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TOPIC HIGHLIGHT

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Chronic complications of spinal cord injury

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Abstract

Spinal cord injury (SCI) is a serious medical condition that causes functional, psychological and socioeconomic disorder. Therefore, patients with SCI experience significant impairments in various aspects of their life. The goals of rehabilitation and other treatment approaches in SCI are to improve functional level, decrease secondary morbidity and enhance health-related quality of life. Acute and long-term secondary medical complications are common in patients with SCI. However, chronic complications especially further negatively impact on patients' functional independence and quality of life. Therefore, prevention, early diagnosis and treatment of chronic secondary complications in patients with SCI is critical for limiting these complications, improving survival, community participation and health-related quality of life. The management of secondary chronic complications of SCI is also important for SCI specialists, families and caregivers as well as patients. In this paper, we review data about common secondary long-term complications after SCI, including respiratory complications, cardiovascular complications, urinary and bowel complications, spasticity, pain syndromes, pressure ulcers, osteoporosis and bone fractures. The purpose of this review is to provide an overview of risk factors, signs, symptoms, prevention and treatment approaches for secondary long-term complications in patients with SCI.

Key words: Spinal cord injury; Chronic complications; Management of complications; Long-term morbidity; Secondary morbidity of spinal cord injury

Core tip: Spinal cord injury (SCI) is a important clinical condition that can lead to lifelong disability. Additionally, the secondary complications following SCI, especially long-term complications, increase morbidity and decrease community participation and health-related quality of life. Improving functional level and quality of life are essential goals of rehabilitation in patients with SCI. Therefore, it is important to be aware of chronic complications of SCI and learn how to manage these complications for the recovery and rehabilitation process. The purpose of this review is to provide an overview of chronic complications of SCI.

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INTRODUCTION

Spinal cord injury (SCI) is a serious medical condition that causes functional, psychological and socioeconomic disorder[1]. Long-term, secondary medical complications are common and play an important role in the continuum of care for patients with SCI[2,3]. Complications are a frequent cause of morbidity and mortality and lead to increased rates of rehospitalization, loss of employability and decreased quality of life[3].

The purpose of this review is to provide an overview of chronic complications of SCI, whether due to trauma or different conditions.

RESPIRATORY COMPLICATIONS

Respiratory complications associated with SCI are the most important cause of morbidity and mortality in both acute and chronic stages[4,5]. The extent of respiratory complications depends on the level of SCI and the degree of motor impairment[4]. Linn and colleagues presented a large investigation assessing pulmonary function in 222 adult outpatients with chronic SCI. They reported that forced vital capacity and forced expired volume (FEV_1) were normal in patients with low-level paraplegia who had never smoked but they found that both decreased with rising SCI level more prominently in patients with tetraplegia[6].

Besides these essential determinants, the effect of duration of injury, smoking history, age and body mass index (BMI) on pulmonary function were also evaluated in various studies in patients with SCI[6,7]. For example, Stepp and colleagues reported that they found a significant decrease in all lung volumes with increasing BMI[7]. Similar results were reported for duration of injury[6,7].

As seen through the literature, SCI often leads to respiratory dysfunction[6,8-10], including insufficiency of respiratory muscles, reduction in vital capacity, ineffective cough, reduction in lung and chest wall compliance and excess oxygen cost of breathing[10]. Due to these problems, atelectasis, pneumonia and respiratory failure are the most common respiratory complications in patients with SCI[4,9].

Pleural effusion, pneumothorax and hemothorax are less common respiratory complications of SCI[9]. Additionally, it is reported that SCI patients have a high prevalence of sleep-related respiratory disorders, particularly obstructive sleep apnea syndrome, which can adversely affect quality of life and rehabilitation[4]. The number of studies of patients with SCI have shown that the syndrome occurs in 25%-45% of those with long-term follow-up[4,11,12].

