: Central vs. peripheral mechanisms. *Current Pain and Headache Reports*, *21*(6), 28. https://doi.org/10.1007/s11916-017-0629-5.

Melzack, R. (1999). From the gate to the neuromatrix. *Pain*, *Suppl. 6*, S121–S126.

Moseley, G. L. (2005). Distorted body image in complex regional pain syndrome. *Neurology*, *65*, 773. https://doi.org/10.1212/01.wnl.0000174515.07205.11.

Moseley, G. L. (2007). Using visual illusion to reduce at-level neuropathic pain in paraplegia. *Pain*, *130*, 294–298. https://doi.org/10.1016/j.pain.2007.01.007.

Özkul, Ç., Kılınç, M., Yıldırım, S. A., Topçuoğlu, E. Y., & Akyüz, M. (2015). Effects of visual illusion and transcutaneous electrical nerve stimulation on neuropathic pain in patients with spinal cord injury: A randomised controlled crossover trial. *Journal of Back and Musculoskeletal Rehabilitation*, *28*, 709–719. https://doi.org/10.3233/BMR-140573.

Pozeg, P., Palluel, E., Ronchi, R., Solcà, M., Al-Khodairy, A. W., Jordan, X., et al. (2017). Virtual reality improves embodiment and neuropathic pain caused by spinal cord injury. *Neurology*, *89*, 1894–1903. https://doi.org/10.1212/WNL.0000000000004585.

Raffin, E., Mattout, J., Reilly, K. T., & Giraux, P. (2012). Disentangling motor execution from motor imagery with the phantom limb. *Brain*, *135*, 582–595. https://doi.org/10.1093/brain/awr337.

Ramachandran, V. S., & Altschuler, E. L. (2009). The use of visual feedback, in particular mirror visual feedback, in restoring brain function. *Brain*, *132*, 1693–1710.

Ramachandran, V. S., & Hirstein, W. (1998). The perception of phantom limbs. *Brain*, *121*, 1603–1630.

Richardson, E. J., Deutsch, G., Deshpande, H. D., & Richards, J. S. (2020). Differences in resting cerebellar and prefrontal cortical blood flow in spinal cord injury-related neuropathic pain: A brief report. *The Journal of Spinal Cord Medicine*. https://doi.org/10.1080/10790268.2020.1786321.

Richardson, C., Glenn, S., Horgan, M., & Nurmikko, T. (2007). A prospective study of factors associated with the presence of phantom limb pain six months after major lower limb amputation in patients with peripheral vascular disease. *The Journal of Pain*, *8*, 793–801.

Richardson, E. J., McKinley, E. C., Fazlur Rahman, A. K. M., Klebine, P., Redden, D. T., & Richards, J. S. (2019). Effects of virtual walking on spinal cord injury-related neuropathic pain: A randomized, controlled trial. *Rehabilitation Psychology*, *64*(1), 13–24. https://doi.org/10.1037/rep0000246.

Richardson, E. J., & Redden, D. T. (2014). Moving towards multiple site outcomes in spinal cord injury pain clinical trials: An issue of clustered observations in trial design and analysis. *Journal of Spinal Cord Medicine*, *37*(3), 278–287. https://doi.org/10.1179/2045772313Y.0000000165.

Richardson, E. J., Richards, J. S., & Boyer, B. A. (2008). Spinal cord injury. In B. A. Boyer, & M. I. Paharia (Eds.), *Comprehensive handbook of clinical health psychology*. Hoboken, NJ: Wiley.

Sayegh, S. A., Filén, T., Johansson, M., Sandström, S., Stiewe, G., & Butler, S. (2013). Mirror therapy for complex regional pain syndrome (CRPS): A literature review and an illustrative case report. *Scandinavian Journal of Pain*, *4*(4), 200–207. https://doi.org/10.1016/j.sjpain.2013.06.002.

Siddall, P. J. (2009). Management of neuropathic pain following spinal cord injury: Now and in the future. *Spinal Cord*, *47*, 352–359.

Siddall, P. J., & Loeser, J. D. (2001). Pain following spinal cord injury. *Spinal Cord*, *39*(2), 63–73. https://doi.org/10.1038/sj.sc.3101116.

Siddall, P. J., McClelland, J. M., Rutkowski, S. B., & Cousins, M. J. (2003). A longitudinal study of the prevalence and characteristics of pain in the first 5 years following spinal cord injury. *Pain*, *103*, 249–257.

Siddall, P. J., Taylor, D. A., & Cousins, M. J. (1997). Classification of pain following spinal cord injury. *Spinal Cord*, *35*, 69Y75.

Siddall, P. J., Taylor, D. A., McClelland, J. M., Rutkowski, S. B., & Cousins, M. J. (1999). Pain report and the relationship of pain to physical factors in the first 6 months following spinal cord injury. *Pain*, *81*, 187–197.

Soler, M. D., Kumru, H., Pelayo, R., Vidal, J., Tormos, J. M., Fregni, F., et al. (2010). Effectiveness of transcranial direct current stimulation and visual illusion on neuropathic pain in spinal cord injury. *Brain*, *133*, 2565–2577.

Soler, D., Moriña, D., Kumru, H., Vidal, J., & Navarro, X. (2021). Transcranial direct current stimulation and visual illusion effect according to sensory phenotypes in patients with spinal cord injury and neuropathic pain. *The Journal of Pain*, *22*, 86–96. https://doi.org/10.1016/j.jpain.2020.06.004.

Sumitani, M., Miyauchi, S., McCabe, C. S., Shibata, M., Maeda, L., Saitoh, Y., et al. (2008). Mirror visual feedback alleviates deafferentation pain, depending on qualitative aspects of the pain: A preliminary report. *Rheumatology*, *47*, 1038–1043. https://doi.org/10.1093/rheumatology/ken170.

Teasell, R. W., Mehta, S., Aubut, J. L., Foulon, B., Wolfe, D. L., Hsieh, J. T. C., et al. (2010). A systematic review of pharmacological treatments of pain following spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *91*, 816–831. https://doi.org/10.1016/j.apmr.2010.01.022.

Trost, Z., France, C. R., Anam, M., & Shum, C. (2020). Virtual reality approaches to pain: Toward a state of the science. *Pain*. https://doi.org/10.1097/j.pain.0000000000002060.

Tsai, I. H., Graves, D. E., Chan, W., Darkoh, C., Lee, M. S., & Pompeii, L. A. (2017). Environmental barriers and social participation in individuals with spinal cord injury. *Rehabilitation Psychology*, *62*, 36–44. https://doi.org/10.1037/rep0000117.

Tsakiris, M. (2017). The multisensory basis of the self: From body to identity to others. *Quarterly Journal of Experimental Psychology*, *70*, 597–609. https://doi.org/10.1080/17470218.2016.1181768.

Villiger, M., Bohli, D., Kiper, D., Pyk, P., Spillmann, J., Meilick, B., et al. (2013). Virtual reality-augmented neurorehabilitation improves motor function and reduces neuropathic pain in patients with incomplete spinal cord injury. *Neurorehabilitation and Neural Repair*, *27*(8), 675–683. https://doi.org/10.1177/1545968313490999.

Vlaeyen, J. W., & Linton, S. J. (2012). Fear-avoidance model of chronic musculoskeletal pain: 12 years on. *Pain*, *153*, 1144–1147. https://doi.org/10.1016/j.pain.2011.12.009.

Wrigley, P. J., Press, S. R., Gustin, S. M., et al. (2009). Neuropathic pain and primary somatosensory cortex reorganization following spinal cord injury. *Pain*, *141*, 52–59.

Yague, J. G., Foffani, G., & Aguilar, J. (2011). Cortical hyperexcitability in response to preserved spinothalamic inputs immediately after spinal cord hemisection. *Experimental Neurology*, *227*, 252–263.

Younger, J., Aron, A., Parke, S., Chatterjee, N., & Mackey, S. (2010). Viewing pictures of a romantic partner reduces experimental pain: Involvement of neural reward systems. *PLoS One*, *5*(10), e13309. https://doi.org/10.1371/journal.pone.0013309.

Chapter 35

Cervical spinal cord injury and thermoregulatory processes: A new narrative

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List of abbreviations

AEE	active energy expenditure
ANS	autonomic nervous system
ASIA	American Spinal Injury Association
BSCB	blood-spinal cord barrier
cSCI	cervical spinal cord injury
MnPO	median preoptic nucleus
NSCISC	National Spinal Cord Injury Statistical Center
REE	resting energy expenditure
SCI	spinal cord injury
SNS	sympathetic nervous system
VO2	oxygen consumption

Introduction

Cervical spinal cord injury (cSCI) is an insult to the cervical region of the spinal cord that can terminate in tetraplegia and even death, depending on the site of injury. The higher the level of injury in the cervical spine, the worse the outcome is. Although uncommon, complete neurological recovery may occur after such insults. According to the National Spinal Cord Injury Statistical Center (NSCISC), there are 17,810 new cases of SCI yearly, with a total approaching 300,000 cases in the United States. Around 80% of the cases are males and the most affected race/ethnicity is the non-Hispanic white population. All age groups are susceptible to the event; however, people in their 40s have the highest tendency to suffer from SCI (National Spinal Cord Injury Statistical Center, 2020). The causes of SCI are many, but motor vehicle accidents have been in the lead for the past 40 years, followed by falls, crimes and violence, sports injuries, medical and surgical complications, among others (Chen, Tang, Vogel, & Devivo, 2013; National Spinal Cord Injury Statistical Center, 2020).

Regardless of the spinal cord injury level, SCI can be classified as either complete or incomplete. According to the American Spinal Injury Association (ASIA), a complete injury refers to the total loss of the sensory and motor functions below the injury level. Whereas, in an incomplete injury, there is the maintenance of certain sensory and/or motor functions below the injury level. SCI can be categorized into 5 grades, according to its severity, as follows:

ASIA A: Complete loss of both motor and sensory functions below the injury level.
ASIA B: Preservation of certain sensory functions with loss of all motor functions below the injury level.
ASIA C: Preservation of certain motor functions below the injury level; more than half of the key muscles have a power grade less than 3.

Cellular, Molecular, Physiological, and Behavioral Aspects of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822427-4.00035-6

ASIA D: Preservation of motor functions below the injury level; at least half of the key muscles have a power grade greater than or equal to 3.
ASIA E: All sensory and motor functions are intact (American Spinal Cord Injury Association, 2019; Martinez-Perez, Cepeda, Paredes, Alen, & Lagares, 2017).

Furthermore, cSCI does not impact motor and sensory functions only; there can be loss of bladder and bowel control, loss of reflexes, sexual dysfunction, respiratory complications, thromboembolic events, spasticity, pain, and physiological and psychological disorders (depression and suicide), depending on the injury level and type (Abrams & Wakasa, 2019). Physiological disturbances are numerous, the most important of which are the disorders caused by the dysfunction of the autonomic nervous system (ANS). The loss of the sympathetic nervous system control and the compensatory attempt by the parasympathetic one may result in bradycardia, hypotension, thermoregulatory disturbances, skin blood flow and microcirculatory system dysfunction, and a fatal complication known as autonomic dysreflexia, among others (Karlsson, 2006; Wecht et al., 2015).

This chapter aims to discuss the thermoregulatory disturbances that develop in individuals with cSCI. The principle of homeostasis and the process of thermoregulation in able-bodied individuals are first introduced for a better understanding of the thermoregulatory changes that occur in cSCI (Figs. 1–4).

Homeostasis

Homeostasis is the ability of an organism to maintain a well-balanced internal environment under varying stress levels. There are a plethora of internal processes finely tuned by homeostasis, among which are the control of the arterial blood pressure and the ionic concentration, the regulation of oxygen and carbon dioxide exchange, the management of the waste products, and the adjustment of the core body temperature, among others (Chovatiya & Medzhitov, 2014; Pear, 2012).

Thermoregulatory process in able-bodied individuals

One of the fundamental homeostatic mechanisms in the body is the regulation of the core body temperature, i.e., the temperature of the internal organs and deeper tissues. Under normal conditions, the core body temperature is 37°C ± 0.5°C, despite any fluctuations in the ambient temperature. A slight deviation from this range may damage the function of the vital organs and disrupt homeostasis (Hall, 2015). On the other hand, the skin temperature is more flexible and adapts to a wider range of ambient temperatures. It is an important factor in aiding the body to acquire or eliminate excess heat (Tansey & Johnson, 2015). The nervous system, principally the hypothalamus, controls the core body temperature. The median preoptic nucleus (MnPO) situated in the anterior hypothalamus is central in the thermoregulatory processes. Inside the MnPO nucleus, heat and cold-sensitive neurons act as sensors for the body temperature. To note that, there exist peripheral thermal receptors that are sensitive to either cold or heat (Mrowka & Reuter, 2016). When the MnPO senses excessive heat, it sends different signals: a signal to terminate thermogenesis, and another one to the cutaneous blood vessels to dilate and induce perspiration, all of which contribute to the body's coolness and restoration of its balance. On the contrary, when the cold sensors detect a drop in temperature, the MnPO sends a stimulus to activate thermogenesis and another one to the skin to constrict its blood vessels and prevent any loss of heat, thereby bringing the temperature back to its set point (Hall, 2015). The diameter of cutaneous blood vessels and consequently the blood flow to the skin are dependent on the autonomic nervous system, specifically the sympathetic nervous system (SNS). Likewise, the sweat glands are also innervated by the sympathetic fibers. Activation of the SNS leads to the vasoconstriction of the cutaneous blood vessels and stimulation of thermogenesis, while its inhibition entails the opposite changes (Tansey & Johnson, 2015). Apart from the SNS, hormonal and behavioral tunings play a role in the regulation of the core body temperature. Hormones like thyroxine, leptin, and neuropeptide Y are among the factors that affect thermoregulation. Furthermore, behavioral adjustments are key components in the adaptation to the weather while supporting the internal mechanisms in maintaining thermoregulatory homeostasis (Hall, 2015).

Differences between healthy individuals and cSCI patients

Alterations in the body composition and energy expenditure after cSCI

There is a decreased level of physical activity and an increased prevalence of corpulence in patients with SCI compared to the general population (Holmlund, Ekblom-Bak, Franzen, Hultling, & Wahman, 2018). In addition to a lower resting energy expenditure (REE) and activity energy expenditure (AEE) in such patients (Jaeger & Blight, 1997), it was also

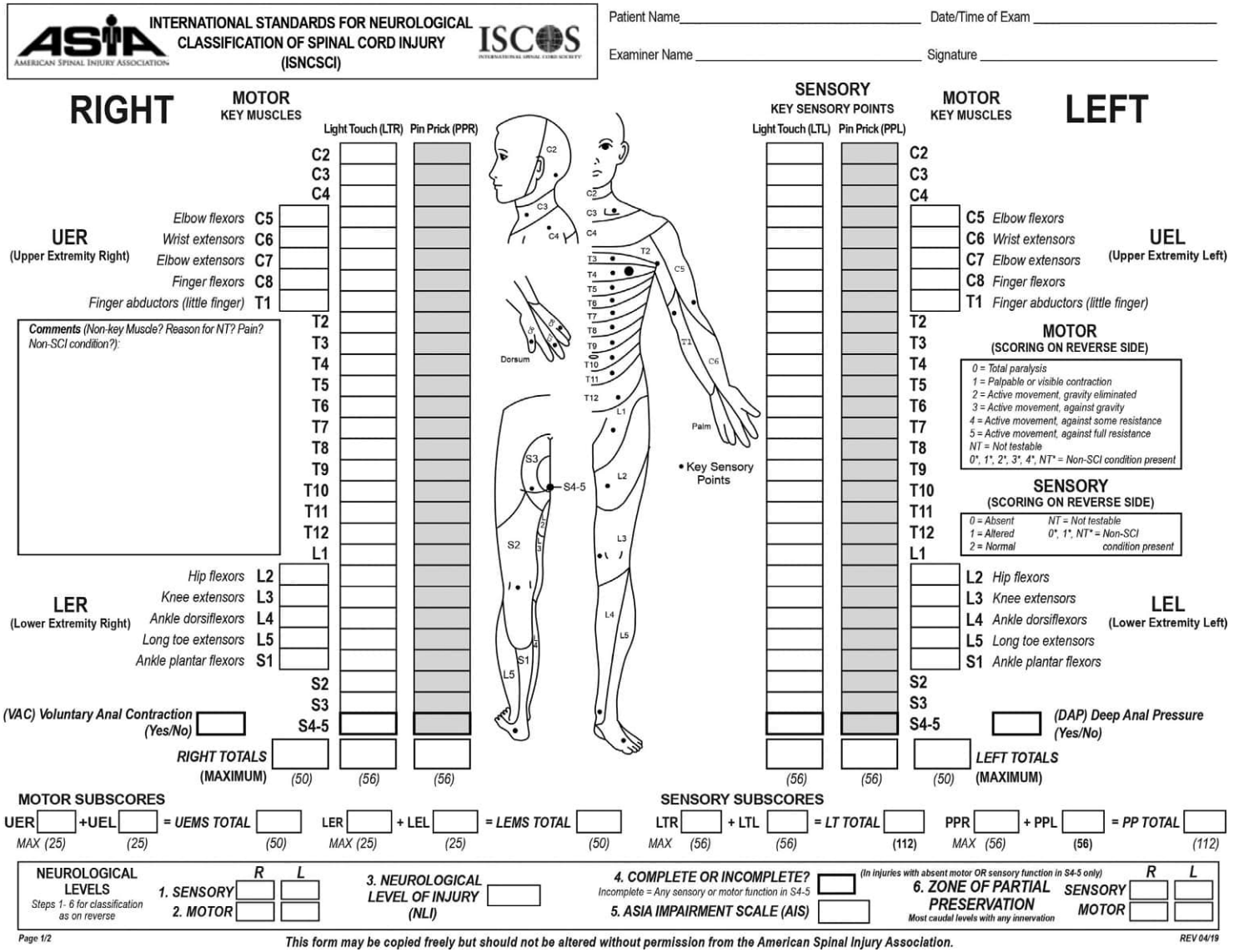

FIG. 1 ASIA grading system. *ANS*, autonomic nervous system; *SNS*, sympathetic nervous system; *BSCB*, blood-spinal cord barrier. *(© 2021 American Spinal Injury Association. Reprinted with permission.)*

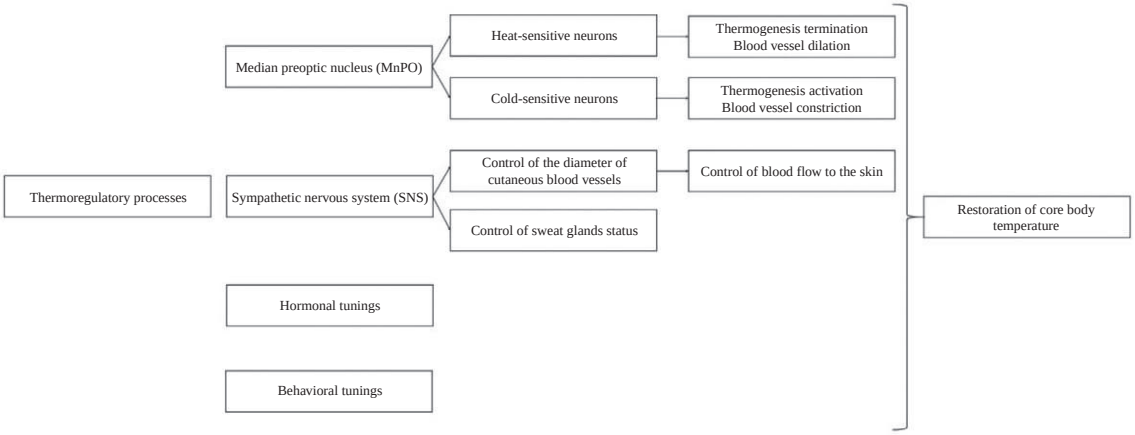

FIG. 2 Thermoregulatory process in able-bodied individuals.

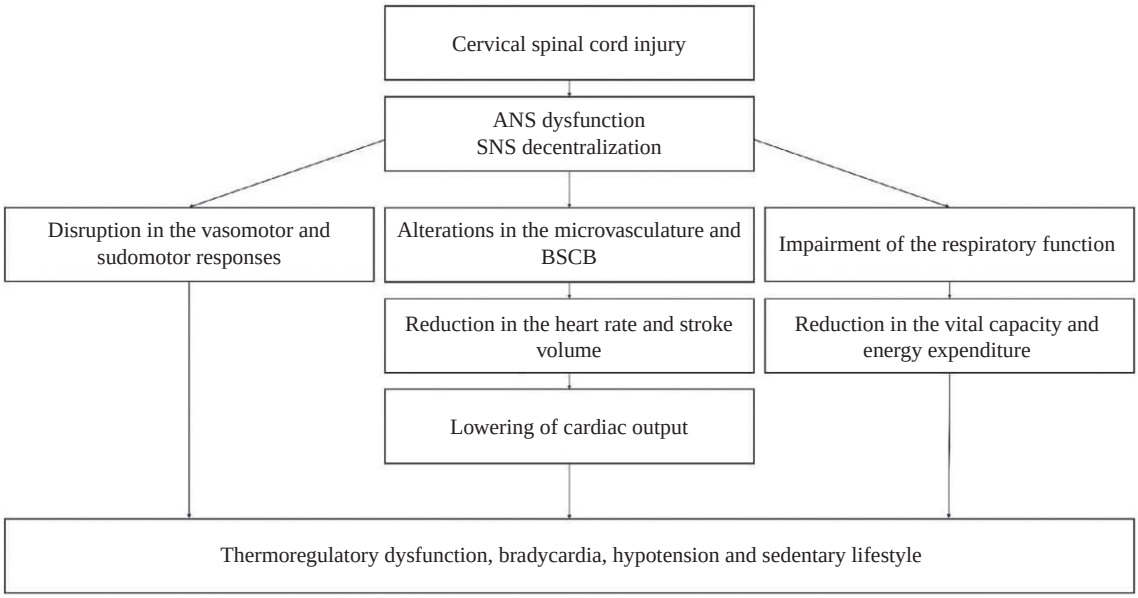

FIG. 3 The negative effects of the cervical spinal cord injury on the human body.

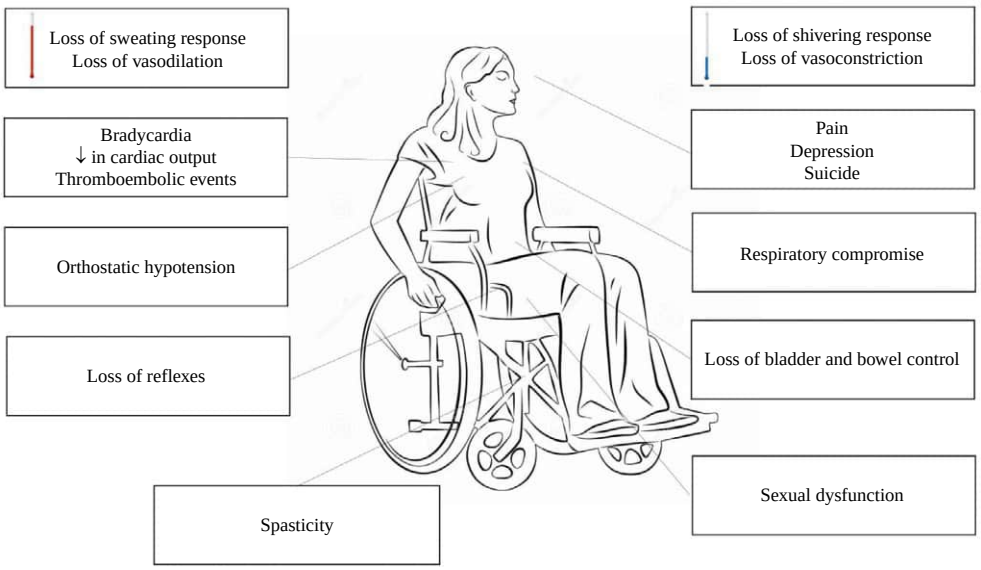

FIG. 4 Detailed negative effects of the cervical spinal cord injury on the human body parts.

shown that it will take a longer time to consume the same amount of energy while performing the same kind of exercise in tetraplegic patients compared to paraplegic patients (Collins et al., 2010). This is because complete motor injuries above thoracic level 6 affect the autonomic nervous system and more muscle tissues (Collins et al., 2010). This will lead to a decrease in the communication between the parasympathetic and the sympathetic nervous systems resulting in an impaired respiratory function with lower vital capacity and maximal heart rate (Currie, West, Hubli, Gee, & Krassioukov, 2015). All of which leads to an energy supply through anaerobic processes with the buildup of lactate, thus affecting the exercise performance and duration (Currie et al., 2015). Holmlund et al. performed a cross-sectional study to compare the resting energy expenditure and VO2 levels for sedentary non-exercise activities and exercise activities in patients with complete motor tetraplegia. They also compared the same parameters between tetraplegic and paraplegic patients. They found out that tetraplegic patients can increase their energy expenditure and VO2 levels three to four times when performing non-exercise physical activity compared to sedentary activities (Holmlund et al., 2018).

In addition, it showed no major differences in resting energy expenditure (REE) between tetraplegic and paraplegic groups. There was an increase in AEE up to 16 times for people with tetraplegia and 14 times for people with paraplegia during exercise activities. This can be attributed to an impairment in the ANS and a greater portion of reduced muscle mass incomplete tetraplegia (Holmlund et al., 2018).

Alterations in the cardiovascular system after cSCI

Traumatic injury to the spinal cord has a profound effect on the microvasculature and the blood-spinal cord barrier (BSCB). It renders the microvasculature permeable to the circulating proteins along the entire axis of the cord not just at the site of injury (Noble, Mautes, & Hall, 1996). Noble et al. demonstrated that in healthy individuals the luminal plasma membranes of the spinal cord show carbohydrate moieties and anionic sites that are like the ones present in the cerebral vessels. However, SCI causes alteration in the composition of the plasma membrane, leading to the loss of the anionic sites with the breakdown of the barrier and an increase in the expression of B-D-galactosamine residues (Noble et al., 1996). Additionally, SCI leads to a reduction in the diameter of blood vessels below the injury level secondary to SNS dysfunction and sedentary lifestyle. This phenomenon will prompt a limitation in the dissipation and preservation of heat resulting in hyperthermia and hypothermia, respectively (Mneimneh, Moussalem, Ghaddar, Aboughali, & Omeis, 2019).

Similar to blood vessel diameter, the cardiac output is also reduced which restricts the individual's tolerance to exercise and culminates in a sedentary lifestyle (Mneimneh et al., 2019).

As previously mentioned, SCI damages the BSCB but in as little as 5 min post-injury (Maikos & Shreiber, 2007). There is a breakdown of this barrier which leads to additional harm to the injured area as well as to the healthy unaffected segments of the spinal cord (Bartanusz, Jezova, Alajajian, & Digicaylioglu, 2011). Several factors are involved in the disruption of this fundamental barrier including the release of toxic free radicals, the disruption of the endothelial tight junctions, and the ischemic condition resulting in the expression of endothelin-1, among many others (Bartanusz et al., 2011).

Disruption in the vasomotor, sudomotor, and shivering responses after cSCI

One of the consequences of cSCI is autonomic dysreflexia (AD), which as the name implies, is the inability of the spinal cord to synchronize the human body sympathetic activity resulting in the disruption of the vasomotor (blood vessel vasodilatation/vasoconstriction) and sudomotor (shivering/sweating) responses. AD, which is potentially fatal, is characterized by bouts of acute hypertension reaching extremely high levels and compensatory bradycardia mediated by the baroreceptors (Eldahan & Rabchevsky, 2018).

Hence, people with tetraplegia are unable to maintain a balanced body temperature due to the loss of the sweating and vasodilatation responses and the vasoconstriction and shivering responses which normally occur when the body temperature is above or below its thermoneutral state, respectively (Gunduz & Binak, 2012). The pathophysiology of such disruption is due to the impairment of the stellate ganglion, a star-shaped sympathetic collection of nerves located in the cervical region, which regulates the involuntary sympathetic nervous system functions such as vaso-regulation, sweating, and pain (Kirshblum et al., 2011).

The sudomotor response is usually activated when the human body temperature is above its thermoneutral state resulting in sweating to cool down the body temperature. It is estimated that 100% of the sudomotor responses are lost in case of complete cSCI compared to 50%–75% loss in case of incomplete cSCI, leading to a disrupted body temperature (Yaggie, Niemi, & Buono, 2002). Hence, damage to the ANS post cSCI hinders the human body's ability from regulating its temperature at extreme thermal stress conditions. Due to the absence of shivering and sweating responses, people with

complete cSCI are at an increased risk of acute and chronic health conditions, such as hyperthermia and hypothermia leading to the disruption of the normal function of the proteins and enzymes leading to cell death, on the molecular level, (Cheung, Lee, & Oksa, 2016) and to multi-organ failure. Hyperthermia, in particular, even in its mildest forms, can lead to cognitive problems including memory and attention deficits, and neurological deficits that can become persistent and even permanent (Walter & Carraretto, 2016). In contrast, hypothermia is more likely to affect the myocardium causing ischemia and infarctions, and the blood causing bleeding diathesis (Sessler, 2001).

Alterations in the blood pressure after cSCI

Due to the loss of the central sympathetic tone (supraspinal neuronal centers), patients with cSCI develop acute hypotension that might require vasopressive treatment to maintain vital blood pressure, although the myogenic (smooth muscle) peripheral tone is preserved in such patients (Piepmeier, Lehmann, & Lane, 1985). Particularly, the development of hypotension occurs in the peripheral blood vessels that are below the lesion. Thus, patients with the highest cervical injuries, develop hypotension the most (West, Mills, & Krassioukov, 2012). Besides resting hypotension, patients with cSCI develop orthostatic hypotension which occurs when they are transferred from supine to an upright position (Mathias & Frankel, 1983). In a healthy individual, orthostatic hypotension is avoided by the sympathetic outflow leading to the baroreflex-mediated peripheral vasoconstriction to preserve blood pressure and cerebral perfusion (Bush, Wight, Brown, & Hainsworth, 2000). It has been suggested that decreased baroreceptor sensitivity and sympathetic hypoactivity are the causes of orthostatic hypotension post cSCI. Besides, disturbed salt/water balance and cardiovascular deconditioning have been also proposed as causes of orthostatic hypotension in such patients (Munakata, Kameyama, Nunokawa, Ito, & Yoshinaga, 2001). To note that problems in orthostasis can last for many years and have the potential to become permanent in tetraplegic individuals (Krassioukov, Eng, Warburton, & Teasell, 2009).

Applications to other areas of neuroscience

In this chapter, we have reviewed the thermoregulatory dysfunctions that occur in patients with cSCI. These changes can be incapacitating to the individuals who might already be suffering on numerous scales including financially, physically, psychologically, and emotionally. Despite this serious unparalleled injury being neglected for years, there are currently hundreds of ongoing research projects worldwide attempting to help individuals live a better quality of life using advanced devices and there are efforts made towards curing this condition using, for example, stem cell technology.

In this section, we will be briefly reviewing some of the advances in the field of treatment of cSCI, and hence in the prevention of thermoregulatory dysfunctions. In addition to the early surgical intervention for decompression which has been proven to improve the outcome (Fehlings et al., 2012; La Rosa, Conti, Cardali, Cacciola, & Tomasello, 2004), there are several clinical trials on pharmacological and non-pharmacological treatment options.

Among the drugs being tested as neuroprotective agents in SCI, we cite glibenclamide (an antidiabetic drug) (Minnema et al., 2019), minocycline (an antibiotic) (Casha et al., 2012), riluzole (a drug for amyotrophic lateral sclerosis) (Fehlings et al., 2016), and certain growth factors such as hepatocyte growth factor, granulocyte colony-stimulating factor, and basic fibroblast growth factor (Badhiwala, Ahuja, & Fehlings, 2018).

The use of cell therapy and stem cell therapy are growing due to their scaffolding, regenerative, and to a lesser extent neuroprotective properties, providing an adequate environment for the spinal cord to heal and regenerate (Badner, Siddiqui, & Fehlings, 2017).

As for the non-pharmacological lines of treatment, there are reports on functional electrical stimulation and cooling of the spinal cord as being effective means to reduce the deleterious effects of cSCI. Functional electrical stimulation was shown to be a safe way to increase the degree of independence and ambulation in SCI, yet larger trials are being conducted to prove its effectiveness (Kapadia et al., 2014; Thrasher, Flett, & Popovic, 2006). On the other hand, inducing hypothermia in SCI using various devices and approaches (e.g. skin surface cooling using jackets or blankets, cooling catheters, chilled saline, and so on) has been assessed in numerous experimental and clinical studies to enhance the outcomes and prevent, or at least halt the progression on the injury (Ahmad, Wang, & Levi, 2014; Zhu, 2018), yet larger studies and randomized control trials are needed to support the adoption of systemic hypothermia as a treatment line in cSCI.

Until the results of large multi-center trials confirm or refute the efficacy of the treatment measures mentioned above, the current guidelines for the treatment of cSCI remain vague.

Mini-dictionary of terms

Tetraplegia: A paralysis due to a spinal cord injury in the cervical region.
Paraplegia: A paralysis due to a spinal cord injury in the thoracic, lumbar, or sacral region.
Thromboembolic events: The movement of a blood clot (thrombus) via blood from one site to another to plug the vessels.
Autonomic nervous system: It is the involuntary nervous system that is responsible for bodily functions, including the heart and respiratory rate, digestion, and urination, among others. It is divided into the sympathetic and parasympathetic nervous systems.
Sympathetic nervous system: It is responsible for the fight and flight responses, including the sudomotor and vasomotor systems.
Parasympathetic nervous system: It is responsible for the rest and digest responses.
Resting energy expenditure: It refers to the amount of energy a body requires during a non-active 24-h period.
Activity energy expenditure: It refers to the energy consumed during planned and unplanned physical activity.
Vital capacity: It refers to the maximal amount of air expelled from the lungs after a full deep breath.

Key facts of spinal cord injury

- SCI is an insult to the spinal cord that can occur at any level.
- The severity of SCI depends on the injury level and type.
- There are profound economic, psychological, and social burdens resulting from SCI.
- Numerous causes have been described but motor vehicle accidents and falls are the most frequently encountered.
- Most of the physiological disturbances are due to the involvement of the autonomic nervous system.
- SCI leads to a variety of dysregulations, most notably, the homeostatic imbalance and thermoregulatory dysfunction.
- People with SCI develop resting and orthostatic hypotension.

Key facts of American Spinal Injury Association

- The American Spinal Injury Association (ASIA) was launched in 1973.
- It is concerned with the care of patients living with spinal cord injury (SCI) and promotes knowledge about SCI both for the public and healthcare personnel.
- It is actively engaged in and encourages research in all fields related to SCI starting with its prevention and not ending with ways to enhance the quality of life of affected patients and finding new therapies.
- It relies on a multidisciplinary approach to SCI.
- It publishes the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI), a widely used assessment tool to determine the level and severity of SCI.

Summary points

- Motor vehicle accidents are the leading cause of traumatic SCI which is increasing every year.
- SCI can be classified into 5 grades depending on the preservation percentage of the sensory and motor functions below the injury level.
- In people with SCI, the sympathetic nervous system loses its function and the parasympathetic one attempts to take control instead.
- People with SCI cannot maintain their core body temperature stable under ambient conditions due to thermoregulatory disturbances.
- Thermoregulatory disruptions are due to the loss of the sudomotor (shivering/sweating) and vasomotor (vasoconstriction/dilation) responses below the injury level.
- People with SCI have a more sedentary lifestyle and thus lower REE and AEE.

References

Abrams, G. M., & Wakasa, M. (2019). In M. J. Aminoff, & M. J. Silveira (Eds.), *Chronic complications of spinal cord injury and disease* UptoDate.

Ahmad, F. U., Wang, M. Y., & Levi, A. D. (2014). Hypothermia for acute spinal cord injury—A review. *World Neurosurgery*, *82*(1–2), 207–214.

American Spinal Cord Injury Association. (2019). *International standards for neurological classification of spinal cord injury*. Retrieved 26/09/2020, from https://asia-spinalinjury.org/international-standards-neurological-classification-sci-isncsci-worksheet/.

Badhiwala, J. H., Ahuja, C. S., & Fehlings, M. G. (2018). Time is spine: A review of translational advances in spinal cord injury. *Journal of Neurosurgery. Spine*, *30*(1), 1–18.

Badner, A., Siddiqui, A. M., & Fehlings, M. G. (2017). Spinal cord injuries: How could cell therapy help? *Expert Opinion on Biological Therapy*, *17*(5), 529–541.

Bartanusz, V., Jezova, D., Alajajian, B., & Digicaylioglu, M. (2011). The blood-spinal cord barrier: Morphology and clinical implications. *Annals of Neurology*, *70*(2), 194–206.

Bush, V. E., Wight, V. L., Brown, C. M., & Hainsworth, R. (2000). Vascular responses to orthostatic stress in patients with postural tachycardia syndrome (POTS), in patients with low orthostatic tolerance, and in asymptomatic controls. *Clinical Autonomic Research*, *10*(5), 279–284.

Casha, S., Zygun, D., McGowan, M. D., Bains, I., Yong, V. W., & Hurlbert, R. J. (2012). Results of a phase II placebo-controlled randomized trial of minocycline in acute spinal cord injury. *Brain*, *135*(Pt. 4), 1224–1236.

Chen, Y., Tang, Y., Vogel, L. C., & Devivo, M. J. (2013). Causes of spinal cord injury. *Topics in Spinal Cord Injury Rehabilitation*, *19*(1), 1–8.

Cheung, S. S., Lee, J. K., & Oksa, J. (2016). Thermal stress, human performance, and physical employment standards. *Applied Physiology, Nutrition, and Metabolism*, *41*(6 Suppl. 2), S148–S164.

Chovatiya, R., & Medzhitov, R. (2014). Stress, inflammation, and defense of homeostasis. *Molecular Cell*, *54*(2), 281–288.

Collins, E. G., Gater, D., Kiratli, J., Butler, J., Hanson, K., & Langbein, W. E. (2010). Energy cost of physical activities in persons with spinal cord injury. *Medicine and Science in Sports and Exercise*, *42*(4), 691–700.

Currie, K. D., West, C. R., Hubli, M., Gee, C. M., & Krassioukov, A. V. (2015). Peak heart rates and sympathetic function in tetraplegic nonathletes and athletes. *Medicine and Science in Sports and Exercise*, *47*(6), 1259–1264.

Eldahan, K. C., & Rabchevsky, A. G. (2018). Autonomic dysreflexia after spinal cord injury: Systemic pathophysiology and methods of management. *Autonomic Neuroscience*, *209*, 59–70.

Fehlings, M. G., Nakashima, H., Nagoshi, N., Chow, D. S., Grossman, R. G., & Kopjar, B. (2016). Rationale, design and critical end points for the Riluzole in Acute Spinal Cord Injury Study (RISCIS): A randomized, double-blinded, placebo-controlled parallel multi-center trial. *Spinal Cord*, *54*(1), 8–15.

Fehlings, M. G., Vaccaro, A., Wilson, J. R., Singh, A. W., Cadotte, D., Harrop, J. S., et al. (2012). Early versus delayed decompression for traumatic cervical spinal cord injury: Results of the Surgical Timing in Acute Spinal Cord Injury Study (STASCIS). *PLoS One*, *7*(2), e32037.

Gunduz, H., & Binak, D. F. (2012). Autonomic dysreflexia: An important cardiovascular complication in spinal cord injury patients. *Cardiology Journal*, *19*(2), 215–219.

Hall, J. E. (2015). Body temperature regulation and fever. In *Guyton and Hall textbook of medical physiology* (p. 1168). Philadelphia, PA: Elsevier.

Holmlund, T., Ekblom-Bak, E., Franzen, E., Hultling, C., & Wahman, K. (2018). Energy expenditure after spinal cord injury in people with motor-complete tetraplegia or motor-complete paraplegia. *Spinal Cord*, *56*(3), 274–283.

Jaeger, C. B., & Blight, A. R. (1997). Spinal cord compression injury in guinea pigs: Structural changes of endothelium and its perivascular cell associations after blood-brain barrier breakdown and repair. *Experimental Neurology*, *144*(2), 381–399.

Kapadia, N., Masani, K., Catharine Craven, B., Giangregorio, L. M., Hitzig, S. L., Richards, K., et al. (2014). A randomized trial of functional electrical stimulation for walking in incomplete spinal cord injury: Effects on walking competency. *The Journal of Spinal Cord Medicine*, *37*(5), 511–524.

Karlsson, A. K. (2006). Autonomic dysfunction in spinal cord injury: Clinical presentation of symptoms and signs. *Progress in Brain Research*, *152*, 1–8.

Kirshblum, S. C., Burns, S. P., Biering-Sorensen, F., Donovan, W., Graves, D. E., Jha, A., et al. (2011). International standards for neurological classification of spinal cord injury (revised 2011). *The Journal of Spinal Cord Medicine*, *34*(6), 535–546.

Krassioukov, A., Eng, J. J., Warburton, D. E., & Teasell, R. (2009). A systematic review of the management of orthostatic hypotension after spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *90*(5), 876–885.

La Rosa, G., Conti, A., Cardali, S., Cacciola, F., & Tomasello, F. (2004). Does early decompression improve neurological outcome of spinal cord injured patients? Appraisal of the literature using a meta-analytical approach. *Spinal Cord*, *42*(9), 503–512.

Maikos, J. T., & Shreiber, D. I. (2007). Immediate damage to the blood-spinal cord barrier due to mechanical trauma. *Journal of Neurotrauma*, *24*(3), 492–507.

Martinez-Perez, R., Cepeda, S., Paredes, I., Alen, J., & Lagares, A. (2017). MRI prognostication factors in the setting of cervical spinal cord injury secondary to trauma. *World Neurosurgery*, *101*, 623–632.

Mathias, C. J., & Frankel, H. L. (1983). Clinical manifestations of malfunctioning sympathetic mechanisms in tetraplegia. *Journal of the Autonomic Nervous System*, *7*(3–4), 303–312.

Minnema, A. J., Mehta, A., Boling, W. W., Schwab, J., Simard, J. M., & Farhadi, H. F. (2019). SCING-spinal cord injury neuroprotection with glyburide: A pilot, open-label, multicentre, prospective evaluation of oral glyburide in patients with acute traumatic spinal cord injury in the USA. *BMJ Open*, *9*(10), e031329.

Mneimneh, F., Moussalem, C., Ghaddar, N., Aboughali, K., & Omeis, I. (2019). Influence of cervical spinal cord injury on thermoregulatory and cardiovascular responses in the human body: Literature review. *Journal of Clinical Neuroscience*, *69*, 7–14.

Mrowka, R., & Reuter, S. (2016). Thermoregulation. *Acta Physiologica*, *217*(1), 3–5.

Munakata, M., Kameyama, J., Nunokawa, T., Ito, N., & Yoshinaga, K. (2001). Altered Mayer wave and baroreflex profiles in high spinal cord injury. *American Journal of Hypertension*, *14*(2), 141–148.

National Spinal Cord Injury Statistical Center. (2020). *Facts and figures at a glance*. Retrieved 22/09/2020, from https://www.nscisc.uab.edu/Public/Facts%20and%20Figures%202020.pdf.

Noble, L. J., Mautes, A. E., & Hall, J. J. (1996). Characterization of the microvascular glycocalyx in normal and injured spinal cord in the rat. *The Journal of Comparative Neurology*, *376*(4), 542–556.

Pear, J. J. (2012). Physiological homeostasis and learning. In N. M. Seel (Ed.), *Encyclopedia of the sciences of learning* (pp. 2628–2631). Boston, MA: Springer US.

Piepmeier, J. M., Lehmann, K. B., & Lane, J. G. (1985). Cardiovascular instability following acute cervical spinal cord trauma. *Central Nervous System Trauma*, *2*(3), 153–160.

Sessler, D. I. (2001). Complications and treatment of mild hypothermia. *Anesthesiology*, *95*(2), 531–543.

Tansey, E. A., & Johnson, C. D. (2015). Recent advances in thermoregulation. *Advances in Physiology Education*, *39*(3), 139–148.

Thrasher, T. A., Flett, H. M., & Popovic, M. R. (2006). Gait training regimen for incomplete spinal cord injury using functional electrical stimulation. *Spinal Cord*, *44*(6), 357–361.

Walter, E. J., & Carraretto, M. (2016). The neurological and cognitive consequences of hyperthermia. *Critical Care*, *20*(1), 199.

Wecht, J., Lafountaine, M., Handrakis, J., West, C., Phillips, A., Ditor, D., et al. (2015). Autonomic nervous system dysfunction following spinal cord injury: Cardiovascular, cerebrovascular, and thermoregulatory effects. *Current Physical Medicine and Rehabilitation Reports*, *3*, 197–205.

West, C. R., Mills, P., & Krassioukov, A. V. (2012). Influence of the neurological level of spinal cord injury on cardiovascular outcomes in humans: A meta-analysis. *Spinal Cord*, *50*(7), 484–492.

Yaggie, J. A., Niemi, T. J., & Buono, M. J. (2002). Adaptive sweat gland response after spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *83*(6), 802–805.

Zhu, L. (2018). Hypothermia used in medical applications for brain and spinal cord injury patients. *Advances in Experimental Medicine and Biology*, *1097*, 295–319.

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Chapter 36

Spinal cord injury and the gut microbiota

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List of abbreviations

ANS	autonomic nervous system
APOA1	apolipoprotein A-I
CFS	chronic fatigue syndrome
CNS	central nervous system
GALT	gut-associated lymph tissue
GI	gastrointestinal
HPA	hippocampus pituitary axis
HDL	high density lipoprotein
KEGG	Kyoto Encyclopedia of Genes and Genomes
LPA	lipoprotein A
MAG	metagenome assembled genome
NAFLD	non-alcoholic fatty liver disease
NE	norepinephrine
SCFA	short-chain fatty acid
SCI	spinal cord injury
SPN	sympathetic pre-ganglionic neuron

Introduction

The gut microbiota comprises all of the bacteria, viruses, fungi, and other microbes that live in the gastrointestinal tract, specifically within the small and large intestines. The density of this community of microbes is at least as numerous as mammalian cells (Sender, Fuchs, & Milo, 2016) and may outnumber them ~10:1 (Gill et al., 2006; Hollister, Gao, & Versalovic, 2014). This diverse ecosystem, and associated genome (i.e., the microbiome), is critical for regulating host metabolism, digestion, nutrient absorption, and immune system development and function (Hooper, Littman, & Macpherson, 2012; Nicholson et al., 2012; Round & Mazmanian, 2009). The types and diversity of microbiota vary as a function of location in the gut. The small intestine has a more limited microbial community structure enriched with Lactobacillaceae and Enterobacteriaceae (Donaldson, Lee, & Mazmanian, 2016; Gu et al., 2013) while a more diverse and abundant microbiome exists in the colon. Because there is lower oxygen tension in the colon, it is enriched with anaerobic microbiota (Donaldson et al., 2016; Gu et al., 2013). In addition to regulating inflammation and GI function, the intestinal microbiota can influence disease development throughout the host, including in the CNS (Collins, Surette, & Bercik, 2012; Wang & Kasper, 2014).

The gut and the CNS communicate with one another via several routes. Gut microbes, through activation of immune cells in the gut-associated lymphoid tissues (GALT) and subsequent release of cytokines, affect CNS function (Bercik et al., 2010). Many (~80%) of the body's immune cells are found in the GALT, and this neuro-immune axis is likely an important route of communication between the gut and brain.

Gut microbes play a role in regulating the body's response to stress, including cortisol release (Crumeyrolle-Arias et al., 2014; Sudo et al., 2004). Germ-free mice develop an exaggerated hypothalamic-pituitary-adrenal (HPA) axis response to stress, which can be completely or partially reversed with a fecal transplant from conventional mice (Sudo et al., 2004). Similar exaggerated stress response has been seen in germ-free rats (Crumeyrolle-Arias et al., 2014), suggesting that the ability of gut microbes to regulate stress is conserved across species.

