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Professional

Bone Health Following Spinal Cord Injury

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Key Points

1.1 Bone Health & Fracture

- Fragility fractures of the distal femur and proximal tibia are common in people with spinal cord injury (SCI).
- Bone health monitoring should begin in the subacute phase after SCI given the anticipated substantial 30-50% declines in hip and knee region bone mass in the first year, and the associated lifetime increased fracture risk (~1-4% per year post-SCI).
- Individuals with chronic SCI and increased risk for lower extremity fragility fractures can be readily identified based on the completion of clinical history and fracture risk factor profile.
- Measuring and monitoring hip and knee region bone mineral density (BMD) after SCI are essential to identify low bone mass and quantify lower extremity fracture risk.
- Biomarkers provide clinical insight into the metabolic activity of bone, while imaging techniques provide insight into bone density, quality, and architecture. To date, no published prospective study has had sufficient power (sample size and study duration) to evaluate fracture risk reduction.

1.2 Bisphosphonates for Prevention of Sublesional Osteoporosis (SLOP) - Benefits

- The efficacy of bisphosphonates for the prevention of SLOP appear greater when administered early after SCI onset
- Oral tiludronate and clodronate prevent a decrease in hip and knee region BMD in men with paraplegia.
- Oral etidronate prevents a decrease in hip and knee region BMD among adults with incomplete paraplegia or tetraplegia who return to walking.
- Oral alendronate once weekly maintains hip region BMD.
- Once yearly intravenous infusion of zoledronate may reduce hip region BMD decline 12 months following administration.
- Pamidronate 30 mg or 60 mg intravenous 4x/year is <u>not</u> effective for the prevention of hip and knee region BMD loss early after SCI among adults with motor complete paraplegia or tetraplegia.
- In summary, there is limited evidence that bisphosphonates are moderately effective at preventing declines in hip and knee region BMD

by mitigating excessive resorption early after SCI among adults with motor complete paraplegia.

1.3 Bisphosphonates for Prevention of SLOP – Side effect control

- Bisphosphonates should be used with caution in 1) premenopausal women due to the unknown teratogenic effects of these medications on the fetus during pregnancy; or 2) patients with a prior history of cancer and radiotherapy due to the increased risk of osteonecrosis of the jaw.

- Short-term side effects of intravenous bisphosphonates include fever and transient low white blood cell count; oral bisphosphonates may cause heartburn, upset stomach and/or joint pain. Patients taking non-steroidal anti-inflammatory medication and /or anti-coagulants concurrently may require gastrointestinal prophylaxis to reduce the risk of developing upper GI bleeding.

- All bisphosphonates (oral or intravenous) may increase the risk of atrial fibrillation, osteonecrosis of the jaw, and atypical femur fracture.

- Treating physicians must weigh the relative risk of fracture versus the adverse sequelae of therapy, prior to prescribing oral or intravenous bisphosphonate therapy.

1.4 Pharmacologic Therapy for Treatment of SLOP

- Alendronate 10 mg daily and calcium 500 mg orally 3x/day is effective for the maintenance of BMD of the total body, hip, and knee region for men with paraplegia.
- Vitamin D supplementation results in maintenance of leg region BMD.

1.5 Non-pharmacologic Therapy for Prevention and/or Treatment of SLOP

- Short-term (6 weeks) therapeutic ultrasound is <u>not</u> effective for preventing BMD decline after SCI.
- Functional electrical stimulation cycling (FES-cycling) does <u>not</u> improve or maintain bone at the tibial midshaft in the acute phase.
- FES-cycling may increase lower extremity BMD over areas stimulated among adults with chronic SCI.

- Six months of activity-based training is effective for increasing spine BMD.
- Neuromuscular electrical stimulation can maintain or increase BMD over the stimulated areas.
- There is inconclusive evidence for reciprocating gait orthoses, long leg braces, passive standing, or self-reported physical activity as a treatment for low BMD.
- There is a lack of definitive evidence supporting non-pharmacological interventions for either prevention or treatment of SLOP after SCI.

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1 Executive Summary

There is overwhelming evidence that supports the importance of addressing bone health issues after spinal cord injury (SCI). Preserving bone mass and maintaining bone architecture are crucial to decrease an individual's future risk of developing a fragility fracture. Much of what we know about sublesional osteoporosis (SLOP) comes from published data about men with motor complete paraplegia of traumatic etiology.

A higher incidence of knee region fractures exists in people who sustain SCI and the majority of fractures occur following transfers or activities that involve minimal or no trauma (Comarr et al. 1962; Ragnarsson & Sell; 1981; Freehafer 1995). The distal femur and proximal tibia (knee region) are typically most at risk.

Sublesional osteoporosis (SLOP) is a condition that causes the weakening of bones in persons with SCI. It is characterized by excessive bone resorption, decreasing bone quality and an increased risk of lower extremity fragility fracture.

1.1 What bone health issues occur after SCI?

Within the first few days following SCI, there is an increase in excreted calcium (known as hypercalciuria) that is 2-4 times that of people without SCI who are confined to prolonged bed rest. Hypercalciuria results in excessive bone resorption or breakdown (Bauman & Spungen 2001).

Longitudinal studies showed a higher rate of hypercalcemia (excessive calcium in the blood) for people with acute SCI. This effect is more rapid in the first 4-6 months post-injury and usually slows for the remainder of the first-year post-injury (Hancock et al. 1979; Frey-Rindova et al. 2000).

Early studies also suggested that bone mineral density (BMD) stabilizes by 1-2 years after SCI at 25-50% below that of non-disabled peers in the hip and knee regions (Griffiths et al. 1976; Hancock et al. 1979; Garland et al.1992). More recent studies suggest a continual decline in BMD implying that a new lower extremity bone mineral homeostasis is not established in the chronic stage of injury (Demirel et al. 1998; Bauman et al. 1999; Eser et al. 2005).

Sublesional osteoporosis develops after SCI in response to several changes in the hormonal, vascular, inflammatory, neuromuscular, and autonomic nervous systems following SCI. In addition, changes to nutritional habits, weight-bearing and the amount of daily physical activity with ageing likely also contribute to SLOP severity. The relative contributions of each factor are not well delineated.

The declines in bone mass and changes in bone quality after SCI make people more susceptible to lower extremity fractures in response to seemingly minor stresses during day-to-day activities (i.e. fragility fracture) where the leg bones are twisted during a transfer or suddenly hyper flexed in a low velocity all from a wheelchair. About 1-4% of people with SCI will get a

Fragility fracture: A fracture occurring spontaneously or following minor trauma such as a fall from standing height or less. (Kanis et al. 2001; Bessette et al. 2008) fracture in any given year (Zehnder et al. 2004a) typically affecting the femur (thigh bone above the knee) and the tibia (shin bone below the knee).

Fragility fractures in persons with SCI are important to prevent because they can affect mobility, the ability to function in daily life, and can be a major cause of medical expenses. Fractures after SCI do not always heal and they may be associated with other complications of immobilization such as deep vein thrombosis, pressure injuries or cellulitis.

1.2 What are the risk factors for SLOP?

There are several risk factors for developing low bone mass after SCI, including female gender, paraplegia, motor complete injury of traumatic etiology and the duration of SCI.

Clinicians and patients should be most concerned about fracture risk, not just low hip and or knee region bone density. A treating clinician can readily identify patients with a high risk of fragility fracture (5 risk factors or **The big 2**) by completing the checklist on the right. Of these fracture risk factors, a prior fragility fracture and a low knee region BMD below the fracture threshold are the most potent predictors of future fracture (**The big 2**).

Lower Extremity Fragility Fracture Risk Factor Checklist after SCI (Craven et al. 2008; Craven et al. 2009; Cervinka et al. 2017)

- ☐ Age at Injury < 16 years
- ☐ Alcohol Intake > 5 servings/day
- ☐ Body Mass Index < 19
- ☐ Duration of SCI ≥ 10 years
- ☐ Woman
- ☐ Motor Complete (AIS A-B)
- ☐ Paraplegia
- ☐ *Prior fragility fracture***
- ☐ Family history of fracture
- ☐ Anticonvulsant use (i.e. - Tegretol, , Gabapentin -
- ☐ Spasticity Medication
- ☐ Heparin use
- ☐ Opioid analgesia use (≥28 mg morphine for a 3 months period)
- ☐ SSRI
- ☐ PPI
- ☐ *Knee region BMD below the fracture threshold***
- ☐ ** "The big 2" **

1.3 What are management options for bone problems?

Screening for secondary causes of osteoporosis, ensuring an adequate but not excessive dietary calcium and vitamin D intake, and completing a fracture risk factor assessment are important first steps.

Measuring and monitoring hip and knee region BMD should begin early following SCI, given the significant declines in hip and knee region bone mass in the first year after injury and the associated lifetime increase in fracture risk.

Biomarkers (urine, blood) provide clinical insight into the metabolic activity of bone, but imaging techniques (e.g. Dual-Energy X-ray Absorptiometry or DXA) provide insight into bone density, quality, and architecture. Conventional tools for predicting fracture risk, such as the Fracture Risk Assessment Tool (FRAX) are only valid among postmenopausal women or men 50 years of age and older.

Pharmacological Options

A number of bisphosphonates have been researched to prevent BMD decline associated with SLOP in persons with SCI. There is Level 1 (Strong) evidence for the prevention and treatment of BMD decline using bisphosphonates (clodronate, etidronate, zoledronate for prevention, and alendronate for treatment) may slow the decline of hip and knee BMD early after SCI or maintain BMD of the hip region in the chronic stage after injury.

Non-pharmacological Options

There is a lack of evidence supporting rehabilitation interventions for the treatment of SLOP after SCI, except neuromuscular electrical stimulation (NMES) and functional electrical stimulation for cycling (FES-cycling), which can maintain or increase BMD over the stimulated areas for as long as the individual persists with the intervention.

Previously, a decision guide has been published for rehabilitation professionals on the identification and management of bone health-related issues for people with SCI (Craven et al. 2008, Craven et al. 2009).

2 Introduction

A significant decline in hip and knee region BMD occurs after motor complete SCI which leads to a lifetime increased risk of lower extremity fragility fracture. Preserving bone mass and maintaining bone architecture are crucial to decrease the risk of lower extremity fragility fractures. Within the first few days following SCI, there is an increase in excreted calcium (known as hypercalciuria) that is 2-4 times that of individuals without SCI who are confined to prolonged bed rest (Bauman & Spungen 2001). Hypercalciuria results in excessive bone resorption (i.e., bone breakdown). Longitudinal studies also highlight a higher rate of hypercalcemia (excessive calcium in the blood) for people after SCI that reflects the rapid bone mineral loss in the first 4-6 months that slow for the remainder of the first-year post-injury (Hancock et al. 1979; Frey-Rindova et al. 2000). Early studies also suggest that BMD stabilizes by 1-2 years after SCI (Griffiths et al. 1976; Hancock et al. 1979; Garland et al. 1992) at 25-50% below that of non-disabled peers in the hip and knee region. Other investigations support a continual loss of bone mass with increases in time post-injury [TPI; (Demirel et al. 1998; Bauman et al. 1999; Eser et al. 2005)] suggesting that lower extremity bone mineral homeostasis is not reached.

The immediate and excessive loss of bone mass post-SCI is believed to result in part from the complete loss of voluntary muscle function and/or weight-bearing capability. Autoimmune, neural, vascular, hormonal, and nutritional changes may also negatively affect bone, but the relative contributions of these factors are unknown (Jiang et al. 2006). The reader is referred to two recent review articles that characterize the regional changes in bone density and architecture (Jiang et al. 2006; Craven et al. 2008). Furthermore, an inadequate dietary calcium intake (Tomey et al. 2005; Miyatani et al. 2014) or insufficient vitamin D may contribute to the rate and severity of BMD decline (Bauman et al. 1995). Aging and inactivity accentuate bone resorption further, resulting in site-specific decreases in bone mineral content (BMC - that is, trabecular bone experiences larger decreases in mineral content than cortical bone).

Additionally, women with motor complete SCI experience regional declines in hip and knee region BMD during menopause that is greater than age-matched non-disabled women (Garland et al. 2001). These changes in bone density and bone architecture contribute to the increased risk of fragility fractures in people with SCI. Fractures after SCI often result in delayed union or non-union and/or complications of immobilization (e.g. deep vein thrombosis, pressure injuries, cellulitis). These fractures are associated with an increase in direct and indirect medical expenses, as well as an increase the individual's morbidity and mortality.

3 Fracture Risk Following SCI

The vast majority of current evidence supports the importance of addressing fracture risk after SCI since there is a higher incidence of fragility fractures in this population (Table 1). The majority of fragility fractures occur following transfers or activities that involve minimal or no trauma (Comarr et al. 1962; Ragnarsson & Sell; 1981; Freehafer 1995; Akhigbe et. al 2015) where the distal femur and proximal tibia (knee region) are most at risk.

Recent findings from review studies in veterans (n=12,162) with SCI have found that 82.6% of all fractures were at the tibia/fibula, femur or hip (Fig 1). Further, individuals with SCI were less likely to receive surgical intervention, than people without SCI, although those with SCI who have surgery did not have increased mortality or adverse event rates (Bishop et. al, 2013; Bethel et. al, 2015). Delayed fracture union is common after SCI (Grassner et al. 2017). Following a fracture there is a five-year increased risk of mortality (Pelletier et al. 2014; Carbone et al. 2014).

Risk factors for fragility fracture after SCI include:

- Sex
- Age at injury
- Time Post-Injury
- Type of impairment
- Low BMI
- Low knee region BMD, and
- Use of anticonvulsants, heparin, or opioid analgesics.

Women are at greater risk compared to men (Vestergaard et al. 1998; Lazo et al. 2001; Nelson et al. 2003; Garland et al. 2004). Increasing age and longer TPI (Frisbie 1997; McKinley et al. 1999; Garland et al. 2004; Garland et al. 2005) increases fracture risk which rises significantly at 10 years post-injury. Further, people with paraplegia have more fractures (Frisbie 1997) and those with complete injuries have greater bone mass loss compared with those with incomplete injuries (Garland et al. 2004; Garland et al. 2005).

Figure 1. Many of the fractures that individuals with SCI sustain occur in the region of the metaphysis and epiphysis. Source: http://sci.washington.edu/info/forums/reports/osteoporosis.asp#dx

A number of concurrent medications a patient is taking can also decrease or substantially increase fracture risk. These include but are not limited to: heparin, benzodiazepines, anticonvulsants, proton pump inhibitors, selective serotonin reuptake inhibitors and opioid analgesics. In a large retrospective cohort study of men with chronic SCI (n=6969, ≥ 2 years post-injury), the use of thiazide-type diuretics was associated with a 25% reduction in the risk of lower extremity fragility fractures (Carbone et al. 2013c). In contrast, the use of heparin (HR 1.48, CI 1.20-1.83), opioid analgesics (HR 1.80, CI 1.57-2.06), or anticonvulsants (HR 1.35, CI 1.18-1.54), especially the benzodiazepine sub-class (HR 1.45, CI 1.27-1.65), was associated with an increased risk of lower extremity fragility fractures in men with chronic SCI (≥ 2 years post-injury) (Carbone et al. 2013a, 2013b). Men with chronic SCI are at a slightly increased risk of lower extremity fragility fractures when exposed to proton pump inhibitors (HR 1.08, CI 0.93-1.25), selective serotonin reuptake inhibitors (HR 1.05, CI 0.90-1.23), or thiazolidinediones (HR 1.04, CI 0.68-1.61) (Carbone et al. 2013a, 2013b). However, these drugs and a prior history of fragility fracture or a history of fracture in a parent are known risk factors for the development of osteoporosis in the general population, and should, therefore, be considered when assessing fracture risk in SCI patients.

Table 1. Fractures and Risk Factors for Fragility Fractures After SCI

First Author Year N Age Range in Years (Mean±SD)	Fractures	Risk Factors
Comarr 1962 N = 1,363 Age - 19-58	109 post-SCI incident lower extremity fractures occurred among 81 out of 1363 participants with traumatic SCI (57% paraplegia, 75% complete). Most common fractures were distal femur (37%), proximal femur (11%)	Motor complete SCI, paraplegia
Ragnarsson 1981 Study 1 N = 578 Age = 4-77 Study 2	33 lower extremity fractures occurred among 23 out of 578 participants (15 men and 8 women) with chronic SCI (78% paraplegia, 91% complete). Most common fractures were supracondylar fractures of femur (33%), femoral shaft (30%) and tibial shaft (18%)	Motor complete SCI

First Author Year N Age Range in Years (Mean±SD)	Fractures	Risk Factors
N = 3,027 Age = 13-77	(National SCI Data Research Centre); 52 lower extremity fractures occurred among 44 out of 3027 participants (37 men and 7 women) with chronic SCI (70% paraplegia, 64% complete). Most common fractures were ankle (24%, tibial shaft (20%) and femoral neck (17%)	N/A
Frisbie 1997 N = 120 Age = 20-77	103 fractures (82% lower extremity) occurred among 40 out of 120 men with chronic SCI (91% traumatic, 30% paraplegia, 80% complete). Most common fracture sites were hip, femoral shaft, supracondylar femur, and tibia. Fracture incidence per age group: 15 fractures/1000 participants years (20-39 years) 31 fractures/1000 participants years (40-59 years) 46 fractures/1000 participants years (60-79 years)	Ageing; with fracture incidence rising with age
Vestergaard 1998 N = 438 Age = 10-80	Overall fracture rate among 438 participants (309 men and 129 women) with SCI (94% traumatic, 55% paraplegia, 68% complete) was 2%/year. cumulative fracture incidence=21%	Women > men; men with a family history of fracture; TPI ≥3 years; level of SCI (cervical lesions with more fractures)*

First Author Year N Age Range in Years (Mean±SD)	Fractures	Risk Factors
McKinley 1999 N = 20,804 population-based all ages	*20,804 participants over a 20-year timeframe* Total number of participants involved in study: 1yr post-SCI, 6,776; 2yrs post-SCI, 5,744; 5 years post-SCI, 4,100; 10yrs post-SCI, 2,399; 15yrs post-SCI, 1,285; 20yrs post-SCI, 500 *Prevalence of lower extremity fractures in women* 1% (5 years post-SCI) 2% (10 years post-SCI) 3% (15 years post-SCI) 6% (20 years post-SCI)	Women > men; TPI
	Prevalence of lower extremity fractures in men 1% (5 years post-SCI) 1% (10 years post-SCI) 2% (15 years post-SCI) 2% (20 years post-SCI)	
Lazo 2001 N = 41 Age = 56±13	41 men with traumatic or Ischemic chronic SCI (57% paraplegia, 93% complete) 26 fractures (82% lower extremity) in 14 participants Most common fracture site was above knee (35%)	Low femoral neck BMD (OR = 2.1, 95% CI = 1.27-3.43; per t-score decrement)
Nelson 2003 N = 23 Age = 39-85	23 participants (22 men and 1 woman) with SCI (44% paraplegia) over 10 years (2.7% of the group). 31 fall-related fractures (97% lower extremity. Most common fracture sites were tibia/fibula (55%) and femoral fractures (35%)	Falls among those age 39-59 years

First Author Year N Age Range in Years (Mean±SD)	Fractures	Risk Factors
Morse 2009b N = 315 Age = 55.0±14.4	39 fractures occurred among 30 men with SCI (50% paraplegia, 83% motor complete) during the first-year post-injury. Most common fracture sites were tibia/fibula (47.5%), distal femoral metaphysis (20%) and proximal femur (15%)	Motor complete SCI; post-injury alcohol consumption > 5 servings*/day
Garland 2004 N = 152 Age = 20-71	9 out of 152 participants with post-SCI fractures (130 men and 22 women) with SCI (54% paraplegia, 67% motor complete). TPI: 12.9 ± 9.3 (range: 1.1 to 44.4) years.	Motor complete SCI; increasing age; low BMI
Zehnder 2004a N = 98 Age = 18-60	39 fractures occurred among 15 paraplegic men with traumatic motor complete SCI. Overall fracture incidence was 2%/year.	TPI strata; 1%/year < 1-year post-SCI 1%/year 1-9 years post-SCI 3%/year 10-19 years post-SCI 5%/year (20-29 years post-SCI) Low knee region BMD;
Eser 2005 N = 99 Age = 19-83	21 out of 99 participants (89 men and 10 women) with traumatic motor complete SCI (72% paraplegia) with lower extremity fractures	TPI; trabecular vBMD less than: 114g/cm^3 distal femur 4% site; 72g/cm^3 distal tibia 4% site;
Garland 2005 N = 168 Age = 26-52	27 of 168 participants with chronic SCI (61% complete) with post-injury lower extremity fracture	Low BMD <25kg/m^2; increasing age; low BMI;

First Author Year N Age Range in Years (Mean±SD)	Fractures	Risk Factors
Carbone 2013a, 2013b N = 7,447 Age = 58±13	892 out of 7447 men with chronic traumatic SCI (56% paraplegia, 37% complete) had incident lower extremity fragility fractures over 5 years (12% of the cohort)	motor complete SCI; use of anticonvulsants;(use of benzodiazepine or use of multiple anticonvulsants), heparin use, opioid analgesia use 28mg of morphine equivalent
Tan et. al 2014 N = 27 Age = 21 - 64	27 men with chronic traumatic SCI (70% paraplegia, 82% complete) 6/27 men with post-SCI osteoporotic fractures	Higher level of adiponectin among wheelchair users Range of values 5657 ± 3003 (wheelchair users with history of fractures)
Akhigbe et. al 2015 N = 140 Age = 56.5±12	140 participants (137 men, 2 women, and 1 unknown) with chronic traumatic SCI (67% paraplegia, 51% complete) with 155 incident lower extremity fractures. Common fracture sites were tibia/fibula (54%) and femur (33%)	Transfers account for 1/3 of fractures
Bethel et. al 2016 N = 22,516 Age = 55±13	3365 participants (3,246 men and 119 women) with chronic SCI and incident fractures (66% traumatic, 44% non-traumatic, 38% with paraplegia, 42% motor complete) A majority ((80%) were lower extremity fractures; tibia/fibula (26%), femur (18%), and the hip (13%)	White race; Traumatic etiology of SCI; paraplegia; Motor complete SCI; TPI; Use of anticonvulsants, Use of opioids Use of benzodiazepines; History of prevalent fractures; higher Charlson Comorbidity Index score; Women aged ≥ 50 years

*1 serving = 341ml of beer, 120ml of wine or 30ml of hard liquor or spirits.

