

Review Article

Osteoporosis after spinal cord injury: aetiology, effects and therapeutic approaches

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Abstract

Osteoporosis is a long-term consequence of spinal cord injury (SCI) that leads to a high risk of fragility fractures. The fracture rate in people with SCI is twice that of the general population. At least 50% of these fractures are associated with clinical complications such as infections. This review article presents key features of osteoporosis after SCI, starting with its aetiology, a description of temporal and spatial changes in the long bones and the subsequent fragility fractures. It then describes the physical and pharmacological approaches that have been used to attenuate the bone loss. Bone loss after SCI has been found to be highly site-specific and characterised by large inter-variability and site-specific changes. The assessment of the available interventions is limited by the quality of the studies and the lack of information on their effect on fractures, but this evaluation suggests that current approaches do not appear to be effective. More studies are required to identify factors influencing rate and magnitude of bone loss following SCI. In addition, it is important to test these interventions at the sites that are most prone to fracture, using detailed imaging techniques, and to associate bone changes with fracture risk. In summary, bone loss following SCI presents a substantial clinical problem. Identification of at-risk individuals and development of more effective interventions are urgently required to reduce this burden.

Keywords: Bisphosphonates, BMD, Disuse Osteoporosis, Electrical Stimulation, Spinal Cord Injury

Introduction

Spinal cord injury (SCI) is a life changing event that has a substantial impact on the individual's physical and mental health. A global annual incidence of 8.0 to 246.0 cases per million inhabitants has been reported¹ with an increase in the percentage of cases of tetraplegia and complete lesions over a 20 years period (1994-2013)^{2,3}. People with SCI experience secondary medical complications such as

those affecting their body composition^{4,5}. They experience extensive declines in bone density and strength that put them at high risk of fragility fractures and associated morbidity and mortality⁶.

This review article summarises different aspects of bone loss and osteoporosis after SCI. It discusses the factors that have been shown to contribute to the SCI-induced bone loss and describes in detail how bone loss develops in the acute and chronic phases of the injury until it reaches its steady state. Factors influencing the large inter-site and inter-individual patterns of bone loss observed in individuals with SCI are also described, in addition to clinical consequences e.g. fractures from SCI-related bone loss and associated complications. It also reviews different physical and pharmacological interventions that have been tested in patients with SCI, to investigate their effectiveness in reversing or attenuating bone loss in acute and chronic phases respectively.

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Aetiology of bone loss after SCI

The type of osteoporosis that develops after spinal cord injury (SCI) has been reported to be induced by a combination of factors. The main causal factor is understood to be from mechanical unloading⁷, that has also been evidenced by the reported bone loss following space flights and bed rest^{8,9}. In addition, neuronal and hormonal changes have been found to contribute to its pathogenesis⁷.

Unloading and the bone formation-resorption imbalance

SCI causes immediate disuse and a subsequent loss of biomechanical stress on bones, which is a substantial stimulus for the bone remodelling process controlled by osteocytes^{7,8,10}. This absence of mechanical loading leads to an adaptive response involving inhibition of osteoblastic bone formation and increases in osteoclastic bone resorption resulting in demineralisation. In some cases, the imbalance between bone formation and resorption is so great and sustained that it leads to severe bone loss.

This has been widely documented in both acute and chronic SCI. Bone resorption biochemical markers in blood and urine, such as total deoxypyridinoline (DPD), N-telopeptide (NTx), serum and urinary type I collagen C-telopeptide (CTX) and hydroxyproline have been found to be significantly increased in acute and chronic SCI¹¹⁻¹⁴, but significantly lower in chronic than in acute SCI¹⁴. Nonetheless, elevated levels of DPD were evident in 30% of patients 10 years or more after injury¹⁵. This significant rise in bone resorption rate after SCI has been found to be associated with a slight increase in osteoblastic bone formation activity, evidenced by minor increases in serum osteocalcin and total alkaline phosphatase¹¹. However, there is no consensus on the significance of these small increases in osteoblastic activity, which were found to be minor in some studies¹¹ but substantial in others^{12,16}.

The increase in bone resorption and the associated calcium efflux from bones after SCI leads to abnormally high concentrations of calcium in blood (hypercalcemia)¹⁷ and urine (hypercalciuria)^{18,19}.

Neurovascular changes

Bone also undergoes neurovascular changes caused by the neurological lesion and the subsequent disturbance of bone tissue innervation⁷. Whilst it is clear that the loss of motor function and the associated reduction in bone loading caused by neural damage contribute substantially to bone loss following SCI, the contribution of other neurally-mediated mechanisms of bone loss is less clear²⁰. Some of the neuronal changes are directly caused by the significant reduction in sensory and autonomic nerve fibres and nerve-derived factors (neuropeptides) which have been documented to regulate and modulate bone metabolism^{7,21,22}.

The autonomic nervous system has been documented to regulate skeletal metabolism through different pathways^{23,24}. Increased activity of the sympathetic nervous

system is known to suppress bone formation and favour bone resorption²³. Subsequently, one would expect that the attenuated sympathetic activity after SCI should increase bone mass instead. It is clear that the extensive bone loss that occurs after SCI cannot be explained directly by the attenuated sympathetic activity²⁵. Furthermore, interruption to the sympathetic system and the subsequent vasomotor irregularity can better (and in part) explain the loss in bone mass²⁶. The interrupted sympathetic nerves (which have their processes distributed along bone vessels²⁷), lead to vascular modification in the sub-lesional areas^{7,28}. Changes in bone blood flow after SCI have been evidenced by high intramedullary pressure and arteriovenous shunting in the legs leading to venous stasis and adverse consequences for bone metabolism^{16,29}. The effect of the reduced parasympathetic activity after SCI³⁰ is an area of active research, and our understanding of its role in regulating bone metabolism is currently limited^{23,25}, which further emphasises the multi-factorial and complex aetiology of bone loss after SCI.

Hormonal changes

Hypercalciuria is prevalent in the acute phase of SCI as a result of the abnormally high ionised calcium levels which are found to get back to normal during the chronic phase³¹. These changes (in the acute phase) are followed by changes in calcium regulatory hormone levels. Serum intact parathyroid hormone (iPTH) level was found to be suppressed in acute and sub-acute SCI as expected for this negative feedback loop (1-4 months)^{11-13,32}. It increases in the chronic phase compared to the acute phase but it stays within or below the lower reference ranges³¹. Only one study reported a decreased level of PTH in the chronic phase, which was associated with normal ionised calcium levels¹⁸. This decline in PTH has been suggested in this study to be driven by "low-grade increased calcium release", which in turn indicates persistently elevated bone resorption even after years of injury¹⁸, a hypothesis that is also supported by the high levels of bone resorption markers reported during the chronic phase³¹.

Reported changes in vitamin D levels in acute SCI, show reduced levels of 1,25(OH)₂ vitamin D (the biologically active form of vitamin D), as a result of bone resorption and the suppression of PTH^{13,32}. However, different results were reported for 25-hydroxyvitamin D (25(OH)D) in the acute phase: with one study reporting normal³², and others reporting low levels^{33,34}. Using different reference values to define normal levels of vitamin D level and other factors such as ethnicity and season might have contributed to this variability in their results. In people with chronic SCI, low levels of 25-hydroxyvitamin D (25(OH)D) have been found to be prevalent³⁴⁻³⁶, which might be accompanied by mild secondary hyperthyroidism³⁷. This could be due to limited exposure to sunlight, prescription of medications that increase vitamin D metabolism and, perhaps, restricted dairy intake³⁶. Only one study reported normal levels of 25(OH)

D in the chronic phase, which was explained by the majority of medically stable and active participants included in this study¹⁸.

SCI is associated with severe muscle atrophy affecting the sublesional areas^{38,39} within the first few days after injury^{40,41}. About one third reduction in thigh muscle cross sectional area (CSA) has been found to occur within only 6 to 24 weeks postinjury^{40,42}. The denervation and atrophy of these muscles (alongside other factors such as reduced physical activity) are believed to be one of the determinants of insulin resistance⁵, which is also associated with increased intra-muscular fat in people with SCI⁴³.

Sex hormones also play a major role in regulating bone metabolism. Oestrogen has been shown to prevent osteocyte apoptosis⁴⁴, and both oestrogen and androgen inhibit bone resorption and promote bone formation via many mechanisms^{45,46}. SCI causes the inhibition of sex hormone production and secretion⁷. In people with acute SCI, testosterone levels were significantly lower than in the uninjured control group, with no further change after week 16 post injury¹³.

When investigating hypothalamus-pituitary-ovary and hypothalamus-pituitary-thyroid axes in women with SCI, approximately 80% women were found to have at least one axis abnormality⁴⁷. These findings suggest that bone loss can be linked to impaired endocrine function in people with SCI.

Structural and geometric changes in bone after SCI

Densitometric assessment of bone parameters after SCI

Most of the studies on bone loss in the early acute phase and throughout the chronic phase following SCI, have used medical imaging technologies such as dual-energy x-ray absorptiometry (DXA) and peripheral quantitative computed tomography (pQCT).

DXA enables scanning of sites that are generally the most susceptible to osteoporotic fractures in the general population such as the vertebrae and proximal femur (hips) and wrist⁴⁸, aiding in detection of osteoporosis and reducing the risk of such clinically and economically costly fractures⁴⁹.

Furthermore, its low radiation dose, low price, wide availability and ease of use have all made it the predominantly used technique to diagnose osteoporosis^{49,50} and assess susceptibility to fractures clinically⁵¹. For similar reasons, it has been the default densitometric technique for measuring bone density in clinical trials⁵⁰ to evaluate the effectiveness of interventions.

However, DXA measures areal BMD, which is highly affected by bone size, leading to larger bones appearing to have a greater density than smaller bones⁴⁹ resulting in both bone loss and fracture risk being underestimated⁵². DXA's inability to extract three-dimensional measurements of bone geometry limits its utility in describing detailed components of bone structure relevant to fracture risk^{49,53}. Moreover, DXA does not distinguish between trabecular and cortical

compartments⁴⁹. This limitation of DXA is particularly relevant in disuse osteoporosis due to the differences in the extent and time-course of bone loss in these two bone compartments.

