

Review

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Effectiveness of FES-supported leg exercise for promotion of paralysed lower limb muscle and bone health—a systematic review

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Abstract: Leg exercises through standing, cycling and walking with/without FES may be used to preserve lower limb muscle and bone health in persons with physical disability due to SCI. This study sought to examine the effectiveness of leg exercises on bone mineral density and muscle cross-sectional area based on their clinical efficacy in persons with SCI. Several literature databases were searched for potential eligible studies from the earliest return date to January 2022. The primary outcome targeted was the change in muscle mass/volume and bone mineral density as measured by CT, MRI and similar devices. Relevant studies indicated that persons with SCI that undertook FES- and frame-supported leg exercise exhibited better improvement in muscle and bone health preservation in comparison to those who were confined to frame-assisted leg exercise only. However, this observation is only valid for exercise initiated early (i.e., within 3 months after injury) and for ≥ 30 min/day for $\geq$ thrice a week and for up to 24 months or as long as desired and/or tolerable. Consequently, apart from the positive psychological effects on the users, leg exercise may reduce fracture rate and its effectiveness may be improved if augmented with FES.

Keywords: functional electrical stimulation; leg exercise; lower limb muscle and bone; spinal cord injury.

Introduction

One major sequela of the inability to perform physical activities requiring lower limbs following spinal cord injury (SCI) is the compromise of muscle function integrity and bone health [1] apart from other degradations [2]. Muscle disuse due to inadequate physical exercise following SCI could lead to atrophy [3]. Atrophic muscles and lack of weight bearing in bones may lead to disuse osteoporosis [3] due to the inactivity and inability of bones to sustain an upright stance. This could readily predispose bones to fracture and increased mortality in persons with SCI [4]. Therefore, bone fractures in this population are associated with a decrease in functional mobility. This clinical condition can promote a dependent lifestyle and a rise in healthcare financing if effective management is sought [5, 6]. Consequently, interventions toward offsetting these clinical challenges are vital for the effective management of persons living with SCI.

Fortunately, the plasticity of neuromuscular systems [7] allows functional electrical stimulation (FES) and related technologies to be useful in preserving muscle and bone health through physical exercises such as those involving legs. Lack of mechanical inducements due to the inability to perform physical activity while bearing body weight in persons with motor paralysis is believed to be a key contributor to a significant decline in their bone mineral density (BMD) [8] and muscle health [9]. Therefore, an exercise intervention that promotes “mechanical loading of bone” and offsets their “calcium loss” [10] is a worthy physical exercise to investigate. Accordingly, healthy muscles and bones, that are fit to support physical activities through a good level of muscle size and strength, amongst other factors, are clinically important as they work together to sustain functional leg exercise such as upright stance. It has also been identified that the largest physiological loads on bone are due to muscle contractions [11]. This is one explanation for a positive linear relationship between bone mineral content (BMC) and muscle cross-sectional area (CSA) [11]. Additionally, a significant positive correlation has been

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reported between bone density and muscle strength/force [5, 12]. Consequently, healthy muscles appear to be a marker of healthy bones. This relationship is also similar for unhealthy muscles and bones secondary to SCI.

Literature evidence suggests that lower limbs are mostly affected by paralysis as SCI victims heavily rely on upper limbs to perform their activities of daily living (ADL) [13]. Although regular and controlled exercise has generally been shown to have certain health benefits [14], its clinical significance on muscle and bone health is debatable [15]. Although FES-supported exercises after SCI preserve muscle and bone health [16, 17], the extent of the accrued benefits associated with FES for leg exercise intervention is not well-known. To increase muscle size, which is a measure of muscle circumference, and strength, which is a measure of muscle force, in people with SCI via FES, a review on the dosage for FES-cycling has been previously reported [18] while another systematic review has shown that FES-cycling promoted lower limb muscle health [19]. Other studies have shown the relevance of intensive leg exercise tasks such as standing for increasing BMD [20–23], muscle mass/volume [9, 24], and/or reducing bone loss [23] in persons with SCI. However, the outcomes and conclusions of these studies are conflicting [25] as some other studies [26–28] have conversely reported a non-significant increase in BMD following a standing task. Also, Zamarioli and colleagues reported a partial preservation of bone strength following standing in complete SCI animals supported by FES- and/or standing frame [29]. These conflicting results make the application of FES technology for the promotion of musculoskeletal integrity speculative in humans with SCI. Panisset and colleagues [30, 31] have attempted to identify the exercise effects on bone and muscle health but their study only considered a limited number of leg exercise methods. Therefore, establishing the effectiveness of common leg exercises by FES or other means of leg exercise support for muscle and bone health preservation or promotion is required to ascertain the clinical relevance of this intervention for wider clinical deployment. As no such information exists in the literature, the present study aimed to comprehensively report the effectiveness of leg exercise in preserving bone and muscle health in persons with SCI.

Methods

Search strategy

Scopus, PubMed, and Google Scholar online literature databases were searched comprehensively for potentially eligible studies from the

earliest return date to January 2022. For wider context, retrieved studies' references and citations were searched on the Google Scholar database. Search phrases and terms used included "Spinal Cord Injury OR Paralysis OR Paraplegia OR Tetraplegia" AND "Functional Electrical Stimulation OR Neuromuscular Electrical Stimulation OR Electrical Muscle Stimulation OR FES OR NMES OR EMS" AND "Stance OR Standing OR Stand" OR "Weight Bearing" OR "Cycling OR Cycle Ergometry" OR "Exercise OR Leg Exercise" AND "Muscle Integrity" OR "Muscle Health" OR "Muscle Size" OR "Thigh Girth" OR "Thigh Circumference" AND "Bone Mineral Density" OR "Bone Density" AND "Bone Health" OR "Osteoporosis" OR "Bone Fracture" OR "Musculoskeletal Outcomes" OR "Musculoskeletal Responses".

Eligibility criteria: The studies included were relevant to the review purpose in relation to the primary outcomes of muscle and bone health preservation following a prominent FES—or FES- and frame—assisted leg exercise, including all forms of leg exercise where frames or parallel bars may be relevant such as standing and walking in persons with SCI. In this study, prominent leg exercise intervention meant well-defined modes of physical exercise targeted at preserving or promoting bone and/or muscle health. Also, promotion of muscle and bone health indicates improvements in body composition in terms of muscle size and bone mineral density, respectively. Studies that only focused on FES for leg intervention, without the specific objective of promoting bone and/or muscle health, were excluded. However, for studies that investigated several muscle outcomes in two or more independent groups of participants that underwent any of the prominent leg exercises, only muscle and bone health outcomes were reported in this review. Also, only changes in muscle mass/volume or thigh circumference/girth, BMD and relevant secondary outcomes reported in persons with SCI recruited in the included studies were presented. For RCTs and other studies with intervention and control groups, only information on the intervention group were reported. In studies where both the results of healthy individuals and those with SCI were presented, only the results of those with SCI were presented in this review. Conference abstracts where participants' demography, clear intervention(s) and outcomes/results could not be obtained were excluded.

Outcomes selection process

To reduce the risk of bias in included studies, two authors, MOI and NAH, independently extracted relevant information from the outcomes of the included studies regarding the focus of the present study. YKA and MOI further evaluated the validity of the extracted data before they were finally compiled. Data retained were mainly on the effectiveness of various leg exercises regarding muscle and bone health.

Results

Characteristics of included studies

Initially, three hundred and seventeen (317) studies were obtained following abstract screening of database while only seventy-eight (78) met the inclusion criteria. These seventy-eight (78) studies were analysed critically for the present

review (Figure 1). Specifically, twelve (12) studies assessed the standing effects on bone and muscle health, forty-nine (49) investigated the cycling, rowing and knee extension effects on bone and muscle health and seventeen (17) appraised the effects of walking on bone and muscle health in persons with SCI. Measured and reported outcome were based on the change in muscle mass/volume and bone mineral density as measured by Computed Tomography

(CT), Magnetic Resonance Imaging (MRI), Dual-Photon X-ray Absorptiometry (DPXA), Dual Energy X-ray Absorptiometry (DEXA), peripheral Quantitative Computed Tomography (pQCT). Subject heterogeneity and diverse experimental methodologies precluded a quantitative/meta-analytical comparison between included studies, and amongst exercise strategies considered. The included studies' characteristics are presented in Tables 1–3.