Fracture thresholds are values below which fragility fractures begin to occur, whereas ***fracture breakpoints*** are values below which the majority of fractures occur (Garland et al. 2005). Knee region areal BMD (aBMD) and volumetric (vBMD) thresholds for fracture and breakpoint have been identified (Mazess 1990; Eser et al. 2005; Garland et al. 2005). BMD thresholds are described on Table 2.

Table 2. BMD thresholds for fracture and fracture breakpoint.

Name	Value	Definition
Fracture threshold	≤ 0.78 g/cm² (aBMD) < 114 mg/cm³ (vBMD-femur) < 72 mg/cm³ (vBMD-tibia)	Knee region BMD values below which fragility fractures occur
Fracture breakpoint	< 0.49 g/cm² (aBMD)	Knee region BMD values at which the majority of fragility fractures occur
BMD = bone mineral density; aBMD = areal BMD; vBMD = volumetric BMD. Reproduced from Craven BC, Robertson LA, McGillivray CF, Adachi JD (page 7).1 © 2009 Thomas Land Publishers, Inc. www.thomasland.com. Reprinted with permission.		

Key Points

Fragility fractures, especially around the knee, are common in people with SCI.

We recommend documenting your patient's fracture risk by completing the risk factor profile checklist (Craven et al. 2008; Craven et al. 2009). We propose that the presence of ≥ 3 risk factors implies a moderate fracture risk, while ≥ 5 risk factors imply a high fracture risk (Table 3).

Table 3. Risk Factors for Lower Extremity Fragility Fracture After SCI

Yes	Risk Factors
☐	Age at Injury < 16 years
☐	Alcohol Intake > 5 servings/day
☐	Body Mass Index < 19
☐	Duration of SCI ≥ 10 years
☐	Woman

Yes	Risk Factors
☐	Motor Complete (AIS A-B)
☐	Paraplegia
☐	Family history of fracture in men
☐	Anticonvulsant use (i.e., Tegretol, Depakote Gabapentin – Neurontin)
☐	Spasticity Medication
☐	Opioid analgesia use (≥28 mg morphine for 3 months)
☐	**Prior fragility fracture****
☐	SSRI
☐	PPI
☐	**Knee region BMD below the fracture threshold****
☐	****The big 2****

4 Gap: Fracture Management After SCI

Source of evidence: At present, there are few studies describing optimal fracture management after SCI. A website with clinical consensus recommendations on Osteoporosis and Fractures in Persons with SCI can be found at: http://sci.washington.edu/info/forums/reports/osteoporosis.asp
Recognizing a fracture A fracture may be evident if there was an incident involving a fall or torsion (twisting motion) of the legs. Symptoms of knee region fracture of the distal femur or proximal tibia may include any of the following: • Swelling, red or warm skin, pain, deformity, autonomic dysreflexia, or increased spasticity.
Management Appropriate fracture management can reduce morbidity and mortality among patients. Here we suggest some principles of fracture risk management for people living with an SCI

General principles include venous thromboembolism prophylaxis, bi-valving the cast or immobilization device, provision of calcium and vitamin D supplementation, and osteoporosis therapy to prevent a future fracture.

Venous thromboembolism prophylaxis with low molecular weight heparin or a direct oral anti-coagulant should follow the current prevention guidelines until the resumption of normal activity.

Anti-embolic stockings or compression wraps can be used for those with regional and/or premorbid dependent edema.

Optimal dietary Calcium and vitamin D supplement intake should be encouraged. The dietary supplementation's efficacy should be checked through serum 25-hydroxyvitamin D level, 30 days after initiating therapy to ensure values are within therapeutic range (>100 nmol/L) for the SCI population.

Osteoporosis therapy to prevent fracture should be considered early post-fracture.

Delayed and non-union fractures could be monitored using portable ultrasound systems.

Most of the injuries above the knee are treated operatively. Injuries below the knee could be managed using bivalve immobilization devices and casts with windows for the malleoli and heel to reduce the incidence of pressure injuries. There may be a need for an elevated leg rest for wheelchair; however, this could increase the risk of falling due to a forward shift in their centre of gravity.

When healing is completed, clinicians should work with patients to restore the range of motion of hip, knee and ankle.

Early recognition and management of tissue injury, persisting edema, and mood disorders can help to optimize fracture outcomes.

First Author Year	N	Age Range in Years (Mean±SD)	Fractures	Risk Factors
Bethel et. al 2015	1,281	56±12	1,281 men with traumatic chronic SCI (57% paraplegia, 54% complete) with 1,979 incident fractures consisting of 345 (17%) upper extremity fractures and 1634 (83%) lower extremity fractures. Most common upper-extremity fracture sites were the humerus (28%) and lower-extremity fracture sites were tibia/fibula (33%), femur (26%) and hip (16%)	Traumatic SCI - TPI > 2 years

Bethel et al. 2015 compared results of incident fracture treatment (surgical vs. non-surgical) among male veterans with chronic SCI. The study comprised 1,979 incident fractures that occurred among 1281 veterans over 6 years. The majority of fractures occurred in lower extremities (~83%), and the majority of these fractures were treated nonsurgically (~90%). The authors reported that there was a significant difference in the level of injury and fracture treatment modality, surgery treatment being used more among individuals with paraplegia ($p = 0.04$). However, there were no significant fracture treatment-related differences in mortality rates.

5 SLOP Detection and Diagnosis

To assess and understand your patient's bone health, it is important to measure their BMD and document their fracture risk. We advocate diagnosing the presence of SLOP based on the following DXA criteria (Table 4).

Table 4. Definition of SLOP

Age Range	Definition
Men ≥ 60 years or postmenopausal women	Hip or knee region *T*-score ≤ -2.5
Men < 59 years or premenopausal women	Hip or knee region *Z*-score < -2.0 with ≥ 3 risk factors for fracture
Men or women age 16–90	Prior fragility fracture and no identifiable etiology of osteoporosis other than SCI

The T-score is the number of standard deviations (SD) BMD is above or below sex-specific young adult mean peak bone mass. The Z-score is the number of SD BMD is above or below that expected for individuals of the same age and sex.

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6 Bone Outcome Measures

There are multiple methods for assessing bone health. Commonly used tools include bone imaging, biochemical markers of bone metabolism, and histomorphometry.

6.1 Imaging Modalities

Bone imaging is typically used to assess BMD, morphology, or microstructure. Imaging modalities that are used for bone health assessment include dual-energy X-ray absorptiometry (DXA), dual-energy photon absorptiometry (DPA), and standard and high-resolution peripheral quantitative computed tomography (pQCT, HR-pQCT). Nevertheless, the availability of pQCT scanners is mainly limited to research institutions in part due to the incompatibility of pQCT data with DXA-derived T-scores, lack of normative studies, and specific treatment thresholds (Engelke et al. 2008, Adams et al. 2014, Zysset et al. 2015). There are more than 50,000 whole-body DXA, approximately 800 pQCT (XCT 2000 and 3000) and just 50 HR-pQCT (XtremeCT and XtremeCT II) scanners used in clinical practice/research worldwide (Shepherd et al. 2014; personal communication with Stratec Medizintechnik GmbH and Scanco Medical).

6.1.1 Dual-Energy Absorptiometry (DXA)

Bone mineral density assessment by DXA imaging is considered by the World Health Organization as the "gold standard" to diagnose osteoporosis and is the most widely used assessment technique for determining treatment effectiveness. DXA is a non-invasive, relatively safe modality for measuring areal BMD (aBMD), which is defined as BMC per unit area in g/cm^2. DPA is an older technology for measuring aBMD that is sometimes reported in studies conducted before the 1990s.

Increases in areal BMD (aBMD) are presumed to be a suitable surrogate outcome for fracture risk reduction when assessing the effectiveness of SLOP therapy. "Optimal therapeutic outcome" would be defined as an *increase* in knee region BMD above the fracture threshold in the absence of fragility fracture.

There are several established methods for measuring BMD at the knee (Garland et al. 1993; Moreno et al. 2001; Eser et al. 2004; Morse et al. 2009b). Regardless of the methodology chosen, assessment of knee region BMD is crucial as it best predicts knee region fracture risk after SCI (Eser et al. 2005; Garland et al. 2005; Lala et al. 2013). Figure 2 displays a sample of a lumbar spine DXA image with vertebral delineation.

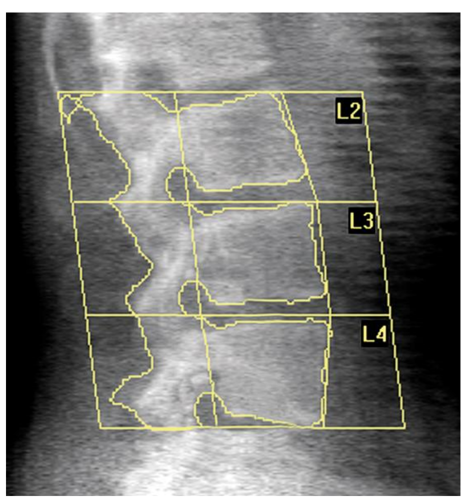


Figure 2. Lumbar spine DXA image with vertebral delineation. Source: https://www.hologic.com/hologic-products/breast-skeletal/horizon-dxa-system#resources

6.1.2 Peripheral Quantitative Computed Tomography (pQCT, HR-pQCT)

Peripheral QCT is another non-invasive, relatively safe imaging modality that can be used to diagnose osteoporosis. Whereas DXA measures areal BMD, pQCT measures volumetric BMD (vBMD), which is defined as bone mineral content (BMC) per unit volume in g/cm^3. vBMD stands alongside aBMD as a surrogate outcome for fracture risk reduction. In addition to assessing volumetric bone density, pQCT can also differentiate cortical bone from trabecular bone and quantify architecture. However, pQCT is available as a clinical diagnostic tool in only a few countries.

High-resolution pQCT (HR-pQCT) improves upon the resolution of standard pQCT imaging and is now available with as fine as 42µm resolution. This imaging modality gives detailed information on the microarchitecture of peripheral bone but is not widely available outside of research applications in North America and is not recommended for cross-sectional studies at this time.

The current official positions of the International Society for Clinical Densitometry (ISCD) (Engelke et al. 2008, Kanis et al. 2015, Adams et al. 2014, Zysset et al. 2015), does not yet recommend routine use of pQCT for diagnosis of osteoporosis, fracture risk prediction or monitoring treatment effectiveness. This position is in part due to the incompatibility of pQCT data with DXA derived T-scores, inconsistency in measurement sites and bone analysis, lack of normative studies, and specific treatment thresholds (Engelke et al. 2008, Adams et al. 2014, Zysset et al. 2015). An example of a pQCT image can be seen in Figure 3.

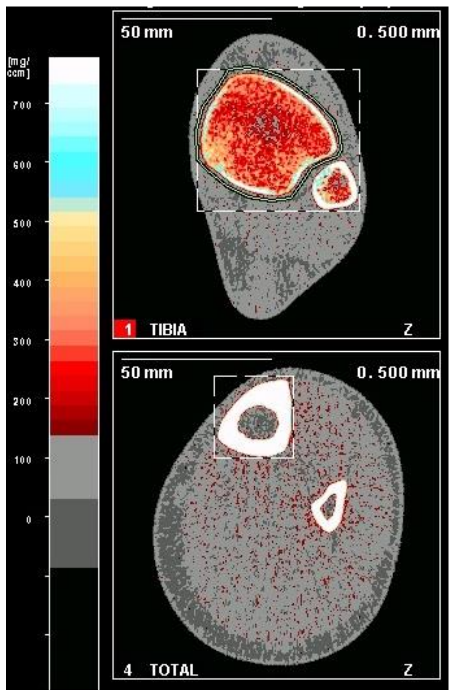


Figure 3. Example of pQCT data. Upper panel represents the tibial epiphysis (predominantly trabecular bone; red colour tones). Lower panel represents the tibial diaphysis (predominantly cortical bone; white colour tones).

6.2 Biochemical Markers

Biochemical markers of bone turnover can be used as an adjunct to DXA in the assessment of bone health among patients with SCI. Serum and urine markers provide useful insight into bone metabolism at specific time points after injury and are an effective tool for selecting patients who would benefit from therapy and monitoring response to therapy. The current therapeutic utility of bone turnover markers is limited by day-to-day, diurnal, inter-individual, and inter-assay variability. For urine markers, results need to be corrected for creatinine (Reiter et al. 2007).

Markers of bone formation include alkaline phosphatase (ALP), bone-specific alkaline phosphatase (BALP), osteocalcin (OC), N-terminal propeptide of type I collagen (P1NP), and C-terminal propeptide of type I collagen (CINP). Markers of bone resorption include urinary free and total pyridinoline (PYD) and deoxypyridinoline (DPD) crosslinks, type 1 collagen C-telopeptide (CTX), and N-telopeptide (NTX). PYD and DPD are molecules that provide stability to collagen and, along with CTX and NTX, are released when collagen is degraded during bone resorption (Brown et al. 2009) (Table 5).

For a bone marker to be useful in assessing the rate of bone turnover and/or monitoring therapy effectiveness, the difference in the rate of bone turnover before and after SCI, as well as the early period versus the late period after SCI, needs to be discernible. Consensus regarding which biomarkers are best to monitor bone turnover is needed in the SCI community. Several authors have suggested candidate biomarkers including sclerostin (Morse et al. 2013) and adiponectin (Doherty et al. 2014). However, due to analytical discordance between the different assay kits) and biological variability (type 2 diabetes, estrogen level, parathyroid hormone etc.), diagnostic performance of these biomarkers has to be yet validated (Wheater et al. 2013, Liu et al. 2013, Durosier et al. 2013, Morris et al. 2017) (Tables 6-8).

The International Osteoporosis Foundation and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC-IOF) Working Group for Standardization of Bone Marker Assays, and the National Bone Health Alliance (NBHA) recommend CTX and P1NP as reference bone markers to inform on fracture risk and efficacy of osteoporosis treatment (Vasikaran et al. 2011, Bauer et al. 2012, Johansson et al. 2014, Morris et al. 2017). This is due in part to their low inter-individual variability, relatively stable nature in serum at room temperature and current availability of reference intervals for these biomarkers for geographic regions and individual assays (Morris et al. 2017). In some clinical studies, however, the urine NTX marker could be preferred due to its lower sensitivity to circadian changes and food intake (Wheater et al. 2013).

Consensus regarding the choice of biomarker and the associated assay techniques are needed to cross-study comparison and future meta-analysis.

Table 5. Bone Formation and Resorption Markers (CTX, NTX, ALP, BALP, PTH, P1NP, CINP, OC, DPD, PYD)

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
Craven et. al, 2017 Canada Randomized Controlled Trial Level 1 N = 34	**Population:** 34 participants (26 men, 8 women) with chronic traumatic SCI; C2-T12; age: 55 years; TPI: 5 years; 13 AIS C, 20 AIS D. **Outcome Measures:** OC was measured with radioimmunoassay, CTX with Roche Elecsys© 2010 immunoassay using electrochemiluminescence	1. OC Range of Values prior intervention [mean±SD]: SCI CONV: 20.1 ± 8.3 ng/ml SCI FES-walking:16.7 ± 6.5 ng/ml Range of Values post-intervention [mean±SD]: SCI CONV: 20.7 ± 8.6 ng/ml SCI FES-walking: 17.8 ± 6.2 ng/ml Normal Range: 24–70 ng/mL for men 18–30 years; 14–42 ng/mL for men 31–

	immunoassay (Roche Diagnostics GmbH, Indianapolis, IN, USA) and serum sclerostin was measured by BIOMEDICA sclerostin ELISA (Alpca Diagnostics, Salem, NH, USA). All markers were assessed at baseline, and 4 months. Treatment: 45 min, 3x/week, 4 months. <u>Control group (CONV)</u>: aerobic (20-25 min, 3-5 Borg; arm or leg bicycling, walking in parallel bars or on the treadmill) and resistance training (2–3 sets of 12–15 maximum repetitions for muscles capable of voluntary contraction). <u>FES-walking with body-weight support group</u>: open-loop FES (8–125 mA, 250–300 µs pulse duration, 20–50 Hz) over the quadriceps, hamstrings, tibialis anterior and gastrocnemius while walking with body weight support.	50 years; 14–46 ng/mL for men 51–70 years and 11–43 ng/mL for premenopausal women 15–46 ng/mL for postmenopausal women MCID/LSC: CV was ~8% 2. CTX Range of values prior intervention [mean±SD]: SCI CONV: 0.24 ± 0.21 ng/ml SCI FES-walking: 0.26 ± 0.15 ng/ml Range of Values post intervention [mean±SD]: SCI CONV: 0.27 ± 0.18 ng/ml SCI FES-walking: 0.24 ± 0.17 ng/ml Normal value: 0.155– 0.873 ng/mL for men 18–30 years; 0.093–0.630 ng/mL for men 31–50 years; 0.035–0.836 ng/mL for men 51–70 years and 0.025–0.573 ng/mL for premenopausal women and 0.104–1.008 ng/mL for postmenopausal women. MCID/LSC: CV was < 10% Important association: - 3. Sclerostin Range of values prior intervention [mean±SD]: SCI CONV: 58.3 ± 12.4 ng/ml SCI FES-walking: 52.9 ± 16.8 ng/ml Range of Values post intervention [mean±SD]: SCI CONV: 61.1 ± 13.5 ng/ml SCI FES-walking: 54.3 ± 20.1 ng/ml Normal value: 0 - 240 pmol/l MCID/LSC: run replicates were <12.5% Important association: -
Invernizzi et. al 2015 Italy Case-Control Study Level 3 N=43	**Population:** 28 participants (23 men, 5 women) with chronic SCI; AIS A-C; C5 – T12; age: 40.5 ± 7.1 years; TPI: 90.8 ± 53.1 months; 24 paraplegic, 4 tetraplegic, 22 motor complete and 6 motor incomplete SCI individuals. 15 healthy controls (5 men, 10 women; age: 28.4 ± 4.1 years). **Outcome Measures:** alkaline phosphate (BALP), parathyroid hormone (PTH) and Beta-CrossLaps (Beta-CTX)	1. Beta-CTX Range of values [mean±SD]: SCI: 461.7 ± 215.5 pg/ml Controls: 399.2 ± 223.9 pg/ml Normal value: - MCID/LSC: - Important association: - 2. BALP Range of values [mean±SD]: SCI: 12.6 ± 4.0 mcg/l Controls: 11.6 ± 6.0 mcg/l Normal value: - MCID/LSC: - Important association: -

		3. PTH Range of values [mean±SD]: SCI: 43.9 ± 13.8 pg/ml Controls: 29.7 ± 6.9 pg/ml Normal value: - MCID/LSC: - Important association: -
Gaspar et. al 2014 Brazil Cross-Sectional Level 5 N= 46	**Population:** 29 sub-acute and chronic men with traumatic SCI; AIS A - B; T2 – T12; age: 32.7 ± 6.9 years; TPI: 5.3 years (range: 0.5 – 24). Control group: 17 non-disabled men (age: 31.9 ± 5.8 years). **Outcome Measures:** collagen type I C-terminal telopeptide (CTX) was measured using commercial chemiluminescence immunoassays (Elecsys Analyzers, Roche), alkaline phosphate (BALP) was assessed by using a colorimetric method (ADVIA1650), PTH measured using an in-house electrochemiluminescence immunoassay	1. CTX Range of values [mean±SD]: SCI: 0.439 ± 0.212 ng/ml Controls: 0.475 ± 0.556 ng/ml Normal value: 0.2 – 0.7ng/ml MCID/LSC: inter-assay CV was 4.7%, intra-assay CV of 4.6% Important association: There was a significant inverse relationship between the CTX values and the duration of injury. 2. BALP Range of values [mean±SD]: SCI: 58.1 ± 11.9 Controls: 89.2 ± 10.6 Normal value: - MCID/LSC: - Important association: - 3. PTH Range of values [mean±SD]: SCI: 34.3 ± 18.2 pg/ml Controls:29.8 ± 8.1 pg/ml Normal value: - MCID/LSC: inter-assay CV was 13.4% and intra-assay CV of 5% Important association: -
Tan et. al, 2014 USA Cross-sectional Level 5 N = 27	**Population:** 27 men with SCI; age: 40.7±11.5 years; AIS A-C; C4 or lower; TPI: 13.2 ± 11.7 (range: 0.12 to 37.5) years; 19 paraplegic, 8 tetraplegic, 22 motor complete and 5 motor incomplete. **Outcome Measures:** Total OC and CTX were measured by electrochemiluminescence immunoassay on a 2010 Elecsys autoanalyzer Roche Diagnostics, Indianapolis, IN).	1. OC Range of Values [mean±SD]: SCI: 22.0 ± 7.5 ng/ml Normal Range: value: - MCID/LSC: CV was < 10% Important Associations: Maximal load was negatively associated with years' post-injury and adiponectin while it was positively associated with lower extremity lean mass 2. CTX Range of values [mean±SD]: SCI: 0.377 ± 0.223 ng/ml Normal value: - MCID/LSC: CV was < 10% Important association: -

* All data expressed as mean±SD, unless expressed otherwise.

Table 6. Sclerostin and Myostatin – Normal range, responsiveness

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
Invernizzi et. al 2015 Italy Case-Control Study Level 3 N=43	**Population:** 28 participants (23 men, 5 women) with chronic SCI; AIS A-C; C5 – T12; age: 40.5 ± 7.1 years; TPI: 90.8 ± 53.1 months; 24 paraplegic, 4 tetraplegic, 22 motor complete and 6 motor incomplete SCI individuals. 15 healthy controls (5 men, 10 women; age: 28.4 ± 4.1 years). **Outcome Measures:** Serum sclerostin was measured by SOST Elisa Kit (Biomedica Gruppe, Vienna, Austria), myostatin quantified by the Elisa assay (MyBioSource, San Diego, CA, USA)	1. Sclerostin Range of values [mean ± SD] SCI: 70 ± 30 pmol/l Controls: 25 ± 5 pmol/l Normal value: 0 - 240 pmol/l MCID/LSC: - Important association: serum sclerostin levels were statistically higher in individuals suffering from SCI compared with healthy controls 2. Myostatin Range of values [mean±SD] SCI: 17 ± 6 ng/ml Controls: 7 ± 6 ng/ml Normal range: 0.625 – 20 ng/ml MCID/LSC: - Important association: myostatin serum levels are significantly higher in individuals with SCI than those in healthy controls; strong correlation with appendicular muscle mass index and moderate correlation with serum sclerostin in motor complete SCI

* All data expressed as mean±SD, unless expressed otherwise.