There is good evidence that, in people with SCI, trabecular bone has a more rapid response to disuse^{15,54-56} and interventions⁵¹ compared to cortical bone (when considering the percentage of the loss in bone). Therefore, it is recommended to obtain separate, detailed trabecular and cortical BMD measurements in order to assess the effectiveness of different bone interventions.

pQCT and high resolution pQCT (HR-pQCT) provide detailed volumetric parameters of trabecular and cortical compartments⁵⁷ making these techniques clinically relevant for this population. They assess volumetric density (vBMD) that considers bone depth (BMC/cm³)⁵¹ and quantify both hard and soft tissues within the region of interest⁵³. pQCT also allows detailed, site-specific examination of regions such as the distal femur and proximal tibia⁵⁸. These areas are particularly prone to fracture in individuals with SCI, who lose bone mass exclusively in sublesional sites⁵⁶ as shown in Figure 1. In contrast, the most commonly performed regional DXA scans focus on the proximal femur and the lumbar spine.

HR-pQCT acquires 3D images of bone microarchitecture which is of importance in assessing bone strength in individuals who are susceptible to fractures^{49,58}, especially people with SCI⁵⁷. It provides trabecular and cortical parameters such as trabecular number, separation, anisotropy and trabecular and cortical thickness⁴⁹, shown to improve fracture risk prediction^{59,60}.

Despite their capabilities, these techniques impose certain practical constraints as imaging of patients with bilateral metal implants or spasticity that could cause movement artefacts is challenging⁶¹. HR-pQCT can only be used to scan peripheral sites such as distal radius and tibia due to its small field of view, which is compromised to achieve the optimum resolution⁵⁸. Moreover, the 140 mm gantry diameter makes it unusable for scanning obese patients or regions such as the thigh and proximal femur⁶¹. Nevertheless, these techniques offer detailed bone microarchitecture measurements for people with SCI, who are of higher risk of sustaining osteoporotic fractures mostly in their lower extremities, compared to the spine and upper extremities that are less prone to fracture^{57,62}. Bone loss after SCI occurs at sublesional sites only, leading to upper limb bone health being preserved in people with paraplegia whilst people with tetraplegia are at risk of developing osteoporosis in both the upper and lower limbs^{63,64}.

Notwithstanding the substantial advantages that pQCT and HR-pQCT offer over DXA, they are not currently recommended to be used routinely by clinicians in the diagnosis of osteoporosis, fracture risk prediction or assessment of bone conditions treatments. This is due to the lack of international standards that regulate its clinical use with regards to aspects such as scanning and analysis protocols and anatomical sites, which were recommended recently by Cervinka et al⁶⁵.

The absence of standards for the clinical use of pQCT,

combined with the ready availability of DXA machines in clinics has driven the development of protocols to make DXA scans more clinically relevant to people with SCI. Different DXA protocols and software have been developed and validated to acquire and analyse images at the knee region, which until now has not been a standard measurement site in DXA. Methods that extract sub-regions from total body DXA scan are not recommended due to their poor repeatability and image resolution⁶⁶. A commercially available GE lunar software for the knee region has FDA approval and is being used for both clinical and research purposes⁶⁷⁻⁶⁹. Few studies investigated the accuracy of conventional DXA software designed for lumbar spine, proximal femur and forearm, in predicting BMD and fracture risk at the knee^{70,71}. A DXA forearm software has been validated by McPherson et al. (2014) to be used to measure BMD at the knee in people with SCI⁷². It was found to be accurate in short-term assessments and has been proposed as a reliable method to assess BMD at the distal femur and proximal tibia using DXA in clinical trials⁷¹. The International Society of Clinical Densitometry recommended a BMD analysis protocol based on lumbar spine software for the calculation of BMD at the knee^{66,73}, until knee-specific software is developed. There remains the need for valid manufacturer-adopted knee software to accurately measure BMD at the distal femur and proximal tibia for clinical use⁶⁶.

Time course of bone changes after SCI

Many longitudinal studies on people with SCI emphasise the substantial effect of time since injury on bone structural and geometric parameters during both the acute (5 weeks-12 months)⁷⁴ and the chronic phases⁷⁵. Bone resorption markers have been shown to increase significantly to maximum levels within 10-16 weeks postinjury¹¹. In the same study, BMD losses in the lower limbs were detected at follow-up (24th week postinjury)¹¹. Bone mass continues to decrease with time throughout the first 8 months⁷⁶, 12 months⁷⁴, 2 years⁷⁷ and even throughout the chronic phase (up to 19-25 years)^{78,79} but at a slower rate in the later phases compared to the rapid loss during acute phase⁵⁴. However, some studies found that bone loss reaches steady-state phase at 3-8 years postinjury depending on the bone parameter measured^{55,75} with about 50% and 60% loss in bone mass in the femoral and tibial epiphyses, and 35% and 25% in the femoral and tibial shafts respectively⁵⁵. Determining the time course of the adaptive modifications in bone geometry and structure is of clinical importance to assess the effectiveness of different rehabilitation interventions in reversing bone loss⁷⁵.

Patterns and time course of loss in cortical and trabecular compartments

Bone loss at epiphyseal sites (which are rich in trabecular bone) has been attributed to the decline in trabecular BMD with comparatively little loss from the outer cortical shell⁸⁰. In contrast, bone loss at diaphyseal sites composed primarily of

cortical bone is suggested to be characterised by a reduction in wall thickness via endocortical resorption in addition to smaller decreases in cortical BMD^{15,53,81} as shown in Figure 2.

Exponential decreases in bone parameters with time postinjury (2 months to 50 years) have been described using pQCT, specifically in bone mass, total and trabecular BMD (BMDtot and BMDtrab, respectively) of the femoral and tibia epiphyses, as well as bone mass and cortical CSA of the diaphysis as shown in Figure 1⁵⁵. In a longitudinal study using pQCT scans, significant decline in cortical BMD and cross sectional area (CSA) has been reported alongside the epiphyseal changes within the first 12 months postinjury⁷⁴. In the acute phase, tibial and femoral cortical BMD losses make a substantial contribution to bone loss at these diaphyseal sites⁷⁴. It has been suggested that acute cortical BMD losses may be transient, resulting from increased remodelling in the early stages post-injury⁵⁵. Indeed, in the chronic phase cortical bone losses at these sites appear primarily attributable to decreased cortical bone cross-sectional area with little or no contribution of BMD losses reported⁵⁵. Nevertheless, the loss in trabecular BMD seems to occur at a more rapid rate acutely and is of greater magnitude in the chronic phase than that in the cortical bone^{55,82} as shown in Figure 1. Lower BMD in the proximal femur^{6,79,83}, femoral shaft and lumbar spine⁸³ have also been correlated with time since injury.

Characteristic temporal and site-specific patterns

Acute SCI

During acute SCI (measured between week 8 and 12 months postinjury), DXA reveals significantly lower BMD in the lower limbs^{11,13}, total body, pelvis¹³, proximal femur¹⁴, midshaft and distal femur⁸⁴ with no difference in the hip (between week 8 and week 24 postinjury¹¹, although BMD loss might have been detected sooner than 24 weeks if the protocol had allowed it), lumbar spine or radius^{11,13,14}. After only one year postinjury the distal femur and proximal tibia lost up to 52% and 70% of their BMD respectively⁶⁴.

pQCT scans during this phase showed a significant decline in tibial trabecular BMD (at 6 and 12 months) as well as in cortical BMD (only at 12 months)^{74,85}. Other epiphyseal (BMC, total BMD) and diaphyseal (BMC, cortical CSA) parameters of the tibia and femur bones also decreased⁷⁴. Lower trabecular BMD was reported in the radius and ulna (at 6 & 12 months) and cortical BMD (at 12 months) in people with tetraplegia with no differences detected at these sites in those with paraplegia⁸⁵. pQCT results in acute SCI further emphasise the rapid rate of trabecular loss compared to cortical loss.

Chronic SCI

Significant decreases in BMD and BMC have been documented at the distal femur⁸⁶⁻⁸⁸, proximal tibia^{86,87,89} proximal femur^{14,90}, femoral neck^{54,87,88,91,92}, femoral shaft⁸⁷ and total femur⁸⁸. This BMD loss seemingly occurs in the lumbar spine as well^{52,93}, but was previously

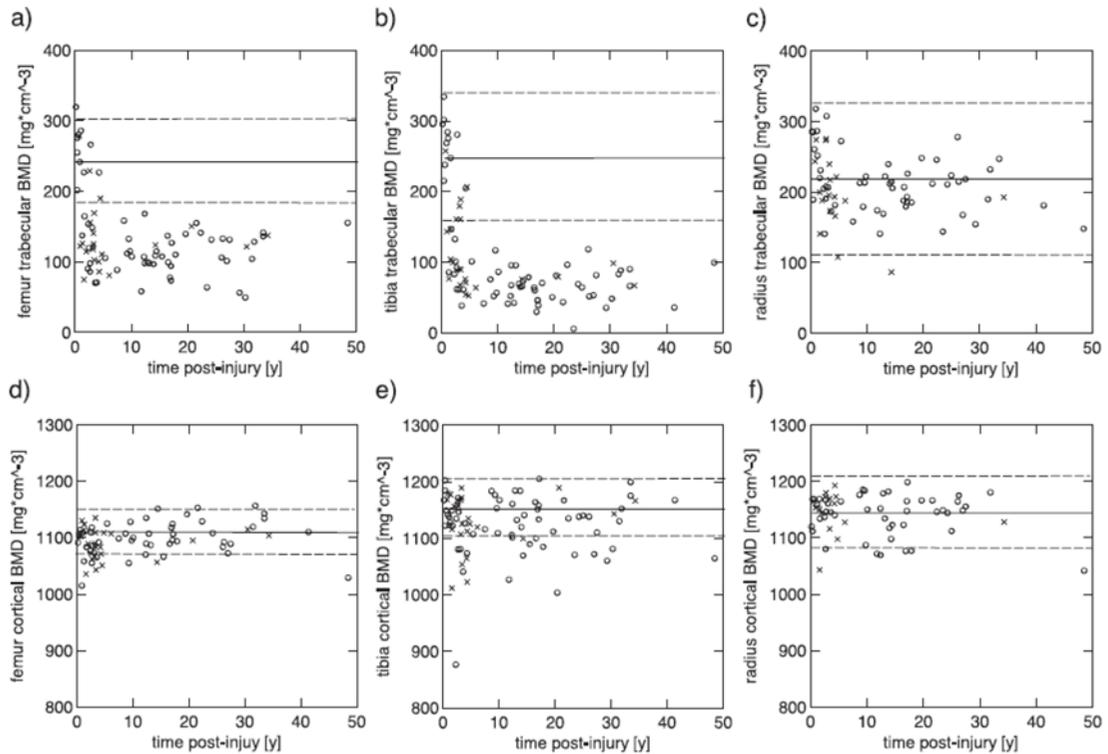


Figure 1. Differences in trabecular (upper row) and cortical (lower row) BMD with time (2 months to 50 years) postinjury in the femur (a,d), tibia (b,e) and radial (c,f) bones within a group of individuals with SCI-induced paraplegia (O) and tetraplegia (x)⁵⁵. (Reproduced with permission).

