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REVIEW

Is body weight-support treadmill training effective in increasing muscle trophism after traumatic spinal cord injury? A systematic review

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Study design: Systematic review.
Objective: To determine the effectiveness of body weight-support treadmill training (BWSTT) for muscle atrophy management in people with spinal cord injury (SCI).
Setting: Studies from multiple countries were included.
Methods: The following databases were consulted from January to October 2013: PubMed, Institute for Scientific Information (ISI), Science Direct and Lilacs. The methodological quality of the articles included was classified according to Jovell and Navarro-Rubio.
Results: A total of five studies were included. These studies reported a significant association between BWSTT and increased trophism of the lower limb muscles of humans with SCI, which was observed as an increase in the cross-sectional area. Moreover, improvements in the ability to generate peak torque, contract the knee extensors and ankle plantarflexors with reduction of body weight support were observed after BWSTT.
Conclusion: The results were considered inconclusive because of the low methodological quality of the articles, which was because of the absence of sample homogeneity, thereby providing a low level of evidence for clinical practice.
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INTRODUCTION

Spinal cord injury (SCI) can be defined as trauma that occurs in any portion of the spinal cord and results in complete or incomplete impairment in motor, sensory and autonomic functions below the injury level.[1] The traumatic SCI primarily affects the population of young men aged 15–34 and has enormous social repercussions.[2,3] Furthermore, in most cases, the neurological deficit contributes to drastic physical activity reduction in individuals with SCI. The inactivity can lead to substantial changes in the body fat content, including the accumulation of intramuscular fat,[4] reduction of bone mineralization[4–6] and muscle atrophy.[7]

The muscle atrophy caused by disuse[8,9] is directly associated with 'morphofunctional' changes in the musculoskeletal system, such as a decrease in the muscle cross-sectional area (CSA)[8] and peak torque[10] and low fatigue resistance from the reduction of the fiber type I;[11] these changes are negatively associated with motor function in individuals with SCI. In addition, muscle atrophy can negatively affect the immune response and wound healing because the fragile muscle is less able to synthesize the proteins that are involved in the production of antibodies and enzymes.[12] It is also associated with decreased bone mineralization density[13–16] and adverse metabolic frames, including glucose intolerance and insulin resistance,[17,18] which are commonly observed in patients with SCI.

To restore/maintain muscle trophism below the injury level after SCI, some therapeutic approaches have been described in the literature, including functional electric stimulation to activate the neuromuscular system, which is usually associated with resistance training with an overload applied during static actions (isometric contraction),[19] cycling[20–23] and lifting ankle weight (isotonic contraction).[24–26] Over the last few decades, activity-based therapy using body weight-support treadmill training (BWSTT) has shown beneficial effects in the motor function recovery of SCI patients and has been widely used.[5,6,26–29]

BWSTT involves the practice of stepping on a motorized treadmill while the individual remains stabilized by a belt connected to a counterweight system that regulates the unloading percentage of body weight on the lower limbs during the stance phase of gait.[30,31] This repetitive locomotor training is associated with sensory stimuli, particularly those related to loading and stretching muscles, and contributes to the refinement of locomotor output after SCI.[32,33] Furthermore, BWSTT has shown beneficial effects on musculoskeletal system adaptation in rats with SCI.[34,35] Such changes have been positively correlated with locomotor activity improvement,[35] particularly for activities related to muscle trophism.

However, it is not clear whether BWSTT used as a therapeutic strategy in SCI rehabilitation is effective for restoring and/or maintaining muscle trophism. Therefore, the purpose of this systematic

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review was to determine the effectiveness of BWSTT for muscle atrophy management in people with SCI.

MATERIALS AND METHODS

Strategies of search

To select the studies, the following databases were consulted from January to October 2013: PubMed, ISI (Institute for Scientific Information), Science direct and Lilacs, using the following terms: '*spinal cord injury*' and '*muscle atrophy*' or '*muscle mass*' or '*muscular atrophy*' and '*locomotor training*' or '*treadmill training*'or '*step training*' or '*gait training*', which were always in combination with the following*: spinal cord injury, locomotor training and muscle atrophy*. In addition, updates in the database researches were performed on August 2014.

Three independent authors performed the search in the databases described above.