Table 7. Vitamin D Data – The prevalence of vitamin D deficiency

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
Tan et. al, 2014 USA Cross-sectional N = 27	**Population:** 27 men with SCI; AIS A-C; C4 or lower; age: 40.7 years; TPI: 13 years; 19 paraplegics, 8 tetraplegics, 22 motor complete and 5 motor incomplete SCI individuals. **Outcome Measures:** 25 OH vitamin D (25(OH)D) was quantified by enzyme immunoassay (Immunodiagnostic Systems Inc., Fountain Hills, AZ).	Range of values [mean±SD]: SCI: 30.9 ± 9.8 ng/ml Normal value: > 30 ng/ml Deficiency (< 30 ng/ml): 55.6% MCID/LSC: CV was < 10% Important association: -

Invernizzi et. al 2015 Italy Case-Control Study N = 43	**Population:** 28 participants (23 men, 5 women) with chronic SCI; AIS A-C; C5 – T12; age: 40.5 ± 7.1 years; TPI: 90.8 ± 53.1 months; 24 paraplegic, 4 tetraplegic, 22 motor complete and 6 motor incomplete SCI individuals. 15 healthy controls (5 men, 10 women; age: 28.4 ± 4.1 years). **Outcome Measures:** 25(OH) Vitamin D (25(OH)D).	Range of values [mean±SD]: SCI: 12.3 ± 6.6 ng/ml Controls: 20.5 ± 7.1 ng/ml Normal value: > 30 ng/ml Deficiency (< 30 ng/ml): SCI: 100% Controls: 80% Deficiency (< 10 ng/ml): SCI: 50% Controls: 0% MCID/LSC: - Important association: 25(OH)D serum levels were also significantly higher in healthy controls compared with individuals with SCI.
Doubelt et. al 2015 Canada Cross-sectional observational study N = 42	**Population:** 34 participants (32 men, 2 women) with chronic SCI; age: 40.0 ± 10.9 years; TPI: 12.7 ± 9.0 years; AIS A-D; C1 – T12; 27 traumatic, 7 nontraumatic; 12 paraplegic, 22 tetraplegic; 17 motor complete and 17 motor incomplete. Control group: 8 matched non-disabled individuals. **Outcome Measures:** plasma 25-hydroxyvitamin D using ultra-high-performance liquid chromatography-tandem mass spectrometry	Range of Values (min – max) SCI: 18 – 120 nmol/L* Controls: 50 – 115 nmol/L* Range of Values [mean±SD]: SCI: 69.3 ± 23.3 nmol/L* Controls: 76.5 ± 19.8 nmol/L* Normal value: > 75 nmol/L* Deficiency SCI: (<75 nmol/L*): 60% (<30 nmol/L*): 10% MCID/LSC: CV was <10% Important associations: *10 nmol/L = 3.145 ng/ml
Javidan et. al, 2014 Iran Cross-sectional study N = 148	**Population:** 148 participants; 116 men [age: 51 years (range 14 – 73)], 32 women [age: 43 years (range: 36 – 54)] with traumatic SCI who had no previous history of endocrine disorders and were not on specific medications. **Outcome Measures:** 25-hydroxyvitamin D [25(OH)D] was assessed by a competitive protein-binding assay	Range of Values: - Normal value: 30 - 74 ng/ml Deficiency (<30 ng/ml): 64.7% MCID/LSC: - Important associations: -
Gaspar et. al 2014 Brazil Cross-Sectional	**Population:** 29 sub-acute and chronic men with traumatic SCI; AIS A - B; T2 – T12; age: 32.7 ± 6.9 years; TPI: 5.3 years (range: 0.5 – 24). Control group: 17 non-disabled men (age: 31.9 ± 5.8 years).	Range of values [mean±SD]: SCI: 22.2 ± 10.2 ng/ml Controls: 205.8 ± 7.3 ng/ml Normal value: >30 ng/ml Deficiency (<30 ng/ml)

N = 46	**Outcome Measures:** 25-hydroxyvitamin D [25(OH)D] were measured using chemiluminescence immunoassay technology (Liaison, DiaSorin).	SCI: 44.4% Controls: 23.5% MCID/LSC: intra-assay CV was 4.6%, inter-assay CV of 8.2% Important associations: There was a significant inverse relationship between the CTX values and the duration of injury. In the controls, the 25(OH)D level was positively correlated with the T and with the lumbar spine BMD, but these correlations were not observed in the individuals with SCI.

* All data expressed as mean±SD, unless expressed otherwise.

- **Clinicians should use a validated** 25-hydroxyvitamin D assay. (Ross et al. 2011)

Table 8. Adipokines and Insulin

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
Tan et. al, 2014 USA Cross-sectional N = 27	**Population:** 27 men with SCI; AIS A-C; C4 or lower; age: 40.7 years; TPI: 13 years; 19 paraplegic, 8 tetraplegic, 22 motor complete and 5 motor incomplete SCI individuals. **Outcome Measures:** Plasma adiponectin level quantified by ELISA assay (Alpco Diagnostics, Salem, NH).	1. Adiponectin Range of values [mean±SD]: SCI in total: 4214 ± 1954 ng/ml SCI with fractures: 5657±3003 ng/ml SCI without fractures: 3802±1380 ng/ml Normal range: - MCID/LSC: CV was < 10% Important association: adiponectin was inversely associated with axial stiffness and maximal load after adjusting for injury duration, and lower extremity lean mass and positively associated with lower extremity lean mass. Participants with osteoporotic fractures had significantly higher adiponectin levels compared to those without an osteoporotic fracture.
Doubelt et. al 2015 Canada Cross-sectional observational study N = 42	**Population:** 34 participants with chronic SCI (AIS A-D, C1 – T12, mean age: 40 years, mean TPI: 12.7 years), 12 paraplegics, 22 tetraplegics, 17 motor complete and 17 motor incomplete SCI individuals. 8 non-SCI	1. Adiponectin Range of values (min – max): SCI: 8 – 200 ng/ml; Controls: 7.2 – 39.9 ng/ml: Range of values [mean±SD]: SCI: 40.5 ± 44.0 ng/ml Controls: 18.7 ± 10.5 ng/ml

	individuals as comparison group - sex, age, waist circumference, and BMI matched **Outcome Measures:** Serum adiponectin, leptin and insulin using the Milliplex Map Kit for Human Adipokine Magnetic bead Panel 2 (Millipore Corporation, Billerica, CA)	Normal Range: - MCID/LSC: - Important association: Adiponectin was positively correlated with lumbar spine aBMD. 2. Leptin Range of values (min – max): SCI: 0.21 – 180 ng/ml Controls: 1 - 16 ng/ml Range of values [mean±SD]: SCI: 14.8 ± 31.4 ng/ml Controls: 5.7 ± 5.2 ng/ml Normal value: - MCID/LSC: - Important association: SCI cohort showed significant associations between aBMD at the femoral neck and lumbar spine with leptin. 3. Insulin: Range of values (min – max): SCI: 58 – 1180 pg/L Controls: 111 – 437 pg/L Range of values [mean±SD]: SCI: 288 ± 234 pg/L Controls: 236 ± 116 pg/L Normal value: - MCID/LSC: - Important associations: SCI cohort showed significant associations between aBMD at the femoral neck and lumbar spine with insulin.
Invernizzi et. al 2015 Italy Case-Control Study N =43	**Population:** 28 participants (23 men, 5 women) with chronic SCI; AIS A-C; C5 – T12; age: 40.5 ± 7.1 years; TPI: 90.8 ± 53.1 months; 24 paraplegic, 4 tetraplegic, 22 motor complete and 6 motor incomplete SCI individuals. 15 healthy controls (5 men, 10 women; age: 28.4 ± 4.1 years). **Outcome Measures:** insulin-like growth factor I	1. Insulin Range of values [mean±SD]: SCI: 177.6 ± 47.7 ng/ml Controls: 241.1 ± 92.8 ng/ml Normal value: - MCID/LSC: - Important associations: -

* All data expressed as mean±SD, unless expressed otherwise.

Alignment of the choice of biomarkers across future bone health studies is critical as it may allow for cross-study comparison, future meta-analyses, and to inform the development of SCI-specific normative datasets. Therefore, we suggest the use of CTX and P1NP bone turnover markers as a future minimum data set and harmonization of units for reporting CTX (ng/L) and P1NP (µg/L) as recommended by IFCC-IOF Bone Marker Standards Working Group (Morris et al. 2017). In addition, adipokines showed promising results; however, more studies are needed to determine their feasibility as primary biomarkers for bone health and osteoporotic fracture risk among individuals with SCI.

The selection of an appropriate analytic assay remains the main limitation of data harmonization as there is an apparent lack of comparability between particular assays, automated (Roche Elecsys/Cobas and IDSiSYS) or manual (Orion Diagnostica). To overcome this issue, the US Foundation of the National Institutes of Health is currently collecting data from all clinical trials in osteoporosis to perform an individual meta-analysis (http://www.fnih.org/what-we-do/current-research-programs/biomarkers-consortium-bone-quality-project) that would overcome the criticisms of inconsistent statistical methodology and small sample size (Morris et al. 2017).

6.3 Histomorphometry

Histomorphometry are measurements from bone biopsies to provide an in-depth understanding of bone. There are two types of bone histomorphometry, dynamic and static. Dynamic histomorphometry involves using substances such as tetracycline to measure tissue growth. Static histomorphometry involves determining the size and types of cells; measurements include length, area or cell counts.

Although bone histomorphometry is considered a valuable tool, it is not always feasible because it requires surgically obtaining bone specimens from consenting participants. As biomarker technology continues to improve, the use of histomorphometry in live human subjects will likely be supplanted by this less invasive testing modality.

7 Clinical Guide

In the following sections, prevention, and treatment interventions for maintaining bone health after SCI are discussed.

Two distinct clinical questions can be posed regarding BMD decline after SCI:

(1) What is the best way to prevent acute regional declines in BMD in the early post-injury period (10-90 days post-injury)?

(2) What are the best treatments for established low bone mass and increased fracture risk of the hip and knee region for individuals with chronic (>2 years) SCI?

Bone loss is greatest in the first year post-SCI. Therefore, this review classifies intervention studies as either *prevention* studies (i.e., the participants are less than 6 months post-SCI) or *treatment* studies (i.e., study participants are ≥1-year post-SCI). Within the prevention and treatment categories, this review discusses (a) pharmacological intervention studies, (b) non-pharmacological intervention studies, and (c) studies of combination interventions (e.g., drug therapy concurrent with a rehabilitation intervention).

When selecting a treatment to offer patients, clinicians seek the best available evidence to support their practice. Ideally, one would like to see three randomized control trials (Level 1 evidence) from separate centres demonstrating the efficacy of therapy prior to routine implementation. Having highlighted this issue, the diversity of interventions, study design and outcome measures make interpretation of the SCI bone health literature challenging and subject to controversy. The following sections attempt to identify the best available literature to address specific clinical questions.

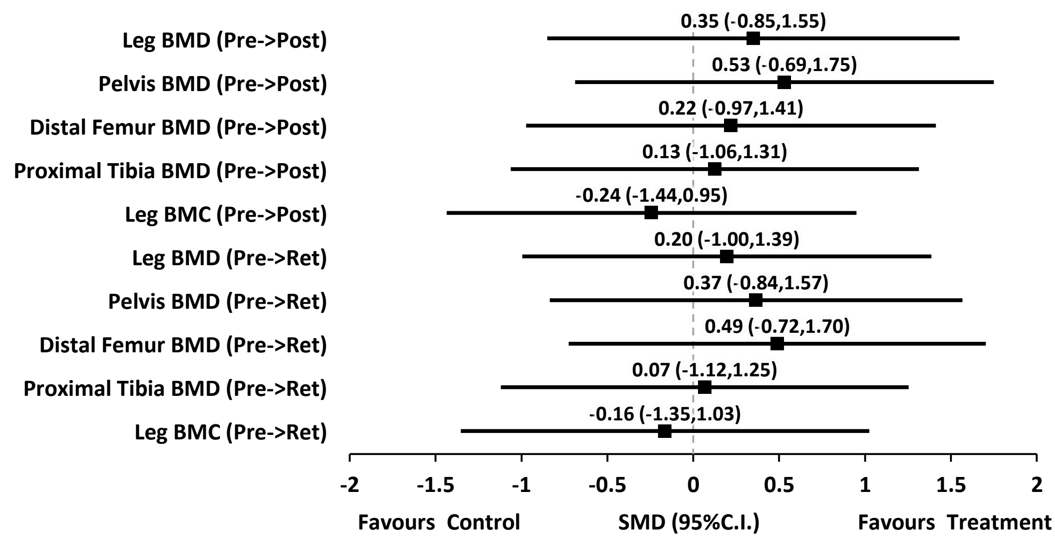
8 Pharmacologic Therapy: Bisphosphonates

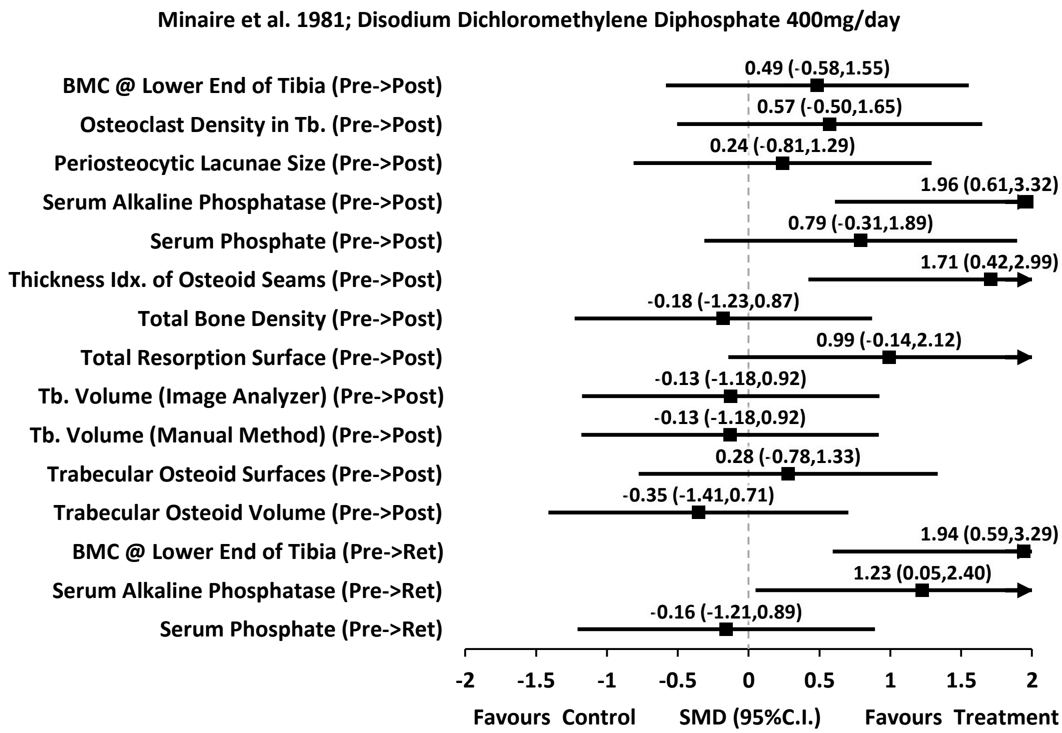
Within weeks after SCI, there is a marked increase in bone resorption (breaking bone down) with a decrease in bone formation. These phenomena are responsible for the significant loss of bone mass that occurs after SCI. Bisphosphonates are a group of medications that are used to prevent declines in bone mass or treat low BMD; they act to slow down excessive bone resorption. They are generally divided into two types, those with or without nitrogen; each type has a different mechanism of action. Etidronate (Didrocal, Didronel), clodronate (Bonefos, Ostac) and tiludronate (Skelid) do not contain nitrogen while pamidronate (Aredia), alendronate (cholecalciferol, Fosamax, Fosamax Plus D, Fosavance), ibandronate (Boniva), risedronate (Actonel, Actonel with Calcium) and zoledronate (zoledronic acid, Aclasta, Reclast, Zomera, Zometa) contain nitrogen. Etidronate, alendronate and risedronate are oral bisphosphonates that are currently approved for the treatment of postmenopausal osteoporosis in Canada (Brown et al. 2002). Clodronate is available intravenously and orally for the treatment of osteoporosis. Tiludronate is available in oral form in the United States. Zoledronate is a newer once-yearly bisphosphonate, administered via intravenous infusion. Concurrent supplementation with calcium and vitamin D has been important to bisphosphonate therapy for postmenopausal osteoporosis (Brown et al. 2002). The concurrent administration of calcium, vitamin D, and bisphosphonates has not been prospectively evaluated in the SCI population but should nonetheless be considered when prescribing oral bisphosphonates for SLOP based on the post-menopausal osteoporosis literature.

8.1 Pharmacologic Therapy: Prevention of Bone Loss (within 12 Months of Injury)

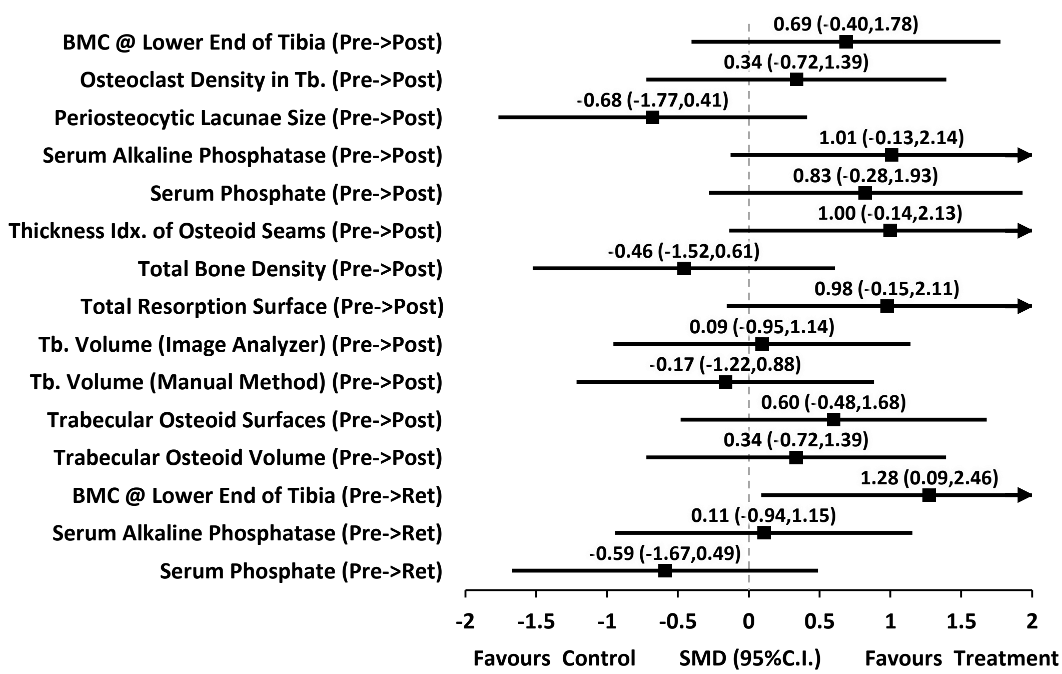
Table 9. Studies of Pharmacologic Therapy for Prevention of Bone Loss in the First Year After SCI

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
Bauman et al. 2005a; USA PEDro=10 RCT Level 1 N=14	**Population:** 14 participants (8 men, 3 women); age: 35 ± 12 years (range: 21–61); motor complete para (n=6) or tetraplegia (n=5); TPI: 44 ± 18 days (range: 22–65). AIS A. **Treatment:** Pamidronate for 12 months. Participants randomized to **1.** 60mg intravenous (n=6) or **2.** Placebo (n=5) **Outcome measures**: BMD by DXA, bone turnover markers at baseline, 1, 2, 3, 6, 9, 12-months post-SCI.	1. There was no significant between-group difference in BMD decline at 1 year. 2. The treatment group had significantly lower 24-hr urinary calcium at 1 month vs. placebo group (P<0.05) and there were no significant changes in markers of bone formation over the 12-month study.
	Effect Sizes: Forest plot of standardized mean differences (SMD ± 95%CI) as calculated from pre- to post-intervention data and pre-intervention to retention/follow-up data	

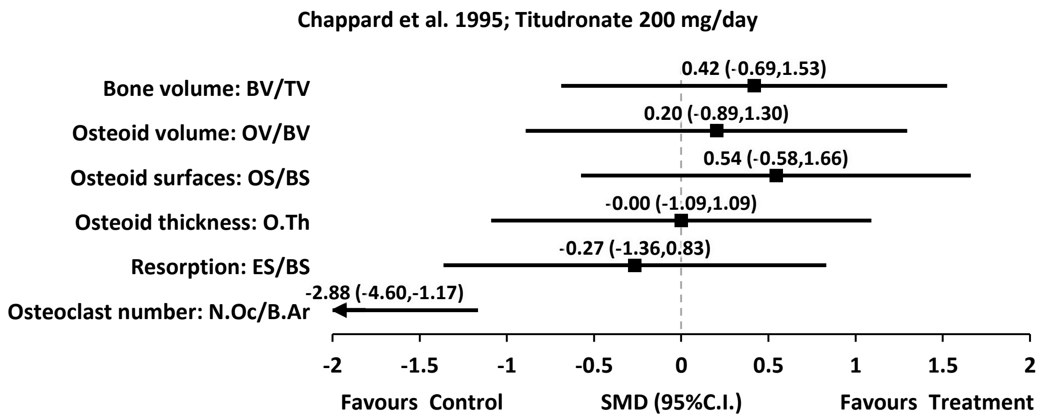
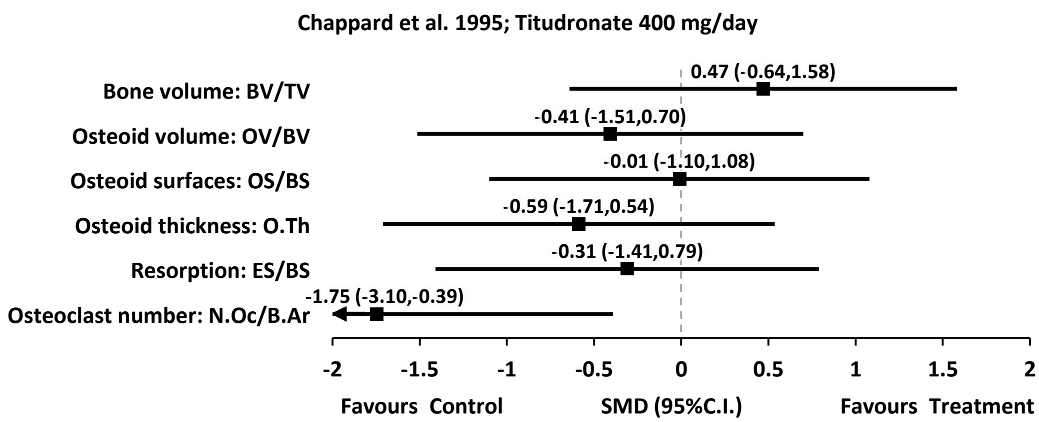
Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
	Bauman et al 2005a; Pamidronate  **12 & 24 months post-baseline data used as post-treatment & retention data, respectively**	
Minaire et al. 1981 France PEDro=10 RCT Level 1 N=21	**Population:** 17 men and 4 women; age: 29 years (range: 15-54); traumatic complete paraplegia; T1 - T12; TPI: 7.6 days (range: 5-29). **Treatment**: Clodronate for 3.5 months. Participants randomized to **1.** 400mg per day (n=7); **2.**1,600 per day (n=7); or ***3.*** Placebo (n=7). **Outcome measures:** BMD by DPA, histomorphometry	1. No reported adverse effects on bone mineralization with intervention. 2. Increase in serum and urine markers in the Placebo group (indicative of increased bone turnover). 3. Effective for acute prevention of declining bone mass and maintenance of BMC of the femur and tibia in the treatment groups.
	Effect Sizes: Forest plot of standardized mean differences (SMD ± 95%CI) as calculated from pre- to post-intervention data and pre-intervention to retention/follow-up data	

