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SPINAL CORD INJURY REHABILITATION EVIDENCE

Bone Health
Following Spinal Cold Injury

B. Cathy Craven, MD FRCPC
Cheryl L. Lynch, PhD
Janice J Eng, PhD BSc (PT/OT)

Key Points

Bone Health & Fracture

- Fragility fractures, of the distal femur and proximal tibia, are common in people with SCI.
- 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 appear greater when medications are administered early after SCI onset
- Individuals with chronic SCI and increased risk for lower extremity fragility fractures can be readily identified based on completion of a clinical history and risk factor profile.
- Measurement and monitoring of hip and knee region 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.

Pharmacologic Therapy for Prevention of Sublesional Osteoporosis (SLOP)

- 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 IV infusion zoledronate may reduce bone loss at the hip during the 12 months following administration.
- Pamidronate 30 mg IV or 60 mg IV 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.
- In summary, there is limited evidence that bisphosphonates prevent declines in hip and knee region bone mass after SCI. However, bisphosphonates are moderately effective at ameliorating the rate of hip and knee region bone mass resorption.

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 analog is effective for maintenance of BMD in the leg.

Non-pharmacologic Therapy for Prevention and/or Treatment

- Short term (6 weeks) therapeutic ultrasound is not effective for preventing bone loss after SCI.
- 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.
- Electrical stimulation can maintain or increase BMD over the stimulated areas.

- FES cycle ergometry may increase lower extremity BMD over areas stimulated.
- 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 a lack of definitive evidence supporting non-pharmacological interventions for either prevention or treatment of bone loss after a SCI.

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Craven C, Lynch CL, Eng JJ (2014). Bone Health Following Spinal Cord Injury. In Eng JJ, Teasell RW, Miller WC, Wolfe DL, Townson AF, Hsieh JTC, Connolly SJ, Noonan VK, Loh E, McIntyre A, editors. Spinal Cord Injury Rehabilitation Evidence. Version 5.0. Vancouver: p 1- 37.

Abbreviations

AB	able-bodied
aBMD	areal bone mineral density
ABT	activity-based therapy
AIS	ASIA Impairment Scale
ASA	acetylsalicylic acid
BALP	bone-specific alkaline phosphatase
BMC	bone mineral content
BMD	bone mineral density
BMI	body mass
BP	bisphosphonate
BW	body weight
CE	cycle ergometer
CSA	cross-sectional area
CT	Type I collagen C-telopeptide levels
CTX	collagen C-telopeptide
DPA	dual energy photon absorptiometry
DOI	duration of injury
DXA / DEXA	dual energy X-ray absorptiometry
EMS	electromyostimulation
ES	electrical stimulation
FES	functional electrical stimulation
HR	high resolution
IGF1	insulin-like growth factor-1
IV	intravenous
NMES	neuromuscular electrical stimulation
NTX	N-telopeptide
OC	osteocalcin
PINP	serum procollagen type I N propeptide
pQCT	peripheral quantitative computed tomography
PTH	parathyroid hormone
QUS	quantitative ultrasound
RCT	randomized controlled trial
RGO	reciprocating gait orthosis
SLOP	sublesional osteoporosis
TSI	time since injury
vBMD	volumetric bone mineral density

Bone Health
Following Spinal Cord Injury

1.0 Introduction

A significant decline in hip and knee region bone mineral density (BMD) occurs after motor complete spinal cord injury (SCI) which leads to a lifetime increased risk of lower extremity fragility or low trauma 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) and reflects excessive bone resorption. Longitudinal studies also highlight a higher rate of hypercalcemia (excessive calcium in the blood) for people after SCI that reflects rapid bone mineral loss in the first 4-6 months that slows for the remainder of the first year post-injury (Hancock et al. 1980; Frey-Rindova et al. 2000). Early studies also suggest that bone mineral density (BMD) stabilizes by 1-2 years after SCI (Griffiths et al. 1976; Hancock et al. 1980; Garland et al.1992) at 25-50% below that of able-bodied peers in the hip and knee region. Other investigations support a continual loss of bone mass with time since injury (Demirel et al. 1998; Bauman et al. 1999; Eser et al. 2005) and suggest that lower extremity bone mineral homeostasis is not reached.

The immediate and excessive loss of bone mass post-SCI is believed to result from a decrease in mechanical loading as a result of reduced or complete loss of muscle function and/or weight-bearing activities. 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 which 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) 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 (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 are greater than age-matched able-bodied women (Garland et al. 2001). These changes in bone density and bone architecture all 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 (DVT, pressure sore, cellulitis). These fractures are associated with an increase in direct and indirect medical expenses, as well as the individual's morbidity and mortality.

2.0 Systematic Review

Table 1: Systematic Review of Bone Health

Author Year; Country Review dates Total Sample Size Score	Methods	Outcome
Ashe et al. 2007; Canada	**Method:** Literature search for English articles exploring prevention or treatment of bone loss after SCI.11 RCTs, 5 non-randomized controlled trials, 15 pre-post trials.	1. There is Level 1 evidence for the prevention and treatment of bone loss using bisphosphonates (clodronate, etidronate and alendronate) that may maintain BMD or slow the decline of BMD after SCI. There is a lack of definitive evidence

Author Year; Country Review dates Total Sample Size Score	Methods	Outcome
Reviewed published articles from 1980 to 2006 N= 31 AMSTAR: 8	Outcome measures include biochemical markers, bone imaging and histomorphometry from bone biopsies. **Databases:** PUBMED/Medline, CINAHL, EMBASE, PsycINFO **Level of Evidence:** SCIRE Procedures- Modified Downs and Black for non-RCTs PEDRo tool for RCTs	supporting nonpharmacological interventions for the treatment of bone loss after an SCI with the exception of muscular electrical stimulation. 2. Level 1 Evidence: – For the first year postinjury, randomized controlled trials show that clodronate prevents a decrease in BMD of the hip and knee region with limited adverse effects on bone mineralization in men living with paraplegia – Oral etidronate prevents a decrease in BMD of the hip and knee region in people living with incomplete paraplegia or tetraplegia who return to walking
Chang et al. 2013; Taiwan Reviewed articles published before Jan. 2013 N = 19 AMSTAR: 8	**Method:** Literature search for English articles related to treatment of post-SCI osteoporosis using bisphosphonates or FES. Bisphosponate treatement: 7 experimental (RCT) studies and 1 quasi-experimental studies. FES treatment: 2 quasi-experimental studies and 9 longitudinal follow-up studies. Outcome measures included percentage BMD change from baseline using DXA or CT at 3, 6, 9, 12, and 18 mos. **Databases:** PubMed, Scopus **Level of Evidence:** Jadad scale for RCTs and quasi-experimental trials; Newcastle-Ottawa scale for longitudinal follow-up studies	1. Bisphosphonate therapy in the early post-injury period attenuated sublesional bone loss, compared to placebo or usual care. 2. Participants with chronic SCI who were exposed to an FES intervention (cycling ergometry or knee resistance exercise) of more than 3 months duration showed a significant increase in knee-region BMD at 3, 6, and 12 mos. post-intervention. 3. Knee-region BMD increases were not maintained after FES therapy was discontinued. In one report, knee-region BMD returned to baseline after 6 months without training. 4. Interventions that provided FES ≥ 5 days/week were likely to be more effective than interventions that used FES ≤ 3 days/week..
Biering-Sorensen et al. 2009; Denmark Reviewed Published articles from 1988 to 2008 N= 45 AMSTAR: 4	**Methods:** Literature search for articles exploring non-pharmacological treatments of osteoporosis after SCI. Interventions include weight-bearing, standing, walking, exercise, electrical stimulation Outcome measures include bone mineral content and bone mineral density. **Database:** PubMed, EMBASE and the Cochrane Controlled Trials Register, PEDro database **Level of Evidence:** SCIRE procedures- PEDro tool	1. No conclusive indication of any effective intervention. 2. Bone mineral should be measured around the knee 3. Length and intensity of non-pharmacological treatment should be sufficiently long and high, and should commence early after SCI. - stimulation used has to be maintained if the positive effect on BMD is to remain
Bryson & Gourlay 2009; USA Reviewed Published articles from 1955 to 2008	**Methods:** Literature search for English articles related to bisphosphonate (BPs) therapy to optimize bone health with experimental, quasi-experimental or controlled observational design	1. Treatment regimens of second-generation BPs administered in the acute stages of SCI attenuated bone hyper-resorption in treated patients compared with placebo during the treatment period in most studies 2. Data were insufficient to recommend routine use of BPs for fracture prevention in SCI patients.

