REVIEW

Does early exercise attenuate muscle atrophy or bone loss after spinal cord injury?

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Objectives: To systematically identify and assess the evidence on the efficacy of exercise initiated early after traumatic spinal cord injury (SCI).

Methods: A comprehensive search (Any-2014) of eleven databases identified studies evaluating exercise interventions initiated within 12 weeks after SCI on muscle and bone loss in paralyzed limbs and comparing with standard care or immobilization. Two reviewers assessed methodological quality. One reviewer extracted data and critiqued results according to the Spinal Cord Injury Rehabilitation Evidence body of evidence framework.

Results: A total of 2811 titles were screened. Eleven studies were included: five randomized controlled trials, four cohort studies and two within-subject control studies. All provided level II evidence with a moderate risk of bias. Two studies found significant positive effects of high-load FES-resisted stance on physiological measures of muscle. Three reported positive effects of 3 months of Functional Electrical Stimulation (FES) on muscle size. Two studies found positive effects of 6-month body-weight supported treadmill training or FES on trabecular bone using pQCT.

Conclusion: We found consistent evidence of positive effects of early exercise on muscle, possibly related to load intensity of the protocol. However, the heterogeneity of interventions and outcomes makes this determination speculative. Evidence for the effectiveness of early exercise on bone is scant and confined to measures of trabecular bone mineral density via pQCT. Transparent reporting of methods and variability of data, combined with standardization of valid and sensitive measures of muscle atrophy and bone loss, could facilitate future meta-analysis on this topic.

Spinal Cord (2016) **54**, 84–92; doi:10.1038/sc.2015.150; published online 8 September 2015

INTRODUCTION

Although evidence supports the positive health effects of exercise interventions in chronic spinal cord injury (SCI),^{1–3} studies using animal models suggest that initiating exercise during a critical early period may optimize clinical outcomes.⁴ The literature reports that substantial atrophy of sub-lesional skeletal muscle takes place within the first 6–12 weeks post injury.^{5–7} Castro *et al.*⁷ reported that, at 6 weeks, thigh muscle cross-sectional area was on average 35% less than that of size- and age-matched controls in the hamstrings and 31% less in the quadriceps; at 11 weeks, the losses had increased to 41 and 38%, respectively. Sadowsky *et al.*⁸ found a 36% mean increase in quadriceps muscle mass, with a concomitant 44% decrease in inter- and intramuscular fat, as well as an average 20-point increase in combined American Spinal Injury Association Impairment Scale (AIS) motor and sensory scores in 25 people with chronic SCI (AIS A–C) following functional electrical stimulation (FES) cycling ergometry (CE). A variety of interventions have been investigated to improve the muscle and bone of paralyzed limbs, with the aim of reducing secondary conditions such as fragility fractures and endocrine-metabolic disease. Some of these methods include FES-rowing, body-weight supported treadmill training (BWSTT), passive CE and robot-assisted ambulation.³

However, the clinical use of exercise during the acute period after SCI varies widely. Concerns about potential triggering of autonomic dysreflexia,⁹ unregulated hyperthermia¹⁰ or other effects of neurogenic shock may deter health professionals from utilizing exercise interventions in the acute phase. Although current clinical guidelines advocate regular exercise for chronic SCI,¹¹ we are not aware of any recommendations regarding exercising early after SCI.

Promising therapies in rodent models have shown synergistic benefits of combining cellular or pharmacological therapies with physical exercise very early after injury.^{12,13} As rehabilitation frequency and duration has been acknowledged as a covariate for functional outcomes,¹⁴ we ought to be knowledgeable about the singular effects of potential adjunct exercise interventions, in order to accurately assess the relative benefits of experimental therapeutic agents in combination treatment protocols. Recent Phase I/IIa clinical studies involve administration of a therapy within 48 h and begin recording outcome measures as early as 1 week to 3 months.¹⁵

The aim of this study was to systematically review the evidence regarding the effects on bone and muscle tissue of exercise interventions involving paralyzed limbs in this early period after traumatic SCI.

