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

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Abstract

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 a SCI especially in the lower extremity. Therefore, 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 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, non-pharmacological evidence for preventing and treating bone loss is limited.

Keywords

Spinal cord injury; osteoporosis; pharmacology; functional electrical stimulation; rehabilitation

INTRODUCTION

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 2–4 times that of people confined to prolonged bedrest but without a SCI¹ 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 months². 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 bone mass⁵ and suggest that a steady-state of lower extremity bone mineral homeostasis is not reached within 3 years⁶.

The immediate and excessive loss of bone mass post 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 unknown. Given the magnitude of response that occurs so rapidly, 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 that may better account for the observed changes.⁷

Fracture risk following a SCI

A high incidence of lower extremity fragility fractures (1–46%) exist in people who sustain a SCI^{8–17} and the majority of fragility fractures occur during transfers or activities that involve minimal or no trauma⁸. The lower extremity is most at risk for this population, consistent with site-specific decreases in bone mineral density such that fractures of the distal femur were 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 (tibia)¹⁸. Recently Garland and colleagues reported fracture thresholds at the knee comparing bone mineral density (BMD) using dual energy X-ray absorptiometry (DXA) and history of fragility fractures in participants with a SCI¹⁹.

There are many notable risk factors for fragility fractures after SCI. There is a greater risk for women compared with men^{12,17}, with increasing age, longer time since injury and low BMI¹⁹. Further, paraplegics have more fractures compared with tetraplegics and those with complete injuries have greater bone loss compared with incomplete injuries¹⁷. 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 SCI²⁰.

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. Areal (i.e., two-dimensional) bone mineral density is quantified non-invasively with imaging technologies such as dual energy X-ray absorptiometry (DXA) and previously with dual energy photon absorptiometry (DPA). Dual energy X-ray absorptiometry is considered by the World Health Organization as the “gold or criterion standard” to diagnose osteoporosis and is the most widely used assessment technique for osteoporosis. Volumetric bone mineral density 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 it at the tissue and cellular level to provide an in-depth 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, using this as the outcome is very difficult for this population due to the large numbers needed to be recruited and followed for an extended period of time. Consequently,

to date there have not been any clinical trials testing interventions and powered for fracture reduction in this population.

Treatment Options for Low Bone Mass after a SCI

In this section we summarize therapies used to optimize bone health after a SCI. We have divided the sections based on the time frame since initial injury because of the more rapid loss of bone early after a spinal cord injury: 1) less than one year since injury and 2) greater than one 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 exists 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 were 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 prescriptions. Intravenous (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 a 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 a SCI for bone health aim to stimulate muscle and encourage weight-bearing. Both muscular electrical stimulation (MES) and functional electrical stimulation (FES) use cyclical patterns of electrical stimulation that simulate muscular activity but FES is directed towards the attainment of purposeful tasks such as cycling or walking. Muscular simulation 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 simulate a cycling pattern. Weight-bearing activities have also been tested for bone health after a SCI. These can include either passive (tilt-table) or active (FES- assisted walking device) weight-bearing activities.

The purpose of this manuscript was to identify and appraise the bone health and SCI literature and to provide best evidence for individuals with a SCI. We have focused on interventions that target two phases of transition for bone mass after a spinal cord injury; i) immediately after the initial injury (acute phase) and ii) greater than 12 months after the injury when low bone mass has been established (chronic phase). In the acute phase the

over-riding goal is to minimize regional declines in bone mass while after this period, treatment is focused on the improvement of bone health and the reduction of risk for fragility fractures. Specifically our guiding questions were, i) What treatments prevents acute regional declines in bone mineral density after a SCI, and ii) How do we treat low bone mass of the lower extremity for people living with longstanding SCI?

METHODS

Search Strategy

A literature search was completed using multiple databases (PUBMED/MEDLINE, CINAHL, EMBASE, PSYCHINFO) to identify all potential trials published from 1980–2006 regardless of study design, focusing on research involving humans and published in English. The keywords 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 and agree by consensus all articles 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 PEDro scale ²¹, while the Downs and Black (D&B) scale was used to assess non-RCTs ²². Table 1 is a summary of the levels of evidence used to critique the literature. A more complete account of the methodology used in this systematic review is found in the first article of this series ²³.