Author Year; Country Review dates Total Sample Size Score	Methods	Outcome
N= 7 AMSTAR: 3	Interventions include bisphosphonates (alendronate, zoledronate, pamidronate, etidronate). 6 experimental (RCT) studies and 1 quasi-experimental study Outcome measures include bone mineral density and histomorphometry bone measures. **Databases:** PubMed/MEDLINE database (1966 through December 2008), ISI database (1955 through December 2008)	3. Fair or poor quality of evidence - 5 studies rated fair - 2 studies rated poor 4. None of the studies included fracture outcomes.

3.0 Fracture Risk Following SCI

There is overwhelming evidence that supports the importance of addressing bone health issues early after SCI. A higher incidence of fragility fractures exist in people who sustain SCI (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). The distal femur and proximal tibia (knee region) are most at risk, consistent with site-specific decreases in BMD to such a degree that fractures of the distal femur were previously referred to as 'the paraplegic fracture' (Comarr et al. 1962).

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 time since injury (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).

BMD *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 aBMD and vBMD thresholds for fracture and breakpoint have been identified (Mazess 1990; Eser et al. 2005; Garland et al. 2005). 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), is associated with an increased risk of lower extremity fragility fractures in men with chronic (≥ 2 yrs injury duration) SCI (Carbone et al. 2013a, 2013b).In a large retrospective cohort study of men with chronic SCI (N = 6969, ≥ 2 yrs 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 the general population, individuals with a prior history of fragility fracture or a maternal history of fracture have an elevated fracture risk; these risk factors should also be considered during a fracture risk assessments among patients with SCI. 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 thiazoledinediones (HR 1.04, CI 0.68-1.61) (Carbone et al. 2013a, 2013b). However, these drugs 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 2: Fractures and Risk Factors for Fragility Fractures after SCI

First Author Year	N	Age	Fractures		Risk Factors
Comarr 1962	1,363	19-58	81 patients with 109 lower extremity fractures (6% of the group)		complete spinal cord injury
Ragnarsson 1981	578	4-77	23 patients with 33 lower extremity fractures (4% of the group)		complete spinal cord injury
	3,027	13-77	(National SCI Data Research Centre);44 patients with 52 lower extremity fractures (1.45% of the group)		N/A
Frisbie 1997	120	20-39	15 fractures/1000 patient years		increasing age
		40-59	31 fractures/1000 patient years		
		60-79	46 fractures/1000 patient years		
Vestergaard 1998	438	10-80	cumulative fracture incidence=21% overall fracture rate 2%/yr		women > men; men with a family history of fractures; time since SCI longer than 3 yrs; level of SCI
McKinley 1999	N/A	population –based all ages	women 1% (5 yrs) 2% (10 yrs) 3% (15 yrs) 6% (20 yrs)		women > men; time since SCI
			men 1% (5 yrs) 1% (10 yrs) 2% (15 yrs) 2% (20 yrs		
Lazo 2001	41	27-83	34% of participants had fractures		low BMD femoral neck
Nelson 2003	889		45 people fractured over 10 years (5% of the group)		women >men; time since injury
Garland 2004	152	19-71	N/A		completeness of injury; increasing age; low BMI
Zehnder 2004	98	18-59	0.4-30 yrs	2%/yr	time since injury; bone loss in lower extremity
			<1 yr	1%/yr	
			1-9 yrs	1%/yr	
			10-19 yrs	3%/yr	
			20-29 yrs	5%/yr	
Eser 2005	99	19-83	21% of the participants had lower extremity fractures		Time since injury; low BMD

First Author Year	N	Age	Fractures	Risk Factors
Garland 2005	28	26-52	N/A	women >men; low BMD; increasing age; low BMI; complete spinal cord injury; duration of injury
Carbone 2013a, 2013b	7447		892 participants had lower extremity fragility fractures over 5 years (12% of the cohort)	Complete SCI; use of anticonvulsants (especially benzodiazepine class), heparin, opioid analgesia

*BMD=bone mineral density; BMI=body mass index; N/A=not available; pt yrs=patient years.

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 implies 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
☐	BMI < 19
☐	Duration of SCI ≥ 10 years
☐	Female
☐	Motor Complete (AIS A-B)
☐	Paraplegia
☐	Prior fragility fracture
☐	Family history of fracture
☐	Anticonvulsant use
☐	Heparin use
☐	Opioid analgesia use

4.0 Sublesional Osteoporosis (SLOP) Detection and Diagnosis

In order 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 Sublesional Osteoporosis (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.

5.0 Bone Outcome Measures

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

5.1 Imaging Modalities

Bone imaging is typically used to assess bone mineral density (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).

5.1.1 Dual-Energy Absorptiometry (DXA, DPA)

BMD assessment by dual energy X-ray absorptiometry (DXA) imaging is considered by the World Health Organisation 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 bone mineral content per unit area in g/cm^2. DPA is an older technology for measuring aBMD that is sometimes reported in studies conducted prior to the 1990's.

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. 2009). 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).

5.1.2 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 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 80 µm resolution. This imaging modality gives detailed information on the microarchitecture of peripheral bone, but is not widely available outside of research applications.