Cellular, Molecular, Physiological, and Behavioral Aspects of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822427-4.00036-8

Finally, gut microbiota produces neuroactive metabolites (i.e., short-chain fatty acids, choline) and neurotransmitters (GABA, noradrenaline, serotonin, dopamine, acetylcholine). These gut metabolites can act locally on neurons and glia that make up the enteric nervous system (Clarke et al., 2014; Tillisch, 2014) but they can also enter the bloodstream. After crossing the blood-brain barrier or by modulating signaling of the afferent vagus nerve in the periphery, circulating metabolites born in the gut can directly influence CNS structure/function (Clarke et al., 2014; Forsythe, Bienenstock, & Kunze, 2014; Wikoff et al., 2009).

In the healthy gut, a symbiosis exists between the gut microbiota, intestinal epithelia, and immune system. Altering the composition of the gut microbiota creates a state of "dysbiosis" where the balance between beneficial and pathogenic or inflammatory bacteria is skewed, usually favoring the latter. Common causes of gut dysbiosis include antibiotic use, stress, and gut dysfunction (Bailey et al., 2011, 2010; El Aidy, van den Bogert, & Kleerebezem, 2015; Hawrelak & Myers, 2004; Hill & Artis, 2010; Hooper et al., 2012; Round & Mazmanian, 2009). Many of these triggers of gut dysbiosis also compromise the mucosal barrier, leading to bacterial translocation, a process whereby gut bacteria migrate from the intestinal lumen into mesenteric lymph nodes and throughout the body (Balmer et al., 2014; Balzan, de Almeida Quadros, de Cleva, Zilberstein, & Cecconello, 2007; Macpherson & Smith, 2006). Gut dysbiosis may also influence the progression of or predispose individuals to develop autoimmune diseases (e.g., multiple sclerosis, type I diabetes, rheumatoid arthritis), allergy or metabolic disorders (Berer et al., 2011; Cao, Feehley, & Nagler, 2014; Kriegel et al., 2011; Lee, Menezes, Umesaki, & Mazmanian, 2011; Tilg & Kaser, 2011). Similarly, dysbiosis has been implicated in the onset or progression of neurological diseases including autism, pain, depression, anxiety, and stroke (Benakis et al., 2016; de Theije et al., 2014; Foster & McVey Neufeld, 2013; Hsiao et al., 2013; Rousseaux et al., 2007; Winek et al., 2016).

Spinal cord injury-induced dysautonomia

Traumatic spinal cord injury (SCI) causes loss of motor and sensory function below the level of the injury, resulting in paralysis and permanent sensory dysfunction. SCI also permanently damages the sympathetic branch of the autonomic nervous system, leading to persistent dysautonomia. SCI-induced dysautonomia contributes to chronic multi-organ pathology and dysfunction including loss of bladder and bowel function, immune suppression, depression and anxiety, fatigue, and cardiovascular dysfunction and disease.

Sympathetic pre-ganglionic neurons (SPNs) reside in the thoracic and upper lumbar spinal cord. SPNs are cholinergic neurons that innervate adrenergic neurons located outside the spinal cord within pre-/post-vertebral ganglia. Post-ganglionic adrenergic sympathetic neurons release norepinephrine (NE) in target organs including (but not limited to) the immune system, liver, cardiovascular system, and the gastrointestinal (GI) tract (Felten, Ackerman, Wiegand, & Felten, 1987; Felten & Olschowka, 1987). SPN neurons can be directly injured during SCI. However, even if SPNs are spared, their function becomes disrupted due to loss or damage to pre-sympathetic axons (from the brain/brainstem) or the intraspinal neuronal networks that regulate autonomic reflexes below the level of injury.

In the gut, sympathetic post-ganglionic innervation controls motility, mucosal secretions, vascular tone, and immune function (Cervi, Lukewich, & Lomax, 2014; Elenkov, Wilder, Chrousos, & Vizi, 2000). SPNs controlling the small and large intestines are located in the intermediolateral cell column in thoracic spinal segments T5–10 and T10-L4, respectively (Fig. 1) (Browning & Travagli, 2014; Levatte, Mabon, Weaver, & Dekaban, 1998; Mabon, LeVatte, Dekaban, & Weaver, 1997). Adrenergic post-ganglionic nerve fibers from the celiac-mesenteric ganglia innervate the stomach, small intestine, and, to some extent, the proximal large intestine. Neurons in the inferior mesenteric ganglia receive input from SPNs located in the T11 and upper lumbar spinal cord then send post-ganglionic projections to innervate the large intestine (Furness & Costa, 1974). Therefore, an injury at any spinal level will adversely affect the GI tract, although these effects are exacerbated when SCI occurs at high spinal levels and progressively more pre-sympathetic control over spinal sympathetic networks that control the gut are lost. Common GI complications after SCI include constipation, fecal incontinence, and decreased colonic transit time (Hou & Rabchevsky, 2014; Qualls-Creekmore, Tong, & Holmes, 2010; Tate et al., 2016). After SCI, impaired autonomic control of gastrointestinal function likely contributes to the development of dysbiosis, which is then maintained or exacerbated by stress and the need for frequent antibiotic use – both are common in people living with SCI (Schönenberg et al., 2014; Wong et al., 2017) (Fig. 1).

Gut dysbiosis after SCI: Pre-clinical studies

SCI-induced gut dysbiosis has been documented in multiple independent pre-clinical studies and, in most cases, 16 s rRNA sequencing was used to analyze the composition and relative abundance of bacteria in fecal samples (Jing et al., 2019; Kigerl et al., 2016; Myers et al., 2019; O'Connor et al., 2018; Schmidt et al., 2020). In SCI mice, robust and lasting

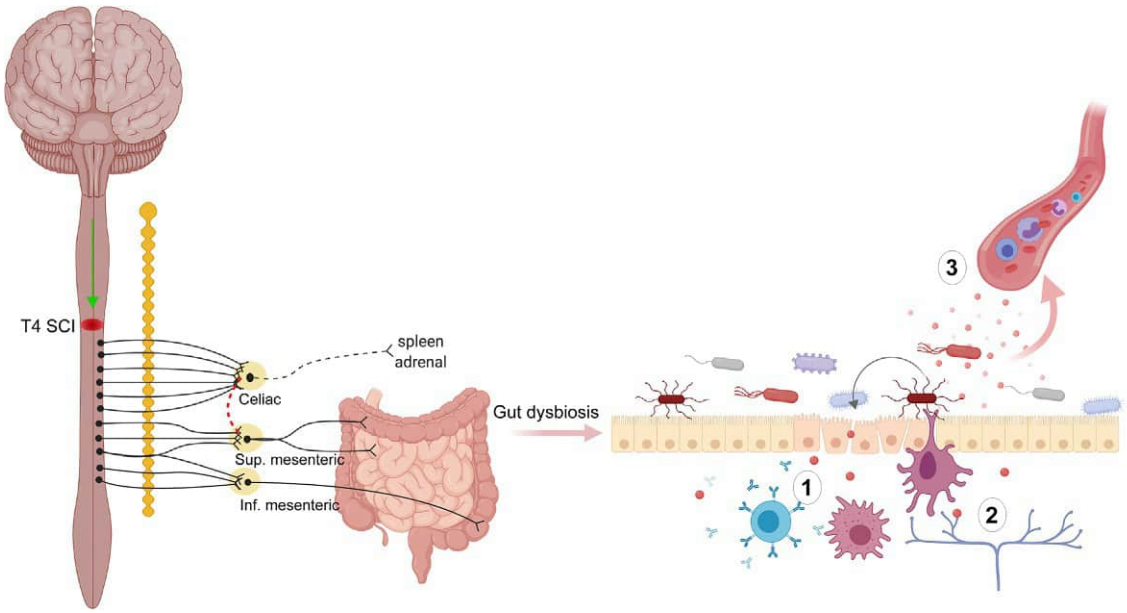

FIG. 1 Spinal cord injury disrupts autonomic control over the gastrointestinal tract, leading to the development of gut dysbiosis. Gut dysbiosis can influence (1) immune system function, (2) vagal signaling, and (3) circulating metabolites that can contribute to the development of common SCI-associated disorders such as immune dysfunction, metabolic and cardiovascular disease, pain, and mood disorders. Created with BioRender.com.

gut dysbiosis develops and is characterized by inverse changes in *Bacteroidales* and *Clostridiales*, the two most prevalent bacterial taxa in mouse gut: *Bacteroidales* decreases while *Clostridiales* increases after SCI (Jing et al., 2019; Kigerl et al., 2016). Minor taxa (*Anaeroplasmatales*, *Turicibacterales* and *Lactobacillales)* also are affected by SCI (Jing et al., 2019; Kigerl et al., 2016). The relative abundance of bacteria from the phylum *Proteobacteria* also increases after SCI in mice (Myers et al., 2019). Gut dysbiosis has similarly been described in SCI rats (O'Connor et al., 2018; Schmidt et al., 2020), in some cases lasting at least 8 weeks post-injury (O'Connor et al., 2018).

In addition to changing the composition and relative abundance of bacteria, SCI increases gut permeability and alters the expression of tight junction proteins in the gut (Jing et al., 2019; Kigerl et al., 2016). Increased gut permeability likely contributes to bacterial translocation (Bai et al., 2011; Kigerl et al., 2016; Liu et al., 2004) and increased levels of circulating endotoxin after SCI (Myers et al., 2019). Combined with gut dysbiosis, bacterial translocation and circulating endotoxin may cause systemic inflammation and contribute to the development of comorbidities associated with SCI, including increased incidence of cardiovascular disease, depression/anxiety, NAFLD, and metabolic syndrome (Foster & McVey Neufeld, 2013; Gérard, 2016; Safari & Gérard, 2019). Schmidt et al. showed that gut dysbiosis contributes to anxiety in SCI rats and this can be reversed by treating SCI rats with a fecal transplant derived from healthy donor rats (Schmidt et al., 2020). Fecal transplantation has been shown to normalize gut dysbiosis and confer therapeutic benefits in recurrent *Clostridium difficile* infection and inflammatory bowel disease. Fecal transplantation is also under investigation for Multiple Sclerosis, Parkinson's Disease, autism, and metabolic syndrome (Vendrik et al., 2020).

The onset of gut dysbiosis after SCI is also associated with intestinal inflammation. Cytokine expression increases in the colon and the GALT after SCI (Jing et al., 2019; Kigerl et al., 2016; O'Connor et al., 2018), and these changes correlate with changes in bacterial taxa (Jing et al., 2019; O'Connor et al., 2018). Increased intestinal permeability and CCL2 expression positively correlate with the abundance of *Clostridiales* and negatively correlate with *Lactobacillales* (Jing et al., 2019). Expression of IL-1β, IL-12, and CXCL2 also correlate with changes in microbiota after SCI (O'Connor et al., 2018). Increased intestinal inflammation, along with the impaired function of the gut microbiome, may exacerbate the gastrointestinal motility deficits caused by SCI. Treatments that reverse gut dysbiosis have been shown to increase gastrointestinal transit time in SCI mice (Jing et al., 2019).

Recently, it has become possible to predict the functional implications of changes in microbial community structure after SCI. Indeed, computational tools now exist that can predict microbial function from 16 s rRNA data (i.e., PICRUSt) or more directly from whole-genome metagenomic sequencing (Langille et al., 2013; Niu et al., 2017). Using these tools, consistent changes were noted in both SCI rats and mice. Notably, SCI appears to affect the gut microbiota's ability to carry out normal carbohydrate metabolism, bile acid biosynthesis, metabolism of cofactors and vitamins, and lipid biosynthesis

(Schmidt et al., 2020; Du et al., 2021). Using metagenome-assembled genomes (MAGs), Du et al. found that a subset of these functions can be attributed to discrete bacterial taxa. Thus, using data from MAGs, one can identify then target specific bacterial taxa to improve or block microbial functions that influence host physiology (Frioux, Singh, Korcsmaros, & Hildebrand, 2020).

So far, only a limited number of pre-clinical studies have tried to manipulate the gut microbiota for therapeutic gain, although those studies have yielded promising results. Post-injury feeding of a medical-grade probiotic formula improved locomotor recovery, reduced lesion pathology and modulated the immune response in the GALT (Kigerl et al., 2016). Fecal suspensions procured from healthy rat donors then transplanted into SCI rats ameliorated SCI-induced gut dysbiosis and reduced anxiety-like behaviors caused by SCI (Schmidt et al., 2020). Melatonin treatment reduced gut dysbiosis, improved gastrointestinal transit time, and modulated intestinal inflammation (Jing et al., 2019). Additional research is needed to further advance our understanding of how the gut microbiota influences neurological recovery and systemic comorbidities after SCI.

Gut dysbiosis after SCI: Clinical studies

SCI also causes gut dysbiosis in humans (Gungor, Adiguzel, Gursel, Yilmaz, & Gursel, 2016; Li et al., 2020; Lin et al., 2020; Zhang et al., 2019, 2018). SCI-induced alterations in the human gut microbiota are long-lasting; the abundance of butyrate-producing gut bacteria was found to be reduced for at least 1-year post-SCI (Gungor et al., 2016). Butyrate and other short-chain fatty acids (SCFAs) have potent immune-modulatory properties and are critical for the maintenance of intestinal epithelium homeostasis (Tan et al., 2014). Other serum metabolites also change after SCI and these changes correlate with altered microbial community structure. For example, Zhang et al. showed that serum glucose, HDL, APOA1, and LPA levels correlate with changes in gut microbiota (based on 16S rRNA sequencing data). Then, using predictive algorithms, they showed that KEGG pathways related to lipid metabolism and fatty acid metabolism decrease in the microbiota of SCI individuals (Zhang et al., 2019). Li et al. reported that bacterial families associated with impaired glucose and lipid metabolism and intestinal inflammation increase in the gut in individuals with SCI (compared to able-bodied controls) (Li et al., 2020). Collectively, these studies suggest that various serum metabolites may serve as biomarkers of SCI-induced changes in gut microbiota and that gut dysbiosis may contribute to metabolic disorders that occur after SCI. Indeed, metabolic function is significantly impaired in paraplegics and tetraplegics; both have higher body fat content compared to able-bodied individuals (Gater, 2007; Gorgey et al., 2014; Gorgey & Gater, 2011). Future studies should determine if gut dysbiosis is causal in the high incidence of metabolic disease and adiposity in SCI individuals (Gorgey and Gater, 2007; Gorgey et al., 2014; Gorgey & Gater, 2011; Manns, McCubbin, & Williams, 2005; Maruyama et al., 2008; Nelson et al., 2007).

Demographic factors (injury level, injury completeness, age, sex)

The magnitude of change and relative composition of the gut microbiota may vary as a function of spinal injury level. Indeed, injuries occurring at high spinal levels will cause more significant or more complete deficits in autonomic tone than an SCI that occurs at lower spinal levels (Holmes & Blanke, 2019). That is because SPNs controlling the small and large intestines are located primarily in thoracic spinal segments T5–10 and T10-L4, respectively (Fig. 1) (Browning & Travagli, 2014; Levatte et al., 1998; Mabon et al., 1997). Consequently, an SCI at or above the most rostrally located SPNs will remove all supraspinal control over spinal sympathetic reflexes, including those that regulate the GI tract. Indeed, using metagenomics to sequence fecal samples obtained from mice with a T4 or T10 SCI, we recently discovered that SCI-induced changes in gut microbial community structure are spinal level-dependent (Du et al., 2021). Although the composition of the gut microbiota in SCI mice was distinct from sham-operated mice, regardless of injury level, gut dysbiosis was exacerbated in T4 SCI mice. These level-dependent differences were evident when evaluating bacterial, functional, and viral components of the microbiome (Du et al., 2021). In clinical studies, gut microbiota composition was also shown to vary as a function of injury level; SCI at cervical or upper thoracic levels produced a gut microbiota that was distinct from that found in individuals with lower thoracic or lumbar SCI (Gungor et al., 2016; Zhang et al., 2018).

Age and sex also influence gut microbial composition (Jašarević, Morrison, & Bale, 2016; Markle et al., 2013; Sheng et al., 2017; Stilling et al., 2015; Thevaranjan et al., 2017). SCI still occurs most often in young adults, but the average age at the time of injury has steadily increased from 29 in the 1970s to 43 in 2015 (National Spinal Cord Injury Statistical Center, 2020). Advanced age at the time of injury is a risk factor for the poorer outcome and increased complications (Devivo, Kartus, Rutt, Stover, & Fine, 1990; Wilson, Cadotte, & Fehlings, 2012). To date, there has been no attempt to evaluate how age at the time of SCI influences the development of gut dysbiosis nor have there been studies that determine

how the gut microbiota changes as people age with SCI. Given the effects of SCI-induced dysautonomia on metabolism, immune function, and gastrointestinal function, the progression of gut dysbiosis in SCI individuals as they age is expected to be unique when compared with age-matched, able-bodied individuals. Likewise, no studies have evaluated whether gut dysbiosis is similarly affected by SCI in males and females. Since published data indicate that the gut microbiota affects serotonin synthesis, metabolism, and neurotransmission differently in males and females, there is reason to predict sex-dependent differences in gut microbial homeostasis after SCI (Bolnick et al., 2014; Clarke et al., 2013; O'Mahony, Clarke, Borre, Dinan, & Cryan, 2015).

Gut dysbiosis and health/disease after SCI

Because gut microbes normally affect the physiological function of organ systems throughout the body, the onset of gut dysbiosis after SCI is likely to cause or contribute to various comorbidities that affect this patient population. Indeed, gut dysbiosis affects able-bodied individuals and has been linked to major depressive disorders and gastrointestinal and metabolic diseases (e.g., obesity, diabetes, Chron's disease, irritable bowel syndrome, etc.) (Carding, Verbeke, Vipond, Corfe, & Owen, 2015; Hsiao et al., 2013; O'Mahony et al., 2015). Dysbiosis and "leaky gut" also have been implicated in the onset and progression of chronic fatigue syndrome (CFS). Chronic fatigue syndrome (CFS) is a multi-system disease characterized by persistent fatigue, cognitive impairment, mood changes, and GI disturbances. Many of these same symptoms also plague people with SCI (Altindag, Karagullu, & Gur, 2014; Jensen, Hirsh, Molton, & Bamer, 2009; Wulff, Gatti, Wettstein, & Foster, 2010). Fatigue affects most SCI individuals (Jensen, Kuehn, Amtmann, & Cardenas, 2007). Fatigue after SCI is contributed to by changes in physiological and behavioral factors including innate neuromuscular ability, motivation, resilience, depressive-like mood swings and is influenced by one's overall sense of the quality of life (Craig, Tran, Wijesuriya, & Middleton, 2012; Wijesuriya, Tran, Middleton, & Craig, 2012). As such, fatigue is closely linked to social and mental health after SCI and gut dysbiosis can significantly affect mental health (Foster & McVey Neufeld, 2013; Jensen et al., 2007).

SCI also enhances the risk or frequency of developing heart disease or metabolic dysfunction (Bauman & Spungen, 2000; Inskip et al., 2010). Although the increased incidence of obesity, diabetes, and liver dysfunction after SCI is often attributed to inactivity, changes in muscle mass and adiposity as well as the onset of insulin resistance and hyperinsulinemia are delayed consequences of SCI. Similarly, cardiovascular disease and the effects of chronic low-grade systemic inflammation do not develop soon after SCI. SCI individuals also suffer from dysfunctional immune responses that exacerbate the above conditions and impair host defense, rendering SCI individuals more susceptible to infection (Brommer et al., 2016; DeVivo, Black, & Stover, 1993; Riegger et al., 2009). This multi-organ "failure", is a slow and insidious disease process that develops in parallel with GI dysfunction, dysbiosis and leaky gut. Although a causal relationship remains unproven, existing therapies could be used to reveal the effects of gut dysbiosis on these disease states. For example, oral probiotics can restore homeostasis to the gut microbiota and in turn, have been shown to positively affect nutrient absorption, mental health, whole-body metabolism, and systemic immune function (Frei, Akdis, & O'mahony, 2015; Judkins, Archer, Kramer, & Solch, 2020; Martin et al., 2008; Mörkl, Butler, Holl, Cryan, & Dinan, 2020). A similar approach might be used to treat people with SCI. We have just begun to understand how changes in the gut microbiome may impact the health of the CNS. Applying newer metagenomic and "multi-omic" tools, it should be possible to reveal how novel, rapidly evolving ecological niches that form in the gut under conditions of dysbiosis, regulate the function and phenotype of cells in the brain or spinal cord. For example, the gut microbiome is already known to shape the transcriptome of adult microglia (Thion et al., 2018), and gut microbiota can alter microglial structure and maturity (Erny et al., 2015). In germ-free mice, adding discrete microbial-derived metabolites (e.g., short-chain fatty acids), even in the absence of the bacteria themselves, can reverse deficits in microglia function (Erny et al., 2015). Under physiological conditions, the gut microbiome regulates the metabolism of several key neurotransmitters. As such, the gut microbiome is intimately associated with normal CNS structure/function. Indeed, most (~90%) of the body's serotonin is produced in the gut (Gershon & Tack, 2007), and its synthesis is regulated by gut microbiota (Wikoff et al., 2009; Yano et al., 2015). Microbe-dependent metabolism of tryptophan also produces small molecules that can directly influence astrocyte function and alter the glial response to neuroinflammation (Rothhammer et al., 2018, 2016). As research continues to identify small molecules produced by gut bacteria and the genes responsible for their production, it will likely become feasible to manipulate these bacteria or their "drug-like" payloads to treat a range of human neurological disorders. Indeed, gut dysbiosis occurs in people with multiple sclerosis, Parkinson's disease, Alzheimer's disease, epilepsy, autism spectrum disorders, and after stroke and brain injury (Cryan, O'Riordan, Sandhu, Peterson, & Dinan, 2020). Interventional trials using probiotics or diet interventions to treat gut dysbiosis have already shown beneficial effects on various clinical aspects of multiple sclerosis, Parkinson's disease, Alzheimer's disease, autism spectrum disorders, and epilepsy (Cryan et al., 2020) demonstrating the breadth of gut microbe effects on brain function.

Mini-dictionary of terms

Gut microbiota: the bacteria, viruses, fungi, and archaea that live in the gastrointestinal tract.
Gut microbiome: the collective genome of the gut microbiota.
Gut dysbiosis: an imbalance in the normal community structure of gut microbes.
Bacterial translocation: the process of gut microbiota moving from the intestinal lumen across epithelial cells into lymphatics, blood, or other tissues in the body.
GALT: The lymphoid tissues, primarily the mesenteric lymph nodes and Peyer's patches, that reside in the gastrointestinal tract.
Dysautonomia: A composite of medical conditions caused by disruption of normal autonomic nervous system function.

Key facts of the gut microbiome

- The gastrointestinal tract is inhabited by trillions of microbes called the gut microbiota. Most of these microbes are located in the colon.
- The collective genomes of these microbes in the gut microbiome, and these genes outnumber genes in the human genome 150:1
- Gut microbiota harvest energy from food, improve gut motiligy, reinforce the gut barrier, and produce metabolites, vitamins and hormones that are important for health.
- Disruption of the composition of gut microbiota is called *gut dysbiosis*. Gut dysbiosis has been linked to the development or worsening of many health conditionings, including those that affect the CNS.

Summary points

- The gut microbiota affects the metabolic function, mental health, and immune function of the host.
- The gut microbiota communicates to the CNS through immune function, the vagus nerve, and microbial-derived metabolites in the circulation.
- Gut dysbiosis develops after SCI in pre-clinical and clinical studies
- Gut dysbiosis correlates with increased intestinal permeability and inflammation after SCI
- Gut dysbiosis is observed in many CNS diseases, and therapies directed at treating gut dysbiosis are beneficial in multiple sclerosis, Parkinson's disease, epilepsy, and autism.

References

Altindag, O., Karagullu, H., & Gur, A. (2014). Sleep disturbances in patients with spinal cord injury. *Orthopedic & Muscular System: Current Research*, *3*, 164.

Bai, C., An, H., Wang, S., Jiang, D., Fan, W., & Nie, H. (2011). Treatment and prevention of bacterial translocation and endotoxemia with stimulation of the sacral nerve root in a rabbit model of spinal cord injury. *Spine (Phila Pa 1976)*, *36*, 363–371.

Bailey, M. T., Dowd, S. E., Galley, J. D., Hufnagle, A. R., Allen, R. G., & Lyte, M. (2011). Exposure to a social stressor alters the structure of the intestinal microbiota: Implications for stressor-induced immunomodulation. *Brain, Behavior, and Immunity*, *25*, 397–407.

Bailey, M. T., Dowd, S. E., Parry, N. M., Galley, J. D., Schauer, D. B., & Lyte, M. (2010). Stressor exposure disrupts commensal microbial populations in the intestines and leads to increased colonization by *Citrobacter rodentium*. *Infection and Immunity*, *78*, 1509–1519.

Balmer, M. L., Slack, E., de Gottardi, A., Lawson, M. A., Hapfelmeier, S., Miele, L., et al. (2014). The liver may act as a firewall mediating mutualism between the host and its gut commensal microbiota. *Science Translational Medicine*, *6*, 237.

Balzan, S., de Almeida Quadros, C., de Cleva, R., Zilberstein, B., & Cecconello, I. (2007). Bacterial translocation: Overview of mechanisms and clinical impact. *Journal of Gastroenterology and Hepatology*, *22*, 464–471.

Bauman, W. A., & Spungen, A. M. (2000). Metabolic changes in persons after spinal cord injury. *Physical Medicine and Rehabilitation Clinics of North America*, *11*, 109–140.

Benakis, C., Brea, D., Caballero, S., Faraco, G., Moore, J., Murphy, M., et al. (2016). Commensal microbiota affects ischemic stroke outcome by regulating intestinal γδ T cells. *Nature Medicine*, *22*, 516–523.

Bercik, P., Verdu, E. F., Foster, J. A., Macri, J., Potter, M., Huang, X., et al. (2010). Chronic gastrointestinal inflammation induces anxiety-like behavior and alters central nervous system biochemistry in mice. *Gastroenterology*, *139*, 2102–2112.

Berer, K., Mues, M., Koutrolos, M., Rasbi, Z. A., Boziki, M., Johner, C., et al. (2011). Commensal microbiota and myelin autoantigen cooperate to trigger autoimmune demyelination. *Nature*, *479*, 538–541.

Bolnick, D. I., Snowberg, L. K., Hirsch, P. E., Lauber, C. L., Org, E., Parks, B., et al. (2014). Individual diet has sex-dependent effects on vertebrate gut microbiota. *Nature Communications*, *5*, 4500.

Brommer, B., Engel, O., Kopp, M. A., Watzlawick, R., Müller, S., Prüss, H., et al. (2016). Spinal cord injury-induced immune deficiency syndrome enhances infection susceptibility dependent on lesion level. *Brain*, *139*, 692–707.

Browning, K. N., & Travagli, R. A. (2014). Central nervous system control of gastrointestinal motility and secretion and modulation of gastrointestinal functions. *Comprehensive Physiology*, *4*, 1339–1368.

Cao, S., Feehley, T. J., & Nagler, C. R. (2014). The role of commensal bacteria in the regulation of sensitization to food allergens. *FEBS Letters*, *588*(22), 4258–4266.

Carding, S., Verbeke, K., Vipond, D. T., Corfe, B. M., & Owen, L. J. (2015). Dysbiosis of the gut microbiota in disease. *Microbial Ecology in Health and Disease*, *26*, 26191.

Cervi, A. L., Lukewich, M. K., & Lomax, A. E. (2014). Neural regulation of gastrointestinal inflammation: Role of the sympathetic nervous system. *Autonomic Neuroscience*, *182*, 83–88.

Clarke, G., Grenham, S., Scully, P., Fitzgerald, P., Moloney, R. D., Shanahan, F., et al. (2013). The microbiome-gut-brain axis during early life regulates the hippocampal serotonergic system in a sex-dependent manner. *Molecular Psychiatry*, *18*, 666–673.

Clarke, G., Stilling, R. M., Kennedy, P. J., Stanton, C., Cryan, J. F., & Dinan, T. G. (2014). Gut microbiota: The neglected endocrine organ. *Molecular Endocrinology*, *28*(8), 1221–1238.

Collins, S. M., Surette, M., & Bercik, P. (2012). The interplay between the intestinal microbiota and the brain. *Nature Reviews. Microbiology*, *10*, 735–742.

Craig, A., Tran, Y., Wijesuriya, N., & Middleton, J. (2012). Fatigue and tiredness in people with spinal cord injury. *Journal of Psychosomatic Research*, *73*, 205–210.

Crumeyrolle-Arias, M., Jaglin, M., Bruneau, A., Vancassel, S., Cardona, A., Daugé, V., et al. (2014). Absence of the gut microbiota enhances anxiety-like behavior and neuroendocrine response to acute stress in rats. *Psychoneuroendocrinology*, *42*, 207–217.

Cryan, J. F., O'Riordan, K. J., Sandhu, K., Peterson, V., & Dinan, T. G. (2020). The gut microbiome in neurological disorders. *Lancet Neurology*, *9*(2), 179–194.

de Theije, C. G., Wopereis, H., Ramadan, M., van Eijndthoven, T., Lambert, J., Knol, J., et al. (2014). Altered gut microbiota and activity in a murine model of autism spectrum disorders. *Brain, Behavior, and Immunity*, *37*, 197–206.

DeVivo, M. J., Black, K. J., & Stover, S. L. (1993). Causes of death during the first 12 years after spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *74*, 248–254.

Devivo, M. J., Kartus, P. L., Rutt, R. D., Stover, S. L., & Fine, P. R. (1990). The influence of age at time of spinal cord injury on rehabilitation outcome. *Archives of Neurology*, *47*, 687–691.

Donaldson, G. P., Lee, S. M., & Mazmanian, S. K. (2016). Gut biogeography of the bacterial microbiota. *Nature Reviews. Microbiology*, *14*, 20–32.

Du, J., Zayed, A. A., Kigerl, K. A., Zane, K., Sullivan, M. B., & Popovich, P. G. (2021). Spinal cord injury changes the structure and functional potential of gut bacterial and viral communities in a spinal-level dependent manner. *mSystems*, *6*(3). https://doi.org/10.1128/mSystems.01356-20, e01356-20.

El Aidy, S., van den Bogert, B., & Kleerebezem, M. (2015). The small intestine microbiota, nutritional modulation and relevance for health. *Current Opinion in Biotechnology*, *32*, 14–20.

Elenkov, I. J., Wilder, R. L., Chrousos, G. P., & Vizi, E. S. (2000). The sympathetic nerve—An integrative interface between two supersystems: The brain and the immune system. *Pharmacological Reviews*, *52*, 595–638.

Erny, D., de Angelis, A. L., Mahlakoiv, T., Buch, T., Chun, E., Schwierzeck, V., et al. (2015). Host microbiota constantly control maturation and function of microglia in the CNS. *Nature Neuroscience*, *18*, 965–977.

Felten, D. L., Ackerman, K. D., Wiegand, S. J., & Felten, S. Y. (1987). Noradrenergic sympathetic innervation of the spleen: I. Nerve fibers associate with lymphocytes and macrophages in specific compartments of the splenic white pulp. *Journal of Neuroscience Research*, *18*(28–36), 118–121.

Felten, S. Y., & Olschowka, J. (1987). Noradrenergic sympathetic innervation of the spleen: II. Tyrosine hydroxylase (TH)-positive nerve terminals form synapticlike contacts on lymphocytes in the splenic white pulp. *Journal of Neuroscience Research*, *18*, 37–48.

Forsythe, P., Bienenstock, J., & Kunze, W. A. (2014). Vagal pathways for microbiome-brain-gut axis communication. *Advances in Experimental Medicine and Biology*, *817*, 115–133.

Foster, J. A., & McVey Neufeld, K. A. (2013). Gut-brain axis: How the microbiome influences anxiety and depression. *Trends in Neurosciences*, *36*, 305–312.

Frei, R., Akdis, M., & O'mahony, L. (2015). Prebiotics, probiotics, synbiotics, and the immune system: Experimental data and clinical evidence. *Current Opinion in Gastroenterology*, *31*, 153–158. 1.

Frioux, C., Singh, D., Korcsmaros, T., & Hildebrand, F. (2020). From bag-of-genes to bag-of-genomes: Metabolic modelling of communities in the era of metagenome-assembled genomes. *Computational and Structural Biotechnology Journal*, *18*, 1722–1734.

Furness, J. B., & Costa, M. (1974). The adrenergic innervation of the gastrointestinal tract. *Ergebnisse der Physiologie, biologischen Chemie und experimentellen Pharmakologie*, *69*(0), 2–51.

Gater, D. R. (2007). Obesity after spinal cord injury. *Physical Medicine and Rehabilitation Clinics of North America*, *18*(333–51), vii.

Gérard, P. (2016). Gut microbiota and obesity. *Cellular and Molecular Life Sciences*, *73*(1), 147–162.

Gershon, M. D., & Tack, J. (2007). The serotonin signaling system: From basic understanding to drug development for functional GI disorders. *Gastroenterology*, *132*, 397–414.

Gill, S. R., Pop, M., Deboy, R. T., Eckburg, P. B., Turnbaugh, P. J., Samuel, B. S., et al. (2006). Metagenomic analysis of the human distal gut microbiome. *Science*, *312*(5778), 1355–1359.

Gorgey, A. S., Dolbow, D. R., Dolbow, J. D., Khalil, R. K., Castillo, C., & Gater, D. R. (2014). Effects of spinal cord injury on body composition and metabolic profile—Part I. *The Journal of Spinal Cord Medicine*, *37*(6), 693–702.

Gorgey, A. S., & Gater, D. R. (2007). Prevalence of obesity after spinal cord injury. *Topics in Spinal Cord Injury Rehabilitation*, *12*, 1–7.
Gorgey, A. S., & Gater, D. R. (2011). Regional and relative adiposity patterns in relation to carbohydrate and lipid metabolism in men with spinal cord injury. *Applied Physiology, Nutrition, and Metabolism*, *36*, 107–114.
Gu, S., Chen, D., Zhang, J. N., Lv, X., Wang, K., Duan, L. P., et al. (2013). Bacterial community mapping of the mouse gastrointestinal tract. *PLoS One*, *8*, e74957.
Gungor, B., Adiguzel, E., Gursel, I., Yilmaz, B., & Gursel, M. (2016). Intestinal microbiota in patients with spinal cord injury. *PLoS One*, *11*, e0145878.
Hawrelak, J. A., & Myers, S. P. (2004). The causes of intestinal dysbiosis: A review. *Alternative Medicine Review*, *9*, 180–197.
Hill, D. A., & Artis, D. (2010). Intestinal bacteria and the regulation of immune cell homeostasis. *Annual Review of Immunology*, *28*, 623–667.
Hollister, E. B., Gao, C., & Versalovic, J. (2014). Compositional and functional features of the gastrointestinal microbiome and their effects on human health. *Gastroenterology*, *146*, 1449–1458.
Holmes, G. M., & Blanke, E. N. (2019). Gastrointestinal dysfunction after spinal cord injury. *Experimental Neurology*, *320*, 113009.
Hooper, L. V., Littman, D. R., & Macpherson, A. J. (2012). Interactions between the microbiota and the immune system. *Science*, *336*, 1268–1273.
Hou, S., & Rabchevsky, A. G. (2014). Autonomic consequences of spinal cord injury. *Comprehensive Physiology*, *4*, 1419–1453.
Hsiao, E. Y., McBride, S. W., Hsien, S., Sharon, G., Hyde, E. R., McCue, T., et al. (2013). Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. *Cell*, *155*, 1451–1463.
Inskip, J., Plunet, W., Ramer, L., Ramsey, J. B., Yung, A., Kozlowski, P., et al. (2010). Cardiometabolic risk factors in experimental spinal cord injury. *Journal of Neurotrauma*, *27*, 275–285.
Jašarević, E., Morrison, K. E., & Bale, T. L. (2016). Sex differences in the gut microbiome—Brain axis across the lifespan. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *371*(1688), 20150122.
Jensen, M. P., Hirsh, A. T., Molton, I. R., & Bamer, A. M. (2009). Sleep problems in individuals with spinal cord injury: Frequency and age effects. *Rehabilitation Psychology*, *54*, 323–331.
Jensen, M. P., Kuehn, C. M., Amtmann, D., & Cardenas, D. D. (2007). Symptom burden in persons with spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *88*, 638–645.
Jing, Y., Yang, D., Bai, F., Zhang, C., Qin, C., Li, D., et al. (2019). Melatonin treatment alleviates spinal cord injury-induced gut dysbiosis in mice. *Journal of Neurotrauma*, *36*, 2646–2664.
Judkins, T. C., Archer, D. L., Kramer, D. C., & Solch, R. J. (2020). Probiotics, nutrition, and the small intestine. *Current Gastroenterology Reports*, *22*(1), 2.
Kigerl, K. A., Hall, J. C. E., Wang, L., Mo, X., Yu, Z., & Popovich, P. G. (2016). Gut dysbiosis impairs recovery after spinal cord injury. *The Journal of Experimental Medicine*, *213*, 2603–2620.
Kriegel, M. A., Sefik, E., Hill, J. A., Wu, H. J., Benoist, C., & Mathis, D. (2011). Naturally transmitted segmented filamentous bacteria segregate with diabetes protection in nonobese diabetic mice. *Proceedings of the National Academy of Sciences of the United States of America*, *108*, 11548–11553.
Langille, M. G. I., Zaneveld, J., Caporaso, J. G., McDonald, D., Knights, D., Reyes, J. A., et al. (2013). Predictive functional profiling of microbial communities using 16S rRNA marker gene sequences. *Nature Biotechnology*, *31*, 814–821.
Lee, Y. K., Menezes, J. S., Umesaki, Y., & Mazmanian, S. K. (2011). Proinflammatory T-cell responses to gut microbiota promote experimental autoimmune encephalomyelitis. *Proceedings of the National Academy of Sciences of the United States of America*, *108*(Suppl), 4615–4622.
Levatte, M. A., Mabon, P. J., Weaver, L. C., & Dekaban, G. A. (1998). Simultaneous identification of two populations of sympathetic preganglionic neurons using recombinant herpes simplex virus type 1 expressing different reporter genes. *Neuroscience*, *82*, 1253–1267.
Li, J., Van Der Pol, W., Eraslan, M., McLain, A., Cetin, H., Cetin, B., et al. (2020). Comparison of the gut microbiome composition among individuals with acute or long-standing spinal cord injury vs. able-bodied controls. *The Journal of Spinal Cord Medicine*, *4*, 1–9.
Lin, R., Xu, J., Ma, Q., Chen, M., Wang, L., Wen, S., et al. (2020). Alterations in the fecal microbiota of patients with spinal cord injury. *PLoS One*, *15*(8), e0236470.
Liu, J., An, H., Jiang, D., Huang, W., Zou, H., Meng, C., et al. (2004). Study of bacterial translocation from gut after paraplegia caused by spinal cord injury in rats. *Spine (Phila Pa 1976)*, *29*, 164–169.
Mabon, P. J., LeVatte, M. A., Dekaban, G. A., & Weaver, L. C. (1997). Identification of sympathetic preganglionic neurons controlling the small intestine in hamsters using a recombinant herpes simplex virus type-1. *Brain Research*, *753*, 245–250.
Macpherson, A. J., & Smith, K. (2006). Mesenteric lymph nodes at the center of immune anatomy. *The Journal of Experimental Medicine*, *203*, 497–500.
Manns, P. J., McCubbin, J. A., & Williams, D. P. (2005). Fitness, inflammation, and the metabolic syndrome in men with paraplegia. *Archives of Physical Medicine and Rehabilitation*, *86*, 1176–1181.
Markle, J. G. M., Frank, D. N., Mortin-Toth, S., Robertson, C. E., Feazel, L. M., Rolle-Kampczyk, U., et al. (2013). Sex differences in the gut microbiome drive hormone-dependent regulation of autoimmunity. *Science*, *339*, 1084–1088.
Martin, F. P. J., Wang, Y., Sprenger, N., Yap, I. K. S., Lundstedt, T., Lek, P., et al. (2008). Probiotic modulation of symbiotic gut microbial-host metabolic interactions in a humanized microbiome mouse model. *Molecular Systems Biology*, *4*, 157.
Maruyama, Y., Mizuguchi, M., Yaginuma, T., Kusaka, M., Yoshida, H., Yokoyama, K., et al. (2008). Serum leptin, abdominal obesity and the metabolic syndrome in individuals with chronic spinal cord injury. *Spinal Cord*, *46*, 494–499.
Mörkl, S., Butler, M. I., Holl, A., Cryan, J. F., & Dinan, T. G. (2020). Probiotics and the microbiota-gut-brain axis: Focus on psychiatry. *Current Nutrition Reports*, *9*, 171–182.
Myers, S. A., Gobejishvili, L., Saraswat Ohri, S., Garrett Wilson, C., Andres, K. R., Riegler, A. S., et al. (2019). Following spinal cord injury, PDE4B drives an acute, local inflammatory response and a chronic, systemic response exacerbated by gut dysbiosis and endotoxemia. *Neurobiology of Disease*, *124*, 353–363.

National Spinal Cord Injury Statistical Center. (2020). *Spinal cord injury facts and figures at a glance 2020 SCI data sheet*.

Nelson, M. D., Widman, L. M., Abresch, R. T., Stanhope, K., Havel, P. J., Styne, D. M., et al. (2007). Metabolic syndrome in adolescents with spinal cord dysfunction. *The Journal of Spinal Cord Medicine*, *30*(Suppl. 1), S127–S139.

Nicholson, J. K., Holmes, E., Kinross, J., Burcelin, R., Gibson, G., Jia, W., et al. (2012). Host-gut microbiota metabolic interactions. *Science*, *336*, 1262–1267.

Niu, S. Y., Yang, J., McDermaid, A., Zhao, J., Kang, Y., & Ma, Q. (2017). Bioinformatics tools for quantitative and functional metagenome and metatranscriptome data analysis in microbes. *Briefings in Bioinformatics*, *19*, 1415–1429.

O'Connor, G., Jeffrey, E., Madorma, D., Marcillo, A., Abreu, M. T., Deo, S. K., et al. (2018). Investigation of microbiota alterations and intestinal inflammation post-spinal cord injury in rat model. *Journal of Neurotrauma*, *35*, 2159–2166.

O'Mahony, S. M., Clarke, G., Borre, Y. E., Dinan, T. G., & Cryan, J. F. (2015). Serotonin, tryptophan metabolism and the brain-gut-microbiome axis. *Behavioural Brain Research*, *277*, 32–48.

Qualls-Creekmore, E., Tong, M., & Holmes, G. M. (2010). Time-course of recovery of gastric emptying and motility in rats with experimental spinal cord injury. *Neurogastroenterology and Motility*, *22*(62–9), e27–e28.

Riegger, T., Conrad, S., Schluesener, H. J., Kaps, H. P., Badke, A., Baron, C., et al. (2009). Immune depression syndrome following human spinal cord injury (SCI): A pilot study. *Neuroscience*, *158*, 1194–1199.

Rothhammer, V., Borucki, D. M., Tjon, E. C., Takenaka, M. C., Chao, C. C., Ardura-Fabregat, A., et al. (2018). Microglial control of astrocytes in response to microbial metabolites. *Nature*, *557*, 724–728.

Rothhammer, V., Mascanfroni, I. D., Bunse, L., Takenaka, M. C., Kenison, J. E., Mayo, L., et al. (2016). Type I interferons and microbial metabolites of tryptophan modulate astrocyte activity and central nervous system inflammation via the aryl hydrocarbon receptor. *Nature Medicine*, *22*, 586–597.

Round, J. L., & Mazmanian, S. K. (2009). The gut microbiota shapes intestinal immune responses during health and disease. *Nature Reviews. Immunology*, *9*, 313–323.

Rousseaux, C., Thuru, X., Gelot, A., Barnich, N., Neut, C., Dubuquoy, L., et al. (2007). *Lactobacillus acidophilus* modulates intestinal pain and induces opioid and cannabinoid receptors. *Nature Medicine*, *13*, 35–37.

Safari, Z., & Gérard, P. (2019). The links between the gut microbiome and non-alcoholic fatty liver disease (NAFLD). *Cellular and Molecular Life Sciences*, *76*(8), 1541–1558.

Schmidt, E. K. A., Torres-Espin, A., Raposo, P. J. F., Madsen, K. L., Kigerl, K. A., Popovich, P. G., et al. (2020). Fecal transplant prevents gut dysbiosis and anxiety-like behaviour after spinal cord injury in rats. *PLoS One*, *15*(1), e0226128.

Schönenberg, M., Reimitz, M., Jusyte, A., Maier, D., Badke, A., & Hautzinger, M. (2014). Depression, posttraumatic stress, and risk factors following spinal cord injury. *International Journal of Behavioral Medicine*, *21*(1), 169–176.

Sender, R., Fuchs, S., & Milo, R. (2016). Revised estimates for the number of human and bacteria cells in the body. *PLoS Biology*, *14*(8), e1002533.

Sheng, L., Jena, P. K., Liu, H. X., Kalanetra, K. M., Gonzalez, F. J., French, S. W., et al. (2017). Gender differences in bile acids and microbiota in relationship with gender dissimilarity in steatosis induced by diet and FXR inactivation. *Scientific Reports*, *7*, 1–12.

Stilling, R. M., Ryan, F. J., Hoban, A. E., Shanahan, F., Clarke, G., Claesson, M. J., et al. (2015). Microbes & neurodevelopment—Absence of microbiota during early life increases activity-related transcriptional pathways in the amygdala. *Brain, Behavior, and Immunity*, *50*, 209–220.

Sudo, N., Chida, Y., Aiba, Y., Sonoda, J., Oyama, N., Yu, X. N., et al. (2004). Postnatal microbial colonization programs the hypothalamic-pituitary-adrenal system for stress response in mice. *The Journal of Physiology*, *558*, 263–275.

Tan, J., McKenzie, C., Potamitis, M., Thorburn, A. N., Mackay, C. R., & Macia, L. (2014). The role of short-chain fatty acids in health and disease. *Advances in Immunology*, *121*, 91–119.

Tate, D. G., Forchheimer, M., Rodriguez, G., Chiodo, A., Cameron, A. P., Meade, M., et al. (2016). Risk factors associated with neurogenic bowel complications and dysfunction in spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *97*, 1679–1686.

Thevaranjan, N., Puchta, A., Schulz, C., Naidoo, A., Szamosi, J. C., Verschoor, C. P., et al. (2017). Age-associated microbial dysbiosis promotes intestinal permeability, systemic inflammation, and macrophage dysfunction. *Cell Host & Microbe*, *21*, 455–466.

Thion, M. S., Low, D., Silvin, A., Chen, J., Grisel, P., Schulte-Schrepping, J., et al. (2018). Microbiome influences prenatal and adult microglia in a sex-specific manner. *Cell*, *172*, 500–516.

Tilg, H., & Kaser, A. (2011). Gut microbiome, obesity, and metabolic dysfunction. *The Journal of Clinical Investigation*, *121*, 2126–2132.

Tillisch, K. (2014). The effects of gut microbiota on CNS function in humans. *Gut Microbes*, *5*(3), 404–410.

Vendrik, K. E. W., Ooijevaar, R. E., de Jong, P. R. C., Laman, J. D., van Oosten, B. W., van Hilten, J. J., et al. (2020). Fecal microbiota transplantation in neurological disorders. *Frontiers in Cellular and Infection Microbiology*, *10*, 98.

Wang, Y., & Kasper, L. H. (2014). The role of microbiome in central nervous system disorders. *Brain, Behavior, and Immunity*, *38*, 1–12.

Wijesuriya, N., Tran, Y., Middleton, J., & Craig, A. (2012). Impact of fatigue on the health-related quality of life in persons with spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *93*, 319–324.