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Received 17 February 2015; revised 27 July 2015; accepted 29 July 2015; published online 8 September 2015

Table 1 Eligibility criteria

Criterion	Inclusion	Exclusion
Participants	Traumatic SCI Adult > 18 years of age ASIA A, B or C	Non-traumatic SCI Animal studies ASIA D
Intervention	Exercise targeting paralyzed limbs initiated within 12 weeks after injury	Volitional exercise of non-paralyzed body (for example, arm ergometry, respiratory training) surgical, diagnostic, pharmaceutical
Comparison	Standard care or immobilization	Outcome measures later than 6 months post-baseline
Outcome measures	Pertaining to neuromuscular or musculoskeletal tissues or function, directly or indirectly (for example, power output)	Psychological Neurological Cardiovascular
Publication	Any-2014 Peer-reviewed journal Abstract available in English	Conference abstracts

Abbreviations: ASIA, American Spinal Injury Association; SCI, spinal cord injury.

MATERIALS AND METHODS

Eligibility criteria

The population intervention comparison outcome method was used to develop eligibility criteria for studies to include in the review. The population was confined to adult humans (age 18+) with acute traumatic SCI. We are aware of several potential interventions utilizing FES, passive ergometry or BWSTT, and new technologies are being developed rapidly. Therefore, the intervention criterion was purposefully broad and included any exercise intervention targeting the paralyzed limbs and initiated within 12 weeks post injury. Studies were sought, which compared early exercise intervention with standard care or immobilization, and reported outcomes measured within 6 months from baseline. The outcomes of interest were also exploratory; any valid measure reflecting muscle atrophy/hypertrophy or bone density/bone loss was eligible for inclusion.

The definition of 'acute' in reference to SCI is evolving.¹⁶ A recent review of exercise interventions defined 'acute SCI' as <12 months post injury, because after this point recovery of function has in large part plateaued.³ Although our choice of 12 weeks to define 'early' is somewhat arbitrary, evidence gleaned from this time frame would be relevant to translational studies of new therapeutics and also based on evidence that, although bone loss occurs immediately and gradually during the first 2 years post injury, thigh muscle atrophy occurs rapidly during the first 11 weeks and continues to decline up to 24 weeks.¹⁷ The National Spinal Cord Injury Statistical Center reports that the median length of stay in the USA over the past four decades for complete tetraplegics is 25 days in acute care followed by 97 days in rehabilitation. For those with incomplete injuries the figures are 14 days in acute and 41–58 days in rehabilitation, depending on level of the lesion. Although length of stay has been decreasing over time, 12 weeks can arguably be considered early for studies conducted in the 1980s when the median rehabilitation stay was 120 days for complete tetraplegics.¹⁸

As we were interested in the effects of exercise on paralyzed limbs, we excluded studies with ASIA D participants. In that patient population, at least 50% of the muscles below the lesion have anti-gravity strength or better. The standard care exercise and activity levels of these individuals could be a significant confounder to the exercise interventions in question. All inclusion and exclusion criteria are presented in Table 1.

Information resources

A comprehensive search (Any- 2014) of eleven databases (Academic Search Complete, CINAHL, Cochrane, DOAJ, MEDLINE (OVID interface), Pedro, PhysEdIndex, PubMed, SCOPUS, Sports & Rehab and SPORTSDiscus), a manual search of relevant clinical trial registers and the references of key papers and previous reviews and a free-text search of Google Scholar identified 2811 titles for screening.

Scope

As pioneering studies, describing the use of FES after SCI, were published as early as 1965, we chose not to limit this search by date of publication. All English-language abstracts were screened, and articles written in languages other than English were not automatically excluded.

Search strategy

Development of the final search strategy was a highly iterative process. An initial search combining the terms 'acute spinal cord injury' and 'exercise' only retrieved three records. Eliminating 'acute' and combining 'spinal cord injury' and 'exercise' generated over 800 citations but failed to identify key articles known to the authors. The final search strategy employed an algorithm for each term, which was fine-tuned for each database, maximizing the use of available filters and qualifiers in order to minimize irrelevant records while still maintaining a broad and therefore comprehensive search (Appendix 1).

Selection process

The primary author eliminated duplicate records, studies without English-language abstracts and irrelevant studies by title. Two reviewers (MGP and MPG) independently evaluated the remaining abstracts for inclusion. Consultation with a third author (DE) provided resolution where the two reviewers were not in agreement. The selection process is illustrated in Figure 1.

Appraisal of evidence

The methodological quality of each paper was assessed using one of the two tools, according to the study design. Randomized controlled trials (RCTs) were appraised using the Physiotherapy Evidence Database (PEDro) tool.¹⁹ A systematic review on the assessment of non-randomized intervention studies identified the Downs and Black checklist as a robust tool for appraisal of non-randomized intervention studies.^{20,21} This scale has been customized for use in similar reviews.^{3,22} The criteria used in this review are included in Appendix 2. The primary author used a standardized data collection form to assess the risk of bias for each study. Uncertainties were resolved through discussion with the other two reviewers.