5.2 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 bone-specific alkaline phosphatase (BALP), osteocalcin (OC), N-terminal propeptide of type I collagen (PINP), and C-terminal propeptide of type I collagen (PICP). Markers of bone resorption include urinary free and total pyridinoline (Pyr) and deoxypyridinoline (DPD) crosslinks, type 1 collagen C-telopeptide (CTX), and N-telopeptide (NTX). Pyr 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).

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). Alignment of the choice of biomarkers across future bone health studies may allow for cross-study comparison or future meta-analyses.

5.3 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 an important 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.

6.0 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 bone loss after SCI: (1) What is the best way to prevent acute regional declines in bone mineral density in the early post-injury period (10-90 days post injury)? and (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 a 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.

7.0 Pharmacologic Therapy: Bisphosphonates

Within weeks after SCI, there is a marked increase in bone resorption (breaking bone down) with a decrease in bone formation (adding new bone). 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 (IV) and orally for the treatment of osteoporosis. Tiludronate is available in oral form in the United States. Zoledronate is a newer once yearly bisphosphonate which is administered via IV infusion. Concurrent supplementation with calcium and vitamin D have been important additions to bisphosphonate therapy for post-menopausal 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.

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

Table 5: 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	**Population:** 14 men and women, ages 21-61, motor complete para or tetraplegia. 3 subjects withdrew from the study before the first time measurement point.	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

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
N=14	**Treatment:** Pamidronate for 12 months. Participants randomized to **1.** 60mg IV (N=6) or **2.** Placebo (N=5) **Outcome measures**: BMD by DXA, bone turnover markers at baseline, 1, 2, 3, 6, 9, 12-mos. post SCI.	vs. placebo group (P<0.05) and there were no significant changes in markers of bone formation over the 12 month study.
Minaire et al. 1981; France PEDro=10 RCT N=21	**Population:** 21 men and women, ages 15-54 years, complete paraplegia. **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 a maintenance of BMC of the femur and tibia in the treatment groups.
Chappard et al. 1995; France PEDro=9 RCT N=20	**Population:** 20 men and women, ages 16-50, 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.	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.
Pearson et al. 1997; Canada PEDro=8 RCT N=13	**Population:** 13 men and women, ages 22-57, injuries between C5-T12, AIS: A or D. **Treatment**: Etidronate for 30 weeks. Participants randomized to **1**.800mg daily (N=6) or **2**. Conventional rehab and calcium 1000mg/day (N=7). **Outcome measures:** DXA and adverse event rate.	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 patients. BMD of lower extremity for the Etidronate-treated AIS D patients were preserved. 2. Oral Etidronate was safe and well tolerated by participants.
Gilchrist et al. 2007; New Zealand PEDro=7 RCT N=31	**Population:** 31 women and men ages 17-55, Type of injury at entry: 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; or 2. Placebo. **Outcome Measures:** BMD and body composition by DXA, ultrasound, bone turnover markers.	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 change in total hip BMD between the two groups. 4. Alendronate compared with placebo induced reductions in urinary calcium excretion and serum C-telopeptide at 3 months only.
Shapiro et al. 2007; USA PEDro=7 RCT N=18	**Population:** 14 men and 4 women, ages 18-60 years. Type of injury: 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 IV 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	1. In treatment group: Six months after zoledronic acid, BMD, cross-sectional area, and sectional modulus increased at the hip and buckling ratio decreased consistent with improved bone outcomes. At 12 months, narrow-neck femur values declined and intertrochanteric and femoral shaft BMD was maintained.

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
	with low serum 25-hydroxyvitamin D received oral supplementation. **Outcome Measures:** bone turnover markers, BMD by DXA	2. Placebo group showed a decrease in bone outcomes and an increase in buckling ratio at the hip at 6 and 12 months.
Minaire et al. 1987; France PEDro=7 RCT N=21	**Population:** 21 men and women, ages 15-54, 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; United Kingdom PEDro=6 RCT N SCI treatment= 7 N SCI control= 7	**Population**: 14 acute SCI patients (Control: 5 male, 2 female; mean age 27 ± 14.4, Treatment: 4 male, 3 female; mean age 31.6 ± 7.1) **Treatment**: 4mg IV zoledronic acid (active treatment group) or standard nursing/medical care (control group) **Outcome Measures**: Bone Mineral Density (BMD) using dual X-ray absorptiometry machine at baseline, 3, 6, 12 months for lumbar spine (L1-4) and hip (total, femoral neck, trochanter); Bone turnover markers (serum CTX and procollagen I N-terminal peptide (PINP) and urinary N-terminal telopeptide/creatine ratio).	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), 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 patients in zolendronic group had flu-like symptoms over 24 hours
Nance et al. 1999; Canada Prospective Controlled trial (nonrandomized) N=24	**Population:** 24 men and women, ages 25-57, injuries between C5-T12, AIS A-D. **Treatment:** Pamidronate for 6 months. Participants randomized to 30mg IV every 4wks x 6doses (total 180mg/participant) (N=14) or conventional rehab (N=10). **Outcome measures:** BMD by DXA, urine biochemical bone markers.	1. There was a lower % decline in BMD in treatment vs. control group. The mean overall bone loss 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.

Discussion

Evidence for pharmacological *prevention* of SCI bone loss includes 8 randomized controlled trials (RCT) (n=152 participants) and 1 non-randomized trial (n=24) (Table 3). These studies were difficult to interpret as a group due to the variability in selection of the pharmacological treatment, primary outcome measure, relatively short durations of follow-up, small sample sizes, and the lack of stratification based on impairment level. Preventing bone loss 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 bone loss compared with a control group. The two studies which report that first generation bisphosphonates (Clodronate) can maintain bone were short in duration (3 month 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 bone loss after 1 year (Baumann 2005). Gilchrist and colleagues noted a

significant difference in BMD at the hip with once weekly Alendronate. Shapiro and colleagues (2007) tested the effect of once yearly IV 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 et al. (2011) also showed that once yearly IV Zolendronate resulted in less bone loss at the spine and hip over 12 months. The investigators also highlighted the added benefits of a once yearly IV administration of bisphosphonate, as this eliminates issues surrounding poor patient adherence and the adverse gastrointestinal effects associated with alternate oral therapies. Although there is evidence that bisphosphonates may reduce bone resorption, current medications do not totally 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 counseled 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 2 RCTs) (Shapiro et al. 2007; Bubbear et al. 2011) that a one-time IV infusion of Zoledronate may reduce bone loss in the hip region during the 12 months following administration.

There is level 1 evidence (from 1 RCT) (Bauman et al. 2005) that Pamidronate 60mg IV seven times per year and level 2 evidence (from 1 non-randomized prospective controlled trial) (Nance et al. 1999) that Pamidronate 30 mg IV six times per year is <u>not</u> 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.

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 IV infusion zoledronate may reduce bone loss at the hip during the 12 months following administration.

