Abstract

Robotic exoskeletons have emerged as rehabilitation tool that may ameliorate several of the existing health-related consequences after spinal cord injury (SCI). However, evidence to support its clinical application is still lacking considering their prohibitive cost. The current mini-review is written to highlight the main limitations and potential benefits of using exoskeletons in the rehabilitation of persons with SCI. We have recognized two main areas relevant to the design of exoskeletons and to their applications on major health consequences after SCI. Clinical trials are currently underway to address some of these limitations and to maximize the benefits in rehabilitation settings. Future directions highlight the need to use exoskeletons in conjunction with other existing and emerging technologies similar to functional electrical stimulation and brain-computer interface to address major limitations. Exoskeletons have the potential to revolutionize rehabilitation following SCI; however, it is still premature to make solid recommendations about their clinical use after SCI.

Key words: Spinal cord injury; Exoskeleton; Robotics; Rehabilitation; Locomotion

Core tip: Robotic exoskeletons have emerged as rehabilitation tool for persons with spinal cord injury (SCI). Clinical evidence related to applications of exoskeletons is still lacking considering their prohibitive cost. Clinical trials are currently underway to address some of these limitations and to maximize their benefits in different rehabilitation settings. Exoskeletons have the potential to revolutionize rehabilitation following SCI; however, it is still premature to make solid recommendations about their clinical use after SCI.
to revolutionize rehabilitation following SCI; however, it is still premature to make solid recommendations about their clinical use after SCI. The current mini-review highlights the basic applications and limitations as well as future directions regarding applications and exoskeletons.

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INTRODUCTION

Robotic exoskeletons or powered exoskeletons are considered wearable robotic units controlled by computer boards to power a system of motors, pneumatics, levers, or hydraulics to restore locomotion[1,2,3]. The topic of exoskeletons is timely given the number of devices currently being studied as well as purchased by facilities for rehabilitation purposes in medical centers or for home use[1-7]. Exoskeletons have emerged as an advantageous rehabilitation tool for disabled individuals with spinal cord injury (SCI)[1]. Rehabilitation specialists, clinicians, researchers, and patients welcome their use for upper ground ambulation[6-7]. Compared to previously existing locomotor training paradigms, exoskeletons may offer a great deal of independence in medical centers and communities including shopping malls, local parks and movie theaters as well as improving the level of physical activity[1,3]. There is a pressing need for this population to improve their levels of physical activity. This feature may encourage continuous usage of exoskeletons in conjunction with wheelchairs.

CURRENT APPLICATIONS OF EXOSKELETONS

Different brands of powered exoskeletons are now commercially available for SCI rehabilitation with different levels of injury[1-7]. However, there is still a limited accessibility to exoskeletons in clinical settings, partly because of their prohibitive cost and the high level of training required before supervising individuals with SCI. Despite these limitations, limited research and anecdotal evidence support the use of exoskeleton to improve quality of life and health related medical conditions after SCI[1-3]. Previous excellent reviews have summarized and highlighted the potential benefits of using exoskeleton for rehabilitation of persons with SCI[2,4]. It is crucial before expanding the applications of exoskeletons that we carefully analyze the available research and clinical evidence regarding this technology. Considering the limited data and/or small sample size of the current published studies, it is premature to draw solid conclusions about the efficacy of exoskeletons in maximizing rehabilitation outcomes or ameliorating several of the health-related consequences following SCI. However, clinical trials are underway to confirm these benefits and to understand the underlying mechanisms that lead to such improvement. Clinical trials site (clinicaltrials.gov) indicated that out of 870 studies for SCIs, there are 28 studies (approximately 3%) addressing different applications of exoskeletons in this population. These statistics may highlight our limited knowledge and the need for additional clinical trials to address the major limitations of exoskeletons. The current use of robotic exoskeletons remains investigational and premature to decide whether exoskeletons are clinically effective in the rehabilitation of persons with SCI. The primary focus of the current review is to allow critical analysis of the available research evidence and to encourage interdisciplinary approach to advance the use of technology in clinical settings. The rehabilitation community should not be discouraged from the use of exoskeletons, but rather to proceed with caution regarding their clinical applications. Moreover, the mini-review will provide the reader with the current pros and cons regarding exoskeletons and will summarize in a non-exhaustive manner the theoretic or potential benefits after recognizing the primary limitations of exoskeletons. It is not the intention of the current review to list types or characteristics of different exoskeletons that were recently published in details[1]. The published work provided details on the average cost per unit and clear illustrations of different exoskeleton units available in rehabilitation settings[1].