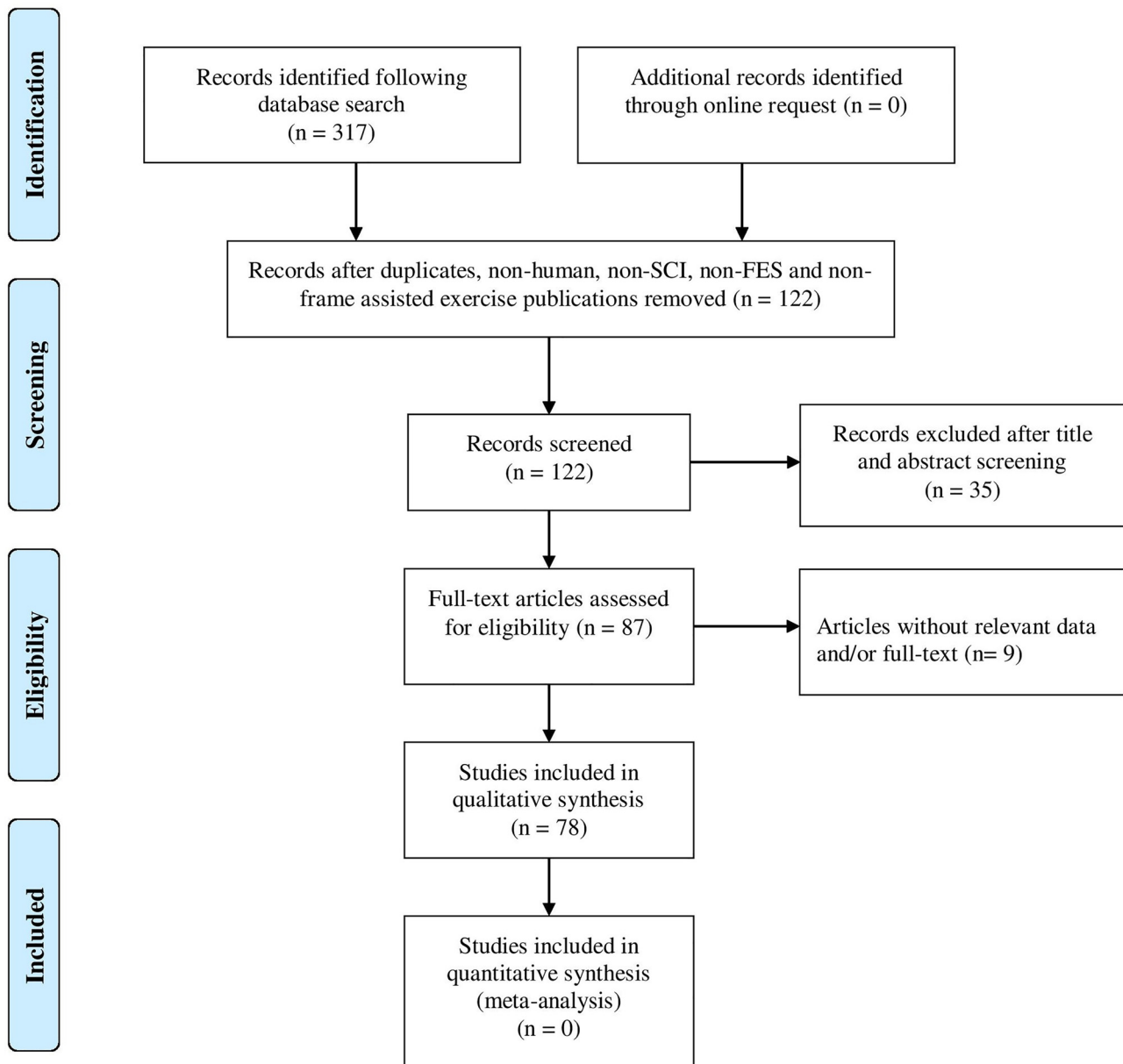


Figure 1: PRISMA flow chart for included and excluded studies in the systematic review. PRISMA was used because it is a standard objective reporting method for article screening process in systematic review studies.

Table 1: Characteristics of included studies on standing effects on muscle and bone health.

Study; Country	Population. <i>n</i> – [neurological level; Age and TSI in mean±SD or (median and range)]	Intervention: frequency and duration of exercise	Exercise aid; stimulation parameters	Muscle mass, volume/BMD. Measurement devices	Outcomes and results	Bone	Muscle
Kunkel et al. [32]; USA	6 – [ND, 4 with SCI; age: 45±6.8years. TSI: 19.3±7.9years]	Stood for an average of 144 h Over a mean of 135 days/6 months	Standing frame; NA	Lumbar spine and femoral neck BMD. DPXA	Only femoral neck BMD was significantly different ($p<0.001$) when compared to those of healthy individuals	✓	–
Taylor et al. [9]; UK	20 – [paraplegics, plus another 7 on FES; age: 28.3±10.7 years & 27.6±7.7 years on FES, TSI: 6.7±7.6 years & 2.1±1.1years on FES]	ND	FES and Oswestry standing frame/calipers; PW: 300 µs; Freq: 20 Hz; Amp/Volt: 150 mA max	Quadriceps muscle thickness. Linear array Ultrasound scanner	About 50% muscle lost in the first 3 weeks Of injury was nearly gained in 240 days of training ($p<0.001$)	–	✓
Goemaere et al. [23]; Belgium	53 – [C6-T12; age: Median: 34.6 range of 20–60 years; TSI: Median: 31.7 range of 12–118 months]	Standing ≤1 h/day, and for infrequent Standing=3 times/week. Duration: ND	Long leg braces, standing frame and wheelchair; NA	BMD of the femoral shaft, lumbar spine, and proximal femur. DPXA	For passive standing group: BMD was preserved in the lumbar spine, decreased (33%) in the proximal femur and by 25% in the femur shaft. For control: Standing SCI and non-standing SCI; only BMD of femur shaft improved ($p=0.009$) and that of lumbar spine marginally improved ($p=0.04$)	✓	–
de Bruin et al. [26]; Switzerland	19 – [C4-L1; Age: 33±10.9 years; TSI: 25 weeks]	Standing for ≥1 h/day for 5 days/week. Duration: ND	Standing frame; NA	BMD of tibia; trabecular and cortical bone. pQCT	No/insignificant ($p>0.05$) decrease in trabecular bone in the intervention group only	✓	–
Frey-Rindova et al. [27]; Switzerland	27 – [C4-L1; age: 33±11.4; TSI: ≥1 month for assessment]	≥3 times/week For 30 min. Duration: 6, 12 and 24 months	Standing frame with hip-suspension; NA	BMD of tibia after 6, 12 and 24 months post injury. pQCT	Insignificant ($p>0.05$) influence on BMD loss for persons with paraplegia in between 6 and 12 months was reported. Also, a significant ($p<0.05$) decrease in the tibia BMD. (trabecular) after 6 and 12 months while the decrease in tibia (cortical) was only after 12 months in all participants. However, in tetraplegic patients, radius ($p<0.01$) and ulna ($p<0.05$) trabecular BMD loss were reported	✓	–

Table 1: (continued)

Study; Country	Population. <i>n</i> – [neurological level; Age and TSI in mean±SD or (median and range)]	Intervention: frequency and duration of exercise	Exercise aid; stimulation parameters	Muscle mass, volume/BMD. Measurement devices	Outcomes and results	Bone	Muscle
Sabo et al. [33]; Germany	46 – [C4-T12 (33 complete and 13 incomplete injury); age: 32±10.7 years; TSI: 1–26 years]	4.1±2.3 weeks of wheelchair confinement or upright standing. Duration: ND	Wheelchair; NA	BMD of distal forearm, lumbar spine and proximal femur. DEXA	BMD was insignificantly affected by the ambulatory status. However, persons with complete lesions had significantly ($p<0.05$) lower BMD in the lumbar spine compared to those with incomplete lesions.	✓	–
Ben et al. [28]; Australia	20 – [ND, paraplegia: 8 and tetraplegia: 12; age: 34±15; TSI: 4±2 years]	Standing (with one leg) for 30 min, 3 times/week for 12 weeks	Tilt-table; NA	BMD of femur. DEXA	No effect on femur BMD	✗	–
Giangregorio et al. [16]; Canada	14 – [ND; age: 29; TSI: 7.7 (range of 1–24) years]	3 times/week for 144 sessions for 12 months	BWSTT; NA	Areal BMD of proximal and distal femur, proximal tibia, and spine, and CSA, volumetric bone density and bone geometry. DEXA and CT	After 12 months of exercise; significant increase in body lean mass ($p<0.003$), muscle CSA increase 4.9% for thigh and 8.2% for lower leg with insignificant BMD or bone geometry were reported. Whole body BMD decreased significantly ($p<0.006$)	✓	✓
Alekna et al. [20]; Lithuania	54 – [C2-L1; standing grp (27, age: 34.6±12.4; TSI: 11.3±3.19); non-standing grp (27; Age: 33.7±11.4 years, TSI: 11.2±3.2 weeks)]	Standing for ≥1 h & not ≤5 days/week. Duration: ≥2years.	Standing frame; NA	BMD of legs, pelvis and lumbar spine. DEXA	First year: the legs' BMD decrease in the standing group was lower than the non-standing group and after 2 years irrespective of the age, gender and level of injury, the leg and pelvis BMD was significant ($p=0.0004$) and ($p=0.014$) higher in the standing group, respectively.	✓	–
Goktepe et al. [21]; Turkey	71 – [Both para and tetraplegia; Age: 18–46 years; TSI: ≥1 year]	3 groups (1: Stood for 1 h Daily; 2: Stood for less than 1 h daily; and 3: No standing grp.). Duration: 4.2 years	Standing frame/ wheelchair or crunches and braces; NA	BMD of lumbar and proximal femoral regions. DEXA	BMD was marginally higher for the group that stood for ≥1 h Daily as compared to non-standing grp.	✓	–
Dudley-Javoroski et al. [22]; USA	28 – [T12-C5/6; age: 35.7±13.6 years; TSI: 4.5±7.0 years]	3 groups (high dose: meant to stand with 150% BW for 5 times/week. Low dose: meant to stand with 40% BW for 30 min in 5 days/week. No standing: 0% BW). Duration: 3 years	FES, standing frame/standing wheelchair; PW: 200 µs. Freq: 20 Hz. Amp/Volt: 200 mA max	BMD of the distal femur. pQCT and high-resolution CT	High dose group's BMD>both low dose and untrained group's BMD ($p<0.05$). Differences between BMD in low dose and untrained groups were insignificant ($p>0.05$)	✓	–