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

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

Table 6: Studies of Pharmacologic Therapy for Treatment of Bone Loss in Chronic SCI

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
Bauman et al. 2005b; USA PEDro=10 RCT N=40	**Population:** 40 subjects with complete motor injuries; 17 participants with tetraplegia and 23 participants with paraplegia. **Treatment:** Vitamin D_2 analog, 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.	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 had a negative effect on increase in percent change of 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.
Zehnder et al. 2004; Switzerland PEDro=7 RCT N=65	**Population:** 65 men, ages 18-60, 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.
Moran de Brioto et al. 2005; Brazil PEDro=6 RCT N=19	**Population:** 19 men (< 50 yrs) and women (< 35 yrs), para/tetraplegia, AIS: A, B, or C. **Treatment:** Alendronate for 6 months. 1. 10mg and calcium 1000 mg bid (N=10) and 2. calcium (1000 mg bid) (N=9). **Outcome measures:** BMD by DXA	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.

Discussion

Evidence for pharmacological *treatment* of SLOP includes 3 RCTs (Zehnder et al. 2004; Bauman et al. 2005b; Moran de Brioto et al. 2005)(n=124 participants). 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. (2004) who found an increase in BMD at the spine with maintenance of BMD at the hip and tibia. In contrast, Moran de Brioto 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 response of outcomes could be a result of the younger participants with less severe injuries in the work by Zehnder and coworkers (2004). Bauman and colleagues (2005b) noted positive results in leg BMD for participants who received vitamin D.

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 4-8oz 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, IV 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 pre-menopausal women due to the unknown teratogenic effects of these medications on the fetus during pregnancy. Patients taking acetylsalicylic acid (ASA), corticosteroids or NSAIDS 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. Zolendronate, an IV 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). Zolendronate 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 osteonecrosis of the jaw and arrhythmia should be discussed during consent for oral or IV 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. 2004) 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.

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

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 analog is effective for maintenance of BMD in the leg.

8.0 Non-Pharmacologic Therapy: Rehabilitation Modalities

Rehabilitation options for bone health after SCI focus on stimulating muscles and encouraging weight-bearing. This section includes six modalities: functional electrical stimulation (FES), electrical stimulation (ES), standing and walking, treadmill training, ultrasound and physical activity. FES is an important option to stimulate muscle with the goal of increasing regional BMD, and involves the use of surface or implanted electrodes to facilitate stimulation-induced standing, ambulation or bicycling

(cycle ergometry). An FES cycle ergometer uses a series of electrodes placed over the hamstrings, quadriceps and gluteal muscles of the legs to stimulate a cycling pattern. Weight-bearing activities 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 have enrolled participants with both acute and chronic injuries and are therefore difficult to classify as pure prevention or treatment interventions. For the purpose of 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.

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

Table 7: 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 Cycle Ergometer		
Lai et al. 2010; Taiwan Prospective controlled Study SCI Treatment (N = 12) SCI Control (N = 12)	**Population:** 24 medically stable SCI patients; 12 treatment and 12 control (10 men, 2 women in each groups); Inclusion criteria: 26-52 days post injury, neurologically complete SCI motor lesion between C5 & T10, muscle responses to trial ES, no prior FES therapy **Treatment**: FES 3 times/week for first 3 months, suspended for next 3 months. Cycling time gradually increased up to 30 min. **Outcome Measures:** DXA in right femoral neck (FN) and distal femur (DF) between femoral condyles and 2cm above knee joint space. Measurements at baseline, end of 3 months cycling program, and 3 months after discontinuation.	1. Baseline: no significant differences in BMD between groups at FN and DF 2. End of 3 months program BMD at FN and DF significantly lower in both groups, but ↓ in DF 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 end of cycling to 3 months after discontinuation, both groups decreased at FN and DF site, with no group differences.
Eser et al. 2003; Switzerland Prospective controlled trial (non-randomized) N=38	**Population:** 38 men and women, mean age = 33, complete injuries between C5-T12, (19 participants, 19 controls). **Treatment**: FES cycle ergometer. Progressive training sessions until able to cycle for 30 mins. Then 3x/wk for 6 mos. from this baseline. On the remaining 2 days of the week there was passive standing. Control group performed 30 mins. of passive standing 5 days/week. **Outcome measures:** CT	1. Both groups had 0-10% decrease in tibial cortical BMD. There was no difference between groups for BMD after the intervention.
Electrical Stimulation (ES)		
Groah et al. 2010; USA PEDro =6 RCT N = 26	**Population**: 26 subjects with traumatic SCI; ≥18 yrs; AIS A or B at time of entry, <12 weeks post injury, spinal cord lesion above T12 **Treatment**: Randomized to usual inpatient SCI program (N=10) or intervention group (N=16). Usual care and addition of 1 hour ES to quadriceps bilaterally (using Complex Motion Stimulator) for 1 hour (or until fatigue) 5 days/week for 6 weeks.	1. No group differences in bone loss or biomarkers over time. However, the ES group experienced 50% less distal femur BMD loss (not significant).

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
	Outcome Measures: Measurements at baseline, post-intervention, 3 months post-intervention. 1) BMD at lumbar spine and bilaterally at femoral neck, distal femur, proximal tibia. 2) Serum osteocalcin (OC) 3) Urinary N-telopeptide and 24 hour urine calcium	
Arija-Blázquez et al. 2013; Spain Repeat-measures N=20 (10 SCI)	**Population:** 10 subjects with recent (8 wks) thoracic SCI (10M, AIS A). Mean (SD) age: 39.4 (12.3); mean (SD) body mass index: 25.1 (3.6) kg/m^2. 10 age-matched AB subjects for comparison; mean (SD) age: 36.7 (8.9), mean (SD) body mass index: 23.3 (3.3) kg/m^2. **Treatment:** Immediately after basal blood samples were drawn, electro-myostimulation (EMS) was conducted (1 set of currents was applied bilaterally at each knee angle; total of 80 contractions; total EMS time was 47 min per subject). **Outcome Measures:** BMD (dual-energy X-ray absorptiometry), muscle cross-sectional area (MRI), testosterone, cortisol and Type I collagen C-telopeptide levels (CT) (blood samples)	1. Basal levels of testosterone were not significantly different in SCI and AB groups. There was a significant decrease in testosterone 15 min post-EMS (SCI = -11.9%, AB=-6.8%). In the SCI group, testosterone remained lowered 30 min post-EMS (-7.4%). No differences in mean testosterone concentrations were observed between SCI and AB groups at any time point. 2. Mean cortisol levels were not significantly different in SCI and AB groups at any time point. In the SCI group, 30 min post-EMS mean cortisol levels dropped significantly (-18.5%). 3. Mean osteocalcin levels were not significantly different between SCI and AB groups at any time point. 4. At all time points, CT levels were significantly higher in the SCI group than AB group. In the SCI group, CT levels significantly declined post-EMS at 0 min (-27.0%), 15 min (-23.4%), 30 min (-27.1%), and 24h post-EMS (-10.2%). In the AB group, CT levels declined at 15 min (-13.7%) and 30 min (-15.6%) post-EMS. 5. No significant differences were observed between right and left muscle cross-sectional areas or between right and left leg BMD.
Dudley-Javoroski & Shields 2008; USA Case control. N = 21 (12 SCI)	**Population:** 12 men with motor complete SCI (C5–T11, AIS A–B; 0.3–22 years after injury; ages 21–72 yrs; 3 subjects in intervention arm, 9 SCI subjects as controls). 9 non-SCI controls between ages 24–61. **Treatment:** Unilateral soleus ES 5x/wk 15 Hz every 2 s for 120 contractions (8000 contractions/mo). **Outcome measures:** pQCT (BMD of distal tibia) of one leg versus the other leg annually for 4–6 years.	1. A sustained between-limb difference in posterior distal tibia BMD of 76.1 mg/cm3 (p = 0.04).
Dudley-Javoroski & Shields 2008; USA Case Report N=1	**Population:** 1 man; T4 AIS A paraplegia; 21 years old; 7 weeks post-injury **Treatment:** Four bouts of 125 soleus contractions over 30 minutes 5 times per week in one leg; actual 8,000 contractions per month	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