BENEFITS AND LIMITATIONS FROM THE DESIGN PROSPECTIVE

Safety and efficacy of exoskeletons
From the clinical health-prospective, several reports have demonstrated that exoskeleton training is safe and likely to be used in different settings to encourage over ground ambulation[1-7]. A recent study that involved nine European rehabilitation centers demonstrated the safety, feasibility and training characteristics in persons with SCI following 8 wk of training[6]. Out of 52 participants, three dropped out following ankle swelling and four presented with grade II pressure injury but managed to continue the study[6]. Personal communication indicated that fracture may occur at the distal tibia or calcaneus bone during exoskeleton walking. Potential health benefits have been highlighted for the use of exoskeletons in rehabilitation settings, and studies have examined the effects of exoskeletons on different health-related outcomes[1,3]. These studies provided preliminary evidence on the efficacy of exoskeletons on cardiovascular health, energy expenditure, body composition, gait parameters, level of physical activity and quality of life[2-9]. Robotic exoskeletons may prove...
an attractive rehabilitation tool not only to restore locomotion but also to improve the level of physical activity years after injury\textsuperscript{[6,7]}. Robotic exoskeletons may decrease seated time, increase standing and walking time as well as social engagements with family and friends\textsuperscript{[6,7]}. Decreased sitting time is likely to ameliorate several of the health-related consequences that negatively impact this population\textsuperscript{[10-15]}.

**Fitting time across different brands**

Most of the current brands require special measurements to custom fit participants before donning/doffing. This may require special adjustments for persons with SCI in case there is leg length discrepancy, pelvic obliquity, severe muscle wasting or even highly sensitive skin; which may require up to 2-3 sessions to accomplish this task (e.g., Rewalk and Ekso)\textsuperscript{[1-9]}. Different brands have different donning/doffing strategies which may range from 10 to 30 min to safely fit subjects before walking (e.g., Indego). After completion of the initial measurements of the participants, exoskeleton fitting may require at least 1 h to safely complete the required checklist steps before standing up and walking. This is usually preceded with detailed physical examination to safely screen participants for eligibility. The detailed physical examination will make a safe clinical decision prior to including or excluding any participants in the program.

After fitting sessions, the time needed to adjust devices to custom fit each participant may also interfere with future training sessions. This has the potential to limit the allotted training time set for each subject as covered by his/her medical insurance. Other available brands have a shorter fitting time and may be as simple as measuring the length from greater trochanter to the knee joint followed by measuring the length from the knee joint to the heel of the patient\textsuperscript{[10]}. Moreover, most of the available brands require transfer to the mat or transfer to piano-type chair to accomplish the fitting purpose which may increase the risk of falling. Many SCI participants with limited hand functions or push-down performance may not be candidates for this technology because of difficulty in achieving safe transfer\textsuperscript{[3,5,7]}. Therefore, future brands need to consider shorter fitting time and allow fitting in wheelchairs without the need to transfer from one place to another. Indego exoskeleton was successful in designing their product into parts that can be easily assembled together while the participants were still in their wheelchairs. This is likely to cut the fitting time and provide safe accessibility to the community. Another aspect is that some brands (e.g., Rewalk) may require higher intellectual capabilities to perform and learn weight shifting and stepping in order to walk or navigate thresholds or carpets. This motor learning capability may vary from one patient to another and may require 3-5 d of continuous training to grasp this procedure. As the technology advances, different manufactures will develop their products to be simply fitted to the participants in a short time and provide variable options for persons with wide motor learning capabilities.