Table 1: (continued)

Study; Country	Population. <i>n</i> – [neurological level; Age and TSI in mean±SD or (median and range)]	Intervention: frequency and duration of exercise	Exercise aid; stimulation parameters	Muscle mass, volume/BMD. Measurement devices	Outcomes and results	Bone	Muscle
Dudley-Javoroski and Shields [34]; USA	24 – [12 with SCI (T12–C5/6; Age: 31.5±8.6 years; TSI: 0.7±0.6 year), and 12 without SCI/control (age: 29.1±7.8 years)]	Active-resisted stance or passive stance for ≤3years. Duration: ≤3years	FES, standing frame/standing wheelchair; PW: ND. Freq: ND. Amp/Volt: ND	BMD of femur. pQCT	For active-resisted stance limb: at >1.5 years, BMD declined over time; At >2 years, BMD was significantly higher (p=0.007)	✓	–

BW, body weight; BWSTT, body weight supported treadmill training; BMD, bone mineral densities; CT, computed tomography; CSA, cross-sectional area; DEXA, dual energy X-ray absorptiometry measures tbBMD, total body bone mineral density; DPXA, dual photon X-ray absorptiometry; MRI, magnetic resonance imaging; NA, not applicable; ND, not described; n, number of participants; pQCT, peripheral quantitative computed tomography— which could differentiate trabecular and cortical bone [34, 35]; TSI, time since injury. ✓: positive change, ✗: negative change, –: unreported.

Table 2: Characteristics of included studies on cycling, rowing and knee extension related effects on muscle and bone health.

Study; Country	Population. <i>n</i> – [neurological level; age and TSI in mean±SD or (median and range)]	Intervention: Frequency and duration of exercise	Exercise mode and aid; Stimulation parameters	Muscle mass, volume/BMD. Measurement devices	Outcomes and results	Bone	Muscle
Fournier et al. [36]; USA	5 – [T2–T12, age: 26.4±3.3. TSI: 3.2±2.1]	An incremental resistance exercise training of 15 min exercise max for 3 days/week For 12 weeks	FES-progressive resistance exercise; PW: ND. Freq: 50 Hz; Amp/Volt: ND	m.Quads. Thigh circumference measuring device	Increase in m. quads bulk was reported	–	✓
Petrofsky et al. [37]; USA	4 – [para- and quadriplegic, age: 21 years Mean. TSI: 4.5 (range: 1.5–7) years.]	3 days/week. For 30 min/day for 30 days @ 15 km/h speed	FES-CE; PW: 1,000 µs. Freq: 50 Hz; Amp/Volt: 0–100 V	Iliacus and m. Quads. Bone densitometer or CAT scanner	Increased muscle size was reported	–	✓
Pacy et al. [38]; UK	4 – [T4/5–T6; Age: Range 20–35years; TSI: 4±2.5years]	LE: 15 min & 5 times/week For 10 weeks LE by 60° against (1.4–11.4 Kg loads). 6 s each for activity and rest. CE: 15 min & 5 times/week For 32 weeks CE at 50 rev/min against (0–18.75 W) workload	FES-LE and -CE; For FES-LE. PW: 0.3 ms, Freq: 40 Hz, Amp/Volt: 65–90 V. For FES-CE. PW: 0.3 ms, Freq: 40 Hz, Amp/Volt: 80–125 V	m.Quads size and BMD of trabecular bone. CT and DPXA	Quads muscle area increased and fat area reduced (p<0.05) and no modification on BMD during exercise were reported	✓	✓
Block et al. [39]; USA	4 – [T4/5–T6; Age: 41±10.2 years; TSI: 11.3±9.1 years]	5 days/week. For 6 weeks	FES-CE; PW: 300 µs, Freq: 30–40 Hz, Amp/Volt: Adjusted to sustain 50 rev/min speed	Midthigh. Quantitative CT	Significant increase in muscle CSA (p=0.042) at distal site of midthigh; and (p=0.019) at a proximal site of the mid-thigh was reported	–	✓
Leeds et al. [40]; USA	6 – [ND, age: ND; TSI: ND]	3 days/week for 6 months	FES-CE; PW: ND, Freq: ND, Amp/Volt: ND	Femoral neck, ward triangle and trochanter BMD. DPXA	No modification on BMD due to CE training was reported	✓	–

Table 2: (continued)

Study; Country	Population. <i>n</i> – [neurological level; age and TSI in mean±SD or (median and range)]	Intervention: Frequency and duration of exercise	Exercise mode and aid; Stimulation parameters	Muscle mass, volume/BMD. Measurement devices	Outcomes and results	Bone	Muscle
Rodgers et al. [41]; USA	12 – [C5-T10, Age: 38.3±12.9 years. TSI: 6.4±6.1 years]	36 sessions of (incremental resistant load from 0 to 15 kg with 0.5 increments) KE exercise @ ≤3 times/week For 12 weeks. KE: 6 kE/min/leg	FES-KE; PW: ND, Freq: ND, Amp/Volt: ND	Trabecular bone density. CT	No decrement of BMD due to KE exercise suggestive of preservation of tibia bone integrity	✓	–
Bremner et al. [42]; Australia	6 – [T6-T12/L1, Age: 27.2±5.9 years. TSI: 13±4.6 years ^a]	20 min max/day, 3 times/week And for 12 weeks of cycling after 12 weeks of strengthening exercise	FES-CE; PW: 298 µs, Freq: 35 Hz, Amp/Volt: 81 mA	Midfemoral muscle CSA, muscle density and thigh circumference. Single energy CT	Total muscle area thigh circumference only increased in 3 participants and this was more evident in “severely weakened muscle”	–	✓
Hangartner et al. [43]; USA	37 (15 selected for FES training) – [C5-T10, age: 19–64 (median-32) years. TSI: 0.1–22.4 (median-4.3) years]	Training involving 3 FES session/week. 6 kE/min/leg for 36 exercise sessions/12 weeks	FES-KE and -CE; PW: 375 µs, Freq: 35 Hz, Amp/Volt: 130 mA max	Tibia bone density. CT	FES intervention promoted bone density (p<0.001)	✓	✓
Sloan et al. [44]; Australia	12 – [C5-T12, Age: 28±11 years. TSI: 3±3 years]	30 min/3 times/week, for 3 months’ period, initially, and continued as tolerable	FES-cycling; PW: 300 µs, Freq: 25 Hz, Amp/Volt: 90 mA max	Thigh muscle area and BMD. CT and DEXA	Quadriceps cross-sectional area (p<0.002) and total thigh muscle (p<0.002) significantly increased. BMD was only promoted in one acute SCI case	✓	✓
Bloomfield et al. [45]; USA	9 – [C5-T7, age: 28.2 years. TSI: 6 years]	12, 40 and 80 FES session within 9 month of cycling and 30 min (expected) per session	FES-CE; PW: 350 ms, Freq: 30 Hz, Amp/Volt: 130 mA max	Lumbar spine, femoral neck, distal femur, and proximal tibia BMD. X-ray absorptiometry	Significant (p<0.05) increase in BMD at the lumbar spine only	✓	–
BeDell et al. [46]; USA	12 – [SCI, Age: 34±6 years. TSI: 9.7±5.1 years]	30 min session for 25±9 weeks max	FES-cycling; PW: 400 µs, Freq: 30 Hz, Amp/Volt: 10–132 mA	BMD of the lumbar spine (L2-4), bilateral trochanters, Ward’s triangles and femoral necks. DEXA	No significant (p=0.056) increase in BMD but a positive trend in lumbar spine was reported	✓	–
Kagaya et al. [12]; Japan	5 – [T6-L2, Age: 38.8±21.2 years. TSI: 1.7±1.8 years]	At the start: 10 min thrice/day then later 10 min every 2 weeks After 10 weeks, it was increased to 60 min intensive training, 3 times daily, for up to 6 months	FES-LCE; PW: 200 µs, Freq: 20 Hz, Amp/Volt: –15 V	CSA of femur head. CT	Significant CSA increase of gluteus medius and para-spinal muscle (p<0.01), the iliopsoas (p<0.05) were reported.	–	✓
Hjeltnes et al. [47]; Norway and Sweden	5 – [C5-C7, age: 35±3 years. TSI: 10.2±3.4 years]	30 min of cycling @ 7 sessions/weeks for 8 weeks	FES-LCE; PW: 350 µs, Freq: 30 Hz, Amp/Volt: 130 mA max	CSA of quadriceps, hamstring and gluteus maximum, medius muscles and LBM. DEXA and CT	Significant (p<0.05) increase in CSA of the listed lower limb muscles, LBM and decrease in whole body fat were reported	–	✓

Table 2: (continued)