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
	Outcome measures: pQCT of one leg versus the other leg after 1 year, 3 years	attributed to posterior portion which lost 2.59%/year.
Clark et al. 2007; Australia Prospective Controlled trial (nonrandomized) N=33	**Population:** 33 men and women; 15 tetraplegia and 18 paraplegia; AIS A-D. **Treatment**: FES, 5 months Low-intensity stimulation to leg muscles, 15 min, 2x/day 5 days/wk, 5 months (n=23); or control group (no treatment) (n=10). **Outcome measures:** DXA at 3 wk, 3 and 6 months post injury.	1. ES 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 USA Pre-Post N=4	**Population:** 4 men with SCI; Age: 52.3±11.2 years; Level of injury: T1-7 (AIS A); TSI: 8.9±4.1 years. **Treatment:** Trained 1 leg using an isometric plantar flexion electrical stimulation protocol (the untrained limb serving as within subject control) for 30min/day, 5 days/wk, for 6 to 11 months. Mean estimated compressive loads delivered to the tibia were ~110% body weight. **Outcome Measures:** BMD by DXA	1. Untrained limb BMD did not differ from trained limb BMD either before or after training. 2. Unchanged BMD of proximal tibia before and after training for trained and untrained limb (p>0.05). Trained limb of 2 subjects had ~0.02g/cm^2 gain in BMD but not statistically significant.
Shields et al. 2006a; USA Prospective Controlled trial (nonrandomized) N=6	**Population:** 6 men with complete injuries from C5-T10; started study within 4.5 months of injury. Within-participant design. **Treatment**: ES at 1.5 times body weight for 3 yrs.Treatment leg only received a home program of ES to stimulate leg plantar flexors with 35-min protocol (4 bouts with 5-min rest between bouts) for 5x/wk. **Outcome measures:** DXA tibial analysis protocol.	1. There was a greater decline in bone mineral loss on the untrained limb compared with the trained limb (10% vs. 25%) (p<0.05)
Shields et al. 2006b; USA Prospective Controlled trial (nonrandomized) N=7	**Population:** 7 men with complete injuries from C5-T10; started study within 4.5 months of injury. Within-participant design. **Treatment**: ES at 1.5 times body weight; 2-3 yrs.Treatment leg only received a home program of ES to stimulate leg plantar flexors with 35-min protocol (4 bouts/d with 5-min rest between bouts) for 5x/wk). **Outcome measures:** pQCT 4%, 38%, and 66% sites of bilateral tibiae.	1. No significant difference at the tibial midshaft but a 31% higher distal tibia trabecular BMD in trained limbs compared with untrained leg.
Standing/Walking		
Ben et al. 2005; Australia PEDro=9 Within-participant RCT N=20	**Population:** 20 men and women; 8 paraplegia, 12 tetraplegia. Within-participant design. **Treatment:** Tilt-table standing, 12 wks. Treatment leg only received weight bearing on a tilt-table for 30 min, 3x/wk. Wedge applied to treatment leg to provide adequate dorsiflexion and weight bearing to the ankle. Control leg was not loaded in standing. **Outcome measures:** DXA proximal femur.	1. No clinically significant effect on proximal femur BMD in treatment group, but a 4 degree improvement in ankle mobility.

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
de Bruin et al. 1999; Switzerland PEDro=6 RCT N=19	**Population:** 19 men, ages 19-59, injuries between C4-T12, AIS: A-D **Treatment:** Standing/Walking. Group 1 had 0-5 hrs per week loading exercises with standing frame. Group 2 had 5+hrs of standing exercises per week (standing). Group 3 had 5+hrs of standing and treadmill (walking). Interventions lasted 25 wks. **Outcome measures:** BMD by pQCT	1. Marked decrease in trabecular BMD at the left tibia for the immobilized group but minimal decrease in trabecular BMD in Group 2 and 3.
Dudley-Javoroski & Shields 2013; USA Mixed cross-sectional and longitudinal N=12 subjects with SCI	**Population:** N=12 (9M 3F) AB controls and N=12 (11M 1F) subjects with SCI. AB controls ranged from 22-48 years old. SCI group ranged from 16-44 yrs old; 11 AIS A, 1 AIS B; 10 out of 12 subjects were <1 year post injury at first scan. **Treatment:** Individuals with SCI experienced active-resisted stance (N=7) or passive stance (N=5) for up to 3 years. **Outcome Measures:** peripheral quantitative computed tomography (pQCT) to assess regional bone mineral density (BMD) of the femur	1. Over 1.5 years, the slope of BMD decline over time was slower at all quadrants for the active-resisted stance limbs. 2. At >2 years of training, BMD was significantly higher for the active-resisted stance group than for the passive stance group. 3. BMD was preferentially spared in the posterior quadrants of the femur with active-resisted stance.
Treadmill Training		
Giangregorio et al. 2005; Canada Pre-post N=5	**Population:** 2 men and 3 women, ages 19-40, injuries between C3-C8, AIS: B and C. no controls. **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/wk-training over a period of 6-8 months. **Outcome measures:** BMD by DXA and CT; bone turnover markers.	1. Decrease in BMD for all participants at almost all lower limb sites after training, ranging from -1.2 to -26.7%. 2. Lumbar spine BMD changes ranged from 0.2 to -7.4%. 3. No consistent changes in bone geometry at distal femur and proximal tibia. 4. Did not alter the expected pattern of change in bone biochemical markers over time.
Ultrasound		
Warden et al. 2001; Australia PEDro=11 RCT N=15	**Population:** 15 men, ages 17-40, injuries between C5-T10, AIS: A-B, (within group design) **Treatment:** Pulsed therapeutic ultrasound. Applied to both calcanei for each participant for 20 min/day, 5x/wk over a consecutive 6-wk period. Right and left calcaneus within each participant was randomized. **Outcome measures:** BMD by DXA and quantitative ultrasound (QUS).	1. For specified dose, no significant effect of QUS for any skeletal measurement parameter ($p>0.05$).