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
		

Tb. = trabecular bone

<table>
<tr><th>Author Year; Country
Score
Research Design
Total Sample Size</th><th>Methods</th><th>Outcome</th></tr>
<tr><td></td><td colspan="2">Minaire et al. 1981; Disodium Dichloromethylene Diphosphate 1600mg/day


Tb. = trabecular bone</td></tr>
<tr><td rowspan="2">[Chappard et al. 1995](#);
France
PEDro=9
RCT
Level 1
N=20</td><td>**Population:** 20 participants (14 men, 6 women), age: 28.0 + 6.4 years; traumatic injuries between C5-T12.
Treatment: Tiludronate for 3 months. Participants randomized to **1**. 400 mg/day (n=7); **2**. 200 mg/day (n=7); or **3**. Placebo (n=6).
Outcome measures: histomorphometry.</td><td>1. There was an increase in total bone volume in the treatment group 1(400mg/day) vs. treatment group 2 (200mg/day) and placebo groups.
2. Increased bone resorption indicators in the placebo group vs. the treatment groups.</td></tr>
<tr><td colspan="2">**Effect Sizes:** Forest plot of standardized mean differences (SMD ± 95%CI) as calculated from pre- and post-intervention data</td></tr>
</table>

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
	 	
Schnitzer et al. 2016; USA PEDro=8 RCT Level 1 N=16	**Population:** 16 participants (15 men, 1 women) with acute SCI; AIS-A/B, or AIS-C; and non-weight-bearing; age: 38.6 ± 16.2 years; 8 cervical, 8 thoracic; TPI: Placebo = 95.3 ± 50.0 days, Zoledronic acid: 35.1 ± 15.4 days. **Treatment:** Infusion of zoledronic acid (5 mg) or placebo (dilutant only) **Outcome measures:** BMD by DXA, bone turnover markers at baseline, 3, 6, 12-months post-treatment.	1. Significant between-group difference at 6 months post-treatment in change of (mean±SD, zoledronic acid vs. placebo): Lumbar spine BMD: +2.4±1.8% vs. -2.5±2.2% Left total hip BMD: -3.7±1.0% vs. -12.3±6.9% Right total hip BMD:

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
		-2.2±3.4% vs. -8.6±3.5% Left femoral neck BMD: -1.1±3.5% vs. -11.1±7.4% Right femoral neck BMD: -5.1±6.5% vs. -20.0±6.4% 2. Zoledronic acid group observed decreased BMD for left & right total hip and femoral neck but observed increased BMD for lumbar spine over 18-24 months post-treatment 3. Elevated levels of serum CTX and P1NP at baseline, and are reduced at 3 months in both zoledronic acid and placebo groups 4. Delayed zoledronic acid infusion in those with >10% BMD loss after 6 months of placebo resulted in stabilization in total hip, left femoral neck, and lumbar spine; however, BMD of left distal femur continued to decline 5. No adverse effects other than temperature elevations (n=3)
	Effect Sizes: Forest plot of standardized mean differences (SMD ± 95%CI) as calculated from pre- and post-intervention data	

<table>
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Score
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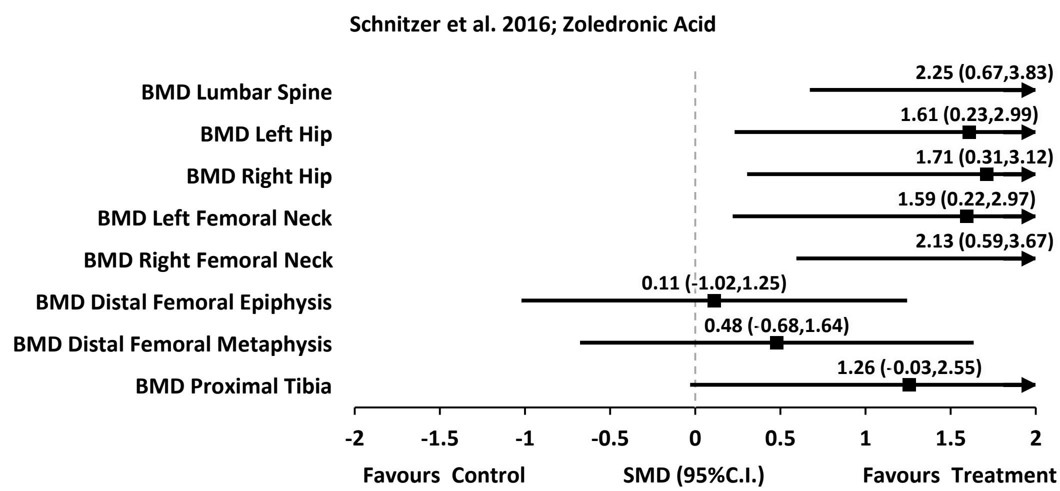
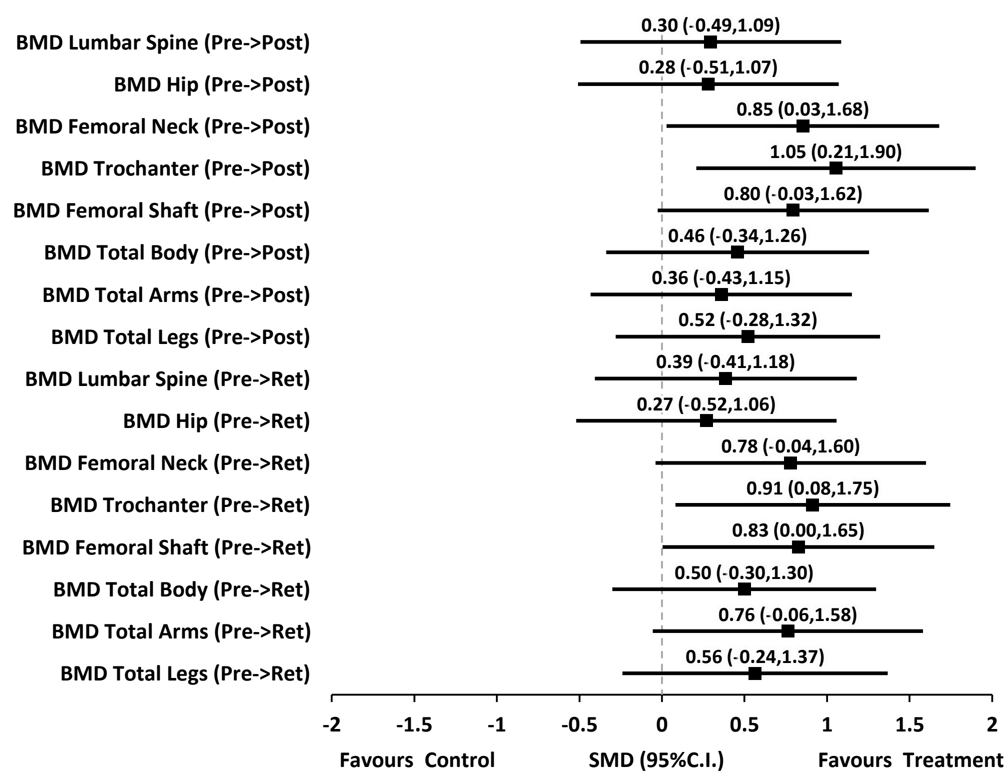
Total Sample Size</th><th>Methods</th><th>Outcome</th></tr>
<tr><td></td><td colspan="2">
</td></tr>
<tr><td>Pearson et al. 1997 Canada
PEDro=8
RCT
Level 1
N=13</td><td>Population: 12 men and 1 woman; age: 22-57 years; injuries between C5-T12; AIS: A or D.

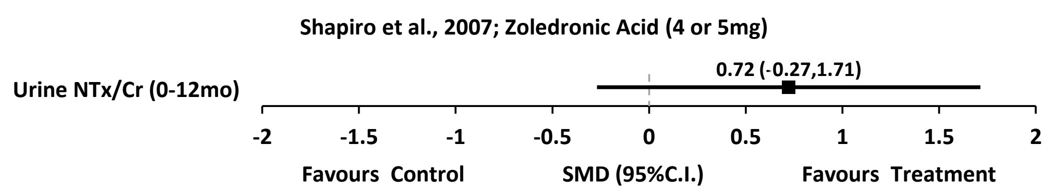
Treatment: Etidronate for 30 weeks. Participants randomized to 1.800mg daily (n=6; 5 men 1 woman; mean age: 35.6 years) or 2. Conventional rehab and calcium 1000mg/day (n=7; 7 men; mean age: 33.6 years).

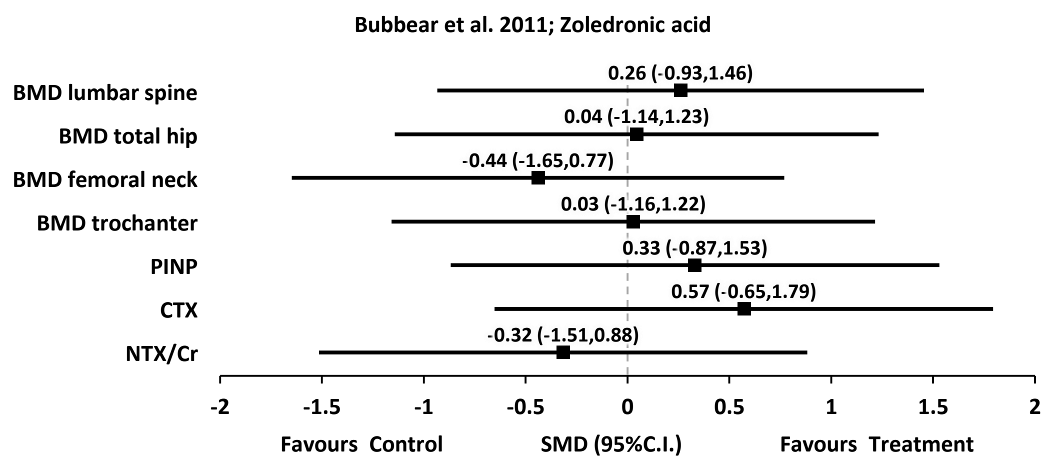
Outcome measures: DXA and adverse event rate.</td><td>1. BMD loss at the distal femur was 26% and 22% at the proximal tibia. The rate of decline in BMD was greatest amongst the AIS A individuals. BMD of lower extremity for the Etidronate-treated AIS D individuals was preserved.
2. Oral Etidronate was safe and well-tolerated by participants.</td></tr>
<tr><td>Gilchrist et al. 2007
New Zealand
PEDro=7
RCT
Level 1
N=31</td><td>Population: 31 participants (22 men, 9 women) age: 17-55 years; 10 AIS A, 1 AIS B, and 3 AIS C.

Treatment: Alendronate (oral) for 12 months within 10 days of acute injury. Participants randomized to 1. 70 mg once weekly (n=15; 10 men and 5 women); or 2. Placebo (n=16; 12 men and 4 women).

Outcome Measures: BMD and body composition by DXA, ultrasound,</td><td>1. BMD at the femoral neck was maintained in the treatment group, and there was less BMD loss at other hip sites compared with the placebo group.
2. BMD at the hip in the Placebo group declined steadily over the 18 months follow-up.
3. At 12 months, there was a 5.3% difference in total body BMD and a 17.6% difference in the percent</td></tr>
</table>

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
	bone turnover markers.	change in total hip BMD between the two groups. 4. Alendronate compared with placebo-induced reductions in urinary calcium excretion and serum CTX at 3 months only.
	Effect Sizes: Forest plot of standardized mean differences (SMD ± 95%CI) as calculated from pre- to post-intervention data and pre-intervention to retention/follow-up data **Gilchrist et al. 2007; Oral Alendronate 70 mg/wk**  **SD calculated from Standard Error of the Mean (SEM)**	
Shapiro et al. 2007	**Population:** 14 men and 4 women with traumatic SCI; age: 18-60 years (Placebo: 28.4 ± 9.4; Treatment: 30.1 ±	1. Treatment group: Six months after zoledronic acid, BMD, bone cross-sectional area, and

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
USA PEDro=7 RCT Level 1 N=18	14.2); tetraplegia (n=5) or paraplegia (n=13); AIS A (n=14) or AIS B (n=4). **Treatment:** Zoledronic acid. Participants randomized to 1. Single-dose intravenous solution either 4mg (n=4) or 5mg (n=4) (Total n=8), or 2. Placebo group received 50ml of normal saline over 15 minutes (n=10) Participants with low serum 25-hydroxyvitamin D received oral supplementation. **Outcome Measures:** bone turnover markers, BMD by DXA	sectional modulus increased at the hip and buckling ratio decreased consistently with improved bone outcomes. At 12 months, narrow-neck femur values declined, and intertrochanteric and femoral shaft BMD was maintained. 2. Placebo group: decrease in bone outcomes and an increase in buckling ratio at the hip at 6 and 12 months.
	Effect Sizes: Forest plot of standardized mean differences (SMD ± 95%CI) as calculated from pre- and post-intervention data 	
[Minaire et al. 1987](#) France PEDro=7 RCT Level 1 N=21	**Population:** 21 men and women; age: 15-54 years, complete paraplegia. **Treatment:** Clodronate for 100 days. Participants randomized to **1.** 400mg per day (n=7); **2.** 1,600 per day (n=7); or **3.** Placebo (n=7). **Outcome measures:** DXA, histomorphometry, bone turnover markers.	1. There was a greater increase in bone removal markers in Placebo group (48%), compared with treatment groups (17-27%). 2. BMD was maintained in treatment groups with a ↓ in placebo group. 3. Lower bone turnover markers in treatment groups.
[Bubbear et al. 2011](#) UK	**Population**: 14 acute SCI participants (Control: 5 men, 2 women; mean age 27 ± 14.4; Treatment: 4 men, 3 women; mean age 31.6 ± 7.1)	1. Significant difference between control and treatment groups over 12 months at lumbar spine (+0.8±4.9% vs. +3.5±3.9%, p = 0.033), total hip (-15.8±8.9% vs. -3.4±3.0%, p=0.005),

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
PEDro=6 RCT Level 1 N = 14	**Treatment:** 4 mg intravenous zoledronic acid (active treatment group) or standard nursing/medical care (control group) **Outcome Measures:** BMD using DXA at baseline, 3, 6, 12 months for lumbar spine (L1-4) and hip (total, femoral neck, trochanter); Bone turnover markers (serum CTX and P1NP) and urinary N-terminal telopeptide/creatine ratio).	trochanter (-17.9±9.4% vs. -4.5±5.7%, p=0.028) 2. No significant difference between groups with femoral neck BMD or with creatine markers. 3. Bone turnover markers normalized within 6 weeks to 3 months in treatment group vs to up to 12 months in control group 4. 5 of 7 participants in zoledronic group had flu-like symptoms over 24 hours
	Effect Sizes: Forest plot of standardized mean differences (SMD ± 95%CI) as calculated from pre- and post-intervention data 	
[Nance et al. 1999](#) Canada Prospective Controlled trial (nonrandomized)	**Population:** 22 men and 2 women, ages 25-57, injuries between C5-T12, AIS A-D. **Treatment:** Pamidronate for 6 months. Participants randomized to 30 mg intravenous every 4 weeks x 6 doses (total 180 mg/participant) [n=14; 30.8 ± 8.3 years (range 20 - 45)] or conventional rehab [n=10; 35.1 ± 10	1. There was a lower % decline in BMD in treatment vs. control group. The mean overall BMD decline was 8.1% in the placebo group but only 2.7% in the treatment group (p=0.02). The average loss of BMD was 3.1% in the AIS D group and 7.7% in the AIS A group.

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
Level 2 N=24	years (range 25 - 57)]. **Outcome measures:** BMD by DXA, urine biochemical bone markers.	

* All data expressed as mean±SD, unless expressed otherwise.

Discussion

Evidence for pharmacological *prevention* of SCI BMD decline includes 9 RCTs (n=168 participants) and 1 non-RCT (n=24) (Table 9). These studies were difficult to interpret as a group due to the variability in selection of the pharmacological treatment, primary outcome measure, relatively short duration of follow-up, small sample sizes, and the lack of stratification based on impairment level. Preventing BMD decline immediately following SCI is challenging given the rapid bone resorption especially in AIS A patients. The majority of studies found bisphosphonates resulted in a reduction of BMD decline compared with a control group. The two studies which report that first generation bisphosphonates (Clodronate) can maintain bone were short in duration (3 months intervention) and participants had less severe injury (paraplegia, incomplete SCI) (Minaire et al. 1981, 1987). In the studies by Pearson and colleagues (1997) and Nance and colleagues (1999), both groups continued to lose bone, except AIS D participants who had bone density preservation in the lower extremity with bisphosphonates while participants with AIS A had the greatest decline in both studies. A recent study which used a second-generation version of the bisphosphonate, Pamidronate, and a longer intervention period found no significant differences between groups for BMD decline after 1 year (Bauman 2005a). Gilchrist and colleagues (2007) noted a significant difference in BMD at the hip with once weekly Alendronate. Shapiro and colleagues (2007) tested the effect of once-yearly intravenous Zoledronate with significant improvement in BMD at the hip at 6 months that returned to baseline values at 12 months; the control group on the placebo treatment lost bone over the 12 months. Bubbear and colleagues (2011) also showed that once-yearly intravenous Zoledronate resulted in less BMD decline at the spine and hip over 12 months. The investigators also highlighted the added benefits of a once-yearly intravenous administration of bisphosphonate, as this eliminates issues surrounding poor patient adherence and the adverse gastrointestinal effects associated with alternate oral therapies. Schnitzer et al. (2016) compared the BMD of people with SCI before and after 12 months of zoledronic acid infusion (5 mg) and only showed increases in lumbar spine BMD. Although there is evidence that bisphosphonates may reduce bone resorption, current medications do not prevent BMD decline. Nonetheless, there is a window of opportunity soon after injury where SLOP prevention may be effective, and there is sufficient evidence of moderate prevention efficacy that patients should be counselled on the available therapies and allowed to make their own decision regarding treatment.

Conclusions

There is level 1 evidence (from 3 RCTs) (Minaire et al. 1981, 1987; Chappard et al. 1995) that oral Tiludronate and Clodronate prevent a decrease in BMD of the hip and knee region with no adverse effects on bone mineralization in men with paraplegia.

There is level 1 evidence (from 1 RCT) (Pearson et al. 1997) that oral Etidronate prevents a decrease in BMD of the hip and knee region in people with incomplete paraplegia or tetraplegia (AIS D impairment) who return to walking within 3 months of the SCI.

There is level 1 evidence (from 1 RCT) (Gilchrist et al. 2007) that once-weekly oral Alendronate maintains hip region BMD.

There is level 1 evidence (from 3 RCTs) (Shapiro et al. 2007; Bubbear et al. 2011) that a one-time intravenous infusion of Zoledronate may reduce BMD decline in the hip region during the 12 months following administration. These results were contradicted by Schnitzer et al. (2016) which showed increases in lumbar spine BMD but not at the hip region.

There is level 1 evidence (from 1 RCT) (Bauman et al. 2005a) that Pamidronate 60mg intravenous seven times per year and level 2 evidence (from 1 non-randomized prospective controlled trial) (Nance et al. 1999) that Pamidronate 30 mg intravenous six times per year is 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.

Key Points

Bone health management should begin early following SCI, given the significant declines in hip and knee region bone mass in the first year and the associated lifetime increased fracture risk.

The efficacy of drug interventions appears to be greater when medications are administered early after SCI onset

Oral tiludronate and clodronate prevent a decrease in BMD of the hip and knee region with no adverse effects on bone mineralization in men with paraplegia.

Oral etidronate prevents a decrease in BMD of the hip and knee region in people with incomplete paraplegia or tetraplegia who return to walking.

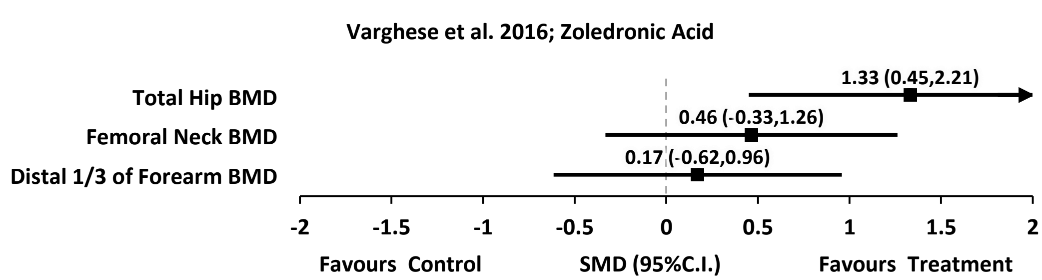
Oral alendronate once weekly maintains BMD at the hip.