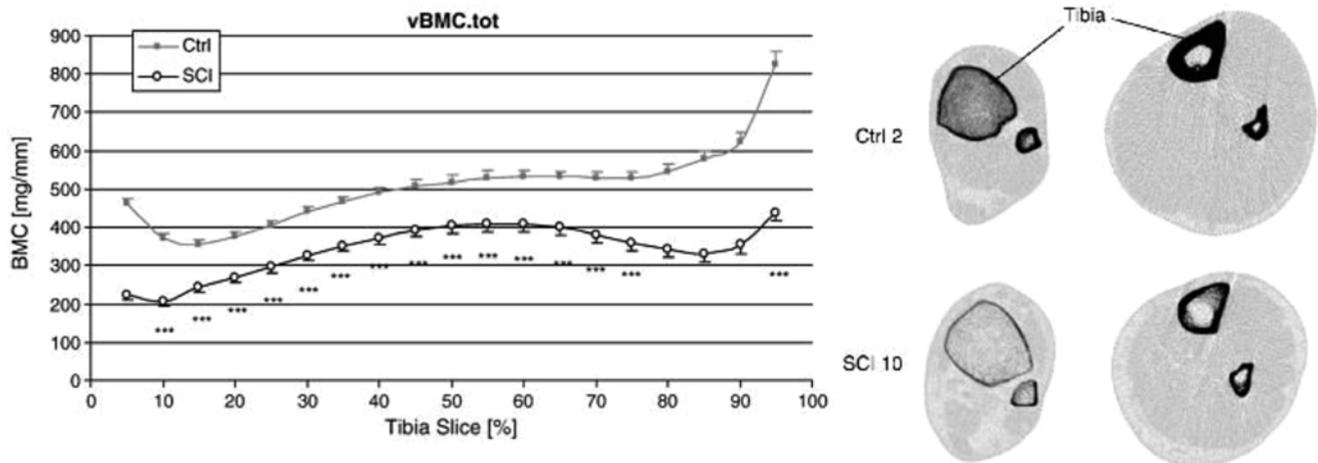


Figure 2. (Left): compares volumetric BMC at different sites along the tibia (starting from distal tibia at 5% of the tibial length and moving toward the proximal epiphysis in steps of 5% (up to 95% of the tibia length) between controls and participants with SCI. It also shows the more pronounced bone loss at the epiphyses compared to the diaphysis between the two groups. (Right): shows pQCT images of the tibia distal epiphysis (left column) and diaphysis (right column) in an uninjured control (upper row) and an individual with SCI (lower row). The decrease in trabecular BMD and the cortical thinning at epiphysis can be seen clearly, alongside the cortical loss/trabecularisation in the diaphysis⁶⁰. (Reproduced with permission).

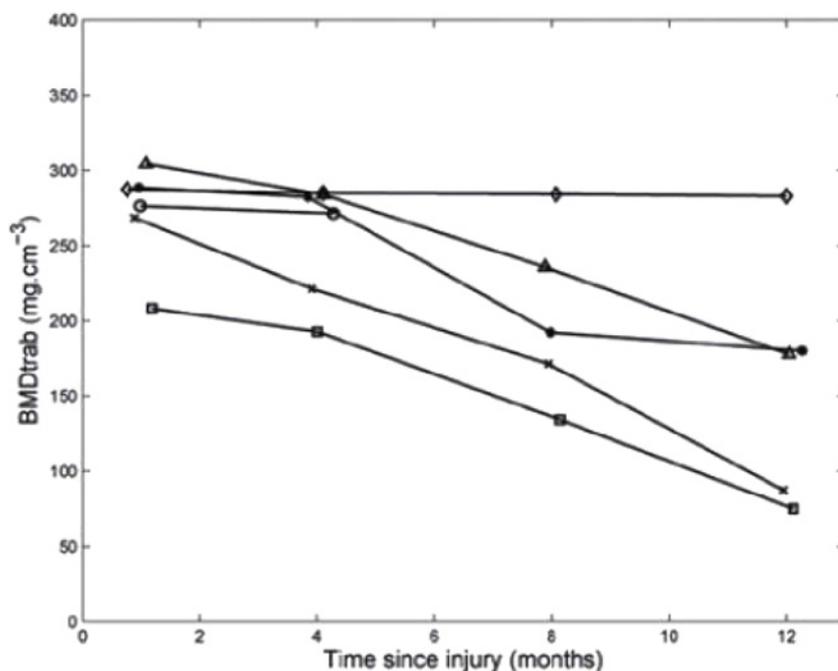


Figure 3. Trabecular BMD of the distal tibia measured in six participants shortly after complete SCI, and 4, 8 and 12 months postinjury⁷⁶.

undetectable by conventional DXA^{14,94}. This was likely due to an overestimate of bone mass resulting from neuropathic calcification and other skeletal abnormalities in the vertebrae of people with SCI⁵².

pQCT scans in people with paraplegia revealed significantly lower tibial total BMD^{80,82}, trabecular BMD, cortical BMD, and cortical thickness, as shown in Figure 2, alongside similar periosteal and increased endosteal circumferences⁸² compared to controls. These findings in cortical parameters further confirm the proposed mechanism of cortical thinning by endocortical resorption⁵⁵.

BMD and BMC at the distal and proximal tibia epiphyses^{77,90} and in the patella have been reported to be significantly less than those in controls. Sabo et al. reported that the cortical area at the distal femur and proximal tibia was lower than that in controls but no difference in cortical BMD was reported in this study⁹⁰. The loss in volumetric BMC was more pronounced at the distal and proximal tibia than in the diaphysis^{77,82}.

Factors influencing rate and magnitude of bone loss following SCI

It has been shown that there are inter-individual and site-specific differences in the rate of bone loss after SCI (Figure 3), with some individuals approaching published BMD fracture thresholds within only 1 year post-injury (around 67% loss in the distal tibia trabecular BMD) while others experience minor BMD reductions within the same period (around 1% in distal tibia trabecular BMD)⁷⁶. Intra-individual

differences have also been reported in another study where bone loss was greater at the proximal tibia compared to the distal tibia and more pronounced in the epiphyses than in the diaphysis (Figure 2)⁸⁰, with evidence that inter-site variance in bone loss may be related to bone geometry^{74,80}.

An inverse relationship was found between BMD and time since injury^{83,88,95}. Unsurprisingly, bone loss has also been found to be influenced by the type, level and completeness of injury (and resulting function). Lower BMD has been reported in the upper extremities^{55,63,95} and lumbar spine⁶³ in people with tetraplegia, compared to those with paraplegia. Patients with complete SCI have been found to have significantly lower BMD than those with incomplete injuries (BMD= -2.29 ± 0.51 in complete versus -0.12 ± 0.22 in incomplete, $P < 0.05$)^{86,95}. Bone loss has also been found to be influenced by the level of injury so that individuals with higher spinal lesions tend to have lower BMD (in the affected skeletal sites) compared to those with lower lesions^{56,87,93}, but this primarily depends on the injury completeness. While it is likely that function linked to lesion level affects the extent of bone loss, to date these associations have not been reported in the literature.

Neither age^{78,86} nor sex have been found to have an effect on bone parameters after SCI⁷⁴. However, a significantly lower cortical BMD has been reported in females compared to males in one study, suggesting a possible effect of gender on cortical bone parameters which was proposed to be influenced by the postmenopausal females participating in this study⁷⁴. The possible effect of spasticity on BMD seems to be unclear with two studies reporting less loss in BMD in spastic compared to flaccid patients^{95,96} and other

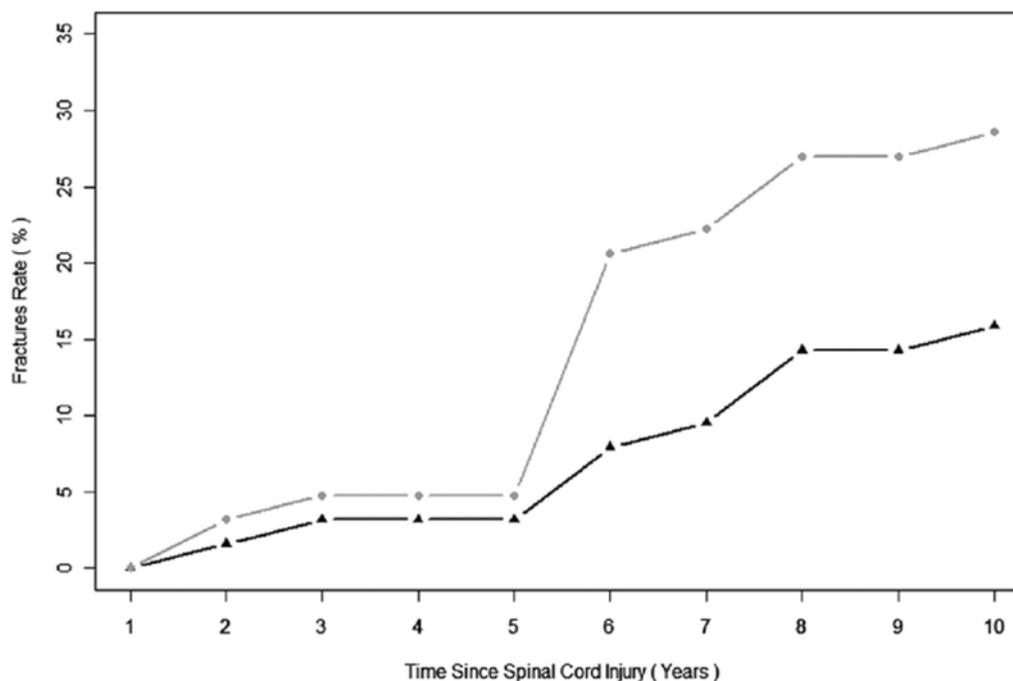


Figure 4. Cumulative rate of fracture recorded during the first 10 years postinjury. The black line with triangles represents the rate of patients sustaining new fractures while the grey line with circles represents the rate of newly sustained fractures per patient⁹⁹. (Reproduced with permission).

studies reporting no differences in BMD^{85,87,97,98} between the two groups. However, in one of the studies that reported a positive effect of spasticity on BMD⁹⁵, the 41 tested participants were a mixture of individuals with paraplegia and tetraplegia, and complete and incomplete SCI. It is clear that the 2 groups (spastic and flaccid) were not matched for these influencing factors.