**Speed and community ambulation**

Exoskeletons offer a range of varying speed and most are characterized by a modest speed that is slightly greater than 0.2 m/sec, which may impede their general use in the community\textsuperscript{[2,3,5]}. Others have demonstrated that speed may exceed 0.7 m/sec especially in persons with incomplete SCI\textsuperscript{[5]}. The slow speed may reduce balance and prevent frequent falling; however, ambulation speed may increase following continuous training. In a case report, we demonstrated the ability of a person with C5 complete SCI to increase his walking speed to 0.4 m/sec\textsuperscript{[7]}. Gaining confidence and securing balance are motor learning strategies that influence walking speed. Most of these brands were primarily tested indoors on tiled surfaces and walking on uneven terrains may impose additional challenges to persons with SCI. Currently, there are two brands that have received Food and Drug Administration approval for personal use\textsuperscript{[5,8]}. Compared to wheelchairs, these brands are still not adequate to provide ambulation on muddy, pebbles, rainy and/or snowy terrains. This may impede their applications in other states or countries having roads or weather conditions not suitable for locomotion with exoskeletons. Development of lighter materials for exoskeletons may facilitate increasing the speed for community ambulation. Current existing brands weigh 50-66 lbs, which may be a hurdle for some individuals with SCI to carry or lift for transportation compared to ultralight wheelchairs\textsuperscript{[3-9]}. Other brands have different components and can be broken down and carried separately\textsuperscript{[8]}. Future designs should focus on choosing highly durable materials that provide less weight and allow faster speed without compromising balance after SCI. Moreover, it is highly recommended to design water-proof brands that can facilitate walking in different weather conditions or on uneven terrains.

**BENEFITS AND LIMITATIONS FROM HEALTH PROSPECTIVE**

**Exoskeletons and levels of SCI**

Persons with tetraplegia represent 55% of the SCI population\textsuperscript{[10]}. The current technology (Ekso) is FDA approved to be used for those with C7 and below SCI, primarily because of safety concerns. The level of injury cut-off was set because reasonable hand functions are required to hold the assistive device (walker or crutches) and to initiate weight shifting during stepping and walking. Lack of appropriate hand grip may eliminate a considerable number of this population from benefitting from this technology. This means that a large segment with C1-C5 level of injury may be ineligible to benefit from this technology. Another brand (REX) has emerged to address this issue and
allows running the machine with a joystick or controller without relying on the participants’ hand functions\cite{12,18}; however, this brand is still not FDA approved and its speed is very limited, less than 0.1 m/sec, to initiate any recognized cardiometabolic benefits compared to a regular standing frame. However, the brand can offer other benefits similar to ambulatory exercise and upper body exercise in upright position\cite{18}. This technology may be beneficial to those with C4-C8 level of SCI or even higher level of injury similar to cases diagnosed with locked-in syndrome. Compared to other approved brands, the REX exoskeleton does not require a two or four point assisted device. In other approved brands, it is crucial to have reasonable hand functions to initiate walking using a controller, to control the assistive device, to help shifting body weight and to provide balance in the standing position. Proactive means of using platforms walker or other devices (e.g., hand splints) are warranted to overcome this problem and to provide safe accessibility in large segment of SCI population despite their level of injury.

**Exoskeletons and body weight / body composition**

Two-thirds of persons with SCI are either overweight or obese\cite{15}. Exoskeletons may facilitate waging the war on obesity syndrome after SCI by helping to decrease sitting time, increase level of physical activity and improve parameters of body composition after SCI. However, the existing technology is only limited to those with body weight less than 100 kg (220 lbs). This may exclude a considerable number of individuals from benefitting from this technology. The weight cut-off may motivate SCI participants to engage in effective dietary plans and participate in SCI wellness and exercise programs to maintain a healthy body weight. Anecdotal evidence supports this notion, several persons with SCI started a rigorous diet program to lose weight after initially being disqualified from enrolling because of exceeding the body weight cut-off limit recommended by the manufacture. Further studies are warranted to investigate whether exoskeleton training may independently help persons with SCI to lose weight especially decreasing percentage of whole body and regional fat mass.

