Prevention and Treatment of Bone Loss After a Spinal Cord Injury: A Systematic Review

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Preserving and maintaining bone mass after a spinal cord injury (SCI) is crucial to decrease the risk of fragility or low trauma fractures – significant health events that occur as a result of minimal trauma such as falling during transfers or from a standing height or less. There is an increased risk for low trauma fractures after an SCI especially in the lower extremity. Therefore, the purpose of this systematic review was to appraise the literature to provide clinical guidance for the optimization of bone health after SCI. The key research questions focused on prevention of acute bone loss after SCI (<1 year) and effective treatment of established low bone mass with long-standing SCI (≥ 1 year). We report moderate evidence for the treatment of bone loss using pharmacology; however, nonpharmacological evidence for preventing and treating bone loss is limited. **Key Words:** *functional electrical stimulation, osteoporosis, pharmacology, rehabilitation, spinal cord injury*

Preserving and maintaining bone mass after a spinal cord injury (SCI) is crucial to decrease the risk of fragility or low trauma fractures – a significant health risk for this population. Following an injury, bone loss is such that within the first few days there is an increase in excreted calcium (known as hypercalciuria) that is two to four times that of people confined to prolonged bedrest but without an SCI[1] and reflects excessive bone resorption. Longitudinal studies in people with SCI highlight a high rate of hypercalcemia (excessive calcium in the blood) with rapid bone mineral loss in the first 4–6 months.[2] Bone mineral density (BMD) is thought to stabilize by 1–2 years[3,4] in the hip and knee region at 25%–50% below that of able-bodied peers. However, more recent investigations support a continual loss of lower extremity bone mass[5] and suggest that a steady state of lower extremity bone mineral homeostasis is not reached within 3 years.[6]

The immediate and excessive loss of regional bone mass after SCI is believed to be caused by a decrease in mechanical loading as a result of reduced or complete loss of muscle function and/or weight-bearing activities, but the exact etiology of bone loss is

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unknown. Given the magnitude and rapidity of the resorption, there must be other contributing factors besides mechanical unloading. It is not surprising therefore that more recent literature suggests a "neurogenic" response to bone cells after SCI that may better account for the observed changes.[7]

Fracture Risk Following an SCI

A high incidence of lower extremity fragility fractures (1%–46%) exists in people who sustain an SCI,[8–17] and the majority of fragility fractures occur during transfers or activities that involve minimal or no trauma.[8] The lower extremity is most at risk for this population, which is consistent with site-specific decreases in BMD such that fractures of the distal femur are referred to as "the paraplegic fracture."[8] More recent investigations highlight a progressive loss of bone mass in the lower extremity from proximal to distal, and the region most at risk is below the knee (proximal tibia).[18] Recently Garland and colleagues examined participants with SCI with and without fractures and reported BMD fracture thresholds at the knee based on dual-energy X-ray absorptiometry (DXA) and history of fragility fractures.[19]

There are many notable risk factors for fragility fractures after SCI. There is a greater risk for women compared with men[12,17] and greater risk with increasing age, longer time since injury, and low body mass index (BMI).[19] Further, persons with paraplegia have more fractures compared with persons with tetraplegia, and persons with complete injuries have lower BMD compared with persons with incomplete injuries.[17] In the general population, individuals with a prior history of fragility fracture or a maternal history of fracture have a greater risk for future fracture, and these risk factors should also be considered in people with SCI.[20]

Evaluation of Bone

Common methods of bone evaluation include biochemical markers, bone imaging, and histomorphometry from bone biopsies. Biochemical markers can be derived from urine or blood serum and reflect bone turnover (formation or resorption). Areal (i.e., two-dimensional) BMD is quantified noninvasively with imaging technologies such as DXA and previously with dual-energy photon absorptiometry (DPA). DXA is considered by the World Health Organization to be the "gold or criterion standard" for diagnosing osteoporosis and is the most widely used assessment technique for diagnosing osteoporosis and monitoring treatment effectiveness. Volumetric BMD is assessed using peripheral quantitative computed tomography (pQCT). Peripheral QCT is a safe and precise technique to differentiate cortical from trabecular bone and assess both bone geometry and volumetric density. Histomorphometry measures bone biopsies and analyzes them at the tissue and cellular levels to provide an indepth understanding. However, it is not always feasible to do histomorphometry, because it requires taking surgically removed bone specimens from willing participants. It is important to note that all of these outcomes are secondary and tertiary surrogates for bone strength. A primary measure of bone health is fracture reduction, however the use of fracture as an outcome is difficult in subjects with a relatively rare condition and the need for a large sample to be recruited and followed for an extended period of time. Consequently, to date there have not been any SCI clinical

trials testing interventions with fracture reduction as the primary outcome measure.

Treatment Options for Low Bone Mass After an SCI

In this section, we summarize therapies used to optimize bone health after an SCI. We have divided the sections based on the time frame since initial injury because of the more rapid loss of bone early after an SCI: (a) less than 1 year since injury, and (b) more than 1 year since injury. We note that the same treatment options have been tested in participants over the continuum of time.

Bisphosphonate therapy

The cellular mechanisms responsible for the regional declines in bone mass early after SCI are a marked increase in bone resorption (osteoclast activity) with a concurrent decrease in bone formation (osteoblast activity). Bisphosphonates have been shown to inhibit bone resorption in other chronic diseases such as postmenopausal and male osteoporosis as well as Paget's disease. There are first-, second-, and third-generation forms of bisphosphonates. First-generation bisphosphonates (*drug name [common trade name]*; etidronate [Didronel, Didrocal] and clodronate [Bonefos, Ostac]) inhibit osteoblast and osteoclast activity and are much less potent than the newer generations. Second (pamidronate [Aredia]) and third-generation bisphosphonates (alendronate [Fosamax], ibandronate [Boniva and IV preparation], risedronate [Actonel], tiludronate [Skelid]) predominantly inhibit osteoclast activity by triggering apoptosis (i.e., early cell death). Dosing regimens of bisphosphonates are flexible, ranging from daily oral preparations to 4x/year intravenous (IV) preparations. IV formulations of bisphosphonates (clodronate, pamidronate, zolendronic acid, ibandronate, tiludronate) are available for the prevention and treatment of declining bone mass for people living with an SCI. The IV preparations are attractive due to the flexibility in dosing regimens, assured compliance, and the reduced relative risk of an adverse upper gastrointestinal event.