Patients with cervical and high thoracic SCI are at higher risk for developing atelectasis and pneumonia due to paralysis of the respiratory muscles below the level of injury, resulting in a weak cough mechanism and difficulty mobilizing lung secretions[13].

Respiratory failure occurs most frequently in the acute period. Atelectasis and pneumonia are mainly seen in the acute stage of SCI but they also can appear as an important chronic respiratory problem in SCI. Chen *et al*[14] reported that individuals with complete tetraplegia are clearly at greatest risk for the development of atelectasis/pneumonia. McKinley *et al*[13] reported that the incidence of atelectasis and/or pneumonia at the first annual follow-up year was 3.5% and there was no significant decrease in follow-up years 2, 5, 10, 15 and 20. Pneumonia/atelectasis was also seen more frequently in persons older than 60 years of age in same model analysis study[3]. Pneumonia is also cited as the primary cause of death during chronic SCI[13,15,16].

In the literature, various recommendations were reported about the management of respiratory complications associated with SCI. They include positioning and postural changes, breathing techniques, spontaneous cough and cough assistance, suctioning, respiratory muscle training, ventilation techniques and education, vaccination agents for influenza and pneumococcal infections and pharmacological interventions. Furthermore, the modifiable risk factors (obesity, smoking, *etc*.) must be addressed, particularly in patients with tetraplegia and of older age[3,7,8,10].

CARDIOVASCULAR COMPLICATIONS

Individuals with SCI have a high risk of cardiovascular complications and their long-term effects such as thromboembolism and autonomic dysreflexia[17]. Common cardiovascular complications in the chronic stage of SCI are orthostatic hypotension (OH), autonomic dysreflexia, impaired cardiovascular reflexes, reduced transmission of cardiac pain, loss of reflex cardiac acceleration, cardiac atrophy with tetraplegia due to loss of left ventricular mass and pseudo-myocardial infarction[17-19].

Orthostatic hypotension

OH is usually seen in both acute and chronic stages following SCI[20,21]. It is defined as a decrease in systolic blood pressure of 20 mmHg or more, or a reduction in diastolic blood pressure of 10 mmHg or more, when the body position changes from supine to upright, regardless of whether symptoms occur[22].

Krassioukov *et al*[23] reported that the low level of efferent sympathetic nervous activity and the loss of reflex vasoconstriction after SCI are among the major causes of OH. OH is particularly common in cervical and high thoracic lesions[24-26]. It is also reported that the prevalence of orthostatic hypotension was 21% and cervical injuries had the highest prevalence in a large cohort study with incomplete SCI[27].

The symptoms associated with orthostatic hypotension include dizziness, light headedness, headache, pallor, yawning, sweating, muscle weakness, fatigue and occasionally syncope[23,28,29]. It is reported that management of OH includes application of pressure stockings and abdominal

binders, adequate hydration, gradual progressive daily head-up tilt and administration of pharmacological agents (salt tablets, midodrine, fludrocortisone, dihydroergotamine, ephedrine or L-DOPS)[23,29].

Autonomic dysreflexia

Autonomic dysreflexia (AD) is a well-known medical emergency. It generally occurs in patients with SCI at levels of T_6 and above[30]. AD is characteristic for the chronic stage but may appear any time after SCI[28]. It is reported that the life time frequency among patients with SCI is 19%-70%. It is more common in patients with cervical and complete lesions[17].

AD is caused by spinal reflex mechanisms initiated by a noxious stimulus entering the spinal cord below the level of injury. This afferent stimulus generates a sympathetic overactivity leading to vasoconstriction below the neurological lesion, along with involvement of splanchnic circulation that causes vasoconstriction and hypertension. The excessive parasympathetic activity (and lack of sympathetic tone) leads to vasodilation above the level of the lesion and is thought to be responsible for headache, flushing, sweating and nasal congestion. The reflex bradycardia is secondary to vagal stimulation[31,32].