Wikoff, W. R., Anfora, A. T., Liu, J., Schultz, P. G., Lesley, S. A., Peters, E. C., et al. (2009). Metabolomics analysis reveals large effects of gut microflora on mammalian blood metabolites. *Proceedings of the National Academy of Sciences of the United States of America*, *106*, 3698–3703.

Wilson, J. R., Cadotte, D. W., & Fehlings, M. G. (2012). Clinical predictors of neurological outcome, functional status, and survival after traumatic spinal cord injury: A systematic review. *Journal of Neurosurgery. Spine*, *17*, 11–26.

Winek, K., Engel, O., Koduah, P., Heimesaat, M. M., Fischer, A., Bereswill, S., et al. (2016). Depletion of cultivatable gut microbiota by broad-spectrum antibiotic pretreatment worsens outcome after murine stroke. *Stroke*, *47*, 1354–1363.

Wong, S., Santullo, P., Hirani, S. P., Kumar, N., Chowdhury, J. R., García-Forcada, A., et al. (2017). Use of antibiotics and the prevalence of antibiotic-associated diarrhoea in patients with spinal cord injuries: An international, multi-centre study. *Journal of Hospital Infection*, *97*(2), 146–152.

Wulff, K., Gatti, S., Wettstein, J. G., & Foster, R. G. (2010). Sleep and circadian rhythm disruption in psychiatric and neurodegenerative disease. *Nature Reviews. Neuroscience*, *11*, 589–599.

Yano, J. M., Yu, K., Donaldson, G. P., Shastri, G. G., Ann, P., Ma, L., et al. (2015). Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis. *Cell*, *161*, 264–276.

Zhang, C., Jing, Y., Zhang, W., Zhang, J., Yang, M., Du, L., et al. (2019). Dysbiosis of gut microbiota is associated with serum lipid profiles in male patients with chronic traumatic cervical spinal cord injury. *American Journal of Translational Research*, *11*, 4817–4834.

Zhang, C., Zhang, W., Zhang, J., Jing, Y., Yang, M., Du, L., et al. (2018). Gut microbiota dysbiosis in male patients with chronic traumatic complete spinal cord injury. *Journal of Translational Medicine*, *16*, 353.

Section D

Behavioral and psychological effects

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Chapter 37

Risk factors and predictors of depression after spinal cord injury: Emphasis on the inflammatory process

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Abbreviations

5-HT	5-hydroxtryptamine or serotonin
ACTH	adrenocorticotropic hormone
AIS	American spinal injury association impairment scale
ASIA	American spinal injury association
BDI	beck depression inventory
CEDS	center for epidemiological depression scale
CRH	corticotropin-releasing hormone
CSS	clinically significant symptomatology
GC	glucocorticoids
GM-CSF	granulocyte macrophage-colony stimulating factor
GR	glucorticoids receptor
HADS	hospital anxiety and depression scale
HPA	hypothalamus-pituitary-adrenal axis
IDO	indoleamine 2,3-dioxygenase
IL	interleukins
IL-2R	interleukin-2 receptor
INF-(γ and α)	interferon-gamma and -alpha
ISNCSCI	international standards for neurological classification of spinal cord injury
MDD	mood depressive disorders
OAHMQ	older adult health and mood questionnaire
PHQ-9	patient health questionnaire–9
PMD	probable major depression
SCI	spinal cord injury
SCI-QOL	spinal cord injury–quality of life
TNF-α	tumor necrosis factor-alpha
YLD	years lived with disability

Introduction

Spinal cord injury (SCI) is a significant public health concern that imposes many challenges on survivors. Individuals face physical limitations, including pain, loss of functional independence, and reduced self-care capacity, with a significant number of patients suffering from mental disorders, such as depression (Bombardier, Richards, Krause, Tulsky, & Tate, 2004; Hoffman, Bombardier, Graves, Kalpakjian, & Krause, 2011; Oh, Shin, Paik, Yoo, & Ku, 2006). Table 1 provides more detail on the clinical aspects of individuals with SCI.

Cellular, Molecular, Physiological, and Behavioral Aspects of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822427-4.00037-X

TABLE 1 Summary of clinical aspects encountered in individuals with spinal cord injury.

Motor outcomes	Muscle weakness	Sensory outcomes	Loss of light touch sensation	Autonomic outcomes	Bowel dysfunction	Mental and cognitive outcomes	Depression
	Muscle atrophy		Loss of proprioception		Bladder dysfunction		Anxiety
	Muscle contracture		Paresthesia		Autonomic dysreflexia		Deficit in information processing speed
	Spasticity		Chronic pain		Orthostatic hypotension		Deficit in learning
	Fatigue		Pressure ulcer		Sexual dysfunction		Decline in verbal fluency

Source: Authors based in Cieza, A., Kirchberger, I., Biering-Sørensen, F., Baumberger, M., Charlifue, S., Post, M. W., et al. (2010). ICF Core sets for individuals with spinal cord injury in the long-term context. *Spinal Cord, 48*(4), 305–312 and Chiaravalloti, N. D., Weber, E., Wylie, G., Dyson-Hudson, T., & Wecht, J. M. (2020). Patterns of cognitive deficits in persons with spinal cord injury as compared with both age-matched and older individuals without spinal cord injury. *The Journal of Spinal Cord Medicine, 43*(1), 88–97.

Research has demonstrated that post-SCI depression negatively affects rehabilitation (Dryden et al., 2005) and the individual's reintegration into society (Craig, Nicholson Perry, Guest, Tran, & Middleton, 2015). This concerning scenario underlines the importance of adequate clinical management of depression, including diagnosis and treatment, in preventing the worsening of adverse motor outcomes in SCI patients.

Although the diagnosis of depression has improved, its etiological factors are still poorly known. Significant efforts have been made to establish a relationship between the physical impairment (injury level and severity) and post-SCI depression (Arango-Lasprilla, Ketchum, Starkweather, Nicholls, & Wilk, 2011; Bombardier et al., 2012; Shin, Goo, Yu, Kim, & Yoon, 2012) but conclusions are yet to be consistent. In contrast, biological factors such as inflammation, which accompanies SCI, have a well-known role in depression (Capuron & Miller, 2011; Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008).

In humans with SCI, increased circulating pro-inflammatory mediators, such as interleukin (IL)-2, IL-6, IL-1α, and TNF-α (tumor necrosis factor-alpha) (Davies, Hayes, & Dekaban, 2007; Gibson, Buchholz, & Ginis, 2008; Hayes et al., 2002), have been previously evidenced and associated with depressive symptoms after SCI (Allison & Ditor, 2015). Similarly, SCI animal models have revealed a correlation between inflammation and depression-like behavior (Do Espírito Santo et al., 2019; Maldonado-Bouchard et al., 2016), and these findings led to the inflammatory process being recently recognized as an etiological agent of depression post-SCI.

This chapter will address the role of the systemic inflammatory process as a robust biological predictor and summarize the demographic, social, environmental, and behavioral risk factors for the development of depression after SCI.

Pathophysiological overview: From local inflammation to systemic inflammation after SCI

Spinal cord injury is a clinical condition with no cure and is usually associated with damage that culminates in numerous symptoms responsible for chronic disability in survivors. As a result, extensive research has been proposed and focused on restorative treatments, such as cellular and molecular therapies and rehabilitation strategies. According to the National Spinal Cord Injury Statistical Center, the incidence of SCI is approximately 54 cases/million population/year in the United States of America, with a prevalence of 285 thousand individuals injured every year (NSCISC, 2016). Furthermore, SCI contributes to increased morbidity and mortality rates in both men and women (aged 32.4 years), although more men are affected than women (ratio 4:1) (Rahimi-Movaghar et al., 2013).

This neurological condition is caused by disruption of ascending and descending white matter tracts in the spinal cord after SCI and is classified using the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) (ASIA and ISCoS, 2019). This standardized method, in association with the American Spinal Injury Association (ASIA) Impairment Scale (AIS), defines the neurological level of injury (tetraplegia or paraplegia) and severity (complete or incomplete) of SCI (Kirshblum, Snider, Rupp, & Read, 2020).

Traumatic SCI is a predominant form of SCI (Halvorsen et al., 2019) whose pathophysiology involves primary mechanical injury (e.g., contusion, compression, and/or laceration) to the spinal cord parenchyma (Kakulas, 2019) and secondary endogenous lesion, which leads to severe tissue damage mainly due to the inflammatory process. Regardless of the type of primary mechanical injury, the initial impact on the spinal cord causes edema, hemorrhage, and necrosis (Kakulas & Kaelan, 2015). Moreover, mRNA transcript levels of pro-inflammatory cytokines increase in the immediate stage of SCI (Bartholdi & Schwab, 1997; Salewski, Emrani, & Fehlings, 2013) (Fig. 1A). The robust inflammation in

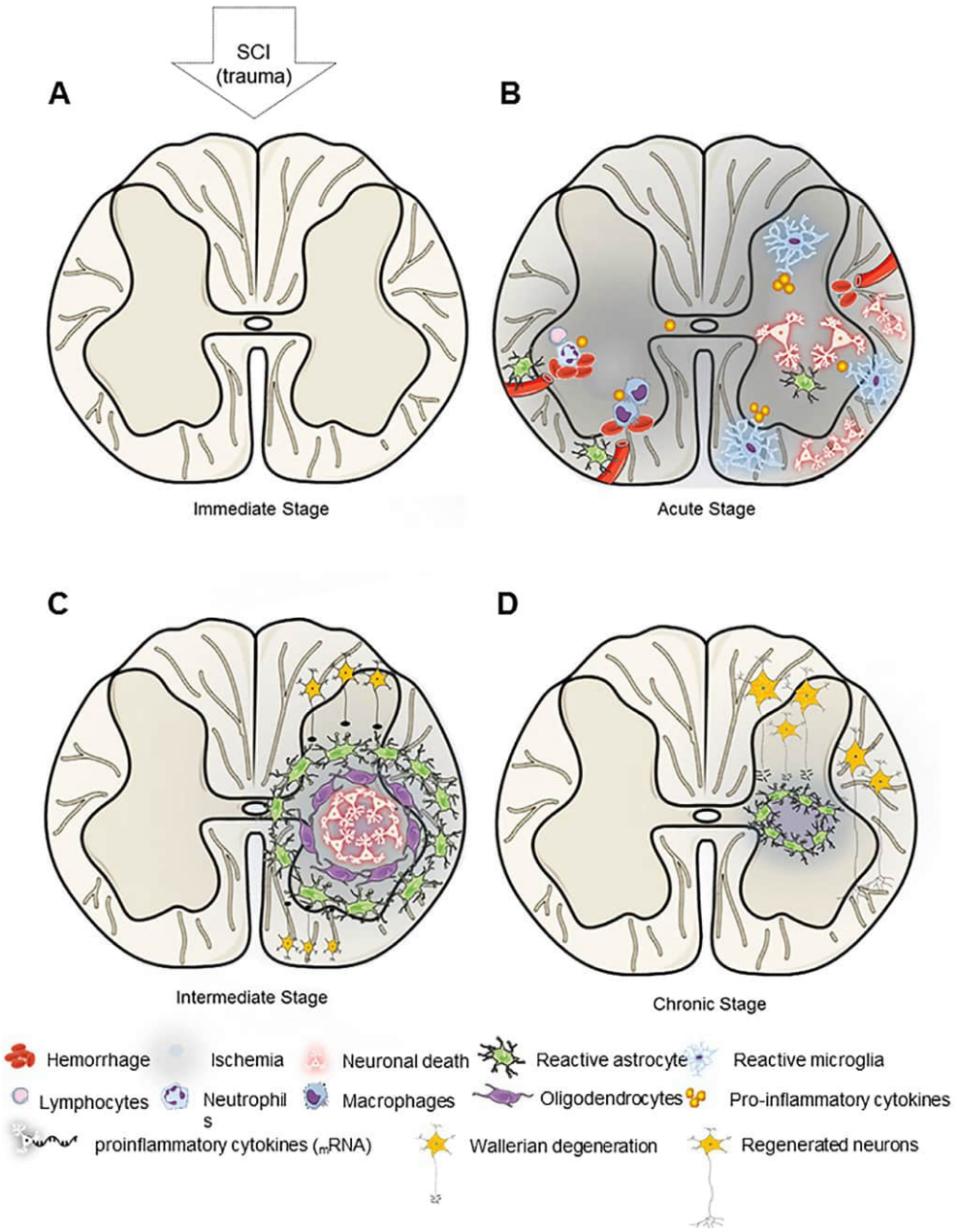

FIG. 1 Pathophysiology of spinal cord injury. Primary and secondary mechanisms of spinal cord trauma. (A) Immediate stage; (B) acute stage; (C) intermediate stage; (D) chronic stage. *Source: Authors.*

response to the immediate events results in secondary endogenous lesion, which is subdivided into acute, intermediate, and chronic phases (Salewski et al., 2013) (Fig. 1B–D).

After SCI, immune system activation is involved in the progression and maintenance of the inflammatory state. The release of TNF-α and IL-1β by resident microglia attracts innate immune cells, including neutrophils and monocytes, to the injury site. The monocyte-derived macrophage increases inflammation by releasing more pro-inflammatory cytokines (David & Kroner, 2011). In addition, T-lymphocyte infiltration increases interferon-gamma (INF-γ) levels (Sun et al., 2018), corroborating macrophage polarization from M1 to M2 phenotype (Kigerl et al., 2009) (Fig. 1B). The hostile microenvironment provokes glial fibrillary acidic protein overexpression, astrocyte proliferation, and astroglial scar formation in the damaged area (Kakulas, 2019; Salewski et al., 2013) (Fig. 1C). In the last stage, injured axons undergo demyelination and fragmentation of the distal segment in a phenomenon described as Wallerian degeneration (Kakulas & Kaelan, 2015; Salewski et al., 2013) (Fig. 1D).

Inflammation is an important part of SCI pathophysiology with evident peripheral immune system involvement in response to spinal cord damage. In addition to local inflammation, there is the occurrence of systemic inflammation, whose causes and consequences are still debatable. Serum concentrations of IL-2, IL-2R, IL-6, TNF-α, IL-1β, and INF-γ are elevated in the acute, subchronic, and chronic stages in animal models (Do Espírito Santo et al., 2019) and humans with SCI (Allison, Josse, Gabriel, Klentrou, & Ditor, 2017; Davies et al., 2007; Hayes et al., 2002).

After SCI, the systemic inflammatory response is counterbalanced by a compensatory anti-inflammatory response responsible for releasing molecules such as IL-10 and glucocorticoids (GC). However, the disruption in central sympathetic control triggers an unregulated anti-inflammatory response (Meisel, Schwab, Prass, Meisel, & Dirnagl, 2005; Schwab, Zhang, Kopp, Brommer, & Popovich, 2014), leading to chronic immune dysfunction, which may alter the functioning of multiple organs, including the brain (Schwab et al., 2014; Sun et al., 2016). Cognitive and psychological dysfunctions observed after SCI point to impairments in distinct brain areas and have been associated with neuroinflammation in the cerebral cortex and hippocampus (Maldonado-Bouchard et al., 2016; Wu et al., 2014), which are both anatomic structures related to emotion (Liu et al., 2017). Together, these findings help illustrate the crosstalk between local inflammation, systemic inflammation, and depressive disorders after SCI.

Depression and spinal cord injury

Epidemiology, assessment, and risk factors of depression after SCI

According to the World Health Organization (WHO), depression is a prevalent mental disorder in the world population. On a global scale, roughly 4.4% of individuals are diagnosed with depression. People of all ages, sexes and social classes are susceptible to developing mental disorders of this nature, although the risk of becoming depressed is more significant in adult women living in underdeveloped and developing countries (WHO, 2017). The concern of these psychiatric disorders is consistent with the high rates of disability in the world (WHO, 2017). The years lived with disability (YLD) represented 7.5% of the years of productive life lost due to depression in 2015. In 2020, depression was predicted to occupy the global position as the second-largest cause of YLD (Ferrari et al., 2013).

Depressive disorders are divided into subcategories, with major depressive disorder (MDD) being the category that best represents the classic scenario of depression. According to the American Psychiatric Association, the presence of at least four symptoms (out of 9 established by the Diagnostic and Statistical Manual of Mental Disorders - DSM–5), besides the core symptoms of depressed mood and anhedonia, serve as a basis for diagnosing MDD. These symptoms occur most of the day, almost every day, for at least 2 weeks (American Psychiatric Association, 2013).

Post-SCI depression has been recognized by specialists for over 40 years, with initial studies dating back to the 1970s. Since then, physical problems and behavioral changes such as reduced social activities, family conflicts, and fewer interactions with friends have been reported in SCI survivors (North, 1999). More current data have shown that the prevalence of MDD after SCI ranges from 18.7% to 26.3% (Williams & Murray, 2015), is estimated as at least three times more frequent than in the world population.

Depressive symptoms can be present in the acute and chronic stages after SCI (Table 2). It is estimated that approximately 10% of patients present depression during rehabilitation in the acute stage, 8.6% in discharge, and 14.1% 6 months after discharge (Craig et al., 2015). After 1 year, depressive symptoms range from 11.9% (Arango-Lasprilla et al., 2011) to 20.6% (Hoffman et al., 2011), while this spectrum varies from 9.7% (Arango-Lasprilla et al., 2011) to 18.1% (Hoffman et al., 2011) at 5 years. Regarding the long-term prevalence of depression, 8.7% of individuals with depression after 1 year remain in similar clinical conditions 5 years after SCI (Hoffman et al., 2011). Additionally, clinically significant symptomatology (CSS) and probable major depression (PDM) 2 years after SCI have higher chances of persisting over time,

TABLE 2 Contribution of neurological condition for developing depressive disorders after spinal cord injury.

Authors	Participants/% of participants with depression	Neurological conditions	Neurological conditions vs depressive symptoms	Risk factors to depression
Krause, Kemp, and Coker (2000)	*n*: 171 participants Clinically significant symptoms[a]: 24% Probable major depression[a]: 24%	+T/P I/+C Chronic SCI	Tetraplegia vs Paraplegia: Ø Complete vs incomplete: Ø	Aged, sex or ethnicity, education and income.
Bombardier et al. (2004)	*n*: 849 participants Mild, moderate and severe[b]: 20%, 11.9% and 4.4%	+T/P +I/C Chronic SCI	Tetraplegia vs Paraplegia: Ø Complete vs incomplete: Ø	–
Oh et al. (2006)	*n*: 102 participants Mild, moderate and severe[c]: 3.9%, 23.5% and 69.9%	T/+P - Chronic SCI	Tetraplegia vs Paraplegia: Ø	Sex and dependence for perform catheterization
Bombardier et al. (2012)	*n*: 244 participants Mild[b]: 39%	+T/P +I/C Acute and chronic SCI	- Complete vs incomplete: ↑ incomplete	Lower availability of reinforcement in the environment (Limited positive reinforced related to health)
Fann et al. (2011)	*n*: 947 participants Moderate[b]: 23% Moderately severe and severe depression[b]: 9%	+T/P - Acute and chronic SCI	Tetraplegia vs Paraplegia: Ø	–
Hassanpour et al. (2012)	*n*: 130 participants Mild[c]: 30% Moderate to severe[c]: < 5%	T/+P +I/C Acute and chronic SCI	Tetraplegia vs Paraplegia: Ø Complete vs incomplete: Ø	–
Arango-Lasprilla et al. (2011)	*n: 2.830 participants* At year 1[b]: 11.9% At year 5[b]: 9.7%	+T/P +I/C Chronic SCI	Tetraplegia vs Paraplegia: ↑ tetraplegia Complete vs incomplete: ↑ complete	Aged (35–55 years old), unemployed, having an indwelling catheter, voiding, no bladder management at discharge, and higher scores on ASIA motor index
Hoffman et al. (2011)	*n*: 1035 participants At year 1[b]: 20.6% At year 5[b]: 18.1%	+T/P +I/C Chronic SCI	Tetraplegia vs Paraplegia: Ø Complete vs incomplete: Ø	Pain, declining health status, and decrease in unsafe alcohol use
Shin et al. (2012)	*n*: 36 participants Mild[c]: 63,9%	+T/P I/C	Tetraplegia vs Paraplegia: Ø Complete vs incomplete: ↑ complete	–
Craig et al. (2015)	*n*: 88 participants Inpatient rehabilitation[d]: 10.3% Discharge[d]: 8.6% 6mo postdischarge[d]: 14.1%	T/+P +I/C Acute SCI	Tetraplegia vs Paraplegia: Ø Complete vs incomplete: Ø	–
Kim, Lee, Park, and Jeon (2020)	*n:* 103 participants -	+T/P I/+C Chronic SCI	Level of the injury was identified as a predictor of depression Complete vs incomplete: Ø	Lower physical activity levels

"–" information not reported; "+" predominant cases; "↑" more depressive symptoms.; "Ø" no clear association between depressive symptoms and the level and/or severity of the injury; *mo*: months; *n*: sample; *P*: paraplegic; *SCI*: spinal cord injury; *T*: tetraplegic.
[a]*OAHMQ: Older Adult Health and Mood Questionnaire.*
[b]*PHQ-9: Patient Health Questionnaire–9.*
[c]*BDI: Beck Depression Inventory.*
[d]*HADS: Hospital Anxiety and Depression Scale.*

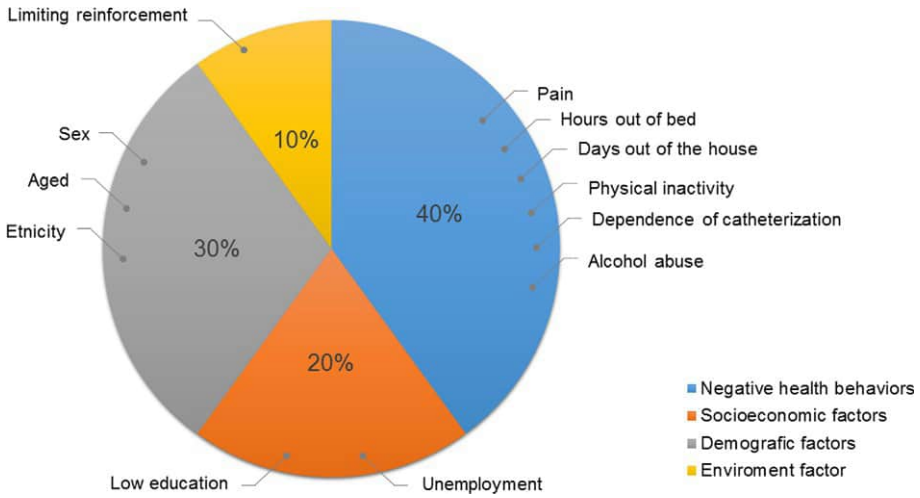

FIG. 2 Risk factors for depression after spinal cord injury. Number of studies (represented in percentage) that reported the risk factors for the development of depression after spinal cord injury (SCI). *Source: Authors based in reference citation Table 2.*

while the likelihood of developing these complications decreases to 20.5% and 8.2%, respectively, in non-depressed patients (Saunders, Krause, and Focht, 2012).

In other clinical conditions such as stroke, higher depressive symptoms are associated with increased illness severity (i.e., predisposition to depression is higher in patients most affected by stroke) (Alghwiri, 2016). Nevertheless, there is still no clear evidence that the severity and/or level of injury are underlying factors of the symptomology of MDD after SCI (Table 2). In contrast, among demographic factors, it is evident that white and black women in the productive age (35–59 years) have higher risks of depression (Krause et al., 2000; Arango-Lasprilla et al., 2011; Saunders, Krause, and Focht, 2012) (Table 2). In addition, research has suggested that the development of MDD post-SCI is associated with adverse health behaviors (Arango-Lasprilla et al., 2011; Hoffman et al., 2011; Kim et al., 2020; Oh et al., 2006; Saunders, Krause, and Focht, 2012), and socioeconomic (Arango-Lasprilla et al., 2011; Krause et al., 2000) and environmental factors (Bombardier et al., 2012) (Table 2; Fig. 2).

It is important to note that the implications of depression can be drastic for individuals with SCI, including elevated stress levels, lower motor scores, and reduced quality of life (Shin et al., 2012). Furthermore, there is a positive correlation between depression and anxiety, limited daily life activity, and general health (Hassanpour et al., 2012). Knowledge concerning the effects of depression on patients comes with the growing number of diagnostic tools to measure depressive symptoms after SCI. Currently, some instruments have been widely used in the literature due to their psychometric properties, including the Older Adult Health and Mood Questionnaire (OAHMQ), Patient Health Questionnaire–9 (PHQ-9), Beck Depression Inventory (BDI), Hospital Anxiety and Depression Scale (HADS), Center for Epidemiologic Studies Depression (CESD) scale, and Spinal Cord Injury–Quality of Life (SCI-QOL) (for more details, see https://www.sralab.org/).

Etiological factors for depression: The role of inflammation

The inflammatory hypothesis proposed by Smith in the 1990s (Smith, 1991) seems to be closely associated with depression. Data compiled from the literature shows that IL-1, INF-α, and TNF-α produced by active macrophages are important mediators of depression since volunteers who received systemic administration of these cytokines showed symptoms of MDD (Smith, 1991). However, the mechanisms of which peripheral cytokines were associated with depression had previously been hypothesized. In 1989, Dantzer and Kelley reported that the systemic administration of pro-inflammatory cytokines induced a non-specific adaptive response known as sickness behavior. Sickness behavior comprises feeling sick, loss of energy or fatigue, loss of interest in usual activities, poor appetite, significant weight loss, sleep changes, and fever, all of which are induced by infectious agents in the periphery (Dantzer & Kelley, 1989). Nonetheless, physiological and behavioral symptoms of sickness are understood by the action of peripherally produced cytokines in the brain (Dantzer et al., 2008). There is a similarity (behaviorally predominant) between sickness behavior and depression. The prominent hypothesis is that depression in humans (or depressive-like behavior in rodents) results from a maladaptive version of cytokine-induced sickness. This maladaptive response is provoked by uncontrolled intensity and/or duration of the innate immune response, leading to the exacerbation of sickness and consequent depression (Dantzer et al., 2008).

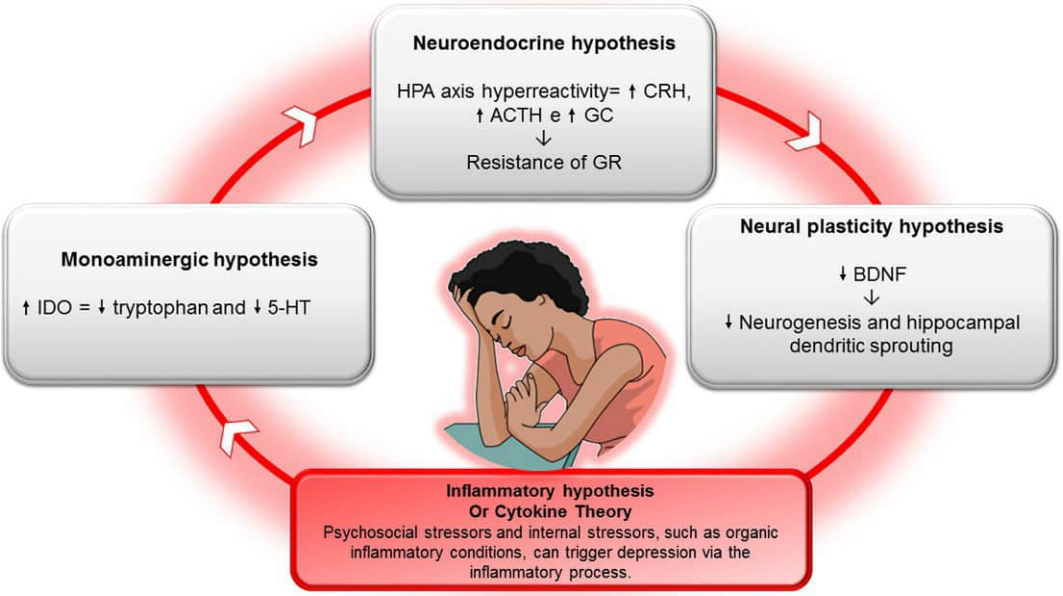

FIG. 3 Flowchart of the inflammatory hypothesis of depression interacting with classic theories postulated for the development of depression (read from left to right). Regarding the monoaminergic hypothesis of depression (*first left arrow*), peripheral cytokines stimulate the enzyme indoleamine 2,3-dioxygenase (IDO), leading to tryptophan depletion. Consequently, serotonin (5-hydroxytryptamine [5-HT]) and tryptophan levels decreased to the detriment of high kynurenine levels. In the neuroendocrine hypothesis, stress-mediated pro-inflammatory signaling directly affects cytokine activation in the hypothalamic and pituitary structures. This provokes the release of the hormones from the corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH), which stimulates the release of glucocorticoids (GC) by the adrenal glands. The hyper-reactivity hypothalamus-pituitary-adrenal (HPA) axis is attributed to glucocorticoid receptor (GR) resistance in the hypothalamus. Lastly, inflammation damages synaptic plasticity, which is mainly due to the loss of neuronal integrity in the hippocampus. It is recognized that kynurenines, high GC levels, and reduced trophic factors, such as brain-derived neurotrophic factor (BDNF), may decrease neurogenesis and dendritic sprouting in the dentate gyrus of the hippocampus. ↑: increase; ↓: reduction. *Source: Authors based in Dantzer, R., O'Connor, J. C., Freund, G. G., Johnson, R. W., & Kelley, K. W. (2008). From inflammation to sickness and depression: When the immune system subjugates the brain.* Nature Reviews Neuroscience, 9*(1), 46–56.; Maes, M., Leonard, B. E., Myint, A. M., Kubera, M., & Verkerk, R. (2011). The new '5-HT' hypothesis of depression: Cell-mediated immune activation induces indoleamine 2, 3-dioxygenase, which leads to lower plasma tryptophan and an increased synthesis of detrimental tryptophan catabolites (TRYCATs), both of which contribute to the onset of depression.* Progress in Neuro-Psychopharmacology and Biological Psychiatry, 35*(3), 702–721.; Capuron, L., & Miller, A. H. (2011). Immune system to brain signaling: Neuropsychopharmacological implications.* Pharmacology & Therapeutics, 130*(2), 226–238.*.

Reports elucidate that abundant peripheral pro-inflammatory cytokines, such as IL-1β, IL-6, and TNF-α (Dowlati et al., 2010; Russo & Nestler, 2013), are found in individuals with depression and have their inflammatory signals transmitted and amplified in different regions of the brain. In response to these signals, important changes in the physiological domains of depression occur, including the metabolism of neurotransmitters (especially serotonin or 5-hydroxytryptamine [5-HT]), neuroendocrine function, and neural plasticity (Capuron & Miller, 2011) (Fig. 3).

Evidence shows that serotonergic transmission in cortico-limbic circuits is susceptible to disruption in the presence of systemic inflammation. In rodents, the elevated TNF-α and IL-1β systemic levels were associated with the stimulation of 5-HT transporter activity in affective processing areas, leading to behavior-like depression, including hopelessness and anhedonia (Zhu et al., 2010). Similarly, a link between depression and stress-induced inflammation is generally accepted. Indeed, tricyclic antidepressant drugs reduce GC and IL-6 plasma levels and social withdrawal provoked by stress, further reinforcing that neuroendocrine dysregulation and inflammation are components of depression-related illness (Ramirez & Sheridan, 2016). Other studies have reported that synaptic plasticity and neurotrophic factor synthesis are effects of prolonged neuroinflammation. Tang, Lin, Pan, Guan, and Li (2016) observed that IL-6, TNF-α, and IL-1β levels in rodent brains were associated with impaired hippocampal neurogenesis during anhedonia, with both conditions being reverted by BDNF administration (Briones & Woods, 2013), suggesting a possible protecting role of BDNF on neuroplasticity hippocampal in depressive-like behavior.

In this context, it is recognized that depression is a complex psychological condition that involves numerous pathophysiological mechanisms, including inflammation. After SCI, the role of the inflammatory process in depression has been expanded to explore a "gap" that still exists regarding the underlying mechanisms of this heterogeneous disease that afflicts part of individuals injured.

Inflammatory aspects of depression after SCI

Research has emphasized that inflammation plays a pivotal role in the development of depression after SCI. Inflammation is a critical component of secondary endogenous injury and potentially leads to the circulation of soluble inflammatory mediators post-trauma. Elevated serum IL-2, IL-2R, IL-6, TNF-α, IL-1β, and INF-γ levels were observed in individuals with subchronic and chronic SCI (Allison et al., 2017; Davies et al., 2007; Hayes et al., 2002). In humans, the chronic systemic inflammatory response has been observed to predispose to depression through a negative correlation between improved mood and tryptophan bioavailability (amino acid precursors of serotonin) and reduced IFN-γ and IL-1β serum levels in patients with chronic SCI submitted to a 12-week anti-inflammatory diet (Allison & Ditor, 2015). Additional data support that women are more vulnerable to psychomotor agitation, anhedonia, and/or mood depression after SCI (Bombardier et al., 2012; Krause et al., 2000; Oh et al., 2006). Healthy women and those with chronic diseases present more mood depression and feelings of social disconnection symptoms in systemic IL-6 and TNF-α responses than men (Moieni et al., 2015). Thus, predisposition to depression may be influenced by sex and inflammatory conditions after SCI.

Animal models of SCI have provided further insight into the development of inflammation-associated depression. Maldonado-Bouchard et al. (2016) showed that immune system reactivity increased in parallel with depressive-like behavior in injured mice. The authors associated hopelessness, social isolation, and psychomotor retardation with higher chemokine and cytokine levels, including granulocyte macrophage-colony stimulating factor (GM-CSF), IL-1β, and TNF-α serum levels, IL-18 and TNF-α in the spinal cord, and IL-1α and TNF-α in the hippocampus in rodents after contusion SCI (Maldonado-Bouchard et al., 2016).

The link between systemic inflammation, neuroinflammation, and depression-like behavior after contusion SCI is also corroborated by Wu et al. (2014, 2016)). The authors reported that reactive microglia co-localized with TNF-α and IL-6 mRNA expressions in the hippocampus increased in rodents with anhedonia and hopelessness (Wu et al., 2014). Besides microglial activation, the impaired hippocampal neurogenesis and increased degeneration in the hippocampus and cerebral cortex were observed in paraplegic mice (Wu et al., 2014, 2016), providing evidence that chronic SCI leads to neuroimmune dysregulation.

Additionally, there is data that neuroinflammation may reduce BDNF levels in the hippocampus and increase corticosterone serum levels in rodents with depressive-like behavior after SCI (Li et al., 2017). Considering that BDNF is involved in synaptic plasticity and is downregulated by corticosterone in response to stress-induced depression (Masi & Brovedani, 2011), Li et al. (2017) showed that treatment with ZBD-2 (a synthetic protein of indirect anti-inflammatory activity) has antidepressant effects able to restore serum corticosterone and hippocampal BDNF levels, reducing microglial reactivity in the spinal cord in rodents with SCI.

In general, the systemic levels and type of pro-inflammatory cytokines tend to vary between SCI stages (acute, subchronic, and chronic) and the animals' psychological well-being (social isolation and anhedonia). However, the early systemic inflammatory peak (48 h after compression SCI) appears to be predictive of developing depressive-like behavior (but not anxiety). In the acute and chronic stages (7 and 35 days post-SCI, respectively), the inflammatory peaks of IL-1β, TNF-α, INF-γ, and IL-6 were negatively correlated with reduced social exploration time. In the subchronic to chronic stages (22 days post-SCI), a similar profile was observed for anhedonia, given that a significant correlation took place between early systemic inflammation and loss of interest/pleasure in rodents (Do Espírito Santo et al., 2019).

Notably, anhedonic behavior has been reported to have lasting effects, enduring for over 2.8 months after secondary SCI-induced neuroinflammation (Wu et al., 2014, 2016), while social isolation manifests for at least 1 month (Do Espírito Santo et al., 2019). Both behavioral conditions have been associated with early and persistent local and systemic inflammatory responses observed in female rats (Do Espírito Santo et al., 2019). These data deserve attention for two reasons: depressive symptoms generally have long-term effects on individuals with SCI, and human studies have not yet been performed on the female sex, although evidence points to this direction.

Lastly, all studies and review articles have a significant scientific value since depression is treatable as long as symptoms and causes are recognized early. Thus, knowledge of biological predictors, including inflammation, may provide an easily accessible prognostic marker for SCI individuals that are more susceptible to inflammation-mediated depression.

Conclusion

For a considerable part of the population of individuals with SCI, physical and psychological problems coexist. In this chapter, the role of inflammation in the etiology of depression was described and the following considered: (1) the risk factors inherent to SCI (age, sex, social status and, less likely, the level and severity of SCI), and (2) the possible biological process in which inflammation overlaps with random depression conditions (monoaminergic system, neuroendocrine function, and neural plasticity). Therefore, there is evidence to support those systemic pro-inflammatory cytokines

propagated at the damage site in the spinal cord have a multifaceted role in SCI and are associated with several behavioral changes, including anhedonia and mood depression (in humans) and anhedonia, social isolation, and hopelessness (in rodents). In this context, it is concluded that chronic inflammation can predispose to depression after SCI.

Applications to other areas of neuroscience

In this chapter, we reviewed the risk factors and predictors of depression after spinal cord injury (SCI) while emphasizing the role of inflammation in the development of depressive symptoms. Depression is a complex, multifactorial clinical condition with the absence of a clear understanding of how it arises and should be treated. Thus, it is speculated that the inaccurate understanding of neurobiological mechanisms may lead to incomplete information to support the etiology of depression (Perugi, Frare, Toni, Ruffolo, & Torti, 2002). This is even more concerning for neurological disorders such as SCI because several maladaptive responses are triggered by spinal cord trauma, including inflammation. Therefore, establishing the relationship between inflammation and depression and exploring the (1) systemic pro-inflammatory cytokines involved, (2) brain areas subject to neuroinflammation caused by traumatic injury, and better understanding (3) inflammation by delving into classic theories regarding the development of depression (all discussed in the present chapter) are important factors that may provide a possible easy-access and low-cost prognostic marker of post-SCI depression.

Furthermore, this knowledge is highly relevant, given that depression is also associated with systemic inflammation in stroke (Chen et al., 2018) and traumatic brain injury (Bodnar, Morganti, & Bachstetter, 2018). Hence, regardless of neurological injury (i.e., trauma or vascular insult to the central nervous system), depression appears to share the same etiologic factor, making inflammation a new target for intervention. Besides inflammation, we also interlink the risk factors inherent to SCI in the development of depression. Indeed, the manifestation of depression is typically masked by behavioral abnormalities (distress, difficulty in dealing with daily life situations, reduced social activities, and family conflicts), consequently delaying diagnosis and treatment. Knowing the demographic factors (age and sex), socioeconomic conditions (education and employment), and social environment is vital to identifying people at risk of developing depression after SCI.

Mini-dictionary of terms

American Spinal Injury Association Impairment Scale: used to classify the severity of spinal cord injury from A to E. A being the most severe, D being the least severe, and E being normal.

Anhedonia: loss of interest or pleasure.

Clinically significant symptoms of depression: presence of depressive symptoms but do not meet the criteria for major depression.

Complete spinal cord injury: the absence of sensory or motor function in the sacral segments (S4-S5).

Cytokines: glycoprotein regulators of the host's defense in response to infection, inflammation, or disease and classified as interleukins, interferons, tumor necrosis factor-alpha, and tumor growth factors.

Hopelessness: similar to behavioral despair in people with depression.

Incomplete spinal cord injury: preservation of any sensory and/or motor function in most caudal sacral segments (S4–S5).

Inflammation: a tissue's response to injury, which is increased by pro-inflammatory cytokines.

Mood depression: a low mood state (i.e., mood disturbance) related to depression.

Paraplegia: paralysis of the lower limbs due to lower cervical cord injury.

Probable major depression: psychological condition attributed by the Patient Health Questionnaire (PHQ-9) and Older Adult Health and Mood Questionnaire that does not meet the criteria for major depression.

Sickness behavior: an adaptive response to pathogenic infection. When the pathogen is cleared, the adaptive response is completely reversed.

Social isolation: reduced social exploration due to loss of motivation.

Tetraplegia: paralysis of all four limbs and torso due to cervical cord injury that may manifest with or without autonomic dysfunctions.

Key facts of depression

- It is estimated to be the second-largest cause of years lived with disability.
- It is prevalent comorbidity in several neurological disorders and negatively affects rehabilitation.

- The biological mechanisms of depression are not entirely understood.
- Systemic inflammation is considered a biological predictor of the onset and/or maintenance of depression.
- Sex, age, ethnicity, income, education, and employment are risk factors for depression.

Summary points

- This chapter focuses on the role of inflammation in the development of depression after SCI.
- Secondary endogenous damage stimulates the activity of the immune system during the pathological stages of SCI.
- Spinal cord injury leads to increased systemic pro-inflammatory cytokines that exert detrimental effects on mental health.
- Cytokines play an important role in the neuroinflammatory responses in depression.
- Women are more susceptible to becoming depressed than men, although other risk factors are associated with depression.

References

Alghwiri, A. A. (2016). The correlation between depression, balance, an physical functioning post stroke. *Journal of Stroke and Cerebrovascular Diseases*, *25*(2), 475–479.

Allison, D. J., & Ditor, D. S. (2015). Targeting inflammation to influence mood following spinal cord injury: A randomized clinical trial. *Journal of Neuroinflammation*, *12*(204), 1–10.

Allison, D. J., Josse, A. R., Gabriel, D. A., Klentrou, P., & Ditor, D. S. (2017). Targeting inflammation to influence cognitive function following spinal cord injury: A randomized clinical trial. *Spinal Cord*, *55*(1), 26–32.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders (DSM-5)* (5th ed.). American Psychiatric Association.

Arango-Lasprilla, J. C., Ketchum, J. M., Starkweather, A., Nicholls, E., & Wilk, A. R. (2011). Factors predicting depression among persons with spinal cord injury 1 to 5 years post injury. *NeuroRehabilitation*, *29*(1), 9–21.

ASIA and ISCoS International Standards Committee. (2019). The 2019 revision of the international standards for neurological classification of spinal cord injury (ISNCSCI)-what's new? *Spinal Cord*, *57*(10), 815–817.

Bartholdi, D., & Schwab, M. E. (1997). Expression of pro-inflammatory cytokine and chemokine mRNA upon experimental spinal cord injury in mouse: An in situ hybridization study. *European Journal of Neuroscience*, *9*(7), 1422–1438.

Bodnar, C. N., Morganti, J. M., & Bachstetter, A. D. (2018). Depression following a traumatic brain injury: Uncovering cytokine dysregulation as a pathogenic mechanism. *Neural Regeneration Research*, *13*(10), 1693–1704.

Bombardier, C. H., Fann, J. R., Tate, D. G., Richards, J. S., Wilson, C. S., Warren, A. M., et al. (2012). An exploration of modifiable risk factors for depression after spinal cord injury: Which factors should we target? *Archives of Physical Medicine and Rehabilitation*, *93*(5), 775–781.

Bombardier, C. H., Richards, J. S., Krause, J. S., Tulsky, D., & Tate, D. G. (2004). Symptoms of major depression in people with spinal cord injury: Implications for screening. *Archives of Physical Medicine and Rehabilitation*, *85*(11), 1749–1756.

Briones, T. L., & Woods, J. (2013). Chronic binge-like alcohol consumption in adolescence causes depression-like symptoms possibly mediated by the effects of BDNF on neurogenesis. *Neuroscience*, *254*, 324–334.

Capuron, L., & Miller, A. H. (2011). Immune system to brain signaling: Neuropsychopharmacological implications. *Pharmacology & Therapeutics*, *130*(2), 226–238.

Chen, H., Luan, X., Zhao, K., Qiu, H., Liu, Y., Tu, X., et al. (2018). The association between neutrophil-to-lymphocyte ratio and post-stroke depression. *Clinica Chimica Acta*, *486*, 298–302.

Craig, A., Nicholson Perry, K., Guest, R., Tran, Y., & Middleton, J. (2015). Adjustment following chronic spinal cord injury: Determining factors that contribute to social participation. *British Journal of Health Psychology*, *20*(4), 807–823.

Dantzer, R., & Kelley, K. W. (1989). Stress and immunity: An integrated view of relationships between the brain and the immune system. *Life Sciences*, *44*(26), 1995–2008.

Dantzer, R., O'Connor, J. C., Freund, G. G., Johnson, R. W., & Kelley, K. W. (2008). From inflammation to sickness and depression: When the immune system subjugates the brain. *Nature Reviews Neuroscience*, *9*(1), 46–56.

David, S., & Kroner, A. (2011). Repertoire of microglial and macrophage responses after spinal cord injury. *Nature Reviews Neuroscience*, *12*(7), 388–399.

Davies, A. L., Hayes, K. C., & Dekaban, G. A. (2007). Clinical correlates of elevated serum concentrations of cytokines and autoantibodies in patients with spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *88*(11), 1384–1393.

Do Espírito Santo, C. C., da Silva Fiorin, F., Ilha, J., Duarte, M. M. M. F., Duarte, T., & Santos, A. R. S. (2019). Spinal cord injury by clip-compression induces anxiety and depression-like behaviours in female rats: The role of the inflammatory response. *Brain, Behavior, and Immunity*, *78*, 91–104.

Dowlati, Y., Herrmann, N., Swardfager, W., Liu, H., Sham, L., Reim, E. K., et al. (2010). A meta-analysis of cytokines in major depression. *Biological Psychiatry*, *67*(5), 446–457.

Dryden, D. M., Saunders, L. D., Rowe, B. H., May, L. A., Yiannakoulias, N., Svenson, L. W., et al. (2005). Depression following traumatic spinal cord injury. *Neuroepidemiology*, *25*(2), 55–61.

Fann, J. R., Bombardier, C. H., Richards, J. S., Tate, D. G., Wilson, C. S., Temkin, N., et al. (2011). Depression after spinal cord injury: Comorbidities, mental health service use, and adequacy of treatment. *Archives of Physical Medicine and Rehabilitation*, *92*(3), 352–360.

Ferrari, A. J., Charlson, F. J., Norman, R. E., Patten, S. B., Freedman, G., Murray, C. J., et al. (2013). Burden of depressive disorders by country, sex, age, and year: Findings from the global burden of disease study 2010. *PLoS Medicine*, *10*(11), e1001547.

Gibson, A. E., Buchholz, A. C., & Ginis, K. M. (2008). C-reactive protein in adults with chronic spinal cord injury: Increased chronic inflammation in tetraplegia vs paraplegia. *Spinal Cord*, *46*(9), 616–621.

Halvorsen, A., Pettersen, A. L., Nilsen, S. M., Halle, K. K., Schaanning, E. E., & Rekand, T. (2019). Non-traumatic spinal cord injury in Norway 2012–2016: Analysis from a national registry and comparison with traumatic spinal cord injury. *Spinal Cord*, *57*(4), 324–330.

Hassanpour, K., Hotz-Boendermaker, S., Dokladal, P., Curt, A., & European Multicenter Study for Human Spinal Cord Injury Study group. (2012). Low depressive symptoms in acute spinal cord injury compared to other neurological disorders. *Journal of Neurology*, *259*(6), 1142–1150.

Hayes, K. C., Hull, T. C. L., Delaney, G. A., Potter, P. J., Sequeira, K. A. J., Campbell, K., et al. (2002). Elevated serum titers of proinflammatory cytokines and CNS autoantibodies in patients with chronic spinal cord injury. *Journal of Neurotrauma*, *19*(6), 753–761.

Hoffman, J. M., Bombardier, C. H., Graves, D. E., Kalpakjian, C. Z., & Krause, J. S. (2011). A longitudinal study of depression from 1 to 5 years after spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *92*(3), 411–418.

Kakulas, B. A. (2019). Spinal cord injuries the facts of neuropathology: Opportunities and limitations. *Current Neuropsychiatry and Clinical Neuroscience Reports*, *1*(1), 1–5.

Kakulas, B. A., & Kaelan, C. (2015). The neuropathological foundations for the restorative neurology of spinal cord injury. *Clinical Neurology and Neurosurgery*, *129*, S1–S7.