Rehabilitation modalities used after an SCI for bone health aim to stimulate osteoblasts through muscle contraction or weight bearing. Both muscular electrical stimulation (MES) and functional electrical stimulation (FES) use cyclical patterns of electrical stimulation to simulate muscular activity, but FES is directed toward the attainment of purposeful tasks such as cycling or walking. MES is focused on producing muscle contractions (isometric, isotonic). In some applications, MES techniques are used as a training stimulus to prepare muscles for a subsequent FES training condition. The FES cycle ergometer uses a series of electrodes placed over the hamstrings, quadriceps, and gluteal muscles of both legs to produce a cycling pattern. Weight-bearing activities have also been tested for bone health after an SCI. These include either passive (tilt-table) or active (FES-assisted walking device) weight-bearing activities.

The purpose of this article was to identify and appraise the bone health and SCI literature and to provide a summary of the current best evidence for the prevention and treatment of low bone mass among individuals with an SCI. We have focused on interventions that target two phases of transition for bone mass after an SCI: (a) immediately after the initial injury (acute phase), and (b) more than 12 months after the injury when low

bone mass has been established (chronic phase). In the acute phase, the overriding goal is to minimize regional declines in bone mass; after this period, treatment is focused on improving BMD or bone architecture and the presumed secondary reduction of risk for fragility fractures. Specifically our guiding questions were the following: What treatments prevent acute regional declines in BMD after an SCI? and How do we treat low bone mass of the lower extremity for people living with long-standing SCI?

Method

Search strategy

A literature search was completed using multiple databases (PUBMED/MEDLINE, CINAHL®, EMBASE, PsychINFO) to identify all potential trials published from 1980 to 2006 regardless of study design, focusing on research involving humans and published in English. The key words used in this search were: osteoporosis, osteopenia, bone health, fractures, functional electrical stimulation (FES), vibration, exercise therapy, alendronate, pamidronate, cyclical etidronate, amino-bisphosphonates, DXA, DEXA, pQCT, spinal cord, spinal cord injury, SCI, paraplegia, tetraplegia, and quadriplegia. We determined a priori that two reviewers would assess all articles and agree by consensus if an article was appropriate for inclusion in the study. When there was a discrepancy between the reviewers, a third reviewer was brought in to make the final decision. All articles chosen for this review were then assessed for quality. Randomized controlled trials (RCTs) were assessed using the Physiotherapy Evidence Database (PEDro) scale,[21] whereas the Downs and Black (D&B) tool was used to assess non-RCTs.[22]

Table 1 is a summary of the levels of evidence used to critique the selected articles. A more complete account of the methodology used in this systematic review is found in the first article of this issue.[23]

Results

There were 313 titles and articles reviewed: 282 articles were removed and only 5 discrepancies resolved. In total, there were 31 articles remaining, including 9 articles related to pharmacology and 22 related to rehabilitation modalities. A summary of the levels of evidence for bone health treatment options is provided in **Table 2**.

Pharmacological interventions in the first year post SCI

Available evidence for pharmacological treatment of bone loss for individuals less than 1 year postinjury included six controlled trials (5 RCTs; $n = 113$ participants)[24–29] (**Table 3**). These studies were difficult to interpret collectively due to the variability in selection of the main outcome measure, relatively short durations of follow-up, small sample sizes, and the lack of stratification based on impairment level. The majority of studies found that bisphosphonates resulted in a reduction of bone loss (i.e., less bone mineral content [BMC] decline) compared with a control group. The two studies that report that the first-generation bisphosphonate clondronate maintained BMD were short in duration (3-month intervention), and participants had less severe motor impairments (paraplegia, incomplete SCI).[25,28] In studies using etidronate[27] (first generation) and pamidronate[29] (second generation), both the control and intervention groups continued to lose BMD, except ASIA D participants who had

Table 1. Levels of evidence used to establish support for treatment options in this systematic review

Level	Research design	Description
Level 1	Randomized controlled trial (RCT)	RCT, PEDro score ≥ 6. Includes within-subjects comparison with randomized conditions and crossover designs
Level 2	RCT	RCT, PEDro score < 6.
	Prospective controlled trial	Prospective controlled trial (not randomized).
	Cohort	Prospective longitudinal study using at least 2 similar groups with 1 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 posttest using a single group of subjects.
	Post-test	A prospective posttest with 2 or more groups – intervention, then posttest (no pretest or baseline measurement) using a single group of subjects.
	Case series	A retrospective study usually collecting variables from a chart review.
Level 5	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.