Fragility fractures after SCI

Osteoporosis is characterised by reduced BMD and deterioration in bone micro-structure that consequently leads to reduced bone strength and increased susceptibility to fracture⁴⁹. The link to fracture risk has been demonstrated as bone geometry parameters⁷³ and BMD were found to be lower in participants with SCI who had lower limb fractures compared to those with no fracture history^{6,15,73,87}.

Fragility fractures are common and unresolved consequences of SCI⁵⁷ and are mostly caused by minor trauma⁹⁹ during transfer between surfaces or turns in bed¹⁰⁰⁻¹⁰² or even during rehabilitation training sessions^{103,104}. They are more frequent in patients with SCI compared to the general population¹⁴ and occur predominantly in the lower extremities^{15,57}; fewer¹⁰⁵ or even no fractures have been reported in the upper limbs^{57,62}. The majority of these fractures occur in the femur and tibia⁹⁹ especially at epiphyseal sites at the ankle and knee joints^{57,105}. This can

be linked to the more dramatic and rapid rate of bone loss documented in these trabecular bone-rich site compared to that in the cortical-rich shaft.

In general, people with SCI are more likely to sustain bone fractures in the chronic phases starting at a mean of 3 to 8.9 years postinjury^{15,62,99} (Figure 4). Annual fracture rates of individuals with a SCI are double those in uninjured (2% and 1% respectively)⁶² but this additional risk is highly site-specific. People with SCI have a 23-fold higher risk of experiencing femur fractures whereas upper limb fracture risk is lower compared to controls⁶².

Fractures risk factors

Fractures are more frequent in women and also in men with a family or personal history of fractures^{62,106}. Fracture risk increases with time since injury^{99,106}, reaching 4.2% per year in individuals who sustained a SCI more than 20 years ago¹⁵. Severity of SCI has also been found to be a contributing risk factor, with fractures found to be more common in patients with complete SCI than in those with incomplete injuries^{99,105,106}. These factors have been shown previously to contribute to the magnitude of bone loss following SCI, illustrating the correlation between severity of bone loss and fracture risk in these patients. Other factors associated with high risk of fracture include white ethnicity¹⁰⁶ and higher alcohol consumption¹⁰⁵.

It is worth pointing out that our understanding of many

Table 1. Summary of studies that used ES- interventions to attenuate the loss in BMD after SCI.

Study	Training Modality	Electrical stimulation parameters	Produced Stress/ power	Training duration/ frequency	Injury duration and level	Imaging modality	Changes in bone parameters	Level of evidence
Pacy et al., 1988 ¹³⁰	Leg raising against load + bicycle ergometer	6s-6s stimulation-rest, 300 μ s, 40 Hz. 65-90 V, for leg raising against load ranging from 1.4-11.4 kg, and 80-125 V for bicycle ergometry.	From 0 to 18.75 W (0-3/8 kilopond)	15 mins, 5 times/week for 10 weeks (leg raising) -15 mins, for 32 weeks (bicycle ergometry), 50 rpm	1, 3 and 4 years, T4-T6 (3 SCI patients) N.B.: 1 patient had hemangioblastoma at T6 for 6 years	DXA	No change in BMC or density	-
Rodgers et al., 1991 ¹²⁸	FNS-induced knee extension (KE)	Progressive resistance load on ankle 0-15 Kg	-	6 KE/min/leg, 3 times/week for 12-18 weeks,	6.4 \pm 6.1 years, C4-T10	QCT	No change in BMD	Poor
Sloan et al., 1994 ¹²³	FES-cycling (Also participating in physiotherapy)	-	50-60 rpm for patients with incomplete and 30-40 rpm for complete SCI	30 min, 3 times/week, for 3 months	0.2-11.6 years, C5-T12	DXA	No change in BMD (BMD tested in only 2 out of 12 patients)	Poor
Bloomfield 1996 ¹²⁵	FES-cycle ergometry	Monophasic, 350 msec duration at 30 Hz and up to 130 mA	Cycling power up to 18 W	30 mins, 3 sessions/week, (80 sessions) for 9 months	6 years, C5 to T7	DXA	Increased by 0.047 \pm 0.010 g/cm ² at the lumbar spine; 78% increase in serum osteocalcin, PTH increased 75% but then declined to baseline	Fair
Mohr et al., 1997 ¹¹⁴	FES-cycling	-	Workload 1/8 Kp- 7/8 Kp, 18 \pm 2 KJ/session	30 min, 3 days/week, for 12 months followed by 6 months of 1 session/ week	12.5 \pm 2.7 years, C6-Th4	DXA	10% increase in PT BMD. This gain faded after 6 months of reduced training	Fair
Belanger 2000 ¹¹¹	Quadriceps contraction (resisted & unresisted)	300- μ sec rectangular pulses delivered at 25Hz with a 5-sec on/5-sec off duty cycle	40 Nm	1-hour a day, 5 days a week, for 24 weeks.	9.6 \pm 6.6 years, C5-T6	DXA	30% of lost BMD recovered in distal femur and proximal Tibia -Large strength gain	Poor
Eser et al., 2003 ¹¹³	FES-cycling and passive standing (2 days/week)	Peak current =140 mA. Pulse width set 0-3- 0-4 ms, frequency set at 30, 50, and 60 Hz	Power output between 0 and 1 kiloponds	30-min, three times a week for 6 months	4.5 weeks	CT	No effect in tibial cortical BMD	Fair
Chen et al., 2005 ¹²⁷	FES-cycling	20 Hz; pulse duration, 300 μ sec; up to 120mA	-	30 minutes/day, 5 days/week, for 6 months	At least 2 years and 7 months, C5- T8	DXA	BMD at DF and PT increased 11.13%, and 12.92% respectively, but decreased at FN	Fair
Shields et al., 2006 ¹¹⁰	ES-isometric plantar flexion	10 pulse train (15 Hz, 667ms) every 2 seconds	Compressive loads: 600 N (90% BW) to 1,107 N (150% BW)	4 bouts/day, each consisting of 120 trains, 5 days/week, for 3 years	4.5 months, C5 and T12	DXA	Decline in trained tibial BMD (10%) less than the untrained (25%)	Fair

Table 1. (Cont. from previous page).

Study	Training Modality	Electrical stimulation parameters	Produced Stress/power	Training duration/frequency	Injury duration and level	Imaging modality	Changes in bone parameters	Level of evidence
Shields and Dudley-Javoroski 2006 ¹²²	ES-isometric plantar flexion	0-200 mA, 400 V, 10 pulse train (15 Hz, 667ms) every 2 seconds	~1-1.5 times BW	4 bouts/day, each consisting of 125 trains, 5 days/week, for ≥2 years	6 weeks, ASIA A	pQCT	31% higher distal tibia Trabecular BMD compared to untrained limb	Fair
Clark et al., 2007 ¹¹²	ES of quadriceps and dorsiflexors	30 Hz, (tetanic) stimulation: rest ratio 4:8 s, supine position, knee flexed at 20°	-	15 min sessions, twice daily, over a 5-day/week, for 5 months	3 weeks, C4-T10, (all with tetraplegia)	DXA	Different total body BMD at 3 months only	Fair
Shields and Dudley-Javoroski 2007 ¹⁰⁸	ES -isometric plantar flexion	0 to 200 mA at 400 V, 10-pulse train (15 Hz; 667ms) every 2s (125 trains in each stimulation bout)	Compressive loads equivalent to 110% of body weight	30 min/day, 5 days a week, for 6-11 months	>2 years ASIA A	DXA	No change in proximal tibia BMD	Fair
Frotzler et al., 2008 ¹¹⁵	FES-cycling	50 Hz, pulse width = up to 500 μs, current amplitude = 80-150 mA	-	58±5 min, 3.7±0.6 sessions/week for 12 months	11.0±7.1 years	pQCT	Increases in distal femoral epiphysis BMD are: 14.4±21.1% in trabecular BMD, 7.0±10.8% in total BMD and 1.2±1.5% in CSA	Fair
Griffin et al., 2009 ¹¹⁹	FES-cycling	50 HZ, up to 140 mA, 49 rpm	0.71-10.51 W	30 min, 2-3 times/week for 10 weeks	11±3.1 years, C4-T7	DXA	No difference in bone mass	Poor
Lai et al., 2010 ¹¹⁷	FES-cycling	20 Hz; 300 μsec, (electrodes at mid quads and hamstrings)	-	30 min, mean of 2.4 sessions/week, for 3 months	26-52 days, C5-T9	DXA	Decreased rate in distal femur BMD less in trained group (2.23% in trained; 6.65% in controls)	Fair
Dudley-Javoroski et al., 2012 ¹⁰⁹	Compressive loads applied during stance by quadriceps ES	60, 100-pulse trains (20 Hz, 200 μs, up to 200 mA), each train followed by 5 s rest	150% body weight (BW)	30 mins, 5 days a week for 3 years	0.19- 24.23 years, C5-T12	pQCT	BMD in limbs that received 40% BW and untrained was 61.1% of that of 150% BW limbs	Poor
Gibbons et al., 2014 ¹²⁹	FES-rowing (1 participant)	50 μsec pulse width, 50 Hz, up to 115 mA unramped stimulation.	-	30-45 mins, For > 8 years	13.5 years, T4	pQCT	PT trabecular BMD was higher in trained participant compared to SCI group but less than able-bodied.	Single case study
Gibbons et al., 2016 ¹¹⁶	FES-rowing	Lower limbs exposed to ~2700 loading cycles/week	-	3 times/week, 30-min rows at 30 strokes/min,	13.5 years, T4	HR-pQCT	Majority of tibial trabecular and cortical measurements were within ~1 s.d. but strength was lower.	Single case study
Johnston et al., 2016 ¹³¹	FES-cycling (compare low and high cadences)	250 μs, 33 Hz, and up to 140 mA	Low: 20 rpm, 2.9±2.8Nm, High: 50 rpm, 0.8±0.2 Nm	56 min, 3 times/week for 6 months	1-27.5 years, C4-T6	DXA and MRI (micro-structure)	Greater decreases in alkaline phosphate and N-telopeptide in low cadence	Fair

aspects of fragility fractures after SCI such as risk factors and fracture thresholds, is limited by the few studies addressing these issues. More studies should be carried out to obtain clarity which should result in the development of effective interventions.