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
Physical Activity		
Astorino et al. 2013; USA Pre-post N=13	**Population:** N=13 subjects with SCI (11M 2F); 2 chronic, 11 acute SCI; mean (SD) age: 29.4 (7.8); mean (SD) DOI: 1.9 (2.7) yrs **Treatment:** 2-3h/day of activity-based therapy (ABT) targeting regions below the level of injury a minimum of 2 days/wk for 6 months. ABT 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:** Serum procollagen type 1 N propeptide (PINP); serum C-terminal telopeptide of type I collagen (CTX); bone mineral density (BMD).	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. Total-body BMC decreased by 2.2% during the study, while spine BMD increased significantly by 4.8%. 3. 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. 1. ABT had no effect on PINP and serum CTX.

Discussion

Evidence for non-pharmacological ***prevention*** of sublesional osteoporosis includes data from sixteen investigations (n=264 participants). This includes four RCTs (80 participants), five non-randomized controlled trials (116 participants) and three pre-post studies (22 participants) (Table 7). 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 five different modalities there is limited evidence available and there was variability in the selection of the primary outcomes. The therapeutic ultrasound study by Warden and coworkers (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. Overall, the evidence suggests that rehabilitation modalities did not prevent bone mass decline in the acute phase after SCI.

Conclusions

There is level 1 evidence (from one RCT) (Warden et al. 2001) that short-term (6 weeks) ultrasound is <u>not</u> effective for treating bone loss after SCI.

There is level 2 evidence (from 1 non-randomized prospective controlled trial) (Shields et al. 2006a) that ES reduced the decline in BMD in the leg.

There is level 2 evidence (from 1 non-randomized prospective controlled trial) (Eser et al. 2003) that FES cycling did <u>not</u> improve or maintain bone at the tibial midshaft in the acute phase.

There is level 4 evidence (from 1 pre-post study) (Giangregorio et al. 2005) that walking and level 1 evidence (from 1 RCT) (Ben et al. 2005) that standing in the acute phase did <u>not</u> differ from immobilization for bone mass decline at the tibia.

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

Short term (6 weeks) therapeutic ultrasound is not effective for preventing bone loss after SCI.

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.

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

In this section, non-pharmacological rehabilitation treatment modalities are divided into six sub-sections: Electrical stimulation, vibration, functional electrical stimulation (FES) cycle ergometry, standing and walking, and physical activity (Tables 8-11). Both ES 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, ES techniques are used as a training stimulus to prepare muscles for a subsequent FES training regimen.

8.2.1 Electrical Stimulation

Table 8: Studies of Electrical Stimulation for Treatment of Bone Loss in Chronic SCI

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
Bélanger et al. 2000; Canada PEDro=11 Prospective Controlled Trial N=28	**Population:** 14 men and women, ages 23-42, complete and incomplete injuries between C5-T6, 14 able-bodied controls. **Treatment**: ES. Quadriceps training was conducted 5 days/wk for 24 wks. 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	1. 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 able-bodied controls. 2. 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 N=12	**Population:** 12 men and women, ages 19-63, para/tetraplegia, complete/incomplete, no controls (only 9 participants had BMD) **Treatment:** ES. Each participant trained for a total of 36 sessions (3x/wk for 12wks) using a progressive intensity protocol for PES stimulated knee extension. This progression was continued to a maximum 15 kg load. **Outcome measures:** BMD by DXA	1. Tibial BMD was not significantly changed after ES protocol ($p>0.05$), but BMD was better than predicted values.

Discussion

Although there were no randomized controlled trials that assessed the effect of electrical stimulation, Bélanger et al. (2000) produced impressive results with a level 2, non-randomized trial which used 1 limb as the treatment and the other as the control limb. Following training, the BMD recovered close to 30% of bone loss when compared with able-bodied values. Stimulation effects only occur over the areas of stimulation and return to baseline within months once stimulation is stopped (Mohr et al. 1997).

Conclusion

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

Electrical stimulation can maintain or increase BMD over the stimulated areas.

8.2.2 Vibration

Table 9: Studies of Vibration Treatment for Bone Loss in Chronic SCI

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
Melchiorri et al. 2007; Italy Pre-Post N=10	**Population:** 10 men with mean age 34±4 yrs; Level of injury: Between 8th and 10th dorsal vertebra; TSI: 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/wk, 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 increased in BMD for both arms.

Discussion

Vibration training is a relatively new treatment option used for potential benefits to muscle and/or bone health.

Conclusion

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

8.2.3 FES Cycle Ergometry

Table 10: Treatment Studies Using FES Cycle Ergometry for Bone Health after SCI

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
Ashe et al. 2010; Canada Case Series N= 3	**Population**: 3 women with chronic motor SCI >1 yr (complete n=2, incomplete n=1); ages 29, 19, 51 **Treatment:** Computer controlled leg FES cycle ergometer 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	1. All three participants had a percentage change in BMD ranging between 1-16% 2. There was maintenance of cortical bone density in all 3 participants at 50% site ranging from 0.51-1.24% 3. 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

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
	(g/mm) and density (mg/cm^3) using pQCT at midshaft (50%) and distal (5%) sites of tibia	
Frotzler et al. 2009; Switzerland/UK Pre-Post N = 5	**Population:** 4 men and 1 woman (mean age 38.6±8.1), with SCI between T4 and T7, ASIA grade A, 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 N = 11	**Population:** 11 participants with SCI between T3 and T12 and ASIA grade 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 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 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.
Chen et al. 2005; Taiwan Pre-post N=30	**Population:** 15 men, ages 23-37, complete, C6-T8. 15 able-bodied controls **Treatment:** FES-cycle ergometer. Participants performed FES-CE exercises with minimal resistance for 30 minutes/day, 5 days/week for 6 months. Follow-up 6 months after intervention. **Outcome measures:** BMD by DXA	1. At baseline, participants' BMD at the femoral neck, distal femur and proximal tibia was lower than controls. 2. 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 N=10	**Population:** 10 men and women, ages 27-45, 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/wk for 6 months, followed by 1x/wk for 6 months. **Outcome measures:** BMD by DXA, bone turnover markers.	1. After 12 mos. of training, there was a significant 10% increase in proximal tibia BMD ($p < 0.05$) but no change at the lumbar spine or femoral neck. 2. After 6 mos. of reduced training, BMD for the proximal tibia returned to baseline. 3. Blood and urine markers were within normal limits at baseline and there was no significant change with FES.
BeDell et al. 1996; USA Pre-post N=12	**Population:** 12 men, ages 23-46, complete injuries between C5-T12, no controls. **Treatment**: FES+ FES-cycle ergometer. Participants participated in a 3-phase training program of FES-CE. Phase 1: quads strengthening. Phase 2: FES-CE progression until 30 min continuously. Phase 3a: 24x 30-mins continuous exercise sessions performed 3x/wk. Phase 3b: An extra 24x 30-min sessions adding	1. At baseline, SCI participants were not significantly different from aged-matched able-bodied 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. 2. Only the L2-L4 values demonstrated a trend ($p=0.056$) for a small positive