Kigerl, K. A., Gensel, J. C., Ankeny, D. P., Alexander, J. K., Donnelly, D. J., & Popovich, P. G. (2009). Identification of two distinct macrophage subsets with divergent effects causing either neurotoxicity or regeneration in the injured mouse spinal cord. *Journal of Neuroscience*, *29*(43), 13435–13444.

Kim, D. I., Lee, J., Park, H., & Jeon, J. Y. (2020). The relationship between physical activity levels and mental health in individuals with spinal cord injury in South Korea. *International Journal of Environmental Research and Public Health*, *17*(12), 4423–4431.

Kirshblum, S., Snider, B., Rupp, R., & Read, M. S. (2020). Updates of the international standards for neurologic classification of spinal cord injury: 2015 and 2019. *Physical Medicine and Rehabilitation Clinics*, *31*(3), 319–330.

Krause, J. S., Kemp, B., & Coker, J. (2000). Depression after spinal cord injury: Relation to gender, ethnicity, aging, and socioeconomic indicators. *Archives of Physical Medicine and Rehabilitation*, *81*(8), 1099–1109.

Li, X. M., Meng, J., Tao Li, L., Guo, T., Yang, L. K., Shi, Q. X., et al. (2017). Effect of ZBD-2 on chronic pain, depressive-like behaviors, and recovery of motor function following spinal cord injury in mice. *Behavioural Brain Research*, *322*, 92–99.

Liu, W., Ge, T., Leng, Y., Pan, Z., Fan, J., Yang, W., et al. (2017). The role of neural plasticity in depression: From hippocampus to prefrontal cortex. *Neural Plasticity*, 1–11.

Maldonado-Bouchard, S., Peters, K., Woller, S. A., Madahian, B., Faghihi, U., Patel, S., et al. (2016). Inflammation is increased with anxiety-and depression-like signs in a rat model of spinal cord injury. *Brain, Behavior, and Immunity*, *51*, 176–195.

Masi, G., & Brovedani, P. (2011). The hippocampus, neurotrophic factors and depression. *CNS Drugs*, *25*(11), 913–931.

Meisel, C., Schwab, J. M., Prass, K., Meisel, A., & Dirnagl, U. (2005). Central nervous system injury-induced immune deficiency syndrome. *Nature Reviews Neuroscience*, *6*(10), 775–786.

Moieni, M., Irwin, M. R., Jevtic, I., Olmstead, R., Breen, E. C., & Eisenberger, N. I. (2015). Sex differences in depressive and socioemotional responses to an inflammatory challenge: Implications for sex differences in depression. *Neuropsychopharmacology*, *40*(7), 1709–1716.

North, N. T. (1999). The psychological effects of spinal cord injury: A review. *Spinal Cord*, *37*(10), 671–679.

NSCISC. (2016). *National Spinal Cord Injury Statistical Center (facts and figures at a glance)*. AL: Department of Physical Medicine and Rehabilitation, University of Alabama at Birmingham.

Oh, S. J., Shin, H. I., Paik, N. J., Yoo, T., & Ku, J. H. (2006). Depressive symptoms of patients using clean intermittent catheterization for neurogenic bladder secondary to spinal cord injury. *Spinal Cord*, *44*(12), 757–762.

Perugi, G., Frare, F., Toni, C., Ruffolo, G., & Torti, C. (2002). Open-label evaluation of venlafaxine sustained release in outpatients with generalized anxiety disorder with comorbid major depression or dysthymia: Effectiveness, tolerability and predictors of response. *Neuropsychobiology*, *46*(3), 145–149.

Rahimi-Movaghar, V., Sayyah, M. K., Akbari, H., Khorramirouz, R., Rasouli, M. R., Moradi-Lakeh, M., et al. (2013). Epidemiology of traumatic spinal cord injury in developing countries: A systematic review. *Neuroepidemiology*, *41*(2), 65–85.

Ramirez, K., & Sheridan, J. F. (2016). Antidepressant imipramine diminishes stress-induced inflammation in the periphery and central nervous system and related anxiety-and depressive-like behaviors. *Brain, Behavior, and Immunity*, *57*, 293–303.

Russo, S. J., & Nestler, E. J. (2013). The brain reward circuitry in mood disorders. *Nature Reviews Neuroscience*, *14*(9), 609–625.

Salewski, R., Emrani, H., & Fehlings, M. G. (2013). Neural stem/progenitor cells for spinal cord regeneration. In S. Wislet-Gendebien (Ed.), *Trends in cell signaling pathways in neuronal fate decision* (pp. 271–304). Crotia: In Tech.

Saunders, L. L., Krause, J. S., & Focht, K. L. (2012). A longitudinal study of depression in survivors of spinal cord injury. *Spinal Cord*, *50*(1), 72–77.

Schwab, J. M., Zhang, Y., Kopp, M. A., Brommer, B., & Popovich, P. G. (2014). The paradox of chronic neuroinflammation, systemic immune suppression, autoimmunity after traumatic chronic spinal cord injury. *Experimental Neurology*, *258*, 121–129.

Shin, J. C., Goo, H. R., Yu, S. J., Kim, D. H., & Yoon, S. Y. (2012). Depression and quality of life in patients within the first 6 months after the spinal cord injury. *Annals of Rehabilitation Medicine*, *36*(1), 119–125.

Smith, R. S. (1991). The macrophage theory of depression. *Medical Hypotheses*, *35*(4), 298–306.

Sun, X., Jones, Z. B., Chen, X. M., Zhou, L., So, K. F., & Ren, Y. (2016). Multiple organ dysfunction and systemic inflammation after spinal cord injury: A complex relationship. *Journal of Neuroinflammation*, *13*(1), 260–271.

Sun, G., Yang, S., Cao, G., Wang, Q., Hao, J., Wen, Q., et al. (2018). γδ T cells provide the early source of IFN-γ to aggravate lesions in spinal cord injury. *Journal of Experimental Medicine*, *215*(2), 521–535.

Tang, M. M., Lin, W. J., Pan, Y. Q., Guan, X. T., & Li, Y. C. (2016). Hippocampal neurogenesis dysfunction linked to depressive-like behaviors in a neuroinflammation induced model of depression. *Physiology & Behavior*, *161*, 166–173.

Williams, R., & Murray, A. (2015). Prevalence of depression after spinal cord injury: A meta-analysis. *Archives of Physical Medicine and Rehabilitation*, *96*(1), 133–140.

World Health Organization. (2017). *Depression and other common mental disorders: Global health estimates*. World Health Organization.

Wu, J., Zhao, Z., Kumar, A., Lipinski, M. M., Loane, D. J., Stoica, B. A., et al. (2016). Endoplasmic reticulum stress and disrupted neurogenesis in the brain are associated with cognitive impairment and depressive-like behavior after spinal cord injury. *Journal of Neurotrauma*, *33*(21), 1919–1935.

Wu, J., Zhao, Z., Sabirzhanov, B., Stoica, B. A., Kumar, A., Luo, T., et al. (2014). Spinal cord injury causes brain inflammation associated with cognitive and affective changes: Role of cell cycle pathways. *Journal of Neuroscience*, *34*(33), 10989–11006.

Zhu, C. B., Lindler, K. M., Owens, A. W., Daws, L. C., Blakely, R. D., & Hewlett, W. A. (2010). Interleukin-1 receptor activation by systemic lipopolysaccharide induces behavioral despair linked to MAPK regulation of CNS serotonin transporters. *Neuropsychopharmacology*, *35*(13), 2510–2520.

Chapter 38

Spirituality, hope, and resilience in the recovery and adaptation process following spinal cord injury

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List of abbreviations

SCI spinal cord injury

Introduction

A spinal cord injury (SCI) is a catastrophic event that abruptly interrupts the lives of an individual and their family, changing everything in a moment (Palmer, Kriegsman, & Palmer, 2008). Described as one of the most devastating conditions to occur in both developed and developing countries, estimates of the global incidence of traumatic SCI range from 3.6 to 195.4 per million across the world (Jazayeri, Beygi, Shokranch, Hagen, & Rahimi-Movaghar, 2015). According to the World Health Organisation (2013), between 250,000 and 500,000 people sustain a SCI every year and most are due to preventable causes. Furthermore, those with SCI are more likely to die prematurely and experience lower rates of economic participation (World Health Organisation, 2013). Damage to the spinal cord may affect an individual's physical functioning in a number of ways, impacting upon mobility, continence, respiration, sexual and reproductive health (Kirshblum & Benevento, 2009; Palmer et al., 2008), as well as triggering neuropathic pain (Hagen & Rekand, 2015).

The substantial psychological impacts of SCI that accompany the bodily impairments and functional alterations have been extensively documented. The prevalence of depression after SCI, as found in a meta-analysis based on 19 studies, is estimated at 22.2%, compared with 16% in the general U.S. population (Williams & Murray, 2015). Furthermore, the risk for suicide is up to five times greater than for the general population (Simpson & Brenner, 2019). The course of psychological distress such as anxiety and depression peaks in the acute stages of treatment just before discharge from hospital (Kennedy & Rogers, 2000), but can last up to 5 years and longer post-SCI (Hoffman, Bombardier, Graves, Kalpakjian, & Krause, 2011). Risk factors for psychological distress include increased pain, worsening health status, and unsafe alcohol use and have all been associated with elevated depression 5 years post-injury (Hoffman et al., 2011). Life satisfaction has also been reported to be affected by SCI, and is significantly determined by the level of injury, pain, and secondary impairments (Van Koppenhagen et al., 2008).

Research examining the impact of an SCI within family members and broader social connections has also emphasized the challenges (Baker, Barker, Sampson, & Martin, 2017). A significant number of studies have reported elevated levels of psychological distress and burden experienced by family caregivers post-SCI (Baker et al., 2017). Furthermore, these impacts may worsen over time, with a rare longitudinal study finding that spouses in the UK who played a caregiving role for their partner with SCI experienced greater depressive affect, physical and emotional stress, burnout, fatigue, and anger and resentment than spouses not in this role (Weitzenkamp, Gerhart, Charlifue, Whiteneck, & Savic, 1997) (see Fig. 1).

Although this body of research is of unquestionable value, the focus on the investigation of psychopathology, embodying deficits and vulnerability-oriented approach, has left other dimensions of the psychological adjustment process post-SCI under-researched and poorly understood (White, Driver, & Warren, 2008). Over the last two decades, alternative paradigms from positive psychology and strengths-based approaches (Saleebey, 2006; Seligman & Csikszentmihalyi,

Cellular, Molecular, Physiological, and Behavioral Aspects of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822427-4.00038-1

FIG. 1 Challenges for family caregivers of relatives with SCI (Weitzenkamp et al., 1997).

2000) have been utilized in broadening our understanding of individual and family adjustment to SCI (White et al., 2008). These involve a shift from a sole emphasis on pathology and deficits to health promotion and the nurturing of strengths (Connor & Davidson, 2003; Richardson, 2002). Research has demonstrated that some individuals and family members have been able to identify positive gains, benefits, and areas of growth after SCI (Byra, 2015; Chun & Lee, 2013; Kalpakjian et al., 2014; Middleton et al., 2014). However, key constructs which may be of importance within such paradigms and their application within the context of SCI are still not well understood.

This chapter, therefore, provides an overview of three central constructs, namely spirituality, hope, and resilience. These constructs all play a mediating role between explanatory factors such as demographic, injury, and psychosocial variables (e.g., sex, age, injury severity, functional status, relationship status, pre-injury psychiatric status) and outcomes such as psychological distress and carer burden post-SCI. Also, the theoretical literature and initial empirical research suggest that these constructs are interrelated.

The first section of this chapter introduces the *quest* narrative, a dynamic context within which to understand the role these constructs play in response to SCI. The following sections will then define each of these constructs and provide a brief outline of the nascent quantitative and qualitative research, both about the person with SCI, and family members. Following this, a model derived from qualitative interviews that integrates spirituality, hope and resilience is outlined, followed by quantitative studies that also demonstrate the inter-relationship among these three constructs. The final section of the chapter highlights approaches to integrating spirituality, hope, and resilience into the clinical practice of SCI rehabilitation.

Responses to trauma: The quest narrative and the role of spirituality, hope, and resilience

Investigations examining the process of adjustment to traumatic events have often characterized this process in terms of a journey (Campbell, 2008). In *The Wounded Storyteller*, Frank (1995) introduces the *quest* narrative as one of three possible narratives for those with a long-standing illness or injury, alongside *restitution* and *chaos* narratives (see Fig. 2). A *restitution* narrative goes "Yesterday I was healthy, today I'm sick, but tomorrow I'll be healthy again" (p. 77). Such a narrative views the body as something needing to be "fixed," like a television set or other piece of equipment. Smith and Sparkes (2005) have suggested that for those with an SCI the restitution narrative is about recovery and "concrete hope," about returning to being able-bodied. The *chaos* narrative is the opposite of the *restitution* narrative. The plot of the *chaos* narrative is that life will never get better and the story is one of "vulnerability, futility, and impotence" (p. 97). Hope is lost and replaced with despair.

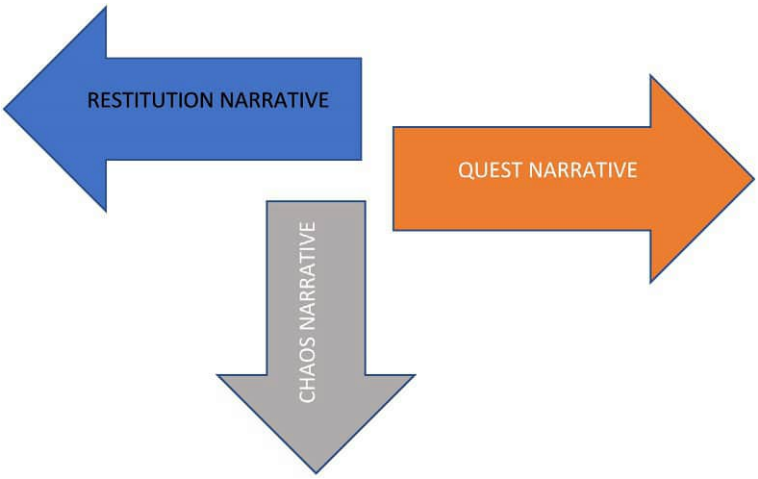

FIG. 2 The three narratives (Frank, 1995).

The *quest* narrative is different from both the *restitution* narrative and the *chaos* narrative. It reframes the interruption to an individual's life as a challenge. Illness or injury becomes a journey, and the teller has a story to tell. According to Frank quest stories meet

> *…suffering head on; they accept illness (or injury) and seek to use it. Illness (or injury) is the occasion of a journey that becomes a quest. What is quested for may never be wholly clear, but the quest is defined by the ill person's belief that something is to be gained through the experience (Frank, 1995, p. 115).*

Smith and Sparkes (2005) suggest that the *quest* narrative fosters a deeper "transcendent hope," one that embraces uncertainty, and moves towards reconstructing identity and meaning. This process of adaptation in response to challenge is also at the heart of resilience, as will be demonstrated through this chapter.

Spirituality after SCI

Spirituality is recognized as playing an important role in enabling individuals with SCI and their family members to thrive and move forward amid adversity (Jones, Dorsett, Simpson, & Briggs, 2018; White, Driver, & Warren, 2010). Spirituality has been defined as "the aspect of humanity that refers to the way individuals seek and express meaning and purpose, and the way they experience their connectedness to the moment, to self, to others, to nature and to the significant or sacred" (Puchalski et al., 2009). This definition implies that spirituality is a broad construct, encompassing a range of different sources of meaning and connection. Religious faith, which is sometimes considered to be interchangeable with spirituality, may be one source of spiritual strength (Davis et al., 2015), however, spirituality may also encompass connection with the natural world, other people, and oneself (Canda & Furman, 2009; Davis et al., 2015) (see Fig. 3). Within the broader healthcare field, there is an increasing awareness and acknowledgment of the importance of spirituality for individuals at times of illness or disability (Cobb, Puchalski, & Rumbold, 2012; Jones, Pryor, Care-Unger, & Simpson, 2018; Puchalski et al., 2009).

Most studies of spirituality after SCI have focused upon the individual with SCI (Jones, Simpson, Briggs, & Dorsett, 2016). A scoping review of the literature (Jones et al., 2016) found among quantitative studies, spirituality was positively associated with other indicators of adjustment after SCI, including life satisfaction, quality of life, and perceived health (see Fig. 4). These findings have been confirmed and extended in recent research (Jones, Simpson, Briggs, Dorsett, & Anderson, 2019; Siddall, McIndoe, Austin, & Wrigley, 2016; Wilson, Forchheimer, Heinemann, Warren, & McCullumsmith, 2017), with spirituality also being associated with lower levels of depression and anxiety. Furthermore, one study (Rahnama et al., 2015) has observed that lower levels of spirituality and negative spirituality may contribute towards greater levels of anxiety and depression.

Two qualitative studies (McColl et al., 2000a; Mundle, 2015) identified in the scoping review (Jones et al., 2016) investigated the concept of spirituality after SCI. The *quest* narrative featured in one of these. Mundle (2015) identified the *restitution, chaos,* and *quest* narratives, during a series of semi-structured interviews with a woman identifying with the

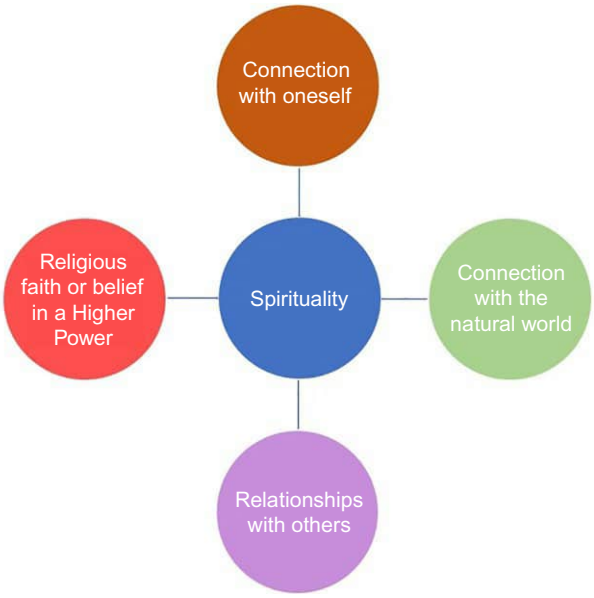

FIG. 3 Possible sources of spiritual strength (Canda & Furman, 2009; Davis et al., 2015).

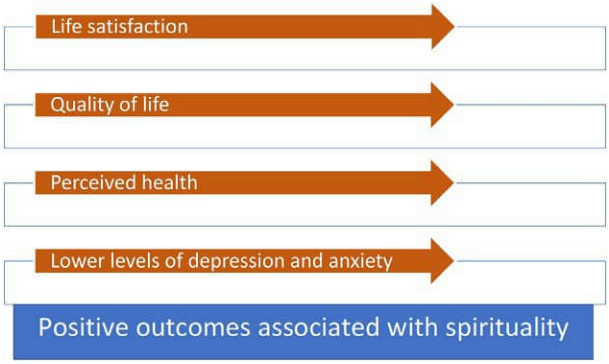

FIG. 4 Positive health outcomes associated with spirituality (Jones et al., 2016; Wilson et al., 2017).

Catholic faith. Mundle suggested that the woman moved from one narrative type to another, eventually arriving at a narrative of "testimony," where others observed her be an "actor in her own healing drama who, in turn, could offer healing and spiritual guidance to others" (p. 41).

The second qualitative study identified to consider spirituality after SCI (McColl et al., 2000a) stands alone as the only one in the scoping review to specifically consider the concept of spirituality as a relational construct. From their interviews with individuals with brain injury or SCI, McColl et al. (2000a) identified five themes which they argued impact upon all aspects of spirituality: (i) awareness, relating to a greater appreciation of life, others, and the world; (ii) closeness, encompassing increased intimacy, particularly within the family; (iii) trust, involving allowing others to provide help due to new dependency and reliance; (iv) vulnerability, as participants "recognised that they were not invincible or immortal"; and (v) purpose, due to the purpose of life which had changed for many participants, with some specifically referring to God or a Creator having a plan for them (p. 821). These findings led to the development of a broad framework for consideration of spiritual issues associated with disability, which encompassed intra-personal, inter-personal, and trans-personal elements (McColl et al., 2000b).

Hope after SCI

Hope has been recognized to be an important element in recovery from SCI (Dorsett, 2010). Hope is "a multi-dimensional dynamic life force characterised by a confident yet uncertain expectation of achieving a future good which….is realistically

possible and personally significant" (Dufault & Martocchio, 1985, p. 380). Dorsett (2010, pp. 85, 86) has suggested that hope "provides a reason to go on living, helps maintain motivation, positive expectations, and may mediate the effect of depression."

Within the field of SCI, hope has played an important role in supporting positive psychological adjustment after SCI. Higher hope agency, as measured by the State Hope Scale (Snyder et al., 1996), has been associated with higher levels of acceptance after SCI (Kennedy, Evans, & Sandhu, 2009). Kortte, Gilbert, Gorman, and Wegener (2010) observed that hope and positive effect demonstrated a significant positive relationship with life satisfaction during the initial period of acute rehabilitation after SCI, and contributed to the prediction of life satisfaction at a three-month follow-up.

A range of qualitative studies have also considered the process of hope for individuals after SCI (Babamohamadi, Negarandeh, & Dehghan-Nayeri, 2011; Dorsett, 2010; Lohne, 2009; Lohne & Severinsson, 2005; Parashar, 2015; Smith & Sparkes, 2005). Hope has been observed to be often associated with a desire for complete recovery (Dorsett, 2010; Parashar, 2015). However, over time, hope has also been expressed for a satisfying quality of life, even in the absence of recovery (Dorsett, 2010; Lohne, 2009; Parashar, 2015). Hope has in some circumstances been closely associated with having religious faith (Babamohamadi et al., 2011).

Smith and Sparkes (2005) observed three kinds of hope among men who sustained SCI through sport: concrete hope, transcendent hope, and despair (loss of hope). Drawing upon the work of Frank (1995) the authors suggested that each kind of hope was shaped by a particular narrative type. Those reflecting the "*restitution* narrative" focused upon walking again, being cured, and returning to their pre-injury lifestyles. The "*quest* narrative," was associated with embracing "uncertainty and finitude, celebrating surprise, play, novelty, mystery, and openness to change" (Smith & Sparkes, 2005, p. 1099). In contrast, the "*chaos* narrative" is characterized as individuals who have experienced a loss of hope, perceiving life to be over as a consequence of SCI.

The presence of hope is common across different spiritual traditions. For example, Babamohamadi et al. (2011) found that hope was one of the most common coping strategies among Muslims in Iran. This included hope for successful surgery, hope in God for divine healing or miracles, hope for medical progress, and hope in the future.

Hope has also been observed independent of religion or spirituality, and something which may change over time. In a series of qualitative studies, Lohne and colleagues (Lohne, 2009; Lohne & Severinsson, 2005) considered hope in people with SCI at different stages post-injury. A year after the SCI, Lohne and Severinsson (2005) observed that individuals with SCI associated the process of hope with will power and struggle. Three to four years after SCI Lohne (2009) identified three main themes from interviews with the same participants; life-related hopes, body-related hopes, and creative and expanding hopes, where hope became about enjoying life within the limits experienced. In another longitudinal study Dorsett (2010) identified three foci of hope: (i) hope for a complete recovery, (ii) hope for a cure, and (iii) hope for a satisfying quality of life. For many participants in this study hope was an important factor in coping with their SCI, and a strong motivator to survive and "get on with life" (p. 95).

Finally, in a longitudinal study conducted over 2 years with individuals with SCI in India, Parashar (2015) considered the continuum of hope and influencers of hope. They found that early in rehabilitation, participants were hopeful and optimistic, which Parashar labeled "inevitable optimism" (p. 566). During this period religion and spirituality were tools several participants relied upon. As time since SCI increased and participants realized more fully the extent of their injury, hope moved to a more "tempered optimism" where the focus shifted from "recovery to rehabilitation" (p. 566). Finally, according to Parashar, the continuum of hope brought participants to a stage of "inevitable realism (p. 567)" where participants "aligned their expectations to the challenges, as well as the possibilities of the present" (p. 567). In the words of one participant, hope "builds onto something else" (p. 567). These longitudinal studies demonstrate how hope can change over time, and although initial hope for recovery may fade, hope does not disappear altogether. Rather it is invested in one's quality of life or returning to activities once previously enjoyed.

Resilience after SCI

Resilience has also been applied to the recovery process after SCI. Historically, resilience was perceived as a personality trait only displayed by a subset of the population. However, research over the past three decades has clarified that resilience is a set of skills that anyone can acquire (Newman, 2005). It is "a dynamic process encompassing positive adaptation within the context of significant adversity" (Luthar, Cicchetti, & Becker, 2000, p. 543), comprising a "a process of coping with disruptive, stressful, or challenging life events in a way that provides the individual with additional protective and coping skills than prior to the disruption" (Richardson, Neiger, Jensen, & Kumpfer, 1990, p. 34). Resilience is relevant to individuals, couples, families, and communities. It entails more than simply bouncing back, but growth in the face of the challenges arising from disruption to an individual's usual life (Richardson, 2002, p. 313).

Resilience after SCI has been positively associated with higher levels of self-efficacy (Driver et al., 2016; Kilic, Dorstyn, & Guiver, 2013), spirituality or religion (Driver et al., 2016; Duggan, Wilson, DiPonio, Trumpower, & Meade, 2016; White et al., 2010), satisfaction with life (Jones et al., 2019; White et al., 2010), positive affect (Jones et al., 2019), hope (Simpson, Anderson, Jones, Genders, & Gopinath, 2020) and social support (Duggan et al., 2016; Monden et al., 2014) as well as lower levels of depression (Driver et al., 2016; Jones et al., 2019; Kilic et al., 2013; Monden et al., 2014; White et al., 2010). The smaller number of studies focused on the experience of family members identified that resilience is closely associated with a positive outlook, increased levels of social support, higher levels of positive affect and lower levels of carer burden and negative affect (Elliot, Berry, Richards, & Shewchuk, 2014; Simpson & Jones, 2013).

The relationship between spirituality, hope, and resilience after SCI

The relationship between spirituality, hope, and resilience has been explored within theoretical frameworks of individual and family adaptation, identified in models generated from the lived experience of people with SCI, and reported by empirical studies. Starting with theoretical frameworks, Walsh (2003) has proposed a model of family resilience that "involves key processes over time that foster the ability to 'struggle well,' surmount obstacles, and go on to live and love fully" (p. 1). Walsh suggests that making meaning out of crises, facilitating a hopeful, positive outlook, and transcendent or spiritual moorings are three key processes that contribute towards family resilience. In the field of traumatic brain injury Nalder, Hartman, Hunt, and King (2019) have suggested that hope and spirituality may be two of several personal characteristics which contribute towards enabling beliefs and resiliency-related outcomes; reconstructing identity, adjusting participation patterns or preferences, and re-engaging in activities.

The interrelationship between spirituality, hope, and resilience has been identified in studies of the lived experience of people with SCI and their family members. The model presented in Fig. 5 brings together concepts of spirituality, hope, and resilience within the dynamic journey of adjustment, drawing upon the lived experience of both the person with SCI and family caregiver (Jones, Dorsett, Simpson, & Briggs, 2018). This model was developed from a study conducted with 10 family dyads at two time points, at a spinal injury unit in Sydney, Australia. The model highlights how people with SCI and their family members can draw upon a range of sources of spiritual strength. These sources of spiritual strength included the natural world, faith in God, oneself, and meaningful connectedness with others. In many cases these sources of spiritual strength can be tested after an SCI, leading to a meaning-making process. For people with SCI meaning-making responses included the perception that they had been given a second chance at life, that they could pray for healing, thinking positively about the situation, and comparing themselves with others who were less fortunate. Three key outcomes associated with these meaning-making responses were gratitude, hope, and deepening relationships with others, each of which may

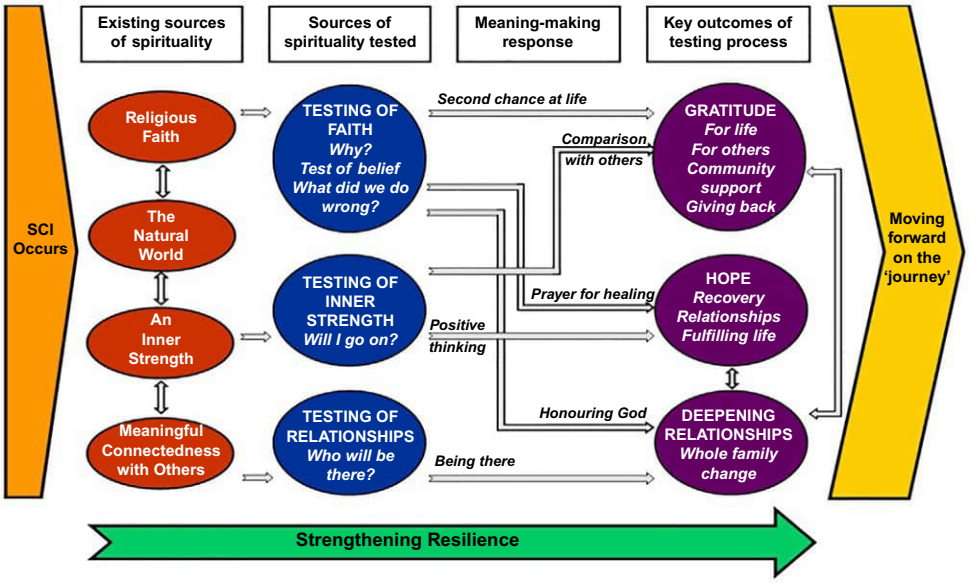

FIG. 5 Family resilience after SCI. *(Adapted from Jones, K. F., Dorsett, P., Simpson, G., & Briggs, L. (2018). Moving forward on the journey: Spirituality and family resilience after spinal cord injury.* Rehabilitation Psychology, 63*(4), 521–531. https://doi.org/10.1037/rep0000229, Figure 1 (p. 6).)*

contribute to the ongoing process of strengthening resilience. Hope included hope for physical recovery, hope for deeper and stronger relationships, and hope for a meaningful life together. Each outcome was observed to contribute to the ongoing process of resilience-building. Like the *quest* narrative, this model reveals that adaptation after SCI can be a journey, with people with SCI and their family members moving forward, stronger together.

The interrelationship between spirituality, hope, and resilience found in this model is echoed in two other qualitative studies. Monden et al. (2014) identified six factors that may contribute to resilience after SCI: spirituality or faith, alongside psychological strength, social support, perspective, adaptive coping, and serving as a role model or inspiring others. In a qualitative study with 475 people with SCI, Duggan et al. (2016), found resilience to be one of eight factors associated with happiness; the others included religion or faith in a higher power, general outlook on life, social support, and social relationships, physical health and functioning, mood, social comparisons, and resources.

Structural equation modeling has found an interrelationship among spirituality, hope, and resilience in two independent samples (Jones et al., 2019; Simpson et al., 2020). In both models, spirituality contributed to resilience, rather than vice versa, with the regression coefficients (ranging from 0.39 to 0.71) indicating a strong relationship. In the second of these studies, hope was also introduced, finding that in addition to the direct relationship between spirituality and resilience, spirituality also had an indirect relationship with resilience mediated by hope (Simpson et al., 2020).

Higher levels of spirituality, hope, and resilience were strongly associated with positive outcomes post-SCI. These included positive affect and satisfaction with life (Jones et al., 2019; Simpson et al., 2020). Higher levels of these three constructs were also associated with lower levels of negative outcomes from SCI, such as depression and negative affect (Jones et al., 2019; Simpson et al., 2020).

Implications for SCI rehabilitation: Person-centered care that embraces spirituality, hope, and resilience

The associations between higher levels of spirituality, hope, and resilience and better outcomes for individuals with SCI and their families need further testing and investigation. If a growing body of evidence supports the associations among these constructs and positive outcomes after SCI, then it raises a number of important implications for clinical practice.

Rehabilitation staff who have been surveyed, generally hold positive attitudes towards spirituality, even those who do not hold personal spiritual beliefs (Jones, Dorsett, Briggs, & Simpson, 2018; Jones, Pryor, Care-Unger, & Simpson, 2020a, 2020b, 2020c). Furthermore, many of them valued rehabilitation approaches that incorporated spirituality as part of a person-centered approach (Jones et al., 2020b). Staff in an SCI unit who participated in two focus groups perceived spirituality as potentially playing an important role in the adjustment of many individuals and their families after SCI (Jones, Dorsett, Briggs, & Simpson, 2018).

Despite the putative importance attributed to the role of spirituality in facilitating the adjustment process following SCI, focus groups and survey data found that few felt equipped to address the spiritual needs of rehabilitation clients and deemed that more training was necessary (Jones et al., 2020b). A brief (two and a half hours) spiritual care training program developed for rehabilitation staff was trialed at Royal Rehab in Sydney Australia. The training comprised a one-hour online self-study component followed by a one and a half hour face-to-face workshop that employed lectures, videoed interviews, role-plays and individual exercises to foster knowledge and skills (Jones et al., 2020c).

The quantitative evaluation of the program revealed that the competency, confidence and comfort levels in delivering spiritual care for those in the intervention group were significantly higher at post and follow-up time points than those in a matched control group (Jones et al., 2020a). An analysis of interviews with 16 participants 6–8 weeks after the training indicated that the overarching take-home message for staff was that “spirituality is everybody’s business” (Jones et al., 2020c). Other themes included increased awareness of the nature of spirituality, realization of the importance of spirituality to clients, a desire to keep spirituality on the radar, identifying barriers to providing spiritual care, incorporating spirituality into practice, and recognizing spirituality as personally meaningful.

These findings suggest that incorporating spiritual care into healthcare practice brings many positives. However, some authors have advised caution. For instance, McSherry and Ross (2002) have highlighted some of the dilemmas of conducting spiritual assessments. These include questions regarding how spirituality is defined, staff motives for undertaking spiritual assessment, the timing and comprehensiveness of assessments, direct questioning versus observation, and which staff should undertake a spiritual assessment.

In addition to spirituality, it is also possible to focus on resilience as a modifiable factor that could be targeted for intervention. For example, the Strength 2 Strength program was developed to build resilience among family members supporting relatives with an SCI or a traumatic brain injury (Simpson et al., 2011). A program that focuses on resilience

could provide options for individuals with SCI or family members who do not identify as having a spiritual dimension to their life. Future research could examine whether increased levels of hope could be a secondary outcome from such programs.

As promising as the current research has been, there are still many questions to be answered. Can programs be developed that support individuals with SCI to draw upon their spirituality to facilitate adjustment to SCI. Will these programs lead to increased levels of hope and resilience? Does the training of rehabilitation staff in spiritual care lead to measurable changes in their practice with clients and can this be captured within the research process? If programs to build resilience demonstrate efficacy among family caregivers supporting individuals with SCI, could such a program have similar benefits for individuals with SCI themselves?

Research into the role of spirituality in facilitating the process of adaptation to SCI is only just beginning. It has a strong potential to expand our understanding of the process of adjustment to SCI. The common references to spirituality in the lived experience accounts of individuals with SCI and their family members provide a strong rationale for continuing to investigate this domain. Observational studies have found strong associations between spirituality and other key clinical constructs such as hope and resilience. In combination, spirituality, hope, and resilience seem to play a significant role in enhancing the quality of life and well-being after SCI and provide a buffer to psychopathology and burden. More sophisticated longitudinal observational studies and experimental trials will be a key to moving this promising area of research forward into the future.

Applications to other areas of neuroscience

This section draws heavily upon Newberg, A. B. (2014). The neuroscientific study of spiritual practices. *Frontiers in Psychology,* 5, 215.

The chapter has focused on research documenting the subjective experience of spirituality within the context of adjustment to SCI. The neurobiological correlates of religious and spiritual phenomena have been investigated, generally among healthy populations, with meditation practices the most frequent area examined. Objective measures have evaluated the association between religious/spiritual practices and/or experiences and physiological parameters such as blood pressure and heart rate, as well as hormone and immune function. Neurobiological parameters such as electroencephalographic activity, cerebral blood flow, cerebral metabolism, and changes in neurotransmitter levels can be measured by techniques including electroencephalography and functional neuroimaging (positron emission tomography, functional magnetic resonance imaging fMRI). These techniques have been found to have both advantages and limitations. For example, fMRI scans require people to lie in a confined space with a significant underlying level of noise. This presents logistic challenges for subjects who are asked to undertake a series of spiritual practices such as prayer while being scanned. Future research could be expanded to include clinical populations, such as individuals with SCI, to help increase understanding of the association between spiritual states, experiences, and the brain.

Mini-dictionary of terms

Spirituality: Spirituality is a broad and dynamic construct that encompasses a range of sources of ultimate meaning-making and connection. Although religious faith may be one source of spirituality, it is not the only one. Other sources of spirituality may include the natural world, music, art, others, and oneself.

Hope: Hope is a dynamic life force focused on achieving something positive or good and is future based. Hope provides motivation and a reason for living.

Resilience: Resilience is a dynamic process that helps a person to overcome adversity and to move forward with growth and adaptation.

Key facts of "Spirituality, hope, and resilience in the recovery and adaptation process following spinal cord injury"

- In 1984 at the 37th World Health Assembly, the spiritual dimension was integrated into the World Health Organisation Member States' strategies for health and understood to play "a great role in motivating people's achievement in all aspects of life."
- In the most comprehensive review of the literature to date, Koenig (2012) identified that in many studies religion/spirituality was significantly associated with better mental health, greater social support, and lower levels of depression, suicide rates and anxiety.

- Hope has been described as understandable, measurable and essential as a coping strategy (Snyder, 1995).
- According to the American Psychology Association (Newman, 2005), resilience is a skill that can be learned by almost everyone.
- A holistic approach to healthcare, which acknowledges the biological, psychological, social and spiritual aspects of a person's well-being, leads to better patient outcomes.

Summary points

- The majority of research associated with coping and adaptation after SCI has focused on the physical, psychological and social challenges confronting the injured person and their family members.
- Recent research has highlighted the potential role that positive attributes such as spirituality, hope, and resilience may play in the process of recovery and adaption from SCI. The quest narrative described by Frank (1995) may be a helpful depiction of this process.
- Spirituality has been associated with a range of positive outcomes after SCI, including greater life satisfaction, quality of life, and lower levels of depression and anxiety.
- Hope has been identified to be an important coping mechanism for people after SCI, and something which may change over time.
- Resilience has been defined as a dynamic growth process, to which spirituality and hope may contribute.
- A study of individuals with SCI and their family members has generated a model of resilience, which depicts the whole family drawing upon different sources of spiritual strength to move forward together on a journey of adaptation and coping.
- A recent spiritual care training program conducted with health professionals has been successful in increasing awareness of the importance of spirituality after traumatic injury, and increasing staff confidence, comfort, and competency levels in spiritual care delivery.

References

Babamohamadi, H., Negarandeh, R., & Dehghan-Nayeri, N. (2011). Coping strategies used by people with spinal cord injury: A qualitative study. *Spinal Cord*, *49*, 832–837.

Baker, A., Barker, S., Sampson, A., & Martin, C. (2017). Caregiver outcomes and interventions: A systematic scoping review of the traumatic brain injury and spinal cord injury literature. *Clinical Rehabilitation*, *31*(1), 45–60.

Byra, S. (2015). Posttraumatic growth in people with traumatic long-term spinal cord injury: Predictive role of basic hope and coping. *Spinal Cord*, *54*, 478–482.

Campbell, J. (2008). *The hero with a thousand faces* (3rd ed.). Novato, CA: New World Library.

Canda, E. R., & Furman, L. D. (2009). *Spiritual diversity in social work practice: The heart of helping*. Cary, NC: Oxford University Press.

Chun, S., & Lee, Y. (2013). "I am just thankful": The experience of gratitude following traumatic spinal cord injury. *Disability and Rehabilitation*, *35*(1), 11–19.

Cobb, M., Puchalski, C. M., & Rumbold, B. (Eds.). (2012). *Oxford textbook of spirituality in healthcare*. Oxford: Oxford University Press.

Connor, K. M., & Davidson, J. R. (2003). Development of a new resilience scale: The Connor-Davidson resilience scale (CD-RISC). *Depression and Anxiety*, *18*, 76–82.

Davis, D. E., Rice, K., Hook, J. N., Van Tongeren, D. R., DeBlaere, C., Choe, E., et al. (2015). Development of the sources of spirituality scale. *Journal of Counselling Psychology*, *62*(3), 503–513.

Dorsett, P. (2010). The importance of hope in coping with severe acquired disability. *Australian Social Work*, *63*(1), 83–102.

Driver, S., Warren, A. M., Reynolds, M., Agtarap, S., Hamilton, R., Trost, Z., et al. (2016). Identifying predictors of resilience at inpatient and 3-month post-spinal cord injury. *The Journal of Spinal Cord Medicine*, *39*(1), 77–84. https://doi.org/10.1179/2045772314Y.0000000270.

Dufault, K., & Martocchio, B. C. (1985). Hope: Its spheres and dimensions. Symposium on compassionate care and the dying experience. *Nursing Clinics of North America*, *20*(2), 379–391.

Duggan, C., Wilson, C., DiPonio, L., Trumpower, B., & Meade, M. A. (2016). Resilience and happiness after spinal cord injury: A qualitative study. *Topics in Spinal Cord Injury Rehabilitation*, *22*(2), 99–110. https://doi.org/10.1310/sci2202-99.

Elliot, T. R., Berry, J. W., Richards, J. S., & Shewchuk, R. (2014). Resilience in the initial year of caregiving for a family member with a traumatic spinal cord injury. *Journal of Consulting and Clinical Psychology*, *82*(6), 1072–1086.

Frank, A. W. (1995). *The wounded storyteller: Body, illness and ethics*. Chicago: University of Chicago Press.

Hagen, E. M., & Rekand, T. (2015). Management of neuropathic pain associated with spinal cord injury. *Pain and therapy*, *4*(1), 51–65. https://doi.org/10.1007/s40122-015-0033-y.

Hoffman, J., Bombardier, C., Graves, D., Kalpakjian, C., & Krause, J. (2011). A longitudinal study of depression 1 to 5 years after spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *92*(3), 411–418.

Jazayeri, S. B., Beygi, S., Shokranch, F., Hagen, E. M., & Rahimi-Movaghar, V. (2015). Incidence of traumatic spinal cord injury worldwide: A systematic review. *European Spine Journal*, *24*, 905–918.

Jones, K. F., Dorsett, P., Briggs, L., & Simpson, G. (2018). The role of spirituality in spinal cord injury (SCI) rehabilitation: Exploring health professional perspectives. *Spinal Cord Series And Cases*, *4*(1), 54. https://doi.org/10.1038/s41394-018-0078-3.

Jones, K. F., Dorsett, P., Simpson, G., & Briggs, L. (2018). Moving forward on the journey: Spirituality and family resilience after spinal cord injury. *Rehabilitation Psychology*, *63*(4), 521–531. https://doi.org/10.1037/rep0000229.

Jones, K. F., Pryor, J., Care-Unger, C., & Simpson, G. (2018). Spirituality and its relationship with positive adjustment following traumatic brain injury: A scoping review. *Brain Injury*, 1–11. https://doi.org/10.1080/02699052.2018.1511066.

Jones, K. F., Pryor, J., Care-Unger, C., & Simpson, G. (2020a). Effectiveness of spiritual care training for rehabilitation professionals: An exploratory controlled trial. *NeuroRehabilitation*. https://doi.org/10.3233/NRE-203221. Advance online publication.

Jones, K. F., Pryor, J., Care-Unger, C., & Simpson, G. (2020b). Rehabilitation health professionals' perceptions of spirituality and spiritual care: The results of an online survey. *NeuroRehabilitation*, *46*(1), 17–30. https://doi.org/10.3233/NRE-192857.

Jones, K. F., Pryor, J., Care-Unger, C., & Simpson, G. (2020c). "Spirituality is everybody's business": An exploration of the impact of spiritual care training upon the perceptions and practice of rehabilitation professionals. *Disability and Rehabilitation*, 1–10. https://doi.org/10.1080/09638288.2020.1820586. Advance online publication.

Jones, K. F., Simpson, G., Briggs, L., & Dorsett, P. (2016). Does spirituality facilitate adjustment and resilience among individuals and their families after SCI? *Disability and Rehabilitation*, *38*(10), 921–935.

Jones, K. F., Simpson, G., Briggs, L., Dorsett, P., & Anderson, M. (2019). A study of whether individual and dyadic relations between spirituality and resilience contribute to psychological adjustment among individuals with spinal cord injuries and their family members. *Clinical Rehabilitation*, *33*(9), 1503–1514. https://doi.org/10.1177/0269215519845034.

Kalpakjian, C. Z., McCullumsmith, C. B., Fann, J. R., Richards, J. S., Stoelb, B. L., Heinemann, A. W., et al. (2014). Post-traumatic growth following spinal cord injury. *The Journal of Spinal Cord Medicine*, *37*(2), 218–225. https://doi.org/10.1179/2045772313Y.0000000169.

Kennedy, P., Evans, M., & Sandhu, N. (2009). Psychological adjustment to spinal cord injury: The contribution of coping, hope and cognitive appraisals. *Psychology, Health & Medicine*, *14*(1), 17–33.

Kennedy, P., & Rogers, B. A. (2000). Anxiety and depression after spinal cord injury: A longitudinal analysis. *Archives of Physical Medicine and Rehabilitation*, *81*(7), 932–937.

Kilic, S. A., Dorstyn, D., & Guiver, N. G. (2013). Examining factors that contribute to the process of resilience following spinal cord injury. *Spinal Cord*, *51*, 553–557.

Kirshblum, S., & Benevento, B. (2009). Understanding spinal cord injury and advances in recovery. In E. Druin, & M. M. Sliwinski (Eds.), *Spinal Cord Injuries: Management and Rehabilitation* (pp. 1–17). Saint Louis: Mosby.

Koenig, H. (2012). Religion, spirituality, and health: The research and clinical implications. *ISRN Psychiatry*, *8*. https://doi.org/10.5402/2012/278730.

Kortte, K. B., Gilbert, M., Gorman, P., & Wegener, S. T. (2010). Positive psychological variables in the prediction of life satisfaction after spinal cord injury. *Rehabilitation Psychology*, *55*(1), 40–47.

Lohne, V. (2009). Back to life again—Patients' experiences of hope three to four years after a spinal cord injury—A longitudinal study. *Canadian Journal of Neuroscience Nursing*, *31*(2), 20–25.

Lohne, V., & Severinsson, E. (2005). Patients' experiences of hope and suffering during the first year following acute spinal cord injury. *Journal of Clinical Nursing*, *14*, 285–293.

Luthar, S. S., Cicchetti, D., & Becker, B. (2000). The construct of resilience: A critical evaluation and guidelines for future work. *Child Development*, *71*(3), 543–562.

McColl, M. A., Bickenbach, J., Johnston, J., Nishihama, S., Schumaker, M., Smith, K., et al. (2000a). Changes in spiritual beliefs after traumatic disability. *Archives of Physical Medicine and Rehabilitation*, *81*(6), 817–823.

McColl, M. A., Bickenbach, J., Johnston, J., Nishihama, S., Schumaker, M., Smith, K., et al. (2000b). Spiritual issues associated with traumatic-onset disability. *Disability and Rehabilitation*, *22*(12), 555–564.

McSherry, W., & Ross, L. (2002). Dilemmas of spiritual assessment: Considerations for nursing practice. *Journal of Advanced Nursing*, *38*(5), 479–488.

Middleton, J., Simpson, G., De Wolf, A., Quirk, R., Descallar, J., & Cameron, I. (2014). Health status, quality of life and strain in carers during community integration after SCI. *Archives of Physical Medicine and Rehabilitation*, *95*, 1312–1319. https://doi.org/10.1016/j.apmr.2014.03.017.