Complications of fractures

About 50% of fractures in individuals with SCI are associated with clinical complications^{99,105} such as infections, pressure ulcers^{101,105}, delayed healing, autonomic dysreflexia, increased muscle spasticity and depression^{105,107}. Delayed union can lead to further surgical interventions and therefore prolonged hospitalisation and increased cost⁵⁷.

Effective interventions that target bone health and attenuate the rapid decline in bone microstructure and geometry should be incorporated into the patient's treatment plan as soon as they are clinically stable. However, there is currently no evidence that supports the effectiveness of any intervention in preventing fragility fractures.

Therapeutic Interventions targeting bone loss after SCI

Different physical and pharmacological interventions have been tested in patients to investigate their effectiveness in reversing or attenuating bone loss in the acute and chronic phases, respectively.

Interventions based on electrical stimulation (ES)

Different ES-induced interventions have been employed to improve muscle and bone health and attenuate their deterioration after SCI by eliciting muscle contractions and thereby restoring bone loading. Functional electrical stimulation (FES) techniques applied to the paralysed limbs of people with SCI use surface electrodes to either activate one muscle group to produce joint extension or flexion¹⁰⁸⁻¹¹², or induce co-ordinated contractions of two or more muscle groups to produce functional movements such as cycling and rowing¹¹³⁻¹¹⁷. While pronounced improvements in body composition^{118,119} muscle geometry^{114,115,120,121} and functional properties^{108,111,121-123} have been widely documented, the evidence for the efficacy of FES interventions in attenuating bone loss is equivocal.

Significant site-specific improvements in BMD (ranging between 7-30% increase in BMD) have been reported in some of these studies^{109-111,115-117} as shown in Figure 5. In contrast, others found no effect on BMD after undergoing 5-12 months of electrical stimulation-induced training^{108,112,113}. Table 1 provides a summary of all studies that used ES- interventions to attenuate the loss in BMD after SCI.

This discrepancy in the documented results of FES on bone health might be due to different factors related to the patient population, intervention protocols and the imaging modalities used to assess changes in bone¹²⁴. For example, a patient's postinjury duration and level of injury seem to influence

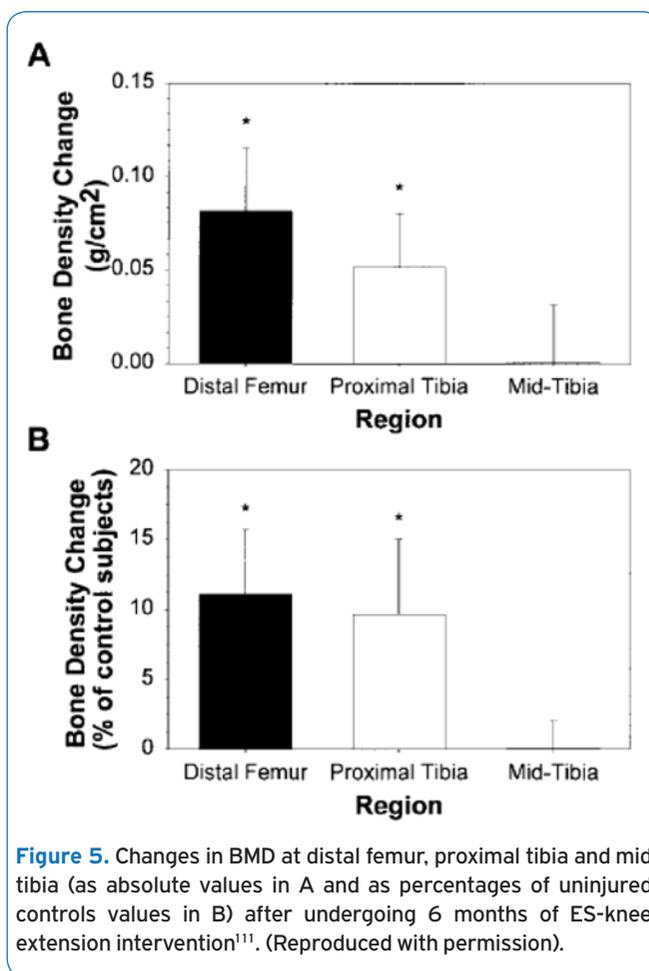


Figure 5. Changes in BMD at distal femur, proximal tibia and mid tibia (as absolute values in A and as percentages of uninjured controls values in B) after undergoing 6 months of ES-knee extension intervention¹¹¹. (Reproduced with permission).

intervention effectiveness considerably. Studies showed that starting FES interventions within the first few weeks (1-7 weeks) after SCI was effective in attenuating BMD decline in trabecular-rich regions of the femur and tibia^{117,122} but with no effect on cortical BMD¹¹³. Individuals with paraplegia seem to achieve greater FES-cycling power when compared with people with tetraplegia (22.5 W and 4.8 W, respectively)¹²⁵. This is likely due to the preserved control of their upper body which enables them to better coordinate movement with the pedalling action of the lower limbs and thereby delay fatigue in the leg muscles.

The magnitude of the elicited muscle forces and the session duration and frequency also influence the intervention results. This is probably because they determine the magnitude of the mechanical loads acting on bone which need to be large enough to exceed the remodelling threshold and induce bone formation¹²⁶. BMD has been reported to be significantly greater in patients who trained at higher cycling power (≥ 18 W)¹²⁵ or received larger compressive loads (150% body weight)¹⁰⁹, compared to that measured at the same sites in patients who trained at lower cycling power (≤ 12 W) and compressive loads (40% BW), respectively. Training paralysed muscles for at least 1 hour per day^{111,115},

for 5 days per week^{109-111,127} seems to be more effective in attenuating BMD loss compared to a training protocol of 30 min, or 3 days per week^{113,119,123,128}. Furthermore, significant improvements have been shown from training interventions that have lasted at least 6 months^{109-111,114,115,122,125,127,129} compared to those lasting less than 6 months and reported no change in bone mass^{119,123,128,130}. This suggests that bone's response to such interventions is highly dose-dependent.

The magnitude of muscle forces elicited by ES has not been reported in many of these studies^{112,115-117,127-129}. However, some studies measured indirect indicators of muscle force such as joint torques (40 Nm¹¹¹ and up to 3 Nm¹³¹) and applied loads as percentages of body weight^{108-110,122} (110%, 150%, 90-150% and 100-150% BW, respectively). These achieved loads are comparable to the compressive forces applied on the knees of uninjured individuals during daily activities such as stair descending (123.58% BW) and walking (101.03% BW)¹³². It has also been suggested that a minimum knee extensor torque of 50 Nm is required to achieve standing and walking using FES¹¹¹ and at least 35.3-49.2 N/kg muscle force of the knee and hip extensors is required to achieve a sit-to-stand movement¹³³.

Other studies reported the achieved cycling cadences^{123,131} (ranging between 20-60 rpm) and power^{119,125,130} (10-18.75 W) as an outcome measure. However, these are not accurate indicators of muscle force and thereby bone loading, because of the inverse relationship between force/load and contraction velocity in skeletal muscles. This concept is demonstrated by considering that high cycling power can be achieved by exerting low force at higher speed as well as by high force and lower speed^{109,110}. It is the latter form of high-power cycling (high force, combined with a low velocity) that has been shown to improve bone parameters most effectively in people with SCI¹³¹.

These different ways of measuring the outcome of the aforementioned interventions do not lend themselves well to quantitative comparisons, in terms of the muscle forces produced. Nevertheless, a qualitative comparison between different training approaches (cycling, rowing and resistance training) can be made. Whereas cycling requires stimulating the quadriceps, hamstrings, gluteal muscles and (in some studies) calf muscles, most of the resistance training studies targeted one muscle group such as the quadriceps^{109,111} or the soleus¹¹⁰. Stimulating one muscle group has been found to mitigate the loss in BMD asymmetrically, on one side/half (posterior) of the lower limb long bones^{134,135}. Accordingly, it might be speculated that stimulating the antagonist muscle pairs could have a more homogenous effect on BMD throughout the different areas of the bone.

The imaging modalities used to evaluate the effectiveness of FES interventions are another important methodological consideration. DXA does not distinguish between trabecular and cortical bone and thereby is not able to detect early potential changes in response to training, which are known to occur more rapidly in trabecular than in the cortical compartments¹¹⁵. This is illustrated in Figure 6, which shows the effect of training on femur trabecular bone using CT²⁰,

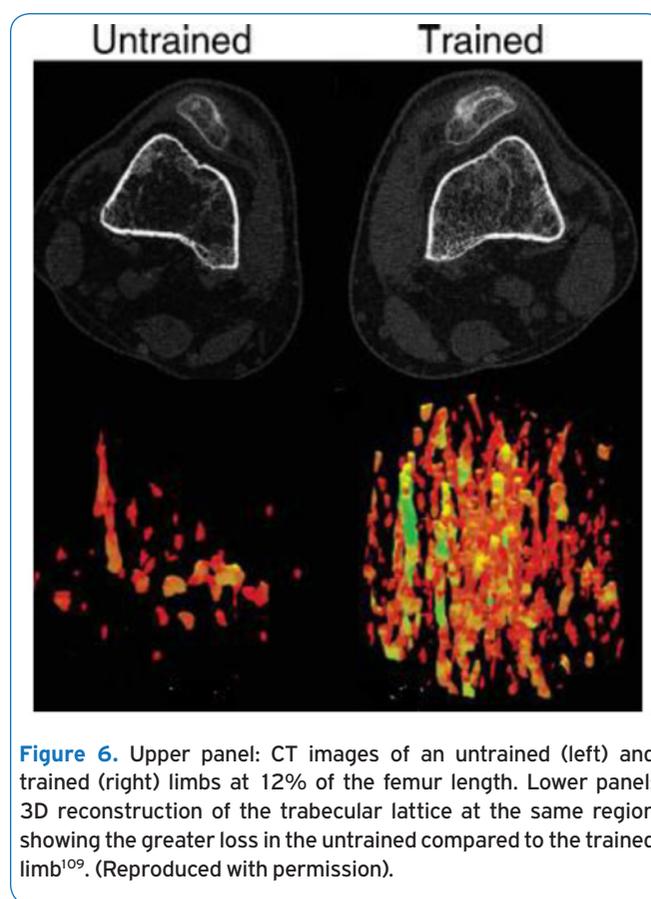


Figure 6. Upper panel: CT images of an untrained (left) and trained (right) limbs at 12% of the femur length. Lower panel: 3D reconstruction of the trabecular lattice at the same region showing the greater loss in the untrained compared to the trained limb¹⁰⁹. (Reproduced with permission).

with no apparent differences in the cortical shell. Moreover, DXA does not typically provide site-specific scans for regions such as distal femur and proximal tibia which are of clinical interest and are likely to be stressed by cycling exercise.