Study; Country	Population. <i>n</i> – [neurological level; age and TSI in mean±SD or (median and range)]	Intervention: Frequency and duration of exercise	Exercise mode and aid; Stimulation parameters	Muscle mass, volume/BMD. Measurement devices	Outcomes and results	Bone	Muscle
Mohr et al. [48]; Denmark	10 – [C6-T4, Age: 35.3±6.9 years. TSI: 12.9±6 years]	≤3 times/week (mean 2.3 times), 30 min/session for 12 months	FES-CE; PW: ND, Freq: 30 Hz, Amp/Volt: ND	Thigh circumference. MRI and CT	Significant increase ($p<0.05$) in muscle mass and 12% CSA of thigh were reported	–	✓
Mohr et al. [49]; Denmark	10 – [C6-Th4, Age: 35.3±2.3 years ^a . TSI: 15.5±2.7 years ^a]	30 min/day, for 3 days/week, for 12 months followed by once a week training for 6 months	FES-CE; PW: ND, Freq: ND, Amp/Volt: ND	Lumbar spine, femoral neck, and proximal tibia BMD. DEXA	No BMD increase ($p>0.05$) in the lumbar spine and femoral neck, but proximal tibia's BMD was partially reversed ($p<0.05$)	✓	–
Baldi et al. [50]; USA	For FES-isometric contractions (IC). 8– [C4-T10, age: 25.8± 4.7 years. TSI: 8.3±3.2 weeks]. For FES-CE. 9– [C5-T10, age: 28.2±6.6 years; TSI: 9.2±3.3 weeks]	FES-IC. 60 min, 5 times/week for 3 months/6 months. FES-CE. 30 min, thrice/week for 3 months/6 months	FES-IC and FES-CE; For FES-IC. PW: 500 µs, Freq: 35 Hz, Amp/Volt: 100 mA; For FES-CE PW: 375 µs, Freq: 60 Hz, Amp/Volt: 140 mA	LBM. DEXA	3 Months exercise prevented muscle atrophy and significant ($p<0.05$) reduction in regionalised LBM was reported	–	✓
Erika scremin et al. [51]; USA	13– [C5/6-T12/L1, age: 34±6.9 years. TSI: 10±5 years]	30min duration for 2.32±0.26 times/week for 52.8 weeks	FES-CE; PW: 300 µs, Freq: 30 Hz, Amp/Volt: ND	Thigh and leg muscle mass. CT	Thigh and leg muscle mass significantly increased ($p<0.001$), with improved “muscle to adipose tissue ratio” were reported	–	✓
Dudley et al. [52]; USA	3 – [ND, Age: ND, TSI: ND]	4 Sets of 10 isometric/dynamic muscle activities twice/week For 8 weeks	FES-isometric contractions @ 60° knee flexion with/without weight attached at the knee; PW: 450 µs, Freq: 30 Hz, Amp/Volt: ND	Quadriceps femoris. MRI	Significant increase ($p=0.0103$) in quadriceps muscle' CSA was reported	–	✓
Chilibeck et al. [53]; Canada	6 – [C5-T10, Age: 31–50 years. TSI: 3–25 years]	30 min thrice per week for 8 weeks	FES-CE. PW: 450 µs, Freq: 30 Hz, Amp/Volt: 10–130 mA	Vastus lateralis. Muscle biopsy examination	Significant increase ($p<0.05$) in muscle fibre was reported	–	✓
Cramer et al. [54]; Australia	6 – [T5-T11, Age: 35±9.2 years. TSI: 2–4 weeks]	1 h training/5 day/weeks for 16 weeks	FES-isokinetic leg extension/flexion; PW: 300 µs, Freq: 35 Hz, Amp/Volt: 70 V DC	Quadriceps and hamstring muscles. Digital image analysis program	Muscle fibre area and type preservation, and connective tissue infiltration's prevention were reported	–	✓
Bélanger et al. [55]; Canada	14 – [C5-T6, Age: 32.4± 5.9 years. TSI: 9.6±6.6 years]	60 min/day (or until fatigue criteria met), five times weekly, for 24 weeks. 93.4%±5.6%	FES-isometric contractions; PW: 300 µs, Freq: 25 Hz, Amp/Volt: 150 mA max	Distal femur, proximal tibia and mid-tibia BMD. !–Para Run-on→DEXA	Partial reversal of the distal femur, proximal. Tibia's bone loss (by approx. 30% recovered, $p<0.05$) and the quadriceps strength loss were reported	–	✓
Sköld et al. [56]; Sweden & USA	15 – [Motor complete SCI; Age: 33 (range 21–48) years. TSI: 9 (range 1–21) years]	30 min of exercise, 3 sessions/week for 6 months	FES-CE; PW: 350 µs, Freq: 30/60 Hz, Amp/Volt: 130 mA max	Leg muscle volume. DEXA	10% increase ($p<0.001$) of leg muscle volume was reported	–	✓

Table 2: (continued)

Study; Country	Population. <i>n</i> – [neurological level; age and TSI in mean±SD or (median and range)]	Intervention: Frequency and duration of exercise	Exercise mode and aid; Stimulation parameters	Muscle mass, volume/BMD. Measurement devices	Outcomes and results	Bone	Muscle
Eser et al. [57]; Switzerland	19 – [C5-T10, Age: 32.9±11.5 years for intervention grp. TSI: 4.5 weeks]	30 min of exercise/ 3 times/week for 6 months (mean)	FES-CE; PW: 300–400 µs, Freq: 30, 50 & 60 Hz, Amp/Volt: 140 mA max	BMD of tibia. CT	Marginal attenuation reduction in tibial cortical BMD was reported and this was linearly related to the initial BMD and age but unrelated to the degree of immobilisation and injury level	✓	–
Chen et al. [58]; Taiwan	15 – [C5-T8, Age: 28.7±3.8 years. TSI: 9.3±3.8 years]	30 min/day in 5 days/week, for 6 months	FES-CE; PW: 300 µs, Freq: 20 Hz, Amp/Volt: 120 mA max	BMD of distal femur & proximal tibia. DEXA	BMD of the distal femur and proximal tibia increased by 11.13±0.80%, and 12.92±2.24%, respectively (p<0.05)	✓	–
Demchak et al. [59]; USA	10 – [C5-T8, Age: 25.7±10.8 years, TSI: 4–6 weeks]	30 min/day, 3 days/week for 13 weeks. ND	FES-CE; PW: ND, Freq: ND, Amp/Volt: 140 mA max	Muscle fibre CSA. Computer software (Bioquant 95, R&B Biometrics, Inc.)	Prevention of muscle fibre CSA loss was reported. CSA increase of 171% (p=0.05) greater than that of the control group was reported	–	✓
Mahoney et al. [60]; USA	5 – [C5-T10, Age: 35.6±4.9 years. TSI: 13.4–6.5 years]	“2 days/week for 4 sets of 10 unilateral, dynamic knee extensions for 12 weeks”	FES-induced resistance training; PW: ND, Freq: ND, Amp/Volt: ND	Thighs (m. Quads) CSA. MRI	Significant increase (p <0.05) in muscle CSA was reported	–	✓
Shields et al. [61]; USA	6 – [C5-T10, Age: 27.7±7.6 years. TSI: 3.2±1 months]	4 Bouts (with 5 min rest in-between)/ approx. 1,680 contractions per week for about 2.5 years	FES-induced isometric plantar flexion; PW: 667 ms, Freq: 15 Hz, Amp/Volt: ND	BMD of spine, bilateral hips, and bilateral knees. DEXA	From the baseline, BMD's percent decline (~10%) for the trained tibia was significantly less (p<0.05) than the untrained tibia (~25%). Partial prevention of the BMD loss was reported	✓	–
Shields et al. [62]; USA	7 – [C5-T12, Age: 29.1±7.8 years. TSI: Within 6 weeks]	4 Bouts (with 5 min rest in-between) of 125 contractions/day X 5 day/week for ≥2 years	FES-induced isometric plantar flexion; PW: 667 ms, Freq: 15 Hz, Amp/Volt: 200 mA max at 400 V	BMD of distal tibia trabecular. pQCT	Distal tibia trabecular's BMD in trained limbs was 31% greater than in untrained limbs. The trained limb was 40 mg/cm ³ higher than untrained limb (p<0.05)	✓	–
Clark et al. [63]; Australia and USA	23 – [C4-T10, age: 28±9 years. TSI: 3 weeks]	Twice 15 min exercise/ limb/day, for 5 days/week, for 5 months	FES-induced isotonic, un-resisted contraction for inner range quadriceps and ankle dorsiflexion; PW: ND. Freq: 30 Hz; Amp/Volt: ND	Total body BMD, lower extremity region, and AP lumbar spine (L2–4), femoral neck and proximal femur. DEXA	Total body BMD only significantly different (p<0.001) at 3 months, and not subsequently, thus, no clinically relevant BMD loss remediation was reported	✓	–

Table 2: (continued)