Monden, K. R., Trost, Z., Catalano, D., Garner, A. N., Symcox, J., Driver, S., et al. (2014). Resilience following spinal cord injury: A phenomenological view. *Spinal Cord*, *52*, 197–201.

Mundle, R. (2015). "I should be closer to god because of this"-a case study of embodied narratives and spiritual reconstruction in spinal cord injury and stroke rehabilitation. *Journal of Disability and Religion*, *19*(1), 30–49.

Nalder, E., Hartman, L., Hunt, A., & King, G. (2019). Traumatic brain injury resiliency model: A conceptual model to guide rehabilitation research and practice. *Disability and Rehabilitation*, *41*(22), 2708–2717.

Newman, R. (2005). APA's resilience initiative. *Professional Psychology: Research and Practice*, *36*, 227–229.

Palmer, S., Kriegsman, K. H., & Palmer, J. B. (2008). *Spinal cord injury: A guide for living*. Baltimore: John Hopkins University Press.

Parashar, D. (2015). The trajectory of hope: Pathways to find meaning and reconstructing the self after a spinal cord injury. *Spinal Cord*, *53*, 565–568.

Puchalski, C., Ferrell, B., Virani, R., Otis-Green, S., Baird, P., Bull, J., et al. (2009). Improving the quality of spiritual care as a dimension of palliative care: The report of the consensus conference. *Journal of Palliative Medicine*, *12*, 885–904.

Rahnama, P., Javidan, A. N., Saberi, H., Montazeri, A., Tavakkoli, S., Pakpour, A. H., et al. (2015). Does religious coping and spirituality have a moderating role on depression and anxiety in patients with spinal cord injury? A study from Iran. *Spinal Cord*, *53*, 870–874.

Richardson, G. E. (2002). The metatheory of resilience and resiliency. *Journal of Clinical Psychology*, *58*(3), 307–321.

Richardson, G. E., Neiger, B. L., Jensen, S., & Kumpfer, K. L. (1990). The resiliency model. *Health Education*, *21*(6), 33–39.

Saleebey, D. (2006). The strengths perspective: Possibilities and problems. In D. Saleebey (Ed.), *The strengths perspective in social work practice* (4th ed., pp. 279–303). Boston: Pearson.

Seligman, M. E., & Csikszentmihalyi, M. (2000). Positive psychology: An introduction. *American Psychologist*, *55*(1), 5–14.

Siddall, P. J., McIndoe, L., Austin, P., & Wrigley, P. J. (2016). The impact of pain on spiritual well-being in people with a spinal cord injury. *Spinal Cord*, 1–7.

Simpson, G., Anderson, M., Jones, K. F., Genders, M., & Gopinath, B. (2020). Do spirituality, resilience and hope mediate outcomes among family caregivers after traumatic brain injury or spinal cord injury? A structural equation modelling approach. *NeuroRehabilitation*, *46*(1), 3–15.

Simpson, G., & Brenner, L. A. (2019). *Suicide prevention after neurodisability: An evidence-informed approach*. New York: Oxford University Press.

Simpson, G., & Jones, K. (2013). How important is resilience among family members supporting relatives with traumatic brain injury or spinal cord injury? *Clinical Rehabilitation*, *27*(4), 367–377.

Simpson, G., Jones, K., Pfeiffer, D., Unger, C., Oosthuizen, H., Francis, J., et al. (2011). *Strength2Strength: Building resilience among families supporting relatives with traumatic injury*. Sydney, Australia: Lifetime Care and Support Authority.

Smith, B., & Sparkes, A. (2005). Men, sport, spinal cord injury, and narratives of hope. *Social Science & Medicine*, *61*, 1095–1105.

Snyder, C. R. (1995). Conceptualizing, measuring, and nurturing hope. *Journal of Counseling and Development*, *73*(3), 355–360. https://doi.org/10.1002/j.1556-6676.1995.tb01764.x.

Snyder, C. R., Sympson, S. C., Ybasco, F. C., Borders, T. F., Babyak, M. A., & Higgins, R. L. (1996). Development and validation of the State Hope Scale. *Journal of Personality and Social Psychology*, *70*(2), 321–335.

Van Koppenhagen, C. F., Post, M. W., Van der Woude, L. H., De Witte, L. P., Van Ashbeck, F. W., De Groot, S., et al. (2008). Changes and determinants of life satisfaction after spinal cord injury: A cohort study in the Netherlands. *Archives of Physical Medicine and Rehabilitation*, *89*, 1733–1740.

Walsh, F. (2003). Family resilience: A framework for clinical practice. *Family Process*, *42*(1), 1–18.

Weitzenkamp, D. A., Gerhart, K. A., Charlifue, S., Whiteneck, G., & Savic, G. (1997). Spouse of spinal cord injury survivors: The added impact of caregiving. *Archives of Physical Medicine and Rehabilitation*, *78*, 822–827.

White, B., Driver, S., & Warren, A. (2008). Considering resilience in the rehabilitation of people with traumatic disabilities. *Rehabilitation Psychology*, *53*(1), 9–17.

White, B., Driver, S., & Warren, A. (2010). Resilience and indicators of adjustment during rehabilitation from a spinal cord injury. *Rehabilitation Psychology*, *55*(1), 23–32.

Williams, R., & Murray, A. (2015). Prevalence of depression after spinal cord injury: A meta-analysis. *Archives of Physical Medicine and Rehabilitation*, *96*(1), 133–140.

Wilson, C. S., Forchheimer, M., Heinemann, A. W., Warren, A. M., & McCullumsmith, C. (2017). Assessment of the relationship of spiritual well-being to depression and quality of life for persons with spinal cord injury. *Disability and Rehabilitation*, *39*(5), 491–496.

World Health Organisation. (2013). *Spinal cord injury*. Retrieved from http://www.who.int/mediacentre/factsheets/fs384/en/.

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Chapter 39

Wellness intervention for persons with spinal cord injury

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List of abbreviations

BCT	behavior change technique
HAPA	health action process model
MS	multiple sclerosis
QOL	quality of life
SCI	spinal cord injury
SCT	social cognitive theory
TBI	traumatic brain injury
TPB	theory of planned behavior
TTM	transtheoretical model

Introduction

Spinal cord injury (SCI), defined by damage to the spinal cord that causes a temporary or permanent change in function, is often a devastating injury that impacts approximately 17,700 people in the United States (US) per year (NSCISC, 2020). From the onset, SCI requires immediate and long-term intervention to address changes in function such as paralysis, loss of sensation, bowel and bladder dysfunction, reduced muscle strength, and pain (NSCISC, 2020). Acquiring an SCI can have a devastating impact on the psychological well-being of a person, with depression, anxiety, a loss of self and identity, and hope for the future (Sparkes & Smith, 2002) being elements of SCI that the majority of people, at some time, will experience. Socially, an SCI can negatively affect an individual's independence, social relationships, and overall quality of life (QOL) (Kennedy, Lude, Elfström, & Smithson, 2011).

Persons with an SCI can, however, live a positive and fulfilling life filled with great meaning and happiness (Chun & Lee, 2020). The process of experiencing long-term wellness after SCI is long, complex, and unique to each individual. The unique nature of SCI regarding the level of injury, degree of completeness, the individual person and immediate social support and surrounding areas underscores the importance of innovative, multifaceted approaches that promote and maintain independence, wellness, and QOL.

This chapter provides readers with tools for designing and assessing wellness interventions that may improve the lives of persons with SCI. We first define wellness and describe unique attributes that distinguish wellness interventions from other health behavior change interventions. Following this, we discuss common measures to assess wellness outcomes of interest. We next present modifiable health-promoting and health-risk behaviors that may be targeted for improving wellness outcomes. We then outline previous literature examining behavior change theories utilized for promoting health behavior change among persons with SCI. We conclude with a brief review of previous wellness interventions and provide considerations that guide the development of future wellness interventions for persons with SCI.

What is wellness?

The concept of wellness has evolved from the mid-20th century to now and differs between health disciplines. In 1948, the World Health Organization defined wellness as a state of complete physical, mental, and social well-being and not merely

Cellular, Molecular, Physiological, and Behavioral Aspects of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822427-4.00039-3

FIG. 1 The six wellness dimensions. The six primary wellness dimensions outlined by Hettler 1980.

the absence of disease or infirmity. With greater political and socio-cultural movements from disability studies, and evolution within psychological health sciences regarding the concepts of wellness and illness (Goodwin & Jamison, 2007), wellness has become a much more multidimensional construct that can mean different things to people from different disciplines. For example, Lebensohn, Dodds, Benn, Brooks, and Birch (2013) defined wellness as "an active process of making choices in multiple dimensions of body, mind, and spirit that lead toward healthier ways of living." Alternatively, from a psychological standpoint, wellness is understood as optimal psychological function and experience (Ryan & Deci, 2001). A hedonic tradition understands wellness to be the pursuit of happiness and seeking to obtain a "good life" (Keyes, Shmotkin, & Ryff, 2002), while a eudemonic tradition defines wellness through realizing one's potential and flourishing (Ryff & Keyes, 1995). Further, wellness is often operationalized into six dimensions: occupational, social, intellectual, physical, emotional, and spiritual (Fig. 1). For this chapter, we define wellness as the existence of positive health in an individual with a focus on functioning, health, and QOL (Corbin & Pangrazi, 2001), but draw upon the aforementioned concepts to highlight the ways interventions can target and enhance the various aspects of wellness among persons with SCI.

Wellness interventions aim to modify behaviors for improving health, functioning, and QOL. In the field of rehabilitation, wellness interventions are specifically characterized by approaches that focus on improving aspects of well-being in the context of a health condition as opposed to concentration on medical management (Stuifbergen, Morris, Jung, Pierini, & Morgan, 2010). Promotion of health behaviors via wellness interventions in persons with SCI are therefore critical given reduced overall QOL reported in this population, both immediately post-injury and long-term. Indeed, persons with SCI report significantly lower overall QOL than the general population as well as higher rates of secondary health conditions such as depression, pain, and cardiovascular disease (Decker & Schulz, 1985; Post, de Witte, van Asbeck, van Dijk, & Schrijvers, 1998). The high incidence of poor QOL, and dramatic changes in life circumstances following SCI, support the interest in wellness interventions targeting health behavior change.

There is an immediate, immense impact of SCI on well-being such that most individuals must learn a completely new way of living. Over the short term during inpatient and acute treatment, healthcare practitioners focus on restoring activities of daily living and minimizing functional impairment through pharmaceutical treatments as well as physical and occupational therapies. Moreover, during the years following acquiring an SCI, a majority of individuals experience clinically significant depressive symptoms and increases in adiposity based on changes in energy expenditure (Gater Jr, 2007; Krause, Kemp, & Coker, 2000). Traditionally, interventions exclude persons with SCI in this sensitive period the first year following injury, yet this period may be a critical gateway for promoting long-term wellness that requires tailored approaches. Further research is needed regarding an appropriate timeline for emphasizing health behaviors in the rehabilitation period following SCI.

Wellness interventions across the lifespan in SCI must consider the changing demographics in the SCI population. Indeed, the average age at injury is now 41 years old compared to 29 years old in the 1970s (NSCISC, 2020). Further, years post-injury, age, gender, marital status, education, employment status, and income are associated with differing levels of QOL among persons with SCI (Dijkers, 1999; Putzke, Elliott, & Richards, 2001; Putzke, Richards, Hicken, & DeVivo, 2002). Such factors may be important considerations when focusing on wellness in diverse groups with SCI. Age may be a focal factor considering life expectancy following SCI has significantly increased based on advances in medicine and assistive device technology. One study of older adults with SCI reported that average activity limitations measured using the Spinal Cord Independence Measure were moderate (mean total score 65.2, range 8–100) and were associated with severity and level of injury (Jörgensen, Iwarsson, & Lexell, 2017). Satisfaction with life among older adults was associated with marital status, vocational status, and bladder functioning (Jörgensen et al., 2017). Collectively, promotion of wellness is important in the SCI population immediately following injury, longitudinally, and among older adults, and innovation strategies may be warranted that address needs and preferences across the lifespan.

Measurement of wellness in SCI

The study of wellness interventions requires appropriate measurement tools, both quantitative and qualitative. From a quantitative perspective, primary outcomes among wellness interventions often focus on QOL, satisfaction with life, or other measures of subjective well-being. This focus is based on the need for global measures that capture an individual's perception of their overall life rather than solely focus on physical functioning. Overall QOL or satisfaction with life is often measured using Diener's 5-item Satisfaction with Life Scale (SWLS) or the 9-item Life Situation Questionnaire (LSQ) (Diener, Emmons, Larsen, & Griffin, 1985; Fugl-Meyer, Bränholm, & Fugl-Meyer, 1991). Health-related QOL (HRQOL) among persons with SCI is widely measured using the SF-12 of SF-36, and SCI-specific measures of QOL have been developed such as the Ferrans and Powers Quality of Life Index (QLI-SCI) (May & Warren, 2002). The focus on HRQOL is based on a need to assess perceptions regarding physical and mental functioning, and overall wellness.

Qualitative methods provide another assessment approach to guide the creation and refinement of wellness interventions. Indeed, exploratory qualitative studies are a crucial first step when designing interventions as they can provide an empirical foundation regarding a person's current wellness state, and identifying preferences for future interventions. Qualitative methods can be incorporated as part of feasibility assessments of interventions, and guide further refinement of interventions for larger clinical trials. Qualitative studies have much to contribute to wellness interventions in SCI as they afford rich detail regarding experience, perceptions, satisfaction, and recommendations for improving an intervention design, delivery, and assessment, mainly through employing interview methods. For example, semi-structured interviews were conducted with four males with SCI following a center-based wellness program and highlighted that the program positively influenced the physical, mental, and social well-being of participants (Ekelman et al., 2017). Findings from this qualitative study contributed to knowledge regarding the utility of the program as well as the value of social and occupational components.

Health behaviors: Targets for wellness interventions

An important consideration of wellness intervention design is the deliberate inclusion of multiple health behaviors to reflect the multifaced nature of wellness. For example, interventions typically target modifiable health-promoting behaviors such as physical activity, nutrition, and stress management as well as health-risk behaviors such as tobacco use. Behaviors of interest may be targeted synchronously or asynchronously. The health behaviors outlined below are but a few samples of possible targets for wellness interventions among persons with SCI.

Physical activity is the most widely studied health-promoting behavior among persons with SCI. Physical activity is broadly defined as any bodily movement produced by skeletal muscles that require energy expenditure – including activities undertaken while working, playing, carrying out household chores, traveling, and engaging in recreational pursuits (WHO, 2018). Exercise is a subset of physical activity that is planned, structured, repetitive, and targets improvements or maintenance of overall fitness (WHO, 2018). Physical activity interventions for persons with SCI may include the promotion of lifestyle physical activity or structured exercise training programs. Exercise training is a key part of rehabilitation immediately following injury and often focuses on functional recovery. Longitudinally, exercise training is essential for persons living with an SCI to increase strength and fitness to maintain and improve independence, participation, and overall health. Physical activity is often targeted as an intervention not only for its purported physical benefits, but also its associations improving subjective well-being in persons with SCI (Ginis, Jetha, Mack, & Hetz, 2010; Warms, Belza, Whitney, Mitchell, & Stiens, 2004). This highlights the potential impact of health-enhancing behaviors on multiple facets of wellness.

Nutrition interventions focus on the adjustment of personal practices and habits to improve nutritional status (WHO, 2020). Such interventions are critical for the persons with SCI to maintain overall health, reduce chances of osteoporosis, and manage bowel and bladder dysfunction. For persons with SCI, these types of interventions may be initiated at various phases of rehabilitation from immediate management of protein needs during the acute phase to the long-term promotion of a balanced diet during the chronic phase. Recent evidence suggests that low carbohydrate or ketogenic diets may improve neurological recovery during the acute phase, immediately following injury (Yarar-Fisher et al., 2018). However, wellness interventions generally focus on healthy eating to promote weight management and overall health for persons living with SCI. One recent systematic review and meta-analysis examining persons with SCI reported imbalances in fiber intake and micronutrients that may be targeted in wellness interventions (Farkas, Pitot, Berg, & Gater, 2019).

Stress management is a critical component of wellness interventions for persons with SCI. Adaptive stress management strategies are key to healthy living following SCI given the traumatic nature of many injuries and the need to adapt to a new life. Individual stress management interventions aim to help individuals identify stressors and develop strategies to cope aiming to reduce stress and increase well-being (Holman, Johnson, & O'Connor, 2018). Group stress management interventions often take the form as support groups for persons with SCI (Holman et al., 2018). One study pilot tested a coping effectiveness training program for persons with SCI that demonstrated reductions in symptoms of anxiety and depression (King & Kennedy, 1999). Stress management is primarily included as part of an intervention targeting other health-promoting behaviors and relevant components for wellness interventions for persons with SCI.

Tobacco use is the primary health-risk behavior of interest in the SCI literature given the prevalence of smoking among persons with SCI is significantly higher than the general population (Saunders, Krause, Saladin, & Carpenter, 2015). Tobacco use is detrimental to rehabilitation following SCI given the nature of CNS dysfunction following injury and preservation of respiratory system function is vital. Smoking behavior may exacerbate secondary health conditions such as pain and impede participation in other health behaviors such as physical activity (Richardson, Richards, Stewart, & Ness, 2012). Smoking cessation has not been a focal target in wellness interventions among persons with SCI. Therefore, tobacco use has been identified as an often overlooked, but vital topic for future wellness interventions.

Behavior change theory for supporting behavior change interventions in SCI

Wellness interventions target change in health behaviors for improving psychosocial outcomes in SCI, and success depends on the actual change and maintenance of behavior change. To that end, such interventions should be informed and supported based on behavior change models or theories. Theory is critical for identifying targets of behavior change and then guiding the selection of behavior change techniques that serve as the active ingredients of the intervention. Common behavior change theories for health promotion among persons with SCI include Social Cognitive Theory, The Transtheoretical Model, Health Action Process Approach Model, and The Theory of Planned Behavior. Researchers should be aware of the underlying assumptions of a theory, its causal structure and variables for behavior change strategies and then align the intervention target, goals, and population with the theory. Theories outlined in this chapter represent the most commonly applied in SCI; however, this is not an exclusive list as there are dozens of theories of human behavior.

Social cognitive theory (SCT) is one of the most widely applied behavior change theories for health promotion among persons with SCI, including wellness interventions (Zemper et al., 2003). The underlying premise of SCT is that behavior is socially constructed through observation (Bandura, 1998). Specifically, behavior is constructed and modified through dynamic interactions among the person, their environment, and behavior (Fig. 2). Self-efficacy is a primary tenet of SCT in which individual confidence in their ability to perform a behavior (i.e., self-efficacy) that guides behavior change and maintenance (Bandura, 1998). Indeed, sources of self-efficacy include mastery experiences, vicarious experiences, verbal persuasion, and physiological or emotional responses (Bandura, Freeman, & Lightsey, 1999). Other central tenets of SCT include outcome expectations, goal setting, barriers, and impediments. Applications of SCT in the assessment of behavior in persons with SCI have largely focused on physical activity behavior (Martin Ginis et al., 2011), however applications to other health behaviors are plausible based on extensive application of SCT in diverse populations.

The Health Action Process Model (HAPA) is a more recent psychological theory that blends components of SCT and the Transtheoretical Model (Fig. 3). The HAPA model includes at least two phases, motivation and volition, and further splits volition phase into planning, action, and maintenance phases (Schwarzer, Lippke, & Luszczynska, 2011). The HAPA model outlines the process of behavior change across various phases (Schwarzer et al., 2011). For example, self-efficacy is highlighted as a crucial component through all phases, whereas risk perceptions play a primary role during the contemplation phase. Schwarzer et al. (2011) provide an overview of how HAPA can be applied in a rehabilitation setting for persons with chronic diseases, such as SCI, however most of the current evidence draws on research in physical activity.

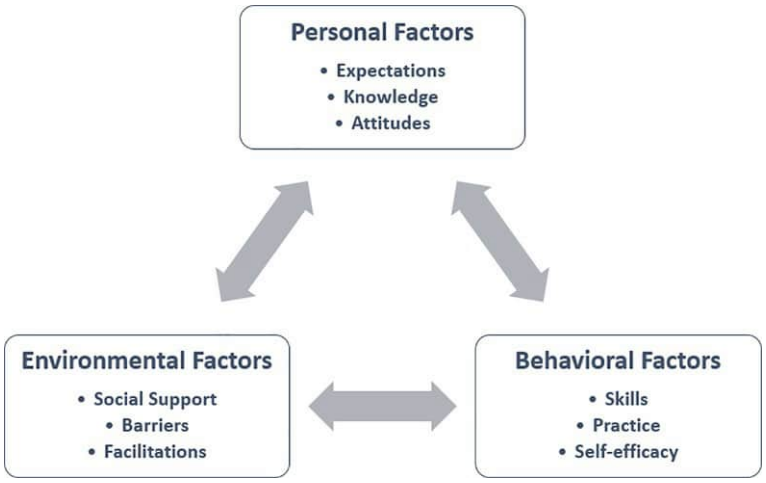

FIG. 2 Social cognitive theory model. Bandura's concept of triadic reciprocal determinism outlines the dynamic interaction between the individual, their environment, and behaviors.

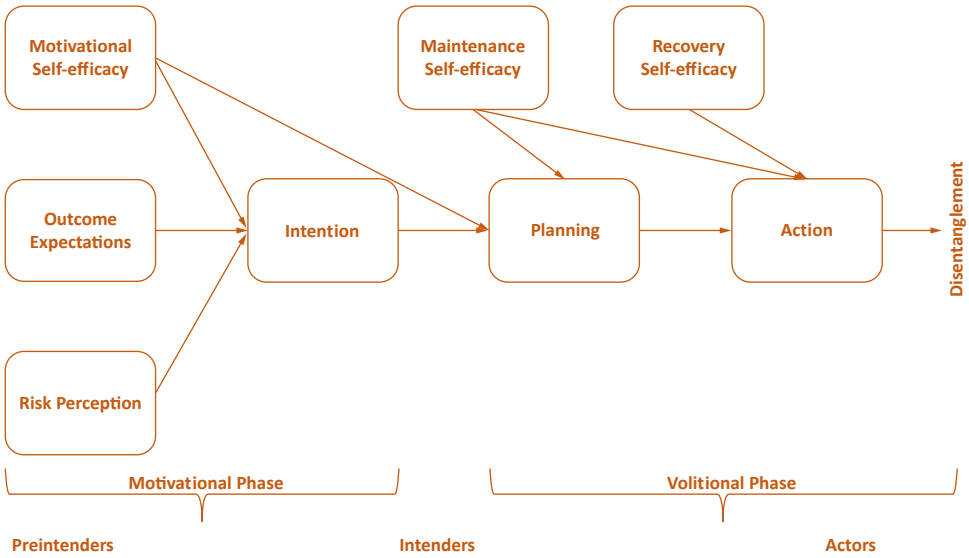

FIG. 3 The health action's process model. The health action's process model outlines various stages and the primary influences that interact within phases that results in actions.

The Transtheoretical Model (TTM) is also known as the Stage of Change Model focuses on the staged and gradual process of health behavior change (Prochaska & Velicer, 1997). TTM was originally developed as a model for smoking behavior change in which individuals change behavior and maintain change based on readiness for change. The stages of change depicted in Fig. 4 include Precontemplation, Contemplation, Preparation, Action, and Maintenance (Prochaska & Velicer, 1997). The stages are predicted by self-efficacy and decisional balance. TTM is unique as its primary utility is to provide a model for the application of behavior change theory along the stages of change. The TTM has been applied in nutrition assessment among adults with SCI as well as physical activity assessment and intervention development (Tsunoda, Inayama, Hata, & Oka, 2015).

FIG. 4 The transtheoretical model. Five discrete stages are outlined in the transtheoretical model, however individuals may progress and regress between stages during various phases of behavior change.

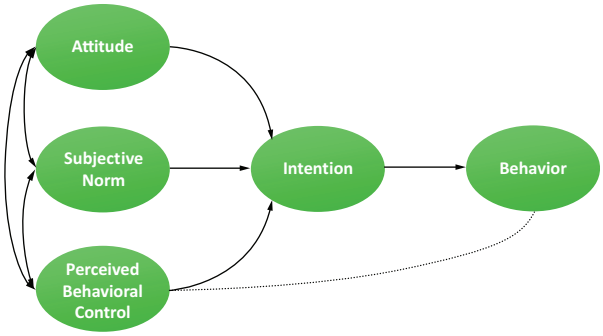

FIG. 5 Theory of planned behavior. The theory of planned behavior model focuses on the influences and factors that guide intentions and subsequent behavior.

The Theory of Planned Behavior (TPB) focuses on behavioral intentions or an individual's plans to engage in a behavior at a specific time and place (Ajzen, 1991). TPB has been widely applied in behavior change interventions for smoking, substance use, health services utilization, and breastfeeding. The two foundational components of TPB are motivation and ability that are guided by perceptions. Underlying concepts associated with TPB are attitudes, intentions, norms (subjective and social), and perceptions of power and behavioral control (Ajzen, 1991) (Fig. 5). TPB has been examined as a determinant of secondary condition management (i.e., skincare) and physical activity in persons with SCI (Latimer & Martin Ginis, 2005; Sheppard, Kennedy, & Mackey, 2006).

Exemplar wellness interventions for persons with SCI: Examples, settings, and results

A thorough background regarding previous wellness interventions for persons with SCI is critical for designing future interventions. The foundational wellness interventions for persons with SCI were delivered via workshops (i.e., short-term educational courses). For example, one randomized controlled trial examined the efficacy of six half-day wellness workshops for adults with SCI over 3 months. Each workshop included an expert-led portion on lifestyle management, nutrition, exercise, and secondary conditions (Zemper et al., 2003). Preliminary results indicated that there were no between-group differences. However, secondary analyses indicated that treatment response among the intervention group participants was related to marital status and age, specifically, single/divorced participants were more likely to not respond to the intervention and further participants who were single/divorced and $\leq$ 50 years old were most likely to not respond to the intervention (Silveira et al., 2020). Overall, short-term workshop interventions are a feasible option for providing wellness information for persons with SCI; however, demographics such as marital status and age may impact response and longitudinal positive impact is not established.

Wellness programs for persons with SCI have been delivered in community fitness settings. Some centers have unique resources such as one-on-one personal trainers who have a background in working with individuals with SCI. A recent qualitative study examined perceptions of four males with SCI following a center-based community wellness program reported positive physical, social, and mental outcomes. Participants reported that the center provided them with "a place for hope" and "a supportive community" (Ekelman et al., 2017). One primary barrier to the implementation of center-based programs is pervasive transportation issues among persons with SCI and the lack of adaptive community centers that are equipped to deliver quality interventions.

Several hospitals are creating wellness programs as part of SCI rehabilitation practices that may be delivered by peers or health care professionals. One recent wellness program created for adults with SCI and spina bifida was delivered through an integrated delivery system and focused on prevention and treatment of pressure sores, depression, neurogenic bladder and bowel, diet, and physical activity (Dicianno et al., 2016). Participants were provided with a wellness practitioner who provided patient education, case management services including goal setting, and incentives for making progress toward goals. Following the 2 year intervention, participants reported better QOL, overall health, lower depressive symptoms, and health care costs were attenuated (Dicianno et al., 2016). The provision of robust integrated delivery system programs is challenging due to time and cost considerations; however, there is some evidence of longitudinal benefits.

Hospital-based wellness programs utilizing a peer mentor approach may help improve self-efficacy to manage life following SCI (Gassaway et al., 2017; Ljungberg, Kroll, Libin, & Gordon, 2011). A recent randomized controlled trial tested the efficacy of an inpatient-based peer mentoring program on self-efficacy and hospital readmissions (Gassaway et al., 2017). Participants in the intervention group received an initial consultation with a peer liaison followed by weekly

meetings with a peer mentor in-person during inpatient care and weekly phone, e-mail, or in-person contact for 90 days following discharge. Positive outcomes were reported with higher rates of self-efficacy in the intervention group compared to the standard-care control group and fewer unplanned hospital stays (Gassaway et al., 2017). Therefore, peer mentoring programs during the initial phases of SCI rehabilitation demonstrate efficacy for improving self-efficacy for managing medical care and life following SCI.

Telehealth approaches to promoting wellness among persons with SCI have received increasing attention. Many telehealth interventions for persons with SCI focus on providing knowledge and resources to manage health promoting behaviors in addition to increased contact with health care providers. For example, CareCall system was created for persons with various spinal cord dysfunctions combining patient education, cognitive-behavioral interventions, screening and referrals, and alerts to a nurse telerehabilitation coordinator for direct non-emergent phone follow-up (Houlihan et al., 2013). Pilot testing of the CareCall system demonstrated efficacy for reducing pressure sores, depression, and patient reports of health care availability, but not health care utilization (Houlihan et al., 2013). Given the efficacy of wellness interventions for persons with SCI, there is a pressing need for further applications of telehealth interventions for promoting health behavior change (McIntyre et al., 2020).

Design of future wellness interventions for persons with SCI

Future wellness interventions for persons with SCI should be founded on behavioral theory and identify behavior change techniques (BCTs) that align with theory. As mentioned, physical activity is currently the most widely researched health-promoting behavior for persons with SCI. Physical activity researchers have provided a roadmap for researchers in other areas to follow and build upon. For example, a review of BCTs in physical activity interventions for persons with SCI coded BCTs based on the BCT Taxonomy V1 and reported the most commonly used were: 4.1. instruction on how to perform the behavior, 1.1. goal setting (behavior), 3.2. social support (practical), 9.1. credible source, 1.2. problem solving, and 1.4. action planning (Tomasone et al., 2018). Compilation of such information is key to identifying the most widely used and the most effective BCTs for future interventions. Separate health behaviors likely require distinctive strategies and techniques for initiating and maintaining health behavior change that aligns with appropriate theory—this is the major challenge for multiple health behavior change interventions.

Multiple health behavior change interventions may further consider aligning with an established model of wellness or QOL. Stuifbergen's Model of QOL in individuals with chronic disabling conditions has established the factors preceding QOL in persons with various chronic disabling conditions, such as SCI (Stuifbergen, Seraphine, & Roberts, 2000) (Fig. 6). This model considers the various interactions among severity of illness/condition, barriers, resources, acceptance, self-efficacy, and health-promoting behaviors. Though more research is needed to determine the validity of the direct versus indirect paths in persons with SCI, the factors of interest are well-established as strong correlates of QOL in persons with SCI. This model is provided as an example in which behavior change theories may be applied for creating theory-based wellness interventions for persons with SCI in various settings.

One primary barrier for creating and disseminating wellness interventions is the timeliness of scientific research to reach community settings. One branch of the Neurorecovery Network aims to provide rapid translation of evidence-based techniques and technologies for promoting health among persons with SCI and other neurological diseases (Tolle et al., 2018).

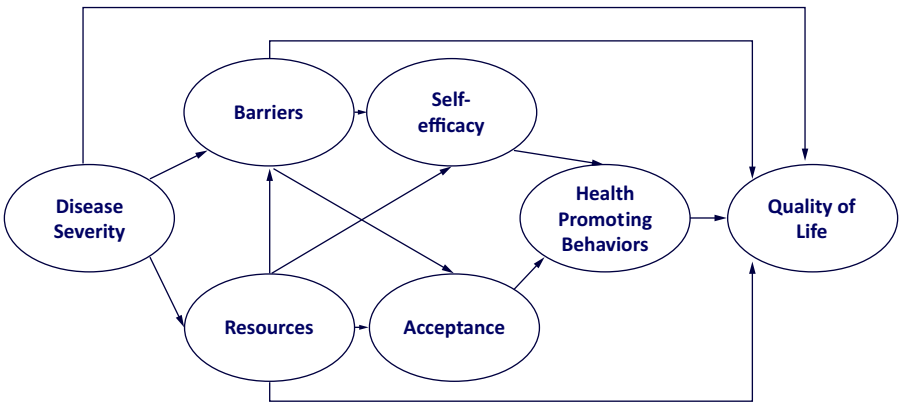

FIG. 6 Model of health promotion and quality of life in chronic disabling conditions. This explanatory model of health promotion and quality of life is a foundation for developing wellness interventions.

The Community fitness and wellness facilities network was created to provide opportunities for promoting wellness across the care continuum (i.e., inpatient through community settings) (Tolle et al., 2018). The network partners utilize standardized intervention strategies and outcome measurements to assess interventions in community settings, bringing together researchers and community partners to bridge the gap between research and practice. The Community fitness and wellness facilities network is an in-person approach wherein individuals work with trained staff and adaptive equipment and therefore is likely not an all-encompassing approach as many individuals with SCI live in rural areas or face significant barriers to transportation; however, this model may be adapted using technology to provide essential wellness resources and support.

Advances in technology provide unique opportunities for telehealth interventions that overcome barriers for persons with SCI such as transportation and accessibility. Researchers and practitioners are examining the efficacy of wellness interventions delivered through various online mediums such as websites and mobile apps. For example, the iMHere system is a website portal and app that includes modules on medication management, skincare, bowel and bladder programs, mood tracking, and messaging that aims to connect people with SCI with their healthcare providers and improve wellness outcomes (Kryger et al., 2019). Preliminary results from the iMHere study indicate reductions in urinary tract infections, but not psychosocial outcomes (Kryger et al., 2019). Such technologies may be a promising foundation for wellness interventions for persons with SCI such that future iterations may include other modifiable behaviors such as nutrition and exercise.

Overall, the design of wellness interventions for persons with SCI is a considerable task that requires inquiry, partnership, and trust among participants, researchers, and the health care community. Mixed-methods approaches are pivotal to the design of wellness interventions that meet the unique needs and preferences of individuals with SCI who differ by demographics, clinical characteristics, and lived experiences. Exploratory Sequential Design is one mixed-method approach that has been recommended for developing self-management interventions for persons with SCI (Munce, Guetterman, & Jaglal, 2020). Exploratory sequential approaches juxtapose qualitative and quantitative methods in the creation of intervention, specifically, researchers inquire about preferences using qualitative methods such as interviews in conjunction with quantitative methods to identify appropriate outcomes such as surveys. This approach allows flexibility to incorporate peers and caregivers to create tailored interventions and has demonstrated efficacy for developing interventions for persons with SCI.

Applications to other areas of neuroscience

Wellness interventions are becoming a pillar of rehabilitation given them potential as second-line approaches for improving symptoms, overall health, and QOL. Wellness interventions for persons with SCI may draw from, or inform, other neurological diseases such as multiple sclerosis (MS), traumatic brain injury (TBI), stroke, and Parkinson's disease. Barriers to engaging in health-promoting behaviors among persons with various neurological diseases overlap such as accessibility, lack of knowledge, transportation, and debilitating symptoms such as pain. Further, as depicted in Stuifbergen's model of QOL, the factors related to QOL overlap in meaningful ways that guided successful wellness interventions for persons with various chronic disabling conditions.

Many wellness interventions have been created for persons with MS that may be adapted for persons with SCI. Symptoms impacting persons with SCI and persons with MS overlap, especially among persons with MS who have lesions in their spinal cord. The National Multiple Sclerosis Society recently convened a Wellness Research Working Group that provides focal reviews of literature regarding physical activity, diet, and emotional well-being (Motl et al., 2017). The Wellness Research Working Group further provided a clear research agenda to guide the development of wellness interventions for persons with MS. The priority questions posited by the Wellness Research Working Group such as "To what extent does resilience affect emotional health and/or the course of the disease" are pressing topics in SCI rehabilitation (Motl et al., 2017).

We underscore the importance to draw on other populations with neurological dysfunction, however note the unique trauma associated with SCI. Persons with SCI often start their rehabilitation journey inpatient with vastly different resources. The rehabilitation journey of each person with SCI may influence the appropriate components of wellness promotion. For example, a person with SCI who experienced a traumatic car accident may require more emotional health resources whereas someone who experiences a fall may require resources focused on mobility and function. In this regard, drawing upon wellness interventions for persons with TBI or stroke may be more appropriate. The period immediately following injury/trauma serves as a sensitive period in which individuals are learning to live a whole new way that warrants focal examination.

Mini-dictionary of terms

Wellness: A multidimensional construct that is characterized by the existence of positive health in an individual with a focus on functioning, health, quality of life.

Well-being: Sense of overall positive health focused on global perceptions of an individual's current status. Well-being has various sub-categories: physical, material, social, productive, emotional, and civic.

Quality of life: Individual evaluation regarding their overall satisfaction with life and health status.

Behavioral intervention: Coordinated sets of activities designed to change specified behavior patterns by providing instruction and application of skills, strategies, and resources for behavior change.

Behavior change techniques: Observable and replicable components are used as strategies in behavioral interventions to initiate or maintain health behavior change. Behavior change techniques are often referred to as the "active ingredients" in behavioral interventions and are frequently used in combination.

Physical activity: Any bodily movement produced by skeletal muscles that require energy expenditure including movements undertaken while working, playing, carrying out household chores, traveling, and engaging in recreational pursuits.

Exercise: A subset of physical activity that is planned, structured, repetitive, and targets improvements or maintenance of overall fitness.

Qualitative research: Research designs that focus on collection and analysis of non-numerical data to understand concepts, develop theories, or inquire about opinions and experiences.

Quantitative research: Research designs that focus on the collection and analysis of numerical data can identify patterns, test causal inferences, and assess generalizability to populations.

Self-efficacy: Individual confidence in ability to follow through on a task or behavior. Self-efficacy is not static and may vary greatly depending on the specific task or behavior.

Key facts of wellness interventions

- Wellness interventions are a second-line approach of interest among persons with spinal cord injury (SCI) and their health care providers for improving outcomes following SCI.
- Wellness interventions focus on behavior change to maximize health within the context of a disease or condition.
- Wellness interventions are not focused on medical management of a specific disease.
- Wellness interventions can be initiated at any time to improve overall health, but may be tailored for different subgroups depending on age, sex, or other demographic and clinical characteristics.
- Wellness interventions may incorporate various health behaviors including behaviors that promote health such as physical activity and nutrition as well as risk behaviors that should be limited such as tobacco use.

Summary points

- Wellness is a major priority for spinal cord injury (SCI) rehabilitation given significant changes in overall health and quality of life.
- Wellness interventions target health behaviors such as physical activity, nutrition, stress management, and tobacco use to improve quality of life over time.
- Rigorous wellness interventions are founded on behavioral theory such as Social Cognitive Theory, the Health Action Process Model, Transtheoretical Model, or Theory of Planned Behavior.
- Previous wellness interventions for persons with SCI have widely been in-person at community centers or hospitals that do not address significant barriers among persons with SCI.
- Future wellness interventions for persons with SCI require qualitative and quantitative approaches for identifying the needs and priorities among persons with SCI and options for optimal delivery within the rehabilitation team.

References

Ajzen, I. (1991). The theory of planned behavior. *Organizational Behavior and Human Decision Processes*, *50*(2), 179–211.

Bandura, A. (1998). Health promotion from the perspective of social cognitive theory. *Psychology and Health*, *13*(4), 623–649.

Bandura, A., Freeman, W., & Lightsey, R. (1999). *Self-efficacy: The exercise of control*. Springer.

Chun, S., & Lee, Y. (2020). "Racing made me feel strong and more positive": Experiencing personal meaning in life through leisure following traumatic spinal cord injury. *Leisure Sciences*, 1–18.

Corbin, C. B., & Pangrazi, R. P. (2001). *Toward a uniform definition of wellness: A commentary*. President's council on physical fitness and sports research digest.

Decker, S. D., & Schulz, R. (1985). Correlates of life satisfaction and depression in middle-aged and elderly spinal cord-injured persons. *American Journal of Occupational Therapy*, *39*(11), 740–745.

Dicianno, B. E., Lovelace, J., Peele, P., Fassinger, C., Houck, P., Bursic, A., et al. (2016). Effectiveness of a wellness program for individuals with spina bifida and spinal cord injury within an integrated delivery system. *Archives of Physical Medicine and Rehabilitation*, *97*(11), 1969–1978.

Diener, E., Emmons, R. A., Larsen, R. J., & Griffin, S. (1985). The satisfaction with life scale. *Journal of Personality Assessment*, *49*(1), 71–75.

Dijkers, M. P. (1999). Correlates of life satisfaction among persons with spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *80*(8), 867–876.

Ekelman, B. A., Allison, D. L., Duvnjak, D., DiMarino, D. R., Jodzio, J., & Iannarelli, P. V. (2017). A wellness program for men with spinal cord injury: Participation and meaning. *OTJR: Occupation, Participation and Health*, *37*(1), 30–39.

Farkas, G. J., Pitot, M. A., Berg, A. S., & Gater, D. R. (2019). Nutritional status in chronic spinal cord injury: A systematic review and meta-analysis. *Spinal Cord*, *57*(1), 3–17.

Fugl-Meyer, A. R., Bränholm, I.-B., & Fugl-Meyer, K. S. (1991). Happiness and domain-specific life satisfaction in adult northern swedes. *Clinical Rehabilitation*, *5*(1), 25–33.

Gassaway, J., Jones, M. L., Sweatman, W. M., Hong, M., Anziano, P., & DeVault, K. (2017). Effects of peer mentoring on self-efficacy and hospital readmission after inpatient rehabilitation of individuals with spinal cord injury: A randomized controlled trial. *Archives of Physical Medicine and Rehabilitation*, *98*(8), 1526–1534. e1522.

Gater, D. R., Jr. (2007). Obesity after spinal cord injury. *Physical Medicine and Rehabilitation Clinics of North America*, *18*(2), 333–351.

Ginis, K. M., Jetha, A., Mack, D., & Hetz, S. (2010). Physical activity and subjective well-being among people with spinal cord injury: A meta-analysis. *Spinal Cord*, *48*(1), 65–72.

Goodwin, F. K., & Jamison, K. R. (2007). *Manic-depressive illness: Bipolar disorders and recurrent depression. Vol. 2*. Oxford University Press.

Holman, D., Johnson, S., & O'Connor, E. (2018). Stress management interventions: Improving subjective psychological well-being in the workplace. In *Handbook of well-being*. Salt Lake City, UT: DEF Publishers.

Houlihan, B. V., Jette, A., Friedman, R. H., Paasche-Orlow, M., Ni, P., Wierbicky, J., et al. (2013). A pilot study of a telehealth intervention for persons with spinal cord dysfunction. *Spinal Cord*, *51*(9), 715–720.

Jörgensen, S., Iwarsson, S., & Lexell, J. (2017). Secondary health conditions, activity limitations, and life satisfaction in older adults with long-term spinal cord injury. *PM & R : The Journal of Injury, Function, and Rehabilitation*, *9*(4), 356–366.

Kennedy, P., Lude, P., Elfström, M. L., & Smithson, E. F. (2011). Psychological contributions to functional independence: A longitudinal investigation of spinal cord injury rehabilitation. *Archives of Physical Medicine and Rehabilitation*, *92*(4), 597–602.

Keyes, C. L., Shmotkin, D., & Ryff, C. D. (2002). Optimizing well-being: The empirical encounter of two traditions. *Journal of Personality and Social Psychology*, *82*(6), 1007.

King, C., & Kennedy, P. (1999). Coping effectiveness training for people with spinal cord injury: Preliminary results of a controlled trial. *British Journal of Clinical Psychology*, *38*(1), 5–14.

Krause, J. S., Kemp, B., & Coker, J. (2000). Depression after spinal cord injury: Relation to gender, ethnicity, aging, and socioeconomic indicators. *Archives of Physical Medicine and Rehabilitation*, *81*(8), 1099–1109.

Kryger, M. A., Crytzer, T. M., Fairman, A., Quinby, E. J., Karavolis, M., Pramana, G., et al. (2019). The effect of the interactive mobile health and rehabilitation system on health and psychosocial outcomes in spinal cord injury: Randomized controlled trial. *Journal of Medical Internet Research*, *21*(8), e14305.

Latimer, A. E., & Martin Ginis, K. A. (2005). The theory of planned behavior in prediction of leisure time physical activity among individuals with spinal cord injury. *Rehabilitation Psychology*, *50*(4), 389.

Lebensohn, P., Dodds, S., Benn, R., Brooks, A. J., & Birch, M. (2013). Resident wellness behaviors. *Family Medicine*, *45*(8), 541–549.

Ljungberg, I., Kroll, T., Libin, A., & Gordon, S. (2011). Using peer mentoring for people with spinal cord injury to enhance self-efficacy beliefs and prevent medical complications. *Journal of Clinical Nursing*, *20*(3–4), 351–358.

Martin Ginis, K. A., Latimer, A. E., Arbour-Nicitopoulos, K. P., Bassett, R. L., Wolfe, D. L., & Hanna, S. E. (2011). Determinants of physical activity among people with spinal cord injury: A test of social cognitive theory. *Annals of Behavioral Medicine*, *42*(1), 127–133.

May, L. A., & Warren, S. (2002). Measuring quality of life of persons with spinal cord injury: External and structural validity. *Spinal Cord*, *40*(7), 341–350.

McIntyre, A., Marrocco, S. L., McRae, S. A., Sleeth, L., Hitzig, S., Jaglal, S., et al. (2020). A scoping review of self-management interventions following spinal cord injury. *Topics in Spinal Cord Injury Rehabilitation*, *26*(1), 36–63.

Motl, R. W., Mowry, E. M., Ehde, D. M., LaRocca, N. G., Smith, K. E., Costello, K., et al. (2017). Wellness and multiple sclerosis: The National MS Society establishes a wellness research working group and research priorities. *Multiple Sclerosis Journal*, *24*(3), 262–267.

Munce, S. E. P., Guetterman, T. C., & Jaglal, S. B. (2020). Using the exploratory sequential design for complex intervention development: Example of the development of a self-management program for spinal cord injury. *Journal of Mixed Methods Research*, 1558689820901936.

National Spinal Cord Injury Statistical Center (NCSISC). (2020). *Spinal cord injury facts and figures at a glance*. https://www.nscisc.uab.edu/Public/Facts%20and%20Figures%202020.pdf.

Post, M. W., de Witte, L. P., van Asbeck, F. W., van Dijk, A. J., & Schrijvers, A. J. (1998). Predictors of health status and life satisfaction in spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *79*(4), 395–401.

Prochaska, J. O., & Velicer, W. F. (1997). The transtheoretical model of health behavior change. *American Journal of Health Promotion*, *12*(1), 38–48.

Putzke, J. D., Elliott, T. R., & Richards, J. S. (2001). Marital status and adjustment 1 year post-spinal-cord-injury. *Journal of Clinical Psychology in Medical Settings*, *8*(2), 101–107.

Putzke, J. D., Richards, J. S., Hicken, B. L., & DeVivo, M. J. (2002). Predictors of life satisfaction: A spinal cord injury cohort study. *Archives of Physical Medicine and Rehabilitation*, *83*(4), 555–561.

Richardson, E. J., Richards, J. S., Stewart, C. C., & Ness, T. J. (2012). Effects of nicotine on spinal cord injury pain: A randomized, double-blind, placebo controlled crossover trial. *Topics in Spinal Cord Injury Rehabilitation*, *18*(2), 101–105.

Ryan, R. M., & Deci, E. L. (2001). On happiness and human potentials: A review of research on hedonic and eudaimonic well-being. *Annual Review of Psychology*, *52*(1), 141–166.

Ryff, C. D., & Keyes, C. L. M. (1995). The structure of psychological well-being revisited. *Journal of Personality and Social Psychology*, *69*(4), 719.

Saunders, L. L., Krause, J. S., Saladin, M., & Carpenter, M. J. (2015). Prevalence of cigarette smoking and attempts to quit in a population-based cohort with spinal cord injury. *Spinal Cord*, *53*(8), 641–645.

Schwarzer, R., Lippke, S., & Luszczynska, A. (2011). Mechanisms of health behavior change in persons with chronic illness or disability: The Health action process approach (HAPA). *Rehabilitation Psychology*, *56*(3), 161.

Sheppard, R., Kennedy, P., & Mackey, C. A. (2006). Theory of planned behaviour, skin care and pressure sores following spinal cord injury. *Journal of Clinical Psychology in Medical Settings*, *13*(4), 358–366.