Note: PEDro = Physiotherapy Evidence Database scale.

better preserved BMD in the lower extremity; participants with ASIA A impairment had the greatest decline in BMD in both studies. A recent study that used the second-generation bisphosphonates (pamidronate) and a longer intervention period found no significant differences between groups for bone loss after 1 year.[24] One study found a significant improvement in histomor-phometric total bone volume using tiludro-nate (third-generation bisphosphonate).[26] Therefore, for *the first year postinjur*y, there is level 1 evidence from randomized controlled trials that clodronate prevents a decrease in BMD of the hip and knee region with limited adverse effects on bone mineralization in men living with paraplegia.[25,28] For first-generation bisphosphonates, there is level 1 evidence from randomized controlled trials that oral etidronate prevents a decrease in BMD of the hip and knee region in people living with incomplete paraplegia or tetraplegia who return to walking within 3 months of the SCI.[27] There is level 1 evidence that tiludronate was

Table 2. Summary of the levels of evidence for bone health treatment options tested in individuals who sustain spinal cord injury

Treatment option	Time phase	Positive result	Levels of evidence
Pharmacology			
Clodronate	Less than 1 year postinjury	Yes	Level 1
Etidronate	Less than 1 year postinjury	Yes	Level 1
Tiludronate	Less than 1 year postinjury	Yes	Level 1
Pamidronate	Less than 1 year postinjury	No	Level 1
Alendronate	More than 1 year postinjury	Yes	Level 1
Vitamin D analog	More than 1 year postinjury	Yes	Level 1
Rehabilitation modalities			
FES cycling	Less than 1 year postinjury	No	Level 2
MES	Less than 1 year postinjury	Yes	Level 2
Standing/walking	Less than 1 year postinjury	No	Level 2, 4
Ultrasound	Less than 1 year postinjury	No	Level 1
FES cycling	More than 1 year postinjury	No	Level 4
MES	More than 1 year postinjury	Yes	Level 4
Standing/walking	More than 1 year postinjury	No	Level 4

Note: FES = functional electrical stimulation; MES = muscular electrical stimulation.

effective in increasing total bone volume using histomorphometry. There is level 1 evidence that pamidronate 30 mg IV or 60 mg IV four times per year was not effective for the prevention of BMD loss at the hip and knee region early after SCI in men and women who have motor complete paraplegia or tetraplegia.[24,29]

Pharmacological treatment strategies in the chronic phase

Evidence for pharmacological treatment for bone loss in individuals more than 1 year postinjury included three RCTs[30–32] (n = 124 participants; **Table 4**). Although two of the studies found less bone resorption with the bisphosphonate alendronate, the imaging measurement sites were different. Zehnder et al.[32] found less loss for the tibia, hip, and trunk but no effects for the wrist. In contrast, Moran de Brito et al.[31] found no changes in the lower extremity or trunk effects, with increases in the upper extremity. These differences could be a result of different patient pools, because Zehnder et al.[32] did not include patients with tetraplegia whereas Moran de Brito et al.[31] did. However, the likelihood of a type II error or detecting no between-group BMD change in the hip or knee region in the study by Moran de Brito et al. is high due to the short duration of the intervention. More recently, Bauman et al. found a significant improvement in bone outcomes using a vitamin D analog, highlighting its potential benefit.[33] Therefore, for people who are more than 1 year postinjury, there is level 1 evidence that alendronate 10 mg daily and calcium 500 mg orally 2x/day was effective for the maintenance of BMD of the wrist, hip, and knee region for men living with paraplegia.[32] Finally, there is level 1 evidence for vitamin D analogs to maintain BMD.[33]

Table 3. Studies using pharmacology for bone health after spinal cord injury in participants who were less than 1 year postinjury

Author, year PEDro or Downs & Black score Design	Method	Results
Bauman et al.,[24] 2005 PEDro = 10 **RCT**	**14 men and women aged 21–61 yrs with motor complete tetra/paraplegia**. Medication: Pamidronate[b], 12 months. Participants randomized to (a) 60 mg IV or placebo (saline) at 1, 2, 3, 6, 9, 12 months post SCI (n = 6) or (b) placebo (n = 5). *Main outcome:* BMD by DXA, bone turnover markers.	No significant between-group differences in BMD loss or bone formation markers at 1 yr. Pamidronate group had significantly lower 24-hr urinary calcium at 1 month compared with placebo group ($p < .05$).
Minaire et al., [25] 1981 PEDro = 10 **RCT**	**21 men and women aged 15–54 yrs with complete paraplegia.** Medication: Clondronate[a], 3.5 months. Participants randomized to (a) 400 mg/d (n = 7), (b) 1,600 mg/d (n = 7), or (c) placebo (n = 7) for 3.5 months. *Main outcome:* Histomorphometry and BMD dual photon absorptiometry.	Clodronate (group 1 and 2) effective for acute prevention of declining bone mass and maintenance of BMC of the femur and tibia compared with placebo. Increased serum and urine markers in the placebo group (suggesting an increase in bone turnover).
Chappard et al.,[26] 1995 PEDro = 9 **RCT**	**20 men and women aged 16–50 yrs with injuries between C5-T12.** Medication: Tiludronate[c], 3 months. Participants randomized to (a) 400 mg/d (n = 7), (b) 200 mg/d (n = 7), or (c) placebo (n = 6). *Main outcome:* Histomorphometry.	Increase in total bone volume in the tiludronate group 1 (400 mg/d) compared with tiludronate group 2 (200 mg/d) and placebo group. Increased bone resorption indicators in the placebo group compared with tiludonrate groups.
Pearson et al.,[27] 1997 PEDro = 8 **RCT**	**13 men and women aged 22–57 yrs with injuries between C5-T12, ASIA A or D**. Medication: Etidronate[a], 30 wks. Participants randomized to (a) 800 mg daily (n = 6) or (b) conventional rehab and calcium 1000 mg/d (n = 7). *Main outcome:* DXA and adverse event rate.	BMD of lower extremity for the etidronate-treated ASIA D patients were preserved compared with other participants. Oral etidronate was safe and well tolerated by participants.

