The impact of walking on spinal cord tissue regeneration in patients with paraplegia following spinal cord Injury

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ABSTRACT

The impact of walking in Spinal Cord Injury can promote axonal growth through directed neuroplasticity. The impact of walking in corticospinal tracts, in combination with proprioception, could be the key to neuroregeneration. Furthermore, growth factors such as brain-derived neurotrophic factor (BDNF) and insulin growth factor -1 (IGF-1) play a crucial role not only in the procedure of axonal growth but also in the remyelination.

Many posttraumatic treatment strategies have been evaluated until now, including pharmacological agents aimingto block the development of secondary apoptotic mechanisms of CNS. The same strategies are simultaneously able to promote the regeneration of neuroaxons. Nevertheless, there is insufficient knowledge concerning the hypothesis that gait training could be applied as a potential therapy for neuroprotection following SCI.

The objective of this review is to assess the impact of assisted walking in paraplegia by consolidating evidence regarding: (a) neuroplasticity (b) tissue regeneration.

Key Words: "SCI", "neuroplasticity", "regeneration", "paraplegia", "proprioception", "gait training"

Introduction

According to the International Spinal Cord Society ISCoS, Spinal cord injury (SCI) is a severe neural trauma that, depending on the severity of the damaged segment, is classified into complete and incomplete. Statistically, it is assessed that 0.0022% of the global population will suffer from a spinal cord injury (SCI), annually [1]. Most of the patients with complete SCI are considered as clinically incomplete due to a few remaining neuron connections based on EMG results [2,3].

Paraplegia refers to the impairment and loss of motor, sensory and/or autonomic function in the thoracic, lumbar or sacral segments [4]. It is a result of severe damage to the spinal cord and the nervous system [5,6]. Recovery following SCI is proved to be perplexed and requires long-term rehabilitation [4]. A hallmark of posttraumatic SCI is neuroplasticity, enabling nervous system to modify and change neural networks to adapt both neuronal structure and function [7-10].

The process of tissue regeneration following SCI

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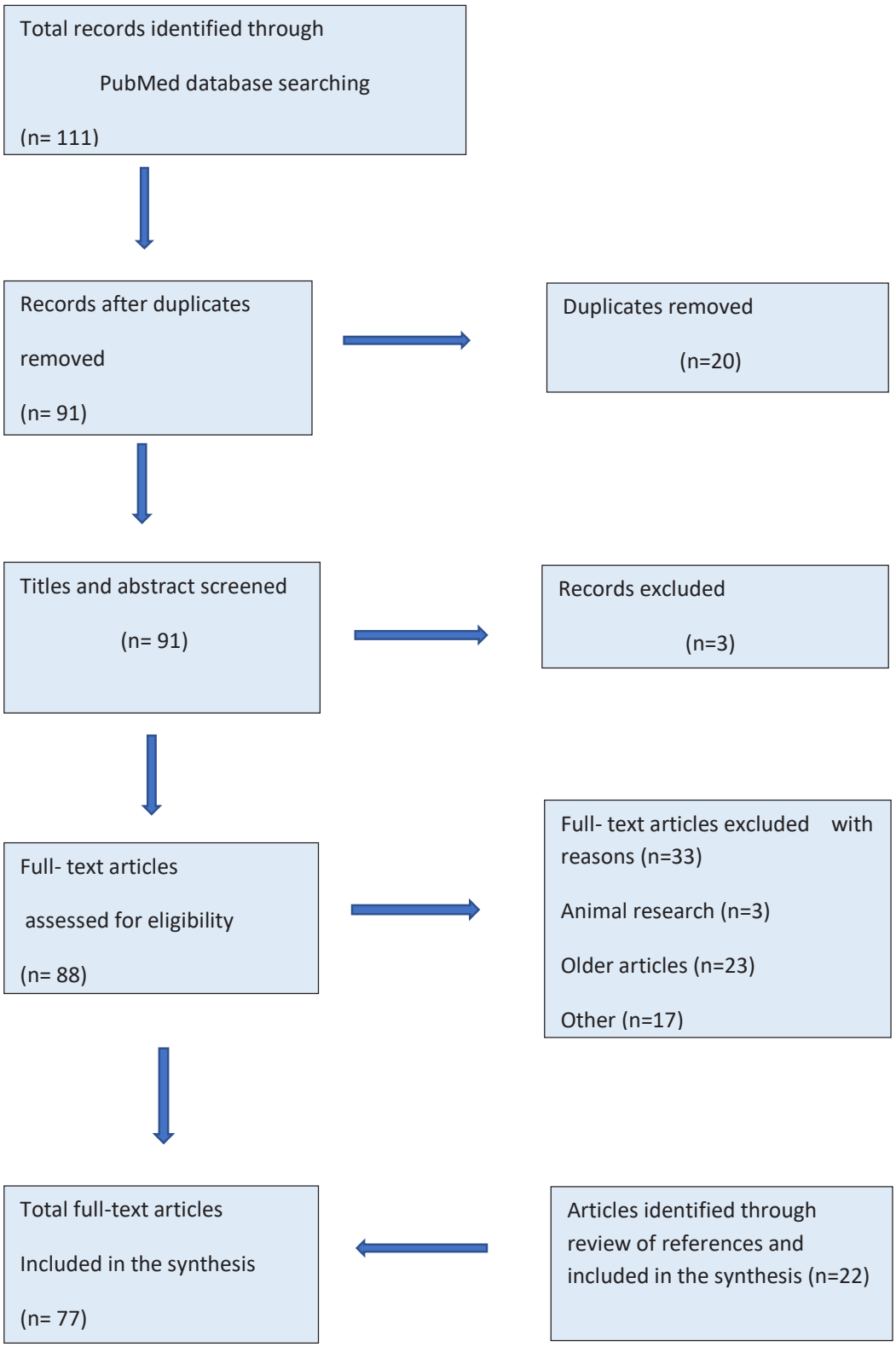