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
	simultaneous arm ergometry (8 participants only). **Outcome measure:** BMD by DPA	effect from training. Further training (Phase 3b) did not demonstrate further increase in BMD at any site.
Hangartner et al. 1994; USA Pre-post N=15	**Population:** 15 men and women, ages 17-46, complete and incomplete injury between C5-T10, no controls. **Treatment:** FES+ FES-cycle ergometer. Either *1.* FES knee extension exercises (n=3) or *2.* FES-CE (n=9) or 3. both (n=3). Sessions were 3x/week for 12 wks except Group 3 had 24 weeks. **Outcome measures:** 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 N=6	**Population:** 6 men, ages 18-27, tetraplegia, no controls. **Treatment:** FES+ FES-cycle ergometer. 1-month quads strengthening exercise, followed by 6 months cycle ergometry (CE). Knee extension sessions were 45 lifts/leg 3x/week for 1month. CE sessions were 3X/wk up to 30 mins for 6 months. **Outcome measures:** BMD by DXA	1. The BMD of the proximal femurs were below normal before commencing exercise intervention (compared with matched able-bodied individuals). 2. After 7 months of exercise training there was no significant difference in BMD for any of the sites of the proximal femurs.
Pacy et al. 1988; UK Pre-post N=4	**Population:** 4 men, ages 20-35, paraplegia, no controls **Treatment:** FES+ FES-CE. Part 1 was quads strengthening with ↑ load ranging from 1.4-11.4 kg bilateral for 15 mins for 5x/wk (10 wks). Part 2 was FES-CE at 50 rpm with resistance (0-18.75 W). Performed for 15 mins, 5x/wk (32 wks). **Outcome measures:** BMD by DXA	1. No significant change in lumbar, femoral shaft, or distal tibia trabecular BMD after the intervention.

Discussion

For FES-Cycling there are mixed results for bone outcomes. Three studies found an increase in BMD (Mohr et al.1997; Chen et al. 2005; Frotzler et al. 2008) at the proximal tibia or distal femur while there was no significant within-participant BMD change at the hip in 3 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 in duration, 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 and colleagues found BMD and BMC were preserved at the distal sites for some participants at 12 months. FES shows promise as an effective treatment around the knee; however the limited availability of cycle ergometry for home or longitudinal use may limit its generalizability if the therapy cannot be sustained outside a clinical trial scenario.

Conclusion

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

FES cycle ergometry may increase lower extremity BMD over areas stimulated.

8.2.4 Standing

Table 11: 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 Mixed cross-sectional and longitudinal N=28 subjects with SCI	**Population:** 28 subjects with SCI (AIS A & B). 14 AB subjects served as normative control condition. **Treatment:** 3 doses of bone compressive loads: no standing, passive standing, quadriceps activation in stance. 7 participants performed unilateral quadriceps stimulation in supported stance (150% body weight compressive load = "High Dose") while opposite leg received 40% body weight = "Low Dose". 5 participants stood passively without applying quadriceps electrical stimulation to either leg (40% body weight load). 16 participants performed no standing (0% body weight load - "untrained"). **Outcome Measures:** Bone mineral density (BMD) assessment between 1-6 times over a 3 yr 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.
Goktepe et al. 2008 Turkey Observational N = 92	**Population:** 71 consecutive adults (18-46 years) and at least 1 year post injury. **Treatment:** Participants were divided into 3 groups: Group A had standing ≥1hr daily, Group B stood <1hr/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)	1. There was no statistically significant difference between the 3 groups in the BMD of any of the regions measured 2. Group A had a tendency to have higher *t*-scores, although the differences were not significant
Needham-Shropshire et al. 1997; USA Pre-post N=16	**Population:** 16 men and women, mean age=29, complete injuries, T4-T11, no controls. **Treatment:** Standing and ambulation. 32 sessions then participants continued ambulation for 8 more weeks. **Outcome measures:** 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 N=6	**Population:** 6 men, ages 36-65, complete and incomplete, C5-T12, 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:** BMD and fracture risk by DPA	1. There was no significant change in fracture risk as measured with BMD for femoral neck or lumbar spine with "standing".

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
Kaplan et al. 1981; USA Pre-post N=10	**Population:** 10 men and women, ages 19-56, 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 groups: **1**) early (within 6 mos of SCI) and **2**) late group (12-18 mos post SCI). **Outcome Measures***:* urinary calcium excretion	1. Significant improvement (p<0.01) in calcium excretion, urinary calcium, and calcium balance for the early group. 2. The late group had a significant improvement for urinary calcium, and calcium balance.
Walking (n=4 studies)		
Carvalho et al. 2006; Brazil Prospective controlled trial N=21	**Population:** 21 men with mean age 31.95 ± 8.01 yrs; Level of injury: C4-C8; TSI: mean 66.42±48.23 months, range 25-180 months. 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 neuromuscular electrical stimulation (NMES). Quadriceps and tibialis anterior stimulated for <5 months before beginning gait training (2x/week) in order to walk for 20 min and support <50% of body weight (pre-gait training) Either 1. NMES for 6 months, 20 min/session,2x/wk (N=11).; or 2. No training (N=10) **Outcome measures:** BMD by DXA, bone markers	1. 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. 2. 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 N=14	**Population:** 14 men and women aged 22-53 yrs with incomplete injuries from C4-T12; AIS B,C; reference control group **Treatment:** Body-weight-supported treadmill training, 12 months. Completed protocol 3x/wk for 144 sessions; intensity increased as tolerated **Outcome Measures:** BMD by DXA, bone markers	1. There were no significant changes in bone density or bone geometry at axial or peripheral sites with the exception of a small but significant decrease in whole body BMD. 2. No significant difference in bone markers.
Thoumie et al. 1995; France Pre-post N=7	**Population:** For bone assessment there were 6 men and 1 woman, ages 26-33, injuries between T2-T10. no controls. **Treatment:** RGO-II hybrid orthosis. Completed the protocol within 3-14 months (2-hr sessions 2x/wk). **Outcome measures:** BMD by DPA	1. At baseline, participants (compared with age-matched Z-score) had no significant change in L-spine BMD but a decrease in femoral neck BMD. 2. After the training program (16 mos), 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 N=4	**Population:** Bone assessment with 2 men and 2 women, ages 16-42, paraplegia. No controls. **Treatment:** Reciprocal gait orthosis. No protocol provided. Quantitative computed tomography repeated every 6 months from the	1. Three of 4 participants increased or maintained femoral neck BMD but no change in lumbar spine.