Bladder distension is the most common triggering factor for AD. The distension can result from urinary retention or catheter blockage and accounts for up to 85% of cases[33]. The second most common triggering for AD is bowel distension due to fecal impaction. Other potential factors include hemorrhoids and anal fissures, gastrointestinal precipitants (appendicitis, cholecystitis, *etc*.), pressure ulcers, ingrown toenails, heterotopic ossification, fractures, menstruation, pregnancy or labor, deep vein thrombosis, pulmonary embolism and sexual activity. Medications, especially nasal decongestants and misoprostol, may also induce AD[31].

An important part of the succesful management of AD is prevention. It is reported that education of the patient, caregivers and family members regarding autonomic dysreflexia is vital to prevent AD and to recognize its occurrence without delay[34]. If AD occurs, the initial management involves non-pharmacological therapeutic interventions. These interventions include placing the patient in an upright position to take advantage of any orthostatic reduction in blood pressure. The next step must be to loosen tight clothing and/or constrictive devices. Blood pressure is controlled at least every 5 min until the patient is stable. It is also necessary to find and eliminate the triggering stimulus which in 85% of patients is related either to bladder distension or bowel impaction[30,35]. These steps will resolve the problem in most patients. It is reported that if non-pharmacological measures fail and arterial blood pressure is 150 mmHg or greater, pharmacological management should be initiated[35]. In general, the predominant medications are antihypertensive agents that have a rapid onset and short duration of action. Nifedipine and nitrates appear to be the most commonly used medications[31]. Additionally, various pharmacological agents (*e.g*., captopril, terazosin, prazosin, phenoxybenzamine, Prostaglandin E2 and Sildenafil) have been proposed for the management of AD episodes[30,35]. The management goals are normalization of the heart rate and blood pressure and clearing the symptoms of AD[19].

URINARY AND BOWEL COMPLICATIONS

One of the most important complications following SCI is the loss of genitourinary and gastrointestinal function[36].

Bladder dysfunction

As with other complications, urological dysfunctions after SCI also increase the risk of long-term complications and decrease psychological and social well-being of the patient[19]. SCI may lead to disturbances of the urinary system. It especially causes bladder dysfunction, often referred to as the neurogenic bladder.

Bladder function is mainly controlled by three areas of the central nervous system: the cerebral cortex, the pontine micturition center and the sacral micturition center[19]. Central lesions can interrupt the pontine and sacral micturition centers. Peripheral lesions also can affect the parasympathetic supply to the detrusor muscle or the sympathetic supply to the bladder neck as well as somatic innervation to the external urethral sphincter in SCI[36].

There are different types of clinical conditions in terms of detrusor and sphincter activity in neurogenic bladder in patients with SCI: (1) hypereflexia of detrusor and sphincter with involuntary contractions, sphincter dyssynergia, reflex incontinence and residual urine; (2) detrusor areflexia with sphincter areflexia. Patients experience stress incontinence and residual urine due to injury to sacral (S2-S4) anterior horn cells or their associated axons, which leads to impaired motor output to the bladder and decreased or absent detrusor contractility (flaccidity); (3) detrusor areflexia with sphincter hyperreflexia with overflow incontinence and urinary retention; and (4) detrusor hyperreflexia with sphincter areflexia with reflex incontinence[36].

It has been reported that the ultimate goals of bladder management after SCI are to preserve upper tract function with low intravesical pressure through adequate bladder drainage and to maintain urinary continence. In patients with SCI, it is generally agreed that urodynamic evaluation is essential to provide a precise diagnosis and treatment options for bladder dysfunction[37]. The urodynamic evaluation is also strongly recommended according to the Autonomic Standards Assessment Form[38]. Time-dependent changes are seen in the level of bladder dysfunction after SCI. Because of that, detailed therapy management should be individualized to the type of voiding dysfunction, level of injury, extent of disability and level of care available to the patient[37].

Treatment methods for neurogenic bladder can be categorized into two groups: therapy to facilitate bladder emptying and therapy to facilitate filling or storage of urine[39].