RESULTS

In total 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 post-injury included 6 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 bisphosphonates resulted in a reduction of bone loss compared with a control group. The two studies which report that first generation bisphosphonate Clondronate maintained bone outcomes were short in duration (3-month intervention) and participants had less severe injuries (paraplegia, incomplete SCI) ^{25, 28}. In studies using Etidronate ²⁷ (first-generation) and Pamidronate ²⁹ (second-generation), both groups continued to lose bone, except ASIA D participants who preserved bone density in the lower extremity while participants with ASIA A had the greatest decline in both studies. A recent study which used second-generation bisphosphonates (Pamidronate) and a longer intervention period, found no

significant differences between groups for bone loss after 1 year²⁴. One study found a significant improvement in histomorphometric total bone volume using Tiludronate (third-generation bisphosphonate)²⁶. Therefore, for *the first year post-injury*, there is Level 1 evidence from randomized controlled trials that Clodronate prevents a decrease in BMD of the hip and knee region with limited side effects on bone 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 SCI²⁷. There is Level 1 evidence that Tiludronate was effective in increasing total bone volume using histomorphometry. There is Level 1 evidence that Pamidronate 30 mg IV or 60mg 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 greater than 1 year post-injury included 3 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 Brioto 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 as Zehnder et al.³² did not include patients with tetraplegia, while Moran de Brioto et al.³¹ did. More recently, Bauman et al. found a significant improvement in bone outcomes using a Vitamin D analog highlighting its potential benefit³³. Therefore, for people who are greater than 1 year post injury, there is Level 1 evidence that Alendronate 10 mg daily and Calcium 500mg orally 3x/day was effective for the maintenance of BMD of the wrist, hip and knee region for men living with paraplegia³². Finally, there is Level 1 evidence for Vitamin D analogs to maintain good bone health³³.

Non-Pharmacological Interventions in the First Year Post-SCI

The evidence for non-pharmacological prevention of SCI bone loss included 8 investigations (n=143 participants). This includes 3 RCTs^{34–36} (54 participants), 4 non-randomized controlled trials^{37–40} (84 participants) and 1 pre-post study⁴¹ (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 needs to be determined. There is Level 2 evidence that MES maintained or improved bone mass. However, in general, the evidence suggests that rehab modalities were not successful in slowing bone loss in the first year following a SCI. There is Level 1 evidence from one RCT that short-term (6 weeks) ultrasound was not effective for treating bone loss³⁶ and Level 2 evidence that FES-cycling did not improve or maintain bone at the tibial midshaft in the first year following a SCI³⁷. There is Level 4 evidence that walking and standing did not maintain bone mass in the first year following a SCI.

Non-Pharmacological Treatment Strategies in the Chronic Phase—The evidence for non-pharmacological treatment of SCI bone loss in participants with injuries greater than one year (chronic phase) 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 (1 limb as the treatment vs. control limb) (Table 6). Following 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 areas⁴².

For FES-Cycling there were conflicting results for bone parameters from the 6 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 stopped⁴⁸ and Chen et al.⁴⁷ found an improvement of BMD at the hip with cycling. The FES-cycling study which reported a positive effect on site-specific bone parameters used a protocol that was 3 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 4 pre-post studies. Therefore there is Level 4 evidence that FES-Cycling did not improve bone mass.

Standing practice has been shown to reduce hypercalciuria⁵¹, 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 bone mineral density.

DISCUSSION

The risk for low trauma fractures after a 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 health¹⁸, and although these guidelines do not specifically address persons with spinal cord injury, they do provide a resource for osteoporosis diagnosis, prevention and treatment. 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 timeframe 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 a spinal cord injury to the slower rate of loss in the chronic phase.

In the past 40 years there have been a number of investigations aimed to maintain or reduce 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 post-injury or treatment interventions in the chronic phase) discussed here report stronger methodologies— these were given PEDro scores

ranging from 6–10 (out of 10) indicating moderate to high quality. In contrast, the studies employing rehab 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 a SCI has a neurogenic response, then it may not be surprising that rehab 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 drawing generalizable conclusions regarding the impact of rehab interventions on bone parameters. Nonetheless, despite the lack of available evidence to establish the effectiveness of these rehab modalities on bone parameters, it 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 health⁵⁵.

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 4–8oz of water, followed by sitting up for one-hour post ingestion prior to taking any other food or medication. Oral bisphosphonate therapy can cause side effects; joint pain and stomach upset being the most frequently reported adverse effects. Intravenous formulations of bisphosphonates are available in daily, monthly and quarterly preparations, and have a greater relative potency and 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 pre-menopausal women due to the unknown effects of these medications on the fetus during pregnancy. Patients taking acetylsalicylic acid (ASA), corticosteroids or NSAIDS may require preventative measures because using these medications with bisphosphonates increases the relative risk of upper gastrointestinal side effects⁵⁶.