Another important consideration is whether exoskeleton training is likely to improve parameters of body composition as indicated by decreased fat mass and increased fat-free mass. Decreased fat mass is likely to improve parameters of cardio-metabolic health after SCI\cite{11}. A recent report demonstrated that improvement in cardio-metabolic health is tightly associated with positive body composition characteristics compared to parameters of physical activity\cite{19}. There is still limited evidence to support the positive effects of exoskeleton ambulation on parameters of body composition. A recent case report demonstrated that 15 wk of exoskeleton training resulted in decreased body mass by 6 kg including 2 kg loss in fat mass and 4 kg loss in fat-free mass in a person with T4 complete SCI\cite{7}.

**Exoskeletons and physical activity**

Physical inactivity is a key feature following SCI, which is likely to lead to a sedentary lifestyle and increased sitting time\cite{12,20-22}. Prolonged sitting time has been shown to be an independent risk factor for cardiovascular disease, cancer as well as a factor for increasing all-cause mortality\cite{10}. A very important point that needs to be considered is low metabolic cost during exoskeleton training. Cardiorespiratory fitness is used as a key feature to determine overall health and inverse relationships were noted between VO₂ max and cardiovascular disorders, insulin resistance and type 2 diabetes mellitus\cite{23}. Recently released ISCoS guidelines recommended that persons with SCI engage in at least 20 min of moderate to vigorous intensity aerobic exercise three times per week to improve cardiorespiratory fitness\cite{20}. This supports the notion adopted by other organizations and research groups on the significance of increasing the level of physical activity to decrease chronic disease risk factors after SCI\cite{10,20-22}. It is unclear whether exoskeleton locomotion may induce this moderate intensity training, but it can definitely decrease sitting time and improve parameters of physical activity as demonstrated by increasing number of steps, duration and distance of walking\cite{6,7}.

According to the World Health Organization, physical activity is defined as the bodily movement resulting from muscle actions that increases energy expenditure. Exoskeletons provide bodily passive movement of the lower extremity without muscle contraction. This is likely to be accompanied with low oxygen uptake and energy expenditure during exoskeleton ambulation\cite{7}. Therefore, incorporating functional electrical stimulation (FES) in conjunction with exoskeleton training may be an effective strategy to offset this problem by initiating muscle contraction and increasing energy expenditure\cite{24,25}. Currently, hybrid exoskeleton brands may offer this feature; however, studies are currently underway to prove the effectiveness of this combination in persons with SCI. The combination of FES and robotic control is a challenging issue, due to the non-linear behavior of muscle under stimulation and the lack of developments in the field of hybrid control\cite{24,25}. The hybrid system may overcome electromechanical timing delays and muscle fatigue as well as balance muscular and robotic actuation during walking.

**Exoskeletons and range of motion**

Joint contractures at the hips, knees and ankle joints are another problem that is likely to disqualify participation from exoskeleton training program\cite{26}. Persons with SCI need to attain hip extension range of motion within 10–15 degrees and knee extension with less than 10 degrees flexion in supine or standing position with ankle joints in neutral position\cite{9}. Participants who fail to attain this range of motion may be encouraged to...
participate in a stretching program to improve muscle flexibility around these joints. This may include the use of standing frame or application of a dyna-splint around the knee joint to provide soft tissue stretching for long duration\[^{[26]}\]. An extensive stretching program may take up to 6 mo to gain 6-10-degree improvement in the range of motion. Because of disuse after high level SCI, persons may also suffer from joint contractures or tenodesis grasp, which may likely limit their ability to use assistive devices and failure to evoke weight shifting during exoskeleton ambulation. Therapists may need to be proactive and use a platform walker or help cufing the hand to the assistive device to overcome these problems. It is worth noting that maintaining functional range of motion during locomotion is essential for neuro-recovery following SCI. Compared to other forms of walking similar to knee-ankle foot orthosis (KAFO) or hip-knee-ankle-foot orthosis (HKAFO), exoskeleton ambulation may facilitate natural recovery over encouraging compensatory techniques of using trunk muscles following SCI. However, further studies are still warranted to support this assertion.