Once yearly intravenous infusion zoledronate may reduce bone loss at the hip during the 12 months following administration.

Pamidronate 30 mg intravenous or 60 mg intravenous 4x/year is not effective for the prevention of BMD loss at the hip and knee region early after SCI people with motor complete paraplegia or tetraplegia.

8.2 Pharmacologic Therapy: Treatment (1 Year Post-Injury and Beyond)

Table 10. Studies of Pharmacologic Therapy for Treatment of Bone Loss in Chronic SCI

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
Varghese et al. 2016 India PEDro=10 RCT Level 1 N=25	**Population:** 25 participants (22 men, 3 women) with traumatic chronic SCI; age: 38.3 ± 10.4 years; TPI: 12.2 (6.8) years; 5 cervical/upper thoracic, 20 lower thoracic/lumbar **Treatment:** Infusion of zoledronic acid (4 mg) or placebo (saline) **Outcome measures:** BMD by DXA at baseline and 12-months post-treatment.	1. Significant within-group decrease in total hip BMD in placebo group only (0.607±0.073 to 0.491±0.169 g/cm²) 2. Significant within-group decreases in femoral neck BMD in placebo (0.548±0.111 to 0.480±0.163 g/cm²) and zoledronic acid group (0.576±0.064 to 0.552±0.074 g/cm²) 3. Significant within-group increases in BMD of distal third of forearm in placebo (0.713±0.031 to 0.747±0.028 g/cm²) and zoledronic acid group (0.717±0.066 to 0.760±0.072 g/cm²) 4. No significant between-group differences in percentage changes of BMD and BMC
	Effect Sizes: Forest plot of standardized mean differences (SMD ± 95%CI) as calculated from pre- and post-intervention data 	

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Score
Research Design
Total Sample Size</th><th>Methods</th><th>Outcome</th></tr>
<tr><td rowspan="2">Bauman et al. 2005b

USA

PEDro=10

RCT

Level 1

N=40</td><td>Population: 40 participants (39 men, 1 woman) with complete motor injuries; age 43 ± 13 years; TPI: 12 ± 10 years (range: 1–34 years); 17 participants with tetraplegia and 23 participants with paraplegia.

Treatment: Vitamin D_2 analogue, 24 months.

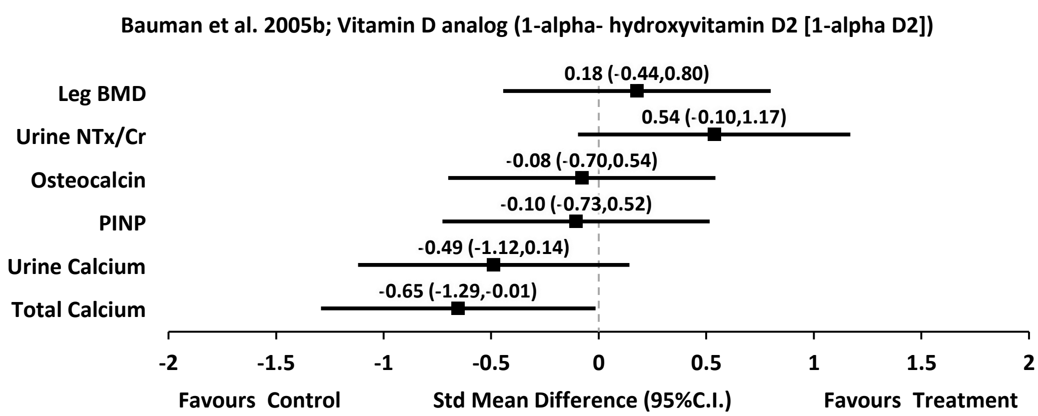
1. Treatment group received calcium 1300 mg daily, vitamin D 800 IU daily, and 1-alpha vitamin D_2 4 µg daily (n = 19).

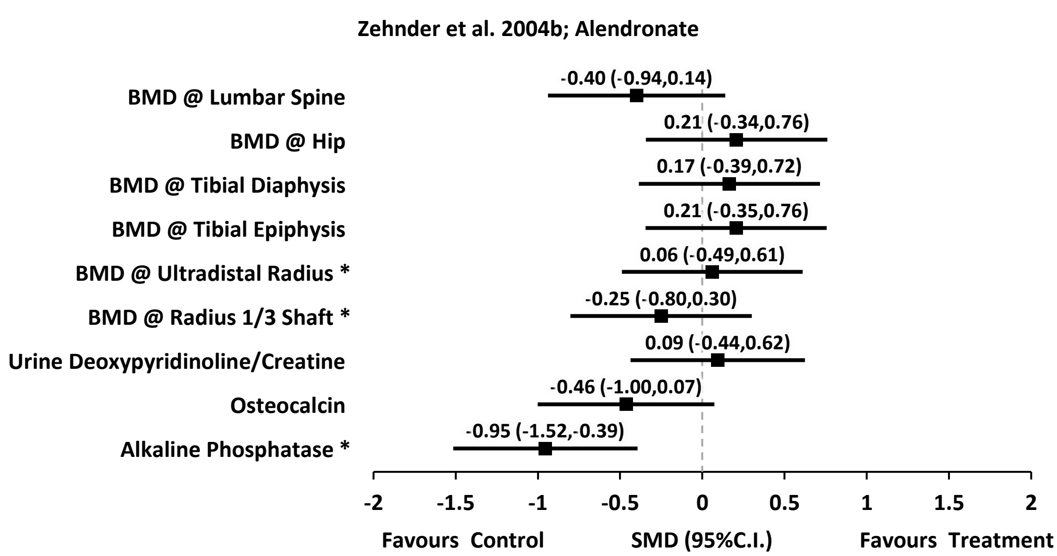
2. Control group received calcium 1300 mg daily, vitamin D 800 IU daily, and placebo in place of vitamin D_2.

Outcome measures: BMD by DXA, biomarkers at 6, 12, 18, and 24 months.</td><td>1. Significant changes noted in leg BMD only in the vitamin D_2 (treatment) group at 6, 12, 18, and 24 months. There was significant interaction for group by time.

2. In the vitamin D_2 (treatment) group, smoking compromised the response to treatment and changes in BMD.

3. In the vitamin D_2 (treatment) group, urinary marker of bone resorption was significantly reduced, but markers of bone formation were not changed.</td></tr>
<tr><td colspan="2">Effect Sizes: Forest plot of standardized mean differences (SMD ± 95%CI) as calculated from pre- and post-intervention data


</td></tr>
</table>

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
[Zehnder et al. 2004b](#) Switzerland PEDro=7 RCT Level 1 N=65	**Population:** 65 men; age: 38.3 years; TPI: 8.7 years (range, 0.1–29.5); traumatic complete injuries between T1-L3; AIS: A, B. **Treatment:** Alendronate for 24 months. 1) 10mg per day plus 500mg calcium per day (n=33) or 2) Calcium alone (500mg per day) (n=32). **Outcome measures:** BMD by DXA and bone turnover markers.	1. Decrease in BMD of the tibia in Calcium group but remained stable in the Treatment group (group difference, p = 0.017). There was no change in wrist BMD and a significant increase in lumbar spine BMD in both groups. BMD of the mid-shaft tibia and hip were maintained in the Treatment group and decreased in the calcium group. 2. Biochemical markers of bone absorption significantly decreased from baseline in the Treatment group.
	Effect Sizes: Forest plot of standardized mean differences (SMD ± 95%CI) as calculated from pre- and post-intervention data  *SMD calculated using SD of pre-post difference instead of baseline SD	

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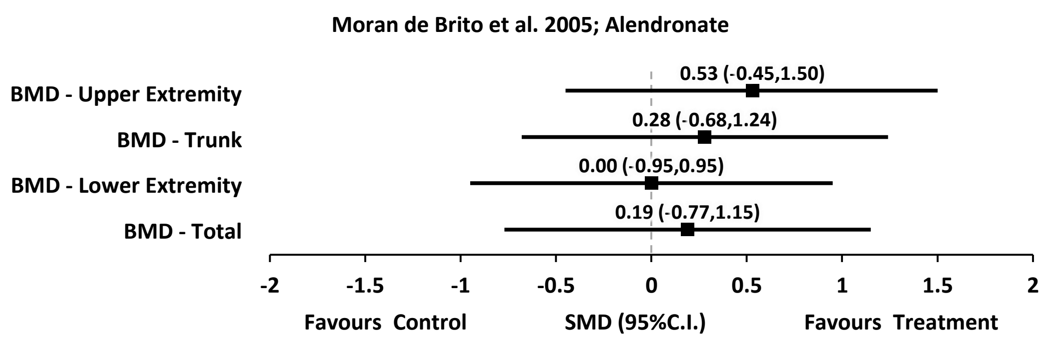
Score
Research Design
Total Sample Size</th><th>Methods</th><th>Outcome</th></tr>
<tr><td rowspan="2">Moran de Brito et al. 2005
Brazil
PEDro=6
RCT
Level 1
N=19</td><td>Population: 15 men and 4 women; age: 30.8 (range: 17-47) years; TPI: 49.8 months (range: 13.1–255.7); 18 traumatic and 1 nontraumatic; para/tetraplegia; AIS: A, B, or C.
Treatment: Alendronate for 6 months.
1. 10 mg and Calcium 1000 mg bid (n=10) and
2. Calcium (1000 mg bid) (n=9).
Outcome measures: BMD by DXA</td><td>1. There was a mean increase in upper extremity BMD that was greater in Treatment vs. calcium group although not statistically significant. There were significant differences for total T-score and BMD.</td></tr>
<tr><td colspan="2">Effect Sizes: Forest plot of standardized mean differences (SMD ± 95%CI) as calculated from pre- and post-intervention data

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</table>

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
Gifre et al. 2016 Spain Post-test Level 4 N=14	**Population:** 14 men with traumatic SCI & osteoporosis; age: 39 ±15 (range: 19-65) years; TPI: 15.2 ± 4 (8-21) months; AIS-A/B/C: 12/1/1; 43% paraplegia, 57% tetraplegia **Treatment:** Denosumab 60 mg every 6 months up to 12 months **Outcome measures:** Biochemical measurements: Serum creatinine, calcium, phosphate, 25OHD Bone turnover markers: Bone ALP, P1NP, serum CTX BMD by DXA at lumbar spine, femoral neck, total hip.	1. Significant within-group increase in BMD at total hip (2.4±3.6%), femoral neck (3.0±3.6%) and lumbar spine (7.8±3.7%) at 12 months 2. Significant within-group decreases in ALP (42%), P1NP (-58%) and serum CTX (-57%) at 12 months 3. BMD changes unrelated to Bone turnover markers or 25OHD changes 4. No serious treatment-related adverse events were noted.

* All data expressed as mean±SD, unless expressed otherwise.

Discussion

Evidence for pharmacological *treatment* of SLOP (Table 10) includes 4 RCTs (Zehnder et al. 2004b; Bauman et al. 2005b; Moran de Brito et al. 2005; Varghese et al. 2016) (n=159) and one prospective observation study (Gifre et al. 2016) (n=14). In these studies, the treatment group experienced improvement or maintenance in bone health at various sites. For the two studies that tested Alendronate, the extent of improvement was greater in the study by Zehnder et al. (2004b) who found an increase in BMD at the spine with the maintenance of BMD at the hip and tibia. In contrast, Moran de Brito et al. (2005) only found a non-significant increase in BMD in the upper extremity and a significant increase in total BMD. The difference in outcomes response could be a result of the younger participants with less severe injuries in the work by Zehnder and colleagues (2004b). Bauman and colleagues (2005b) noted positive results in leg BMD for participants who received vitamin D. Varghese et al. (2016) showed significant reductions in hip and femoral neck BMD one year after zoledronic acid infusion (4 mg). Sixty milligrams of Denosumab evoked significant increases in the hip, femoral neck, and lumbar spine BMD after one year (Gifre et al. 2016).

This review has provided conflicting support for using first- and second-generation oral bisphosphonates for prevention of low bone mass and some support for treatment of 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 one-hour post ingestion, prior to taking any other food or medication. About 1% of the ingested oral bisphosphonate is absorbed in the upper intestine, yet it remains in the body in an inactive form for several months or years thereafter. Oral bisphosphonate therapy can cause side effects; joint pain, stomach upset and diarrhea being the most frequently reported adverse effects. Intravenous formulations of bisphosphonates are available in monthly, quarterly and annual preparations, and have a greater relative potency. Although their common short-term side effects include fever, low serum calcium and transient decrease in white blood cells, intravenous preparations are attractive due to the flexibility in dosing regimens, assured adherence to therapy and the reduced relative risk of an adverse upper gastrointestinal event.

Bisphosphonates should be used with caution in premenopausal women due to the unknown teratogenic effects of these medications on the fetus during pregnancy. Patients taking acetylsalicylic acid, corticosteroids or non-steroidal anti-inflammatory medication may require gastrointestinal prophylaxis as these medications in combination with bisphosphonates increase the relative risk of developing a gastric ulcer or bleeding. Many questions regarding the safety of these medications among people with SCI and the optimal duration of therapy remain. Zoledronate, an intravenous bisphosphonate, has been reported to increase the incidence of serious atrial fibrillation resulting in hospitalization or disability among 1-3% of elderly non-SCI patients (HORIZON study, Black et al. 2007). Zoledronate should be used with caution in elderly patients or patients with premorbid atrial fibrillation or arrhythmia secondary to autonomic dysfunction after SCI. The risk of osteonecrosis of the jaw is highest among people with a prior history of cancer or radiotherapy. Both osteonecroses of the jaw and arrhythmia should be discussed during consent for oral or intravenous bisphosphonate therapy.

It has been shown that oral bisphosphonates may be taken safely without adverse effects on bone metabolism for 10 years in postmenopausal women (Bone et al. 2004). Data from postmenopausal non-SCI women suggests BMD should be monitored at least alternate years in patients who stop taking oral bisphosphonates; those with a rapid decline in BMD of >10% in two years or >5% from baseline should be switched to alternate treatment or resume bisphosphonate therapy (Colon-Emeric 2006).

Conclusion

There is level 1 evidence (from 1 RCT) (Zehnder et al. 2004b) that Alendronate 10 mg daily and calcium 500mg orally 3x/day is effective for the maintenance of BMD of the total body, hip and knee region for men with paraplegia.

Sixty milligrams of Denosumab evoked significant increases in hip, femoral neck, and lumbar spine BMD after one year (Gifre et al. 2016). Further validation of treatment efficacy in a randomized trial is needed.

There is level 1 evidence (from 1 RCT) (Bauman et al. 2005b) that vitamin D analogue is effective for maintaining leg BMD.

Key Points

Alendronate 10 mg daily and calcium 500 mg orally 3x/day is effective for the maintenance of BMD of the total body, hip and knee region for men with paraplegia.

Vitamin D analogue is effective for maintenance of BMD in the leg.

9 Non-pharmacologic Therapy: Rehabilitation Modalities

Rehabilitation options for bone health after SCI focus on the application of electrical stimulation of the lower limb muscles and encouraging weight-bearing. This section includes six modalities: NMES, FES, standing and walking, treadmill training, ultrasound and physical activity/exercise. NMES is characterized by the application of high intensity, intermittent stimulation to produce strong visible isometric muscle contractions to elicit regional gains in strength with repeated stimulus exposure. (Maffiuletti et al. 2017). In contrast, FES consists of delivering moderate surface stimulation over specific muscles to replicate voluntary movements such as cycling, walking or rowing with the main goal of restoring function (Maffiuletti et al. 2017). These lifelong types of NMES and FES protocols are dedicated to maintaining neuromusculoskeletal health and are intended to be a substitute for a functional activity for patients that can no longer perform these movements by themselves in the absence of the device. On the other hand, FES-therapeutic (FES-T) is a form of FES where voluntary movement of a limb is initiated prior to application of the electrical stimulation in a specific pattern to augment voluntary movement, with the aim of withdrawing the device after 3-6 months of therapy and persistence of the movement is anticipated thereafter.

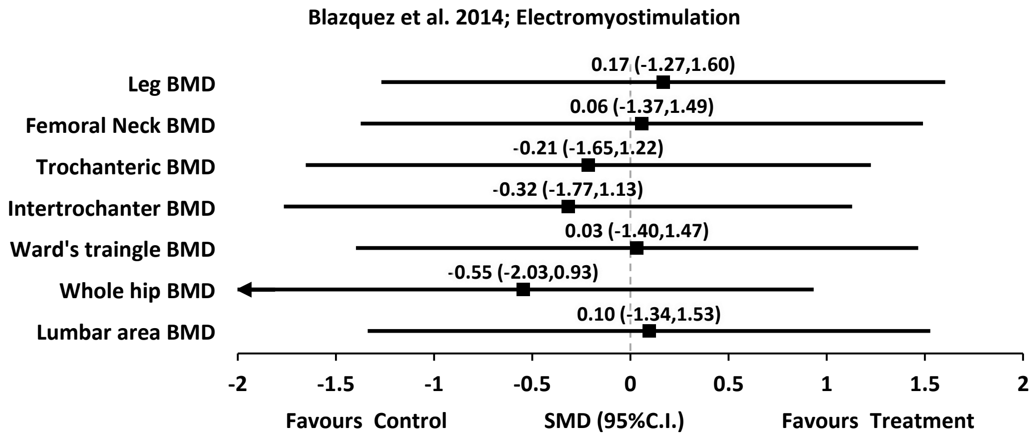
Weight-bearing activities, such as walking and standing, are also used for bone health after SCI; these modalities include either passive (tilt-table or standing frame) or active weight-bearing activities with or without assistance from FES. Many FES studies and weight-bearing studies have enrolled participants with both acute and chronic injuries and are therefore difficult to classify as pure prevention or treatment interventions. For this review, studies that enrolled participants that ranged from the acute phase to > 1 year were included with the treatment literature, as the majority of their participants were in the chronic phase.

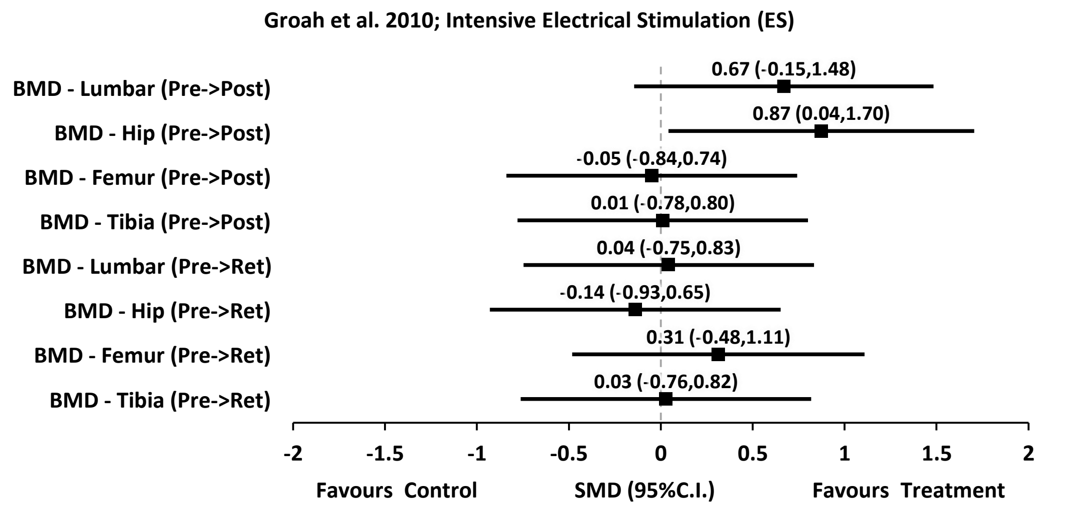
9.1 Non-pharmacologic Therapy: Prevention of Bone Loss (within 12 Months of Injury)

Table 11. Studies of Rehabilitation Modalities for Prevention of Bone Loss in the First Year after SCI

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
FES-Cycling		
Lai et al. 2010 Taiwan Prospective controlled Study Level 2 N = 24	**Population:** 24 participants; 12 treatment (10 men, 2 women; age: 28.9 ± 5.3 years; TPI: 35.3 ± 6.1 days; C5 – T7) and 12 control (10 men, 2 women; age: 28.2 ± 5.7 years; TPI: 34.9 ± 8.0 days; C5 – T7). **Treatment**: FES-cycling 3x/week for first 3 months, suspended for next 3 months. Cycling time gradually increased up to 30 min. **Outcome Measures:** Right femoral neck BMD and distal femur BMD between femoral condyles 2cm above knee joint space (DXA). Measurements at baseline, after 3-month intervention, and 3 months post-intervention	1. Baseline: no significant differences in BMD between groups at femoral neck and distal femur 2. End of 3 months program BMD at femoral neck and distal femur significantly lower in both groups, but ↓ in distal femur BMD absolute values significantly lower in FES group than control (0.02 g/cm^2 (SD 0.01) vs. 0.07 g/cm^2 (SD 0.01), p<0.01) 3. From the end of cycling to 3 months after discontinuation, both groups decreased at the femoral neck and distal femur site, with no group differences.
Eser et al. 2003 Switzerland Prospective controlled trial Level 2 N=38	**Population:** 38 participants (34 men, 4 women); age: 32.9 years; complete traumatic injuries between C5-T12, (19 participants, 19 controls). **Treatment**: FES-cycling. Progressive training sessions until able to cycle for 30 minutes, then 3x/week for 6 months from this baseline. On the remaining 2 days of the week, there was passive standing. Control group performed 30 min of passive standing 5 days/week.	1. Both groups had 0-10% decrease in tibial cortical BMD at 3-10 months. There was no difference between groups for BMD after the intervention.