Weld and Dmochowski reported clean intermittent

catheterization (CIC) as the safest bladder emptying method for SCI patients in terms of urological complications[40]. It was also shown to be the optimal method for assisted bladder voiding after SCI by Shen *et al*[41]. CIC requires education and support, particularly during the initial stages and follow-up. Patients with sufficient hand function using CIC are able to empty the bladder regularly, with a lower urinary tract infection rate and good continence between catheterization[39].

Emptying the bladder with a permanent indwelling urethral or suprapubic catheter or reflex voiding may be an option for some patients with SCI[19]. Indwelling urethral catheters are used in the acute phase of injury but they are not recommended for long-term use because of the high risk for urinary complications (*e.g.*, urinary tract infection, calculi, urethral damage, renal dysfunction and bladder cancer)[42]. Singh *et al*[43] reported an indwelling catheter as the most prevalent risk indicator of urinary tract infection in SCI patients. The risk of urinary tract infection increases with the increasing duration of catheterization.

In spite of the risks, there are times when the use of an indwelling catheter is necessary. For example, it may be used transiently to assist wound healing and prevent contamination in patients with stage 3 or 4 perineal pressure ulcers. Long-term indwelling catheterization may be used for tetraplegic patients who do not have adequate upper limb function and assistance of a caregiver[37,42].

The Crede maneuver is not recommended for bladder emptying in the long-term because it raises intravesical pressures against a closed bladder outlet, raising the risk of vesicoureteral reflux, hernia, rectogenital prolapse and hemorrhoids[42]. Reflex voiding is not recommended in SCI patients with AD, voiding with high pressure, incomplete emptying and in female patients[37]. It may be a viable option for tetraplegic men who are unable to self-catheterization[42].

The other treatment options for bladder management in SCI include pharmacological interventions (anticholinergic medications, α-blockers, botulinum toxin) and surgical procedures (urethral stents, transurethral sphincterotomy, electric stimulation and posterior sacral rhizotomy, bladder augmentation, continent urinary diversion, cutaneous ileovesicostomy)[2].

Regular monitoring and suitable management for bladder dysfunction are important to prevent long-term complications (*e.g.*, infections, vesicouretheral reflux, renal failure, renal calculi, bladder cancer) and provide a better quality of life in patients with SCI.

NEUROGENIC BOWEL

Neurogenic bowel (NB) is a major problem in terms of physical and psychological aspects for people with SCI[44]. Liu *et al*[45] reported NB as a very common complication in patients with SCI, affecting nearly half of those with SCI (46.9%). It has also been shown that a high level of cord lesion, completeness of cord injury and longer duration of injury (≥ 10 years) can predict the severity of NB in patients with SCI[46].

A neurogenic bowel occurs when there is a dysfunction of the colon due to lack of nervous control[36,44]. Two main types of neurogenic bowel presented as upper motor neuron (UMN) bowel syndrome and lower motor neuron (LMN) bowel syndrome, reported by Stiens *et al*[47].

The UMN bowel syndrome or hyperreflexic bowel results from a lesion of the spinal cord above the conus medullaris. The defecatory maneuver cannot be performed due to lack of functioning abdominal musculature. There is increased colonic wall and anal tone. The voluntary control of the external anal sphincter is interrupted and the sphincter remains tight, thereby retaining stool. The UMN bowel syndrome leads to constipation and fecal retention, at least in part due to the external sphincter activity. The LMN bowel syndrome or areflexic bowel results from a lesion affecting parasympathetic cell bodies at the conus, cauda equina or the pelvic nerve. This syndrome is characterized by the lack of spinal cord-mediated reflex peristalsis and slow stool propulsion. There is an increased risk of incontinence because of the denervated external anal sphincter. The LMN bowel syndrome is correlated with constipation and a significant risk of incontinence due to the atonic external anal sphincter and lack of control over the levator ani muscle[36,44,47,48].