Study selection

Two independent authors performed the selection of the titles and abstracts of scientific articles in the literature to determine whether the inclusion and exclusion criteria were met. The selected studies were compared, and differences were resolved by discussion until the investigators reached consensus.

Eligible studies

The inclusion/exclusion eligibility criteria are presented in Table 1.

Methodological quality assessment

The initial exploration of the literature showed that randomized clinical trials were scarce. Therefore, we also included nonrandomized clinical trial and case studies. To obtain insight into the methodological quality of the included trials, the studies were classified according to Jovell and Navarro-Rubio[36] by the type of study design (see Kloosterman *et al.*[37]).

We made sure that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed in all of the studies selected for this systematic review.

RESULTS

The initial search resulted in 420 titles. Four hundred and fifteen of these were excluded, leaving only five articles[5,6,10,27,28] that fulfilled the selection criteria, which were therefore included in the present review (Figure 1).

An overview of the characteristics of the reviewed articles is presented in Table 2.

Table 1 Eligibility criteria

Inclusion criteria	*Exclusion criteria*
Participants	
Eighteen-year-old	Other associated diseases
Clinical diagnosis of SCI, either chronic or acute, of traumatic origin	
Injury level: paraplegia or tetraplegia	
Severity level: complete or incomplete	
In any stage of locomotor recovery	
Titles	
Full articles in scientific journals	Reviews
Published in English	Animal studies
Those who included an analysis of morphological changes of the musculoskeletal system after BWSTT	Articles that lacked a group that had undergone BWSTT therapy alone

Abbreviation: BWSTT, body weight-support treadmill training; SCI, spinal cord injury.

Methodological quality judgment

Three[5,10,27] of the selected studies received a methodological score of IX, indicating a poor strength of evidence for a case report and case series. The remaining two studies by Giangregorio *et al.*[6] and De Abreu *et al.*[28] received scores of VI and III, respectively, indicating fair and good to fair levels of evidence according to Jovell and Navarro-Rubio.[36,37]

Patients

We found one case report,[27] two case series[5,10] and two nonrandomized clinical trials.[6,28] The samples ranged from 1 to 15 individuals with SCI and an average age of 33 years; most of the individuals were male. The neurologic level ranged from C3 to T12, and there was a predominance of cases of motor-incomplete tetraplegia. Only one case series[10] and one nonrandomized clinical trial[6] included subjects with paraplegia. Regarding the time of injury, only two studies[5,10] included individuals with acute SCI (injury time of less than a year). The remaining studies had samples of individuals with chronic SCI and a maximum injury time of 24 years.[6]

Characteristics of the intervention with BWSTT

As shown in Table 2, the period of intervention with BWSTT therapy ranged from 9 to 48 weeks, with a minimum session number of 45 and a maximum of 144, and a mode of 48 sessions was the predominant quantity number. The frequency of therapeutic approach ranged from two to five times a week, and there was a predominance of two sessions per week, lasting a minimum of 5 min (initial sessions) and a maximum of 30 min. In two studies,[5,28] the intervention period and the frequency of the therapeutic approach were exactly equal, at 24 weeks and twice a week, respectively.

In four of the five selected articles,[5,6,10,27] the BWS and treadmill speed were mentioned as parameters modulating the intensity of the

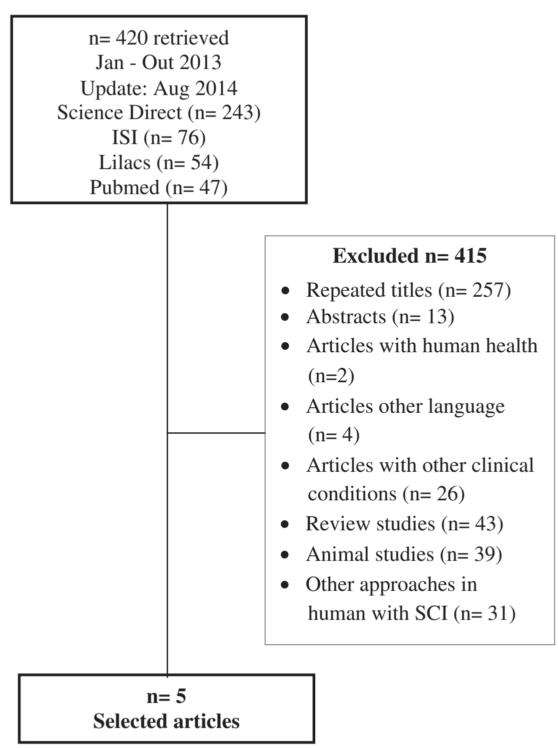

Figure 1 Diagram summarizing the selection process of the studies included in the systematic review.