The primary author performed data extraction. Results are reported as mean difference between groups (percentage change from baseline) and 95% confidence interval, where data were reported or able to be calculated. Confidence intervals were calculated using a confidence interval calculator available for download free from the PEDro website; <http://www.pedro.org.au>.²³ Cohen's *d* was calculated using a web-based effect size calculator.²⁴ The level of evidence was determined according to the Spinal Cord Injury Rehabilitation Evidence (SCIRE) method.²²

RESULTS

Study selection

Out of 2811 titles screened, 420 English-language abstracts were assessed, yielding 144 papers that required review via full-text. The majority of the exclusions thereafter occurred because the intervention

Figure 1 Flow chart of selection process.

was initiated after 12 weeks post injury as indicated by a detailed review of each paper ($n = 84$). Five studies met the early intervention and outcome criteria, but two of them had no control group,^{25,26} one did not provide outcome measures prior to 1 year,²⁷ one involved only participants with AIS C and D combined,²⁸ and one study was reported via conference abstract only, and did not include point estimates or raw data for each group.²⁹ Figure 1 illustrates the selection process. Eleven papers met all inclusion criteria.

Study characteristics

Study design, methodological quality scores and participant and intervention characteristics for each study are presented in Table 3. Our review included five RCTs,^{30–34} four cohort studies^{35–37} and two within-subject control studies.^{38,39} All studies provided Level II evidence according to the SCIRE framework. All of the RCTs had a moderate-to-high risk of bias, with PEDro scores ranging from 3 to 5 out of 9. None of the RCTs utilized concealed allocation or intent-to-treat analysis, nor did they blind subjects or therapists. Two used blinded assessors and achieved baseline comparability.^{30,34} All of them provided point estimates and variability, but the two smaller studies did not provide group estimates.^{32,34} Six prospective studies had an average Downs and Black score of 16.8 out of 27. Risk of bias was highest for external validity (28%), selection bias (50%), reporting of adverse events (0 studies) and providing actual *P*-values (2 studies). Higher scores indicated lower risk of bias in the reporting (71%) and internal validity categories (81%). The scores for each study can be found in the first column of Tables 2–4.

Interventions

Four studies examined FES-CE.^{31,33,36,37} All FES-CE protocols were performed for 30 min, 3 times per week. These studies used similar stimulation protocols but employed varying intensities, ranging from a mean power output of 2.2 W³¹ to 24.5 W³³ after 12–13-week training. Two studies continued the intervention duration to achieve a mean power output of 12.7 ± 6.3 W after 4–9 months³⁶ and a range of 11–35 W after 6 months.³¹ One study did not report power intensity.³⁷ We categorized these interventions as having low-to-moderate load, because although 24.5 W is considerably more load than 2.2 W, it is less than exercise intensity prescribed for a patient with congestive heart failure.⁴⁰

One study⁴¹ examined the effects of BWSTT. Subjects exercised 3 times per week for 3–6 months. Because the body-weight support ranged from 20 to 80%, this protocol was considered low load.

Table 2 Levels of evidence as used by SCIRE

Level	Research design	Description
Level 1	RCT	RCT, PEDro score ≥ 6 . Includes within subjects comparison with randomized conditions and cross-over designs
Level 2	RCT	RCT, PEDro score < 6 .
	Prospective controlled trial	Prospective controlled trial (not randomized)
	Cohort	Prospective longitudinal study using at least two similar groups with one exposed to a particular condition.
Level 3	Case control	A retrospective study comparing conditions, including historical controls
Level 4	Pre–post	A prospective trial with a baseline measure, intervention, and a post-test using a single group of subjects.
	Post-test	A prospective post-test with two or more groups—intervention, then post-test (no pre-test or baseline measurement) using a single group of subjects.
Level 5	Case series	A retrospective study usually collecting variables from a chart review.
	Observational	Study using cross-sectional analysis to interpret relations.
	Clinical consensus	Expert opinion without explicit critical appraisal, or based on physiology, biomechanics or ‘first principles’
	Case report	Pre–post or case series involving one subject

Abbreviation: RCT, randomized controlled trial.