It is reported that bowel dysfunction caused major restrictions in social activities and in the quality of life in 39% of patients with SCI. The management of this problem is fairly important because it can be a greater problem than both bladder and sexual dysfunction[45].

There are various interventions used for management of bowel dysfunction in patients with SCI. The non-surgical treatment methods include high dietary fiber intake[49], abdominal massage[50], digital rectal stimulation[51], manual evacuation[52], oral laxatives[52], transanal irrigation[53], rectal suppository[54] and other pharmacological agents (stool softeners, colonic stimulants, contact irritants, bulk formers)[46] and functional electrical and magnetic stimulation of skeletal muscles[44].

Conservative or pharmacological interventions are successful in the management of neurogenic bowel dysfunction in 67% of the SCI population and when conservative management is ineffective, surgical interventions provide an option. Surgical treatments include sacral nerve stimulation with implantation of electrical stimulation systems, colostomy and Malone antegrade continence enema[44].

SPASTICITY

Spasticity is a common secondary impairment after SCI characterized by hypertonus, increased intermittent or sustained involuntary somatic reflexes (hyperreflexia), clonus and painful muscle spasms[55]. Spasticity affects 70% of patients with SCI and causes considerable disability for many[56,57].

The pathogenesis of spasticity in patients with SCI remains uncertain. An alteration in the excitability of various supraspinal inhibitory nerve paths used to be the

main explanation[57]. Although spasticity has often been viewed as a factor that can negatively affect functional level after SCI[56], light to moderate spasticity may have a positive impact on functional activities, including standing, transfers and ambulation. Additionally, it contributes to better peripheral circulation, thereby avoiding edema and reducing the risk of deep vein thrombosis[56,57].

Severe spasticity may contribute to increased functional impairment, contractures, ulcers, posture disorders and pain. Treatment should start as soon as possible to prevent such negative effects [57].

Management options of spasticity involve the elimination of exacerbating factors (such as urinary tract infection, constipation, ingrown nails, pulmonary infection, pressure ulcers, *etc.*) and the use of physical agents (heat, cold) and physical techniques, systemic medications, chemical neurolysis, intrathecal agents, electrical stimulation and surgical interventions[13,57,58].

Commonly used antispastic medications are baclofen, tizanidine, botulinum toxin, benzodiazepine, dantrolene sodium, gabapentin and pregabalin. Baclofen is a gamma-aminobutyric acid (GABA) agonist. It inhibits the excitatory activity at the spinal reflexes. In addition to an oral form, baclofen has been reported to effectively manage spasticity when used intrathecally. The use of baclofen can be limited because of its adverse effects (*e.g.*, sedation, fatique, drowsiness, ataxia and mental confusion)[55,59].

Tizanidin is a centrally acting α_2-adrenergic agonist involved in presynaptic inhibition[13]. Mirbagheri *et al*[60] reported that tizanidine acts to reduce reflex mechanical responses substantially without inducing comparable changes in intrinsic muscle properties in individuals with SCI.

Botulinum toxin is an injectible medication that acts on the neuromuscular junction to inhibit the release of acetylcholine. A chemical denervation occurs with botulinum toxin in intrafusal and extrafusal muscle fibers and its effect is reversible. The major side effect is excessive weakness of the treated muscle. Another antispastic medication is benzodiazepine. The presumed action mechanism of benzodiazepines is to enhance the binding efficacy of $GABA_A$ receptors. Dantrolene sodium is a unique agent that affects the level of skeletal muscles directly but it tends to cause generalized weakness of muscles, which can affect the patient's participation in a rehabilitation program[55].

Gabapentin and pregabalin were developed for the treatment of epilepsy but are widely used for the treatment of neuropathic pain. Their mechanisms of action require the binding to the high affinity α_2- delta subunit protein of the voltage gated Ca^{2+} channels, thereby decreasing release of excitatory neurotransmitters in the central nervous system[55].