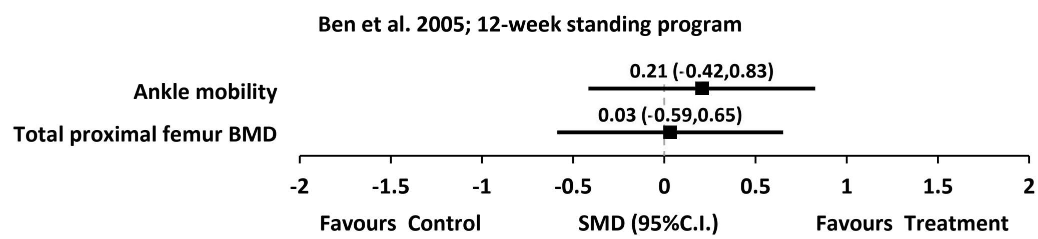
	Outcome measures: cortical BMD of right tibia diaphysis (50% site, and 5cm proximal and distal to the 50% site) computed tomography (CT)	
	NMES	
Arija-Blázquez et. al 2014 Spain RCT Level 1 PEDro = 8 N=8	**Population:** 8 men with acute motor complete traumatic SCI were allocated to Treatment group (n=5; AIS A; T4 – T 12; age: 42 years; TPI: 5.5 weeks) or Control group (n=3; age: 36years; TPI: 5.8 weeks). **Treatment:** 14 weeks of NMES training (47 minutes/day, 5 days/week). One session consisted of 80 muscle contractions during 47 minutes divided into 10 contraction sets with a 60-second rest between sets. Every 2 sets, knee angle was changed throughout 10°, 35°, 60°, and 85° (0° full extension). NMES (T-ONE MEDIPRO, Electromedical Mediterranea, S.L., Spain): electrodes were located over the rectus femoris, vastus medialis and vastus lateralis. Stimulation pattern: 200 μs pulse duration, at 30 Hz and with a maximum current of 140 mA. Amplitude was adjusted in the Treatment group to elicit similar isometric torque during the 14 weeks. **Outcome Measure:** Bone mineral density (BMD; DXA): legs from whole-body scan, lumbar spine, total hip, femoral neck, trochanteric and intertrochanteric areas. Bone biomarkers: Serum cortisol (ARCHITECT c4000 (Abbott Laboratories S.A, Madrid, Spain), Serum OC (Diasource kit (DIAsource ImmunoAssays S.A., Barcelona, Spain) and Serum CTX (E 170 module for MODULAR ANALYTICS - Roche Diagnostics, S.L., Madrid, Spain).	1. No difference in mean group change in BMD (g/cm^2) and T-score between pre vs pre and pre vs post-NMES treatment between two groups. In fact, both groups showed a trend (i.e. not significant) for BMD decline in all areas (e.g. Treatment group: leg=-2.92%; trochanteric=-9.94%; Control group: leg=-3.34%; trochanteric=-8.12%), except lumbar (+3.47%). 2. Although serum OC increased >50% (pre: 10.64±5.5 ng/ml) and CTX and serum cortisol decreased by >26 (pre: 1.26±0.6 ng/ml) and >20% (pre: 13.5 ±3.6 ug/dl), respectively, these differences were not statistically significant.

	Effect Sizes: Forest plot of standardized mean differences (SMD ± 95%CI) as calculated from pre- and post-intervention data 	
[Groah et al. 2010](#) USA PEDro =6 RCT Level 1 N=26	**Population**: 26 participants (22 men, 4 women) with traumatic SCI; age: ≥18 years; AIS A or B at time of entry, TPI: 39.5 days; above T12. **Treatment**: Randomized to usual inpatient SCI program [n=10; 26.2 years (range 19-71), 15 men and 1 woman] or intervention group [(n=16; 31.1 years (range 18-44), 7 men and 3 women]. Usual care and additional 1-hour NMES to quadriceps bilaterally (using Complex Motion Stimulator) for 1 hour (or until fatigue) 5 days/week for 6 weeks. **Outcome Measures**: Measurements at baseline, post-intervention, 3 months post-intervention. 1) BMD at lumbar spine and bilateral femoral neck, distal femur, proximal tibia (DXA). 2) Serum OC 3) Urinary NTX and 24-hour urine calcium	1. No group differences in BMD decline or biomarkers over time. However, the NMES group experienced 50% less distal femur BMD loss (not significant).
	Effect Sizes: Forest plot of standardized mean differences (SMD ± 95%CI) as calculated from pre- to post-intervention data and pre-intervention to retention/follow-up data	

		
Arija-Blázquez et al. 2013 Spain Prospective Controlled Trial Level 2 N=20 (10 SCI)	**Population:** 10 participants with recent traumatic thoracic SCI (10 men, AIS A); age: 39.4 ± 12.3 years; TPI: 8 weeks; BMI: 25.1 ± 3.6 kg/m^2. 10 age-matched non-disabled participants for comparison; age: 36.7 ± 8.9 years, BMI: 23.3 ± 3.3 kg/m^2. **Treatment:** Immediately after basal blood samples were drawn, NMES was conducted (1 set of currents was applied bilaterally at each knee angle; total of 80 contractions; total NMES time was 47 min per participant). **Outcome Measures:** BMD lower limb, total hip, femoral neck, intertrochanteric region (DXA), muscle cross-sectional area (MRI), testosterone, cortisol, and Type I collagen CTX (blood samples)	1. No significant differences between right and left leg BMD. 2. Basal levels of testosterone were not significantly different in SCI and non-disabled groups. There was a significant decrease in testosterone 15 min post-NMES (SCI = -11.9%, non-disabled=-6.8%). In the SCI group, testosterone remained lowered 30 min post-NMES (-7.4%). No differences in mean testosterone concentrations were observed between SCI and non-disabled groups at any time point. 3. Mean cortisol levels were not significantly different in SCI and non-disabled groups at any time point. In the SCI group, 30 min post-NMES mean cortisol levels dropped significantly (-18.5%). 4. Mean OC levels were not significantly different between SCI and non-disabled groups at any time point. 5. At all time points, CTX levels were significantly higher in the SCI group than non-disabled group. In the SCI group, CTX levels significantly declined post-NMES at 0 min (-27.0%), 15

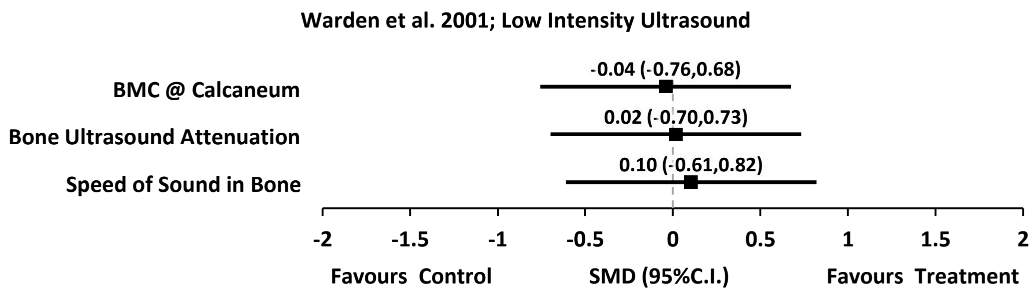
		min (-23.4%), 30 min (-27.1%), and 24h post-NMES (-10.2%). In the non-disabled group, CTX levels declined at 15 min (-13.7%) and 30 min (-15.6%) post-NMES.
Dudley-Javoroski & Shields 2008a USA Case-control Level 3 N=19 (12 SCI)	**Population:** 12 men with motor complete SCI; age: 21–72 years; TPI: 0.3–22 years; C5–T11; AIS A–B; 9 matched SCI subjects as controls. 7 matched non-SCI controls. **Treatment:** Unilateral soleus NMES 5x/week 15 Hz every 2 s for 120 contractions (8000 contractions/month). **Outcome measures:** pQCT (trabecular vBMD of distal tibia 4% site) of one leg versus the other leg annually for up to 6 years.	1. A sustained between-limb difference in posterior distal tibia trabecular vBMD of 76.1 mg/cm3 (p = 0.04).
Dudley-Javoroski & Shields 2008b USA Case Report Level 5 N=1	**Population:** 1 man; T4 AIS A traumatic paraplegia; age: 21 years; TPI: 7 weeks. **Treatment:** Four bouts of 125 soleus contractions over 30 minutes 5 times per week in one leg; actual 8,000 contractions per month **Outcome** measures: trabecular vBMD of distal tibia 4% site (pQCT) of one leg versus the other leg after 1 year, 3 years	1. After 1 year, no difference in trabecular architecture; 4.5% difference in trabecular vBMD After 3 years, 15%/year vBMD decline in of untrained tibia and 7.6%/year vBMD decline in trained limb. Lower decline attributed to posterior portion which lost 2.59%/year.
Clark et al. 2007 Australia Prospective Controlled trial Level 2 N=33	**Population:** 33 participants; 15 tetraplegia and 18 paraplegia; AIS A-D. **Treatment**: NMES, 5 months Low-intensity stimulation to leg muscles, 15 min, 2x/day 5 days/week, 5 months (n=23; age 28.6 ± 8.6 years; C4–T10, 13 tetraplegic; ; n=21 traumatic; n=2 nontraumatic); or control group (no treatment) (n=10; age: 31.0 ± 10.7 years; C5–T12, 4 tetraplegic; n=9 traumatic; n=1 nontraumatic). **Outcome measures:** total body, lumbar spine and hip BMD (DXA) at 3 weeks, 3- and 6-months post-injury.	1. NMES was safe and well-tolerated, but there was only a minimal difference between groups for total body BMD only at 3 months post-injury (p<.01). Other DXA measures (hip and spine BMD) did not differ between groups at any time point.
Shields et al. 2007	**Population:** 4 men with SCI; age: 52.3 ± 11.2 years; T1-7; AIS A; TPI: 8.9 ± 4.1 years. **Treatment:** Trained 1 leg using an isometric	1. Unchanged BMD of proximal tibia before and after training for trained and untrained

USA Pre-Post Level 4 N=4	plantarflexion NMES protocol (the untrained limb serving as within-subject control) for 30min/day, 5 days/week, for 6 to 11 months. Mean estimated compressive loads delivered to the tibia were ~110% body weight. **Outcome Measures:** BMD of the proximal tibia by DXA at baseline and post-intervention.	limb ($p>0.05$). Trained limb of 2 subjects had ~0.02g/cm^2 gain in BMD but not statistically significant. 2. Untrained proximal tibia BMD did not differ from trained limb proximal tibia BMD either before or after training.
Shields et al. 2006a USA Prospective Controlled trial Level 2 N=6	**Population:** 6 participants with complete injuries from C5-T10; age: 27.6 years (range: 21-43); TPI: 2.1 months; 70% training compliance. Within-participant design. **Treatment**: NMES at 1.5 times bodyweight for 3 years. Treatment leg only received a home program of NMES to stimulate leg plantar flexors with a 35-min protocol (4 bouts with 5-min rest between bouts) for 5x/week **Outcome measures:** BMD of the spine, hips and knee regions (proximal tibial analysis protocol) by DXA at baseline and 1,2 and 3 years.	1. There was a greater decline in tibia BMD of the untrained limb compared with the trained limb (10% vs. 25%) ($p<0.05$)
Shields et al. 2006b USA Prospective Controlled trial Level 2 N= 7	**Population:** 7 men with complete injuries from C5-T10; age: 29.1 years (range: 21-43); TPI: < 4.5 months. Within-participant design. **Treatment**: NMES at 1.5 times body weight; 2-3 years. Treatment leg only received a home program of NMES to stimulate leg plantar flexors with a 35-min protocol (4 bouts/day with 5-min rest between bouts) for 5x/week). **Outcome measures:** cortical BMD of the tibia bilaterally at the 4%, 38%, and 66% sites (pQCT).	1. No significant differences in cortical BMD of the tibia at the 38% and the 66% sites 2. Higher distal tibia trabecular BMD at 4% site in trained compared with untrained limb.
Standing/Walking		

<table>
<tr>
<td rowspan="2">Ben et al. 2005
Australia
PEDro=9
Within-participant RCT
Level 2
N=20</td>
<td>Population: 20 participants (16 men and 4 women); TPI: 4 ± 2 months; age: 34 ± 15; 8 paraplegia, 12 tetraplegia. Within-participant design.
Treatment: Tilt-table standing, 12 weeks
Treatment leg only received weight-bearing on a tilt-table for 30 min, 3x/week. Wedge applied to treatment leg to provide adequate dorsiflexion and weight-bearing to the ankle. Control leg was not loaded in standing.
Outcome measures: BMD of proximal femur (DXA).</td>
<td>1. No difference in proximal femur BMD between the treatment and the control leg.</td>
</tr>
<tr>
<td colspan="2">Effect Sizes: Forest plot of standardized mean differences (SMD ± 95%CI) as calculated from pre- and post-intervention data


Both heels of each subject randomized to different groups (control or intervention) such that each sucject acts as his/her own control</td>
</tr>
<tr>
<td>de Bruin et al. 1999
Switzerland
PEDro=6
RCT
Level 1
N=19</td>
<td>Population: 19 men; ages 19-59; traumatic injuries between C4-T12; AIS: A-D.
Treatment: Standing/Walking. Group 1 had 0-5 hour per week loading exercises with a standing frame. Group 2 had 5+hour of standing exercises per week (standing). Group 3 had 5+hours of standing and treadmill (walking). Interventions lasted 25 weeks
Outcome measures: trabecular BMD, cortical BMD moment of inertia of the left tibia proximal to the ankle joint line and in the diaphysis (pQCT).</td>
<td>1. Marked decrease in trabecular BMD. (site not specified) at the left tibia for the immobilized group but minimal decrease in trabecular BMD in Group 2 and 3</td>
</tr>
<tr>
<td></td>
<td>Population: 12 participants (9 men, 3 women; age: 22-48 years) non-disabled controls and 12 (11 men, 1 woman; age: 16-44 years old; 11 AIS A, 1 AIS B; 10 out of 12</td>
<td>1. Over 1.5 years, the slope of distal femur trabecular MD decline over time was slower at all quadrants for the active-resisted stance limbs.</td>
</tr>
</table>

Dudley-Javoroski & Shields 2013 USA Longitudinal Level 2 N=12	subjects had TPI <1-year at first scan) participants with SCI. **Treatment:** Individuals with SCI experienced active-resisted stance with FES of the quadriceps (n=7) or passive stance (n=5) for up to 3 years. **Outcome Measures:** trabecular BMD of the distal femur 12% femur length measured distal to proximal (pQCT)	2. At >2 years of training, trabecular BMD was significantly higher for the active-resisted stance group than for the passive stance group. 3. Trabecular BMD was preferentially spared in the posterior quadrants of the femur with active-resisted stance.
Treadmill Training		
Giangregorio et al. 2005 Canada Pre-post Level 4 N=5	**Population:** 5 participants (2 men, 3 women); age: 19-40 years, traumatic injuries between C3-C8; AIS: B and C; no controls; TPI: 114.2 days. **Treatment:** Body-weight supported treadmill training. Initial session started at 5mins and was increased gradually to 10-15 mins in all but 1 participant during 48 sessions of 2x/week-training over 6-8 months. **Outcome measures:** BMD lumbar spine, hip, distal femur and proximal tibia by DXA and mid femur 60% site and proximal tibia 66% site CT; bone turnover markers (osteocalcin, DPD).	1. Lumbar spine BMD changes ranged from 0.2 to -7.4%. 2. Decrease in BMD for all participants at almost all lower limb sites after training, ranging from -1.2 to -26.7% (DXA). 3. No consistent changes in bone geometry at distal femur and proximal tibia (pQCT). 4. Did not alter the expected pattern of change in biochemical bone markers over time.
Ultrasound		
Warden et al. 2001 Australia PEDro=11 RCT Level 1 N=15	**Population:** 15 men; age: 29 years (range: 17-40); traumatic injuries between C5-T10; AIS: A-B; TPI: 110.3 days; within-group design. **Treatment:** Pulsed therapeutic ultrasound. Applied to both calcanei for each participant for 20 min/day, 5x/week over a consecutive 6-week period. Right and left calcaneus within each participant was randomized. **Outcome measures:** BMD of the calcaneus by DXA and quantitative ultrasound of the calcaneus (QUS).	1. For the specified dose of pulsed ultrasound, no significant effects were on BMD measured via DXA or QUS for any parameter (p>0.05).
	Effect Sizes: Forest plot of standardized mean differences (SMD ± 95%CI) as calculated from pre- and post-intervention data	

<table>
<tr><td></td><td colspan="2">

Both heels of each subject randomized to different groups (control or intervention) such that each sucject acts as his/her own control</td></tr>
<tr><td colspan="3">Physical Activity</td></tr>
<tr><td>Astorino et al. 2013
USA
Pre-post
Level 4
N=13</td><td>Population: 13 participants with SCI (11 men, 2 women); 2 chronic, 11 acute SCI; age: 29.4 ± 7.8 years; TPI: 1.9 ± 2.7 years.
Treatment: 2-3h/day of activity-based therapy targeting regions below the level of injury a minimum of 2 days/week for 6 months. Activity-based therapy consisted of the following modalities: active assisted exercise, upper/lower body and core resistance training, load-bearing, cycle ergometry, gait training and vibration.
Outcome measures: BMD of the whole body, lumbar spine, right and left total hip, femoral neck and intertrochanteric region distal femur, proximal tibia (DXA) at baseline, 3 and 6 months.
Serum P1NP; serum CTX;</td><td>1. Total-body BMD significantly declined (2.5%) from 0 to 6 months, accompanied by reductions in total hip BMD, right and left femoral neck BMD, and right and left trochanter BMD.
2. The two participants with chronic SCI showed increased total body (1.0 and 1.8%), total femur (0.5 and 1.3%) and trochanter BMD (2.6 and 6.8%) in response to training.
3. Activity-based therapy had no effect on P1NP and serum CTX.</td></tr>
</table>

* All data expressed as mean±SD, unless expressed otherwise.

Discussion

Evidence for non-pharmacological ***prevention*** of SLOP includes data from seventeen investigations (n=270 participants). This includes five RCTs (88 participants), five non-randomized controlled trials (160 participants) and three pre-post studies (22 participants) (Table 11). As with pharmacological studies, there were difficulties with interpretation because of low numbers of participants and variability with the primary outcome measures. For each of the different rehab modalities, there is limited evidence available and there was variability in the selection of the primary outcomes. The therapeutic ultrasound study by Warden and colleagues (2001) found no significant improvement in bone health after a 6-week intervention. Although prospective observational data (Frey-Rindova et al. 2000) highlight the loss of bone in the early phase (first 6-months post-SCI), there was no significant influence of self-reported physical activity level. Training adherence was: 78.4% for FES-cycling, 79.4% for NMES, 94.4 for standing/walking and 100% for ultrasound and physical activity. Overall, the evidence suggests that rehabilitation modalities did not prevent bone mass decline in the acute phase after SCI, although general training compliance was relatively high.

Conclusions

There is level 1 evidence (one RCT) that 6 weeks of pulsed calcaneal ultrasound has no effect on calcaneal BMD measured by DXA or QUS. (Warden et al. 2001)

There is level 1 evidence (one RCT) that NMES training of quadriceps 5 days per week for 14 weeks did not result in significant changes in lower limb or hip region BMD. (Arija-Blázquez et al. 2014)

There is level 2 evidence (from 1 non-randomized prospective controlled trial) that NMES of plantar flexors for 2-3years initiated after 2-4 months of injury reduced the decline in tibia vBMD (Shields et al. 2006a; 2006b).

There is level 2 evidence (from 1 non-randomized prospective controlled trial) that FES-cycling 30 minutes thrice weekly for 6 months did not improve or maintain cortical BMD of the right tibial diaphysis in the acute phase. (Eser et al. 2003)

There is level 1 evidence (from 1 RCT) that standing thrice weekly for 12 weeks initiated within 4-6 months of injury did not prevent proximal femur BMD decline (Ben et al. 2005).

There is level 3/4 evidence that active-assisted standing (FES) with for 2-3 years was effective in mitigating BMD decline of the trabecular BMD of the distal femur (Dudley-Javoroski & Shields 2013).

There is level 4 evidence (from 1 pre-post study) that BWSTT twice weekly for 6-8 months more than three months post-injury did not prevent declines in hip or knee region bone mineral density (DXA or QCT). (Giangregorio et al. 2005)

There is level 4 evidence (from 1 pre-post study) that activity-based training 2-3 hours/day for a minimum of 2 days a week for 6 months increased spine BMD (Astorino et al. 2013).

Key Points

Interventions, beyond 6 months in duration, with an adequate sample size, are needed to determine the efficacy of rehabilitation intervention for prevention or treatment of SLOP.

FES-cycling FES-cycling does not improve or maintain bone at the tibial midshaft in the acute phase.

Activity-based training (6 months) is effective for increasing spine BMD.SLOP.
There may be a role for longterm(2-3 years) of NMES in mitigating BMD decline

9.2 Non-pharmacologic Therapy: Treatment (1 Year Post-Injury and Beyond)

In this section, non-pharmacological rehabilitation treatment modalities are divided into six sub-sections: NMES, vibration, FES-cycling, standing, and walking, and physical activity (Tables 12-16). Both NMES and FES use cyclical patterns of electrical stimulation that simulate muscular activity. However, FES is directed towards the attainment of purposeful tasks such as cycling or walking. Electrical stimulation, on the other hand, is focused on producing muscle contractions (isometric, isotonic). In some interventions, electrical stimulation techniques are used as a training stimulus to prepare muscles for a subsequent FES training regimen.

9.2.1 NMES

Table 12. Studies of NMES for Treatment of Bone Loss in Chronic SCI

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
Bélanger et al. 2000 Canada Prospective Controlled Trial Level 2 N=28	**Population:** 14 participants (11 men, 3 women); age: 32.4 ± 5.9 (range: 23-42) years; complete and incomplete injuries between C5-T6. 14 non-disabled matched controls. **Treatment**: NMES. Quadriceps training was conducted 5 days/week for 24 weeks. Participants trained for 1hr/day or until fatigue. Right quadriceps were stimulated with no resistance (but against gravity) while the left quadriceps were stimulated against a resistance. **Outcome measures:** BMD by DXA	At baseline BMD from the experimental group was lower at the distal femur, proximal tibia, and mid-tibia (decreased range: 25.8% to 44.4%) than non-disabled controls. Increased BMD with training ($p<0.05$) for both sides of SCI participants, but the type of training had no effect (resistance vs. no resistance). There was a significant increase in the BMD of the distal femur and proximal tibia, but not in the mid-tibia.
Rodgers et al. 1991; USA Pre-post Level 4 N=12	**Population:** 9 men and 3 women; age: 38.3 ± 12.9 years; TPI: 6.4 ± 6.1 years; para/tetraplegia; complete/incomplete; no controls (only 9 participants had BMD) **Treatment**: Knee extension NMES. Each participant trained for a total of 36 sessions (3x/week for 12 weeks) using a progressive intensity protocol. This progression was continued to a maximum 15 kg load. **Outcome measures:** BMD of the tibia by DXA	Tibial BMD was not significantly changed after NMES protocol ($p>0.05$), but BMD was better than predicted values.