Figure 1: Flowchart of the Article Selection and Review Process

could be differentiated into two phases, the subacute and the chronic phase [5]. The subacute phase refers to some weeks following injury and the chronic to some months-years post-trauma [9]. Walking has been always a goal of the chronic-phase SCI rehabilitation program, concerning locomotion function [11-13]. Nonetheless, there are questions on how walking can affect neuroplasticity and tissue regeneration. This is a potential oversight to assume walking as a therapy.

The main purpose of this review is to provide proof that locomotion training on the treadmill [61], gait-assisted orthosis such as Locomat and wearable exoskeleton robots are capable to foster spinal cord tissue regeneration and promote neuroplasticity through re-learning gait, in individuals with SCI [10]. Although the existing data about this issue is limited and quite perplexing, especially in human subjects, there are some research articles, meta-analysis and systematic reviews that could prove this hypothesis. Successful and functional nerve tissue regeneration should be supported from supraspinal tracts [62], spinal and peripheral inputs to be long- lasting and functional [63].

Pubmed database was reviewed to identify ways that walking can foster spinal cord tissue regeneration and promote neuroplasticity. The key words "SCI", "neuroplasticity", "regeneration", "paraplegia", "proprioception" and "gait training" were used. Search parameters were specific regarding date of publication (from 1995 until 2022) and relevance. The process of identification and the criteria of inclusion-exclusion are described on the following flowchart (Figure 1).

Discussion

The initial electronic database search resulted in a total of 111 articles, of these, 77 were considered for inclusion in this review (Figure 1).

Pathophysiology of Spinal Cord Injury

SCI consist of two major pathophysiological mechanisms, primary and secondary [5,6,14]. The primary refers to the immediate mechanical traumatic damage of spinal cord, leading to demyelination and axotomy [15-17]. Secondary injury involves the presence of free radicals due to the long ischemia and hypoxia [4-6]. Neurotransmission is impaired, lipid peroxidation and calcium influx contribute to apoptosis and axonal demyelination [4,14-17]. Finally, scar and cavitation are formed, inhibiting myelin regeneration and limiting axon growth [4,5].

Neuroplasticity of Spinal Cord

Based on the metaplasticity theory, morphology and function of a synapse can change over time [9,18]. Following SCI, the following plasticity includes the neural circuit reconstruction, activation of neurons and nerve conduction [8,19]. The regulation of microenvironment and molecularis aim at neuroprotection of intact axons and gene regulation [20,21]. Specifically, neurotrophic factors such as the brain derived nerve factor–BDNF and insulin growth factor-1 (IGF-1) have been proved to promote adaptive spinal plasticity [20,21,28]. As an adaptive spinal plasticity can be referred as task-dependent plasticity which can be succeed by special forms of training such as stepping [11,19,22].

In patients with paraplegia, stepping may be an effective approach to direct and enhance plasticity however the major question is how [25]. Assisted walking can be defined as a direct-task plasticity specific training of motor function [25]. Hence, the improvement of functional ability of individuals with paraplegia can be translated into enhancement in neuroplasticity. The parameters of these indications are gait speed, intensity, and duration of gait training [25,27]. Literature data support that the improvement of intensity and gait speed are proved to be an indicator of increased plasticity [27].