**Exoskeletons and bone health**

Sixty percent of individuals with SCI suffer from osteopenia or osteoporosis; a progressive disease that leads to bone loss, especially in the distal femur and proximal tibia\[^{[27]}\]. Bone remodeling and demineralization is a continuous process and it is a function of both osteoblastic and osteoclastic activities. The pattern of bone loss in persons with SCI differs from other clinical population and it is commonly referred to as neurogenic osteoporosis\[^{[27]}\]. Bone loss occurs sublesionally at a rapid rate and approaching 1% of bone mineral density per week\[^{[27]}\]. Most of bone loss occurs within the first 12 to 24 mo after SCI and reaches steady state within 3-8 years post-injury\[^{[27]}\]. Furthermore, persons with SCI are likely to experience lower extremity fracture that may require close to several months to one year to re-initiate weight bearing using a standing frame or any other assistive devices. The high susceptibility of fracture in these regions may lead to other health consequences following immobilization similar to joint contractures and pressure injuries. Imaging techniques are now available to provide clinicians with insights regarding bone health after SCI. These techniques include X-rays, dual energy X-ray absorptiometry (DXA), quantitative computed tomography (CT), magnetic resonance imaging (MRI)\[^{[27]}\]. The first two techniques provide two-dimensional assessment of bone health and the latter ones provide 3-dimensional volumetric assessment of bone architecture. A recent review has clearly demonstrated the differences among imaging approaches in highlighting the risk of fractures after SCI\[^{[27]}\]. Longitudinal monitoring of bone health in persons with SCI has become a crucial element for any rehabilitation program. This may ensure safe standing and weight bearing prior to locomotion programs including exoskeleton.

Recommendations based on early evidence suggest that a BMD below 0.6 g/cm\(^2\) of the knee joint (i.e., distal femur and proximal tibia) or T-scores less than 3.5 standard deviations at the hip joints or femoral neck can be used as cut-offs to exclude individuals from participating in standing activities. This is likely to exclude a considerable number of participants from engaging in exoskeleton training programs. Moreover, these cut-offs do not guarantee certainty that fracture at any of these sites may not occur\[^{[27-29]}\]. Bone biomarkers have been previously used in rehabilitation programs to highlight these activities\[^{[10]}\]. These biomarkers are not widely introduced and underutilized in clinical settings. Therefore, it is highly recommended that all persons with SCI undergo DXA scans for knees and hips as well as X-ray at the ankle joints prior to exoskeleton training. It is essential to conduct X-ray exam at the ankle joints to assess participants’ risk of fracture at the distal tibia or calcaneus bone during standing or walking training with exoskeleton. Moreover, evidence-based guidelines need to be established on what clinical biomarkers should be utilized to decrease the risk of bone fracture. It is still unclear, based on available evidence, whether incorporating pharmacological intervention with or without neuromuscular electrical stimulation can alleviate the problem of osteoporosis after SCI.

**Exoskeleton and pressure injuries**

It is well documented that 70%-75% of persons with SCI experience pressure injuries during their lifetime with dramatic changes in their skin structures that are likely to break down with a minimal amount of shear\[^{[21,31]}\]. This should make us cautious about choosing the appropriate candidate, utilizing their past medical history to identify those likely to benefit from exoskeleton use without exposure to such shear stress. Powered exoskeletons are likely to have straps to help maintaining static and dynamic posture during standing and walking\[^{[17]}\]. With diminished sensation and impaired peripheral circulation, these straps are likely to cause excessive shears to the surrounding soft tissues and may lead to pressure injuries\[^{[17]}\]. To circumvent this problem, researchers developed pressure sensors to monitor pressure exerted by physical human-machine interfaces and provide feedback about levels of skin/body pressure in fastening straps\[^{[17]}\]. These pressure sensors are likely to protect against ischemia and necrosis by maintaining pressure in range of 30-35 mmHg to allow for adequate circulation or below 50 mmHg to maintain tissue oxygenation\[^{[17]}\]. Pressure heat maps were recently measured in one person with SCI performing exoskeleton locomotion. The authors highly suggested that thigh straps may induce pressures ranging from 80-120 mmHg while performing upright locomotion. Anecdotal unpublished evidence supports that extensive strapping may result in cyst formation at the pressure site\[^{[17]}\]. Therefore, clinicians working with exoskeletons...
need to check different pressure skin zones especially when working with complete SCI.