Table 2 Characteristics of the included papers

Study			Participants						Study Details					
Author	Quality study[37]	n	Age	AIS	Level	TSI (months)	Design	Groups	Intervention				Outcomes	Significant results
									Period (weeks)	Frequency (days per week)	Speed/time training	%BWS***		
Giangregorio et al.[5]	IX—Poor	5	29.6 ± 8.7	B–C	C3–C8	< 2	LPCS	BWSTT therapy	24	2	Initial/end speed: 0.2 ± 0.05 $m s^{-1}$/0.4 ± 0.17 $m s^{-1}$ Initial time: 5 min End time: 10–15 min	Initial: Minimum 60% End: mean 42%	CSA CSA_{fat}	↑ ↑
Giangregorio et al.[6]	VI—Fair	9	28.8 ± 8.1	B–C	C4–T12	< 24	CC	BWSTT therapy	48	3	Initial/end speed: 0.2 $m s^{-1}$/ increased at each level of BWS. Initial time: 5 a 15 min End time: ~40 min	Initial: 60% End: ~30%	CSA	↑
		3	38.0 ± 4.1	B–D				No intervention	—	—	—	—	CSA	↓
Jayaraman et al.[10]	IX—Poor	5	41.4 ± 13.9	C–D	C4–T4	< 8	LPCS	BWSTT therapy	9–11	5	Initial/end speed: 0.7 ± 0.33 $m s^{-1}$/ 1.1 ± 0.13 $m s^{-1}$ Time: 30 min	Initial: 40% End: mean 10%	CSA MVC MVA	↑ ↑ ↑
Adams et al.[27]	IX—Poor	1	27	B	C4	< 12	CS	BWSTT therapy	16	3	Adaptation: 0.14 $m s^{-1}$ Initial/end speed: 0.3 $m s^{-1}$/0.7 $m s^{-1}$ Initial time: 15 min End time: not mentioned	Initial: 59% End: 59%	CSA	↑
Carvalho et al.[28]	III—Good to fair	8	32.3 ± 3.5	A	C4–C7	< 24	nRCT	BWSTT therapy +NMES	24	2	Initial speed: 0.03 $m s^{-1}$ End speed: 0.09 m/s Time: 20 min	30–50%	CSA	↑
		7	32.8 ± 3.5		C5–C7			Traditional therapy[a]	24	2	—	—	CSA	=
		7[b]						BWSTT therapy without NMES	24	2	Initial/end speed: 0.03 m s^{-1}/ 0.09 $m s^{-1}$ Time: 20 min	30–50%	CSA	=

Abbreviations: AIS, ASIA impairment scale; BWS, body weight support; BWSTT, body weight-support treadmill training; CC, case–control; CS, case study; CSA, muscle cross-sectional area; CSA_{fat}, fat cross-sectional area; LPCS, longitudinal prospective cases series; MVA, muscle voluntary activation; MVC, muscle voluntary contraction (included the peak isometric torque); NMES, neuromuscular electrical stimulation; nRCT, not a randomized clinical trial; TSI, time since injury; =, no significant change; ↑, significant increase; ↓, significant decrease.

[a]Traditional therapy: passive movements of the hips, knees and ankles and strengthening of every muscle group involved in the movements. Elbow and wrist movements were performed depending on the extent of the injuries. Adoption of the orthostatic position.

[b]After 24 weeks, the traditional therapy group performed an additional 6 months of BWSTT without NMES.

training, meaning that, during the training period, the BWS decreased while the speed increased. Therefore, the initial BWS ranged from 30 to 60%, according to the severity of the injury; it was higher for individuals with complete SCI and lower at the end of the sessions, reaching a minimum support of 10% in the study by Jayaraman *et al.*[10] It is important to clarify that the aim of the initial BWS was the proper positioning of the participant on the treadmill, prioritizing an upright trunk, knee in extension and heel strike with the ground during the stance phase of gait.