Study; Country	Population. <i>n</i> – [neurological level; age and TSI in mean±SD or (median and range)]	Intervention: Frequency and duration of exercise	Exercise mode and aid; Stimulation parameters	Muscle mass, volume/BMD. Measurement devices	Outcomes and results	Bone	Muscle
Liu et al. [64]; Taiwan	18 – [C3-L1, age: 40±11.3 years. TSI: 3.2±2.1 years]	30 min of thrice/week for 8 weeks FES-CE	FES-CE; PW: 300 µs, Freq: 30 Hz, Amp/Volt: 10–132 mA	Thigh and calf girths. Flexible meter	Significant ($p \leq 0.05$) thigh girth and insignificant bone mass reported after 4 weeks of FES-cycling	✓	✓
Kakebeeke et al. [65]; Switzerland and UK	1 – [C6, age: 31 years. TSI: 3 years]	60 min for 5 times/week for 12 months	FES-CE; PW: 300 µs. Freq: 50 Hz; Amp/Volt: 140 mA max	BMD of distal femoral epiphysis. pQCT	BMD increased by 3.9% after the training	✓	–
Frotzler et al. [66]; Switzerland and UK	12 – [T3-T9, age: 41.9±7.5 years. TSI: 11±7.1 years]	Initially: 14±7 weeks of FES for muscle conditioning, followed by 58±5 min per session for average of 3.7±0.6; FES-cycling sessions/week, for 12 months. Average of 76.6–79.3%	FES-cycling; PW: 500 µs, Freq: 50 Hz. Amp/Volt: As tolerable	Trabecular and cortical parameters (BMD) of the femur and tibia, and their fat and muscle tissue parameters (CSA). pQCT	Significant increase ($p \leq 0.05$) in BMD of the bones and muscle CSA of the thigh ($p=0.003$) was reported	✓	✓
Frotzler et al. [67]; Switzerland and UK	5 – [T4-T7, age: 38.6±8.1 years. TSI: 11.4±7 years]	≤5 sessions/week, for 12 months, for further 24 months for monitoring (including intensive FES-cycling training and detraining/reduced FES intensity). ND	FES-cycling; PW: ND. Freq: ND. Amp/Volt: ND	Total and trabecular BMD of the tibial and femoral epiphyses, thigh shank muscle and fat CSA. pQCT	Improvement of bone and muscle parameters was reported	✓	✓
Griffin et al. [68]; USA	18 – [C4-T7, age: 40±2.4 years ^a . TSI: 11±3.1 years ^a]	30 min for 2–3 times/week for 10 weeks	FES-cycling; PW: ND. Freq: 50 Hz, Amp/Volt: 140 mA max	Total body mass and lean muscle mass. DEXA	Significant ($p \leq 0.05$) increase in total and lean muscle mass but no change in bone and adipose mass were reported	✓	✓
Lai et al. [69]; Taiwan	12 – [C5-T8, age: 28.9±5.3 years. TSI: 35.3–6.1 days]	30 min for 3 times/week for 3 months initially and discontinued for another 3 months	FES-CE; PW: 300 µs. Freq: 20 Hz; Amp/Volt: ND	BMD of distal femur and femoral neck. DEXA	Partial attenuation ($p < 0.01$) of BMD loss of only distal femur in the early stage of training was observed	✓	–
Groah et al. [70]; USA	16 – [C4-T12, age: 26.2±12.8 years. TSI: 35.9±16.9 days]	Stimulation for 60 min/until muscle fatigue for 5 day/week for 6 weeks	FES-KE; PW: 300 µs; Freq: 25 Hz. Amp/Volt: 125 mA max	BMD of lumbar spine femoral neck, distal femur, and proximal tibia. DEXA	Attenuation of BMD loss in distal femur was reported	✓	–
Astorino et al. [71]; USA	13 – [C4-T12, age: 29.7±7.8 years. TSI: 1.9±2.7 years]	For ABT: 2–3 h/day/week For 6 months. FES-cycling: 30 min/week	ABT and FES-cycling; PW, Freq and amp/Volt were set as tolerable.	BMD of lumbar spine (L1–L4), proximal femur, and knee. DEXA	Inability of the chronic ABT to reverse BMD loss ($p > 0.05$) was reported, although BMD reduction was less than the expected values in recent SCI cases	✓	–

Table 2: (continued)

Study; Country	Population. <i>n</i> – [neurological level; age and TSI in mean±SD or (median and range)]	Intervention: Frequency and duration of exercise	Exercise mode and aid; Stimulation parameters	Muscle mass, volume/BMD. Measurement devices	Outcomes and results	Bone	Muscle
Sadowsky et al. [72]; USA	45– [C1-L5, age: 36±12.2 years. TSI (range): 85.8 (16–519) months]	45–60 min duration, thrice/week For mean duration of 29.5 months. With 29.1 months mean duration of follow up	FES-CE; PW: 500 µs. Freq: 100 Hz. Amp/Volt: 140 mA max	Quadriceps muscle mass, total thigh muscle, intra- and intermuscular fat volumes. MRI and DEXA	No significant (p=0.24) increase in total thigh volume but significant (p=0.001; 0.005) volume increase in anterior and posterior thigh compartment muscles were reported. BMD was not significantly different	✓	✓
Fornusek et al. [73]; Australia	8 – [C7-T11, age: 39±14 years. TSI: ≥1 year]	30 min and thrice/week for 6 weeks exercise	FES-CE, PW: 250 µs, Freq: 35 Hz; Amp/Volt: Linearly ramped from 40 to 140 mA	Thigh girth. Cloth measuring tape	Significant (p=0.08) increase of thigh girth was reported	–	✓
Kuhn et al. [74]; Germany & Austria	30 – [C4-L5, age: 44±15.5 years. TSI: (2: 1.0–4.25 i.e. median: IQR) months]	20 min and twice/week for 4 weeks exercise.	FES-cycling; PW: 250 µs; Freq: 30 Hz; Amp/Volt: 10–130 mA max	Rectus femoris muscle CSA and leg circumference. Tape measure	Significant (p<0.05) increase of thigh girth was reported	–	✓
Gibbons et al. [75]; UK	1 – [T4, age: 58 year. TSI: 13 year]	ND	FES-rowing; PW: ND; Freq: ND; Amp/Volt: ND	BMD of proximal tibial trabecula. pQCT	Improved BMD reported after the training	✓	–
Arija-Blázquez et al. [1]; Spain	10 – [T4-T12, age (intervention grp): 41.7±12 years. TSI: 8<weeks]	80 electrically induced isometric contractions/day, 47 min/day, 5 days/week for 14 weeks. ND	FES-isometric contractions; PW: 200 µs; Freq: 30 Hz; Amp/Volt: 140 mA max	CSA of quadriceps femoris muscle; BMD. MRI and DEXA	Significant (p<0.05) muscle size increase, but not bone tissue/CSA were reported	✓	✓
Johnston et al. [76]; USA	17– [C4-T6, age: 42±12 years; TSI: 12±10 years]	Low cadence cycling (20 rpm) and high cadence (50 rpm) cycling thrice/week for 6 months. i.e., 56 min for 63–78 sessions within 6 months	FES-cycling; PW: 250 µs; Freq: 33 Hz; Amp/Volt: 140 mA max	Distal femur and trabecular, cortical bones and thigh muscle volume. DEXA and MRI	Muscle volume increase within each group but not between groups (p=0.32) was reported. Increase bone volume (10% & 19% for the 2 groups) and general improved bone health were reported	✓	✓
Gibbons et al. [77]; UK & USA	1– [T4, age: 59 years. TSI: 14 years]	30 strokes/min for 30 min and thrice per week for 24 months i.e. approx. 2,700 loading cycles/week	FES-rowing; PW: ND; Freq: ND; Amp/Volt: ND	BMD of ultra-distal radius and tibia pQCT	BMD loss was prevented with the rowing exercise	✓	–
Deley et al. [78]; France	1 – [T4/T5, Age: 36 years; TSI: 2 years]	12 months training (i.e. 3 times/week 3 months of knee extension exercise, and rowing of 30 min for 3 times/week for 9 months).	FES-strengthening and rowing; PW: 450 µs; Freq: 40 Hz; Amp/Volt: 110 mA max	BMD and thickness of m. Quads and thigh circumference. B-mode ultrasonography machine and DEXA	Increased muscle thickness (136%), thigh circumference (14%) and BMD (19%) were reported	✓	✓

Table 2: (continued)

Study; Country	Population. <i>n</i> – [neurological level; age and TSI in mean±SD or (median and range)]	Intervention: Frequency and duration of exercise	Exercise mode and aid; Stimulation parameters	Muscle mass, volume/BMD. Measurement devices	Outcomes and results	Bone	Muscle
Draghici et al. [79]; USA	13 – [C4-T8, Age: 31.9±10 years, TSI: 1.6±1.6 years]	FES-rowing to achieve 462±478 km for 1.7±1.5 years	FES-rowing; PW: ND; Freq: ND; Amp/Volt: ND	BMD of distal tibia and radius. pQCT	Trabecular thickness ($R^2=0.72$; $p<0.01$) and volumetric BMD are positively correlated with duration of rowing. Thus, regular exercise reverses BMD loss	✓	–
Lambach et al. [80]; USA & UK	4 – [C7-T12, age: 32.5±7.4 years; TSI: 12.5±2.3 months]	90 sessions i.e., 30–60 min for 3 times/week for 9–12 months	FES-rowing; PW: 450 μ s. Freq: 40 Hz; Amp/Volt: 120 mA max	BMD of distal femur and tibia. pQCT	Initial BMD loss reversal was reported with exercise progression. Bone stimulus significant correlation with femoral trabecular BMD changes ($R_2=0.458$; $p=0.016$) was reported	✓	–
Farkas et al. [81]; USA	6 – [T4-T10, Age: 38.8±19.9 years. TSI: ND]	80 sessions i.e., for 40 min of cycling @ 50 rpm in 5 day/week for 16 weeks	FES-cycling; PW: 450 μ s; Freq: 60 Hz; Amp/Volt: 140 mA max	Total body fat (TBF) and BMD. DEXA	The reported reduction in % body fat was significant ($p=.008$). Significant ($p=.04$) increase in BMD was also reported	✓	✓
Afshari et al. [82]; USA	18 – [C & T levels], Age: 29.06±5.4 years. TSI: ≤24 months]	For strength training: 3 times/week for 2–3 weeks until able to perform 30 min without rest. For FES-rowing: 30–40 min, 3 times/week for 26 weeks	FES-rowing; PW: ND; Freq: ND; Amp/Volt: ND	Total and regional lean mass, fat mass, fat percentage, visceral adipose tissue (VAT), BMD and bone mineral content (BMC). DEXA	Significant ($p<0.05$) increase in total and leg lean mass; and reduction ($p<0.05$) in pelvis and total BMD decline were reported	✓	✓