(continued)

Table 3. Continued

Author, year PEDro or Downs & Black score Design	Method	Results
Minaire et al.,[28] 1987 PEDro = 7 **RCT**	**21 men and women aged 15–54 yrs with complete paraplegia.** Medication: Clondronate[a], 100 d. Participants randomized to (a) 400 mg/d (n = 7), (b) 1,600 mg/d (n = 7), or (c) placebo (n = 7). *Main outcome:* Histomorphometry, DXA, biochemical bone turnover markers.	Greater increase in bone removal markers in placebo group (48%) compared with clodronate groups (17%–27%). BMD was maintained in clodronate groups with a decrease in placebo group.
Nance et al.,[29] 1999 D&B = 13 **Controlled trial (nonrandomized)**	**24 men and women aged 25–57 yrs with injuries between C5-T12, ASIA A-D.** Medication: Pamidronate[b], 6 months. Participants given (a) 30 mg IV every 4 wk x 6 doses (total 180 mg/participant) (n = 14) or (b) conventional rehab (n = 10). *Main outcome:* BMD by DXA and urine biochemical bone markers.	Mean overall bone loss was 8.7% in placebo group but only 2.7% in the pamidronate group (p = .02).

Note: ASIA = American Spinal Injury Association Classification; BMC= bone mineral content; BMD = bone mineral density; d = day; DXA = dual-energy X-ray absorptiometry; hr = hour; IV= intravenous; PEDro = Physiotherapy Evidence Database scale; RCT = randomized controlled trial; wk = week; yrs = years.

[a]First-generation bisphosphonate. [b]Second-generation bisphosphonate. [c]Third-generation bisphosphonate.

Table 4. Studies using pharmacology for bone health after spinal cord injury in participants who were more than 1 year postinjury

Author, year PEDro score Design	Method	Results
Bauman et al.,[33] 2005 PEDro = 10 **RCT**	**40 subjects with complete motor injuries; 17 participants with tetraplegia and 23 participants with paraplegia.** Medication: Vitamin D analog, 24 months. 1) Vitamin D: 4 µg 1-alpha D(2) (n = 19); 2) Placebo (n = 21) was administered daily for 24 months; or 3) Both groups received calcium and vitamin D. *Main outcome:* BMD by DXA, biomarkers at 6, 12, 18, and 24 months.	Significant changes noted in leg BMD only in the vitamin D group at 6, 12, 18, and 24 months. There was a significant interaction for group by time. In the vitamin D group, smoking had a negative effect on increase in percent change of BMD. In the vitamin D group, urinary marker of bone resorption was significantly reduced, but markers of bone formation were not changed.
Zehnder et al.,[32] 2004 PEDro = 7 **RCT**	**65 men aged 18–60 yrs with complete injuries between T1-L3 ASIA A, B.** Medication: Alendronate[a], 24 months. 1) 10 mg/day plus 500 mg calcium per day (n = 33) or 2) calcium alone (500 mg/d) (n = 32) for 6 months. *Main outcome:* BMD by DXA and bone turnover markers.	Decreased tibal BMD in calcium-only group but remained stable in the alendronate group (p = .017). Significant increase in lumbar spine BMD but no change in wrist BMD in both groups. BMD of the mid-shaft tibia and hip were maintained in the alendronate group but decreased in the calcium-only group. Biochemical markers of bone absorption were significantly decreased from baseline in the alendronate group.
Moran de Brito et al.,[31] 2005 PEDro = 6 **RCT**	**19 men < age 50 and women < age 35 with para/tetraplegia (ASIA A, B, or C).** Medication: Alendronate[a], 6 months. 1) 10 mg and calcium 500 mg bid (n = 10) or 2) calcium-only (500 mg bid) (n = 9). *Main outcome:* BMD by DXA	Mean increase in upper extremity BMD that was greater in alendronate compared with calcium-only group. No group differences for BMD of the lumbar spine, lower extremity, or whole body and lower extremity T-score.

Note: ASIA = American Spinal Injury Association Classification; BMD = bone mineral density; DXA = dual-energy X-ray absorptiometry; PEDro = Physiotherapy Evidence Database scale; RCT = randomized controlled trial; yrs = years.

[a]Third-generation bisphosphonates.

Nonpharmacological interventions in the first year post SCI

The evidence for nonpharmacological prevention of SCI bone loss included eight investigations (n = 143 participants). This includes three RCTs[34–36] (54 participants), four nonrandomized controlled trials[37–40] (84 participants), and one pre-post study[41] (5 participants) (**Table 5**). As with pharmacology studies, there were interpretation difficulties because of low numbers of participants and variability with the primary outcome. Shields et al.[39] found a significant increase in trabecular bone BMD at the distal tibia (but not cortical bone at the midshaft tibia) using MES to apply compressive loads to the tibia equivalent to 1.5 times body weight. However, the clinical significance of this finding needs to be determined. There is level 2 evidence that MES maintained or improved bone mass. However, in general, the evidence suggests that rehabilitation modalities were not successful in slowing bone loss in the first year following an SCI. There is level 1 evidence from one RCT that short-term (6 weeks) ultrasound was not effective for treating bone loss[36] and level 2 evidence that FES cycling did not improve or maintain bone at the tibial midshaft in the first year following an SCI.[37] There is level 4 evidence that walking and standing did not maintain bone mass in the first year following an SCI.

Nonpharmacological treatment strategies in the chronic phase

The evidence for nonpharmacological treatment of SCI bone loss in participants with injuries occurring more than 1 year (chronic phase) previously included 14 investigations[7,42–54] (n = 169 participants) using MES, FES cycle ergometry, standing, or walking (**Tables 6–8**); they were all pre-post studies. Although there were no RCTs that assessed the effect of MES, the work by Bélanger et al.[42] completed a within-participant trial (one limb as the treatment vs. control limb) (**Table 6**). After training, BMD regained almost 30% of lost bone mass when compared with able-bodied reference scores. Therefore, there was level 4 evidence that MES either increased or maintained BMD over the stimulated areas.[42]

For FES cycling there were conflicting results for bone parameters from the six studies (**Table 7**). One study found a 10% increase in BMD at the proximal tibia during the treatment protocol, but these positive results returned to baseline within months after FES cycling was stopped.[48] Chen et al.[47] found an improvement of BMD at the hip with cycling. The FES cycling study that reported a positive effect on site-specific bone parameters used a protocol that was three sessions/week for at least 6 months in duration. That is, there was an increase in bone parameters over areas directly affected by stimulated muscles (e.g., quads, distal femur, and proximal tibia), and the FES cycling intervention needed to be maintained or bone gains were lost. There was no significant within-participant change in BMD for the remaining four pre-post studies. Therefore there is level 4 evidence that FES cycling did not improve bone mass.