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 especially since all used secondary or tertiary surrogates for bone strength. When measuring parameters such as urine or blood biomarkers, studies of short duration may yield significant results. However, using imaging, cortical bone remodelling can take at least 6 months in order to observe 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. Importantly all outcomes for bone health after a 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 non-pharmacological) 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 to be able to determine the clinical significance of the interventions.

Future Directions

Despite the evidence discussed in this manuscript, more research is essential to understand the etiology of bone loss as well as bone response to interventions after a SCI. In particular, our understanding of bone response to a SCI would be greatly enhanced with a large prospective longitudinal investigation (such as a national registry) to provide a foundation to understand bone loss, injury patterns and mechanisms. This paper 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, however, 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. Importantly, in order to understand what bone improvements mean for this population, more research is essential to understand a clinically significant difference. For example, if an individual loses a significant proportion of bone mass after a SCI, does 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 fall⁵⁸.

Conclusion

There is a significant risk for lower extremity fragility fractures after a 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 slow the loss of BMD after SCI. There is Level 1 evidence that ultrasound does not prevent bone loss in the first year following a SCI but a lack of definitive evidence supporting non-pharmacological interventions for the treatment of bone loss after a SCI with the exception of MES. The rehab 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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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)	Randomized controlled trial, PEDro score ≥ 6. Includes within subjects comparison with randomized conditions and cross-over designs
Level 2	RCT	Randomized controlled trial, PEDro score < 6.
	Prospective controlled trial	Prospective controlled trial (not randomized)
	Cohort	Prospective longitudinal study using at least 2 similar groups with one exposed to a particular condition.
Level 3	Case control	A retrospective study comparing conditions, including historical controls
Level 4	Pre-post	A prospective trial with a baseline measure, intervention, and a post-test using a single group of subjects.
	Post-test	A prospective post-test with two or more groups – intervention, then post-test (no pre-test or baseline measurement) using a single group of subjects.
	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

Table 2

Summary of the Levels of Evidence for bone health treatment options tested in individuals who sustain a SCI.

Treatment Option	Time Phase	Positive Result	Levels of Evidence
Pharmacology			
Clodronate	Less than < 1 year post-injury	Yes	Level 1
Etidronate	Less than 1 year post-injury	Yes	Level 1
Tiludronate	Less than 1 year post-injury	Yes	Level 1
Pamidronate	Less than 1 year post-injury	No	Level 1
Alendronate	Greater than 1 year post-injury	Yes	Level 1
Vitamin D Analog	Greater than 1 year post-injury	Yes	Level 1
Rehab Modalities			
FES-Cycling	Less than 1 year post-injury	No	Level 2
MES	Less than 1 year post-injury	Yes	Level 2
Standing/Walking	Less than 1 year post-injury	No	Level 2, 4
Ultrasound	Less than 1 year post-injury	No	Level 1
FES-Cycling	Greater than 1 year post-injury	No	Level 4
MES	Greater than 1 year post-injury	Yes	Level 4
Standing/Walking	Greater than 1 year post-injury	No	Level 4

FES= functional electrical stimulation; MES= muscular electrical stimulation

Table 3

Studies using pharmacology for bone health after a SCI in participants who were less than 1 year post-injury.