Table 3 Characteristics of included studies

First author (Downs and Black or PEDro score)	Study design	Groups	n	ASIA percentage complete (A:B:C:D)	Neurological level (percentage cervical)	Time since injury (weeks)	Intervention (muscle groups)
Arija-Blazquez (<i>P</i> =5)	RCT	Intervention	5	100% (5:0:0:0)	0%	5.5 ± 1.1	FES (Quads)
		Control	3	100% (3:0:0:0)	0%	5.8 ± 1.7	Sham FES
Baldi (<i>P</i> =4)	RCT	Intervention (High)	9	100% (NR)	56%	9.2 ± 3.3	FES-CE (Quads, HS and Gluteals)
		Intervention (low)	8	100% (NR)	38%	8.3 ± 3.2	FES-IC (Quads, HS and Gluteals)
		Control	9	100% (NR)	11%	8.4 ± 3.5	SC
Clark (<i>D&B</i> =15)	Non-concurrent cohort	Intervention	23	100% (NR)	57%	3	FES (Quads and DF)
		Control	10	80% (NR)	20%	3	SC
Cramer (<i>P</i> =3; <i>D&B</i> =16)	RCT	Intervention	4	100% (NR)	0%	2–4	FES (Quads and HS)
		Control	2	100% (NR)	0%	2–4	SC
de Bruin (<i>D&B</i> =14)	Cohort	Intervention (high)	4	0% (0:0:3:1)	75%	2–4	BWSTT
		Intervention (low)	5	100% (4:1:0:0)	0%	1–3	SS
		Control: SCI	4	75% (1:2:1:0)	75%	NR	SS
Demchak (<i>P</i> =5)	RCT	Intervention	5	100% (4:1:0:0)	60%	4–6	FES-CE (Quads, HS and Gluteals)
		Control - SCI	5	100% (4:1:0:0)	40%	4–6	SC
		Control: uninjured	5	NA	NA	NA	NA
Dudley-Javoroski (<i>D&B</i> =19)	Within-subject control	Intervention (high)	7	100% (7:0:0:0)	14%	< 12 (<i>n</i> =2)	FES-RS (Quads)
		Opposite leg (low)	5	100% (4:1:0:0)	0%	< 12 (<i>n</i> =1)	SS
	Cohort	Control: SCI	16	100% (14:2:0:0)	6%		SC
		Control: uninjured	14	NA	NA	NA	NA
Eser (<i>D&B</i> =14)	Cohort	Intervention	19	100% (NR)	42%	2.6 ± .9	FES-CE (Quads, HS and Gluteals)
		control	19	100% (NR)	42%	4.5 ± 3.3	SS
Groah (<i>P</i> =4)	RCT	Intervention	16	100% (15:1:0:0)	56%	< 12	FES-AG (Quads)
		control	10	100% (8:2:0:0)	30%	< 12	SC
Lai (<i>D&B</i> =16)	Matched cohort	Intervention	12	100% (12:0:0:0)	42%	4–7	FES-CE (Quads and HS)
		Control	12	100% (12:0:0:0)	42%	4–7	SC
Shields (<i>D&B</i> =20)	Within-subject control	Intervention	7	100% (7:0:0:0)	29%	< 6	FES-RS (Soleus)
		Opposite leg					SS

Abbreviations: ASIA, American Spinal Injury Association; BWSST, body-weight supported treadmill training; CE, cycle ergometry; *D&B*, Downs and Black Score; DF, dorsiflexors; FES, Functional Electrical Stimulation; HS, hamstrings; NA, not available; NR, not reported; *P*, PEDro score; Quads, quadriceps; RCT, randomized controlled trial; RS, resisted stance; SC, standard care; SCI, spinal cord injury; SS, supported standing.

Two studies^{38,39} employed functional electrical stimulation in resisted stance (FES-RS) to provide loading to the muscles and bone of one lower limb, up to 1.5 × body weight, using the participant's untrained limb as the comparator. These studies were considered high-load interventions. FES was applied to the quadriceps in one study (15 min, 3–5 times per week),³⁸ whereas, the soleus muscle was targeted in the other (30 min, 4–5 times per week).³⁹ Both studies also examined the effects of passive standing in the untrained limbs of these participants for a within-subject control comparison.