Research conducted by Leech et al investigated that high-intensive treadmill training in patients with incomplete chronic SCI has an important influence on serum concentration of the brain-derived neurotrophic factor BDNF [28]. The authors demonstrated increased levels of peripheral sBDNF after acute intensive gait training of 11 individuals with SCI [28]. Except from sBDNF, the researchers proved that treadmill training can also affect IGF-1 serum concentration levels [28]. Although there was no correlation between speed and intensity and serum levels of IGF-1, treadmill training increased the levels of IGF-1 following exercise in general [28]. Taking into consideration that insulin-growth factor-1 (IGF-1) is involved in synaptic protein synthesis and interacts with BDNF [20,21], this means that neuroregeneration can be promoted also on a molec-

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ular level. Neurotrophic factor BDNF promotes adaptive plasticity which is required for the creation of functional neural connections in SCI [28].

From Tissue Regeneration to Functional Synapsis

The scientific issue of neurogenesis and neuroregeneration in neuroscience has not been completely solved [23,24]. Nowadays, there is limited research data on neural repair following SCI and the mechanisms underneath axon restoration and reconstruction [23]. Nevertheless, the function and efficiency of tissue regeneration mechanisms is still under investigation [5]. Anatomically, there are three broad routes to successfully achieving restitution of functional circuitry [6,18]. The one is the regeneration of damaged axons in long distance, the other is sprouting of lesioned neuron and get connected with the intact ones or alternatively sprouting of undamaged axons and properly joined with the cut neuron [6,18]. The three broad routes alone are inadequate for functional synapsis [18]. Hence, there are some presuppositions that contribute to functional restitution [6,76]. The damaged axons must appropriately guide to the right direction, maintain a long-distance axon growth, circumvent the glial scars, develop mechanisms of remyelination and finally form functional synapses with the intact neurons [18,77].

The remyelination of axons after SCI is an overly complex process [15]. Nevertheless, it is generally accepted that the trophic factor BDNF, Schwann cells and oligodendrocyte precursor cells are involved in remyelinating spared axons, thereby contributing to tissue regeneration [15,16,26]. The growth factor BDNF has been proved to promote adaptive spinal plasticity, thus it can be assumed that there is an interaction between the process of neuroplasticity of spinal neurons and myelin production [28,29].Furthermore, Schwann cells are well known as the myelinating cells of peripheral nervous system [29,30]. However, they can gain access to spinal axons and assist in forming myelin [30]. This means that peripheral nervous system can influence in a positive way the damaged spinal circuits as far as myelin regeneration is concerned [15]. Eventually, oligodendrocyte precursor cells (OPCs) which originate both from the subventricular zone (SVZ) and locally, migrate to the SCI lesion site to differentiate into myelin-producing oligodendrocytes [15,31,32].

Axon outgrowth can be sustained only if axonal debris of the damaged neurons can be surpassed. Microglia is the major innate immune cell class in the brain and spinal cord [33]. Using its phagocytosis function, microglia could participate in the maintenance of structural and functional homeostasis of the central nervous system, such as normal myelin turnover and activity-dependent synaptic plasticity [33]. This phagocytosis is significantly up-regulated after injury, as a part of the injury-associated inflammatory responses, to engulf damaged neuronal and axonal debris [33].

Proprioceptive Afferent Promote Neuroplasticity

Proprioceptive feedback incorporated signals from ankle extensors during stance and swing phases of walking [19,34,35]. To begin with, the leg extensor muscles provide load-related afferent information to the spinal cord [36,37]. The activation of these muscles is produced through loading of the sole of the foot during stance phase [37,38]. These activations occur a hip-joint related afferent input, which are appropriate for the initiation of the swing phase [38,39,40]. A study demonstrated that without loading the sole of the foot during the stance phase, no meaningful leg muscle activation occurs in people with complete paraplegia during supporting stepping [41].

Another principal factor that depends on afferent proprioception is the automatism of moving limbs [42]. Spinal automatism is provided during stepping, influencing the coordination of the limbs during locomotion [19,36,42]. In SCI, there is need for training, imitating the automatism and coordination of normal stepping [19,42]. Thus, a basic requirement to induce a locomotion pattern in the thoracolumbar spinal cord can be an assisting training, providing sufficient proprioceptive feedback [36].

Training effects in patients with SCI depend on some number of physiological prerequisites necessary to evoke a pattern of muscle activation like those individuals without SCI to promote adaptive neuroplasticity [19,43,44]. A fundamental factor that is required to trigger a locomotor EMG pattern in SCI patients is an afferent input from load receptors [39,45]. Proprioceptive inflow from leg extensor muscles and mechan-

oreceptors in the sole of the foot, provide load-related afferent information [19,41]. Hip joint-related afferent inputs also play a major role in the generation of a locomotor EMG pattern, in individuals with incomplete spinal cord injury [19,41].

The activation of load receptors and hip-joint related proprioceptive receptors (hip extension) lead to a physiological leg muscle activity pattern during stepping [38]. The research proved that proprioceptive input produced during assisted walking led to targeted leg muscle activation. Electromyographic activity (EMG) of patients with SCI showed great improvement and similarities to normal walking [34,40,46].