Authors, Year PEDro Downs & Black Score, Design	Methods	Results
Bauman et al.²⁴ 2005 PEDro=10 RCT	14 men and women aged 21–61 years with motor complete tetra/paraplegia. Medication: Pamidronate ⁺ , 12 months. Participants randomized to 1) 60mg IV or placebo (saline) at 1, 2, 3, 6, 9, 12 months post SCI. (N=6) or 2) Placebo (N=5). <i>Main outcome:</i> BMD by DXA, bone turnover markers.	No significant between group differences in BMD loss or bone formation markers at 1 year. Pamidronate Group had significantly lower 24-hour urinary calcium at one month compared with Placebo Group ($p < 0.05$).
Minaire et al.²⁵ 1981 PEDro=10 RCT	21 men and women aged 15–54 years with complete paraplegia. Medication: Clodronate [*] , 3.5 months. Participants randomized to 1) 400mg per day (N=7), 2) 1,600 mg per day (N=7) or 3) Placebo (N=7) for 3.5 months. <i>Main outcome:</i> 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 years with injuries between C5-T12. Medication: Tiludronate [*] , 3 months. Participants randomized to 1) 400 mg/day (N=7), 2) 200 mg/day (N=7) or 3) Placebo (N=6). <i>Main outcome:</i> histomorphometry.	↑ in total bone volume in the Tiludronate Group 1(400mg/day) compared with Tiludronate Group 2 (200mg/day) and Placebo group. Increased bone resorption indicators in the Placebo group compared with Tiludronate groups.
Pearson et al.²⁷ 1997 PEDro=8 RCT	13 men and women aged 22–57 with injuries between C5- T12, ASIA A or D. Medication: Etidronate [*] , 30 weeks. Participants randomized to 1) 800mg daily (N=6) or 2) Conventional rehab and calcium 1000mg/day (N=7). <i>Main outcome:</i> 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.
Minaire et al.²⁸ 1987 PEDro=7 RCT	21 men and women aged 15–54 years with complete paraplegia. Medication: Clodronate [*] , 100 days. Participants randomized to 1) 400mg per day (N=7), 2) 1,600 mg per day (N=7) or 3) Placebo (N=7). <i>Main outcome:</i> histomorphometry, DXA, biochemical bone turnover markers.	Greater ↑ 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 (non-randomized)	24 men and women aged 25–57 with injuries between C5-T12, ASIA A–D. Medication: Pamidronate ⁺ , 6 months. Participants given 1) 30mg IV every 4 weeks × 6 doses (total 180mg/participant) (N=14) or 2) Conventional rehab (N=10). <i>Main outcome:</i> 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 ($p=0.02$).

BMD= bone mineral density; DXA=dual energy X-ray absorptiometry; ASIA= American Spinal Injury Association Classification.

^{*} First generation bisphosphonate;

⁺ Second generation bisphosphonate;

Third generation bisphosphonate.

Table 4
Studies using pharmacology for bone health after a SCI in participants who were greater than 1 year post-injury.

Authors, Year PEDro Score, Design	Methods	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 µgms 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. <i>Main outcome:</i> 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 years with complete injuries between T1-L3 ASIA A,B. Medication: Alendronate , 24 months 1) 10mg per day plus 500mg Calcium per day (N=33) or 2) Calcium alone (500mg per day) (N=32) for 6-months. <i>Main outcome:</i> BMD by DXA and bone turnover markers.	Decreased tibial BMD in Calcium-only Group but remained stable in the Alendronate Group (p = 0.017). 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 decrease 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 , 6 months. 1) 10mg and Calcium 500mg bid (N = 10) or 2) Calcium-only (500mg bid) (N=9). <i>Main outcome:</i> 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 BMD and lower extremity T-score.

BMD= bone mineral density; DXA=dual energy X-ray absorptiometry; ASIA= American Spinal Injury Association Classification.;

Third generation bisphosphonates.

Table 5

Studies using rehabilitation modalities for bone health after SCI for participants less than 1 year post-injury.

Authors, Year PEDro/Downs & Black Score Design	Methods	Results
FES- Cycle ergometer		
Eser et al. ³⁷ 2003 D&B=14 Controlled trial (non- randomized)	38 men and women mean age 33 years 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 minutes, then 3 days FES-cycle and 2 days passive standing per week. The Control Group performed 30 minutes of passive standing 5 days a week. <i>Main outcome:</i> 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 2006 D&B=21 Controlled trial (non- randomized)	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 day, 5 day/week, 5 months (n=23); or Control Group (no treatment) (n=10). <i>Main outcome:</i> DXA at 3 weeks, 3 and 6 months post-injury.	MES was safe and well tolerate but there was only a minimal difference between groups for total body BMD only at 3 months post injury (p<0.01). Other DXA measures (hip, spine BMD, FM) did not differ between groups at any time.
Shields et al. ⁴⁰ 2006a D&B=15 Controlled trial (non- randomized)	6 men with complete injuries from C5-T10; started study within 6 weeks of injury. Within-participant design. Modality: MES at 1.5 body-weight; 3 years. 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/week. <i>Main outcome:</i> 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 < 0.05).
Shields et al. ³⁹ 2006b D&B=15 Controlled trial (non- randomized)	7 men with complete injuries from C5-T10; started study within 6 weeks of injury. Within-participant design. Modality: MES at 1.5 body-weight; 2–3 years. Treatment leg only received a home program of MES to stimulate leg plantar flexors with 35 min protocol (4 bouts/day with 5 min rest between bouts) for 5x/week. <i>Main outcome:</i> 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 weeks. Treatment leg only received weight-bearing on a tilt-table for 30 minutes, 3X/week. Wedge applied to treatment leg to provide adequate dorsiflexion and weight bearing to the ankle. Control leg was not loaded in standing. <i>Main outcome:</i> DXA proximal femur	No clinically significant effect on proximal femur BMD in treatment group, but a 4° improvement in ankle mobility.
de Bruin et al. ³⁵ 1999 PEDro=6 RCT	19 men aged 19–59 years with injuries between C4-T12, ASIA A-D. Modality: Standing/Walking, 25 weeks. Control Group 1 had 0–5 hrs per week loading exercises with standing frame. Group 2 had 5+hours of standing exercises per week (standing), and Group 3 had 5+hours of standing and treadmill (walking). Interventions lasted 25 weeks. <i>Main outcome:</i> 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<0.05).