* All data expressed as mean±SD, unless expressed otherwise.

Discussion

Although there were no RCTs that assessed the effect of NMES, Bélanger et al. (2000) produced impressive results with a level 2, non-randomized trial which used one limb as the treatment and the other as the control. Following training (93.4% compliance), the BMD recovered close to 30% of BMD decline when compared with non-disabled values. Stimulation effects only occur over the areas of stimulation and returned to baseline within months once stimulation is stopped (Mohr et al. 1997). However, there is a clear need for further studies, especially RCTs, testing the long-term effects of NMES with weight-bearing on bone health.

Conclusions

There is level 2 evidence (from 1 prospective controlled trial) (Bélanger et al. 2000) that NMES either increased or maintained BMD over the stimulated areas.

Key Points

NMES can maintain or increase BMD over the stimulated areas.

9.2.2 FES-Cycling

Table 13. Treatment Studies Using FES-Cycling for Bone Health After SCI

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
Craven et. al 2017 Canada PEDro = RCT Level 1 N=34	**Population:** 34 participants (26 men, 8 women) with chronic traumatic SCI; C2-T12; age: 55 years; TPI: 5 years; 13 AIS C, 20 AIS D. **Outcome Measures:** OC was measured with radioimmunoassay, CTX with electrochemiluminescence immunoassay Roche Diagnostics GmbH and Serum sclerostin was measured by BIOMEDICA sclerostin ELISA. All markers were assessed at baseline, and 4 months. aBMD of total hip, distal femur and proximal tibia were assessed by DXA (4500A, Hologic Inc., Waltham, MA, USA). PQCT scan measured total vBMD, cortical vBMD, trabecular vBMD, cortical thickness	1. Participants in the FES-walking arm had a decrease in CTX (0.26 – 0.24 ng/ml, p = 0.05) and a significant increase in OC (16.7 – 17.8, p = 0.02) at intervention completion. 2. No significant biomarker change was observed in CONV arm at intervention completion. 3. No within or between-group differences were observed in sclerostin at intervention completion 4. No between-group differences were observed in aBMD of total hip, distal femur, or proximal tibia at any point

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
	(CoTh), strength-strain index and polar moment of inertia, at sites 4% and 38% of total tibia length **Treatment:** 45 min, 3x/week, 4 months. Control group (CONV): aerobic (20-25 min, 3-5 Borg; arm or leg bicycling, walking in parallel bars or on the treadmill) and resistance (2–3 sets of 12–15 repetitions maximum resistance for muscles capable of voluntary contraction) exercise program. FES-walking with bodyweight support group: open-loop FES (8–125 mA, 250–300 µs pulse duration, 20–50 Hz) over the quadriceps, hamstrings, tibialis anterior and gastrocnemius while walking with body weight support.	5. No between-group differences were observed in vBMD of the tibia 4% and 38% site or pQCT bone architecture outcomes at any point
Johnston et al. 2016 USA PEDro = 5 RCT Level 1 N=17	**Population:** 17 participants (14 men, 3 women); age: 42 ± 12 years; TPI: 12 ± 10 years; 8 cervical, 9 thoracic; AIS-A/B. Treatment: FES-cycling 1h per session, 3 times per week for 6 months Low cadence group: n=8 at 20 RPM High cadence group: n=7 at 50 RPM n=2 withdrew due to personal reasons Outcome Measures: Trabecular bone micro-architecture (apparent trabecular number; apparent trabecular separation; apparent bone volume to total volume), BMD by DXA, serum bone-specific ALP, urine NTX, other biochemical markers & muscle volume	No significant between-group or within-group differences for bone micro-architecture measures Large effect sizes seen for distal femur apparent trabecular number, apparent trabecular separation and a moderate effect size were seen for apparent bone volume to total volume Significantly greater decrease between-groups in bone ALP in low cadence group Low cadence group decreased bone ALP by 15.5%, whereas high cadence group increased by 10.7% Significant within-group decrease in NTX in low cadence group 1. Low cadence group decreased NTX by 34%, whereas high cadence group decreased by 10%

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
Hammond et. al 2014 USA Cross-sectional Level 5 N=364	**Population:** 364 participants with SCI; age 39.8 ± 16.1 years; 276 traumatic, 88 nontraumatic; 79 ambulatory; 202 FES users; TPI: 6.9 (range: 1-8) years; 178 AIS A and B, 184 AIS C and D. Treatment: N/A **Outcome Measures:** The prevalence of osteoporosis, defined as having ≥1 region of interest on a DXA (Hologic Discovery equipment and software) examination with a T score ≤2.5, based on FES-cycling usage (RT 300 SL). General FES-cycling parameters: maximal intensity of 140 mA, 500 μs pulse duration, 30 to 40 Hz frequency, with a target goal of 50 revolutions per minute, 30-60 min/session). Other data recorded: age, sex, level and severity of injury as per the American Spinal Injury Association (ASIA) Impairment Scale (AIS), TPI, ambulatory status, FES usage, daily calcium and vitamin D intake, and anticonvulsant drug use.	1. Prevalence of osteoporosis was 34.9% (n=127). Osteopenia (defined as a T score between >-1 and -2.4) was present in 46.7% (n=170) of participants, and BMD was normative in only 18.4% (n=67). 2. FES-cycling usage [mean (confidence interval - CI)]: 20.2 (1.0-24.0) weeks, 2.3 (1.0-3.0) sessions per week, average distance of 8.1 (4.7-10.5) km, average energy per hour 61,412.8 kJ/h, average stimulation level (% range 0-100) 83.2 (76.4-99.0) and average charge level 28.8 (17.5-34.7) μC. 3. FES-cycling was associated with 31.2% prevalence of osteoporosis compared with 39.5% among persons not using FES. FES use was associated with 42% decreased odds (Odds Ratio/OR = 0.58; 95% confidence interval (CI) = 0.35-0.99) of osteoporosis after adjusting for sex, age, BMI, type and duration of injury, Lower Extremity Motor Scores (LEMS), ambulation, previous bone fractures, and use of calcium, vitamin D and anticonvulsant. 4. Healthy BMI (from 25-40) showed 58% decreased odds of osteoporosis in adjusted analysis (OR = 0.42; 95% CI = 0.24-0.73) 5. Duration of injury >1 year was associated with a 3-fold increase in odds of osteoporosis compared with individuals with <1 year. 6. Type and severity of injury, calcium and vitamin D intake, use of anticonvulsant therapy, and previous bone fractures were not associated with the likelihood of having osteoporosis.

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
Ashe et al. 2010 Canada Case Series Level 4 N= 3	**Population**: 3 women with traumatic chronic motor SCI; TPI: >1 year; complete n=2, incomplete n=1; ages: 29, 19, 51 years. **Treatment:** Computer-controlled leg FES-cycling training for 6 months, 3 times a week. Including habituation and training phases **Outcome Measures:** Pre-post BMD (g/cm^2) using DXA (lower extremity); pre-post differences in bone health i.e. total content (g/mm) and density (mg/cm^3) using pQCT at midshaft (50%) and distal (5%) sites of tibia	All three participants had a percentage change in BMD ranging between 1-16% There was maintenance of cortical bone density in all 3 participants at 50% site ranging from 0.51-1.24% At distal site, all three participants responded differently. Increase in BMD in both legs n=1, increase in right leg n =1, increase in left leg n=1
Frotzler et al. 2009 Switzerland/UK Pre-Post Level 4 N = 5	**Population:** 4 men and 1 woman with traumatic SCI; age: 38.6 ± 8.1 years; T4-T7; ASIA grade A; TPI: 11.4 years (range 3.6–19.8); who showed significant effects on bone parameters due to high-volume FES-cycling **Methods:** Follow-up on Frotzler et al. 2008: 4 participants stopped FES-cycling and 1 had reduced training (two-three 30-minute sessions/week) **Outcome Measures:** Trabecular and total BMD and BMC by pQCT.	**Participants who stopped training:** *Distal femur:* 73%±13.4% of total gain in BMDtrab; 63.8%±8.0% in BMDtot, and 59.4%±3.9% in BMC were preserved after 12 months of detraining **Participant with reduced training:** 96.2% of total gain in BMDtot and 95% of gain in BMDtrab in the distal femur were preserved
Frotzler et al. 2008 Switzerland/UK Pre-Post Level 4 N=11	**Population:** 11 participants (2 women, 9 men) with traumatic SCI; T3-T12; age: 41.9 ± 7.5 years; TPI: 11.0 ± 7.1 years; AIS A. **Treatment:** FES-cycling, five 60-min sessions per week for 12 months **Outcome Measures:** Femur and tibia: trabecular, cortical, and total BMD, BMC and total bone cross-sectional area by pQCT.	Distal Femur: 1. Trabecular BMD increased by 14.4±21.1% 2. Total BMD increased by 7.0±10.8% 3. Total bone cross-sectional area increased by 1.2±1.5% Femoral Shaft: 1. Cortical BMD decreased by 0.4±0.4% 2. BMC decreased by 1.8±3.0% **Tibia:** No significant changes in bone parameters.

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
Chen et al. 2005 Taiwan Pre-post Level 4 N=30	**Population:** 15 men, age: 28.67 (range: 23 ± 37) years; TPI: 9.3 ± 3.9 years; complete, C6-T8. 15 matched non-disabled controls. **Treatment:** FES-cycling. Participants performed FES-cycling exercises with minimal resistance for 30 minutes/day, 5 days/week for 6 months. Follow-up 6 months after intervention. **Outcome measures:** BMD of the hip. Femoral neck, distal femur and proximal tibia by DXA	At baseline, participants' BMD at the femoral neck, distal femur and proximal tibia was lower than controls. After 6 months, BMD of the distal femur and proximal tibia increased significantly (p<0.05). BMD in the distal femur, proximal tibia, and heel decreased significantly after 6 months without intervention (p<0.05). The BMD of the femoral neck decreased progressively throughout the treatment (p>0.05).
Mohr et al. 1997 Denmark Pre-post Level 4 N=10	**Population:** 10 men and women; age: 27-45 years, injuries either C6 or T2, no controls. **Treatment:** FES. Sequential electrical stimulation of the quadriceps, hamstrings, and gluteal muscle groups to generate a cycling motion for 30 min, 3x/week for 6 months, followed by 1x/week for 6 months. **Outcome measures:** Lumbar spine, femoral neck, distal femur, proximal tibia and BMD by DXA and bone turnover markers (osteocalcin and deoxypyridinoline).	After 12 months of training, there was a significant 10% increase in proximal tibia BMD (p < 0.05) but no change in 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 were no significant changes with FES.
BeDell et al. 1996 USA Pre-post Level 4 N=12	**Population:** 12 men; age: 34 ± 6 years (range: 23-46); complete traumatic injuries between C5-T12; TPI: >2 years; no controls. **Treatment**: FES-cycling. Participants participated in a 3-phase training program. Phase 1: quadriceps strengthening through NMES. Phase 2: FES-cycling progression until 30 min continuously. Phase 3a: 24x 30-mins continuous FES-cycling sessions performed 3x/week. Phase 3b: An extra 24x 30-min FES-cycling sessions	At baseline, SCI participants were not significantly different from age-matched non-disabled ambulatory men for lumbar-spine BMD. However, BMD was significantly lower for participants at the hip (p<0.025) for bilateral trochanters, Wards triangles, and femoral necks. Only the L2-L4 values demonstrated a trend (p=0.056) for a small positive effect from training. Further training (Phase 3b) did not demonstrate further increase in BMD at any site.

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
	adding simultaneous arm ergometry (8 participants only). **Outcome measure:** lumbar spine and hip BMD by DPA	
Hangartner et al. 1994 USA Pre-post Level 4 N=15	**Population:** 15 participants; age: 17-46 years; complete and incomplete injury between C5-T10; no controls. **Treatment:** NMES and FES-cycling. 1. NMES knee extension exercises (n=3); 2. FES-cycling (n=9); or 3. both (n=3). Sessions were 3x/week for 12 weeks except Group 3 had 24 weeks. **Outcome measures:** tibia BMD specify site (proximal and distal) via CT	1. 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.
Leeds et al. 1990 USA Pre-post Level 4 N=6	**Population:** 6 men; ages 18-27; C4-C6; traumatic tetraplegia; no controls. **Treatment:** NMES and FES cycle ergometry. 1-month quads strengthening exercise (NMES), followed by 6 months of FES-cycling. Knee extension sessions were 45 lifts/leg 3x/week for 1month. FES-cycling sessions were 3X/week up to 30 mins for 6 months. **Outcome measures:** Hip BMD by DXA	The BMD of the proximal femurs were below normal before commencing exercise intervention (compared with matched non-disabled individuals). After 7 months of exercise training, there was no significant difference in BMD for any of proximal femur sites
Pacy et al. 1988 UK Pre-post Level 4 N=4	**Population:** 4 men; age: 20-35 years; paraplegia; no controls. **Treatment:** NMES and FES-cycling. Part 1 was NMES of quads strengthening with ↑ load ranging from 1.4-11.4 kg bilateral for 15 mins for 5x/week (10 weeks). Part 2 was FES-cycling at 50 rpm with resistance (0-18.75 W). Performed for 15 mins, 5x/week (32 weeks). **Outcome measures:** Lumbar spine, hip, and distal tibia BMD by CT.	No significant change in lumbar, femoral shaft, or distal tibia trabecular BMD after the intervention.

* All data expressed as mean±SD, unless expressed otherwise.

Discussion

There are mixed results for bone outcomes after FES-cycling. Three studies reported a regional increase in BMD (Mohr et al.1997; Chen et al. 2005; Frotzler et al. 2008) at the distal femur or proximal tibia, while there was no significant within-participant BMD change at the hip in three pre-post studies (Pacy et al. 1988; Leeds et al.1990; and BeDell et al.1996). The FES-cycling studies which reported a positive effect on bone parameters used protocols that were at least 3 sessions/week for 6 months and increased bone parameters over areas directly affected by stimulated muscles (e.g., quads, distal femur and proximal tibia). Although one study showed that FES-cycling intervention needed to be maintained or bone gains were lost (Chen et al. 2005).

Frotzler et al. (2008) found BMD and BMC were preserved at the distal sites for some participants at 12 months. Hammond et al. (2014) suggested that FES-cycling may reduce the prevalence of osteoporosis in people with SCI compared to people with SCI that do not use FES-cycling; however, no minimal FES requirements (i.e. intensity, duration or frequency) were provided. Craven et. al, (2017) and Johnston et al. (2016) however, showed no difference in BMD after 4-6 months of FES-walking and FES-cycling, respectively. In summary, longitudinal FES-cycling shows promise as an effective treatment for regional BMD maintenance (around the knee, where fracture risk is highest). The limited availability of FES-cycling for home or longitudinal use may limit its' generalizability outside a clinical trial scenario.

Conclusions

There is level I evidence that FES-walking did not elicit significant changes in bone biomarkers or BMD after 4 months of training (Craven et. al, 2017)

Johnston et al. (2016) showed that 6 months of FES-cycling did not produce significant changes in bone architecture.

Hammond et. al, 2014 suggested a decrease in the prevalence of osteoporosis after FES-cycling.

There is level 4 evidence (Mohr et al.1997; Chen et al. 2005; Frotzler et al. 2008) that FES-cycling increased regional lower extremity BMD over areas stimulated.

Key Points

FES-cycling may increase lower extremity BMD over stimulated areas for the duration of the intervention.

Serial DXA assessment of treatment effectiveness among individuals with SCI should include evaluation at the total hip, distal femur, and proximal tibia, following a minimum of 12 months of therapy at 1- to 2-year intervals.

9.2.3 Vibration

Table 14. Studies of Vibration Treatment for Bone Loss in Chronic SCI

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
Dudley-Javoroski et al. 2016 Pre-post 2016 USA N=7	**Population:** 7 participants (5 men, 2 women); age: 38.1 ± 19.6 years; TPI: 5.9 (range: 0.1-29.2); 6 thoracic, 1 cervical; AIS-A/B: 5/2; TPI at first pQCT: 5.6 ± 6.5 years; TPI at first CT: 7.4 ± 4.9 years. **Treatment:** n=6; 12 months of vibration; mean of > 2.14 sessions/week, for 112-152 sessions One leg of each participant underwent vibration (+ cycles of 10-35% body weight), the other acted as control n=1 did not participate in vibration (participant 1); followed-up at 2.7 years post-SCI (first pQCT & CT @ 0.14 & 0.36 years post-SCI) **Outcome Measures:** BMD and bone micro-architecture variables including network length, plate volume fraction, and others. Variables measured via peripheral quantitative CT (pQCT) and high-resolution CT (CT). CT analyzed at multiple regions and peel* modes *Removal of voxels corresponding to 30, 45, and 60 % from the trabecular envelope; peripheral peel = removal of 60% peel from 30% peel.	1. pQCT found no significant training (yes/no) x time (pre/post) interaction for BMD of either tibia or femur 2. CT found significant training x time and training x region interactions only for certain variables at certain peels and regions of tibia and femur 3. pQCT found a significant decline in distal femur & tibia BMD post-training but found no overall decline femur or tibia BMD 4. CT found significant post-training decreases in BMD and network length with 30% peel at distal tibia & femur 5. CT found a mean post-training decrease of 24.3% in BMD and 14.4% in NL across all regions of tibia, and 29.5% and 35.5% for femur. 6. pQCT found a mean follow-up** BMD decrease of 55.9% for distal tibia, and 73.4% for distal femur. 7. CT found a mean follow-up** decrease of 48.1% in BMD, and 41.9% in NL distal tibia, and 53.6% in BMD, 38.1% in NL & 2,9% in PVF for distal femur. 8. Loss** of BMD and architecture greatest at ultra-distal tibia and central epiphysis of femur **Follow-up of participant 1 at 2.7 years post-SCI
Wuermser et al. 2015 USA 2015 Pre-post N=9	**Population:** 9 participants (5 men, 4 women) with chronic traumatic motor complete paraplegia; age: 42 ± 8 years; TPI: 2-27 years; AIS- A or B; BMI: 22.3 ± 4.1 kg/m^2. **Treatment:** Whole-body low-magnitude vibration (Juvent Medical, Somerset, NJ,	1. Average use of the whole-body vibration platform: 20-60 min per day, 5x per week. 2. aBMD: no significant change at the proximal femur sites (baseline: 0.75 ± 0.20 g/cm^2; post-intervention: 0.74± 0.18 g/cm^2).

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
	USA; model Juvent 1000) using a standing frame for 20 minutes per day, 5 days a week, and for 6 months. The vibrating plate provides a 0.3 g, 34 Hz vertical sinusoidal movement of ~50 µm. **Outcome measure:** Areal bone mineral density (aBMD; DXA, Lunar Prodigy system, GE Healthcare, Madison, WI, USA) at the proximal femur; distal tibia total trabecular and cortical volumetric BMD (vBMD; HRpQCT (XtremeCT, Scanco Medical AG Brüttisellen, Switzerland), and bone microstructure; bone turnover biomarkers: C-terminal telopeptide of type I collagen (CTX; Roche Cobas e411 (Roche Diagnostics, Indianapolis, IN, USA), amino-terminal pro-peptide of type I collagen (, P1NP; double-antibody radioimmunoassay, Orion Diagnostica, Espoo, Finland) and serum, sclerostin (enzyme-linked immunosorbent assay, Biomedica, Wien, Germany; distributed in USA by ALPCO, Salem, NH, USA);) and body composition measurements: total body lean mass (kg) and total body fat mass (kg) and BMI (kg/m^2). Assessed at baseline, 3 and 6 months during the intervention and 6 months after the intervention.	However, three subjects had an increase in total hip aBMD that was greater than the minimal detectable difference. 3. vBMD and microstructure: no significant differences in either the trabecular (Tibia: trabecular thickness baseline: 0.04 ± 0.03 mm; post-intervention: 0.04 ± 0.03 mm) or cortical compartments (Tibia cortical thickness pre: 0.80 ± 0.28 mm; post-intervention: 0.78 ± 0.31 mm). No change greater than the minimal detectable difference was identified. 4. No significant improvement in aBMD at the proximal femur or vBMD after 6 months of intervention, or any relevant changes 6 months following the discontinuation of the low-magnitude vibration. 5. No significant change or relevant trend in bone turnover biomarkers or total or lower extremity, lean mass or fat mass over follow-up.
Melchiorri et al. 2007 Italy Pre-Post N=10	**Population:** 10 men; age: 34 ± 4 years; traumatic SCI; Level of injury: between 8th and 10th dorsal vertebra; TPI: 8 ± 3 yrs. **Treatment:** Vibration using handlebars and four series of maximal speed arm curls with the load being increased with each series to 5,8,10, and 15% of individual's body weight (handlebar and extra load together) at frequency of 30 Hz. Subjects exposed to vibrations for 12 weeks, 5x/week, 5min/session. **Outcome measures:** BMC and BMD by DXA (total body)	1. Total DXA measurements corresponding to BMC and BMD showed no statistically significant differences between three-time points. Segmental analysis showed a non-significant increase in BMD for both arms.

* All data expressed as mean±SD, unless expressed otherwise.

Discussion

Vibration training is a relatively new treatment option used for potential benefits to muscle and/or bone health. However, none of the current evidence supports its efficacy in improving bone health.

Conclusion

There is level 4 evidence (from 2 pre-post studies) (Wuermser et al. 2015; Dudley-Javoroski et al. 2016) that standing on a low-magnitude vibration plate did not improve BMD or microstructure at the proximal femur or distal tibia and did not significantly change bone turnover biomarkers.

There is level 4 evidence (from 1 pre-post study) (Melchiorri et al. 2007) that vibration training did not improve or maintain BMC in the arms.

9.2.4 Standing

Table 15. Treatment Studies Using Standing or Walking for Bone Health After SCI

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
Standing (n=5 studies)		
Dudley-Javoroski et al. 2012 USA Longitudinal Level 2 N=28	**Population:** 28 participants (24 men, 4 women) with SCI; AIS A & B; age: 16-64 years. 14 non-disabled control participants (11 men, 3 women; age: 22-50 years). **Treatment:** 3 doses of bone compressive loads: no standing, passive standing, quadriceps activation during stance. 7 participants performed unilateral quadriceps stimulation in supported stance (150% body weight compressive load = "High Dose") while the opposite leg received 40% body weight = "Low Dose". 5 participants stood passively without applying quadriceps NMES to either leg (40% body weight load). 16 participants performed no standing (0% body weight load - "untrained"). **Outcome Measures:** BMD assessment between 1-6 times over a 3-year training protocol.	1. BMD for the High dose group significantly exceeded BMD for both the Low Dose and Untrained groups. 2. BMD for participants performing passive stance did not differ from individuals who performed no standing. 3. High-resolution CT imaging of one High Dose participant revealed 86% higher BMD and 67% higher trabecular width in the High Dose limb.