ABT, activity-based therapy; AP, anteroposterior; BW, body weight; BWSTT, body weight supported treadmill training; BMD, bone mineral densities; CT, computed tomography; CSA, cross-sectional area; CE, cycle ergometry; DEXA, dual energy X-ray absorptiometry measures tbBMD, total body bone mineral density; DPXA, dual photon X-ray absorptiometry; IQR, interquartile range; KE, knee extension; LBM, lean body mass; LE, leg extension; MRI, magnetic resonance imaging; *n*, number of participants; ND, not described; pQCT, peripheral quantitative computed tomography—which could differentiate trabecular and cortical bone [34, 35]; SE, Standard Error; TSI, time since injury. ^a – with the assumption that the study was conducted in the year of article publication. ✓: positive change, ✗: negative change, –: unreported.

Standing effects on bone and muscle health in persons with SCI

Four studies [20, 21, 23, 32] reported a preservation or significant increase in the femoral neck and/or lumbar spine's BMD following ≥6 months of frame-assisted (i.e., standing frame, long leg brace, and standing wheelchair) upright standing exercise in persons with chronic SCI. These studies found that the bone loss sequel is site-specific in SCI with that

of the lower extremities being the highest. The researchers also observed that standing with a frame only could preserve bone health but may be unable to improve it. The studies reported here advanced the feasibility of the positive effects of frame-assisted standing on the BMD of SCI participants especially for standing initiated early after injury and/or sustained for a long time.

Conversely, with frame-assisted upright standing training, five studies [16, 26–28, 33] reported an insignificant increase or reduction in targeted lower limb BMD in persons

Table 3: Characteristics of included studies on walking effects on muscle and bone health.

Study; Country	Population. n – [neurological level; age and TSI in mean±SD or (median and range)]	Intervention: frequency and duration of exercise	Exercise mode and aid; Stimulation parameters	Muscle mass, volume/BMD. Measurement devices	Outcomes and results	Bone	Muscle
Ogilvie et al. [83]; UK	4 – [ND, paraplegic; Age: 16–42 years. TSI: ND]	3 h For average of 5 months, repeated every 6 months follow p duration of 18–30 months	Walking orthosis with RGO. NA	Femoral neck and lumbar vertebrae; Quantitative CT	Slight improvement on BMD was reported.	✓	–
Thoumie et al. [84]; France	21 – [C8-T12, SCI; Age: 33 (20–50 years). TSI: 26 (4–72) months; mean (range)]	2 h, thrice/week for 3–14 months	RGO-II hybrid orthosis. NA	Lumbar spine and femoral neck BMD; DPXA	Lack of improvement on BMD was reported at lumbar and BMD decrease at femoral neck was significant. The result suggests the corrections of the effect of immobilization by this exercise	✓	–
Needham-Shropshire et al. [85]; USA	16 – [T4-T10, age: 28.8 years. TSI: 3.8 years]	32 FES ambulation sessions plus another 8 weeks before BMD measurements	Parastep® and walking frame; PW: ND; Freq: ND; Amp/Volt: ND	Femoral head, neck, and Ward's BMD; DP3 dual-photon densitometer	By week 7, weight bearing (for more than 90 min/session) through the legs in 9 out of 16 participants were reported. By week 10, 10 out of 16 participants could ambulate for more than 120 min/session. However, insignificant changes in BMD were reported	✓	–
Klose et al. [86]; USA	16 – [T4-T10, age: 28.4±6.6 years; TSI: 4±3.5 years]	Thrice weekly of 32 FES-gait sessions for 11 weeks	Parastep®, frame walker and ankle-foot orthosis; PW: 150 µs; Freq: 24 Hz; Amp/Volt: 0–300 mA max	Thigh CSA, and calculated lean tissue and the thigh, calf and certain anatomical positions' circumference; X-ray and DPXA	Significant increase (p=0.001) in thigh CSA and lean tissue but decrease in the skin fold of the skin were reported	–	✓
Stewart et al. [87]; Canada and USA	9 – [C4-T10, age: 31±3 years; TSI: 8.1± 2.5 years]	68 sessions in 6 months (2.8±0.2 training sessions/week)	BWST gait; NA	Vastus lateralis CA; Muscle biopsy examination	Significant (p=0.001) increase in muscle fibre area and oxidative capacity of the muscle were reported	–	✓
Giangregorio et al. [88]; Canada	5 – [C3-C8, age: 29.6±7.8 years. TSI: 114.2± 3 42.2 days]	twice/week 48 sessions	BWST gait; NA	Proximal femur, distal femur, proximal tibia and lumbar spine BMD and CSA; DEXA and CT scan	About 3.8–56.9% increase in muscle CSA and reduction of – 1.2–26.7% in BMD were reported	✗	✓
Carvalho et al. [89]; Brazil	21 – [C4-C8, Age: 31.95±8.0 years. TSI: 66.42±48.2 months]	20 min of gait twice/week for 6 months with 30–60% body weight support	FES-gait on treadmill; PW: 300 µs; Freq: 25 Hz; Amp/Volt: 200 V max	Lumbar spine, femoral neck, trochanteric area, and total femur BMD; DEXA	Increase in bone formation markers was reported in 81.8% of participants. BMD improvement was indicated	✓	–

Table 3: (continued)

Study; Country	Population. n – [neurological level; age and TSI in mean±SD or (median and range)]	Intervention: frequency and duration of exercise	Exercise mode and aid; Stimulation parameters	Muscle mass, volume/BMD. Measurement devices	Outcomes and results	Bone	Muscle
de abreu et al. [90]; Brazil	15 – [C4-C7, age: 31.95± 8 years. TSI: 66.43± 48.2 months]	20 min/session 2 times/week for 6 months to achieve 0.5–1.4 km/h max after 6 months	FES-gait on treadmill; PW: 300 ms; Freq: 25 Hz; Amp/Volt: 200 V max	CSA of m. Quads; MRI	CSA of m. Quads was significantly (p=0.01) higher after 6 month of FES-gait from the baseline	–	✓
Forrest et al. [91]; USA and Canada	1 – [C6, Age: 25 years. TSI: 1 year]	2 blocks of locomotor training for 9 months (i.e., 35 session block, and 8.6 weeks of rest followed by a 62-session block)	Locomotor training with BWS treadmill; NA	BMD of femoral neck and lumbar spine; and total LBM; DEXA	Total (1.54%) and regional (legs: 6.72%). BMD decrease was reported	✗	–
Jayaraman et al. [92]; USA	5 – [C4-T4, Age: 41.4±12.4 years. TSI: 19.5± 10.5 months.]	9 weeks of stepping training involving 45 sessions of 5 times/week	Locomotion training; PW: ND; Freq: ND; Amp/Volt: ND	CSA of knee-extensor (KE) and plantar-flexor (PF); MRI	Increased in PF (between 6.8 and 21.8%) CSA was reported	–	✓
Coupaud et al. [93]; UK	1 – [T6, Age: 40 years. TSI: 14.5 year]	7 months of gait training	Partial BWSTT; PW: 117–351 µs; Freq: 40 Hz; Amp/Volt: 40 mA	Tibial epiphyses and the distal femoral epiphysis BMD and muscle CSA; pQCT	5% (right) and 20% (left) increase of trabecular BMD in the distal tibia only and slight increase in CSA of thigh were reported	✓	✓
de abreu et al. [94]; Brazil	15– [C4-C7, 8 SCI control grp: Age: 32.3±3.5 years. TSI: 64.1±96.2 months.]	Gait training for 20 min/session twice per week for 6 months	FES-gait training with treadmill; PW: 300 ms; Freq: 25 Hz; Amp/Volt: 200 V	Quadriceps CSA. MRI	Muscle CSA increase from 49.8± 9.4 cm ² to 57.3± 10.3 cm ² was observed due to FES-gait training.	–	✓
Craven et al. [95]; Canada	17 – [C2-T12, age: 56.59±14 years. TSI (Median (IQR): 5±6.6 years]	45 min/session and thrice week for 4 months	FES-walking with body weight support with harness; PW: 250–300 µs; Freq: 20–50 Hz; Amp/Volt: 8–125 mA	Total hip, distal femur and proximal tibia BMD. DEXA an pQCT	Enhanced bone turnover (p<0.05)) was reported	✓	–
Karelis et al. [96]; Canada and Brazil	5 – [C5-T5, SCI: Age: 60.4±6.1 years. TSI: 7.6±4.6 years]	≤60 min/session, 3 sessions/week for 6 weeks	Robotic exoskeleton; NA	Lean body mass (LMB), BMD, muscle mass and calf CSA. DEXA an pQCT	Significant increase (p= 0.01) in leg and appendicular lean body mass, total, leg and appendicular fat mass, and the calf mass CSA were reported	✓	✓
Terson de Paleville et al. [97]; USA	4 – [C5-T5, SCI: Age: 27.3±3.7 years; TSI: 30.8±3.1 months]	Task specific training with epidural stimulation involving 160 sessions	Epidural stimulation supported locomotion; PW: ND; Freq: 10–45 Hz; Amp/Volt: ND	Lean body mass and % of body fat. DEXA	Increase in body weight due to increase in fat-free mass, increased lean body mass with decreased % of body fat were reported for all participants	–	✓