Standing practice has been shown to reduce hypercalciuria[51]; however, passive standing[49,50] and walking studies (via braces, partial weight-bearing treadmill practice)[52–54] provide level 4 evidence that these modalities do not maintain or improve BMD in the hip or knee region.

Table 5. Studies using rehabilitation modalities for bone health after spinal cord injury for participants less than 1 year postinjury

Author, year PEDro or Downs & Black score Design	Method	Results
FES cycle ergometer		
Eser et al.,[37] 2003 D&B = 14 **Controlled trial (nonrandomized)**	**38 men and women mean age 33 yrs with complete injuries between C5-T12: 19 participants and 19 controls**. Modality: FES cycle ergometer, 6 months. Progressive training sessions until able to cycle for 30 min, then 3 days FES cycle and 2 days passive standing per week. Control group performed 30 min of passive standing 5 d/wk. *Main outcome:* Computed tomography.	Both groups had a 0%–10% decrease in tibial cortical BMD. There was no difference between groups for BMD after the intervention.
MES		
Clark et al.,[38] 2007 D&B = 21 **Controlled trial (nonrandomized)**	**33 men and women; 15 tetraplegia and 18 paraplegia; ASIA A-D.** Modality: MES, 5 months. Low-intensity stimulation to leg muscles, 15 min, 2x/d, 5 d/wk, 5 months (n = 23); or control group (no treatment) (n = 10). *Main outcome:* DXA at 3 wk and 3 and 6 months postinjury.	MES was safe and well tolerated, but there was only a minimal difference between groups for total body BMD only at 3 months postinjury ($p < .01$). Other DXA measures (hip and spine BMD) did not differ between groups at any timepoint.
Shields et al.,[40] 2006 D&B = 15 **Controlled trial (nonrandomized)**	**6 men with complete injuries from C5-T10; started study within 6 wks of injury. Within-participant design.** Modality: MES at 1.5 body weight; 3 yr. Treatment leg only received a home program of MES to stimulate leg plantar flexors with 35-min protocol (4 bouts with 5-min rest between bouts) for 5x/wk. *Main outcome:* DXA tibial analysis protocol.	There was a greater decline in bone mineral loss on the untrained limb compared with the trained limb (10% vs. 25%) ($p < .05$).

(continued)

Table 5. Continued

Author, year PEDro or Downs & Black score Design	Method	Results
Shields et al.,[39] 2006 D&B = 15 **Controlled trial (nonrandomized)**	**7 men with complete injuries from C5-T10; started study within 6 wks of injury. Within-participant design.** Modality: MES at 1.5 body weight; 2–3 yrs. Treatment leg only received a home program of MES to stimulate leg plantar flexors with 35-min protocol (4 bouts/d with 5-min rest between bouts) for 5x/wk. *Main outcome:* pQCT 4%, 38%, and 66% sites of bilateral tibiae.	No significant difference at the tibial midshaft but a 31% higher distal tibia trabecular BMD in trained limbs compared with untrained leg.
Standing/walking		
Ben et al.,[34] 2005 PEDro = 9 **Within-participant RCT**	**20 men and women; 8 paraplegia, 12 tetraplegia. Within-participant design.** Modality: Tilt-table standing, 12 wks. Treatment leg only received weight bearing on a tilt-table for 30 min, 3x/wk. Wedge applied to treatment leg to provide adequate dorsiflexion and weight bearing to the ankle**.** Control leg was not loaded in standing. *Main outcome:* DXA proximal femur.	No clinically significant effect on proximal femur BMD in treatment group, but a 4º improvement in ankle mobility.
de Bruin et al.,[35] 1999 PEDro = 6 **RCT**	**19 men aged 19–59 yrs with injuries between C4-T12, ASIA A-D.** Modality: Standing/walking, 25 wks. Control group 1 had 0–5 hr/wk loading exercises with standing frame; group 2 had 5+ hr of standing exercises per week (standing); and group 3 had 5+ hr of standing and treadmill (walking). Interventions lasted 25 wks. *Main outcome:* BMD by pQCT.	Decrease in trabecular BMD at the left tibia for the control group but minimal decrease in trabecular BMD in groups 2 and 3 ($p < .05$).

Treadmill training		
Giangregorio et al., [41] 2005 D&B = 13 **Pre-post**	**2 men and 3 women aged 19–40 yrs with injuries between C3-C8 ASIA B and C. No controls.** Modality: Body-weight–supported treadmill, 6–8 months. Session started at 5 min and was increased gradually to 10–15 min in all but 1 participant during 48 sessions of 2x/wk. *Main outcome:* BMD by DXA and computed tomography.	Decrease in BMD for all participants at almost all lower limb sites after training, ranging from –1.2% to –26.7%. Lumbar spine BMD changes ranged from 0.2% to –7.4%. No consistent changes in bone geometry at distal femur and proximal tibia. Did not alter the expected pattern of change in bone biochemical markers over time.
Ultrasound		
Warden et al.,[36] 2001 PEDro = 10 **RCT**	**15 men aged 17–40 yrs with injuries between C5-T10 ASIA A-B. Within-group design.** Modality: Pulsed therapeutic ultrasound, 6 wk. Applied to both calcanei for each participant for 20 min/d, 5x/wk. Right and left calcanei within each participant was randomized. *Main outcome:* BMD by DXA and QUS.	For specified dose, no significant effect of therapeutic ultrasound for any skeletal measurement parameter ($p > .05$).