Finally, four studies^{30–32,34,35} administered FES to lower limb muscles without resistance or load (FES-IC) and one employed FES to extend the knee, lifting the leg against gravity (FES-AG).³⁴ These we classified as low-load interventions. The majority of these studies stimulated the quadriceps muscles either alone or in combination with the hamstrings. In one study, the quadriceps were stimulated along with the ankle dorsiflexors.³⁵ Protocol frequency for FES-IC was consistent across these studies at 5 times per week. In the study by Clark *et al.*,²⁴ compliance with the protocol was weakest (61%). Although others ranged from 68 to 83% compliance, 6 of the studies did not report on compliance levels.

Adverse events

Out of 16 studies, including the 5 early intervention studies that were excluded due to lack of comparators, only nine studies reported monitoring for adverse events. All of these reported that no adverse

events were associated with early exercise. Where monitoring was not reported, authors were contacted for further information, resulting in an additional two studies confirming an absence of adverse events. The total combined number of participants who safely participated in exercise within 12 weeks post injury in these sixteen studies included 28 who performed FES-CE, 11 who performed BWSTT and 43 who underwent FES-IC. Given that this information is not reported for 5 studies, the risk of reporting bias should be noted. Likewise, one must always consider that publishing bias favors positive results.⁴²

Muscle function and body composition

Table 4 summarizes the results of the interventions for all muscle outcomes. Two studies found significant positive effects on physiological measures of muscle contractions with 6 months of high-load FES-resisted stance^{38,39} using a within-subject control design. Three studies^{30,31,33} found evidence of positive effects on muscle and body composition after 12–14 weeks of exercise intervention. Moderate intensity FES-CE³³ resulted in significant increases in muscle power after only 5 weeks. Muscle biopsy showed that this protocol was accompanied by significant increases in muscle fiber cross-sectional area (CSA) after 13 weeks, compared with controls. A low-intensity FES-CE protocol showed a significant increase in lean body mass after 6 months.³¹ Results from unloaded FES protocols were inconsistent. One study found unloaded FES performed an average of 4 h per week over 14 weeks, led to an increase in thigh muscle CSA, visualized by

Table 4 Summary of muscle outcomes in order of methodological quality

First author, year (Downs and Black or PEDro score)	Intervention (mus- cles)	Work load	Frequency per week × min	Duration (compliance)	Outcome mea- sure	Between-group tests	Estimated mean difference (confidence intervals)	Effect Size (Cohen's d)
Demchak, 2005 (<i>P</i> =5)	FES-CE (Quads, HS and Gluteals)	Mod (24.5 ± 3.2 W)	3 × 30	13 weeks (NR)	Muscle fiber CSA	↑ FES-CE (+63%) Control (−72%)	^	Very large (3.2) Non-normalized PIV CSA
					Muscle fiber type	#	^	^
Arija-Blazquez, 2014 (<i>P</i> =5)	FES-IC (Quads)	Unloaded	5 × 47	14 weeks (NR)	Average CSA of quads (MRI)	↑	24.8% (13–36.7%)	Very large (3.6)
					Max CSA of quads (MRI)	↑	30.6% (7.2–54%)	Large (2.2)
Baldi, 1998 (<i>P</i> =4)	FES-CE (Quads, HS and Gluteals)	Low (2.2 ± 1.1 W)	3 × 30	3 months (NR)	LBM: gluteal (DXA)	↑	◆	^
					LBM: LL (DXA)	↑	◆	^
				6 months (NR)	LBM: Gluteal (DXA)	↑	34.5% (31–38%)	Very large (9.3)
					LBM - LL (DXA)	↑+	30.7% (26–35.5%)	Very large (6.4)
	FES-IC	Unloaded	3 × 30	3 and 6 months (NR)	LBM: LL (DXA)	#	◆	^
Shields, 2006 (<i>D&B</i> =20)	FES-RS (Soleus)	High (150% BW)	5 × 30	6 months (83%)	Peak torque contractions #1–5	↑	34% ◆	^
					Fatigue index	↑	◆	^
					Torque rise time	↑	◆	^
Dudley-Javoroski, 2012 (<i>D&B</i> =19)	FES-RS (Quads)	High (150% BW)	3–5 × 15	6 months (68%)	Quads force	↑**	^	^
					Fatigue index	↑	^	^
Cramer, 2000 (<i>P</i> =3; <i>D&B</i> =16)	FES-IC (Quads and HS)	Unloaded	5 × 60	4 months	Muscle fiber CSA	#	^	^
					Muscle fiber type changes	#	^	^