Chemical neurolysis is usually used for localized spasticity. In this intervention, phenol or ethanol solution is used to constitute a nonselective destruction of the nerve axon or motor point that can decrease spasticity. Poor localization of the nerve or an inadequate dose causes treatment failure[13,58].

Surgical approaches include many orthopedic procedures (*e.g.*, tendon extension, tendon plasty or osteotomy) and the ablation of motor nerves and/or rhizotomy of sensory spinal roots. Surgical treatment of spasticity leads to irreversible changes and can often be avoided if other methods are used at an early stage[57,58].

PAIN SYNDROMES

Chronic pain is one of the frequent secondary complications for individuals with SCI, with up to 80% of patients with SCI reported to suffer from it[61]. Chronic pain may lead to functional disability and emotional discomfort and may impact negatively on community participation and quality of life[13,62].

The International Association for the Study of Pain has proposed a taxonomy of pain with a tiered classification of pain related to SCI in which pain types are divided into two main groups: nociceptive (musculoskeletal or visceral) and neuropathic (either above level, at level or below level of injury)[63].

Nociceptive pain

After SCI, chronic musculoskeletal pain, a type of nociceptive pain, may occur with abnormal posture, gait and overuse of structures such as the arm and shoulder. For example, using a manually operated wheelchair increases the risk of developing shoulder pain. Carpal tunnel syndrome and ulnar nerve entrapment at the cubital tunnel and Guyon canal are also seen. Muscle spasm pain is another type of musculoskeletal pain that is often seen in patients with incomplete SCI[2,13,61,63].

Visceral pain is a less distinct category of SCI-related pain. It arises from damage, irritation or distention of internal organs. This type of pain is reported in 15% of patients with chronic SCI[2,13].

Neuropathic pain

Neuropathic pain can occur above the level, at the level or below the level of injury. Above the level neuropathic pain may arise from complex regional pain syndromes and compressive mononeuropathies. At the level neuropathic pain may be due to damage to either nerve roots or the spinal cord itself. In the presence of late onset neuropathic pain, post-traumatic syringomyelia must be considered[61,63].

Below the level neuropathic pain is also referred to as central dysesthesia syndrome or deafferentation pain and often presents diffusely caudal to the level of SCI. It is generally characterized as a burning, aching, tingling or stabbing sensation[63].

Identifying the characteristic features of pain is important for determining suitable treatment.

Pain treatment

The use of simple analgesics, non-steroidal anti-inflammatory drugs and opioids are frequently reported for treatment of patients with musculoskeletal pain after SCI[2,61,63,64]. Pain relief medication combined with non-pharmacological

Table 1 Classification of pressure ulcers[76]