Note: ASIA = American Spinal Injury Association Classification; BMD = bone mineral density; d = day; DXA = dual-energy X-ray absorptiometry; FES = functional electrical stimulation; hr = hour; MES = muscular electrical stimulation; min = minute; PEDro = Physiotherapy Evidence Database scale; pQCT = peripheral quantitative computed tomography; QUS = quantitative ultrasound; wk = week.

Table 6. Studies using muscular electrical stimulation for bone health after spinal cord injury in participants who were more than 1 year postinjury

Author, year Downs & Black score Design	Method	Results
Belanger et al.,[42] 2000 D&B = 11 **Pre-post**	**14 men and women aged 23–42 yrs with complete and incomplete injuries between C5-T6: 14 able-bodied controls. Able-bodied controls as reference values.** Modality: MES, 24 wks. Quadriceps MES was conducted 5 d/wk. Participants trained for 1 hr/d or until fatigued. Right quadriceps stimulated with no resistance (against gravity) while the left quadriceps stimulated against resistance. *Main outcome:* BMD by DXA.	At baseline, BMD from the SCI group was lower at the distal femur, proximal tibia, and mid-tibia (decrease ranged from 25.8% to 44.4%) than able-bodied controls. Increased BMD at distal femur (.082 g/cm^2) and proximal tibia (.052 g/cm^2), but not mid-tibia with MES ($p < .05$) for participants with SCI. MES with and without resistance were equally effective.
Rodgers et al.,[43] 1991 D&B = 10 **Pre-post**	**12 men and women aged 19–63 with para/tetraplegia complete and incomplete; only 9 participants had BMD measures. No controls.** Modality: MES, 12 wks. Each participant trained for a total of 36 sessions (3x/wk) using a progressive intensity protocol for MES stimulated knee extension. This progression was continued to a maximum 15-kg load. *Main outcome:* BMD by DXA.	Although tibial BMD was not changed after MES protocol ($p > .05$), it was better than predicted values.

Note: BMD = bone mineral density; d = day; DXA = dual-energy X-ray absorptiometry; MES = muscular electrical stimulation; PEDro = Physiotherapy Evidence Database scale; wk = week; SCI = spinal cord injury; yr = year.

Table 7. Studies using FES cycle ergometry for bone health after SCI in participants more than 1 year postinjury

Author, year Downs & Black score Design	Method	Results
Leeds et al.,[44] 1990 D&B = 12 **Pre-post**	**6 men aged 18–27 yrs with tetraplegia; no controls.** Modality**:** MES + FES cycle ergometer, 6 months. One month quads strengthening exercise, followed by 6 months of cycle ergometry. Knee extension sessions were 45 lifts in each leg 3x/wk for 1 month. Cycle ergometry sessions were 3x/wk; 30 min for 6 months. *Main outcome:* BMD by DXA.	The BMD of the proximal femurs were below normal before commencing exercise intervention (compared with matched able-bodied individuals). No significant change in BMD for any of the sites of the proximal femurs after training.
Pacy et al.,[45] 1988 D&B = 10 **Pre-post**	**4 men aged 20–35 yrs with paraplegia; no controls.** Modality: MES + FES cycle ergometer, up to 32 wk. Part 1: quadriceps strengthening with increased load ranging from 1.4 to 11.4 kg bilaterally for 15 min for 5x/ wk (10 wks). Part 2: cycle ergometer at 50 rpm with resistance (0–18.75 W), 15 min, 5x/wk (32 wks). *Main outcome:* BMD by DXA.	No significant change in lumbar spine and femoral shaft and/or distal tibia trabecular BMD after training.
BeDell et al., [7] 1996 D&B = 10 **Pre-post**	**12 men aged 23–46 yrs with complete injuries between C5-T12; no controls**. Modality: MES + FES cycle ergometer, 24–48 wk. 3-phase program. Phase 1: quadriceps muscle strengthening; Phase 2: FES cycling progression until 30 continuous minutes; Phase 3a: 30-min continuous FES-cycling 3x/wk for 24 sessions; Phase 3b: extra 30-min sessions of FES cycling with simultaneous arm ergometry, 3x/wk for 24 sessions. *Main outcome:* BMD by DXA.	At baseline, BMD was significantly lower for participants at the hip ($p < .025$) for bilateral trochanters, Ward's triangles, and femoral necks, but not lumbar spine compared with able-bodied reference values. Only the L2-L4 values had a positive training gain of .02 g/cm^2 ($p = .056$). Further training (Phase 3b) did not demonstrate further increase in BMD at any site.

(continued)