Abbreviations: AG, against gravity; BMD, bone mineral density; BW, body weight; CSA, cross-sectional area; *D&B*, Downs and Black Score; DF, dorsiflexors; DXA, dual x-ray absorptiometry; FES, functional electrical stimulation; CE, cycle ergometry; HS, hamstrings; IC, isometric contractions; LBM, lean body mass; Mod, moderate; NR, not reported; *P*, PEDro score; pQCT, peripheral quantitative-computed tomography; Quads, quadriceps; RS, resisted stance. †significant benefit compared with controls, +significant difference compared with low-intensity exercise group (*P*<0.05); **significant difference between groups (*P*<0.01); # no significant difference; ^ unable to calculate; ◆ data in graphs only.

MRI, which was associated with healthier baseline blood glucose levels and improved carbohydrate metabolism.³⁰ However, two other studies found no significant differences in muscle outcomes after 4–9 months, although these studies were of poorer methodological quality.^{31,32}

Outcomes of bone measurements

Table 5 summarizes the results of the interventions for all bone outcomes. Eight studies examined the effects of early exercise on bone tissue. Five measured bone mineral density with dual x-ray absorptiometry (DXA) and found no significant differences. Two studies measured cortical bone changes at the mid-shaft of the tibia, via CT and pQCT, and found no effect. Two studies measured the effect of BWSTT⁴¹ or FES-RS³⁹ on trabecular bone of the tibia using pQCT, and both found a significant positive effect after 6 months of intervention.

DISCUSSION

The aim of this review was to identify and synthesize all information published to date regarding the efficacy of early exercise interventions targeting the paralyzed limbs, initiated within the first 12 weeks after traumatic SCI. An exhaustive search found 16 papers that met these

criteria; however, five were thereafter excluded for not meeting the criterion for reporting of comparison data.

Eleven out of those sixteen studies monitored adverse events and found none. This is consistent with reports from the SCI Locomotor Trial, a multisite RCT that found no increase in adverse events with BWSTT, initiated an average of 4.5 weeks post SCI (AIS B–D), compared with conventional physical therapy.⁴³ However, there remains considerable risk of reporting and publication bias on this important matter.

Overall, the body of evidence presented here would be considered level II evidence based on study design, according to the SCIRE methodology. However, there was a moderate risk of bias in all studies, primarily for selection bias and external validity. The methodological quality of the reviewed studies was fair, but the majority of the studies had only a small sample size, a common problem when studying this population.¹⁶ Ideally, a meta-analysis would be able to combine multiple small studies to build a more robust base of evidence. However, only half of the studies reported sufficient data to allow confidence intervals and effect sizes to be calculated. Furthermore, the variety of interventions, with varying intensities (0–24 W), durations (4 weeks–3 years) and outcome measures precluded a meta-analysis in this review.

Table 5 Summary of bone outcomes in order of methodological quality

First author, year (Downs and Black or PEDro score)	Intervention (muscles)	Work load	Protocol fre- quency per week x minutes	Duration (compliance)	Outcome measure	Between-group tests (comments)	Estimated mean difference (confi- dence intervals)	Effect size (Cohen's d)
Arija-Blazquez, 2014 (<i>P</i> =5)	FES-IC (Quads)	Unloaded	5×47	14 weeks (NR)	Leg BMD (DXA)	#	0.4% (–12 to 11%)	Trivial (0.06)
Groah, 2010 (<i>P</i> =4)	FES-AG (Quads)	Low (weight of lower leg)	5×60	6 weeks (NR)	Distal femur (DXA)	# FES-AG –4%, Control –3.5%	^	^
					Proximal tibia (DXA)	# FES-AG –0.9%, Control –4.6%	^	^
					Hip (DXA)	# FES-AG –1.85%, Control –12.5%	^	^
Shields, 2006 (<i>D&B</i> =20)	FES-RS (Soleus)	High (150% BW)	5×30	6 months (83%)	Trabecular bone tibia (pQCT)	↑	31% ◆	^
					Cortical bone tibia (pQCT)	#	^	^
Dudley-Javoroski, 2012 (<i>D&B</i> =19)	FES-RS (Quads)	High (150% BW)	3–5×15	6 months (68%)	Distal femur (DXA)	Rate of bone loss (slope of data) 3× lower than control	◆	^
					Proximal tibia (DXA)	Rate of bone loss 25.1% lower than control	◆	^
					Distal tibia (DXA)	Rate of bone loss 14.4% lower than control	◆	^
Eser, 2003 (<i>D&B</i> =17)	FES-CE (Quads, HS and Gluteals)	Mod (12.7±6.3 W)	3×30	4–9 months (73%)	Cortical bone tibia (CT) %Δ per month	#	32% (–0.8 to 0.15%)	Small (0.44)
Lai, 2010 (<i>D&B</i> =16)	FES-CE (Quads and HS)	NR	3×30	3 months (80.3%)	Distal femur (DXA)	Rate of loss after cessation of FES-CE was same for both groups at both locations	4.4% (3.8–5.1%)	Very large (5.7)
					Femoral neck (DXA)		0.6% (0.1–1.1%)	Large (1.1)
Clark, 2007 (<i>D&B</i> =15)	FES-AG (Quads and DF)	Low	10×15	3 months (61%)	Leg BMD (DXA)	#	–0.1% (–2.3 to 2.5%)	Trivial (.03)
		Low	10×15	6 months (61%)	Leg BMD (DXA)	#	–2.4% (–0.1 to –4.7%)	Large (–0.82) §
de Bruin, 1999 (<i>D&B</i> =14)	BWSTT	Low (40% BW)	3×30	6 months (NR)	Trabecular bone tibia (pQCT)	↑	7.6% (5.9–9.3%)	Very large (9.6)
					Cortical bone tibia (pQCT)	#	0.75% (–0.4 to 1.9%)	Large (1.3)