Table 3: (continued)

Study; Country	Population. n – [neurological level; age and TSI in mean±SD or (median and range)]	Intervention: frequency and duration of exercise	Exercise mode and aid; Stimulation parameters	Muscle mass, volume/BMD. Measurement devices	Outcomes and results	Bone	Muscle
Asselin et al. [98]; USA	8 – [C8/T8-T11, SCI: Age: 47±12 years. TSI: 6±4 years]	≤2 h/session, 3 times/week of 40 sessions	Powered exoskeleton-supported locomotion; NA	Lean body mass and total body fat mass (TBFM) and visceral adipose tissue (VAT). DEXA	Significant reduction of TBFM ((−1.8±1.2 kg, p=0.004); marginally loss of VAT (−0.141 kg, p=0.06) for 6 out of 8 participants was also reported	–	✓
Sutor et al. [99]; USA	8 – [C5 - T11, SCI: Age: 36.7±13.7 years. TSI: 8.5±6 years]	EAW & TSS: 10 min walk test (10 MWT), 2–3 times/week for 12 weeks	Exoskeleton-assisted walking (EAW) & Trans-spinal stimulation (TSS) for subset of the participants (i.e., n=3); PW: 250–300 µs; Freq: 20–50 Hz; Amp/Volt: 8–125 mA	Body fat %, total body, legs and trunk's lean and total mass. DEXA	Reduction in % fat from baseline was reported for the total body (−1.4%, (p=0.018)), leg (−1.3%, (p=0.018)), and trunk (−2%, (p=0.036)) regions	–	✓

ABT, activity-based therapy; BW, body weight; BWSTT, body weight supported treadmill training; BMD, bone mineral densities; CT, computed tomography; CSA, cross-sectional area; CE, cycle ergometry; DEXA, dual energy X-ray absorptiometry measures tbBMD, total body bone mineral density; DPXA, dual-photon X-ray absorptiometry; IQR, Interquartile range; MRI – magnetic resonance imaging; NA, not applicable; ND, not described; n, number of participants; pQCT, peripheral quantitative computed tomography—which could differentiate trabecular and cortical bone [34, 35]; TSI, time since injury. ✓: positive change, ✗: negative change, –: unreported.

with acute [26, 27] and chronic [16, 28, 33] SCI. The studies reported here generally showed that standing with frames had no clinically significant effects on BMD for both acute and chronic SCI cases.

Studies that have looked into the effect of FES-supported standing on BMD and muscle mass preservation were sparse. In persons with chronic SCI, two studies [22, 34], reported “lowest rate of femur BMD decline across time” and significantly lower BMD decline over time at >2 years of FES- and frame-supported standing task [34] under unilateral high-dose quadriceps stimulation. These two studies confirmed the relevance of FES-supported standing in bone health promotion and also affirmed that long term exercise is needed for significant BMD improvement following leg exercise. One study by Taylor et al. [9] investigated the impact of standing by Oswestry standing frame (i.e., an adjustable and customised standing frame) on quadriceps muscle and found that ~50% of muscle lost in the first 3 weeks of injury could nearly be regained in 240 days of FES-standing training in persons with SCI.

These studies suggested that the positive effects of FES on muscle health may appear earlier before that of BMD. Table 1 presents the reported effects of standing on muscle and bone health.

Cycling, rowing and knee extension effects on bone and muscle health in persons with SCI

Twenty-one studies [12, 36–39, 42, 44, 47, 48, 50, 51, 53, 56, 59, 64, 66–68, 72–74] submitted that 1–12 months of FES-cycling exercise resulted in a marginal or significant increase in CSA of Iliacus [37], quadriceps muscles [36–38, 47, 44], vastus lateralis [45], gluteus medius [12, 44], paraspinal muscles [12], lean body mass [44, 50, 68], iliopsoas [12] and thigh circumference [42, 44, 48, 51, 64, 66, 67, 72–74] and leg muscle volume [56] in persons with SCI. Here, an increase in muscle CSA has been reported in FES-cycling exercise for at least 3 months and leading to better results if conducted for longer duration. Two out of these studies [46, 75] also reported significant improvement of FES-cycling exercise on BMD. In one study, the improvement in BMD was only observed in one acute SCI case [44] and in another study, no change in bone and adipose mass were reported [68].

Ten studies [43, 49, 57, 58, 65–67, 69, 76] reported significant preservation and improvement of FES-cycling on lower limb BMD and specifically presented partial reversal of proximal tibial BMD [43, 49], distal femoral's BMD [66, 67]

and improvement of lumbar spine BMD [45]. However, partial attenuation [69], no influence [38, 40] or an insignificant but positive trend on BMD improvement [46] were reported in four studies [38, 40, 46, 69] mostly in acute SCI cases [69].

Five studies [75, 77, 79, 80] reported BMD loss attenuation and muscle thickness [78], following a prolonged FES-rowing in individuals with chronic SCI. Apart from FES-cycling and -rowing exercises, 10 studies [41, 52, 54, 55, 60–63, 79, 71] reported other FES-supported leg exercise modalities. For example, Dudley et al. [52] showed significant increase in quadriceps muscles CSA following intermittent FES-isometric contractions to elicit high force contraction. Bélanger et al. [55] demonstrated a partial reversal of BMD loss of lower limb bones following FES-isokinetic knee extension/flexion for 24 weeks in persons with chronic SCI. Groah et al. [70] demonstrated the possibility of FES-induced knee extension to attenuate the loss of lower extremities BMD in persons with acute SCI. Shields et al. [61] reported a partial prevention of the BMD loss following FES-induced isometric plantar flexion against a compressive load of up to twice of body weight in persons with acute SCI.

In a similar study by Shields et al. [62], it has been demonstrated that isometric plantar flexion against a compressive load of up to 1.5 of body weight could promote BMD in acute SCI individuals. Preservation of tibia bone integrity was reported by Rodgers et al. [41] following 12 weeks of knee extension exercise. Cramer et al. [54] reported the preservation of muscle fibre area and type, and prevention of connective tissue infiltration in acute SCI cases. Also, Mahoney et al. [60] reported significant increase in quadriceps muscles' CSA following 12 weeks of FES-resistance training in persons with chronic SCI. However, Clark et al. [63] reported that 5 months of FES-induced isotonic contractions could not preserve lower extremities' bone loss/BMD in persons with acute SCI. Also, Astorino et al. [71] conducted a six-month activity-based therapy (ABT) which included standing, gait training and FES-cycling training in both acute and chronic SCI cases, and found that the ABT was unable to attenuate the bone loss. Two recently published studies by Farkas et al. [81]; and Afshari et al. [82] also showed significant improvement of BMD and muscle mass after a cycling and rowing intervention respectively through reduction of total body fat in persons with SCI. Table 2 summarises the results of studies on cycling, rowing and knee extension related effects on muscle and bone health. In summary, the studies reported here claimed that the accrued improvements through FES-supported training could only be maintained if the intervention is sustained for as long as feasible. Some studies

also showed that exercise intervention may not positively impact both bone and muscle health.

Effects of walking on bone and muscle health in persons with SCI

Five studies [83, 84, 87, 88, 96] reported increase in BMD [83, 84, 88] and muscle CSA [96] or muscle fibre area [87] and three studies [85, 87, 88] reported no impairment/reduction in BMD following walking with walking aids (i.e. RGO, BWST) after SCI gait on a treadmill without FES. Seven studies [86, 89, 90, 92, 94, 95, 97] demonstrated that FES-walking promoted BMD/bone turnover/lean body mass [89, 95, 97] and muscle CSA [86, 90, 92, 94] in chronic SCI individuals while only one study [85] reported insignificant effect of this exercise on BMD [87]. Also, only one study [93] reported an increase in both the BMD and muscle CSA following FES-supported walking in persons with SCI. Asselin et al. [98] and Sutor et al. [99] recently reported a significant positive effect of exoskeleton-assisted walking on muscle through the reduction total body fat percentage in persons with chronic SCI while the effects of this exercise on bone were unreported. Table 3 depicts the results of studies on effects of walking on muscle and bone health.

Discussion

This review sought to synthesise published outcomes' conclusions on the effectiveness of prominent lower limb exercise modes with and/or without the aid of FES on the preservation of muscle and bone health in persons with SCI. This is an important research study as the evidence on the effectiveness of FES to preserve muscle and bone health in persons with SCI was inconclusive [15]. Through this study we have been able to ascertain that both muscle and bone health outcomes were correlated in studies that reported both findings except a few studies. It was also observable that positive changes in muscle health were more prominent compared to bone health improvements, which may take longer time or requires higher exercise dose than needed for muscle health improvement.