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
	1st referral, orthotic fitting and training, to independent and regulator ambulation (mean=5 months). The RGO was used daily on average for 3 hrs. **Outcome measures:** BMD by QCT	

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 longitudinal study found that participants who underwent quadriceps activation in stance with 150% body weight compressive load had significantly higher BMD than participants who underwent quadriceps activation in 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 bone loss 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 in stance with 150% body weight compressive load to increase BMD.

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.

8.2.5 Physical Activity

Table 12: 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 N=25	**Population:** 25 subjects with quadriplegia (25M). 2 groups: active (n=10) and sedentary (n-15). Sedentary: Mean (SD) age = 36(11); Mean (SD) DOI = 15(9) Active: Mean (SD) age = 30(9); Mean (SD) DOI = 8(7) **Treatment:** No treatment - comparison of active vs. sedentary groups. Active group practiced regular adapted physical exercise at least 150min/wk divided in at least 3 days/wk for at least 3 consecutive months.	1. After adjusting for DOI, 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, IGF1 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

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
	Outcome Measures: Total bone mineral content (BMC); bone mineral density (BMD) of total body, lumbar spine, total proximal femur, femoral neck and 33% radius; serum calcium; serum intact parathyroid hormone (iPTH); 25-hydroxyvitamin D (25(OH)D); insulin-like growth factor-1 (IGF1); osteocalcin; type I collagen.	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.

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 actually had significantly higher lumbar spine BMD.

Conclusion

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

9.0 Combination Interventions

As this chapter goes to press, the first generation of studies of combination interventions for treatment of bone loss 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 parathyroid hormone (rPTH, Forteo) in combination with weight bearing. Table 13 describes the early results from one such trial.

Table 13: 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 test study N = 12	**Population:** Convenience sample of 12 nonambulatory subjects (2 women) with chronic SCI (5 AIS A, 3 AIS B, 4 AIS C) and low total hip bone mass (DXA T-score < 2.5 or Z-score < 1.5), injury level C1 to T10, ≥ 1 year post-injury, mean age 34 ± 8 yrs. **Treatment:** teriparatide (PTH 1-34) 20 µg daily x 6 mos, calcium 1000 mg daily x 6 mos, vitamin D 1000 IU daily x 6 mos, and treadmill stepping 3 times/wk (20 to 40 min. stepping time at 1.8 to 2.5 km/h) for 6 mos. 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 mos; micro-MRI of distal tibia at baseline, 3, 6, and 12 mos; serum bone	1. Positive but non-significant changes in lumbar spine & total hip BMD were observed at 6 mos. 2. Teriparatide was well tolerated.

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
	markers BAP, CTX-1, PINP, and osteocalcin at baseline, 3, 6, and 12 mos.	

Discussion

One study of concurrent teriparatide and body-weight supported treadmill stepping did not provide evidence in support of this combination intervention for treatment of bone loss in SCI. However, this study used a convenience sample with a small N, and was not powered to detect significant intervention effects.

Conclusion

There is no evidence to support concurrent treatment of low bone mass with teriparatide and body-weight supported treadmill training.

10.0 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 14 describes several such studies.

Table 14: 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 N = 21	**Population:** 21 adults (17 men) with acute SCI (6 to 122 days post-injury, median 26 days post-injury), mean age 34 years; 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 IV 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 calcium, phosphorus, intact PTH, 25-D, 1,25-D.	1. Calcitriol-pamidronate therapy decreased urinary NTx excretion by 71% ($p < 0.001$), and urinary calcium excretion by 73% ($p < 0.001$). 2. Calcitriol-pamidronate therpay increased serum PTH ($p < 0.05$) and 1,25-D ($p < 0.005$). 3. Post-therapy hypocalcemia or hypophosphatemia occurred in 44% ($p < 0.01$) and 53% ($p < 0.01$) of participants, respectively.
Mechanick et al. 2006 USA Case series N = 32	**Population:** 32 adults (25 men) with acute traumatic SCI; mean age 42 yrs; 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 IV on day 4 **Outcome measures:** Serum calcium, phosphorus, and albumin; urinary calcium and NTx, serum intact PTH, 25-D, 1,25-D	1. 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. 2. Post-therapy hypocalcemia or hypophosphalemia occurred in 75% ($p<0.02$) and 22% ($p<0.02$) of participants, respectively. 3. Single-dose pamidronate is associated with increased incidence of fever (78%) compared to 30 mg daily x 3 days

Author Year; Country Score Research Design Total Sample Size	Methods	Outcome
		dosing regimen (20%).
Bauman et al. 2009 USA Case series N = 8	**Population:** 8 men with chronic SCI (12 ± 8 yrs post-injury) and low vitamin D (25[OH]D ≤ 20 ng/mL) and/or elevated serum PTH (>55 pg/mL) , age 34 ± 7 yrs; paraplegia (n=6), tetraplegia (n=2) **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 hrs. **Outcome measures:** Serum total calcium, creatinine, NTx, and PTH at baseline, 2, 4, and 6 hrs post-infusion.	1. 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. 2. Calcium gluconate infusion reduced bone collagen catabolism during calcium infusion.

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.

11.0 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 spinal cord injury. 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. 2008; 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 provides a description of the results based on whether the goal of therapy is prevention or

treatment of SLOP. In the past 40 years there have been a number of 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, time since injury 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, FES-cycling may have small effects on bone, but this modality has been shown to have large effects on cardiovascular health (Jacobs & Nash 2004).

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 aging 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 remodeling. 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 bone loss with aging rather, only a slower phase of bone loss 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 dual photon absorptiometry [DPA], DXA or pQCT, urine or blood markers) 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 remodeling can take at least 9 months in order to observe changes within participants over time. Consequently, investigations that did not maintain an intervention for at least 6 months may not show changes, 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 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 bone loss 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 is limited by small samples, diverse treatment protocols, heterogeneous samples (in terms of 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.

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.

12.0 Summary

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 2 RCTs) (Shapiro et al. 2007; Bubbear et al. 2011) that a one-time IV infusion of Zoledronate may reduce bone loss in the hip region during the 12 months following administration.

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

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

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

There is level 1 evidence (from 1 RCT) (Warden et al. 2001) that short-term (6 weeks) ultrasound is not effective for treating bone loss after SCI.

There is level 2 evidence (from 1 non-randomized prospective controlled trial) (Shields et al. 2006a) that ES reduced the decline in BMD in the leg.

There is level 2 evidence (from 1 non-randomized prospective controlled trial) (Eser et al. 2003) that FES cycling did not improve or maintain bone at the tibial midshaft in the acute phase.

There is level 4 evidence (from 1 pre-post study) (Giangregorio et al. 2005) that walking and level 1 evidence (from 1 RCT) (Ben et al. 2005) that standing in the acute phase did not differ from immobilization for bone mass decline at the tibia.

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

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

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

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 for quadriceps activation in stance with 150% body weight compressive load to increase BMD.

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

There is no evidence to support concurrent treatment of low bone mass with teriparatide and body-weight supported treadmill training.

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.

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