The treadmill speed, another parameter of training intensity, was initially established at an average of $0.3\,m\,s^{-1}$. For two studies,[5,6] the reduction of the BWS resulted in increased speed; however in one article,[6] the final speed was omitted. The average of the final evaluated speed was $0.6\,m\,s^{-1}$.

All protocols of BWSTT included at least two therapists to assist with the positioning of the lower limbs and to facilitate trunk control in individuals with SCI during gait training. Only one study[27] guided the participants to swing their arms and/or use parallel support for balance only. In addition, a single study employed overground training immediately following step training on the treadmill.[10] Overground training incorporated the use of assistive devices; however, the participants were bearing full weight on their lower extremities.

Outcome measures

Muscle changes

Morphological changes related to muscle trophism. For a morphological analysis of muscle trophism, were measured the CSA of muscle fibers obtained after biopsy[27] and of the great muscle groups[5,6,10,28] using imaging, such as computed tomography and magnetic resonance imaging.

In acute incomplete SCI, the CSA of the thigh muscles and calf increased in 12 and 14% of the participants, respectively, compared with baseline.[5] This increase was more pronounced in the plantarflexors[5,10] after treadmill step training.

Furthermore, in chronic incomplete SCI, BWSTT was also effective for increasing the muscle trophism of the lower limbs (thigh and calf), and the values increased from 2.3 to 16.8%, compared with the reference group that did not receive locomotor training.[6] The analysis of the muscle biopsy showed that atrophic fibers of the vastus lateralis experienced an overall increase of 27.1% in CSA, which was primarily because of hypertrophy of fiber types IIa and IIx. In a more detailed observation of each muscle fiber, BWSTT reduced the CSA of type I fibers and increased the CSA of type IIa and IIx fibers. However, training significantly increased the distribution of type I fibers with a reduction in the percentage of both type IIa and IIx fibers. The expansion of the type I fiber distribution promoted an increase in the total area occupied by type I fibers, which is characterized by the sum of each muscle fiber.[27]

Contrary to what has already been stated in this paper, De Abreu *et al.*[28] reported that 6 months of BWSTT alone were not sufficient to cause any significant change in the CSA of the quadriceps muscle ($41.81 \pm 8.45\,cm^2$ before versus $41.75 \pm 7.87\,cm^2$ after BWSTT). However, the authors noted that further studies with larger samples are needed to achieve more reliable conclusions. In their study, muscle trophism was only observed when BWSTT was combined with NMES, where the quadriceps CSA increased from 49.81 ± 9.36 to $57.33 \pm 10.32\,cm^2$.[28]

Changes in the peak isometric force, voluntary activation and contraction related to muscle function. Jayaramam *et al*[10] in addition to investigating the muscle morphological changes, examined the implication of BWSTT on muscle function. The findings of this study showed that all subjects demonstrated improvement in their ability to generate peak torque and contract the knee extensors and ankle plantarflexors after BWSTT, whereas in plantarflexors the torque production was more robust and accompanied by increases in the CSA of these muscles.[10]

DISCUSSION

To the best of our knowledge, this is the first systematic review to examine the efficacy of BWSTT in morphological changes, particularly those related to muscle trophism in individuals with acute and chronic SCI. Overall, the evidence concerning the effects of BWSTT of increasing the muscle trophism in individuals with traumatic SCI was characterized as low quality, according to the scientific rigor in the design of selected studies: only one study[28] received a 'good' score according to the classification scheme developed by Jovell and Navarro-Rubio.[36] The failure of most studies is primarily associated with small sample sizes, absence of follow-up and problems related to internal validity (bias), such as a lack of study subjects who are blind to the intervention, researchers who are blind to the main outcomes of the intervention and randomization into intervention groups.

Although the extracted data suggested that BWSTT was able to provoke musculoskeletal system changes and improve the treadmill performance and walking ability of subjects with SCI in both the acute and chronic stages, these findings are not conclusive because of the low quality of the studies that were eligible for this review. In the muscular system, there were increases in the CSA of the thigh and calf muscles, particularly demonstrated by increasing the trophism of type IIa and IIx fibers and increasing the representation of type I fibers. Morphological changes were accompanied by improvement in muscle function, which was characterized by increases in the peak torque and voluntary muscle activation. In addition, there was improvement in treadmill performance, including increased gait speed, distance walking/session and reduced BWS levels provided during training; however, the improvement in the overground ambulatory capacity was limited to a few patients with incomplete SCI. For the skeletal system, BWSTT was inefficient because it did not prevent the reduction in bone mass in the chronic and acute stages of SCI.