Silveira, S. L., Ledoux, T. A., Johnston, C. A., Kalpakjian, C., O'Connor, D. P., Cottingham, M., et al. (2020). Differences among participants' response to a wellness intervention for individuals with spinal cord injuries. *Disability and Health Journal*, *13*(1), 100842.

Sparkes, A. C., & Smith, B. (2002). Sport, spinal cord injury, embodied masculinities, and the dilemmas of narrative identity. *Men and Masculinities*, *4*(3), 258–285.

Stuifbergen, A. K., Morris, M., Jung, J. H., Pierini, D., & Morgan, S. (2010). Benefits of wellness interventions for persons with chronic and disabling conditions: A review of the evidence. *Disability and Health Journal*, *3*(3), 133–145.

Stuifbergen, A. K., Seraphine, A., & Roberts, G. (2000). An explanatory model of health promotion and quality of life in chronic disabling conditions. *Nursing Research*, *49*(3), 122–129.

Tolle, H., Rapacz, A., Weintraub, B., Shogren, C., Harkema, S. J., & Gibson, J. L. (2018). Establishing the neurorecovery network community fitness and wellness facilities: Multi-site fitness facilities provide activity-based interventions and assessments for evidence-based functional gains in neurologic disorders. *Disability and Rehabilitation*, *40*(25), 3086–3093.

Tomasone, J. R., Flood, S. M., Ma, J. K., Scime, N. V., Burke, S. M., Sleeth, L., et al. (2018). Physical activity self-management interventions for adults with spinal cord injury: Part 1–A systematic review of the use and effectiveness of behavior change techniques. *Psychology of Sport and Exercise*, *37*, 274–285.

Tsunoda, N., Inayama, T., Hata, K., & Oka, J. (2015). Vegetable dishes, dairy products and fruits are key items mediating adequate dietary intake for Japanese adults with spinal cord injury. *Spinal Cord*, *53*(11), 786–790.

Warms, C. A., Belza, B. L., Whitney, J. D., Mitchell, P. H., & Stiens, S. A. (2004). Lifestyle physical activity for individuals with spinal cord injury: A pilot study. *American Journal of Health Promotion*, *18*(4), 288–291.

World Health Organizaion (WHO). (2018, February 23). *Physical activity*. https://www.who.int/news-room/fact-sheets/detail/physical-activity.

World Health Organization (WHO). (2020). *Nutrition interventions*. https://www.who.int/elena/intervention/en/.

Yarar-Fisher, C., Kulkarni, A., Li, J., Farley, P., Renfro, C., Aslam, H., et al. (2018). Evaluation of a ketogenic diet for improvement of neurological recovery in individuals with acute spinal cord injury: A pilot, randomized safety and feasibility trial. *Spinal Cord Series And Cases*, *4*(1), 88.

Zemper, E. D., Tate, D. G., Roller, S., Forchheimer, M., Chiodo, A., Nelson, V. S., et al. (2003). Assessment of a holistic wellness program for persons with spinal cord injury. *American Journal of Physical Medicine & Rehabilitation*, *82*(12), 957–968.

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Chapter 40

Sexual life in individuals with spinal cord injury and management

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List of abbreviations

AD	autonomic dysreflexia
ED	erectile dysfunction
EEJ	electro-ejaculation
ICI	intracavernous injections
IIEF	International Index of Erectile Function
IPP	inflatable penile implants
L	lumbar
PDE5-Is	phosphodiesterase 5-inhibitors
PM	prostate massage
PPI	penile prosthesis implantation
PVS	penile vibrator stimulation
S	sacral
SCI	spinal cord injury
T	thoracal

Introduction

Significant physiological changes related to sensory, voluntary motor, and autonomic functions developing due to spinal cord injury (SCI) affect sexual interest and satisfaction negatively by causing problems in sexual arousal, orgasm potential, ejaculation in men, and sexual position for both genders (Stoffel, Van der Aa, Wittmann, Yande, & Elliott, 2018). SCIs usually occur in separate regions of the neuraxis, and their effects on sexual function can be predicted depending on the spinal motor and autonomic pathways that are affected. Three spinal segments are particularly important for sexual function: T11-L2, sympathetic; S2-S4, parasympathetic; and somatic centers. Depending on the level of injury and severity of these pathways, some changes in genital sexual arousal (erection problems in men and decreased lubrication in women) occur (Stoffel et al., 2018). Besides, bladder and bowel incontinence and related problems affect sexual self-esteem, sexual expression, and sexual satisfaction as secondary health consequences of SCI including autonomic dysreflexia, nociceptive and neuropathic pain, depression, and pharmacological management of such conditions (Adriaansen et al., 2016; Courtois, Alexander, & McLain, 2017).

Several studies reported that sexual dysfunctions experienced in SCI are associated with psychiatric outcomes, such as poor quality of life, anxiety, depression, and changes in personality structure (Choi, Kang, & Shin, 2015; Cramp, Courtois, & Ditor, 2015; Le & Dorstyn, 2016). Therefore, sexual satisfaction is an important aspect of the life of people with SCI, and it is important to diagnose and manage sexual dysfunctions with a multidisciplinary approach to improve the quality of life of these individuals (Elliott, Hocaloski, & Carlson, 2017). In this section, the problems experienced in sexual life after SCI and their management are examined separately for men and women as a guide for health professionals (Fig. 1).

Cellular, Molecular, Physiological, and Behavioral Aspects of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822427-4.00040-X

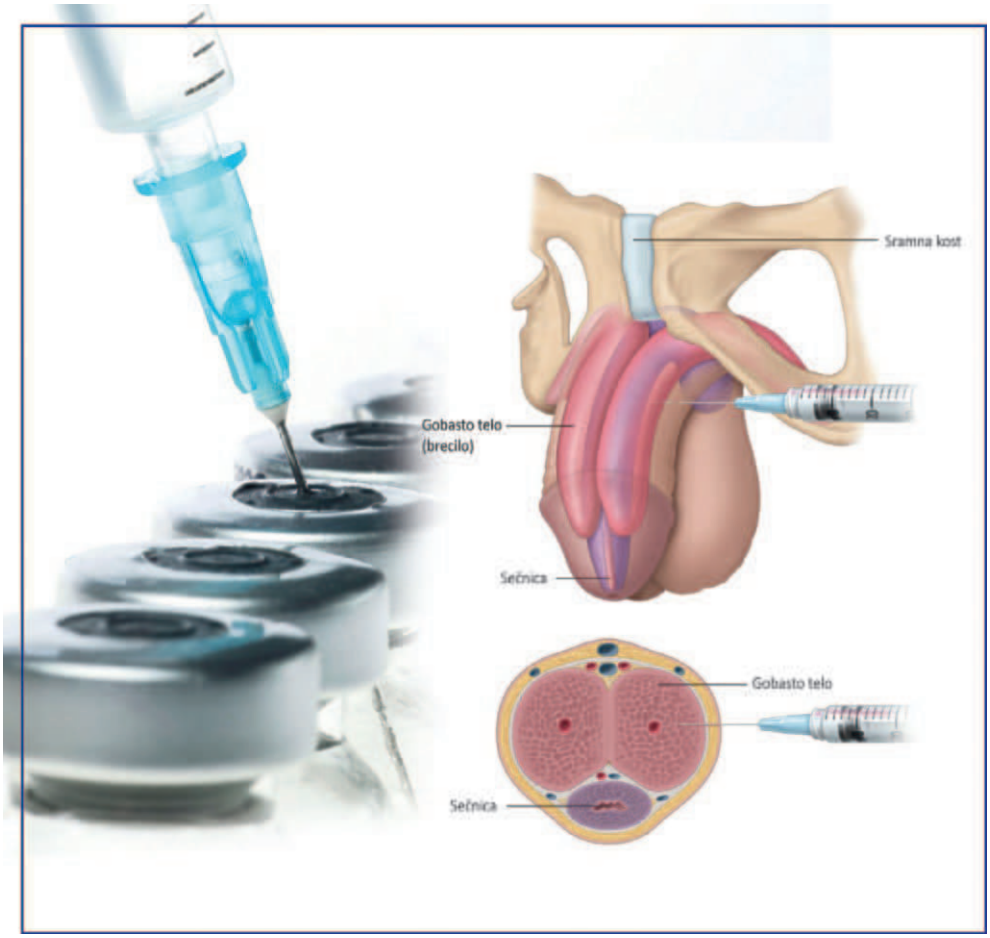

FIG. 1 Intracavernous injections.

Sexual life in men with SCI

It is estimated that 35%–80% of men become inactive after SCI. Following (Choi et al., 2015; Dahlberg, Alaranta, Kautiainen, & Kotila, 2007; Gomes et al., 2017) SCI, most men experience severe impairment in their sexual health and reproductive function due to erectile and/or ejaculatory dysfunction and semen abnormalities (Aikman, Oliffe, Kelly, & McCuaig, 2018). Male sexual dysfunction includes erectile dysfunction, decreased libido, and abnormal ejaculation. The normal male sexual function requires interactions between vascular, neurological, hormonal, and psychological systems (Courtois & Charvier, 2015). The first requirement for male sexual activity is the achievement and maintenance of penile erection (Afferi et al., 2020). In this section, first, the physiology of normal sexual function is explained so that sexual dysfunction in men with SCI can be understood (Fig. 2).

Physiology of normal sexual function

Parasympathetic innervation

The preganglionic neurons of parasympathetic efferents come out of the intermediolateral region at the level of sacral 2–4 (S2–4) segments of the spinal cord known as the sacral parasympathetic nucleus, reach the pelvic plexus, and feed the lower urinary system and genital system. Parasympathetic efferent stimulation loosens up corpus cavernosum and vascular (cavernosal artery) smooth muscles in the penis, which results in blood filling (erection) into the penis (Elliott, 2018; Sabharwal, 2013).

FIG. 2 Vacuum device.

Sympathetic innervation

Sympathetic efferents emerge from thoracal 10 and lumbar 2 (T10-L2) spinal segments and feed the bladder floor, internal sphincter, proximal urethra, prostate, penis, and smooth muscles of seminal tract in men. Sympathetic efferent stimulation contracts bladder outlet, prostate, and seminal tract smooth muscles, cavernosal tissue and vascular smooth muscles in the penis, epididymis, vas deferens, and seminal vesicle smooth muscles through alpha 1 adrenergic receptors (Alwaal, Breyer, & Lue, 2015; Elliott, 2018). Thus, while sympathetic innervation suppresses erection, it plays an important role in the formation of the emission phase of urine storage and ejaculation (Krassioukov & Elliott, 2017; Sabharwal, 2013).

Neurophysiology of erection

Erections can be psychogenic or reflexogenic. Normally, these two mechanisms act in synergy. Sensory stimulation of the genitals leads to reflexogenic erection in men. This reflex occurs at the S2–S4 level of the spinal cord. Afferents are the pudendal nerve that carries sensory transmitters from the genitals, and the efferent pathway passes through the pelvic nerve. Psychogenic erection, on the other hand, involves more complex pathways (Alwaal et al., 2015; Elliott, 2018). In psychogenic erection, various audio, visual, tactile, and/or creative afferent stimuli are processed centrally. After passing through different paths, these fibers move through the hypogastric nerve, reaching the pelvic plexus where the action is integrated with the parasympathetic function (Krassioukov, 2009) (Fig. 3).

Ejaculation

Ejaculation is a neurologically more complex phenomenon and relies on the coordination of the sympathetic (T11-L2) and parasympathetic nervous systems (S2–4) in addition to the somatic nervous system using the pudendal nerve (S2–5). Semen ejection occurs by the rhythmic contraction of the urethral smooth muscle (via sympathetic innervation) and the ischiocavernosus and bulbocavernosus muscles (somatic innervation). The autonomic component of ejaculation is emission, and its somatic component is expulsion. The emission phase of ejaculation describes the accumulation of epididymis, seminal vesicles, and prostate secretions in the posterior urethra, while the expulsion phase describes the excretion

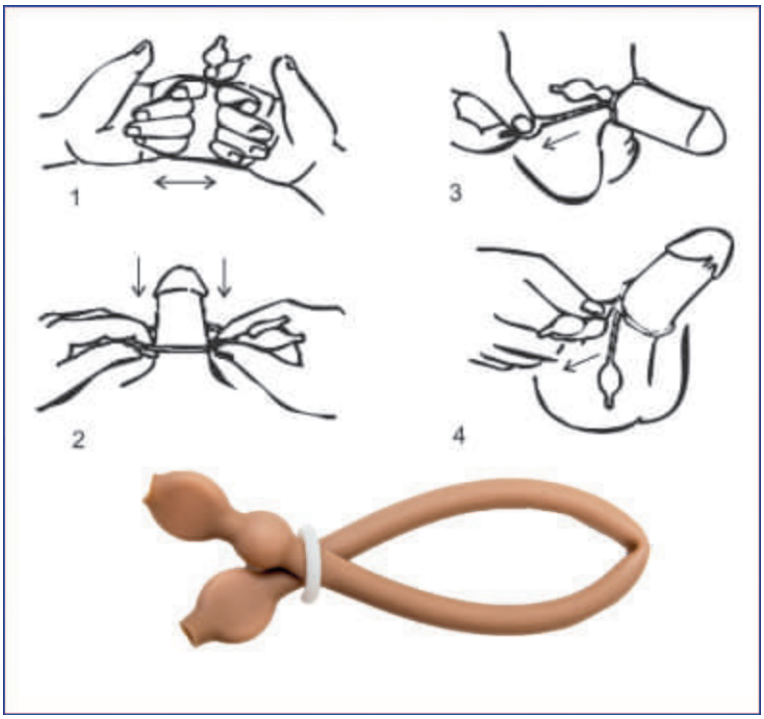

FIG. 3 Penile rings.

of the accumulated seminal secretion from the urethra (Alwaal et al., 2015). Both parasympathetic and sympathetic tonus that provide ejaculation are achieved by integrating genital sensory and/or cerebral erotic stimuli at the spinal cord level (Sabharwal, 2013).

Problems affecting sexual life in men with SCI

Erectile dysfunction in men with SCI

Erectile dysfunction is defined as constant or recursive inadequacy that leads to a failure in achieving or maintaining an erection with full rigidity and duration for sexual intercourse (Burnett et al., 2018). Depending on the innervation of the male genitals, the erectile potential following SCI may be affected by the level and completeness of the lesion. As a general rule, while higher lesions retain better reflex activity and greater sexual potential (especially through multiseptic reflexes), lower lesions impair reflex activity and only retain psychogenic potential. Higher lesions in the cervical or thoracic spinal segments preserve all reflexes beneath the lesion, including multisegmental reflexes. Reflex erections are therefore possible. In contrast, psychogenic erection usually disappears (Aikman et al., 2018; Courtois & Charvier, 2015; Everaert et al., 2010).

While reflex erections are seen in spinal cord lesions between the thoracolumbar region and sacral centers, psychogenic erections do not usually occur (Courtois & Charvier, 2015; Elliott, 2018; Ibrahim, Lynne, & Brackett, 2016). While psychogenic erections persist in spinal cord lesions of the sacral center and below this center, reflex erections disappear (Courtois & Charvier, 2015; Elliott, 2018; Ibrahim et al., 2016).

Ejaculation disorders in men with SCI

The potential for discharge following SCI is similarly affected by the level and completeness of the lesion (Aikman et al., 2018). Accordingly, while autonomic ejaculation is possible in the thoracolumbar region or in a lesion above, nocturnal ejaculation does not occur. Autonomic, somatic, nocturnal, and vibro ejaculations disappear in spinal cord lesions under the thoracolumbar region, but electro-ejaculations can be seen because postsynaptic fibrils remain intact (Alexander, Aisen, Alexander, & Aisen, 2017; Courtois & Charvier, 2015).

Orgasm in men with SCI

Orgasm is the sexual cycle phase accompanied by spinal cord reflexes showing up with subjective pleasure, delight, and relaxation that occurs with the activation of the amygdala and hippocampus in the brain at the end of ejaculation (Alwaal et al., 2015). Studies conducted on men with SCI show that they can experience orgasm even with complete lesions in the spinal cord (Alexander et al., 2017; Courtois & Charvier, 2015; Krassioukov & Elliott, 2017). The responses in individuals with SCI (especially those with lesions above T6) are similar to symptoms of autonomic hyperreflexia during orgasm in healthy individuals (Alexander et al., 2017; Courtois & Charvier, 2015; Krassioukov & Elliott, 2017).

Semen abnormalities and infertility

Although sperm concentration is less affected, impaired sperm motility is common after SCI. The causes are probably multifactorial and have not been fully understood. Immotility of semen associated with seminal vesicle dysfunction has been documented. High levels of cytokines and leukocytes have been reported in semen, suggesting an inflammatory component (Aikman et al., 2018; Ibrahim et al., 2016; Sabharwal, 2013; Stoffel et al., 2018). Only a small percentage of men with SCI can become a father without medical intervention (Sabharwal, 2013).

Management of sexual problems in men with SCI

The management of sexual problems in individuals with SCI should be handled with a holistic approach, and this is possible with a multidisciplinary or interdisciplinary teamwork. Although an interdisciplinary approach in patient-centered care is recommended for a more holistic approach, some patients may prefer limited, individual multidisciplinary appointments to team evaluations due to the sensitivity of the issue of sexuality. The members of a multidisciplinary team usually consist of doctors, nurses, occupational therapists, physiotherapists, psychologists, sexual therapists, social service experts, and peer support workers (Elliott et al., 2017).

Evaluation of neurological factors and medical conditions that may affect sexual function is an important aspect of the management of sexual problems. A detailed neurological, musculoskeletal, and functional evaluation should be made. Examination that is carried out using the International Standards for the Neurological Classification of SCI should include special attention to sensory protection coming from T10-L2 and S2–5, as well as determining the presence of voluntary anal contraction and reflexes to assess sexual function (Sabharwal, 2013).

The most widely employed method for evaluating sexual function is the International Index of Erectile Function (IIEF) in men. IIEF is a self-administered scale consisting of 15 questions and five sub-dimensions, including erectile dysfunction, orgasm function, sexual desire, sexual intercourse satisfaction, and general satisfaction. IIEF is recommended for use in male individuals with SCI to evaluate sexual dysfunction. Another assessment scale is the four-point Erection Hardness Grading Scale, developed for use in various drug studies (Alexander et al., 2009; Steadman & Hubscher, 2016). There is no scale to evaluate ejaculation capacity in men with SCI. Clinically, reflex assessments allow men to predict ejaculatory capacity. The bulbocavernosis reflex can be visualized by stimulating the glans penis and recording the responses of the bulbospongiosus muscle or anal sphincter via electromyography. The presence of the bulbocavernosis reflex indicates that the S2-S4 level is intact. The hip flexor response is a pathogenic reflex initiated by stimulation of the sole that leads to hip flexion typically seen in individuals with SCI. This reflex suggests lesions at the S2-S4 level, if present. The presence of both bulbocavernosis reflex and hip flexor response indicates that the individual can ejaculate with the help of PVS (Penile Vibratory Stimulation). These spinal reflex assessments are therefore clinically useful as indicators of sexual prognosis and as a tool to assist in the selection of future treatment plans (Courtois & Charvier, 2015; Steadman & Hubscher, 2016).

Treatment of erectile dysfunction

Treatment options for Erectile Dysfunction (ED) range from Phosphodiesterase 5-inhibitors to Intracavernous Injections (ICI), vacuum devices, penile rings, and penile prostheses. The choice of treatment depends on individual factors and patient compliance; yet, usually, the least invasive is the first option (Afferi et al., 2020).

Phosphodiesterase 5-inhibitors (PDE5-Is)

PDE5-Is (Sildenafil, Tadalafil, and Vardenafil) are recommended as first-level therapy in men with neurogenic ED (Afferi et al., 2020). The effectiveness of this drug in managing ED depends on the extent and location of the neurological lesion.

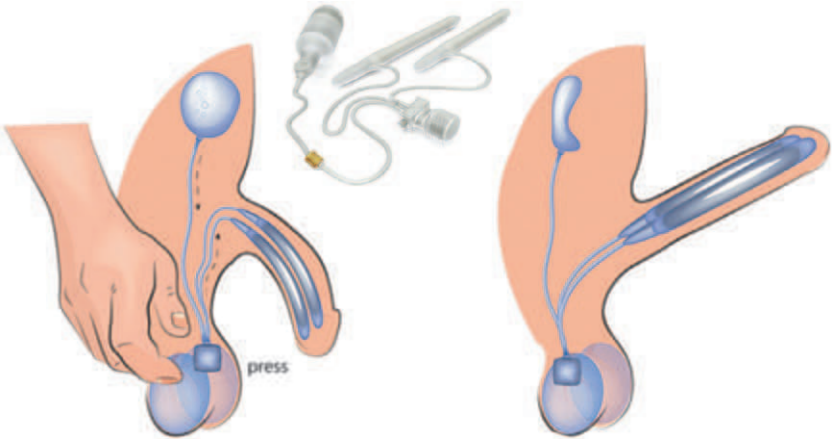

FIG. 4 Penile prostheses.

PDE5I is highly effective in the population with SCI, except for people with cauda equina and conus medullaris injuries (Courtois & Charvier, 2015; Sabharwal, 2013; Stoffel et al., 2018) (Fig. 4).

Intracavernous injections (ICI)

Intracavernosal vasoactive agent injections can be used in patients who do not respond to oral treatments, use nitrates, or cannot achieve reflexogenic erections. Particularly, patients with SCI who have lower lesion levels are more likely to respond to ICI compared to oral pharmacotherapy (Groen et al., 2016). The first product tested in ICI was phentolamine, followed by papaverine and prostaglandins. All of these trigger an erection without the need for sexual stimulation. Self-injections begin with minimal dosages (usually fail), then continue in small increments (0.1 mL increments) until a satisfactory dose is reached (Afferi et al., 2020; Pawar et al., 2019). Patients who start injection therapy should be warned especially about the risk of hematoma and priapism. (Afferi et al., 2020; Courtois & Charvier, 2015; Sabharwal, 2013).

Intraurethral medication

Alprostadil can be used intraureterally for the treatment of erectile dysfunction. Intraurethral administration of alprostadil is less invasive than intracavernosal injection. (Afferi et al., 2020; Courtois & Charvier, 2015).

Vacuum device and penile rings

With the help of a pump, a vacuum is created that promotes an increase in cavernous blood flow, thus causing penile erection. Placing a constriction ring at the base of the penis prevents venous outflow and thus maintains erection. The constriction ring should never be left in place for more than 30 min. The device requires hand skill or partner assistance to some degree. The use of anticoagulant medication is a contraindication (Afferi et al., 2020; Ibrahim et al., 2016; Sabharwal, 2013).

Penile prostheses

The last level of treatment in ED treatment is Penile Prosthesis Implantation (PPI). Penile prostheses are divided into two types: inflatable and malleable. Malleable prostheses consist of semi-rigid rods that can bend upwards during sexual intercourse. The disadvantages of malleable prostheses are the constant rigidness, which can irritate the user and cause him to become asocial. Inflatable Penile Implants (IPP) consist of two cylinders that are placed in the scrotum and provide fluid transfer from the balloon to the cylinder chambers when erection is desired, a reservoir balloon, and a pump. This implant has the advantage of providing a rigid erection on demand and better flaccidity when deflated (Afferi et al., 2020; Courtois & Charvier, 2015; Ibrahim et al., 2016).

Ejaculation dysfunction treatment

The main methods used for sperm retrieval in patients with SCI include penile vibrator stimulation (PVS), electroejaculation (EEJ), prostate massage (PM), and surgical sperm retrieval technique (Fenstermaker, Dupree, Hadj-Moussa, & Ohl, 2018).

Penile vibrator stimulation

Penile Vibrator Stimulation (PVS) is recommended as the first choice for anejaculation in patients with SCI due to its reliability, provision of the highest rate of sperm retrieval as antegrade ejaculation, and cost-effectiveness. PVS can be applied in supine or sitting position. The vibrator is placed in the dorsum, frenulum, or both sides of the penis. If there is no ejaculation within 2 min, the procedure is stopped and continued after a 1–2 min interval. In this way, a total of 10 min of stimulation can be maintained. Meanwhile, the penile skin is checked for edema and abrasions (Courtois & Charvier, 2015; Fenstermaker et al., 2018; Ibrahim et al., 2016).

Electroejaculation

Electroejaculation can be preferred in patients in whom a penile vibrator has not been successful. In this case, semen is retrieved by giving an electrical stimulation through an electrical probe placed in the rectal mucosa in the prostate and seminal vesicle localization from the rectal route. The procedure may be uncomfortable for patients; in this case, spinal or general anesthesia may be needed (Alwaal et al., 2015; Ibrahim et al., 2016).

Prostate massage (PM)

Prostate massage is a simple method of semen extraction applied by a doctor who presses the prostate and seminal vesicles with a finger through the rectum in men with spinal cord injuries. In cases where PVS fails and EEJ is unavailable or requires anesthesia, this method can be recommended as another option before surgical sperm retrieval (Ibrahim et al., 2016).

Surgical sperm retrieval

If PVS, EEJ, and PM are unsuccessful or contraindicated, surgical sperm retrieval methods can be used as the last option for sperm retrieval. Surgical sperm retrieval is more costly and more invasive than PVS and EEJ methods (Ibrahim et al., 2016).

Psychological support

Beyond the well-known physiological changes that cause sexual dysfunction in men with traumatic spinal cord injuries, other factors have been reported to have a potential effect on sexual responses and function. These factors include individual characteristics, such as post-injury self-esteem and body image problems, relationship status, previous sexual attitudes and experiences, and openness to the sexual experience (Cehic et al., 2016; Eisenberg, Andreski, & Mona, 2015). For example, studies have shown that men who adhere to masculine norms and are overly self-confident increase their negative perceptions of their physical limitations after SCI, inhibit their desire to engage in emotional and social support, and end up with higher rates of depression (Burns, Hough, Boyd, & Hill, 2010). To address these concerns, interventions, including sexual training, counseling (both individual and couple counseling), cognitive behavioral therapy, sex therapy, and peer support, are often helpful (Aikman et al., 2018; Eisenberg et al., 2015).

Sex life in women with SCI

Women with SCI need information and counseling about sexual life as well as all their life experiences. Women experience some problems in their sexual life after SCI. These problems include physiological changes, such as difficulty in genital arousal, reduced sensation or loss of sensation, vaginal dryness, difficulties in reaching orgasm, bladder and bowel incontinence, movement and self-positioning difficulty, as well as multidimensional psychological changes, such as unattractiveness or feeling less attractive, lower self-esteem, and maintaining relationships with the partner or finding a partner (Ferreiro-Velasco et al., 2005). Women also need more support and follow-up than other women's processes regarding their fertility status, contraception methods, and gestational periods (Bertschy et al., 2020; Bertschy, Bostan, Meyer, & Pannek, 2016) (Fig. 5).

FIG. 5 Penile vibrator stimulator.

Problems affecting sexual life in women with SCI and their management

Compared to the options available for the treatment of sexual dysfunction in men, the treatment options available to women are rather limited. To improve sexual life and sexual motivation in women, it is very important to first manage the conditions that affect sexual life. Managing biological or medical factors (e.g., low testosterone or estrogen replacement), treating depression (for low libido and poor genital arousal), handling bladder or bowel incontinence, and managing fatigue or pain positively affect sex life and sexual motivation to a great extent (Stoffel et al., 2018). Problems that occur in the lives of women with SCI and their management are discussed in the following sections.

Difficulty in genital arousal

Women with SCI experience physical and psychological genital arousal difficulties (Otero-Villaverde et al., 2015). Tingling sensations (35.3%) and spasms (35%) are the most frequently reported physical sensory problems in women with SCI (Stoffel et al., 2018). In coping with this problem, it may be recommended to try positions and activities different from pre-injury sexual intercourse positions. The multidisciplinary team can support women with SCI and their partners to talk about their needs and aspirations for these new activities and positions. PDE5 inhibitors are used to treat erectile dysfunction in men. These oral medications have been tested in women to increase sexual responses such as arousal. The use of these drugs in women has been reported to increase blood flow in the perineum and vaginal stimulation, which affects sexual satisfaction positively (M. S. Alexander, Biering-Sorensen, Elliott, Kreuter, & Sonksen, 2011; Otero-Villaverde et al., 2015).

Orgasm

One of the important sexual life problems experienced by women after SCI is the difficulty in reaching orgasm. Orgasm is associated with mental excitement. It is reported that in approximately 40–50% of women with spinal cord injuries, the stimulation required to reach orgasm is prolonged compared to pre-injury experiences. Women with SCI can achieve self-defined or laboratory-recorded orgasmic release despite this prolonged orgasm process (Alexander & Rosen, 2008). In women with SCI, conditions such as complete or partial injury and having genital sensation affect orgasm (Stoffel et al., 2018). The use of vibrators may be recommended by a multidisciplinary team for injuries below the T6 level. Counseling can be provided as to whether the drugs used by women can be adjusted to minimize the effect on sexual responses (Courtois et al., 2017).

Another condition that affects orgasm is Autonomic Dysreflexia (AD). Sympathetic activity, which is activated by a stimulus such as genital stimulation, cannot be controlled by the upper centers, causing a continuous and strong sympathetic release (Krassioukov, 2009). Although hypertension is life-threatening, it may not always progress with the same clinical picture and the same severity. Systolic blood pressure in these patients can reach up to 300 mmHg and is important for the diagnosis of AD. Bradycardia, tachycardia, flushing, headache, sweating, tremors, nasal congestion, weakness, blurred vision, spasms are other symptoms of AD (Khastgir, Drake, & Abrams, 2007). AD can make sex unappealing or lead to active abstinence from having sex in some patients with SCI. It is important to give couples time to find the best position for sexual stimulation and orgasm. Longer foreplay and stimulation of body senses (breast, ear lobes, inner thigh) may be recommended for sexual pleasure (Hess & Hough, 2012; Taylan, Gozuyesil, Manav, & Isik, 2019).

Position problems

Positioning problems during foreplay and sexual intercourse are among the most important changes affecting the sexual life of women with SCI. It is important to give couples time to find the best position for sexual stimulation and orgasm. Studies have recommended putting a pillow under the hips to relieve the pressure experienced regarding the position and to provide support during sexual intercourse. Women must be encouraged to try different positions (Courtois et al., 2017; Hess & Hough, 2012).

Psychosocial problems

Apart from the level of injury, some determinants related to the psychosocial life of the person also affect sexual life. In patients with SCI, having a supportive partner (Valtonen, Karlsson, Siosteen, Dahlof, & Viikari-Juntura, 2006), partner satisfaction, and the quality of the relationship (Hess & Hough, 2012) positively affect sexual life. It is emphasized that especially patients with partner support have a better adaptation to their sexual life over time (Valtonen et al., 2006). It is important that women speak openly and honestly to their partners about their sexual needs and desires, and that the partner is understanding and sensitive to these needs. Women may take on the role of giving pleasure to their partner instead of getting pleasure (Taylan et al., 2019). Therefore, the greatest sexual concern of women after injury may include feelings, such as the inability to achieve sexual satisfaction, abandonment by their spouse, emptiness, and exclusion (Maasoumi, Zarei, Merghati-Khoei, Lawson, & Emami-Razavi, 2018).

It is very important to support socialization in coping with psychological difficulties, which draws attention to the fact that SCI affects sexual life in women. Regarding sexual rehabilitation, supporting women in terms of depression and stress, attractiveness, self-esteem, and the ability to overcome the difficulties of managing their relationship with their partner, or finding a partner is important in raising their attention to their preserved sensations during sexual activity (Taylan et al., 2019). For this reason, the multidisciplinary team should provide partner cooperation, including the partner in training and consultancy services, and provide consultancy for appropriate communication by supporting communication between spouses (Stoffel et al., 2018).

Bowel and bladder incontinence

Bowel and bladder continence problems are among the most important problems affecting the sexual life of women with SCI. Urinary incontinence is more common especially in women with complete tetraplegia (Lombardi, Del Popolo, Macchiarella, Mencarini, & Celso, 2010). Bladder management is a source of concern for most women with SCI. It is important to provide counseling to reduce the possibility of urinary accidents during sexual activities. Fluid intake before sexual intercourse can be limited (Hubscher et al., 2018). Women using intermittent catheterization for bladder treatment can empty their bladder before engaging in sexual activity. Women who use suprapubic or Foley catheters may have concerns about the presence of the catheter. Women with SCI can be informed that the Foley catheter is attached to the urethra, the urethra is a separate region from the vagina, and that it will not interfere with sexual intercourse (Lombardi et al., 2010). During sexual intercourse, women may be recommended to fix (using some adhesive tape) the Foley catheter to the thigh or abdomen, taking care not to bend it, and to attach an empty urine bag to the tip of the Foley. If they have the opportunity to reattach the Foley catheter after sexual intercourse, they may also have the option of pulling the Foley catheter before sexual intercourse (Hubscher et al., 2018).

Bowel management is another problem that affects the sex life of women with SCI. The best way to prevent incontinence during sex is to establish a consistent bowel management program. Once a routine has been established, an accident is

much less likely to occur. For greater confidence, it is important to empty the bowel before sexual intercourse and to avoid eating before sexual intercourse (Hubscher et al., 2018).

Fertility

SCI also affects fertility as well as sexual life in both men and women. Neither the level of injury nor the completeness of the lesion appears to have an effect on the menstrual cycle over time (Stoffel et al., 2018). However, most women with SCI experience a brief pause in their menstrual cycle after SCI. This pause is normal and can last up to 6 months after injury (Bertschy et al., 2020). Women with SCI may experience menstrual symptoms, such as increased bladder and muscle spasms, before and during menstruation. Injury can rarely cause menopause in premenopausal women. Except for an increase in mood disorders, menopausal symptoms are similar to those of other women (Stoffel et al., 2018).

Fertility treatment strategies in individuals with SCI are similar to those of the general population. However, it is important to understand the options, consequences, and potential complications that may be specific to SCI, and to inform women about these possible changes (Stoffel et al., 2018).

Birth control

After a period of transient amenorrhea, most women with SCI return to their fertile state before the injury. Although hormonal birth control can be administered to women with SCI, the increased thromboembolic risk should be taken into account. Hormonal contraception should be avoided in women with SCI who continue to smoke and have a history of cardiovascular circulation problems (Stoffel et al., 2018).

Pregnancy

SCI does not necessarily reduce a woman's desire or capacity to give birth. However, several factors, including urological complications, thromboembolism, and autonomic dysfunction, should be considered during pregnancy and delivery (Bertschy et al., 2020). Pregnancy complications with a relatively higher risk of occurrence compared to other pregnant women are urinary tract infections, pyelonephritis, venous thrombosis, pulmonary embolism, premature rupture of membrane, and preterm delivery (Bertschy et al., 2016). Women with SCI often take more than one medication because of the associated symptoms. Therefore, they should have a planned pregnancy. Early prenatal anesthetic consultation is recommended. Anesthetic difficulties may arise, especially in the case of AD. The absence of contractions in women with injuries above T 10 can result in unplanned home births and unattended hospital births. Pregnant women with SCI should be trained about uterine palpation techniques to detect contractions at home (Bertschy et al., 2020).

Maternity care for women with SCI is unavailable in the structural and procedural processes of many high-income countries. Different care philosophies in gynecology/obstetrics and rehabilitation medicine can cause miscommunication, tension, and even antagonism in the continuity of care. These issues must be resolved to benefit women with SCI. In this period, gynecology/obstetrics should be included in the multidisciplinary team (Bertschy et al., 2020).

Conclusion

Problems that may occur in sexual life after injury in individuals with SCI are among the primary issues that should be addressed in both sexes. Treatment options, problems with sexual function and fertility, and possible complications should be addressed with a multidisciplinary approach. It is important that the multidisciplinary team should be aware of the feelings and problems experienced by patients and that patients should be provided with counseling about appropriate coping methods. Informing individuals about possible changes in sexuality and methods for handling them after SCI, and supporting individuals in managing this process will alleviate their pain and anxiety and enable them to be more motivated in their sexual lives (Table 1).

Applications to other areas of neuroscience

As in spinal cord injuries, sexual life problems are common in neurological disorders. Interruption of the long spinal cord pathways between the cortex and sacral cord or pelvic autonomic nerves affects genital blood circulation, erections, ejaculation, and orgasm. Neurological disorders; Intimacy during sexual activity can make it difficult to maintain sexual arousal, sexual intercourse and urinary and bowel continence.

TABLE 1 Problems affecting their sexual life in individuals with spinal cord injuries.

	Physical problems	Psychological problems
Male	Erectile dysfunction Decreased libido Abnormal ejaculation	Anxiety Low self-esteem Depression Decreased sexual satisfaction Changes in personality structure
Female	Genital arousal reduced sensation or loss of sensation Vaginal dryness Difficulties in reaching orgasm Bladder and bowel incontinence Movement and self-positioning difficulty	

Sexual problems experienced in individuals with neurological disorders such as stroke, severe brain trauma, epilepsy, Parkinson's, multiple sclerosis, cauda equina syndrome, perpheric neuropathy are similar to those with spinal cord injuries. Problems such as difficulty in genital arousal, orgasm problems, position problems, bowel and bladder incontinence are common in women. Problems such as erectile dysfunction, ejaculation disorders, orgasm problems, semen abnormalities and infertility are experienced in men. All these problems in both sexes affect the sexual life satisfaction of individuals.

As in SCI individuals, it is important to be aware of the sexual problems of individuals with neurological disorders and to be managed with the same approach. Management of sexual problems should be handled with a holistic approach. Because reduced body image, fatigue, loss of independence, depression, and changes in interpersonal relationships can damage sexual function as much or more than impaired neural circuits. In addition to medical treatment options, patients should be provided with psychological support, talk about their sexual problems, and provide counseling in solving these problems. Although an interdisciplinary approach in patient-centered care is recommended for a more holistic approach, some patients may prefer limited, individual multidisciplinary appointments for team evaluations due to the sensitivity of sexuality.

Mini-dictionary of terms

Autonomic dysreflexia: It is a clinical picture that occurs as a result of uncontrollable sympathetic activity, usually triggered by a sensory stimulus, in spinal cord injuries with injury level T6 and above.
Bladder incontinence: The involuntary leakage of urine.
Bowel Incontinence: The loss of bowel control and causes unexpected stool excretion.
Bulbocavernosus reflex: It is an involuntary reaction that contracts the breech muscles due to stimulation of the clitoris or glans penis.
Ejeculation dysfunction: The inability to efficiently ejaculate sperm from the penis at the time of sexual orgasm.
Erectile dysfunction: It is that the duration and strength of erection in the penis is not sufficient for sexual intercourse.
Neuropathic pain: Type of pain caused by damage or disease affecting the somatosensory nervous system.
Nociceptive pain: The type of pain caused by structural dysfunction is.
Orgasm: It is the sexual cycle phase accompanied by subjective pleasure, pleasure, and relaxation that occurs with the activation of the amygdala and hippocampus in the brain.
Phosphodiesterase 5-inhibitors (PDE5-Is): The first-line drugs used in the treatment of erectile dysfunction (ED).
Priapism: It is a prolonged erection of the penis that is not caused by sexual arousal.
Psychogenic erection: It is an erection that results from audiovisual stimuli or fantasies that generate an impulse from the brain to the spinal erection centers.
Reflexogenic erection: It is an erection caused by direct stimulation of the penis.
Sexual arousal: It is the stimulation of sexual desire during or anticipation of sexual activity.
Sexual dysfunction: It is the difficulty experienced by an individual or a couple at any stage of normal sexual activity, including physical pleasure, desire, preference, arousal, or orgasm.

Key facts of sexual life in individuals with SCI and management

- Spinal cord injuries greatly affect the sexual lives of both men and women.
- The degree of individual sexual dysfunction depends on the level and severity of the SCI.

- It is estimated that 35%–80% of men become inactive after SCI Following.
- Tingling sensations (35.3%) and spasms (35%) are the most frequently reported in women with SCI.
- Male sexual dysfunction includes erectile dysfunction, decreased libido, and abnormal ejaculation.
- Female sexual dysfunction includes difficulty in genital arousal, vaginal dryness, difficulty reaching orgasm.
- Interventions for patients' sexual life, including sexual education, counseling cognitive behavioral therapy, are often helpful

Summary points

- In this section, the effects of SCI on sexual life are discussed.
- It includes male sexual dysfunction, erectile dysfunction, decreased libido, and abnormal ejaculation.
- Female sexual disorders are physiological problems, feeling less attractive, and lack of self-confidence.
- Sexual dysfunctions experienced are associated with psychiatric consequences such as low quality of life, anxiety.
- It is important to diagnose and manage sexual dysfunctions with a multidisciplinary approach.

References

Adriaansen, J. J., Ruijs, L. E., van Koppenhagen, C. F., van Asbeck, F. W., Snoek, G. J., van Kuppevelt, D., et al. (2016). Secondary health conditions and quality of life in persons living with spinal cord injury for at least ten years. *Journal of Rehabilitation Medicine*, *48*(10), 853–860.

Afferi, L., Pannek, J., Burnett, A. L., Razaname, C., Tzanoulinou, S., Bobela, W., et al. (2020). Performance and safety of treatment options for erectile dysfunction in patients with spinal cord injury: A review of the literature. *Andrology*, 1–14. https://doi.org/10.1111/andr.12878.

Aikman, K., Oliffe, J. L., Kelly, M. T., & McCuaig, F. (2018). Sexual health in men with traumatic spinal cord injuries: A review and recommendations for primary health-care providers. *American Journal of Men's Health*, *12*(6), 2044–2054.

Alexander, M. S., Aisen, C. M., Alexander, S. M., & Aisen, M. L. (2017). Sexual concerns after spinal cord injury: An update on management. *NeuroRehabilitation*, *41*(2), 343–357. https://doi.org/10.3233/NRE-172202.

Alexander, M. S., Biering-Sorensen, F., Elliott, S., Kreuter, M., & Sonksen, J. (2011). International spinal cord injury female sexual and reproductive function basic data set. *Spinal Cord*, *49*(7), 787–790. https://doi.org/10.1038/sc.2011.7.

Alexander, M. S., Brackett, N. L., Bodner, D., Elliott, S., Jackson, A., Sonksen, J., et al. (2009). Measurement of sexual functioning after spinal cord injury: Preferred instruments. *The Journal of Spinal Cord Medicine*, *32*(3), 226–236. https://doi.org/10.1080/10790268.2009.11760777.

Alexander, M., & Rosen, R. C. (2008). Spinal cord injuries and orgasm: A review. *Journal of Sex & Marital Therapy*, *34*(4), 308–324. https://doi.org/10.1080/00926230802096341.

Alwaal, A., Breyer, B. N., & Lue, T. F. (2015). Normal male sexual function: Emphasis on orgasm and ejaculation. *Fertility and Sterility*, *104*(5), 1051–1060.

Bertschy, S., Bostan, C., Meyer, T., & Pannek, J. (2016). Medical complications during pregnancy and childbirth in women with SCI in Switzerland. *Spinal Cord*, *54*(3), 183–187. https://doi.org/10.1038/sc.2015.205.

Bertschy, S., Schmidt, M., Fiebag, K., Lange, U., Kues, S., & Kurze, I. (2020). Guideline for the management of pre-, intra-, and postpartum care of women with a spinal cord injury. *Spinal Cord*, *58*(4), 449–458. https://doi.org/10.1038/s41393-019-0389-7.

Burnett, A. L., Nehra, A., Breau, R. H., Culkin, D. J., Faraday, M. M., Hakim, L. S., et al. (2018). Erectile dysfunction: AUA guideline. *The Journal of Urology*, *200*(3), 633–641.

Burns, S. M., Hough, S., Boyd, B. L., & Hill, J. (2010). Men's adjustment to spinal cord injury: The unique contributions of conformity to masculine gender norms. *American Journal of Men's Health*, *4*(2), 157–166.

Cehic, E., Kasum, M., Simunic, V., Oreskovic, S., Vujic, G., & Grgic, F. (2016). Fertility in men with spinal cord injury. *Gynecological Endocrinology*, *32*(12), 937–941. https://doi.org/10.1080/09513590.2016.1202231.

Choi, Y., Kang, J., & Shin, H.-I. (2015). Sexual activity and sexual satisfaction in Korean men with spinal cord injury. *Spinal Cord*, *53*(9), 697–700.

Courtois, F., Alexander, M., & McLain, A. B. J. (2017). Women's sexual health and reproductive function after SCI. *Topics in Spinal Cord Injury Rehabilitation*, *23*(1), 20–30. https://doi.org/10.1310/sci2301-20.

Courtois, F., & Charvier, K. (2015). Sexual dysfunction in patients with spinal cord lesions. *Handbook of Clinical Neurology*, *130*, 225–245.

Cramp, J. D., Courtois, F. J., & Ditor, D. S. (2015). Sexuality for women with spinal cord injury. *Journal of Sex & Marital Therapy*, *41*(3), 238–253.

Dahlberg, A., Alaranta, H., Kautiainen, H., & Kotila, M. (2007). Sexual activity and satisfaction in men with traumatic spinal cord lesion. *Journal of Rehabilitation Medicine*, *39*(2), 152–155.

Eisenberg, N. W., Andreski, S.-R., & Mona, L. R. (2015). Sexuality and physical disability: A disability-affirmative approach to assessment and intervention within health care. *Current Sexual Health Reports*, *7*(1), 19–29.

Elliott, S. (2018). *Sexual dysfunction and infertility in individuals with spinal cord disorders*. *Spinal cord medicine* (pp. 411–435). Springer Publishing Company.

Elliott, S., Hocaloski, S., & Carlson, M. (2017). A multidisciplinary approach to sexual and fertility rehabilitation: The sexual rehabilitation framework. *Topics in Spinal Cord Injury Rehabilitation*, *23*(1), 49–56.

Everaert, K., De Waard, W., Van Hoof, T., Kiekens, C., Mulliez, T., & D'herde, C. (2010). Neuroanatomy and neurophysiology related to sexual dysfunction in male neurogenic patients with lesions to the spinal cord or peripheral nerves. *Spinal Cord*, *48*(3), 182–191.

Fenstermaker, M., Dupree, J. M., Hadj-Moussa, M., & Ohl, D. A. (2018). Management of Erectile Dysfunction and Infertility in the male spinal cord injury patient. *Current Urology Reports*, *19*(7), 47. https://doi.org/10.1007/s11934-018-0806-z.

Ferreiro-Velasco, M. E., Barca-Buyo, A., de la Barrera, S. S., Montoto-Marques, A., Vazquez, X. M., & Rodriguez-Sotillo, A. (2005). Sexual issues in a sample of women with spinal cord injury. *Spinal Cord*, *43*(1), 51–55. https://doi.org/10.1038/sj.sc.3101657.

Gomes, C. M., Miranda, E. P., de Bessa Jr, J., Bellucci, C. H. S., Battistella, L., Abdo, C. H. N., et al. (2017). Erectile function predicts sexual satisfaction in men with spinal cord injury. *Sexual Medicine*, *5*(3), e148–e155.

Groen, J., Pannek, J., Castro Diaz, D., Del Popolo, G., Gross, T., Hamid, R., et al. (2016). Summary of European Association of Urology (EAU) guidelines on neuro-urology. *European Urology*, *69*(2), 324–333. https://doi.org/10.1016/j.eururo.2015.07.071.

Hess, M. J., & Hough, S. (2012). Impact of spinal cord injury on sexuality: Broad-based clinical practice intervention and practical application. *The Journal of Spinal Cord Medicine*, *35*(4), 211–218. https://doi.org/10.1179/2045772312Y.0000000025.

Hubscher, C. H., Herrity, A. N., Williams, C. S., Montgomery, L. R., Willhite, A. M., Angeli, C. A., et al. (2018). Improvements in bladder, bowel and sexual outcomes following task-specific locomotor training in human spinal cord injury. *PLoS One*, *13*(1). https://doi.org/10.1371/journal.pone.0190998, e0190998.

Ibrahim, E., Lynne, C. M., & Brackett, N. (2016). Male fertility following spinal cord injury: An update. *Andrology*, *4*(1), 13–26.