Table 7. Continued

Author, year Downs & Black score Design	Method	Results
Hangartner et al.,[46] 1994 D&B = 9 **Pre-post**	**15 men and women aged 17–46 yrs with complete and incomplete injury between C5-T10; no controls**. Modality: MES + FES cycle ergometer, 12–24 wks. Group 1: MES knee extension exercises ($n = 6$); group 2: FES cycling ($n = 9$). Sessions were 3x/wk for 12 wk; 9/15 had additional 12 wks with 3 of the MES switching to FES cycling. *Main outcome:* Computed tomography.	Participants in the exercise groups continued to lose bone at the distal and proximal end of the tibia, but it was less than expected from the regression lines.
Chen et al.,[47] 2005 D&B = 9 **Pre-post**	**15 men aged 23–37 yrs with complete injuries between C6-T8; 15 able-bodied controls as reference values**. Modality: FES cycle ergometer, 6 months. Participants performed FES cycling exercises with minimal resistance for 30 min/d, 5 d/wk for 6 months. Follow-up 6 months after intervention. *Main outcome:* BMD by DXA.	At baseline, SCI participants' BMD at the femoral neck, distal femur, and proximal tibia was lower than able-bodied controls. After 6 months, significant increase BMD of the distal femur (.0798 g/cm^2) and proximal tibia (.0715 g/cm^2) ($p < .05$) and calcaneus showed a trend (.0112 g/cm^2, $p > .05$) toward increasing with FES cycling. Significant decrease BMD in the distal femur, proximal tibia, and heel during 6 months following end of intervention ($p < .05$). Progressive nonsignificant decrease of BMD of the femoral neck during 6 month FES cycling program ($p > .05$).
Mohr et al.,[48] 1997 D&B = 9 **Pre-post**	**10 men and women aged 27–45 yrs with injuries either C6 or T2; no controls.** Modality: FES cycle ergometer, 12–18 months. Stimulated the legs for 30 min, 3x/wk for 12 months, followed by 1x/wk for 6 months. *Main outcome:* BMD by DXA, biochemical markers.	After 12 months of training, there was a significant 10% increase in proximal tibia BMD ($p< .05$) but no change at the lumbar spine or femoral neck. After 6 months of reduced training, BMD for the proximal tibia returned to baseline. Blood and urine markers were within normal limits at baseline and there was no significant change with FES.

Note: BMD = bone mineral density; d = day; DXA = dual-energy X-ray absorptiometry; FES = functional electrical stimulation; MES = muscular electrical stimulation; SCI = spinal cord injury; wk = week; yr = year.

Table 8. Studies using standing or walking for bone health after spinal cord injury in participants more than 1 year postinuury

Author, year Downs & Black score Design	Method	Results
Standing (n = 4 studies)		
Kunkel et al.,[49] 1993 D&B = 12 **Pre-post**	**6 men aged 36–65 yrs with complete and incomplete C5-T12; no controls.** Modality: Passive standing frame, 5 months. Increased gradually until able to "stand" 30 min 3x/d. Progressed to 45 min 2x/d then participants maintained 45 min of standing 2x/d for 5 months. *Main outcome:* BMD and fracture risk by DPA.	No significant change in fracture risk as measured with BMD for femoral neck or lumbar spine with "standing."
Needham-Shropshire et al.,[50] 1997 D&B = 10 **Pre-post**	**16 men and women mean age 29 yrs with complete injuries between T4-T11; no controls.** Modality: Standing and ambulation, 32–40 wks. 32 sessions then continued ambulation for 8 more wks. *Main outcome:* BMD by DPA.	No significant changes in BMD in the femoral neck, Ward's triangle, or trochanter.
Kaplan et al.,[51] 1981 D&B = 8 **Pre-post**	**8 men and women aged 19–56 yrs with incomplete tetraplegia; no controls.** Modality: Tilt-table weight bearing and strengthening exercises. Each tilt table session lasted ≥20 min 1x/d and the tilt-table angle attained was ≥45°. Two groups: (a) early = within 6 months of SCI, and (b) late group = 12–18 months post SCI. *Main outcome:* Urinary calcium excretion.	Significant improvement ($p < .01$) in calcium excretion, urinary calcium, and calcium balance for the early group. The late group had a significant improvement for urinary calcium and calcium balance.
Walking (n = 3 studies)		
Giangregorio et al.,[52] 2006 D&B = 20 **Pre-post**	**14 men and women aged 22–53 yrs with incomplete injuries from C4-T12; ASIA B, C; no controls.** Modality: Body-weight–supported treadmill training, 12 months. Completed protocol 3x/wk for 144 sessions; intensity increased as tolerated. *Main outcome:* DXA, CT, serum and urinary bone markers at baseline and after 6 and 12 months of training.	There were no significant changes in bone density or bone geometry at axial or peripheral sites with the exception of a small but significant decrease in whole body BMD. No significant difference in bone markers.

(continued)

Table 8. Continued

Author, year **Downs & Black score** **Design**	**Method**	**Results**
Ogilvie et al.,[53] 1993 D&B = 8 **Pre-post**	**Bone assessment with 2 men and 2 women aged 16–42 yrs with paraplegia; no controls.** Modality: Reciprocal gait orthosis (RGO). No protocol provided. QCT repeated every 6 months from the first referral, orthotic fitting and training, to independent ambulation (mean 5 months). The RGO was used daily on average for 3 hr. *Main outcome:* BMD by QCT.	3 of 4 participants increased or maintained femoral neck BMD but no change in lumbar spine.
Thoumie et al.,[54] 1995 D&B = 8 **Pre-post**	**For bone assessment, there were 6 men and 1 woman aged 26–33 yrs with injuries between T2-T10; no controls.** Modality: Reciprocal gait orthosis (RGO)-II hybrid orthosis. Completed the protocol within 3–14 months (2-hr sessions 2x/wk). *Main outcome:* BMD by DPA.	At baseline, participants (compared with age-matched *Z* score) had no significant change in lumbar spine BMD but a decrease in femoral neck BMD. After the training program (16 months), no consistent changes at the femoral neck BMD among participants (4 participants decreased BMD, 1 participant increased BMD, and no change in 2 participants).

Note: BMD = bone mineral density; d = day; DPA = dual photon absorptiometry; DXA = dual-energy X-ray absorptiometry; min = minute; QCT = quantitative computed tomography; SCI = spinal cord injury; wk = week.