Only one study estimated the effect of ES-training on bone strength¹¹⁶, reporting increases in multiple trabecular and cortical parameters after ES-rowing intervention. However, bone strength (which was estimated using computational modelling from biomechanical indices such as stiffness (-3 SD) and predicted failure load (-3.5 SD)) was lower than non-SCI controls; this was proposed to be related to the larger percentage cortical porosity (+4.6 SD) and mean pore diameter (+3.7 SD)¹¹⁶. More studies are required to investigate the effect of ES-interventions on bone strength alongside structural and geometric parameters (as no effect was found in the latter in one study¹¹⁴) to assess their effectiveness in preventing fragility fractures.

Different forms of ES-interventions seem to partially reverse BMD when applied intensively over the long-term in people with chronic SCI. However, these improvements have not been shown to lead to fracture risk reduction (which would be considered the desired and clinically relevant outcome). The biomechanical loads/forces elicited by these interventions should be measured and further tested to find out how could they be delivered effectively and safely. Ideally,

the ES-interventions would mimic the voluntary muscle loading exerted by able-bodied individuals during daily activities. Additional research is also needed to determine whether it is possible to identify a 'loading dose threshold' above which fracture risk could be significantly minimised.

Other physical interventions

Weight bearing

Other forms of physical training interventions include weight-bearing activities such as standing and walking, which aim to load the lower limb bones through axial compression, bending and torsional stresses that would normally act on the lower extremities during standing and ambulation.

Most of the reviewed studies (11 out of 16 studies) based on conventional standing training (using standing frames, wheelchairs and leg braces)^{64,87,136-139}, exoskeletons¹⁴⁰⁻¹⁴³ or treadmill walking^{144,145} did not show improvements in BMD, either during the acute phase^{137,139,144} or during the chronic phase^{64,87,136,138,140,141,145}. Only four studies showed positive results in bone parameters by preventing bone loss in the acute to sub-acute phase (standing and treadmill walking)¹⁴⁶ and increasing BMD in the chronic phase (treadmill training)¹⁴⁷ (passive standing)^{148,149}. The participants recruited were full-time wheelchair users with complete SCI in some of these studies^{136,139-142,148,149}, or had incomplete injuries (or a mixture of both) in other studies^{64,87,137,138,144-147}. Only three studies reported that the recruited participants were already physically active before their recruitment^{144,147,149}. Two of these studies reported a positive impact of the intervention on BMD^{147,149}, which suggests that being active might have improved their muscle health and attenuated their atrophy which in turn optimised their force production and subsequently their impact on bone stimulation.

These improvements range from 7-9% larger BMD at different sites in the lower limbs in standing groups compared to controls. However, one of these studies was a single case study recruiting a subject with motor-incomplete SCI (achieving a 20% increase in tibial trabecular BMD)¹⁴⁷, which in itself is known to lead to less bone loss than complete SCI^{86,95}. Goemaere et al reported an improvement in femoral shaft BMD but not in the proximal femur¹⁴⁹. These results were explained by a possible difference between cortical and trabecular bone in the minimal effective strain for initiating bone remodelling (being reached more rapidly in cortical bone)¹⁴⁹, although recent evidence suggests that there are regional variations (regardless of bone type) in strain thresholds within the same bone¹⁵⁰. In this study, however, the effect of standing was not investigated at the sites that are known to be most prone to fragility fractures in people with SCI (distal femur, proximal tibia and distal tibia). The last study reported attenuation of bone loss based on bone formation and resorption biomarkers but BMD results did not always match the biomarker results¹⁵¹.

To summarise, to achieve significant improvements in BMD in the lower limbs from standing and walking, long-term training sessions should start within the first few weeks after

the injury onset^{146,148}. Combining ES with weight bearing activities may have a greater positive effect on bone than performing these activities on their own¹⁴⁷. While the duration of the ES-training has been shown to have an impact on BMD¹⁵², standing for different durations (<1 hour, 1 hour and >1 hour)^{64,138} and frequencies (daily standing versus standing for 3 times/week)¹⁴⁹ seems to have no significant effect on BMD. This might indicate that the compression stresses produced during standing alone are insufficient to stimulate lower limb bones even when applied for longer durations.

Similarly, bone stresses delivered through treadmill walking seem to be insufficient to induce adequate bone stimulation. This is, likely because of partial bodyweight support and low treadmill speeds used compared to normal walking speed¹⁴⁴, which would result in lower bone strains¹⁵³. It should also be noted that the atrophied muscles of patients with SCI would produce smaller bone strains when contracting which would make them less effective in inducing osteogenic effects in the bones of the paralysed limbs¹⁴². Again, as seen with FES interventions, the dosage of the mechanical loading acting on bone that is required to attenuate or reverse bone loss effectively is yet to be ascertained¹⁵⁴.

Additional studies are also needed to determine whether partial body-weight supported treadmill training and other gait rehabilitation orthoses are more effective in terms of bone stimulation than conventional training¹⁴⁴ and whether they could be used safely for long term intervention, as home-based rehabilitation devices¹⁴¹.

Ultrasound

As high-frequency mechanical waves, ultrasound was thought to be a potential technique to stimulate bones with mechanical signals. This concept is based on results of a number of *in-vitro* trials where low-intensity pulsed ultrasound has been reported to induce osteogenic responses^{155,156}. However, in the published literature there is only one study that investigated its effect on bone health in people with SCI. The study found no significant effect of applying pulsed ultrasound for 6 weeks on calcaneal bone loss¹⁵⁷, although the short trial duration likely limited the relevance of the study. Further investigation should be carried out to study the effects of varying ultrasound parameters, as well as, the intervention duration and frequency on its effectiveness in treating bone loss after SCI.

Whole Body Vibration

Whole body Vibration systems have been used in people with SCI to deliver vertical or side-alternating oscillations throughout the long bones using a vibrating plate upon which the feet are situated, either while the participant is sitting¹⁵⁸ or passively standing¹⁵⁹. In the former, the limb is fixed using external compressive loads (35% BW) in order to optimise the transmission and effectiveness of the vibrations¹⁵⁸. It has been reported that neither 6 months¹⁵⁹ nor 12 months¹⁵⁸ of applying whole body vibration combined with weight-bearing activities has induced any improvements in BMD

Table 2. Summary of studies that used other physical interventions (without electrical stimulation) to attenuate the loss in BMD after SCI.

Study	Training modality	Produced Stress/power	Training duration/frequency	Injury duration and level	Imaging modality	Changes in bone parameters	Level of evidence
Biering-Sørensen et al., 1988 ⁸⁷	Standing or walking using long leg braces	-	For at least 1 hour daily	2-25 years, C7-L3	DXA	No effect on BMC	-
Kunkel et al., 1993 ¹³⁶	Standing in frame	-	45 min/twice daily for 5 months (144 h over 135 days)	10-39 years, C6-T12, (4 SCI, 2 multiple sclerosis patients)	DXA	No change in BMD	Fair
Goemaere et al., 1994 ¹⁴⁹	Passive Standing using: 1. long leg braces, 2. standing frames, 3. standing wheelchairs)	-	Daily standing for 1 hour in 1 group and 3 times/week in the second group	12-118 months. Complete paraplegia	DXA	BMD better at femoral shaft but not proximal femur compared to non-standing	Fair
Thoumie et al., 1995 ¹⁴¹	Gait rehabilitation with hybrid orthosis	-	2 hours, 3 times/week, for 16 months	15-60 months, T2-T10	DXA	Significant decrease in BMD at femoral neck and no change at lumbar spine	Poor
Needham-Shropshire et al., 1997 ^{142,143}	Standing and walking using a device that combined ES and a modified walker	-	3 times/week, 12-20 weeks, (mean of 143.6±86.4 mins per session)	At least 6 months, T4-T11	DXA	No significant change in BMD at FN, neck, and Ward's triangle	Fair
de Bruin et al., 1999 ¹⁴⁶	Standing and treadmill walking	Treadmill speed= 1.3 km/h	30min standing, 30 min walking, 5 days/week for 6 months	1-4 weeks, C4-L1	pQCT	Almost no loss in tibia trabecular BMD in trained group compared to -6.9% to -9.4% loss in trabecular bone	Fair
Dauty et al., 2000 ⁶⁴	Passive standing	-	Daily for: 1. less than 1 h, 2. 1 h, 3. More than 1h	68.3±74.7 months	DXA	No effect on BMC	-
Frey-Rindova et al., 2000 ¹³⁷	Standing using frame (for complete SCI) and treadmill walking (for incomplete SCI)	-	At least 30min, 3 times/week for 2 and half years (treadmill speed 1.3 km/h)	1-4 weeks	pQCT	No effect on BMD	-
Warden et al., 2001 ¹⁵⁷	Pulsed US	-	20 min, 5 days/week for 6 weeks US settings: 10 µsec 1.0 MHz sine waves, 3.3 kHz	1-6 months, C5-T10	DXA	No effect on calcaneal bone parameters	Fair
Ben et al., 2005 ¹³⁹	Standing on 1 leg (on tilt table)	17 Nm dorsiflexion torque	30 min, 3 times/week, for 12 weeks	4±2 months	DXA	Little or no effect on femur BMD	Good
Giangregorio et al., 2005 ¹⁴⁴	Body weight supported treadmill	-	Less than 1hour, 2 times/week (48 sessions in 8 months) (speed= 0.7-2 km/h)	2-6 months, C3-C8	DXA and CT	No effect on BMD (proximal and distal femur, PT, spine) or CSA (mid-femur, PT)	Poor

Table 2. (Cont. from previous page).