Category/stage Ⅰ: Non-blanchable erythema
Intact skin with non-blanchable redness of a localized area usually over a bony prominence. Darkly pigmented skin may not have visible blanching; its color may differ from the surrounding area. The area may be painful, firm, soft, warmer or cooler as compared to adjacent tissue. Category I may be difficult to detect in individuals with dark skin tones. May indicate "at risk" persons
Category/stage Ⅱ: partial thickness
Partial thickness loss of dermis presenting as a shallow open ulcer with a red pink wound bed, without slough. May also present as an intact or open/ruptured serum-filled or sero-sanginous filled blister. Presents as a shiny or dry shallow ulcer without slough or bruising[1]. This category should not be used to describe skin tears, tape burns, incontinence associated dermatitis, maceration or excoriation
Category/stage Ⅲ: Full thickness skin loss
Full thickness tissue loss. Subcutaneous fat may be visible but bone, tendon or muscle are not exposed. Slough may be present but does not obscure the depth of tissue loss. May include undermining and tunneling. The depth of a Category/Stage Ⅲ pressure ulcer varies by anatomical location. The bridge of the nose, ear, occiput and malleolus do not have (adipose) subcutaneous tissue and Category/Stage Ⅲ ulcers can be shallow. In contrast, areas of significant adiposity can develop extremely deep Category/Stage Ⅲ pressure ulcers. Bone/tendon is not visible or directly palpable
Category/Stage Ⅳ: Full thickness tissue loss
Full thickness tissue loss with exposed bone, tendon or muscle. Slough or eschar may be present. Often includes undermining and tunneling. The depth of a Category/Stage Ⅳ pressure ulcer varies by anatomical location. The bridge of the nose, ear, occiput and malleolus do not have (adipose) subcutaneous tissue and these ulcers can be shallow. Category/Stage Ⅳ ulcers can extend into muscle and/or supporting structures (*e.g.*, fascia, tendon or joint capsule) making osteomyelitis or osteitis likely to occur. Exposed bone/muscle is visible or directly palpable
Additional categories/Stages for the United States
Unstageable/unclassified: Full thickness skin or tissue loss - depth unknown
Full thickness tissue loss in which actual depth of the ulcer is completely obscured by slough (yellow, tan, gray, green or brown) and/or eschar (tan, brown or black) in the wound bed. Until enough slough and/or eschar are removed to expose the base of the wound, the true depth cannot be determined but it will be either a Category/Stage Ⅲ or Ⅳ. Stable (dry, adherent, intact without erythema or fluctuance) eschar on the heels serves as "the body's natural (biological) cover" and should not be removed
Suspected deep tissue injury - depth unknown
Purple or maroon localized area of discolored intact skin or blood-filled blister due to damage of underlying soft tissue from pressure and/or shear. The area may be preceded by tissue that is painful, firm, mushy, boggy, warmer or cooler as compared to adjacent tissue. Deep tissue injury may be difficult to detect in individuals with dark skin tones. Evolution may include a thin blister over a dark wound bed. The wound may further evolve and become covered by thin eschar. Evolution may be rapid exposing additional layers of tissue even with optimal treatment

[1]Bruising indicates deep tissue injury.

treatment such as physiotherapy is also reported[61].

Neuropathic pain relief in patients with SCI can be complex and requires a multifaceted approach. Medications, surgical interventions, the use of modalities and psychotherapy are included in this approach[2].

In the literature, the use of anticonvulsants[65-67], antidepressants[68,69], opioid and other analgesics[64,70-72] and antispasticity medications[73] were reported with different effects on neuropathic pain relief of SCI patients. It is also reported that nonpharmacological treatment such as transcutaneous electrical nerve stimulation, acupuncture, spinal cord stimulation and surgical procedures may be effective for some patients with SCI-related neuropathic pain[63].

PRESSURE ULCERS

Pressure ulcers are an important and potentially life-threatening secondary complication of SCI. They can lead to further functional disability and fatal infections and surgical interventions can be required[74]. Diseases of skin (including pressure ulcers) were reported as the second most common etiology for rehospitalization at most time intervals (years 1, 10, 15, 20) in a multicenter analysis with SCI patients[75].

Pressure ulcers have been defined as a localized injury to the skin and/or underlying tissue, usually over a bony prominence, as a result of pressure or pressure in combination with shear[76].

A common classification system for pressure ulcers has been developed by the National Pressure Ulcer Advisory Panel (NPUAP) and European Pressure Ulcer Advisory Panel (EPUAP). They have agreed on four levels of injury which range in severity from category/stage I (intact skin with non-blanchable erythema) to category/stage Ⅳ (full thickness tissue loss). Recognizing that the terms unclassified/unstageable and deep tissue injury are generally graded as "Ⅳ" in Europe, NPUAP has agreed to put them separately (Table 1)[76].

It is reported that the most common locations for pressure ulcers after 2 years of SCI are the ischium (31%), trochanters (26%), sacrum (18%), heel (5%), malleolus (4%) and feet (2%)[3]. Hoff *et al*[77] also reported that risk factors for pressure ulcers are immobility, reduced activity, lack of sensibility, moisture due to urinary and fecal incontinence, muscle atrophy, prolonged time since injury, depression, smoking and poor nutrition.