Khastgir, J., Drake, M. J., & Abrams, P. (2007). Recognition and effective management of autonomic dysreflexia in spinal cord injuries. *Expert Opinion on Pharmacotherapy*, *8*(7), 945–956. https://doi.org/10.1517/14656566.8.7.945.

Krassioukov, A. (2009). Autonomic function following cervical spinal cord injury. *Respiratory Physiology & Neurobiology*, *169*(2), 157–164. https://doi.org/10.1016/j.resp.2009.08.003.

Krassioukov, A., & Elliott, S. (2017). Neural control and physiology of sexual function: Effect of spinal cord injury. *Topics in Spinal Cord Injury Rehabilitation*, *23*(1), 1–10.

Le, J., & Dorstyn, D. (2016). Anxiety prevalence following spinal cord injury: A meta-analysis. *Spinal Cord*, *54*(8), 570–578.

Lombardi, G., Del Popolo, G., Macchiarella, A., Mencarini, M., & Celso, M. (2010). Sexual rehabilitation in women with spinal cord injury: A critical review of the literature. *Spinal Cord*, *48*(12), 842–849. https://doi.org/10.1038/sc.2010.36.

Maasoumi, R., Zarei, F., Merghati-Khoei, E., Lawson, T., & Emami-Razavi, S. H. (2018). Development of a sexual needs Rehabilitation framework in women Post-spinal cord injury: A study from Iran. *Archives of Physical Medicine and Rehabilitation*, *99*(3), 548–554. https://doi.org/10.1016/j.apmr.2017.08.477.

Otero-Villaverde, S., Ferreiro-Velasco, M. E., Montoto-Marques, A., Salvador de la Barrera, S., Arias-Pardo, A. I., & Rodriguez-Sotillo, A. (2015). Sexual satisfaction in women with spinal cord injuries. *Spinal Cord*, *53*(7), 557–560. https://doi.org/10.1038/sc.2015.53.

Pawar, P., Patil, S., Tamhankar, A., Kulkarni, V., Savalia, A., Shah, N., et al. (2019). An audit of andrological needs in traumatic paraplegic male patients: Five year assessment in a single paraplegic Centre. *Journal of Clinical and Diagnostic Research*, *13*(12).

Sabharwal, S. (2013). *Essentials of spinal cord Medicine*. New York: Demosmedical.

Steadman, C. J., & Hubscher, C. H. (2016). Sexual function after spinal cord injury: Innervation, assessment, and treatment. *Current Sexual Health Reports*, *8*(2), 106–115.

Stoffel, J. T., Van der Aa, F., Wittmann, D., Yande, S., & Elliott, S. (2018). Fertility and sexuality in the spinal cord injury patient. *World Journal of Urology*, *36*(10), 1577–1585. https://doi.org/10.1007/s00345-018-2347-y.

Taylan, S., Gozuyesil, E., Manav, A. I., & Isik, E. I. (2019). An evaluation of the factors that affect the sexual satisfaction of people with spinal cord injuries. *The Journal of Spinal Cord Medicine*, 1–8. https://doi.org/10.1080/10790268.2019.1672955.

Valtonen, K., Karlsson, A. K., Siosteen, A., Dahlof, L. G., & Viikari-Juntura, E. (2006). Satisfaction with sexual life among persons with traumatic spinal cord injury and meningomyelocele. *Disability and Rehabilitation*, *28*(16), 965–976. https://doi.org/10.1080/09638280500404362.

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Chapter 41

Depressive symptoms in rehabilitation post-spinal cord injury

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Abbreviations

ABI	acquired brain injury
CBT	cognitive behavioral therapy
CES-D	Center for Epidemiologic Studies Depression Scale
DSM5	diagnostic and statistical manual of mental disorders
HPA	hypothalamic-pituitary-adrenal
MDD	major depressive disorder
MINI	Mini-International Neuropsychiatric Interview
NIH PROMIS	National Institutes of Health Patient-Reported Outcomes Measurement Information System
PHQ-2, PHQ-9	Patient Health Questionnaire-2 and -9
SCI	Spinal Cord Injury
SCID-5	Structured Clinical Interview for DSM5
SNRI	serotonin-norepinephrine reuptake inhibitors
SSRI	serotonin reuptake inhibitors
TBI	traumatic brain injury

Introduction

Depression is a common concern among persons with spinal cord injury (SCI). Given the losses and innumerable adjustments required, individuals with an SCI will likely encounter repeated strains upon their available coping resources. As many as 40% of people suffering an SCI experience depression during rehabilitation and around 1 in 5 people experience depression a year after the injury (Williams & Murray, 2015). The experience of depression interferes with rehabilitation efforts, and compromises capacity building, thereby impeding the potential to prevent complications. Depression after SCI is associated with several negative outcomes post-injury including longer hospitalization, decreased longevity, higher levels of pain, increased rates of suicide, reduced health, daily functioning, and limited community participation; it is likely best viewed as a secondary complication or sequelae rather than part of an adaptive process facilitating overall emotional adjustment (Consortium for Spinal Cord Medicine, & Paralyzed Veterans of America, 1998). Depression post-SCI can interfere with recovery and rehabilitation and is related to longer hospital stays, higher levels of pain, and lower quality of life after injury. Management of depression post-SCI is often overlooked due to failure to recognize symptoms and/or access to appropriate services (Paralyzed Veterans of America, 2020). SCI rehabilitation should focus not only on acute care but also on longer-term psychological care (Craig, Tran, & Middleton, 2009). Failure to adopt a multi-modal approach to SCI rehabilitation, one that also targets psychological distress may result in added pressures to health care resources (Craig et al., 2009.; Tate & Pledger, 2003). This chapter summarizes the state of depression among persons with SCI and reviews evidence for its management.

Cellular, Molecular, Physiological, and Behavioral Aspects of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822427-4.00041-1

Screening and assessment of depression post-SCI

While depression was once considered a universal aspect of grieving and adjustment following catastrophic SCI illness or injury (Hohmann, 1975), the adverse impact of clinical depression upon the course of recovery has been more recently well established. Depression is associated with fewer functional improvements and longer inpatient rehabilitation lengths of stay (Dobrez, Heinemann, Deutsch, Durkin, & Almagor, 2010). When compared with non-depressed peers, persons living with SCI in the community encounter greater health-related complications (e.g., pressure ulcers and urinary tract infections) and associated medical costs (Craig et al., 2009). A recent (2015) meta-analysis estimates that the prevalence rates for depression in persons with spinal cord injury to be between 19% and 26% (Williams & Murray, 2015). Depression is not a necessary consequence of SCI. Longitudinal profiles of those with SCI have found that there is a gradual increase in depressive symptoms between 24 and 48 weeks post-injury; followed by a significant decrease post-discharge (Kennedy & Rogers, 2000; Fig. 1). Unfortunately, evidence indicates persons with SCI and significant depression often go unrecognized, or when identified, may not receive sufficient pharmacologic or psychological intervention. In one study, only 29% of persons with probable major depressive disorder (MDD) received anti-depressants and 11% received psychotherapy within the past 3 months (Fann et al., 2011).

From a practical perspective, how best to identify individuals with SCI who are experiencing significant depressive symptoms has long been a focus of clinical concern in rehabilitation. In 2020, the Consortium for Spinal Cord Medicine published a set of clinical practice guidelines for health care providers specific to the management of mental health disorders, substance use disorders, and suicide in adults with spinal cord injury (Karnes et al., 2020). It was recommended that individuals with SCI be screened for major depression early during the initial inpatient hospital or rehabilitation stay, with repeated screening to monitor symptoms at the initial follow-up post-discharge as well as annually (or more frequently) thereafter. Factors including premorbid mental health issues, positive depression screenings following the onset of SCI, and significant chronic pain (Craig et al., 2013) should be considered in determining an individualized screening strategy. The process of regular symptom monitoring can offer an opportunity for earlier intervention to potentially reduce morbidity and mortality in persons "at risk" for developing depressive symptoms following SCI. In a recent study, suicide mortality among those with SCI decreased over three injuries, but it still remained three times higher than that of the general population (Cao, Massaro, Krause, Chen, & Devivo, 2014).

Structured diagnostic interviews (e.g., Structured Clinical Interview for DSM5 (SCID-5) or the Mini-International Neuropsychiatric Interview (MINI)) are often considered the "gold standard" for establishing mental health diagnoses (First, Williams, Karg, & Spitzer, 2016; Sheehan et al., 1998) (Table 1); however, the specialized staff training and burden to clients required to complete these assessments can be impractical in high volume settings such as acute care, rehabilitation, or outpatient clinic settings. Accordingly, a simpler screening strategy to identify depressive symptoms in individuals with a possible diagnosis and facilitate ongoing monitoring becomes of obvious importance in providing ongoing care for

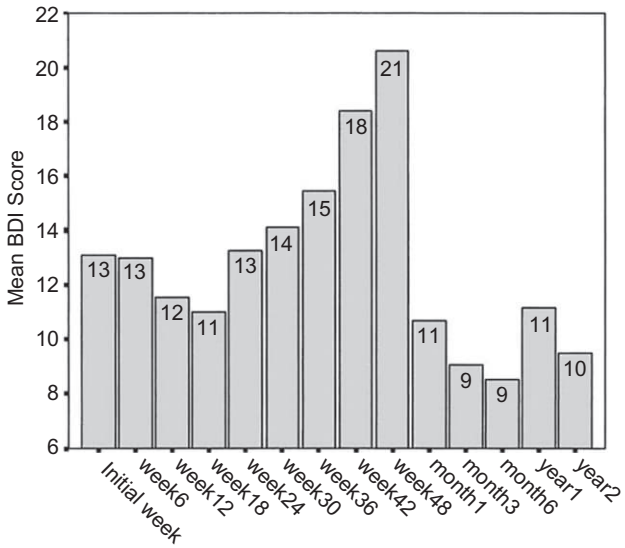

FIG. 1 Mean scores on Beck Depression Inventory over 2 years among those with SCI; Clinical cut-off at >14. *Reprint from: Kennedy, P., & Rogers, B. A. (2000). Anxiety and depression after spinal cord injury: a longitudinal analysis.* Archives of Physical Medicine and Rehabilitation, 81*(7), 932–937.*

TABLE 1 DSM-5 major depressive disorder diagnostic criteria.

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. Note: Do not include symptoms that are clearly attributable to another medical condition.
1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful). (Note: In children and adolescents, can be irritable mood.)
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).
3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month) or decrease or increase in appetite nearly every day. (Note: In children, consider failure to make expected weight gain.)
4. Insomnia or hypersomnia nearly every day.
5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
6. Fatigue or loss of energy nearly every day.
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.
B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
C. The episode is not attributable to the physiological effects of a substance or another medical condition.
Note: Criteria A–C represent a major depressive episode.
Note: Responses to a significant loss (e.g., bereavement, financial ruin, losses from a natural disaster, a serious medical illness or disability) may include the feelings of intense sadness, rumination about the loss, insomnia, poor appetite, and weight loss noted in Criterion A, which may resemble a depressive episode. Although such symptoms may be understandable or considered appropriate to the loss, the presence of a major depressive episode in addition to the normal response to a significant loss should also be carefully considered. This decision inevitably requires the exercise of clinical judgment based on the individual's history and the cultural norms for the expression of distress in the context of loss. In distinguishing grief from a major depressive episode (MDE), it is useful to consider that in grief the predominant affect is feelings of emptiness and loss, while in an MDE it is persistent depressed mood and the inability to anticipate happiness or pleasure. The dysphoria in grief is likely to decrease in intensity over days to weeks and occurs in waves, the so-called pangs of grief. These waves tend to be associated with thoughts or reminders of the deceased. The depressed mood of an MDE is more persistent and not tied to specific thoughts or preoccupations. The pain of grief may be accompanied by positive emotions and humor that are uncharacteristic of the pervasive unhappiness and misery characteristic of an MDE. The thought content associated with grief generally features a preoccupation with thoughts and memories of the deceased, rather than the self-critical or pessimistic ruminations seen in an MDE. In grief, self-esteem is generally preserved, whereas in an MDE feelings of worthlessness and self-loathing are common. If self-derogatory ideation is present in grief, it typically involves perceived failings vis-à-vis the deceased (e.g., not visiting frequently enough, not telling the deceased how much he or she was loved). If a bereaved individual thinks about death and dying, such thoughts are generally focused on the deceased and possibly about "joining" the deceased, whereas in an MDE such thoughts are focused on ending one's own life because of feeling worthless, undeserving of life, or unable to cope with the pain of depression.
D. The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.
E. There has never been a manic episode or a hypomanic episode.

This table is recreated from the American Psychiatric Association (2013). Diagnostic and statistical manual of mental disorders (5th ed.). https://doi.org/10.1176/appi.books.9780890425596

persons with SCI. In a practical two-stage strategy, individuals who test positive on short screening tools can then be more carefully (re)evaluated to confirm the persistence of symptoms, understand factors underlying them, arrive at a diagnosis (e.g., MDD, adjustment disorder, other) and then determine appropriate interventions.

The need for a brief, valid measure of depression with established sensitivity and specificity has long been sought. A wide variety of self-report depression measures have been employed in studies with persons following spinal cord injury

TABLE 2 Validity of depression screeners compared with major depression diagnosis.

Study	Screening measure	Cut point	Criterion measure	Sensitivity %	Specificity %	PPV	NPV	Prevalence %	N
Radnitz et al. (1996)	BDI	≥18	SCID DSM-III-R	83.3	90.8	50.0	98.1	9.7	124
Tate, Forchheimer, Maynard, Davidoff, and Dijkers (1993)	Zung SDS	≥55	DSM-III-R	86.0	67.0	42.9	93.8	23	30
Bombardier et al. (2012)	PHQ-9	≥10	SCID DSM-IV	100	80	36.0	100	10	142
Bombardier et al. (2012)	PHQ-9	≥11	SCID DSM-IV	100	84	40.0	100	10	142
Krause et al. (2009)	QAHMQ	≥11	PHQ-9	89.7	88.8	48.4	98.6	10.7	727

Abbreviations: *BDI*, Beck Depression Inventory; *NPV*, negative predictive value; *OAHMQ*, Older Adult Health and Mood Questionnaire; *PHQ-9*, 9-item Patient Health Questionnaire-9; *PPV*, positive predictive value; *SCID DSM-III-R*, Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised; *SCID DSM-IV*, Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, 4th edition; *Zung SDS*, Zung Self-Rating Depression Scale.
This table is recreated from Paralyzed Veterans of America. (2020). Management of mental health disorders, substance use disorders, and suicide in adults with spinal cord injury. Retrieved from https://www.iscos.org.uk/uploads/sitefiles/Newsletters/PVA_CPG_Mental_Health_and_substa.pdf

(Table 2). A longstanding concern is an impact of including somatic symptoms of depression (e.g., low energy/fatigue, sleep, and appetite disturbances) in screening measures—and the apparent risk that such "transdiagnostic" or overlapping symptoms may serve to inflate depression scores when used with persons with spinal cord injury. A 2017 study of retrospective responses to the CES-D, PHQ-9, and the NIH PROMIS depression scales supported an "inclusive" view toward somatic symptomatology (regardless of etiology) and did not find these three depression scales to have performed differently in persons with SCI when compared to general and community samples. Accordingly, the authors offered that these measures can be applied with greater confidence in helping to identify persons with MDD providing an endorsement of at least one of the two cardinal symptoms (anhedonia; low mood) (Cook et al., 2017).

Other concerns regarding the use of "case finding" screening measures of depression in general, and in persons following SCI include the range of length of the surveys, issues involving manual dexterity when completing pencil/paper assessments, social desirability, accurate item comprehension, or reading challenges. Further, many of the screening measures do not map easily onto established diagnostic classification (DSM5) systems (symptoms and/or time frames) and intervention planning. The PHQ-9 has the advantages of broad clinical application, brevity, no cost, and the 9-item version corresponds directly to the symptoms of MDD in the DSM5. Enhancing its clinical utility, the measure is appropriate for adults and adolescents (as young as 12 years of age), is available in multiple languages and has been widely used across a variety of rehabilitation settings (including acquired brain injury (ABI) and stroke populations). It has been well investigated in persons with SCI (both in inpatient rehabilitation and community samples) and demonstrates strong psychometric properties in identifying clinical cases—though evidence for PHQ-9 as a severity measure and aid to monitoring treatment outcomes is less clear (Pettersson, Boström, Gustavsson, & Ekselius, 2015). Importantly, it includes an item specific to identifying self-destructive ideation. Scores can range from 0 (none)—27 (severe) with 5-point increments in severity. A process that employs an initial screen using the 2-item Patient Health Questionnaire (PHQ-2) can offer further efficiency, such that if neither anhedonia nor depressed mood is endorsed, screening can be discontinued, while if present, the remaining PHQ-9 items can be administered.

In general use, a score of 10 on the PHQ-9 is considered of "moderate" severity prompting consideration of a treatment plan (psychological and/or pharmacological), and a score of 5–9 warrants a discussion of symptoms with their provider and periodic monitoring of their ongoing adjustment. For persons with SCI, it has been suggested that an optimal cut off for detecting major depression with the PHQ-9 during inpatient rehabilitation is a score of 11 (or higher) acknowledging the potential impact of non-specific factors during inpatient rehabilitation and resulting in 100% sensitivity and 84% specificity with persons endorsing at least 1 cardinal symptom of depression (Bombardier et al., 2012). Further investigation into the implementation and outcomes of routine depression screening in persons with SCI is viewed as critical toward supporting emotional well-being and preventing the negative consequences of untreated depression on health and community participation (Titman, Liang, & Craven, 2019).

Theoretical correlates of depression post-SCI

As mentioned previously, depression is not inevitable following SCI, thus it is noteworthy that depression is related to modifiable factors that play a role in its development and maintenance. Several factors, including demographics, injury characteristics, pre-injury behaviors and psychopathology, personality factors, social/environmental factors, and pathophysiology, have been implicated as correlates of depression post-SCI.

Personal factors such as pre-injury psychological distress and psychiatric disorders as well as post-injury difficulties adjusting to SCI have often been shown to be correlated with the presence of depressive symptoms (Arango-Lasprilla, Ketchum, Starkweather, Nicholls, & Wilk, 2011; Krueger, Noonan, Williams, Trenaman, & Rivers, 2013; Williams, Smith, & Papathomas, 2014). Secondary physical complications such as the presence of pain, spasticity, bowel/bladder dysfunction have also been associated with greater levels of depressive symptoms (Hartoonian et al., 2014). However, the self-management model demonstrates that individuals with greater levels of self-efficacy in managing the physical complications of SCI are less likely to experience depression and/or depressive symptoms (Hartoonian et al., 2014). Studies have demonstrated that those that have strong problem-solving skills and self-confidence report fewer symptoms of depression (Elliott, Godshall, Herrick, Witty, & Spruell, 1991).

A higher proportion of depressive symptoms have been correlated with race, particularly Latinos reporting greater level of depressive symptoms compared to African American or Caucasians (Kemp, Krause, & Adkins, 1999). Socioeconomic status, specifically having lower income, has been shown to predict high scores on self-reported depression after controlling for demographic and injury characteristics (Khazaeipour, Taheri-Otaghsara, & Naghdi, 2015). There is conflicting evidence for the role of gender in the prevalence of depression. While some studies indicate women experience greater rates of depression (Khazaeipour et al., 2015), others indicate that there's no significant difference in prevalence rates based on gender (Kalpakjian & Albright, 2006). Environmental factors such as lack of social support or having difficulty having care needs met have been associated with depressive symptoms (Khazaeipour et al., 2017; Zürcher et al., 2019).

There is limited clinical research on pathophysiological models of depression post-SCI. Depression is characterized by changes in neurochemical and neuroendocrine systems, including monoaminergic systems and the hypothalamic-pituitary-adrenal (HPA) axis (Brown, Steinberg, & Van Praag, 1994). These factors are reported in clinical and animal studies during various conditions that result in immunity system activation. In the non-SCI clinical population, studies have found an association between elevated levels of pro-inflammatory cytokines and depression (Dowlati, Herrmann, Swardfager, Reim, & Lanctot, 2010; Liu, Ho, & Mak, 2012). Animal models indicate that among those with a depression-like profile there are higher levels of pro-inflammatory cytokines peripherally. These changes in inflammation were not associated with severity of injury indicating that the correlation between inflammation and depression-like behaviors is independent of impairment (Maldonado-Bouchard et al., 2016). In addition, chronic microglia activation resulting from sustaining an SCI has been shown to increase cognitive dysfunction and depression-like symptoms in mouse models (Wu et al., 2014). Thus there may be a role for the immune system in the development of depression-like symptoms. It is important to keep in mind that these pathophysiological factors alone do not result in decreased emotional well-being. Rather, they may interact with existing maladaptive environmental and psychosocial factors that lead to increased distress (Maldonado-Bouchard et al., 2016).

Management of depression post-SCI

Based on the biopsychosocial model, appropriate management of depression and related secondary complications should be through a multi-disciplinary approach that is best able to deal with a complex number of diverse variables beyond just the actual SCI. Multi-disciplinary SCI rehabilitation programs based on a biopsychosocial model are effective (Budh, Kowalski, & Lundeberg, 2006; Perry, Nicholas, & Middleton, 2010). However, resource limitations can restrict the ability of service providers to deliver these integrative biopsychosocial approaches in the community.

Pharmacological

As there is a lack of studies specific to the SCI population for pharmacologic management of depression, treatment decisions usually follow the basic principles that guide the management of depression in the general population. Psychotherapy and pharmacotherapy in combination are more effective than either alone; they should be offered together if possible (Cuijpers, Dekker, Hollon, & Andersson, 2009; Paralyzed Veterans of America, 2020; Richelson, 2001). Specific studies within the SCI population demonstrate improvements in mood following combined treatment with pharmacotherapy and

CBT/supportive psychotherapy (Judd, Stone, Webber, Brown, & Burrows, 1989; Kahan, Mitchell, Kemp, & Adkins, 2006; Kemp, Kahan, Krause, Adkins, & Nava, 2004).

In general, the addition of pharmacotherapy is recommended in those with at least moderate depression based on symptom severity scales and/or functional impairment (Kennedy et al., 2016). Anti-depressant management in those with mild depression may be considered in certain cases, including patient preference, past response to anti-depressants, and failure of non-pharmacologic management (Kennedy et al., 2016).

Pharmacologic targets for depression management have primarily focused on the neurotransmitters dopamine, serotonin, and dopamine (Richelson, 2001). Anti-depressants may block different neurotransmitter receptors, block the reuptake of different neurotransmitters, or inhibit monoamine oxidase (a mitochondrial enzyme) (Richelson, 2001). This alters the magnitude of neurotransmitter response at the synapse (Richelson, 2001).

In general, first-line pharmacologic treatments include selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), agomelatine, bupropion, mirtazapine, and vortioxetine (Kennedy et al., 2016). When choosing an anti-depressant, factors such as patient preference, prior medication response, relative efficacy and effectiveness, safety, tolerability, anticipated side effects, co-occurring psychiatric and medical conditions, drug interactions, ease of use, half-life, and cost should be considered (Gelenberg et al., 2010; Kennedy et al., 2016). The selection of a first-line treatment for depression is individualized, as differences between these medications are small (Kennedy et al., 2016).

Venlafaxine, an SNRI, is the only anti-depressant that has demonstrated improvement in depressive symptoms when assessing pharmacology-only depression management after SCI (Fann et al., 2015). In those with nociceptive pain, venlafaxine has also been shown to improve pain interference of mood (Richards et al., 2015). Amitriptyline, gabapentin, and carbamazepine have not demonstrated an effect on depressive symptoms after SCI, but the evidence is limited (Rintala et al., 2007; Salinas, Lugo, & García, 2012). Bupropion, mirtazapine, and vortioxetine have not been systematically evaluated within the SCI population (Paralyzed Veterans of America, 2020) nor has agomelatine.

Within the SCI population, caution should be exercised with the SSRI fluoxetine (Paralyzed Veterans of America, 2020), as increased spasticity risk has been described in a case report (Stolp-Smith & Wainberg, 1999). Tricyclic anti-depressants, which are considered second-line for depression in the general population (Kennedy et al., 2016), should also be used with caution in those with SCI given their anticholinergic side effects. An increased risk of certain anti-depressant side effects after SCI may also result from polypharmacy, including prolonged QTc interval and serotonin syndrome (Paralyzed Veterans of America, 2020).

Given the potential for increased risk of side effects from anti-depressants after SCI, frequent monitoring after initiation of treatment is recommended (Paralyzed Veterans of America, 2020). Initiation of anti-depressants at half their usual dose with titration at half the usual rate is also recommended (Paralyzed Veterans of America, 2020).

Non-pharmacological

Evidence for non-pharmacological management of depression post-SCI is limited. However, recent clinical practice guidelines recommend cognitive behavior therapy (CBT) (Paralyzed Veterans of America, 2020). The application of CBT-based approaches has been widely used on a range of psychosocial issues associated with SCI. CBT has been shown to improve an individual's psychological health by modifying maladaptive emotional, behavioral, and cognitive responses (Tolin, 2010). CBT aims to teach specific coping strategies to manage stressful stimuli and develop strategies to help modify an individual's response to the stressor (Kennedy, 2008). CBT also focuses on problem-solving, cognitive restructuring, increasing access and willingness to engage in rewarding activities, relaxation training, as well as self-efficacy and coping (Swett & Richardson, 2004). Several systematic reviews among the SCI population demonstrate that CBT facilitates adjustment and has been found effective in improving psychological outcomes such as depression, anxiety, coping, and self-efficacy for up to 6 months in follow-up (Dorstyn, Mathias, & Denson, 2010; Mehta et al., 2011). More recent studies have found that online psychological interventions are effective for reducing depressive symptoms among adults with SCI who struggle with mild to moderate depressive symptoms (Burke et al., 2019; Dear et al., 2018; Mehta et al., 2020; Migliorini, Sinclair, Brown, Tonge, & New, 2016). With online interventions, persons with SCI may be able to access therapy that otherwise would have been inaccessible in person.

Other management non-pharmacological management strategies include exercise programs which included stretching, aerobic arm ergometry, and resistance exercises among those with SCI. The studies found a significant reduction in depressive symptoms post-SCI after exercise treatment (Crane, Hoffman, & Reyes, 2017; Hicks et al., 2003; Latimer, Ginis, Hicks, & McCartney, 2004; Ginis et al., 2003). There is limited evidence for external brain stimulation interventions including repetitive transcortical magnetic stimulation or transcranial direct current stimulation in decreasing depressive

symptoms with comorbid pain (Defrin, Grunhaus, Zamir, & Zeilig, 2007; Fregni, Boggio, Nitsche, Rigonatti, & Pascual-Leone, 2006; Tan, Hartung, Sharp, & Temel, 2011). However, follow-up times for these treatments have been relatively short (6 weeks); long-term effectiveness is yet to be determined. In addition, access to these forms of treatments may be limited.

Applications to other areas of neuroscience

Other neurological conditions such as traumatic brain injury (TBI), stroke, multiple sclerosis, epilepsy, Alzheimer's diseases also experience a higher prevalence of depressive symptoms compared to the general population (Bulloch et al., 2015) with impaired physical health and quality of life across these neurological conditions (Prisnie et al., 2018). The dispositional factors and pathophysiological pathways are seen in the development of depressive symptoms among those with SCI have also been implicated among other neurological conditions. Consistent findings have linked the presence of depressive symptoms with the hyperactivity of the HPA axis and activation of specific immune responses across neurological disorders (Benedetti, Bernasconi, & Pontiggia, 2006).

Several management strategies reviewed in the current chapter are also translatable among other neurological conditions. Similar to the management of depression among those with SCI, recommendations include the use of SSRIs and CBT among other neurological conditions (Benedetti et al., 2006; Fernie, Kollmann, & Brown, 2015; Hellmann-Regen et al., 2013). Though these management strategies are effective across neurological conditions, several differences exist. Pharmacological treatments like SSRIs (e.g., fluoxetine) may be more tolerable among certain neurological conditions such as with TBI without the risk of spasticity seen among those with SCI (Fann, Hart, & Schomer, 2009). In addition, management strategies involving a strong cognitive component such as CBT may not be appropriate for individuals with severe cognitive or linguistic impairments such as those seen in Alzheimer's disease, TBI, and stroke. Given these differences, it's important to examine the distinct profiles of each neurological condition when developing personalized management plans.

Mini-dictionary of terms

- **Adjustment**: adjustment in a psychological setting, is the process by which an individual attempt to adjust to the challenges from their environment.
- **Anhedonia**: a condition in which an individual is unable to experience pleasure from pleasurable experiences.
- **Cytokines**: a variety of substances that are secreted by cells of the immune system and affect other cells.
- **Depression**: a common medical condition that negatively affects how the individual feels, thinks, and acts.
- **Dispositional Factors**: internal factors or individual characteristics that affect the individual's behavior and actions.
- **Half-life**: the length of time it takes for the concentration of a drug to decrease to half of its starting dose.
- **Hypothalamic pituitary adrenal (HPA) axis**: comprises the hypothalamus, the pituitary gland, and the adrenal glands. It plays an important role in homeostasis and the body's response to stress.
- **Monoaminergic systems**: are a network of neurons that use monoamine neurotransmitters and are important mediators of emotion, arousal, and certain types of memory.
- **Neurotransmitters**: are chemical agents released by neurons to stimulate neighboring neurons or muscle cells, resulting in the transmission of impulses from one cell to the next.
- **QT interval**: is a measurement of the total time from ventricular depolarization to complete repolarization.
- **Sensitivity**: is the proportion of people with the condition who test positive on a specific test.
- **Specificity**: is the proportion of people without the condition who test negative on a specific test

Key facts of screening and diagnosis

- Depression is a common secondary condition post-SCI.
- It can be a complicated process that significantly impedes adjustment and activities of daily living.
- Depression is not universal and though many experience grief after SCI, not everyone experiences persistence of these symptoms into depression once in the community.
- Identifying symptoms of depression can be difficult since comorbid physical concerns may endorse similar somatic symptoms (e.g., fatigue, insomnia, changes in appetite).
- Self-report measures are important screening tools to help clinicians identify any psychosocial distress. These should be followed up with an appropriate referral to management.

Key facts of management

- Combined psychotherapy and pharmacotherapy are effective at managing depression post-SCI than either alone.
- Pharmacological management of depression post-SCI is primarily through SSRIs and SNRIs.
- Due to the increased risk of side effects, it is important to monitor treatment.
- The current recommendation for non-pharmacological management include CBT to improve depression post-SCI
- There is limited evidence for other non-pharmacological strategies including exercise and physical stimulation interventions such as trans magnetic stimulation and transcranial direct current stimulation.

Summary points

- This chapter focuses on depression which is a common secondary condition post-SCI with a prevalence of up to 29%.
- Depression impedes recovery post-SCI and results in several negative outcomes including increased hospitalization, increased morbidity, greater levels of pain, reduced quality of life, and decreased functional capacity.
- Clinical practice guidelines recommend regular screening and monitoring of depressive symptoms among those with SCI.
- Screening should be followed by appropriate diagnosis using the SCID-5 or MINI which is considered the gold standard for establishing diagnoses.
- Due to the existence of transdiagnostic somatic symptoms of depression among persons with SCI, there is a potential for inflation of depression scores while using some outcome measures; however, measures such as the CES-D, PHQ-9, and NIH PROMIS depression scales were found to be psychometrically sound in persons with SCI regardless of the presence of somatic symptoms.
- Several factors have been established as correlates of depression post-SCI including pre-injury psychological distress, race, secondary physical complications, socioeconomic status, gender, and neurotransmitters.
- Optimal management should include both psychotherapy and pharmacotherapy. In terms of pharmacotherapy, current CPGs recommend the use of SSRIs and SNRIs as first-line treatments. CBT is the primary non-pharmacological strategy recommended by the CPGs.
- The depression profile of those with SCI is similar to other neurological condition populations. However, it is important to examine the differences among each condition when developing a personalized management plan.

References

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). American Psychiatric Publishing, Inc.

Arango-Lasprilla, J. C., Ketchum, J. M., Starkweather, A., Nicholls, E., & Wilk, A. R. (2011). Factors predicting depression among persons with spinal cord injury 1 to 5 years post injury. *NeuroRehabilitation*, *29*(1), 9–21.

Benedetti, F., Bernasconi, A., & Pontiggia, A. (2006). Depression and neurological disorders. *Current Opinion in Psychiatry*, *19*(1), 14–18.

Bombardier, C. H., Kalpakjian, C. Z., Graves, D. E., Dyer, J. R., Tate, D. G., & Fann, J. R. (2012). Validity of the patient health questionnaire-9 in assessing major depressive disorder during inpatient spinal cord injury rehabilitation. *Archives of Physical Medicine and Rehabilitation*, *93*(10), 1838–1845.

Brown, S. L., Steinberg, R. L., & Van Praag, H. M. (1994). The pathogenesis of depression: Reconsideration of neurotransmitter data. In *Handbook of depression and anxiety: A biological approach* (pp. 317–347). New York, NY: Marcel Dekker, Inc.

Budh, C. N., Kowalski, J., & Lundeberg, T. (2006). A comprehensive pain management programme comprising educational, cognitive and behavioural interventions for neuropathic pain following spinal cord injury. *Journal of Rehabilitation Medicine*, *38*(3), 172–180.

Bulloch, A. G., Fiest, K. M., Williams, J. V., Lavorato, D. H., Berzins, S. A., Jetté, N., … Patten, S. B. (2015). Depression—A common disorder across a broad spectrum of neurological conditions: A cross-sectional nationally representative survey. *General Hospital Psychiatry*, *37*(6), 507–512.

Burke, D., Lennon, O., Blake, C., Nolan, M., Barry, S., Smith, E., … Fullen, B. M. (2019). An internet-delivered cognitive behavioural therapy pain management programme for spinal cord injury pain: A randomized controlled trial. *European Journal of Pain*, *23*(7), 1264–1282.

Cao, Y., Massaro, J. F., Krause, J. S., Chen, Y., & Devivo, M. J. (2014). Suicide mortality after spinal cord injury in the United States: Injury cohorts analysis. *Archives of Physical Medicine and Rehabilitation*, *95*(2), 230–235.

Consortium for Spinal Cord Medicine, & Paralyzed Veterans of America. (1998). *Depression following spinal cord injury: A clinical practice guideline for primary care physicians*. Consortium for Spinal Cord Medicine.

Cook, K. F., Kallen, M. A., Bombardier, C., Bamer, A. M., Choi, S. W., Kim, J., … Amtmann, D. (2017). Do measures of depressive symptoms function differently in people with spinal cord injury versus primary care patients: The CES-D, PHQ-9, and PROMIS®-D. *Quality of Life Research*, *26*(1), 139–148.

Craig, A., Tran, Y., & Middleton, J. (2009). Psychological morbidity and spinal cord injury: A systematic review. *Spinal Cord*, *47*(2), 108–114.

Craig, A., Tran, Y., Siddall, P., Wijesuriya, N., Lovas, J., Bartrop, R., & Middleton, J. (2013). Developing a model of associations between chronic pain, depressive mood, chronic fatigue, and self-efficacy in people with spinal cord injury. *The Journal of Pain*, *14*(9), 911–920.

Crane, D. A., Hoffman, J. M., & Reyes, M. R. (2017). Benefits of an exercise wellness program after spinal cord injury. *The Journal of Spinal Cord Medicine*, *40*(2), 154–158.

Cuijpers, P., Dekker, J., Hollon, S. D., & Andersson, G. (2009). Adding psychotherapy to pharmacotherapy in the treatment of depressive disorders in adults: A meta-analysis. In *Database of abstracts of reviews of effects (DARE): Quality-assessed reviews [internet]* Centre for Reviews and Dissemination (UK).

Dear, B. F., Fogliati, V. J., Fogliati, R., Gandy, M., McDonald, S., Talley, N., … Jones, M. (2018). Transdiagnostic internet-delivered cognitive-behaviour therapy (CBT) for adults with functional gastrointestinal disorders (FGID): A feasibility open trial. *Journal of Psychosomatic Research*, *108*, 61–69.

Defrin, R., Grunhaus, L., Zamir, D., & Zeilig, G. (2007). The effect of a series of repetitive transcranial magnetic stimulations of the motor cortex on central pain after spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *88*(12), 1574–1580.

Dobrez, D., Heinemann, A. W., Deutsch, A., Durkin, E. M., & Almagor, O. (2010). Impact of mental disorders on cost and reimbursement for patients in inpatient rehabilitation facilities. *Archives of Physical Medicine and Rehabilitation*, *91*(2), 184–188.

Dorstyn, D. S., Mathias, J. L., & Denson, L. A. (2010). Psychological intervention during spinal rehabilitation: A preliminary study. *Spinal Cord*, *48*(10), 756–761.

Dowlati, Y., Herrmann, N., Swardfager, W. L., Reim, E. K., & Lanctot, K. L. (2010). Efficacy and tolerability of antidepressants for treatment of depression in coronary artery disease: A meta-analysis. *The Canadian Journal of Psychiatry*, *55*(2), 91–99.

Elliott, T. R., Godshall, F. J., Herrick, S. M., Witty, T. E., & Spruell, M. (1991). Problem-solving appraisal and psychological adjustment following spinal cord injury. *Cognitive Therapy and Research*, *15*(5), 387–398.

Fann, J. R., Bombardier, C. H., Richards, J. S., Tate, D. G., Wilson, C. S., Temkin, N., & PRISMS Investigators. (2011). Depression after spinal cord injury: Comorbidities, mental health service use, and adequacy of treatment. *Archives of Physical Medicine and Rehabilitation*, *92*(3), 352–360.

Fann, J. R., Bombardier, C. H., Richards, J. S., Wilson, C. S., Heinemann, A. W., Warren, A. M., … Tate, D. G. (2015). Venlafaxine extended-release for depression following spinal cord injury: A randomized clinical trial. *JAMA Psychiatry*, *72*(3), 247–258.

Fann, J. R., Hart, T., & Schomer, K. G. (2009). Treatment for depression after traumatic brain injury: A systematic review. *Journal of Neurotrauma*, *26*(12), 2383–2402.

Fernie, B. A., Kollmann, J., & Brown, R. G. (2015). Cognitive behavioural interventions for depression in chronic neurological conditions: A systematic review. *Journal of Psychosomatic Research*, *78*(5), 411–419.

First, M. B., Williams, J. B., Karg, R. S., & Spitzer, R. L. (2016). *SCID-5-CV: Structured clinical interview for DSM-5 disorders, clinician version*. American Psychiatric Association Publishing.

Fregni, F., Boggio, P. S., Nitsche, M. A., Rigonatti, S. P., & Pascual-Leone, A. (2006). Cognitive effects of repeated sessions of transcranial direct current stimulation in patients with depression. *Depression and Anxiety*, *23*(8), 482–484.

Gelenberg, A. J., Freeman, M. P., Markowitz, J. C., Rosenbaum, J. F., Thase, M. E., Trivedi, M. H., … Silbersweig, D. A. (2010). Practice guideline for the treatment of patients with major depressive disorder third edition. *The American Journal of Psychiatry*, *167*(10), 1.

Ginis, K. A. M., Latimer, A. E., McKechnie, K., Ditor, D. S., McCartney, N., Hicks, A. L., … Craven, B. C. (2003). Using exercise to enhance subjective well-being among people with spinal cord injury: The mediating influences of stress and pain. *Rehabilitation Psychology*, *48*(3), 157.

Hartoonian, N., Hoffman, J. M., Kalpakjian, C. Z., Taylor, H. B., Krause, J. K., & Bombardier, C. H. (2014). Evaluating a spinal cord injury–specific model of depression and quality of life. *Archives of Physical Medicine and Rehabilitation*, *95*(3), 455–465.

Hellmann-Regen, J., Piber, D., Hinkelmann, K., Gold, S. M., Heesen, C., Spitzer, C., … Otte, C. (2013). Depressive syndromes in neurological disorders. *European Archives of Psychiatry and Clinical Neuroscience*, *263*(2), 123–136.

Hicks, A. L., Martin, K. A., Ditor, D. S., Latimer, A. E., Craven, C., Bugaresti, J., & McCartney, N. (2003). Long-term exercise training in persons with spinal cord injury: Effects on strength, arm ergometry performance and psychological well-being. *Spinal Cord*, *41*(1), 34–43.

Hohmann, G. W. (1975). Psychological aspects of treatment and rehabilitation of the spinal cord injured person. *Clinical Orthopaedics and Related Research*, *112*, 81–88.

Judd, F. K., Stone, J., Webber, J. E., Brown, D. J., & Burrows, G. D. (1989). Depression following spinal cord injury: A prospective in-patient study. *The British Journal of Psychiatry*, *154*(5), 668–671.

Kahan, J. S., Mitchell, J. M., Kemp, B. J., & Adkins, R. H. (2006). The results of a 6-month treatment for depression on symptoms, life satisfaction, and community activities among individuals aging with a disability. *Rehabilitation Psychology*, *51*(1), 13.

Kalpakjian, C. Z., & Albright, K. J. (2006). An examination of depression through the lens of spinal cord injury: Comparative prevalence rates and severity in women and men. *Women's Health Issues*, *16*(6), 380–388.

Karnes, J. H., Rettie, A. E., Somogyi, A. A., Huddart, R., Fohner, A. E., Formea, C. M., … Callaghan, J. T. (2020). Clinical pharmacogenetics implementation consortium (CPIC) guideline for CYP2C9 and HLA-B genotypes and phenytoin dosing: 2020 update. *Clinical Pharmacology and Therapeutics*.

Kemp, B. J., Kahan, J. S., Krause, J. S., Adkins, R. H., & Nava, G. N. (2004). Treatment of major depression in individuals with spinal cord injury. *The Journal of Spinal Cord Medicine*, *27*(1), 22–28.

Kemp, B., Krause, J. S., & Adkins, R. (1999). Depression among African Americans, Latinos, and Caucasians with spinal cord injury: A exploratory study. *Rehabilitation Psychology*, *44*(3), 235.

Kennedy, S. H., Lam, R. W., McIntyre, R. S., Tourjman, S. V., Bhat, V., Blier, P., … CANMAT Depression Work Group. (2016). Canadian network for mood and anxiety treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: Section 3. Pharmacological treatments. *The Canadian Journal of Psychiatry*, *61*(9), 540–560.

Kennedy, F. (2008). The use of formulation in inpatient settings. In *Cognitive behaviour therapy for acute inpatient mental health units* (pp. 57–80). Routledge.

Kennedy, P., & Rogers, B. A. (2000). Anxiety and depression after spinal cord injury: A longitudinal analysis. *Archives of Physical Medicine and Rehabilitation*, *81*(7), 932–937.

Khazaeipour, Z., Ahmadipour, E., Rahimi-Movaghar, V., Ahmadipour, F., Vaccaro, A. R., & Babakhani, B. (2017). Association of pain, social support and socioeconomic indicators in patients with spinal cord injury in Iran. *Spinal Cord*, *55*(2), 180–186.

Khazaeipour, Z., Taheri-Otaghsara, S. M., & Naghdi, M. (2015). Depression following spinal cord njury: Its relationship to demographic and socioeconomic indicators. *Topics in Spinal Cord Injury Rehabilitation*, *21*(2), 149–155.

Krause, J. S., Saunders, L. L., Reed, K. S., Coker, J., Zhai, Y., & Johnson, E. (2009). Comparison of the Patient Health Questionnaire and the Older Adult Health and Mood Questionnaire for self-reported depressive symptoms after spinal cord injury. *Rehabilitation Psychology*, *54*(4), 440–448. https://doi.org/10.1037/a0017402.

Krueger, H., Noonan, V. K., Williams, D., Trenaman, L. M., & Rivers, C. S. (2013). The influence of depression on physical complications in spinal cord injury: Behavioral mechanisms and health-care implications. *Spinal Cord*, *51*(4), 260–266.

Latimer, A. E., Ginis, K. A. M., Hicks, A. L., & McCartney, N. (2004). An examination of the mechanisms of exercise-induced change in psychological well-being among people with spinal cord injury. *Journal of Rehabilitation Research and Development*, *41*(5).

Liu, Y., Ho, R. C. M., & Mak, A. (2012). Interleukin (IL)-6, tumour necrosis factor alpha (TNF-α) and soluble interleukin-2 receptors (sIL-2R) are elevated in patients with major depressive disorder: A meta-analysis and meta-regression. *Journal of Affective Disorders*, *139*(3), 230–239.

Maldonado-Bouchard, S., Peters, K., Woller, S. A., Madahian, B., Faghihi, U., Patel, S., … Hook, M. A. (2016). Inflammation is increased with anxiety- and depression-like signs in a rat model of spinal cord injury. *Brain, Behavior, and Immunity*, *51*, 176–195.

Mehta, S., Hadjistavropoulos, H., Nugent, M., Karin, E., Titov, N., & Dear, B. F. (2020). Guided internet-delivered cognitive-behaviour therapy for persons with spinal cord injury: A feasibility trial. *Spinal Cord*, *58*(5), 544–552.

Mehta, S., Orenczuk, S., Hansen, K. T., Aubut, J. A. L., Hitzig, S. L., Legassic, M., & Teasell, R. W. (2011). An evidence-based review of the effectiveness of cognitive behavioral therapy for psychosocial issues post-spinal cord injury. *Rehabilitation Psychology*, *56*(1), 15.

Migliorini, C., Sinclair, A., Brown, D., Tonge, B., & New, P. (2016). A randomised control trial of an internet-based cognitive behaviour treatment for mood disorder in adults with chronic spinal cord injury. *Spinal Cord*, *54*(9), 695–701.

Paralyzed Veterans of America. (2020). *Management of mental health disorders, substance use disorders, and suicide in adults with spinal cord injury*. Retrieved from https://www.iscos.org.uk/uploads/sitefiles/Newsletters/PVA_CPG_Mental_Health_and_substa.pdf.

Perry, K. N., Nicholas, M. K., & Middleton, J. W. (2010). Comparison of a pain management program with usual care in a pain management center for people with spinal cord injury-related chronic pain. *The Clinical Journal of Pain*, *26*(3), 206–216.

Pettersson, A., Boström, K. B., Gustavsson, P., & Ekselius, L. (2015). Which instruments to support diagnosis of depression have sufficient accuracy? A systematic review. *Nordic Journal of Psychiatry*, *69*(7), 497–508.

Prisnie, J. C., Sajobi, T. T., Wang, M., Patten, S. B., Fiest, K. M., Bulloch, A. G., … Jette, N. (2018). Effects of depression and anxiety on quality of life in five common neurological disorders. *General Hospital Psychiatry*, *52*, 58–63.

Radnitz, C. L., Broderick, C. P., Perez-Strumolo, L., Tirch, D. D., Festa, J., Schlein, I. S., et al. (1996). The prevalence of psychiatric disorders in veterans with spinal cord injury: A controlled comparison. *Journal of Nervous and Mental Disease*, *184*(7), 431–433. https://doi.org/10.1097/00005053-199607000-00006.

Richards, J. S., Bombardier, C. H., Wilson, C. S., Chiodo, A. E., Brooks, L., Tate, D. G., … Fann, J. R. (2015). Efficacy of venlafaxine XR for the treatment of pain in patients with spinal cord injury and major depression: A randomized, controlled trial. *Archives of Physical Medicine and Rehabilitation*, *96*(4), 680–689.

Richelson, E. (2001). Pharmacology of antidepressants. In *Vol. 76. Mayo Clinic Proceedings* (pp. 511–527). Elsevier. No. 5.

Rintala, D. H., Holmes, S. A., Courtade, D., Fiess, R. N., Tastard, L. V., & Loubser, P. G. (2007). Comparison of the effectiveness of amitriptyline and gabapentin on chronic neuropathic pain in persons with spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *88*(12), 1547–1560.

Salinas, F. A., Lugo, L. H., & García, H. I. (2012). Efficacy of early treatment with carbamazepine in prevention of neuropathic pain in patients with spinal cord injury. *American Journal of Physical Medicine & Rehabilitation*, *91*(12), 1020–1027.