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
Goktepe et al. 2008 Turkey Observational Level 5 N=92	**Population:** 71 participants (60 men, 11 women; 64 traumatic, 7 nontraumatic); age: 30.9 years (range: 18-46), TPI: 4.5 years and AIS A (n=64) – B (n=7). **Treatment:** Participants were divided into 3 groups: Group A had standing ≥1hr daily, Group B stood <1hour/day, and Group C did not stand at all. **Outcome Measures:** BMD by DXA of bilateral hips (Ward's triangle and femoral neck) and spine (L2 to L4)	There was no statistically significant difference between the 3 groups in the BMD of any of the regions measured Group A tended to have higher *t*-scores, although the differences were not significant
Needham-Shropshire et al. 1997 USA Pre-post Level 4 N=16	**Population:** 13 men and 3 women; age: 28.4 ± 6.6 years; TPI: 4.0 + 3.5 years; complete injuries; T4-T11; no controls. **Treatment:** Standing and ambulation. 32 sessions then participants continued ambulation for 8 more weeks. Outcome measures: Hip BMD by DPA	1. There were no significant changes in BMD in the femoral neck, Ward's triangle, or the trochanter.
Kunkel et al. 1993 USA Pre-post Level 4 N=6	**Population:** 6 men; age: 49 years (range: 36-65); complete and incomplete; C5-T12; 4 traumatic and 2 nontraumatic (multiple sclerosis); no controls. **Treatment:** Passive standing frame. Increased gradually until able to "stand" 30 mins 3x/day. Progressed to 45 mins 2x/day then participants completed 45 mins of standing 2x/day for 5 months. **Outcome measures:** Lumbar spine and femoral neck BMD and fracture risk by DPA	There was no significant change in fracture risk as measured with BMD for femoral neck or lumbar spine with "standing".
Kaplan et al. 1981 USA Pre-post Level 4	**Population:** 8 men and 2 women; age: 19-56 years; incomplete tetraplegia; no controls. **Treatment**: Tilt-table weight-bearing and strengthening exercises. Each tilt table session lasted at least 20mins 1x/day, and the tilt table angle attained was ≥45^{0}. Two	Significant improvement ($p<0.01$) in calcium excretion, urinary calcium, and calcium balance for the early group.

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
N=10	groups: **1**) early (within 6 months of SCI) and **2**) late group (12-18 months post SCI). **Outcome Measures**: urinary calcium excretion	The late group had a significant improvement in urinary calcium and calcium balance.
Walking (n=4 studies)		
Carvalho et al. 2006 Brazil Prospective controlled trial Level 2 N=21	**Population:** 21 men; age: 31.95 ± 8.01 years; C4-C8; TPI: 66.42 ± 48.23 months (range: 25-180). Two groups: In the treatment group, all individuals had a complete lesion; in the control group individuals had an incomplete lesion (AIS B) **Treatment:** Treadmill gait training provided by NMES. Quadriceps and tibialis anterior stimulated for <5 months before beginning gait training (2x/week) to walk for 20 min and support <50% of body weight (pre-gait training) Groups were: 1. NMES for 6 months, 20 min/session,2x/week (n=11).; or 2. No training (n=10) **Outcome measures:** BMD by DXA, bone markers	Increase in bone formation markers after gait training occurred in 81.8% (9/11) of the participants, with 66.7% (8/11) had a decrease in bone resorption markers. In the control group, no changes were observed in three people; two people had an increase in bone formation markers; while three people had a decrease in bone resorption markers.
Giangregorio et al. 2006 Canada Pre-post Level 4 N=14	**Population:** 11 men and 2 women; age: 22-53 years; TPI: 7.4 years (range 1.2-24); with incomplete traumatic injuries; C4-T12; AIS B-C; matched control group. **Treatment:** Body-weight-supported treadmill training, 12 months. Completed protocol 3x/week for 144 sessions; intensity increased as tolerated **Outcome Measures:** BMD by DXA, bone markers	There were no significant changes in bone density or bone geometry at axial or peripheral sites except for a small but significant decrease in whole-body BMD. No significant difference in bone markers.

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
[Thoumie et al. 1995](#) France Pre-post Level 4 N=7	**Population:** For bone assessment, there were 6 men and 1 woman; age: 31 years (range: 26-33); TPI: 29 months (range: 15-60); T2-T10. **Treatment:** reciprocating gait orthosis - II hybrid orthosis. Completed the protocol within 3-14 months (2-hour sessions 2x/week). Outcome measures: 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).
[Ogilvie et al. 1993](#) England Pre-post Level 4 N=4	**Population:** Bone assessment with 2 men (25 and 28 years) and 2 women (16 and 42 years), with traumatic paraplegia. **Treatment:** Reciprocal gait orthosis. No protocol provided. Quantitative computed tomography repeated every 6 months from the 1st referral, orthotic fitting and training, to independent and regulator ambulation (mean=5 months). The reciprocating gait orthosis was used daily on average for 3 hours. **Outcome measures:** Lumbar spine and hip BMD by QCT	Three of 4 participants increased or maintained femoral neck BMD but no change in lumbar spine.

* All data expressed as mean±SD, unless expressed otherwise.

Discussion

There is inconclusive evidence for Reciprocating Gait Orthosis, long leg braces or passive standing as a treatment for low bone mass after SCI. One mixed cross-sectional and a longitudinal study found that participants who underwent quadriceps activation during stance with 150% body weight compressive load, had significantly higher BMD than participants who underwent quadriceps activation during stance with 40% body weight compressive load and passive standing. One cross-sectional study (Goemaere et al. 1994) used a self-report physical activity measure to highlight the potential for standing to reduce BMD decline at the femoral shaft; patients with long leg braces had a significantly higher trochanter and total BMD compared with standing frame or standing wheelchair. In contrast, another cross-sectional investigation of bone outcomes and self-report physical activity measures found no effect of activity on lower extremity bone parameters (Jones et al. 2002).

Conclusions

There is inconclusive evidence for Reciprocating Gait Orthosis, long leg braces, passive standing, or self-reported physical activity as a treatment for low bone mass.

There is level 4 evidence (Dudley-Javoroski et al. 2012) for quadriceps activation during stance with 150% body weight compressive load to increase BMD.

Key Points

There is inconclusive evidence for Reciprocating Gait Orthosis, long leg braces, passive standing or self-reported physical activity as a treatment for low bone mass.

9.2.5 Physical Activity

Table 16. Treatment Studies Using Physical Activity for Bone Health After SCI

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
Chain et al. 2012 Brazil Cross-sectional Level 5 N=25	**Population:** 25 men with traumatic quadriplegia. 2 groups: Active (n=10; age: 30 ±9 years; TPI: 8 ± 7 years) and Sedentary (n=15; age: 36 ± 11 years; TPI: 15 ± 9 years. **Treatment:** No treatment - comparison of active vs. sedentary groups. Active group practiced regular adapted physical exercise at least 150min/week divided in at least 3 days/week for at least 3 consecutive months. **Outcome Measures:** Total BMC; BMD of total body, lumbar spine, total proximal femur, femoral neck and 33% radius; serum calcium; serum intact PTH; 25-hydroxyvitamin D (25(OH)D); insulin-like growth factor-1; OC; type I collagen.	1. After adjusting for TPI, total body mass and calcium intake, no differences were observed between groups for any bone parameter except for the lumbar spine BMD, which was significantly higher in the sedentary group. 2. Serum concentrations of total calcium, 25(OH)D, insulin-like growth factor-1 and PTH were on average within normal range and were similar between sedentary and active groups. 3. In active subjects, serum concentrations of 25(OH)D were associated positively with hours of physical exercise per week (r=0.59). Serum concentrations of PTH were associated negatively with hours of physical exercise per week (r=-0.50). 4. No significant associations between habitual calcium intake and bone parameters were observed for the whole group.

* All data expressed as mean±SD, unless expressed otherwise.

Discussion

There is no evidence to support physical activity as a treatment for low bone mass after SCI. One cross-sectional study (Chain et al. 2012) used a self-report physical activity measure to highlight the differences in BMD between self-reported "active" and "sedentary" patients; active patients did not differ from sedentary patients in any bone parameter, and the sedentary group had significantly higher lumbar spine BMD.

Conclusion

There is no evidence to support physical activity as a treatment for low bone mass after SCI.

10 Combined Interventions

As this chapter goes to press, the first generation of studies of combination interventions for the treatment of BMD decline in chronic SCI are being completed. These studies evaluate the concurrent administration of pharmacological therapy with non-pharmacological rehabilitation interventions. Some examples of registered trials include studies of zoledronate in combination with FES-rowing and recombinant PTH (Forteo) in combination with weight-bearing. Table 17 describes the early results from one such trial.

Table 17. Studies of Combination Interventions for Treatment of Bone

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
Gordon et al. 2013 USA Pre-post Level 4 N=12	**Population:** 12 nonambulatory participants (10 men, 2 women) with chronic SCI; age: 34 ± 8 years; TPI: 7.7 years; 5 AIS A, 3 AIS B, 4 AIS C; low total hip bone mass (DXA T-score < 2.5 or Z-score < 1.5); C1-T10. **Treatment:** teriparatide (PTH 1-34) 20 μg daily x 6 months, calcium 1000 mg daily x 6 months, vitamin D 1000 IU daily x 6 months, and treadmill stepping 3 times/week (20 to 40 min. stepping time at 1.8 to 2.5 km/h) for 6 months using Lokomat driven gait orthosis and partial body-weight support **Outcome measures:** BMD of spine, total hip, and femoral neck by DXA at baseline, 3, 6, and 12 months; micro-MRI of distal tibia at baseline, 3, 6, and 12 months; serum bone markers BAP, CTX-1, P1NP, and OC at baseline, 3, 6, and 12 months	1. Positive but non-significant changes in lumbar spine & total hip BMD were observed at 6 months 2. Teriparatide was well tolerated.

* All data expressed as mean±SD, unless expressed otherwise.

Discussion

One study of concurrent teriparatide and body-weight supported treadmill stepping did not provide evidence in support of this combination intervention for the treatment of BMD decline in SCI. However, this study used a convenience sample with small sample size and was not powered to detect significant intervention effects. Three months of electroacupuncture and combination therapy seem to be sufficient to produce positive adaptations in BMD compared to individuals who received combination therapy only.

Conclusion

There is no evidence to support concurrent treatment of low bone mass with teriparatide and body-weight supported treadmill training (Gordon et al. 2013).

11 Interventions with Bone Biomarker Outcomes

As biomarker science improves, the utility of urinary and serum biomarkers of bone turnover continues to increase. While BMD is considered the gold standard outcome measure for bone health interventions, this outcome is not always available. In particular, retrospective studies may not have access to BMD data, and may, therefore, report only biomarker outcomes. Table 18 describes several such studies.

Table 18. Studies of Bone Health Interventions with Biomarker Outcomes

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
Chen et al. 2001 USA Case series Level 4 N=21	**Population:** 21 participants (17 men, 4 women) with acute SCI; age: 34 (range, 16- 78) years; TPI: 26 days (range: 6 to 122); AIS A (n = 17), AIS B (n = 2), AIS C or D (n = 2). **Treatment:** 0.5 µg calcitriol daily x 6 days; 1250 mg calcium carbonate BID x 6 days; 30 mg pamidronate intravenous daily x 3 days (administered on days 4, 5, and 6 of study) **Outcome measures:** Within 2 weeks prior to baseline, and again within 2 weeks following study completion: 24-hour urine calcium and creatinine; spot urine NTX; serum	Calcitriol-pamidronate therapy decreased urinary NTx excretion by 71% ($p < 0.001$), and urinary calcium excretion by 73% ($p < 0.001$). Calcitriol-pamidronate therapy increased serum PTH ($p < 0.05$) and 1,25-D ($p < 0.005$). Post-therapy hypocalcemia or hypophosphatemia occurred in 44% ($p < 0.01$) and 53% ($p < 0.01$) of participants, respectively.

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
	calcium, phosphorus, intact PTH, 25-D, 1,25-D.	
[Mechanick et al. 2006](#) USA Case series Level 4 N=32	**Population:** 32 adults (25 men, 7 women) with acute traumatic SCI; age: 42 years; paraplegia (n=8), tetraplegia (n=13); AIS A (n=22), AIS B (n=5), AIS C (n=5). **Treatment:** calcium 1000 mg daily and calcitriol 0.25 µg daily x 17 days, pamidronate 90 mg intravenous on day 4 **Outcome measures:** Serum calcium, phosphorus, and albumin; urinary calcium and NTX, serum intact PTH, 25-D, 1,25-D	Single-dose calcitriol-pamidronate therapy decreased urinary NTX excretion by 64% ($p<0.001$) and urinary calcium excretion by 50% ($p<0.002$) in acute SCI. Post-therapy hypocalcemia or hypophosphalemia occurred in 75% ($p<0.02$) and 22% ($p<0.02$) of participants, respectively. Single-dose pamidronate is associated with increased incidence of fever (78%) compared to 30 mg daily x 3 days dosing regimen (20%).
[Bauman et al. 2009](#) USA Case series Level 4 N = 8	**Population:** 8 men with chronic SCI; age: 34 ± 7 years (range: 23–43); TPI: 12 ± 8 years (range: 3–27); paraplegia (n=6), tetraplegia (n=2); low vitamin D (25[OH]D ≤ 20 ng/mL) and/or elevated serum PTH (>55 pg/mL). **Treatment:** Calcium gluconate bolus (0.025 mmol elemental calcium/kg) over 20 min followed by calcium gluconate infusion (0.025 mmol/kg/hr) for 6 hours. **Outcome measures:** Serum total calcium, creatinine, NTX, and PTH at baseline, 2, 4, and 6 hours post-infusion.	At 2 hr time point, PTH dropped from 70 ± 25 pg/mL to 18 ± 12 pg/mL, and NTx dropped from 21 ± 8 nM bone collagen equivalent (BCE) to 17 ± 5 nM BCE. Calcium gluconate infusion reduced bone collagen catabolism during calcium infusion.

* All data expressed as mean±SD, unless expressed otherwise.

Discussion

Two retrospective case series studies (Chen et al. 2001; Mechanick et al. 2006) provide Level 4 evidence supporting the use of calcitriol-pamidronate therapy to reduce urinary excretion of calcium and NTX in acute SCI, which are biomarkers of bone resorption. Single-dose infusion of pamidronate was associated with increased incidence of fever compared to infusion on three consecutive days. However, single-dose pamidronate may be a more efficient use of patients' time during ever-shorter inpatient rehabilitation stays.

One study (Bauman et al. 2009) provided Level 4 evidence that calcium gluconate infusion may reduce transient bone collagen catabolism in men with chronic SCI.

Conclusion

There is Level 4 evidence (Chen et al. 2001; Mechanick et al. 2006) to support the use of calcitriol-pamidronate therapy to reduce bone resorption in acute SCI.

12 General Discussion

The risk for fragility fractures after 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 (Brown et al. 2002). Currently, these guidelines do not specifically address persons with SCI. While, they do provide a resource for osteoporosis diagnosis, prevention and treatment, the lack of SCI-specific, consensus-based guidelines for SLOP, has resulted in diverse SLOP screening, prevention, and treatment practices among SCI clinicians (Morse et al. 2009a; Ashe et al. 2009). Hopefully, future national guidelines will provide recommendations for people who have SCI and diverse impairments that lead to reduced weight-bearing, muscle activity and physical activity levels. Recently a decision guide has been published for rehabilitation professionals on the identification and management of bone health-related issues for people with SCI (Craven et al. 2008, Craven et al. 2009).

In this review, we note some support for pharmacological agents, but less support for rehabilitation modalities for the prevention and management of bone health in people with SCI. Our results have some similarities with the recent systematic review by Bryson and Gourlay (2009). Our results for the non-pharmacological treatment of bone health are consistent with the review by Bering-Sorensen and colleagues (2009) highlighting promise with some modalities. However, this review differs by reporting evidence for early (acute) and late (>12 months) intervention with rehabilitation modalities and therefore describes the results based on whether the goal of therapy is prevention or treatment of SLOP. In the past 40 years, there have been several interventions (both pharmacological and rehabilitation modalities) aimed to maintain or slow down bone mass decline after SCI yet consistent methodological oversights have emerged including: small sample sizes and broad inclusion criteria that do not always account for sex, TPI or impairment differences between participants.

The pharmacological interventions (either prevention or treatment interventions) discussed here report stronger methodologies— all except one were RCTs with PEDro scores ranging from 6-10 indicating moderate to high quality. In contrast, the studies employing rehabilitation modalities had low numbers of participants and only 3 of the 31 studies were RCTs. These factors contribute to difficulties drawing generalizable conclusions regarding the impact of rehab interventions on bone parameters.

Nonetheless, despite the lack of 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, NMES and FES-cycling may have small effects on bone but have been shown to have large effects on muscular and cardiovascular health (Jacobs & Nash 2004).

There is a large body of studies that suggest an infinite number of combinations of NMES/FES types and stimulation parameters that could be used during FES/NMES-training. This may be one of the causes of the large heterogeneity of the results when using these techniques. It has long been suggested that the individual capacity of generating relevant torque amplitudes during electrically-evoked contractions is the main factor to maximize training effectiveness (Lieber et al. 1991). As elegantly discussed by Maffiuletti et al. (2017), future NMES-based studies should reduce their focus on NMES types and parameters and increase the emphasis on clinically desired outcomes taking into consideration individual- and impairment-specific requirements. Moreover, the participant's tolerance to NMES should be taken into consideration since not everyone can tolerate or increase their tolerance over time (i.e., responders vs non-responders). It was suggested that a minimum of >15% of a maximal voluntary contraction is necessary to reach the therapeutic window range (Maddocks et al. 2016).

There are a few key points to consider when interpreting the results from interventions designed to maintain and/or improve bone parameters after SCI. These include biological differences in bone development and maintenance between men and women, the natural decline in bone mass with ageing and the selected primary outcome measure. Age-related changes in bone mass affect both women and men but the pattern of change is different because estrogen plays such a dominant role in bone remodelling. Consequently, in women, the loss of estrogen at menopause initiates a rapid loss of bone that eventually slows but continues throughout life. Men generally do not experience the rapid phase of BMD decline with ageing rather, only a slower phase of BMD decline is observed. Therefore, keeping in mind that bone mass declines over time, a study that reports no significant difference in BMD between two time periods 6 months apart may be interpreted as positive because of the anticipated loss.

Due to the diversity of primary outcomes (BMD by DPA, DXA or pQCT, urine or blood markers and NMES/FES/vibration types and parameters), it is difficult to pool the results from multiple studies. 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 9 months to observe changes within participants over time. Consequently, investigations that did not maintain an intervention for at least 6 months may not show changes, and the results cannot be interpreted as negative. Importantly, all primary outcomes for bone health after 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 fracture reduction. Fracture reduction studies are somewhat infeasible due to cost and the large number of participants that would be needed and followed longitudinally. Consequently, the clinical significance of the interventions based on fractures for this population remains to be determined. Prospective multicentre intervention studies using common interventions and outcome assessments are urgently needed.

Conclusion

There is a significant risk for fragility fractures after SCI; the risk increases for women, people with motor complete injuries (AIS A and B), longer duration of injury, and with use of benzodiazepines, heparin, or opioid analgesia. Early assessment and ongoing monitoring of bone health are essential elements of SCI care.

There is Level 1 evidence for the prevention and treatment of BMD decline using medications; however, non-pharmacological evidence for preventing a decline in bone mass and treating low bone mass is poor. Interpretation and pooling of bone health studies are limited by small samples, diverse treatment protocols, heterogeneous samples (regarding impairment and injury duration) and short treatment durations given the time required to detect improvements in bone parameters and variability associated with different imaging technologies. As noted in two publications (Craven et al. 2008, Ashe et al. 2009), a consensus regarding the ideal duration of therapy and choice of outcome measures would advance the field.

Key Points

Early assessment and monitoring of bone mass after SCI are essential to identify low bone mass and quantify risk of lower extremity fragility fracture.

Prevention with oral bisphosphonates (Tiludronate, Clodronate and Etidronate) may slow the early decline in hip and knee region bone mass after SCI. There is limited evidence that treatment with oral bisphosphonates maintains hip and knee region bone mass late after SCI.

There is a lack of definitive evidence supporting non-pharmacological interventions for either prevention or treatment of bone loss after SCI.

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Abbreviations

25(OH)D	25-hydroxy vitamin D
aBMD	areal bone mineral density
AIS	American Spinal Injury Association Impairment Scale
ALP	alkaline phosphatase
BALP	bone-specific alkaline phosphatase
BMC	bone mineral content
BMD	bone mineral density

BMI	body mass index
CI	confidence interval
CINP	C-terminal propeptide of type I collagen
CT	computed tomography
CTX	Type I collagen C-telopeptide
CV	coefficient of variation
DPA	dual-energy photon absorptiometry
DPD	deoxypyridinoline
DXA	dual-energy X-ray absorptiometry
FES	functional electrical stimulation
HR	hazard ratio
HR-pQCT	High-resolution peripheral quantitative computed tomography
IFCC-IOF	International Osteoporosis Foundation and the International Federation of Clinical Chemistry and Laboratory Medicine
ISCD	International Society for Clinical Densitometry
LSC	least significant change
MCID	minimal clinically important difference
MRI	magnetic resonance imaging
NBHA	National Bone Health Alliance
NMES	neuromuscular electrical stimulation
NTX	N-telopeptide
OC	osteocalcin
OR	odds ratio
P1NP	procollagen Type I N propeptide obtained from serum
pQCT	peripheral quantitative computed tomography
PTH	parathyroid hormone
PYD	total pyridinoline
QCT	quantitative computed tomography
RCT	randomized controlled trial
SCI	spinal cord injury
SD	standard deviation
SLOP	sublesional osteoporosis
TPI	time post-injury
TNF	tumour necrosis factor α
vBMD	volumetric bone mineral density