Prevention of pressure ulcers begins at the time of injury and is a lifelong commitment for those living with SCI or their caregivers[74]. Pressure ulcer management includes daily inspection of skin, keeping skin clean and dry, avoidance of excessive pressure or shearing, proper pressure relief techniques, individually prescribed equipment (*e.g.*, wheelchair cushions), well-balanced nutrition, early recognition and treatment[74,75].

A treatment plan for pressure ulcer following SCI outlined in the Consortium Guideline includes cleansing, debridement (autolytic, enzymatic, mechanical, sharp,

surgical), dressing (transparent films, hydrocolloids, hydrogels, foams, alginates, gauze dressings), nutritional support, management of tissue loads (bed positioning, using pressure-reducing bed and wheelchair support surfaces, avoiding the individual's postural alignment) and surgery[78].

Furthermore, Regan *et al*[74] reported that there was level 1 evidence to support the use of electrical stimulation, ultrasound/ultraviolet light C and non-thermal pulsed electromagnetic energy treatment as adjunctive therapies to standard wound management.

OSTEOPOROSIS AND BONE FRACTURES

Osteoporosis, a condition characterized by low bone mass and deterioration of the skeletal microarchitecture, is a well-known complication of SCI[79]. It occurs rapidly in the first 12-18 mo but continues for several years[62]. A significant decrease in bone mineral density has been reported in chronic SCI patients[80-82].

The mechanism involved in the development of SCI-induced osteoporosis is complex and multifactorial. Disuse may play an important role in the pathogenesis of osteoporosis but non-mechanical factors also appear to be important. These factors may include insufficient nutritional support, disordered vasoregulation, hypercortisolism (either therapeutic or stress-related), alterations in gonadal function and other endocrine disorders[79].

Bone loss after SCI leads to increased risk of low impact fractures (those occurring spontaneously or from a transfer from bed to chair)[83]. The most common fracture sites appear to be those around the knee, such as the distal femur or proximal tibia[82-85]. A number of factors appear to have an influence on bone mass in patients with SCI. The level of the lesion, the extent of functional impairment, muscular loading of the bones, the duration of injury and aging are included in these factors. The degree of bone loss may be more severe in patients with complete SCI than with incomplete SCI[79,84]. The bone mass tends to reduce with increasing time post-injury and age in patients with SCI[79,86]. Muscular loading of the bones has been considered to play a role in the maintenance of bone density[79].

There is generally no standardized treatment guidelines for management of osteoporosis in patients with SCI[83,87]. In the literature, pharmacological and rehabilitation-oriented approaches were reported[79,84].

Pharmacological interventions for osteoporosis after SCI have focused on reversing bone resorption[88]. The bisphosphonates, the most studied pharmacological agents in the treatment of SCI-induced osteoporosis. They strongly inhibit bone resorption (79). The efficacy of bisphosphonates to decrease bone loss has been reported in both the acute and chronic period[85].

Gilchrist *et al*[88] concluded that alendronate 70 mg orally per week for 1 year initiated soon after acute SCI prevents bone loss. Zehnder *et al*[89] also reported that SCI bone loss was stopped at all measured cortical and trabecular infralesional sites over 2 years with alendronate 10 mg daily in a group of paraplegic men.

In a recent study, zoledronic acid, the newest generation of bisphosphonates, was reported to be an effective and well-tolerated treatment to prevent bone mineral density loss at the total hip and trochanter for up to 1 year following SCI[90].

Non-pharmacological treatment methods such as standing-up, orthotically aided walking, weight - bearing physical exercises, functional electrical stimulation and pulsed electromagnetic fields have been studied in the literature. Charmetant et al reported that mechanical and rehabilitational approach aimed at stimulating sublesional bone segments may be a useful adjunct to drug treatment. In various studies standing-up and orthotically-aided walking seem to have a favorable effect during the early phase of SCI[79,84,91,92].

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