Following a comprehensive literature search, this study included 78 papers after applying the exclusion criteria. 12 out of those studies (15%) were on standing effects on muscle and bone health with or without FES. With only three studies on FES-supported standing to improve muscle (i.e., two studies) [9, 34] and bone health (i.e., one study) [22] in

persons with SCI, there is a need for further investigation to support the body of evidence on this topic for effective clinical decisions. This is important as only the exercise effects on quadriceps muscle thickness and femur BMD were reported in the three available studies. While the mode of intervention was not reported in one study [9], FES-standing training involving high-dose and active resistance stance for a minimum duration of ≤ 3 years appeared to be necessary for a significant benefit of FES-supported standing on muscle and bone health. The studies reported here majorly recruited persons with chronic SCI. Also, the recruited individuals were with paraplegia and some with high tetraplegia (i.e. one study [19] with C2 and three studies [26, 27, 33] with C4). The population selected and intervention adopted may be due to the fact that sufficient trunk stability was required for upright stance and this was lacking in most people with high tetraplegia from C1-C4 [100]. Among the remaining studies, 1 h of frame-assisted/treadmill standing, thrice weekly for a minimum of 6 months was generally reported with some muscle and/or bone health benefits except in a few acute SCI cases [26, 27] where no/insignificant benefits were reported. In situations where significant benefits were found in acute SCI cases, the training was sustained for ≥ 2 years [20].

It appeared that more than 24 months [34] of standing training may be needed before clinically worthwhile bone health preservation could be achieved in specific cases of standing initiated soon after SCI. As bone mechanical loading may not reduce BMD loss after several months of immobilisation due to osteoporosis after SCI [23], it was evident that early standing intervention after SCI may likely reduce the rate of BMD decline. This intervention should be sustained for long-term to promote bone mineralization [33]. There seemed to be preliminary evidence to ascertain that leg exercise supported by FES promote bone health. One important information from the few available studies showed that the effect of standing training was muscle (i.e., muscle tissue properties) [9] and time since injury dependent. Further evaluation of the standing modality for bone health preservation is warranted before objective generalisation could be made. On the other hand, evidence of standing effect on muscle mass or volume was generally scarce and in fact, no recent study on this topic could be found in the literature. However, a positive effect of standing supported by FES and standing frame on the participants' muscle mass preservation was one important suggestion from the study of Taylor et al. [9].

Forty-nine out of the remaining studies (63%) were on cycling, rowing and knee extension related effects on muscle and bone health with or without FES. All the 49 studies here applied FES to support the exercise intervention. One explanation for this could be that the exercise under this category

cannot be executed without FES, since the target population lack voluntary motor activity, if improved muscle and bone health were sought. The subjects recruited for the studies reported here had paraplegia and few with tetraplegia with injury levels between C1-L5. This may suggest that cycling, rowing and knee extension exercise targeted at preserving or promoting health in persons with SCI could only be effective if supported with FES technologies. Out of the 49 studies under this category only four studies [56, 39, 45, 62] reported no benefits of the exercise interventions. The probable explanations for this observation appeared to be "insufficient" duration of the intervention, training intensiveness, time after injury of the participants and the injury severity. In general cycling/cycle ergometry with FES-support that accounted for 63% of all included studies happened to be the most common mode of muscle and both health preservation.

The remaining 17 studies (22%) were on walking effects on muscle and/or bone health with or without FES. Except in one study [85], FES-supported walking generally has a positive effect on muscle and/or bone health following intensive training. Walking with BWSTT/robotic exoskeleton appeared to be promising too as most studies reported here with participants with injury ranges from C3-T10 showing positive health benefits on lower limb's muscle and bone. These outcomes suggest that walking exercise with or without FES should be promoted in lower limb rehabilitation in persons with SCI. This is suggested to be preceded by clinical assessment of relevant bones for suitability.

It is evident that the skeletal muscle contractions and the consequent tension on the skeleton, elicited by FES may aid the preservation of muscle integrity and bone health [101]. Based on the available studies on FES-supported exercises on muscle and bone health preservation, it can be deduced that FES combined with standing frame/walking treadmill better preserves lower limb muscle and bone health in individuals with motor paralysis in comparison to the exercise intervention that rely only on frame standing/walking treadmill support. This information is useful to ascertain the potential of lower limb exercise in impacting musculoskeletal integrity to promote modest independent living in persons with SCI. Furthermore, the available evidence did not describe the potential complication or adverse effects associated with the exercise interventions described in this study. However, it is evident that clinical assessment before lower limb exercise may be required to exclude patients with bones that may be prone to spontaneous fracture due to a significant loss of BMD and muscle atrophy after SCI especially in the chronic phase of injury. A simple clinical task such as FES-supported knee extension exercise may precede challenging lower limb physical exercises, especially for habituation to prepare the bone for the challenging

mechanical bone loading due to these exercises for prevention of spontaneous bone fracture.

Overall, a significant delay of bone loss and improved muscle integrity appeared to improve with longer exercise duration and higher exercise intensity. At minimum, a marginal improvement in bone and muscle health following an increase in BMD and muscle bulk, respectively, due to lower limb exercise, has generally been observed. For example, as the diagnosis of osteoporosis potential in patients, areal bone mineral density is conventionally used as a predictor for the development of osteoporosis in the clinical and experimental settings. Furthermore, the accrued BMD increase due to FES-supported lower limb has been shown to be prominent in distal femur [66, 102] and proximal tibia [66], known to be mostly susceptible to fractures [102]. This development further buttresses the clinical usefulness of lower limb exercise intervention in clinical rehabilitation.

The most commonly reported stimulation parameter adopted in the reviewed studies included the stimulation frequency that ranged between 20 and 35 Hz (≤ 58 studies) while other studies applied 15 Hz (2 studies), 40 Hz (5 studies), 50 Hz (7 studies), and 60 Hz (2 studies). Also, the pulse width of the stimulation pulse mostly ranged between 200 and 400 μ s (≤ 64) while other studies used 450 μ s (4 studies), 500 μ s (3 studies), 667 ms (2 studies), and 1,000 μ s (1 study). Furthermore, 300 mA was the highest stimulation current for current controlled stimulation. The combination of these common parameters appeared to have yielded optimum stimulation outcomes due to their promotion of efficient motor unit recruitment strategies.

Effects of bone and muscle health promotion on spasticity

Spasticity is a common clinical condition in persons with SCI confined to wheelchair and it adversely affects their response to functional rehabilitation, especially, the range of motion [32]. Although spasticity can promote muscle trophism [103] and bone density [104], if not properly managed, its primary complication may include contracture leading to discomfort while its secondary complication may lead to pain and impaired function execution [105]. This may be especially evident during lower limb exercise. Thus, rehabilitation physicians and allied health professionals are interested in methods to reduce this clinical condition in order to promote rehabilitation outcomes in lower limbs. Therefore, a reduction of spasticity may be an additional benefit for the patients following leg exercise to improve bone and muscle health. Several adjustment strategies to reduce the influence of spasticity or “hamstring tightness”

during leg exercise have been promoted. This knowledge is based on the study of Bekhet and colleagues [106] where effectiveness of FES for managing spasticity had been proposed with proper stimulation strategies. For example, during knee extension exercise training, a sitting position that ensured that the hip joint flexion is set at $\sim 110^\circ$ [77] has been promoted. Although passive standing exercise may reduce spasticity [107], Kunkel and colleagues [32] suggested the application of FES-standing exercise for reducing spasticity as passive frame-assisted standing may be less effective. Also, FES-supported cycling [108] and locomotion [87, 109, 110] may reduce spasticity. It appeared that exercises involving active muscle movement elicited by FES or muscle stretching such as those described in this review could be used to reduce spasticity.

It must however be emphasized here that persons with peripheral nerve lesions (i.e., leading to lower motor neuron lesion) may have limited improvement and effectiveness of the various lower limb exercises reviewed in this study. This is because although FES is believed to “promote nerve regeneration and functional recovery”, it is largely relevant if the transected nerve has been surgically or otherwise repaired [111]. Even with this, one challenge of nerve transection or grafting is that the motor function may be largely unrecovered [112]. This is believed to be the major issue with using FES-supported rehabilitation for functional restoration in persons with peripheral nerve lesions. However, one recent study [113] have reported a promotion of muscle size and health following the deployment of “long pulse width stimulation” strategy. As this topic is beyond the scope of this study, further investigation may be of interest.

Conclusions

Evidence seems to be emerging to affirm that a rigorous and controlled high intensity frame- and/or FES-supported leg exercise is a possible “non-pharmacological” means of preventing muscle atrophy, osteoporosis and bone fracture in persons with SCI. Responses of bone and muscle integrity to exercise interventions appear to be heavily influenced by injury duration and how early the exercise is commenced as well as exercise duration and frequency of training. Affirmative comments on this may be justified by more studies especially RCTs. This stems from the fact that FES- and/or frame-supported leg exercises have been shown in this study to provide certain benefits, especially regarding musculoskeletal health promotion. FES-supported leg exercise may, therefore, serve as a useful augmentation for other traditional leg exercise aids. This may have significant and positive effects if combined with pharmacological means for

preservation of muscle and bone integrity. The present study could guide clinical rehabilitation professionals to make an evidence-based decision on the need to promote FES- and frame-supported leg exercise as a standard and viable clinical rehabilitation modality for muscle and bone health preservation in order to aid its wider clinical deployment. This study is also vital for understanding the clinical significance of leg exercise for muscle and bone health promotion and associated secondary benefits in the management of persons with SCI especially those with motor paralysis.

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