Study	Training modality	Produced Stress/power	Training duration/frequency	Injury duration and level	Imaging modality	Changes in bone parameters	Level of evidence
Carvalho et al., 2006 ¹⁵¹	Treadmill gait training	30-50% BW supported	20 min, 2 times/week for 6 months	25-180 months, C4-C8	DXA	Most of the participants showed increased bone formation and decreased bone resorption (BMD results did not always match biomarkers results)	Poor
Giangregorio et al., 2006 ¹⁴⁵	Body weight supported treadmill	-	3 times/week, For 12 months (144 sessions)	1-24 years (all Incomplete)	DXA and CT	No effect on BMD (at proximal and distal femur, PT, spine) or CSA (mid-femur, PT)	Poor
Alekna et al., 2008 ¹⁴⁸	Passive standing in frame	-	For at least 1 hour/day, no less than 5 days/week	8-12 weeks, C2-L1	DXA	Higher BMD in lower limbs after 2 years in standing group (1.018 compared to 0.91 g/cm ²)	Fair
Goktepe et al., 2008 ¹³⁸	Any form of Standing: 1. More than 1hour, 2. Less than 1hour, 3. No standing	-	Daily standing	At least 1 year, ASIA A, B	DXA	No significant difference between groups in BMD at PT and lumbar spine	Fair
Coupaud et al., 2009 ¹⁴⁷	Partial body-weight supported treadmill training (BWSTT) + FES on one side (bisphosphonate + Vitamin D prescribed independently)	30% BW support -Speed increased from 0.1 m/s to 0.3 m/s	Muscle conditioning over 2 months Target increased for 15 min to 30 min, 3 time/week for 5 months. FES: 40Hz, 40mA, and 117-351µs	14.5 years, T6 (incomplete) (one subject)	pQCT	Increase of 5% (right) and 20% (left) in DT trabecular BMD. Changes are negligible in PT and DF	Single case study
Davis et al., 2010 ¹⁶⁰	3 phases of training: 1. standing only, 2. partial standing/WBV (foot only on plate), 3. standing with vibration	-	1. Phase 1: 40 min, 3 times/week, for 10 weeks, 2. Phase2: 20/20 mins, 3 times/week, 3. Phase3: 7 mins/session, 3 times/week	4 years, T10 (incomplete), (single case)	DXA	Improvement in BMD in the trunk and spine after phase 3 only. No effect on legs	Single case study
Wuermser et al., 2015 ¹⁵⁹	Low-magnitude whole body Vibration+ passive standing	About 76-86% BW	20 mins, 5 days/week, for 6 months (0.3 g, 34 Hz, 50 µm.)	2-27 years, T3-T12	DXA and HR-pQCT	No effect on BMD at PF or microstructure at DT	Fair
Dudley-Javoroski et al., 2016 ¹⁵⁸	Body Vibration	35% BW applied during the vibration training	3 times/week, for 12 months Vibration parameters: 0.6g, 30 Hz, 20 min, three times weekly)	0.1 to 29.2 years, C7-T4	pQCT	No effect on trabecular microstructure or BMD at DT and DF	Fair
Karelis et al., 2017 ¹⁴⁰	Walking with a robotic exoskeleton	-	Up to 60 min, 3 times/week for 6 weeks Mean standing time/session: 48.4 min, walking time: 27.0 min	7.6 ± 4.6 years, C7-T10	DXA	No significant change in BMD	Fair

or microstructure of the lower extremities. Only one study reported an improvement from whole body vibration (when combined with standing) in BMD (using DXA) in the spine (8.3%) and trunk (5.5%), but not in the lower extremities¹⁶⁰.

Whole body vibration has been incorporated into the rehabilitation programmes of some patients with SCI very recently, but the number of studies that have investigated its effect on bone health is very limited. A summary of the studies that investigated the effect of weight bearing exercises, ultrasound and whole-body vibration on BMD after SCI, can be found in Table 2.

To summarise, most of the physical interventions had limited effects on bone health. This may be related to an inability of current methods to develop or safely apply large internal muscle forces or external forces to bone. For those with chronic SCI, treatments aimed at reversing osteoporosis should be considered, but are less likely to be effective in restoring BMD values to within the normal range¹⁵². This has been proposed to be due to the weaker bone losing its ability to adapt to applied strains¹⁰⁸ which might be due to the cellular accommodation phenomenon¹⁶¹ or osteocyte apoptosis¹⁶². Moreover, patellar tendon stiffness was found to be reduced by up to 77% in people with chronic SCI compared to uninjured controls¹⁶³. This would make force transmission from muscles to bones through tendons more difficult and less efficient¹⁶³.

Pharmacological interventions (Bisphosphonates)

A wide range of pharmacological treatments for osteoporosis are currently available, such as strontium ranelate¹⁶⁴, denosumab¹⁶⁵, selective oestrogen receptor modulator drugs¹⁶⁶ and bisphosphonates. The latter are the most commonly prescribed treatments for osteoporosis in women¹⁶⁷⁻¹⁶⁹ and men^{170,171}, and have been found to be effective in attenuating bone resorption, restoring BMD and preventing fractures¹⁷².

Bisphosphonates are anti-resorptive agents that reduce the bone resorption rate by targeting osteoclasts, inhibiting their activity and subsequently reducing their number in the long term¹⁷³. They are administered either orally on a daily or weekly basis¹⁷⁴ or as an annual single^{67,175} or multiple (every month or 3 months)^{176,177} intravenous injection. Patients taking bisphosphonates on a weekly basis have been found to be more compliant and to persist with the treatment compared to those who take a daily dose¹⁷⁴.

However, bisphosphonates studies conducted in patients with acute SCI showed mixed results, with 5 out of 9 studies reporting positive effects. Alendronate (weekly for 12 months) has been found to preserve total body and leg BMD¹⁷⁸. Intravenous bisphosphonates such as zoledronate and pamidronate have been shown to have positive effects on BMD in the lower limbs¹⁷⁷, hip and spine^{67,179}. One study reported little effect of disodium dichloromethylene diphosphonate on BMD at the distal tibia¹⁸⁰.

These agents resulted in a lower limb BMD that was 7-17% higher compared to untreated controls. However, it should be

pointed out here that in three of these studies, about one third of the participants were classified as having an incomplete SCI (with good preservation of motor function) and were not full time wheelchair users¹⁷⁷⁻¹⁷⁹. With only two studies reporting positive results in participants with complete SCI^{67,180}; one reported only a marginal effect on BMC at the distal tibia (7%)¹⁸⁰ while the other reported about 12% greater BMD at the hip⁶⁷. The reduction in bone loss in the acute phase after pamidronate and zoledronate administration (administered once a year) has been reported in some studies to be temporary, lasting 6 months (after the annually administered dose)¹⁷⁵ although the treatment was not discontinued in one study¹⁷⁶. This might indicate that the dose or the frequency of administration could be further investigated to prolong their effect. Another study reported no effect of the treatment at the knee which might suggest that such treatment is effective in attenuating cortical but not trabecular bone loss¹⁷³.

Based on the results reported in these studies, there is little current evidence that supports the effectiveness of bisphosphonates in attenuating/preventing bone loss in the acute phase of complete SCI at the lower extremities. It was apparent that most studies did not investigate the effect of these treatments in the sites that are most prone to fracture, in part because these sites were only identified relatively recently. However, a number of these studies have been carried out since the fracture-prone sites after SCI were identified and published^{15,55,181} and so, this is unlikely to explain all the lack of relevant evidence for the effectiveness of pharmacological intervention to treat bone loss after SCI. Furthermore, these findings are possibly due (in part) to the measurement technique used and the lack of studies that investigated these sites using a 3D imaging technique (e.g. pQCT). Positive changes might have been achieved in the trabecular bone (which responds to interventions faster than cortical bone), but it was not possible to observe it with DXA imaging.

Fewer studies investigated the use of bisphosphonates in the chronic phase of SCI^{173,182,183} and one study included a mixed patient group with acute and chronic SCI¹⁸⁴. The effects of alendronate on leg BMD seem to be influenced by treatment duration. A daily dosage of alendronate administered orally had no effect on lower limb BMD¹⁷¹ over 6 months, but it attenuated bone loss by 9%¹⁸⁴ when administered for 2 years.

As one of the only two studies that reported significant effects of bisphosphonates in the chronic phase, was a single case study of a patient with incomplete SCI¹⁸², it can be concluded that there is no sufficient data to assess their effectiveness for osteoporosis in chronic SCI. It is clear that the positive effect of bisphosphonates on BMD in the chronic phase of SCI is limited when used as the only intervention. Furthermore, and crucially, it does not exceed keeping BMD within its current level without restoring what has been lost, which could be less effective in the chronic phase (after reaching steady state) compared to the acute phase

A number of issues can be highlighted after reviewing the use of bisphosphonates in people with SCI. Firstly,

Table 3. Summary of studies that used pharmacological treatments to attenuate the loss in BMD after SCI.