FUTURE DIRECTIONS IN EXOSKELETON AMBULATION

Current challenges facing community use
The transition from hospital setting to rehabilitation use or community ambulation requires the need of a well-trained caregiver \(^1,5\). It is likely to be challenging for persons with SCI to identify a dedicated caregiver, who is willing to dedicate the time and effort to support their partner during exoskeleton ambulation. Work related commitment, divorce, liability in case of falling or injury have been identified as precluding factors to having a committed caregiver. Moreover, it is the total responsibility of a certified exoskeleton trainer to provide hands-on training for the caregiver and ensure that the patient is safe before getting released in the community. There is increased prevalence of SCI with aging; as a result of falling or cervical myelopathy that may prevent baby-boomers with SCI to benefit from this technology.

Their next of kin is likely to be older or unable to provide the time to be qualified as a trained caregiver. Designing systems that do not require or decrease reliance on a caregiver may be an advantageous future goal in the rehabilitation of persons with SCI.

The cost and standard wheelchair
Finally, the current cost of this equipment is prohibitive and may interfere with accessibility in the developed countries as well as less developed parts of the world. The cost may drop with increased numbers of emerging brands and studies demonstrating their efficacy. However, policy makers and governments need to determine whether the technology deserves wide spread application such that medical insurance can offer an exoskeleton unit per patient similar to a wheelchair. As of now, it remains unclear whether this emerging technology offers benefits beyond the existing standard of care, such as a regular wheelchair or a standing frame. Current research is underway to answer these questions. It should be noted that someone who has been in a wheelchair for 20-30 years may not be willing to make daily lifestyle changes to adopt the new technology. Current technology may offer accessibility in the community, but it is still limited in its ability to navigate special terrains, climb stairs, or move in water. It has yet to be determined whether persons with SCI are willing to compromise his/her comfort zone of using his daily wheelchair over experiencing the luxury of ambulating in a costly robotic suit. From the recreational point of view, recreation programs may need to encourage community trips using exoskeletons to help increasing public awareness and facilitate their use in conjunction with wheelchairs. It is highly recommended to encourage exoskeleton sports during the annual wheelchair games similar to power wheelchair soccer or other activities. This is likely to provide competitions among the available brands and increase their popularity in recreational settings.

Future directions may need to consider a number of research questions including the effects of exoskeleton training on acute compared to chronic injury and weather early use is likely to attenuate or slow the changes that occur in body composition after SCI. A recent study demonstrated that those with an acute injury (< 1 year) showed improvement in parameters of gait function by 36% compared to only 3% for those with chronic injury \(^9\). Moreover, it is still unclear whether exoskeleton training can be used as a task specific training to reinforce neural plasticity and recovery of gait especially in persons with incomplete SCI. Implementing the exoskeleton technology with electrical stimulation, epidural stimulation and brain-computer interphase (BCI) may be available features in future brands \(^33\). This may provide the end-user with a control over the robotic limbs via the use of electrical stimulation, BCI or both \(^30,31,33,34\). The technology of the exoskeleton is likely to evolve as more partnerships developed to produce future generations that are likely to be lighter and faster. Moreover, robotic exoskeletons may need to be considered within developmental stages to help children with SCI and other clinical population \(^35,36\). This is highly important to provide early weight bearing and avoid postural abnormalities or deformities. The National Institutes of Health just released an attempt to help kids with cerebral palsy to walk on their feet and prevent crouched gait \(^35,36\). As cheaper brands of exoskeletons become available, participants may continue to use them in conjunction with wheelchairs because of their recognized benefits on spasticity, physical activity, bowel movement and quality of life after SCI.

CONCLUSION

The current review may raise the awareness of the SCI community about the use of exoskeletons in the rehabilitation of persons with SCI. We should strive for an interdisciplinary team approach to provide greater accessibility to this technology and further our knowledge on how to expand its use to the general population of SCI by overcome some of the existing limitations that were highlighted. Exoskeletons may improve several physiologic and psycho-somatic outcomes. Moreover, it is time to establish round table discussions including individuals with SCI (consumers), government and health policy makers, researchers and rehabilitation specialists to develop rigorous plans for the future of exoskeletons. As our knowledge and experience increase, more individuals with SCI should become eligible to gain the benefits of this promising technology.

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