Authors, Year PEDro/Downs & Black Score Design	Methods	Results
Treadmill training		
Giangregorio et al. ⁴¹ 2005 D&B=13 Pre-post	2 men and 3 women aged 19–40 years with injuries between C3–C8 ASIA B and C; No controls. Modality: Body-weight supported treadmill, 6–8 months. Session started at 5 minutes and was increased gradually to 10–15 minutes in all but 1 participant during 48 sessions of 2x/week. <i>Main outcome:</i> 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 years with injuries between C5–T10 ASIA A–B (Within group design). Modality: Pulsed therapeutic ultrasound, 6 weeks. Applied to both calcanei for each participant for 20 minute/day, 5x/week. Right and left calcanei within each participant was randomized. <i>Main outcome:</i> BMD by DXA and QUS.	For specified dose, no significant effect of therapeutic ultrasound for any skeletal measurement parameter (p>0.05).

FES= functional electrical stimulation; MES= muscular electrical stimulation; BMD= bone mineral density; DXA=dual energy X-ray absorptiometry; pQCT= peripheral quantitative computed tomography; ASIA= American Spinal Injury Association Classification; QUS= quantitative ultrasound.

Table 6

Studies using Muscular Electrical Stimulation (MES) for bone health after SCI in participants who were greater than 1 year post-injury.

Authors, Year Downs & Black Score Design	Methods	Results
Bélanger et al. ⁴² 2000 D&B=11 Pre-post	14 men and women aged 23–42 years with complete and incomplete injuries between C5-T6: 14 able-bodied controls: Able bodied controls as reference values. Modality: MES, 24 weeks. Quadriceps MES was conducted 5 days/week. Participants trained for 1 hr/day or until fatigued. Right quadriceps stimulated with no resistance (against gravity) while the left quadriceps stimulated against resistance. <i>Main outcome:</i> BMD by DXA	At baseline, BMD from the SCI group was lower at the distal femur, proximal tibia and mid-tibia (decrease ranged: 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<0.05) for participants with SCI, but 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 weeks. Each participant trained for a total of 36 sessions (3x/week) using a progressive intensity protocol for MES stimulated knee extension. This progression was continued to a maximum 15 kg load. <i>Main outcome:</i> BMD by DXA	Although tibial BMD was not changed after MES protocol (p>0.05), it was better than predicted values.

SCI= spinal cord injury; MES= muscular electrical stimulation; BMD= bone mineral density; DXA=dual energy X-ray absorptiometry.

Table 7

Studies using FES Cycle Ergometry for bone health after SCI in participants greater than 1 year post-injury.