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., … Dunbar, G. C. (1998). The Mini-international neuropsychiatric interview (MINI): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *The Journal of Clinical Psychiatry*, *59*(Suppl 20), 22–33.

Stolp-Smith, K. A., & Wainberg, M. C. (1999). Antidepressant exacerbation of spasticity. *Archives of Physical Medicine and Rehabilitation*, *80*(3), 339–342.

Swett, S. E., & Richardson, W. S. (2004). Cognitive-behavioral therapy. In F. Chan, N. L. Berven, & K. R. Thomas (Eds.), *Counseling theories and techniques for rehabilitation health professionals* (pp. 159–176). NewYork, NY: Springer Publishing Co.

Tan, S. K., Hartung, H., Sharp, T., & Temel, Y. (2011). Serotonin-dependent depression in Parkinson's disease: A role for the subthalamic nucleus? *Neuropharmacology*, *61*(3), 387–399.

Tate, D. G., Forchheimer, M., Maynard, F., Davidoff, G., & Dijkers, M. (1993). Comparing two measures of depression in spinal cord injury. *Rehabilitation Psychology*, *38*(1), 53–61. https://doi.org/10.1037/h0080287.

Tate, D. G., & Pledger, C. (2003). An integrative conceptual framework of disability: New directions for research. *American Psychologist*, *58*(4), 289.

Titman, R., Liang, J., & Craven, B. C. (2019). Diagnostic accuracy and feasibility of depression screening in spinal cord injury: A systematic review. *The Journal of Spinal Cord Medicine*, *42*(sup1), 99–107.

Tolin, D. F. (2010). Is cognitive–behavioral therapy more effective than other therapies?: A meta-analytic review. *Clinical Psychology Review*, *30*(6), 710–720.

Williams, R., & Murray, A. (2015). Prevalence of depression after spinal cord injury: A meta-analysis. *Archives of Physical Medicine and Rehabilitation*, *96*(1), 133–140.

Williams, T. L., Smith, B., & Papathomas, A. (2014). The barriers, benefits and facilitators of leisure time physical activity among people with spinal cord injury: A meta-synthesis of qualitative findings. *Health Psychology Review*, *8*(4), 404–425.

Wu, J., Zhao, Z., Sabirzhanov, B., Stoica, B. A., Kumar, A., Luo, T., … Faden, A. I. (2014). Spinal cord injury causes brain inflammation associated with cognitive and affective changes: Role of cell cycle pathways. *Journal of Neuroscience*, *34*(33), 10989–11006.

Zürcher, C., Tough, H., Fekete, C., & SwiSCI Study Group. (2019). Mental health in individuals with spinal cord injury: The role of socioeconomic conditions and social relationships. *PLoS One*, *14*(2), e0206069.

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Chapter 42

Self-harm behaviors in patients with spinal cord injuries: From non-adherence to suicide

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List of abbreviations

SCI spinal cord injury

Introduction

Harming oneself seems unnatural. Yet, many people knowingly engage in behaviors that are not in their best interest and, if prolonged, some behaviors can result in serious harm to oneself, hence "self-harm." In medical settings, self-harm can emerge in an assortment of behaviors and range from mismanaging medications, failing to attend medical or mental health appointments, sleeping too much or little—to frank self-neglect, complete social isolation, overuse of pain medication, deliberate alcohol and illicit drug abuse, candid "giving up", decisions to medically hasten death, or suicide attempts.

Spinal cord injury (SCI) forces people to suddenly learn how to do everything in their lives in new ways, an abundantly stressful event for most people. Many factors affect a person's response after SCI—physical health, economic and social factors, comorbid psychological and substance use disorders, and more (Craig, Tran, & Middleton, 2017; Kishi, Robinson, & Kosier, 2001; Martz, Livneh, Priebe, Wuermser, & Ottomanelli, 2005; Pollard & Kennedy, 2007). Olkin (1993) states these influences on adaptation persist with a "…response curve, while steeper at first, does not ever level off at some mythical stage of adjustment and acceptance" (p. 15). Rather, "adaptation" (preferred term over adjustment) to SCI is a continuous process in a non-linear fashion (Craig et al., 2017; Pollard & Kennedy, 2007) and is intensely personal.

Physicians, nurses, psychologists, social workers, and other health care providers (referred to as "clinicians" going forward) have an ethical obligation to benefit the patient (beneficence), avoid or minimize harm, and respect patients' values and preferences (Beauchamp & Childress, 2009; Torke & Sachs, 2008). Under most contexts, patients are presumed to want help to improve their health and well-being. However, sometimes patients decline or ignore vital medical interventions and act in ways that can or do cause themselves harm, interfering with the clinician's obligation for beneficence. This can be a source of pointed frustration, realistic concern, and/or moral distress for clinicians (Torke & Sachs, 2008).

Self-harm behaviors and suicidal behaviors

"Self-harm" is usually automatically associated with suicide and an intent to die. However, there are additional forms of self-harm that have been less well described but potentially as lethal (Bostwick, 2015; Bostwick & Cohen, 2009). Some self-harm behaviors are conscious choices or expressions of autonomous self-determination. Some behaviors are to seek attention or help, to escape a challenging situation, or to express "just how bad" things are for them. Whatever the underlying source, self-harm behaviors can be symptomatic of treatable conflicts and problems such a depression, misinformation, hampered mastery and autonomy, or social or financial concerns.

Cellular, Molecular, Physiological, and Behavioral Aspects of Spinal Cord Injury. https://doi.org/10.1016/B978-0-12-822427-4.00042-3

A category of patients theoretically mislabeled as suicidal can be non-adherent patients. World Health Organization defines adherence as "the extent to which a person's behavior—taking medication, following a diet, and/or executing lifestyle changes corresponds with agreed recommendations from a health care provider" (World Health Organization, 2003). Medications, rehabilitation therapies, and self-care behaviors will not work if patients do not follow prescribed plans. In addition to clinicians' frustrations when patients act directly against their best interest, persistent self-harm behaviors pose ethical and practical challenges for clinicians because not intervening would be violating our duties to avoid or mitigate harm when possible (Torke & Sachs, 2008).

When chronic or severe enough, the fears of clinicians and loved ones are realistic: a patient's behaviors can produce serious self-harm or even death. Bostwick and Cohen (2009) catalogued two accounts that can help distinguish true suicide from other forms of self-harm by exploring the presence of (1) a death wish or intent to die, and, (2) complicity or collaboration with clinicians and/or family members. Particularly applicable to medical settings, these two criteria help disentangle authentic suicide from non-adherence, physician-assisted suicide, and palliative/hospice care (Bostwick, 2015). A true suicide has both (1) an intent to die, and, (2) is not collaborative with clinicians or loved ones. Many self-harm behaviors observed in medical settings, such as non-adherence, are not directed at death, and clinicians and loved ones are not complicit with patient's poor choices. Other "self-harm" behaviors such as declining life-sustaining interventions may be motivated toward death yet do not have the secrecy and exclusion of clinicians as in suicide.

Chapter clarifications

This chapter speaks to clinical experiences about a selection of self-harm behaviors observed in SCI populations. Building on the work of Macleod (Macleod, 1988), behaviors are conceptualized as a sign of core conflicts signifying clinical needs that SCI clinicians can detect and with which they can empathize, and consequently treat. As such, self-harm behaviors can be symptomatic of treatable circumstances such as problems with adapting to a disability, depression, existential drives, medical mistrust, or authentic patient preferences. The goal is to expand a clinician's understanding and repertoire of responses when patients with SCI make choices that may result in self-harm, including suicidal behaviors.

The term "self-harm" is used broadly, with an assumed range of severity and types of behavior, and without suggestion of causation nor attention to idiosyncratic situations or individual attributes. Individuals with cognitive problems, delirium, or psychopathologies may require different approaches. There is no one-size-fits-all clinical response, and numerous factors influence a patient's self-care decisions (e.g., medical status, state of well-being, time since injury, pain, coping abilities, financial security, social support) that are too vast to consider here. In addition, suggested responses for each self-harm behavior are not exhaustive and will overlap (e.g., strength-focused, patient-centered reactions apply to all). Lastly, the ideas are offered with the utmost respect and acknowledgment that most people adapt well to SCI, without psychopathology, and with amazing stability over time (Pollard & Kennedy, 2007). Nevertheless, adopting "different" ways to conceptualize self-harm behaviors observed in SCI clinics can enhance appreciation and stimulate an array of approaches to hopefully halt further serious or devasting harm.

Regarding language in this chapter, the term "adherence" is preferred over "compliance" because adherence retains focus on the patient as an active collaborator rather than "obeying" the clinician (Merbitz, 2016). The term "adapting" is preferred over "adjustment" based on the literature from people with disabilities (Olkin, 1993).

Self-harm behaviors as presenting symptoms

Mark Twain said, "Actions speak louder than words." Self-harm *behavior* is a multi-dimensional phenomenon symptomatic of countless contributors**.** Five select examples underlying self-harm behaviors to enhance understanding and inform clinician responses are described: 1. Problems related to adapting to disability; 2. Major depression; 3. An existential wish to not live; 4. Medical mistrust; and, 5. A conscientious lifestyle choice. General information from the literature relating each issue to SCI will be presented along with various core tensions, behavioral signs, and ideas for clinician responses. Comments applying and contrasting Bostwick's (2015) criteria for true suicide (intention to die and caregiver corroboration) versus other self-harm behaviors are incorporated. Table 1 summarizes the five self-harm behaviors, possible etiologies, and clinical responses.

Adapting to disability

Numerous factors can disturb adaptation to SCI that emanate from self-harm behaviors. Frequently cited obstacles to adaption are premorbid mental health problems, and substance abuse (Craig et al., 2017; Kolakowsky-Hayner et al.,

TABLE 1 Self-harm Behaviors: Underlying causes and conflicts, presenting symptoms and interventions.

Possible etiology	Core conflicts/tensions	Behaviors	Clinician responses
Adapting to disability	Loss of autonomy and individuation; external locus of control; limited coping resources for the demands	Anger, indifference, non-adherence, or inconsistent compliance	Promote mastery of new and existing life-valued activities; bolster coping skills; instruct how to direct one's care; supportive therapy; peer support; meaning-making
Depression	Feelings of loss; Feeling hopeless; Inappropriate guilt; Suicidal ideation	Agitation; negative withdrawal; "giving up"; suicidal talk	Anti-depressants; evidence-based psychotherapies; supportive therapy; process grief; increase or expand life valued activities; practice gratitude; identify future goals of value
Existential/ palliative or hospice	Informed choice for personal quality of life; preference of quality over quantity of life; self-determination; Skewed perception of living with disability	Decline rehabilitation services; decline medical interventions; act personally resolved with their decision; appear righteous	Confirm informed consent; comprehensively address physical, emotional, and social needs; consult ethics committees; family meetings; peer support; therapeutic trial period
Medical mistrust	Feel compelled to be guarded/overly cautious; defensive; fear someone will harm or impede their autonomy	Act in anger; withdrawal; dismiss recommendations; negative expectations; miss appointments; question motives	Validate mistrust; validate prior experiences; appreciate cultural factors in context; educate with facts; offer options; bolster therapeutic alliance
Patient preferences	Not wanting to change; Angry with the interference of SCI on quality of life; Latent fears or misperceived expectations about living with SCI	Same pre-injury behavior; non-standard or inconsistent healthcare adherence; resign themselves to a victim/sick role.	Evaluate capacity; continue to offer interventions while respecting autonomous choices; persist with healthy recommendations and excellent care; peer support if they agree; collaborative care plans; accentuate values for life and living

Examples of core tensions, behavioral signs, and ideas for clinician responses.

2002; Martz et al., 2005). Poor self-care happens when SCI challenges the availability of coping resources for people with prior mental health issues. Excessive stress impacts mental health symptoms, in general, and especially for those predisposed (Russell, Turner, & Joiner, 2009).

Substance use is repeatedly associated with SCI. It has been reported that at the time of acquiring their SCI, 31%–50% of individuals were abusing alcohol, 16%–33% were using illegal drugs, and 26% were using a combination of each (Tétrault & Courtois, 2014). A considerable number of people with SCI continue to use alcohol or drugs after SCI (Kolakowsky-Hayner et al., 2002), placing themselves at risk for secondary problems with physical and mental health, managing pain, and social and other life challenges (Skidmore & Budd, 2016). Cumulatively, untreated mental health and substance abuse issues complicate self-management, and mental and physical health consequences can be severe if mismanaged (Furlanetto & Stefanello, 2011; Kishi et al., 2001). Also impacting adaptation to SCI are reduced social participation and autonomy, fatigue, loss of employment, secondary infections, pain (Craig et al., 2017; Martz et al., 2005) self-efficacy, and social support (Bhattarai, Jin, Smedema, Cadel, & Baniya, 2021; Kishi et al., 2001; Russell et al., 2009).

Underlying poor adaptation to SCI can be conflicts with loss of autonomy and individuation leaving some feeling a "helpless dependence." Patients may withdraw, acting in anger or indifference. Nonadherence behaviors give people an element of control and autonomy over their situations (MacLeod, 1998). Self-harm behaviors stemming from problems with adapting to SCI may be a form of suicide if the intention is to "give up" on living while not being forthcoming with clinicians and loved ones about their intention (e.g., could constitute a passive form of suicide).

Treatments to facilitate adaptation to SCI include promoting a sense of mastery by encouraging personal responsibility, cultivating self-efficacy (Bhattarai et al., 2021), and collaboration with planning and making decisions for the future

(Russell et al., 2009). Specifically, individuals with SCI desire more focus on well-being interventions, financial and other social worries, assistance with bowel and bladder concerns, increased physical activity, occupation guidance, and peer and family support (Simpson, Villeneuve, & Clifton, 2020). Attending to these while validating the scope and intensity of the challenges, and teaching how acceptance of disability changes over time, can proffer empathy and hope (Craig et al., 2017; Kripke, 2017; Ubel, Loewenstein, Schwarz, & Smith, 2005).

Depression

Underlying depression can manifest a range of behaviors for people with SCI. Pollard and Kennedy's (2007) 10-year longitudinal study determined about 30% of people with SCI are depressed after SCI, and these rates of depression are consistent over time in this population (Craig et al., 2017). Coping at 12-weeks post-injury was most predictive of lasting depression, indicating a need for early detection and intervention (Pollard & Kennedy, 2007).

Depression has been associated with self-harm behaviors ranging from poor self-care to severe self-neglect, and suicidal ideation to suicidal behaviors (Bostwick, 2015; Kishi et al., 2001). A history of depression increases the risk of depression after SCI. People with depression exhibit pervasively low mood and energy, disturbed sleep and appetite, suicidal ideation, and expressed negativism, all of which consume personal resources. Caring for oneself with SCI requires a certain amount of energy and diligence. Even minor inattention can worsen situations. For example, ignoring pressure relief or improper cushion inflation for 1 day can result in pressure ulcers affecting mobility, impacting participation [that can have further ramifications] and future ulcers (Sprigle, McNair, & Sonenblum, 2020). In general, prolonged inattention to self-care contributes to feelings of hopelessness. Self-harm behaviors driven by clinical depression demands immediate attention and comprehensive assessment to rule out suicidal ideation, intention, and plans. Unfortunately, an expectation of depression following SCI may delay appropriate diagnosis and needed treatment (Craig et al., 2017).

Accurate depression diagnosis and treatment can be critical (Kishi et al., 2001; Lewis, Anderson, & Feuchtinger, 2014). Fortunately, combined anti-depressant and psychotherapy interventions frequently resolve depression and the patient resumes more healthful behaviors (Kishi et al., 2001). See the chapter on Depression in this book for a comprehensive review of depression and SCI.

Existential (palliative/hospice)

Individuals with an existential self-harm/neglect are less common (Macleod, 1988). Self-harm behaviors with an underlying existential element may encompass requests like ventilation removal, or voluntary cessation of eating and drinking. These individuals express a forthright desire for death despite the absence of clinical depression. If their situation were different, these individuals would not be contemplating life-ending activities. Applying Bostwick and Cohen's (2009) criteria, this is not suicide. These patient's meaning to hasten death is based on intense circumstances and correlated life values. Unlike the devastation following a death by suicide, the patient's survivors usually proactively collaborate with these thoughts and accept the arrangement. These decisions carry ethical and moral conflicts. A thorough assessment is warranted before deciding to assist or oppose death-hastening behaviors. Notably, existential choices are not "passive suicide" but a non-punitive selection of autonomy (Macleod, 1988) for how they want to live their lives, and perhaps die.

Ethically and legally, choices to decline treatment or stop an existing treatment are permissible if the person has decision-making capacity demonstrating an appreciation, understanding, and rational reasoning of the risks and benefits of their choices, even if it causes harm, or result in death (Beauchamp & Childress, 2009).

Motivations to medically hasten death are often when the patient wants to exercise self-determination and elect death over a life that they perceive as more burdens and less quality than they want to experience. Supporters are usually proponents of physician-assisted suicide and "rational suicide." Commonly, like depression, these plans are often transient and ameliorate over time and many people ultimately elect to live (Kishi et al., 2001; Pollard & Kennedy, 2007).

Suggested treatments for these patients involve addressing physical needs (e.g., pain control), maximizing social and clinical support, and discussing the impact of decisions with loved ones. Consult hospital ethics committees and conduct team-family meetings for thoroughness. Repeat offers of recommended care with non-judgmental acceptance of their choice (i.e., giving the patient the right to say "no" may sway them to say "yes"). Encourage a trial period of living with disability and educate that disability is not a disease (Kripke, 2017), and describe the occurrence of the "Disability Paradox"—i.e., most people with SCI experience a good quality of life; until they were disabled, they too believed it impossible (Ubel et al., 2005).

Medical mistrust

Patient trust is central to therapeutic relationships and treatment adherence to materialize best outcomes (Suchman & Matthews, 1988); behaviors in response to medical mistrust can spawn unintended self-harm. Previous medical mistakes or bad experiences may have disenfranchised the patient for years before SCI. Now with SCI, medical needs are inescapable, and there are no options but reliance on medical experts and dependence upon others for assistance. This may be especially applicable for patients in marginalized populations or certain cultural groups (Gonzalez et al., 2018). Disbelieving their SCI and prognosis (Craig et al., 2017), reading misinformation on the internet, and clinician attitudes (VanPuymbrouck, Friedman, & Feldner, 2020) also can generate mistrust, affect the therapeutic relationship, and influence clinical decision-making (Baron & Berinsky, 2019; Suchman & Matthews, 1988). Self-harm behaviors emitted from medical mistrust are not suicidal because the person prefers to live, but they are guarded and reluctant to fully trust medical recommendations. To them, they are not the ones precipitating the self-harm.

In any group, prior unpleasant encounters or medical mistakes may make one delay care or affect medical decision making and selecting care (Eipper-Mains, Kao, Gitlin, & Peteet, 2019). Medical distrust is a protective defense with pathways to mend (Baron & Berinsky, 2019).

If medical mistrust is suspected, validate the apprehensions and attempt to understand the patient's decision-making process in the context of the specific medical need. Maximize control whenever possible while furthering patient understanding and appreciation of medical facts. Explain medical details about interaction effects with concerning behaviors. Practice shared-decision making and offer all alternative solutions, even if a compromise is less than ideal to both parties (Suchman & Matthews, 1988).

Patient preferences

Some behavioral choices can deviate far from medical recommendations and have the potential to cause serious self-harm. Some patients choose to mix alcohol with certain medications or refuse a procedure or treatment that would help them, for example. Patient-centered care is grounded on a balance of deep respect for the uniqueness of the person and empirically scientific generalizations, balanced in the context of that person and that situation (Epstein & Street, 2011). Ethically and legally, patients with decision-making capacity have the right to accept or refuse offered treatment interventions, including in circumstances in which the decision to forgo treatment may be dangerous or even result in death (Beauchamp & Childress, 2009). Decisions to decline care are supported ethically under the strongly held principle of patient autonomy. Patients have the right to make unhealthy choices.

However, honoring patient preferences occurs at the same time clinicians honor the integrity of their profession. Patients do not always know what is best, and our duty is to offer specialized services along with benefits and risks for choosing or declining. For example, a drug may be what a patient wants but not what they need. We welcome their participation but can only offer treatments fitting within professional standards of care, which they can decline or accept. The goal is a partnership, solidarity, and collaboration with both parties having autonomous roles.

Electing harmful behaviors over healthier options may not have suicidal intentions, but rather reflect an unwillingness to change a pre-injury lifestyle. For them, quality of life has personal benefits (pleasures congruent with lifelong values) that outweigh prospects for consequential self-harm. For example, a young man who designed his life as a professional gambler traveling across the country becomes paraplegic. Doctors warn against this lifestyle due to a host of pre-existing problems combined with SCI. The man continues life-valued activities despite risks and the likelihood of additive harm. This can be distinguished from suicide because he has no intention to die, and he likely shares his preferences with clinicians and loved ones.

Clinical responses to scenarios of behaviors precipitated by patient preferences are shared with approaches when existential motivations underly self-harm (e.g., confirm decision-making capacity; respect autonomy; persist with healthy recommendations) along with peer support and concentration on the hierarchy of the person's values to aid in decision-making.

Suicide behaviors and SCI

While the majority adapt well, individuals with SCI are at increased risk for suicide when compared with the general population. Suicide is the 7th leading cause of death in traumatic SCI, befalling 4%–11% of people with SCI (Kennedy & Garmon-Jones, 2017). Prominently, 91% of suicides happen within the first 10 years after injury then recedes the years following (Savic et al., 2018). The risk for suicide is more pronounced when SCI was caused by a suicide attempt

(Kennedy & Garmon-Jones, 2017) and when there were prior attempts (Furlanetto & Stefanello, 2011). The means of committing suicide depends upon accessibility and the person's physical abilities. For example, firearms are rather accessible in the US and used more frequently than in Europe, where drug poisoning/overdose (Savic et al., 2018) was a common method for suicide for people with SCI. Associations of the level of injury and suicide are too mixed to be conclusive (Kennedy & Garmon-Jones, 2017).

Risk mitigation

Warning signs for suicide

Consider as suicidal all self-harm behaviors that (a) have an intention for dying, and (b) are not corroborative with caregivers/clinicians (Bostwick, 2015). Since secretive in nature, we must look for other signs of suicidal self-harm. Changes in behavior, thoughts, or emotions can be warning signs. Look for medication non-adherence, increased substance use, disengagement from social contacts, increased verbal or physical aggression, mood swings, and preparatory behaviors (e.g., selling belongings, researching ways to die by suicide, purchasing firearms, hoarding pills). The types of thoughts and the way the person experiences thoughts can also be warning signs. For example, concerning thoughts include passive suicidal thoughts about preferring to be dead, desiring peace or a sense of control, experiencing many thoughts rapidly, feeling overwhelmed, or of their "mind going blank." Emotional changes to watch for include shame, hopelessness, guilt, anger, sadness, anxiety, irritability. See Table 2.

What to assess

Psychological, social, and medical risk factors should be assessed along with protective factors (see Fig. 1). Psychological risk factors include current suicidal ideation, prior suicide attempts, mood or substance abuse disorders, personality disorders, hopelessness, and prior psychiatric hospitalization (Fuller-Thomson, Tulipano, & Song, 2012; Kennedy & Garmon-Jones,

TABLE 2 Suicidal self-harm behaviors: underlying causes and conflicts, presenting symptoms and interventions.

Possible etiology	Core conflict	Behaviors	Interventions
SCI is perceived as a fate worse than death; Financial anxieties; Residential options	Existential conflict of life not being worth living; perceived burdensomeness; catastrophizing pain experience; desiring peace or sense of control; shame; hopelessness; guilt; anger; sadness; anxiety; financial and social concerns	Changes in behavior—disengagement from others, extreme irritability, or aggression; Hoarding guns or medications; selling or giving away belongings; mood swings; increased substance use; researching ways to die; suicidal ideation, statements, or attempt	Mental health evaluation or hospitalization; treat any mental health conditions; Safety planning; reduce all lethal means—lock or give away firearms; restrict medication access; rally support system; all other self-harm interventions can apply; focus on reasons for living

Examples of core tensions, behavioral signs, and ideas for clinician responses.

FIG. 1 Risk and protective factors for suicide. As protective factors increase, risk factors decrease. As Protective Factors increase, Risk Factors decrease.

2017). Social risk factors include stressful life events (e.g., loss of a relationship; illness of self or family member), financial problems, legal problems, lack of social support). A new diagnosis of a major illness is a suicide risk factor, along with chronic pain, worsening medical illness, or functional limitation.

Assessment of biopsychosocial risk factors for suicide is beneficial for risk mitigation. For example, attention to intrapsychic factors such as mental health symptomatology can reduce emotional distress while at the same time enhance a sense of connectedness with a helping professional, building a channel for reaching out in times of crisis. Reflecting on core values advances relatedness to life- as opposed to death-orientation. Simple authentic interest in listening about someone's psychic pain can decrease the experience of loneliness and foster hope.

Social isolation

Social support is key to providing patients with SCI with appropriate emotional, educational, and instrumental (e.g., caregiver) resources to meet physical, functional, and emotional needs. One area often associated with elevated suicide risk is feeling like a burden (Joiner, 2005). Whether perceived burdensomeness reflects a primary intrapsychic struggle or an actual interpersonal conflict, demands exploration. Reconciling being dependent on others as a previously independent adult is fundamental to SCI adaptation, and its intensity and persistence vary among individuals based on many factors. The "usefulness" or "value" that someone places on themself, if unemployed, warrants consideration in the context of their culture. Research has increasingly demonstrated the association of work and psychosocial health in SCI (Goetz, Ottomanelli, Barnett, Sutton, & Njoh, 2018).

Reduced social isolation's protection for suicidal risks may be evidenced indirectly in other studies. For example, employment's negative association with suicide is perhaps because of the increased socialization while working. Studies that suggested tetraplegics have reduced risk of suicide is because their reliance on other people for activities of daily living requires much human interaction (Kennedy & Garmon-Jones, 2017).

Addressing environmental and social factors cannot be overlooked. There is great significance for emotional functioning and psychosocial adjustment associated with the stability, or lack thereof, of accessible housing and transportation, caregiver arrangements, and access to valued leisure and recreational activities.

Reduce access to lethal means

Conversations about and direct action regarding lethal means are vital. As stated, the most common methods of suicide are gunshots and drugs. Firearm access is an independent suicide risk factor independent of age, gender, and mental health diagnosis (Studdert et al., 2020). Importantly, any action that increases the time from suicidal ideation to availability of means reduces the risk for completion. Examples include storing firearms in a locked safe, separating ammunition and firearm, removing firing pins, and giving the firearm safe key to a trusted person. Reduce medication as a lethal choice by limiting supplies, using pill bubbles and less toxic medicines, or holding them safely. The main point is to add time for reconsideration of suicide, and hopefully focus on better solutions.

Applications to other areas of neuroscience

Patients with other neurological disorders share similar psychological responses, and risks for self-harm as people with SCI – pre-injury personality, chronic pain, level of independence, use of alcohol and other substances, cognitive appraisals, sleep quality, perceived social supports, social conditions, and financial considerations—are all pertinent both at the time of diagnosis and throughout their lives. All underlying symptoms and ideas to manage self-harm behaviors discussed for SCI apply to other neurological populations. Many physical, mental, and social stressors are similar and also contextual.

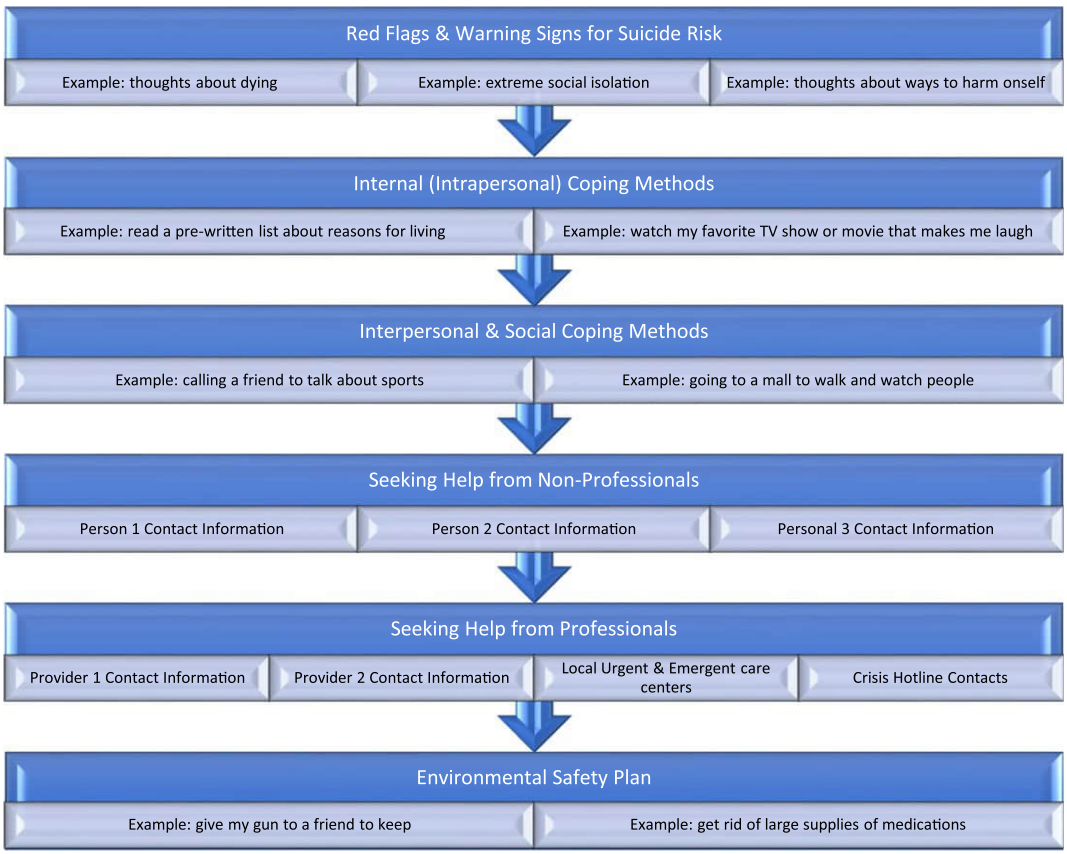
The initial months following a neurological diagnosis pose the highest risk for suicide (Kishi et al., 2001), particularly for patients with multiple hospitalizations (Roy-Byrne, 2020), unmarried (Russell et al., 2009), Caucasian, and younger age (Fuller-Thomson et al., 2012; Furlanetto & Stefanello, 2011). Roy-Byrne (2020) recently determined suicidal risks were largest for amyotrophic lateral sclerosis and Huntington disease followed by multiple sclerosis, head injury, epilepsy, and stroke. Common risk factors for suicidal ideation in neurological patients are hopelessness, depression, social isolation (Kishi et al., 2001; Lewis et al., 2014), and functional limitations (Fuller-Thomson et al., 2012). However, like SCI, over time most people with a new onset of a neurological disorder do adapt after a period of shock and suicide risks decrease (Kripke, 2017). Depression, if present, is considered the most important factor in preventing self-harm and suicidal ideation and behaviors (Kishi et al., 2001). It is important to not assume clinical depression is a normal reaction and that depression does not need to be assessed and addressed.

Three of four top correlates for suicidal ideation in medical patients are modifiable—anxiety, depression, and poor social support (Furlanetto & Stefanello, 2011). The fourth factor, prior suicide attempts, is unmodifiable but with further exploration with the patient, discussion can yield valuable information for a personalized approach. Concentrated treatments can perhaps halt further or future suicidal ideation.

Identifying depression is critical. As stated, depression is a known and treatable, risk factor for suicide for people with neurological problems. Kishi et al. (2001) found 25% of people with an acute medical illness with depression had suicidal ideation, of these 7.3% had suicidal plans. Depressed people perceive events more negatively, and thus may perceive their medical condition as a stressor beyond their capacity to manage (Furlanetto & Stefanello, 2011; Russell et al., 2009). Studies show treatment of depression ameliorates related suicidal ideation in medical populations (Kishi et al., 2001).

Suicide mitigation safety planning for all populations

When a patient is at risk for suicide or self-harm behaviors but is not considered a level of severity for involuntary hospitalization, a Safety Plan can be lifesaving. Safety plans help people identify risks and help individuals develop personalized plans that describe warning signs, internal coping strategies, external factors to provide healthy distractions, people to contact (friends, family, professionals), and ways to make the environment safe. See Fig. 2 for content inclusion and examples.



Safety Plan content includes: Warning signs for suicide risk, plus ways to mitigate risk by making a plan highlighting Internal Coping Methods, Social Coping Methods, Self-help Seeking from non-professionals and professionals, and keeping the environment safe.

FIG. 2 Suicide mitigation strategies.

Conclusion

Suicide is "transdiagnostic"—suicidal ideation and behaviors cross medical, mental, and behavioral health diagnoses and 54% of suicides were not associated with mental health conditions. Rather, contributors were relationship issues, substance use, health, and financial problems (Stone et al., 2018), not depression (Kishi et al., 2001). This suggests that suicide prevention strategies do not limit assessment to individuals with known mental health diagnoses. It has been documented that suicidal patients in medical settings have different profiles from suicidal patients in psychiatric hospitals (Furlanetto & Stefanello, 2011; Russell et al., 2009).

Behaviors can be informative and add precision in our care. Identifying sources motivating self-harm behaviors can promote a more compassionate understanding of a patient's core tensions and problems and generate interventions relevant to each situation. A key element is a therapeutic relationship. Empathic validation and genuine shared-decision making often dissipate distress and increases openness toward healthier behaviors. Self-harm behaviors fitting under the rubric of classic suicide are behaviors with a goal of death and are not corroborative with caregivers/loved ones (Bostwick, 2015). Self-harm and suicide are often extreme acts to get relief. Multiple biological, psychological, and social factors affect one's response to serious neurological disorders (Martz et al., 2005), and this chapter was directed to increase understanding about some reasons some people may indulge in the gamut of self-harm behaviors. Rather than ask why the suicide or self-harm, ask, what are the struggles or challenges driving it?

Mini-dictionary of terms

Adherence: "the extent to which a person's behavior—taking medication, following a diet, and/or executing lifestyle changes corresponds with agreed recommendations from a health care provider" (World Health Organization).
Beneficence: the state of producing or doing good; state of being beneficent.
Patient-centered care: the patient's specific health needs and their desired outcomes are the mainspring for health care decisions and assessment. Patient preferences are respected but within an acceptable scope of the clinician's practice, balanced in the context of that person and that situation.
Self-harm: any type of self-injurious behavior along a continuum of severity ranging from medical non-adherence to passive or active suicide.
Suicidal ideation: thoughts about or considering suicide.
Suicide: the act of taking one's life.

Key facts of self-harm

- It is a myth that asking someone about suicide makes things worse; discussing suicide is the most helpful way to get the person's help.
- There are often no notes before a suicide attempt.
- Clinicians must be aware of bias in assessing self-harm in people with spinal cord injury because either under-or over-estimating risk can harm the therapeutic relationship (Budd, Haque, & Stein, 2020).
- CDC and Joint Commission (2019) recommend universal suicide risk screening for all patients in medical settings, across the lifespan and regardless of the time since disability.
- All patients who screen positive should have a safety plan, resources (National Suicide Lifeline, 1–800-273-TALK (8255), and Crisis Text Line, Text HOME to 741–741), and means restriction education.
- Focusing on reasons for living is a strength-based approach to facilitate motivation toward healthful behaviors.
- ASQ toolkit www.nimh.gov/asq includes scripts, flyers, and resources in several languages for youth and adults in three settings: Emergency Department; Inpatient Medical/Surgical Unit; Outpatient Primary Care/Specialty Clinics.

Summary points

- Human behaviors may be symptomatic of an underlying treatable problem.
- Self-harm phenomena in SCI medical settings can take a variety of forms.
- Identification and addressing underlying problems can ameliorate self-harm behaviors.
- People with SCI experience a significantly higher quality of life than clinicians expect, which can affect the options presented and decision-making.
- A person can be suicidal without a diagnosed mental health condition.

- A new diagnosis of a major illness is a suicide risk factor, along with chronic pain, worsening medical illness, or functional limitation.
- Good therapeutic relationships yield the best outcomes.
- Self-harm behaviors that *are* suicidal have (a) an intent to die and (b) no complicity or corroboration with caregivers.
- Depression and social circumstances are key risk factors for suicide in neurological populations.
- People who survive a suicide attempt are more likely to do it again, more if their neurological injury was caused by a suicide attempt.

References

Baron, R. J., & Berinsky, A. J. (2019). Mistrust in science—A threat to the patient–physician relationship. *The New England Journal of Medicine*, *381*(2), 182–185. https://doi.org/10.1056/NEJMms1813043.

Beauchamp, T. L., & Childress, J. F. (2009). *Principles of biomedical ethics*. New York: Oxford University Press.

Bhattarai, M., Jin, Y., Smedema, S. M., Cadel, K. R., & Baniya, M. (2021). The relationships among self-efficacy, social support, resilience, and subjective well-being in persons with spinal cord injuries. *Journal of Advanced Nursing*, *77*(1), 221–230. https://doi.org/10.1111/jan.14573.

Bostwick, J. M. (2015). When suicide is not suicide: Self-induced morbidity and mortality in the general hospital. *Rambam Maimonides Medical Journal*, *6*(2), 1–6. https://doi.org/10.5041/RMMJ.10197.

Bostwick, J. M., & Cohen, L. M. (2009). Differentiating suicide from life-ending acts and end-of-life decisions: A model based on chronic kidney disease and dialysis. *Psychosomatics*, *50*(1), 1–7.

Budd, M. A., Haque, O. S., & Stein, M. A. (2020). Biases in the evaluation of self-harm in patients with disability due to spinal cord injury. *Spinal Cord Series And Cases*, *6*(1), 43. https://doi.org/10.1038/s41394-020-0293-6.

Craig, A., Tran, Y., & Middleton, J. (2017). Theory of adjustment following severe neurological injury: Evidence supporting the spinal cord injury adjustment model. In A. Costa, & E. Villalba (Eds.), *Horizons in neuroscience research* (pp. 117–139). Nova Science Publishers.

Eipper-Mains, J. E., Kao, L. E., Gitlin, D. F., & Peteet, J. R. (2019). Life-threatening mistrust: Assessing and enhancing capacity to trust. *Psychosomatics*, *60*(6), 606–611. https://doi.org/10.1016/j.psym.2019.02.001.

Epstein, R. M. M. D., & Street, R. L. P. (2011). The values and value of patient-centered care. *Annals of Family Medicine*, *9*(2), 100–103. https://doi.org/10.1370/afm.1239.

Fuller-Thomson, E., Tulipano, M. J., & Song, M. (2012). The association between depression, suicidal ideation, and stroke in a population-based sample. *International Journal of Stroke*, *7*(3), 188–194. https://doi.org/10.1111/j.1747-4949.2011.00702.x.

Furlanetto, L., & Stefanello, B. (2011). Suicidal ideation in medical inpatients: Psychosocial and clinical correlates. *General Hospital Psychiatry*, *33*(6), 572–578. https://doi.org/10.1016/j.genhosppsych.2011.08.002.

Goetz, L. L., Ottomanelli, L., Barnett, S. D., Sutton, B., & Njoh, E. (2018). Relationship between comorbidities and employment among veterans with spinal cord injury. *Topics in Spinal Cord Injury Rehabilitation*, *24*(1), 44–53. https://doi.org/10.1310/sci16-00047.

Gonzalez, C. M., Deno, M. L., Kintzer, E., Marantz, P. R., Lypson, M. L., & McKee, M. D. (2018). Patient perspectives on racial and ethnic implicit bias in clinical encounters: Implications for curriculum development. *Patient Education and Counseling*, *101*(9), 1669–1675. https://doi.org/10.1016/j.pec.2018.05.016.

Joiner, T. (2005). *Why people die by suicide*. Harvard University Press.

Kennedy, P., & Garmon-Jones, L. (2017). Self-harm and suicide before and after spinal cord injury: A systematic review. *Spinal Cord*, *55*(1), 2–7. https://doi.org/10.1038/sc.2016.135.

Kishi, Y., Robinson, R. G., & Kosier, J. T. (2001). Suicidal ideation among patients with acute life-threatenng physical illness: Patients with stroke, traumatic brain injury, myocardial infarction, and spinal cord injury. *Psychosomatics*, *42*(5), 382–390. https://doi.org/10.1176/appi.psy.42.5.382.

Kolakowsky-Hayner, S. A., Iii, E. V. G., Kreutzer, J. S., Marwitz, J. H., Meade, M. A., & Cifu, D. X. (2002). Post-injury substance abuse among persons with brain injury and persons with spinal cord injury. *Brain Injury*, *16*(7), 583–592. https://doi.org/10.1080/02699050110119475.

Kripke, C. (2017). Patients with disabilities: Avoiding unconscious bias when discussing goals of care. *American Family Physician*, *96*(3), 192–195. https://www.aafp.org/afp/2017/0801/p192.html.

Lewis, D. S., Anderson, K. H., & Feuchtinger, J. (2014). Suicide prevention in neurology patients: Evidence to guide practice. *The Journal of Neuroscience Nursing*, *46*(4), 241–248. https://doi.org/10.1097/JNN.0000000000000062.

Macleod, A. D. (1988). Self-neglect of spinal injured patients. *Spinal Cord*, *26*(5), 340–349. https://doi.org/10.1038/sc.1988.48.

Martz, E., Livneh, H., Priebe, M., Wuermser, L. A., & Ottomanelli, L. (2005). Predictors of psychosocial adaptation among people with spinal cord injury or disorder. *Archives of Physical Medicine and Rehabilitation*, *86*(6), 1182–1192. https://doi.org/10.1016/j.apmr.2004.11.036.

Merbitz, N. (2016). Treatment adherence. In M. A. Budd, S. Hough, S. T. Wegener, & W. Stiers (Eds.), *Practical psychology in medical rehabilitation* Springer. https://doi.org/10.1007/978-3-319-34034-0_28.

Olkin, R. (1993). Crips, gimps and epileptics explain it all to you. *Readings*, *8*, 13–17.

Pollard, C., & Kennedy, P. (2007). A longitudinal analysis of emotional impact, coping strategies and post-traumatic psychological growth following spinal cord injury: A 10-year review. *British Journal of Health Psychology*, *12*(3), 347–362. https://doi.org/10.1348/135910707X197046.

Roy-Byrne, P. (2020). Heightened risks for suicide in patients with neurological disorders. *NEJM Journal Watch. Psychiatry*. https://www.jwatch.org/na50835/2020/02/12/heightened-risks-suicide-patients-with-neurological.

Russell, D., Turner, R. J., & Joiner, T. E. (2009). Physical disability and suicidal ideation: A community-based study of risk/protective factors for suicidal thoughts. *Suicide & Life-Threatening Behavior*, *39*(4), 440–451. https://doi.org/10.1521/suli.2009.39.4.440.

Savic, G., DeVivo, M. J., Frankel, H. L., Jamous, M. A., Soni, B. M., & Charlifue, S. (2018). Suicide and traumatic spinal cord injury-a cohort study. *Spinal Cord*, *56*(1), 2–6. https://doi.org/10.1038/sc.2017.98.

Simpson, B., Villeneuve, M., & Clifton, S. (2020). The experience and perspective of people with spinal cord injury about well-being interventions: A systematic review of qualitative studies. *Disability and Rehabilitation*, 1–15. https://doi.org/10.1080/09638288.2020.1864668. Advance online publication.

Skidmore, W. C., & Budd, M. A. (2016). Alcohol and substance use disorders in medical rehabilitation. In M. A. Budd, S. Hough, S. T. Wegener, & W. Stiers (Eds.), *Practical psychology in medical rehabilitation* Springer. https://doi.org/10.1007/978-3-319-34034-0_28.

Sprigle, S., McNair, D., & Sonenblum, S. (2020). Pressure ulcer risk factors in persons with mobility-related disabilities. *Advances in Skin & Wound Care*, *33*(3), 146–154. https://doi.org/10.1097/01.ASW.0000653152.36482.7d.

Stone, D. M., Simon, T. R., Fowler, K. A., Kegler, S. R., Yuan, K., Holland, K. M., et al. (2018). Vital signs: Trends in state suicide rates—United States, 1999-2016 and circumstances contributing to suicide—27 states, 2015. *MMWR. Morbidity and Mortality Weekly Report*, *67*(22), 617–624. https://doi.org/10.15585/mmwr.mm6722a1.

Studdert, D. M., Zhang, Y., Swanson, S. A., Prince, L., Rodden, J. A., Holsinger, E. E., et al. (2020). Handgun ownership and suicide in California. *New England Journal of Medicine*, *382*(23), 2220–2229. https://doi.org/10.1056/NEJMsa1916744.

Suchman, A. L., & Matthews, D. A. (1988). What makes the patient-doctor relationship therapeutic? Exploring the connexional dimension of medical care. *Annals of Internal Medicine*, *108*(1), 125–130. https://doi.org/10.7326/0003-4819-108-1-125.

Tétrault, M., & Courtois, F. (2014). Use of psychoactive substances in persons with spinal cord injury: A literature review. *Annals of Physical and Rehabilitation Medicine*, *57*(9), 684–695. https://doi.org/10.1016/j.rehab.2014.10.002.

The Joint Commission. (2019). *National Patient Safety Goals (Report No. 15.01.01)*. https://www.jointcommission.org/resources/patient-safety-topics/suicide-prevention/.

Torke, A. M., & Sachs, G. A. (2008). Self-neglect and resistance to intervention: Ethical challenges for clinicians. *Journal of General Internal Medicine*, *23*(11), 1926–1927. https://doi.org/10.1007/s11606-008-0807-6.

Ubel, P. A., Loewenstein, G., Schwarz, N., & Smith, D. (2005). Misimagining the unimaginable: The disability paradox and health care decision making. *Health Psychology*, *24*(4S), S57–S62. https://doi.org/10.1037/0278-6133.24.4.S57.

VanPuymbrouck, L., Friedman, C., & Feldner, H. (2020). Explicit and implicit disability attitudes of healthcare providers. *Rehabilitation Psychology*, *65*(2), 101–112. https://doi.org/10.1037/rep0000317.

World Health Organization. (2003). *Adherence to long-term therapies: Evidence for action*. World Health Organization. https://www.who.int/chp/knowledge/publications/adherence_report/en/.

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Index

Note: Page numbers followed by *f* indicate figures and *t* indicate tables.

B

C

D

E

F

G

H

I

K

L

M

Q

R

S

T

U

V

W

X

Y

Z

CELLULAR, MOLECULAR, PHYSIOLOGICAL, AND BEHAVIORAL ASPECTS OF SPINAL CORD INJURY

THE NEUROSCIENCE OF SPINAL CORD INJURY

EDITED BY
RAJKUMAR RAJENDRAM, VICTOR R. PREEDY, AND COLIN R. MARTIN

Spinal injury affects about 10 million people annually worldwide, impacting on the family unit and causing lifelong disabilities, with varied symptoms including paresthesia, spasticity, loss of motor control, and often severe pain. ***Cellular, Molecular, Physiological, and Behavioral Aspects of Spinal Cord Injury*** will enhance readers' understanding of the biological and psychological effects of spinal cord injury. Featuring chapters on gene expression, metabolic effects, and behavior, this volume discusses in detail the impact of spinal cord injury to better understand the underlying pathways and processes. The book has applicability for neuroscientists, neurologists, clinicians, and anyone working to better understand these injuries.

Key Features:

- Summarizes the neuroscience of spinal cord injury, including cellular and molecular biology
- Contains chapter key facts, dictionary, and summary points to aid understanding
- Features chapters on signaling and hormonal events
- Includes plasticity and gene expression
- Examines health and stress behaviors after spinal cord injury

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TITLE ISBN
ISBN 978-0-12-822427-4
9 780128 224274

SET ISBN
ISBN 978-0-323-99198-8
9 780323 991988