Abbreviations: AG, against gravity; BMD, bone mineral density; BW, body weight; BWSTT, body-weight supported treadmill training; *D&B*, Downs and Black Score; DF, dorsiflexors; DXA, dual x-ray absorptiometry; FES, functional electrical stimulation; CE, cycle ergometry; CT, computed tomography; HS, hamstrings; IC, isometric contractions; Mod, moderate; NR, not reported; *P*, PEDro score; pQCT, peripheral quantitative-computed tomography; Quads, quadriceps; RS, resisted stance. †significant benefit compared with controls, +significant difference compared with low-intensity exercise group (*P*<0.05); **significant difference between groups (*P*<0.01); #no significant difference; ^unable to calculate; ◆data in graphs only; §opposite of expected.

The results from our review appear nonetheless to support literature, indicating that paralyzed muscle tissue can hypertrophy with FES within a 3-month time frame.⁴⁴ Some large effect sizes were reported in muscle outcomes at 3-month follow-up points. The magnitude of muscle hypertrophy may be related to either the amount of resistance and/or the length of intervention, but given the diversity of outcome measures such comparisons remain speculative. One included study showed that improvements in muscle tissue correlated with improved metabolic indicators.³⁰ This is consistent with studies of similar interventions in the chronic SCI population.^{8,45} Further research is warranted to determine the clinical relevance of gaining or maintaining muscle tissue in the early period post SCI.

In contrast to the results seen with muscle outcomes, there was minimal evidence in this review of any exercise attenuating bone loss. This may be expected, as bone loss in acute SCI occurs at a much slower rate of 3–4% per month in the first half year⁴⁶ when compared with the rate of muscle atrophy, which is as much as 40% in the first 11 weeks.⁷ There is an increased possibility of type II error in studies using DXA to measure changes in BMD, as pQCT measures of trabecular bone have been shown to be the most sensitive predictor of fractures in SCI.⁴⁷ In particular, two studies that used whole lower limb BMD (DXA)^{30,35} may have been unable to detect an effect because others have shown smaller effect sizes distal to the site of FES.^{34,37} Edwards *et al*⁴⁸ observed that a decline of 2% in BMD after acute SCI correlated to a 7% loss in CT-based finite element modeling

of femoral strength; thus, even a seemingly small change in DXA values could be clinically meaningful. A recent retrospective cross-sectional study determined that the use of FES was associated with a lower prevalence of osteoporosis in chronic SCI.⁴⁹

Limitations

Limitations of this review are in part due to the nature of the studies that were included. Small sample size, poor reporting and risk of bias were common. This review was purposefully broad in its scope; however, the resulting heterogeneity of interventions and outcomes precluded a synthesis of the evidence. Although every effort was made for quality control, one author undertook data extraction.

CONCLUSION

We found some consistent level II evidence of a positive effect of early exercise on muscle tissue within the first 3–6 months post SCI, possibly related to load and intensity of the exercise protocol. However, the heterogeneity of interventions and outcome measures used makes this determination speculative.