Locomotion Rehabilitation Influence Plasticity and Regeneration

It appears that, through gait training, the spinal cord acquires the ability to respond to the imposed patterns of sensory inputs [47,48]. The aim is to retrain the nervous system, stimulating a form of learning that regenerates the surviving circuits and promotes new neuronal connections [22,48]. Stepping, as a spinal learning process, can strengthen the efficacy of neural pathways [47].

Neural excitability within the spinal cord is regulated by motoneurons / interneurons [49]. Khan et al demonstrated that intensive walking training counterpoise the abnormal H-reflex, clonus and stretch reflex following SCI [41,49-52]. Furthermore, the increased impact of corticospinal inputs to interneurons [53] due to training strengthened the inhibitory control of spinal circuits [49]. Additional research demonstrated that gait-assisted training generated and modulated soleus H-reflex [54,66]. Consequently, gait training strengthens spinal descending control and promotes adaptive plasticity [50,51,52].

Cortical and spinal excitability must be increased to activate pyramidal axons and interneurons including spinal intrinsic networks [65,67]. Thomas et al., examine the impact of intensive treadmill training on human spared corticospinal pathways directly [68] and not only based on walking function parameters [11,13]. The authors evaluated patients with chronic SCI and demonstrated that corticospinal tract function was enhanced after intensive daily treadmill training for several months [68]. The researchers used the system of TMS-evoked MEPs to measure corticospinal excitability, which was quite increased after training. Moreover, the patients were examined again after 2,5 years, and the results were maintained [68]. Therefore, the results of motor evoked potentials (MEP) might be an indication of nerve sprouting on spinal level [57,64].

Spared corticospinal tract (CST)[65] and proprioceptive afferent (PA) axons are both able to sprout after injury and contribute to rewiring spinal circuits, affecting motor recovery [70]. Proprioceptive afferents and descending motor pathways, including the CST, are the two major classes of extrinsic inputs to spinal segmental motor circuits [70,71]. They closely interact with each other during postural control, locomotion, and voluntary movements [70-72]. Both ipsilateral CST and PA axons are very sparse in lamina V to VII of spinal cord and there is minimal overlap between them [70-72]. Taking this fact for granted, it can be a parallel sprouting of proprioceptive afferents and CST axons [27].

Robot- assisted gait training in Paraplegia

Robot-assisted gait training (RAGT) is separated into two categories: the grounded exoskeleton robots (Locomat) [22,34,55] and the wearable exoskeleton robots [76] such as ReWalk [56], Ekso, REX, Indego, and HAL [13,57]. FDA or CE officially approves all [22]. The major difference of these two robot systems is that Locomat is a stationary walking system including a grounded exoskeleton based on a treadmill, whereas the wearable exoskeleton utilizes various environments for gait training [22]. The main purpose of the two exoskeleton robots is to support SCI patients' bodyweight to re-educate walking [58]. Studies proved that RAGT improve neuromuscular relearning in patients with SCI [55,59,60].

Important research with 11 incomplete patients with paraplegia provided supportive evidence for the clinical potential of gait–assisted training with an exoskeleton. Particularly, all participants were trained with the assistance of BWSTT with HAL exoskeleton for 12 weeks [57]. The authors reported that plastic changes appeared in sensorimotor cortical region (S1) after training and long ago after it [57]. Nevertheless, more research is required in this field.

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A case study with four patients with tetraplegia evaluated brain plasticity after training with body weight-supported treadmill (BWSTT) and Locomat orthosis [69]. Evidence of great significance was found by the investigators, who demonstrated supraspinal plasticity after 12-week training [69]. The assessment was made with fMRI imaging, proving an increased activation of sensorimotor cortical region (S1,S2) [12,69]. Furthermore, for the participants who achieved functional improvement in over-ground locomotion, the fMRI depicted an enhanced activation of cerebellum [69]. Therefore, it can be assumed that these results may be a consequence of axonal regeneration on spinal level. Consequently, further research should be performed to investigate whether spinal tissue regeneration can be associated with previous results.

Limitations

One limitation of this study is that there was limited exclusive data available on paraplegic patients, since most of research papers also include quadriplegics due to the difficulty of finding subjects for research. Another restriction was the diversity of evaluating techniques used in the studies. For instance, some researchers use fMRI depiction and others measure the concentration of molecules in serum levels.

Conclusion

This review is the first to refer to locomotion rehabilitation as a method to promote nerve tissue regeneration. There are many presuppositions for a successful sprouting and nerve connection. The overall approach of supraspinal, spinal and peripheral tracts can be the key to directed plasticity.

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