Authors, Year Downs & Black Score Design	Methods	Results
Leeds et al. ⁴⁴ 1990 D&B=12 Pre-post	6 men aged 18–27 years 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/week for 1 month. Cycle ergometry sessions were 3X/week, 30 minutes for 6 months. <i>Main outcome:</i> 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 years with paraplegia: No controls. Modality: MES+ FES-cycle ergometer, up to 32 weeks. Part 1: quadriceps strengthening with ↑ load ranging from 1.4–11.4 kg bilaterally for 15 minutes for 5x/week (10 weeks). Part 2: cycle ergometer at 50 rpm with resistance (0–18.75 W), 15 minutes, 5x/week (32 weeks). <i>Main outcome:</i> 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 years with complete injuries between C5–T12: No controls. Modality: MES+ FES-cycle ergometer, 24–48 weeks. 3-phase program. Phase 1: quadriceps muscle strengthening. Phase 2: FES cycling progression until 30 continuous minutes. Phase 3a: 30-minutes continuous FES-cycling 3x/week for 24 sessions. Phase 3b: An extra 30-minute sessions of FES-cycling with simultaneous arm ergometry, 3X/week for 24 sessions. <i>Main outcome:</i> BMD by DXA	At baseline, BMD was significantly lower for participants at the hip ($p<0.025$) for bilateral trochanters, Wards 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 ($p=0.056$). Further training (Phase 3b) did not demonstrate further increase in BMD at any site.
Hangartner et al. ⁴⁶ 1994 D&B=9 Pre-post	15 men and women aged 17–46 years with complete and incomplete injury between C5–T10: No controls. Modality: MES+ FES-cycle ergometer, 12–24 weeks. <i>Group 1:</i> MES knee extension exercises (n=6); <i>Group 2:</i> FES cycling (n=9); Sessions were 3x/week for 12 weeks; 9/15 had additional 12 weeks with 3 of the MES switching to FES cycling.. <i>Main outcome:</i> 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 years 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 minutes/day, 5 days/week for 6 months. Follow-up 6 months after intervention. <i>Main outcome:</i> 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 ↑ BMD of the distal femur (.0798 g/cm ²) and proximal tibia (.0715 g/cm ²) ($p<0.05$) and calcaneus showed a trend (.0112 g/cm ² , $p>0.05$) toward increasing with FES-cycling. Significant ↓ BMD in the distal femur, proximal tibia, and heel during 6 months following end of intervention ($p<0.05$). Progressive non- significant ↓ of BMD of the femoral neck during 6 month FES-cycling program ($p>0.05$).
Mohr et al. ⁴⁸ 1997 D&B=9 Pre-post	10 men and women aged 27–45 years with injuries either C6 or T2: No controls. Modality: FES cycle ergometer, 12–18 months. Stimulated the legs for 30 min, 3x/week for 12 months, followed by 1x/week for 6 months. <i>Main outcome:</i> BMD by DXA, biochemical markers.	After 12 months of training, there was a significant 10% ↑ in proximal tibia BMD ($p<0.05$) but no change at the lumbar spine or femoral neck. After 6 months of reduced training, BMD for the proximal tibia returned to

Authors, Year Downs & Black Score Design	Methods	Results
		baseline. Blood and urine markers were within normal limits at baseline and there was no significant change with FES.

SCI= spinal cord injury; FES= functional electrical stimulation; MES= muscular electrical stimulation; BMD= bone mineral density; DXA=dual energy X-ray absorptiometry; ↑ = increase; ↓ =decrease; QUS= quantitative ultrasound.

Table 8

Studies using standing or walking for bone health after SCI in participants greater than 1 year post-injury.

Authors, Year Downs & Black Score Design	Methods	Results
Standing (n=4 studies)		
Kunkel et al. ⁴⁹ 1993 D&B=12 Pre-post	6 men aged 36–65 years with complete and incomplete C5–T12: No controls. Modality: Passive standing frame, 5 months. Increased gradually until able to “stand” 30 minutes 3x/day. Progressed to 45 minutes 2x/day then participants maintained 45 minutes of standing 2x/day for 5 months. <i>Main outcome:</i> 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 years with complete injuries between T4–T11: No controls. Modality: Standing and ambulation, 32–40 weeks. 32 sessions then continued ambulation for 8 more weeks. <i>Main outcome:</i> 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 years with incomplete tetraplegia: No controls. Modality: Tilt-table weight-bearing and strengthening exercises. Each tilt table session lasted 20 minutes 1x/day and the tilt table angle attained was 45°. Two groups: 1) early = within 6 months of SCI and 2) late group=12–18 months post SCI. <i>Main outcome:</i> urinary calcium excretion	Significant improvement ($p<0.01$) 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 years with incomplete injuries from C4–T12: ASIA B, C: No controls. Modality: Body weight supported treadmill training, 12 months. Completed protocol 3x/week for 144 sessions; intensity increased as tolerated. <i>Main outcome:</i> 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.
Ogilvie et al. ⁵³ 1993 D&B=8 Pre-post	Bone assessment with 2 men and 2 women aged 16–42 years 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 hours. <i>Main outcome:</i> BMD by QCT	Three 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 was 6 men and 1 woman aged 26–33 years with injuries between T2–T10: No controls. Modality: Reciprocal Gait Orthosis (RGO)-II hybrid orthosis. Completed the protocol within 3–14 months (2- hour sessions 2x/week). <i>Main outcome:</i> BMD by DPA	At baseline, participants (compared with age- matched Z-score) had no significant change in L- 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).

SCI= spinal cord injury; BMD= bone mineral density; DPA=dual photon absorptiometry; QCT= quantitative computed tomography