Study	Treatment	Injury duration and level	Dose, Duration & frequency	Imaging device	Changes in BMD	Supplements	Level of evidence
Minaire et al., 1981 ¹⁸⁰	disodium dichloromethylene diphosphonate	Acute SCI, T1-T12, (all with complete paraplegia)	400 or 1600 mg/day for 3.5 months	Photon absorptiometry	Little effect in BMC at distal tibia (for 400 mg)	-	Fair
Pearson et al., 1997 ¹⁸⁷	Cyclical Etidronate	Within 6 weeks, C5-T12	Orally 800mg/day for 2 weeks, this was repeated after 13 weeks	DXA	BMD maintained only in ambulatory treated patients	-	Poor
Nance et al., 1999 ¹⁷⁷	Intravenous Pamidronate	6 weeks, C4-T12	30-mg infusion/month for 6 months	DXA	Greater BMD at hip, femoral and tibial diaphyses, femoral and tibial epiphyses (less bone loss in ambulatory)	Calcium: 1000 mg daily	Poor
Sniger and Garshick, 2002 ¹⁸²	Alendronate	27 years, C4 (incomplete), (single case)	Daily: 1. Alendronate: 10mg, 2. Vitamin D: 400mg, 3. Calcium carbonate 500mg, daily for 2 years	DXA	Increased BMD at spine and lower legs	Vitamin D: 400 mg/d Calcium carbonate: 500 mg/d	Single case study
Zehnder et al., 2004 ¹⁸⁴	Alendronate	0.1-29.5 years, T1-L3, (all with complete SCI)	10mg + 500 mg calcium daily for 24 months	DXA	BMD at distal tibia, tibial diaphysis and total hip remained stable compared to control group	Elemental calcium: 500g/d	Fair
Bauman et al., 2005 ¹⁷⁶	Intravenous Pamidronate	22 to 65 days, ASIA A, Acute SCI	60 mg given at 1, 2, 3, 6, 9, 12 months	DXA	No changes in long term (12, 18,24 months) although reported early (1,3,6 months) reduction in bone loss in total leg BMD	Calcium: at least 700 mg/d in diet	Fair
de Brito et al., 2005 ¹⁷³	Alendronate	13.1-255.7 months, ASIA A, B, C	10 mg (+1000 mg Calcium), daily for 6 months	DXA	General increase in BMD	Calcium: 1000 mg/d	Fair
Mechanick et al., 2006 ¹⁸⁶	Intravenous Pamidronate	Acute SCI, AIS A, B, C	90 mg over 4 hours (single dose)	-	Reduced bone resorption biomarkers, BMD not tested	-Calcium: 1,000 mg daily, -Calcitriol: 0.25 µg daily	-
Gilchrist et al., 2007 ¹⁷⁸	Alendronate	Within 10 days, C4-L2	70 mg once weekly, for 12 months	DXA	Total and hip BMD was 5.3% and 17% greater in intervention group respectively. Effects sustained for more 6 months after treatment discontinued	-	Fair
Shapiro et al., 2007 ¹⁷⁵	Intravenous Zoledronate	10-12 weeks, C2 to T12	4 or 5 mg (administered once)	DXA	BMD and CSA increased at proximal femur only at 6 months, and for 12 months at the femoral shaft	Calcium: 800 mg, Vitamin D: 800 IU (both from diet)	Fair
Bubbear et al., 2011 ¹⁷⁹	Intravenous Zoledronate	Within 3 months, C4-L3	4 mg (administered once)	DXA	Higher BMD at total hip (12.4%) trochanter (13.4%), and lumbar spine (2.7%) up to 12 months	-	Fair
Bauman et al., 2015 ⁶⁷	Intravenous Zoledronate	Within 3 months ASI A, B (all with complete SCI)	5 mg (administered once)	DXA	Reduction of BMD loss at the hip but not at the knee	Calcium carbonate: 1250 mg/d Vitamin D: only for participants with levels <20 ng/ml	Poor
Haider et al., 2019 ¹⁸⁵	Teriparatide (in previous study) followed by oral alendronate	15±9 years, ASI A, B, C (C1-L5)	Teriparatide: 12-24 months Alendronate: 70 mg once weekly for 12 months	DXA	Significant increase in aBMD at the spine 2.5% and in BMC at femoral epiphysis, metaphysis, and diaphysis, 15%, 7.7%, 3.0%, respectively, - no clear results at the tibia	Vitamin D (cholecalciferol 1000 IU) daily -calcium carbonate: 1000 mg daily	Fair
Gifre et al., 2016 ¹⁹¹	Denosumab	15±4 months, C4-T8 (ASIA 12A, 1B, 1C)	60 mg every 6 months for up to 12 months	DXA	Increases in lumbar (8%) and femoral BMD (3%)	Calcium and Vitamin D	Fair

most of these studies tested these treatments in patients with different ambulatory capabilities and injury severity^{173,177-179,185-187}. Some of these studies showed more pronounced improvements in ambulatory compared to non-ambulatory participants^{177,187}. Despite the fact that there appear to be comparable numbers of studies with mixed and complete SCI that reported positive results of pharmacological interventions (4 studies with mixed group (complete and incomplete SCI) and 3 studies of complete SCI only), testing these agents on only non-ambulatory patients with complete SCI would give a clearer indication of their effectiveness in restoring BMD and preventing fractures^{67,188}. As a minimum, where mixed patient groups are used, completeness of injury should be included in the data analysis and reporting of findings.

Secondly, very few studies investigated the effect of these treatments on BMD at the sites that are most susceptible to fracture in people with SCI^{67,180,184}, such as the distal femur and proximal and distal tibia⁵⁷. Furthermore, the use of pQCT (instead of DXA) could provide more quantitative insights into whether cortical bone and trabecular bone respond to such agents to similar or different extents.

Although these studies reported no^{173,178} or only acute mild side effects^{179,186}, osteonecrosis of the jaws¹⁸⁹ and spontaneous fractures¹⁹⁰ are considered as rare side effects of using oral bisphosphonates in osteoporotic patients. Other clinical treatments have therefore been suggested to be tested on people with SCI such as the anti-resorptive denosumab and anabolic therapies such as sclerostin antibodies⁶⁷. Gifre et al reported an increase in lumbar and femoral BMD (8% and 3% BMD respectively) after administering Denosumab in people with acute SCI for 12 months¹⁹¹. This was the only study testing Denosumab in people with SCI. Table 3 provides a summary of all studies that used pharmacological treatments to attenuate the loss in BMD after SCI.

Combination treatment interventions

Despite the reported mitigated bone resorption in the acute phase^{67,177,178} and the stabilised BMD in the chronic phase^{183,184} in many of these studies, no increase in BMD has been reported, indicating a need for an intervention with an anabolic effect that can be combined (or used sequentially) with anti-resorptive agents to boost their effect^{183,192}. The additive effect of anti-resorptive medications combined with the anabolic stimulus of physical activity may explain results from a number of bisphosphonate studies reporting more pronounced improvements in BMD in ambulatory individuals than in full time wheelchair users^{177,187}. Furthermore, combining exercises with anti-resorptive therapies has been reported to have a greater effect on BMD compared to using antiresorptives alone in different models of osteoporosis^{193,194} but the number of studies examining such approaches is small¹⁹⁵.

Remembering the significant role of mechanical stresses in preserving/losing BMD might suggest that bisphosphonates should be accompanied by physical training in order to achieve

optimum benefits in people with SCI¹⁹⁶. Hypothetically, by combining these interventions, the anti-resorptive agent would target the inhibition of osteoclastic activity, while the skeletal loading could have a role in stimulating osteoblasts, thus mitigating the imbalance between bone formation and resorption caused by the SCI. In a recent study, significant increases in geometric cortical bone parameters (cortical bone volume, cortical thickness index, and buckling ratio) were reported at the distal femur and proximal tibia in the group that had FES-rowing training combined with zoledronate administration compared to the group that performed FES-rowing alone¹⁹⁷. This is clinically-relevant as reductions in these geometric cortical bone parameters after SCI are thought to be associated with osteoporotic fractures in this patient group¹⁹⁷.

The anabolic parathyroid hormone teriparatide has been also investigated in combination with gait training¹⁹², with vibration¹⁹⁸ and following 12 months of bisphosphonates treatment¹⁸⁵. The first study reported no effect on BMD (i.e. with gait training)¹⁹². The second study reported that the combination of vibration with teriparatide did not augment its effect on BMD¹⁹⁸, while in the latter (involving combination with bisphosphonates), an increase in BMC ranging between 3-15% was reported in different parts of the femur¹⁸⁵. Studies that tested these combined treatments in people with SCI are summarised in Table 4.

Levels of evidence

After reviewing all available interventions aiming to mitigate bone loss in people with SCI, the quality of these studies was assessed. Only studies that investigated BMD as their primary outcome were included in this assessment, due to the well-documented link between BMD and fracture incidence in people with SCI^{6,15}. Furthermore, it is the most commonly measured bone parameter among all studies in the SCI population.

The levels of evidence were assessed following the approach described by Bryson et al., 2009¹⁸⁸ which was based on the Delphi list 9 items. Each of these items (listed in Tables 5,6,7 (provided in Online Resource 1)) was given a subscore of either 1 (not reported), 2 (fair) or 3 (good), except for the randomisation item which was given a score of 0 (if the study was not randomised). Items 5,6,7 were all merged together under one category due to the small numbers of studies that reported blinding of the patient (which was difficult to achieve especially for physical interventions), assessor or the caregiver. All subscores were summed to determine the overall quality rating (poor, fair, good).

All the reviewed studies were either of a poor or fair quality except one study that tested the effect of standing and was of a good quality¹³⁹. For both the ES and the pharmacological interventions studies, 30% were of poor quality while about 70% were of fair quality. Other physical interventions (such as weight bearing) studies showed comparable levels of evidence with 25% poor, 67% fair and 8% good quality. The

Table 4. Summary of studies that used physical interventions combined with pharmacological treatments to attenuate the loss in BMD after SCI.

Study	Intervention	Protocol	Physical Training parameters	Injury duration and level	Imaging device	Changes in BMD	Level of evidence
Gordon et al., 2013 ¹⁹²	Parathyroid hormone and gait training	20 µg/day and robotic-assisted stepping for 6 months, followed by 6 months of teriparatide alone	40 minutes/session, 3 times/week, at speed 2.0-2.5 km/h, <50% BW support	>1 year, C1-T10	DXA (hip and spine) and MRI (microarchitecture of distal tibia)	No change in spine and total hip BMD. Positive anabolic effect significant at 3 but not 6 months	Fair
Edwards et al., 2018 ¹⁹⁸	3 groups: 1. Teriparatide + sham vibration, 2. placebo + vibration, 3. Teriparatide + vibration	Teriparatide: 20 µg/d Vibration: 10 min/d -Additional 12 months of Teriparatide treatment	Vibration: 30 Hz, acceleration amplitude = 0.5 g	19±13.8 years, ASIA A, B, C, D	DXA and CT	Increase in groups that used teriparatide: 4.8% - 5.5% increase in spine BMD -Vibration did not augment teriparatide effect. -Small increase in knee cortical bone in all groups. - the additional 12 months of Teriparatide resulted in 7.1-14.4% increase from baseline)	Good
Morse et al., 2019 ¹⁹⁷	Intravenous Zoledronate and FES-Row	12-month FES-rowing program and single dose of zoledronate	30 min, 3 days/week at an intensity of 75% to 85% of peak heart rate	0.4-37.9 years, 75% had a motor-complete injury	DXA for BMD, QCT	Greater cortical bone volume, cortical thickness index and buckling ratio at proximal tibia and distal femur metaphysis	Fair

quality of most of physical interventions studies were found to be limited by the absence of randomisation and blinding which were difficult to achieve due to ethical and practical reasons, respectively. Also, many studies were not controlled, comparing baseline with post-intervention measures, making item 2 (allocation concealment) and item 9 (intention-to-treat analysis) not applicable.

Conclusions

To summarise, this review article has discussed the aetiology, development and consequences of bone loss in people with SCI. Furthermore, the most commonly used imaging modalities to assess bone loss after SCI and available therapeutic approaches have been evaluated.

It is clear that bone loss that develops in the paralysed limbs after SCI is highly site-specific, progressing with different patterns and timelines in cortical and trabecular bone compartments. In addition, rates of bone loss differ substantially between individuals but to date there is little understanding of the mechanisms responsible for this variation. Most of the physical and pharmacological interventions developed and evaluated to date appear to have a limited effect on bone health, but the poor quality of published studies in this area limits our ability to draw

clear conclusions. More high-quality observational and interventional studies, with appropriate outcome measures targeting fracture-prone site, are needed.

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