Evidence for the effectiveness of these interventions on bone is scant and confined to measures of trabecular bone mineral density via pQCT in two studies.^{39,41} This may be a type II error, resulting from insensitive measures. In particular, the use of DXA measures of BMD, which was common in these studies, has been shown to be inferior to pQCT measures of trabecular bone in the SCI population.⁴⁷

Further work is needed to identify valid and sensitive outcome measures of muscle atrophy and bone loss, which could be standardized for use in clinical trials in order to facilitate future meta-analysis, as has been done with other outcome domains with the Comprehensive International Classification of Functioning, Disability and Health (ICF) Core Set.⁵⁰ In order to make use of such measures, future studies must also maintain scientific rigor, utilize transparent reporting of methods and include confidence intervals and effect estimates. Only then can the data from small studies be utilized and built upon.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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APPENDIX 1

Search strategy

Construct	Database	Search terms	Qualifiers
Acute SCI	All	Spinal Cord Injuries OR Parapleg* OR tetrapleg* OR quadripleg* AND Humans AND Adult	AND NOT (TOPIC =chronic OR com- munity OR wheel- chair OR athlete) AND NOT (Topic = resp* OR pulm* OR bladder OR bowel OR urin* OR sexual OR ejacula*)
Exercise	All	Rehabilitation OR exercise OR activity OR electric* OR sti- mulat* OR FES OR resist* OR train* OR cycling OR rowing OR ergometry OR contin- uous passive motion OR continuous pas- sive movement OR gait	
Exercise	CINAHL SPORTS-DISCUS Sports & Rehab Academic Search Complete	Rehabilitation OR exercise OR activity OR electric*OR sti- mulat* OR resist*OR train*OR cycling OR rowing	Narrow by Subject- Major: Rehabilitation, Elec- tric stimulation, Elec- trical stimulation functional, Physical therapy, Therapeutic exercise, Gait train- ing, Physical Activity, Exercise, Rehabilita- tion patients
Musculo-skeletal Outcome		AND (therapy OR physiopathology OR	

	Medline PubMed DOAJ CINAHL SPORTS-DISCUS Sports & Rehab Academic Search Complete	physiology OR rehabilitation)	
Musculo-skeletal outcome			Narrow by Subject- Major: Outcome assessment, Treatment outcomes, Recovery, Exercise physiology, Muscle (skeletal), Spasticity, Instrument validation
Musculo-skeletal outcome	SCOPUS	Title, Abstract, Key- word: atrophy OR muscle OR muscular OR body composition OR fat-free mass OR bone OR osteop* OR strength OR power OR cross-sectional area	Limit to Subject Areas: MEDI OR HEAL OR NEUR OR NURS

APPENDIX 2

Modified Downs and Black tool

Reporting

1. Is the aim, hypothesis or objectives of the study clearly stated?
2. Are the outcomes to be measured clearly described?
3. Are the characteristics of the participants adequately reported?
4. Are the interventions of interest clearly described?
5. Is the distribution of principal confounders in each group of participants adequately reported?
6. Are the main findings of the study clearly reported?
7. Does the report indicate the extent of random variability in the data for the main outcomes?
8. Were adverse events monitored and adequately reported?
9. Are drop-outs and participants lost to follow-up reported and adequately described?
10. Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes, except where the probability value is less than 0.001?

External validity

11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?
12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?
13. Were the staff, places and facilities where the patients were treated, representative of the treatment the majority of patients receive?

Internal validity—bias

14. Were measurement protocols of the main outcome measures standardized and automated or performed by blind assessors?
15. If any of the results of the study were based on 'data dredging', was this made clear?

16. Were the follow-up measures taken across the same time period or, if not, were the analyses adjusted?
17. Were appropriate statistics employed?
18. Was compliance reliable (>85%)
19. Were the outcome measures reliable and valid?
23. Was the randomized intervention assignment concealed from both patients and health-care staff until recruitment was complete and irrevocable?
24. Were confounders stratified or adjusted for in the main analyses?
25. Were participant drop-outs or losses to follow-up taken into account in the analysis?

Internal validity—confounding (selection bias)

20. Were all participants recruited from the same population?
21. Were all participants recruited over the same period of time?
22. Were participants randomized to intervention groups?

Power

26. Did the study have sufficient power to detect a clinically important effect where the probability of a difference being due to chance is less than 5%?