The relative contributions of BWSTT in the musculoskeletal dysfunction of humans with SCI emerged from animal models that had a close relationship between treadmill step training and increased muscle trophism.[34,35,38] BWSTT in rats with incomplete, acute SCI provoked significant increases in the CSA hind limb muscles immediately after the onset of training.[35] However, Liu *et al.*[38] showed that this training effectively recovers the soleus fiber size in the locomotor-trained group compared with the control group: reversion of muscle atrophy was observed following moderate contusion. In humans, the chronic state of SCI does not prevent the promotion of morphological changes in muscles with training, indicating that BWSTT can be a therapeutic tool for individuals who have a higher injury time.[6,10,27,28]

However, the level of neurological involvement interfered with the ability of the muscle to undergo plastic adaptations related to trophism. De Abreu *et al.*[28] observed that tetraplegic subjects with ASIA impairment scale (AIS) category A had an increase in the CSA of quadriceps of ~15% (49.81 ± 9.36 to $57.33 \pm 10.32\,cm^2$) only when BWSTT was associated with neuromuscular electrical stimulation (NMES). Dudley *et al.*[19] also assessed the trophic effects of NMES in individuals with complete motor SCI and observed that 8 weeks of encouraging the isometric or dynamic contraction of the quadriceps muscle was sufficient to increase the average CSA. Although it is already known that NMES is capable of increasing the muscle trophism, we cannot affirm that BWSTT depends on NMES to provoke hypertrophy in the muscles of patients with motor complete SCI. This finding is reinforced by the study by Forrest *et al.*,[39] who showed that BWSTT can modify the corporal composition, thereby increasing the lean mass in 4% in both legs, and that of Adams *et al.*,[27] who reported an increase of 27.1% in the CSA of the vastus lateralis in individual tetraplegic subjects with AIS B.

After analyzing the results, it also became clear that the number of BWSTT sessions necessary to cause changes in the CSA of the lower limb muscles is directly proportional to the severity of neurological injuries (see Table 2). While patients with tetraplegia AIS category C required 144 sessions to increase the CSA of the quadriceps by 4.9% and plantarflexors by 8.2%,[6] patients with tetraplegia AIS category D received only one-third of this number to increase these CSA values by 6.8% and 21.8%, respectively.[10] This suggests that the degree of preservation of motor and sensory functions significantly contributes to plastic changes related to the muscle trophism induced by BWSTT.

The muscle growth provoked by BWSTT in atrophic muscle may be mediated by the expanded intramuscular protein content[40] and is possibly because of the activation/proliferation of the satellite cells required to increase muscle trophism in response to functional overload.[41] This functional progressive applied overload in both lower limbs during BWSTT is proportional to decreases in the BWS levels, as observed in three of the five studies included in this systematic review.[5,6,10] Because they had a greater ability to support their own body weight at the end of their sessions, patients with tetraplegic AIS category D averaged 90%,[10] followed by individuals with AIS C at 70% [6] and those with AIS B at 58%.[5]

Increasing muscle trophism and muscle strength can improve a patient's ability to support their weight and training time on the treadmill[42] and they are necessary to restore the locomotor function of individuals with SCI.[43] In this context, Wirtz *et al.*[44] stated that individuals with tetraplegia need to reach a functional level of muscle contraction in their lower limbs to allow for locomotor function. Although it is not the main objective of this review, it is noteworthy to observe that none of the selected studies were able to establish a positive, significant correlation between the functional improvement of overground walking and muscle changes related to muscle trophism.

CONCLUSION

Although all of the studies selected for inclusion in this systematic review reported increased muscular trophism, measured by the CSA of the lower limb muscles of humans with SCI in acute and chronic stages after BWSTT, we suggest that these results are inconclusive. This is because of the lower methodological quality of the articles, which is associated with the absence of sample homogeneity, thereby providing a low level of evidence for clinical practice. Furthermore, additional studies, particularly randomized clinical trials, need to be performed to clarify the effectiveness of BWSTT in morphological changes related to muscle trophism in individuals with SCI.

DATA ARCHIVING

There were no data to deposit.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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