Discussion

The risk for low trauma fractures after an SCI has been established, and low bone mass is an important factor to be considered. In 2002, the Canadian Medical Association published clinical practice guidelines for prevention and treatment of bone health[18]; although these guidelines do not specifically address persons with SCI, they do provide a resource for osteoporosis diagnosis, prevention, and treatment. Extrapolating from these guidelines to the SCI population may not be valid given the unique mechanisms underlying osteoporosis following SCI and the varying responses to treatment. For example, weight bearing has been shown to be effective in other populations but not with individuals with SCI. Future guidelines should provide recommendations for people who have paralysis such as after a stroke, SCI, multiple sclerosis, or other neurological impairments that lead to reduced weight bearing, muscle activity, and physical activity levels. We chose to separate the studies based on the time since injury. Although the separation point (1 year) is somewhat arbitrary, we did not want to compare studies attempting to prevent the rapid bone loss immediately following an SCI to the slower rate of loss in the chronic phase.

In the past 40 years, there have been a number of investigations aimed at maintaining or reducing bone loss after SCI, yet consistent methodological oversights have emerged including small sample sizes and broad inclusion criteria that do not always account for gender, time since injury, or impairment differences between participants. The pharmacological interventions (either prevention in the first year postinjury or treatment interventions in the chronic phase) discussed here report stronger methodologies— these were given PEDro scores ranging from 6 to 10 (out of 10) indicating moderate-to-high quality. In contrast, the studies employing rehabilitation modalities had very low numbers of participants and few control groups; only 3 of the 22 studies were RCTs. In addition, if indeed the rapid loss of bone mass after an SCI has a neurogenic response, then it may not be surprising that rehabilitation modalities that are based on mechanical loading may not be effective. Alternatively, the loading may not have been sufficiently high, as some recent studies[39,40] show promising success with muscle stimulation applying large compressive forces (1.5 times body weight). These factors contribute to difficulties in drawing generalizable conclusions regarding the impact of rehabilitation interventions on bone parameters. Nonetheless, the lack of available evidence to establish the effectiveness of these rehabilitation modalities on bone parameters does not negate these treatments as beneficial to other body systems. For example, FES cycling may have small effects on bone, but this modality has been shown to have significant effects on cardiovascular health.[55]

This review has provided support for using first-generation oral bisphosphonates for prevention and third-generation bisphosphonates for treatment for low bone mass. Despite the benefits of these medications, they are not without their complications. Oral bisphosphonates must be ingested on an empty stomach, with 4–8 oz of water, followed by sitting up for 1-hour after ingestion prior to taking any other food or medication. Oral bisphosphonate therapy can cause side effects. Joint pain and stomach upset are the most frequently reported adverse effects, and avascular necrosis of the jaw and gastric

ulcer are the most serious adverse effects. Intravenous formulations of bisphosphonates are available in daily, monthly, and quarterly preparations and have a greater relative potency. They are attractive due to the flexibility in dosing regimens, assured compliance, and the reduced relative risk of an adverse upper gastrointestinal event. Common short-term side effects of IV bisphosphonates include fever, low serum calcium, and transient decrease in white blood cells. They should be used with caution in premenopausal women due to the unknown effects of these medications on the fetus during pregnancy. Patients taking acetylsalicylic acid (ASA), corticosteroids, or nonsteroidal anti-inflammatory drugs (NSAIDS) may require preventative measures, because using these medications with bisphosphonates increases the relative risk of upper gastrointestinal side effects.[56]

Due to the nature of different bone outcomes (BMD by DPA, DXA, CT, QCT or pQCT, urine or blood markers), it can be difficult to compare across studies because all use secondary or tertiary surrogates for bone strength. When parameters such as urine or blood biomarkers are measured, studies of short duration may yield significant results. However, with imaging, cortical bone remodelling can take at least 6 months in order to demonstrate changes within participants over time. Consequently, investigations that did not maintain an intervention for at least 6 months may not show changes, but the results cannot necessarily be interpreted as negative. All outcomes for bone health after an SCI are surrogate measures, that is, there has yet to be a study published in this area that investigates the effect of an intervention (either pharmacological or nonpharmacological) on reducing low trauma fractures. Although costly due to the large number of required participants and long follow-up time, studies based on fracture as the primary outcome are the next step in determining the clinical significance of the interventions.

Future directions

Despite the evidence discussed in this article, more research is essential to understand the etiology of bone loss as well as bone response to interventions after an SCI. In particular, our understanding of bone response to an SCI would be greatly enhanced with a large prospective longitudinal investigation (such as a national registry) to provide a foundation of knowledge about bone loss, injury patterns, and mechanisms. This article also highlights measurement limitations that currently exist for measuring bone outcomes. Almost all of the previous studies that used imaging used total leg DXA variables, but recently researchers have used a DXA method to target just the knee area.[40,57] If we are not measuring directly over the relevant areas, we may miss an effect of the intervention. To understand what bone improvements mean for this population, more research is essential to define a clinically significant difference. For example, if an individual loses a significant proportion of bone mass after an SCI, is an intervention that only provides a 10% increase in bone density sufficient to protect against a future fragility fracture? As low-trauma fractures occur as a result of diminished bone mass and propensity to fall, a comprehensive rehabilitation program is essential to educate about bone loss, teach safe transferring skills, and review potential fracture signs and symptoms to observe after a fall.[58]

Conclusion

There is a significant risk for lower extremity fragility fractures after an SCI; the risk increases with gender, severity of initial injury, and time since injury. Early assessment and ongoing monitoring of bone health is an essential element of SCI care. There is level 1 evidence for the prevention and treatment of bone loss using bisphosphonates (clodronate, etidronate, and alendronate) that may maintain BMD or slow the decline of BMD after SCI. There is level 1 evidence that ultrasound does not prevent bone loss in the first year after an SCI but a lack of definitive evidence supporting nonpharmacological interventions for the treatment of bone loss after an SCI with the exception of MES. The rehabilitation treatment literature is limited by small studies, different treatment protocols, participant groups that are heterogeneous, relatively short treatment sessions given the time required to detect improvements in bone parameters, and variability with imaging technologies and measured primary regions of interest.

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