Clinical Reviews in Bone and Mineral Metabolism (2019) 17:94–108
https://doi.org/10.1007/s12018-019-09265-z

TREATING BONE LOSS IN CHALLENGING SITUATIONS

Osteoporosis in Veterans with Spinal Cord Injury: an Overview of Pathophysiology, Diagnosis, and Treatments

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Published online: 2 August 2019

Abstract

Immediately after spinal cord injury (SCI), approximately 75% of patients suffer rapid and severe loss of bone mineral density (BMD) below the lesion level (i.e., sublesional), leading to osteoporosis (OP) in ~ 60% 1-year post-injury. The distal femur (DF) and proximal tibia (PT) are most commonly involved, and 70% of SCI patients sustain a low impact fracture at some point in their lifetime, adding disability to an already physically challenged population. Unfortunately, OP treatments for post-menopausal women are not as effective for OP post-SCI. Mechanisms of new agents targeting the neurogenic etiology of bone resorption (i.e., denosumab and anti-sclerostin antibodies) may hold greater potential and are discussed. Furthermore, standardized DXA protocols with normative BMD values for the DF and PT sites have not been established, so diagnosing OP is problematic. This review will summarize the pathophysiology of sublesional OP after SCI, the unique challenges of diagnosing and managing OP in SCI patients and provide recommendations for future studies. Given the Veterans Health Administration (VA) is the largest health care system in the world for persons with SCI, it is well-equipped to add to gaps in the literature.

Keywords Spinal cord injury · Neurogenic osteoporosis · Dual energy x-ray absorptiometry · Bone mineral density · Fractures

Introduction

Spinal cord injury (SCI) results in varying degrees of impairment of sensation, motor control, and autonomic function. Seventy-eight percent of SCI patients are male and about 30% endure motor complete injuries, with complete loss of sensation and motor function below the level of injury. Motor complete injuries are classified as the highest level of functional impairment [1]. SCI occurs in 17,500 individuals per year in the USA and affects 12 to 57.8 per 1 million people worldwide [1, 2]. The United States Veterans Health Administration (VA) provides primary and chronic care to over 27,000 SCI patients and is the largest health care system in the world providing lifelong care to these patients. The VA Spinal Cord Injury/Disorders system of care consists of 24 centers of excellence, or "hubs," that provide support and guidance to "spokes." Medical care for the SCI population is improving and as such, life expectancy of this population is slowly approaching that of persons without SCI [3]. Primary providers within the VA manage long-term sequela of SCI and are often faced with treating secondary conditions associated with prolonged survival. Loss of bone mineral density (BMD) after SCI is a common secondary sequela that occurs in about 75% of persons with motor complete injuries. Unlike trabecular bone loss in the spine and proximal femur in post-menopausal women, trabecular bone loss after SCI is limited to bones below the neurological level of injury, or "sublesional" areas. Most notably, the bone loss is seen at peri-knee regions of the distal femur (DF) and proximal tibia (PT) [4]. Bone resorption begins immediately after SCI and is most rapid and severe within the first 3–6 months but continues for 3–8 years post-SCI eventually culminating in $\geq$ 50% loss of BMD and fractures at the DF and PT sites [5], increasing morbidity in this functionally disabled population [6, 7]. Managing bone loss and sequela is an integral component of practice for VA clinicians who provide care for SCI patients.

Rapid and severe loss of BMD after SCI was initially described as "immobilization osteoporosis" suggesting that the primary cause was the decrease in mechanical stress on the bone. However, emerging evidence suggests that denervation and vascular changes due to a decentralized sympathetic

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nervous system, and hormonal aberrations are also implicated. Loss of mechanical loading or immobilization alone cannot explain the sublesional osteoporosis following SCI [8–11].

. The purpose of this article is to review the pathophysiology of BMD loss in the acute (< 1-year post-SCI) and chronic (> 1-year post-SCI) stages, diagnostic imaging techniques, therapies, and future directions.

Loss of Bone Mineral Density Within 1-Year Post-SCI

Immediately after SCI, there is a rapid decline in BMD of 1% per week (for months) due to increased osteoclastic activity of bone resorption coupled with decreased osteoblast activity/impaired bone formation [6, 12, 13]. In contrast to global bone loss seen in post-menopausal women or non-paralyzed immobilized individuals, bone loss due to SCI primarily affects bone below the level of SCI. Sublesional bone loss occurs most rapidly in the tibia (proximal tibial epiphysis > diaphysis), femur (distal femur > proximal femur), and upper extremities, respectively, and is relatively preserved in the LS unlike that seen in post-menopausal women [5] (Fig. 1). Demineralization at the most affected sites of the DF and PT is more rapid and severe post-SCI when compared to the rate and severity seen in immobility (0.1% per week), anti-gravity (0.25% per week), or post-menopausal (3–5% per year) conditions [14].

Bone Resorption Markers

Hypercalciuria with or without hypercalcemia peaks at 1 to 4 weeks after the injury remains high for up to 16 weeks then levels off 24–36 weeks post-injury [15–17]. Hypercalcemia does not always occur but is seen within 2 weeks to 6 months post-injury [18]. Deoxypridinoline (DPD) and N-telopeptide (NTX) increase up to 10 times normal values as early as 1 to 2 weeks post-injury, with DPD remaining 5-fold higher than normal within the first 1 year [12, 13]. Serum and urine

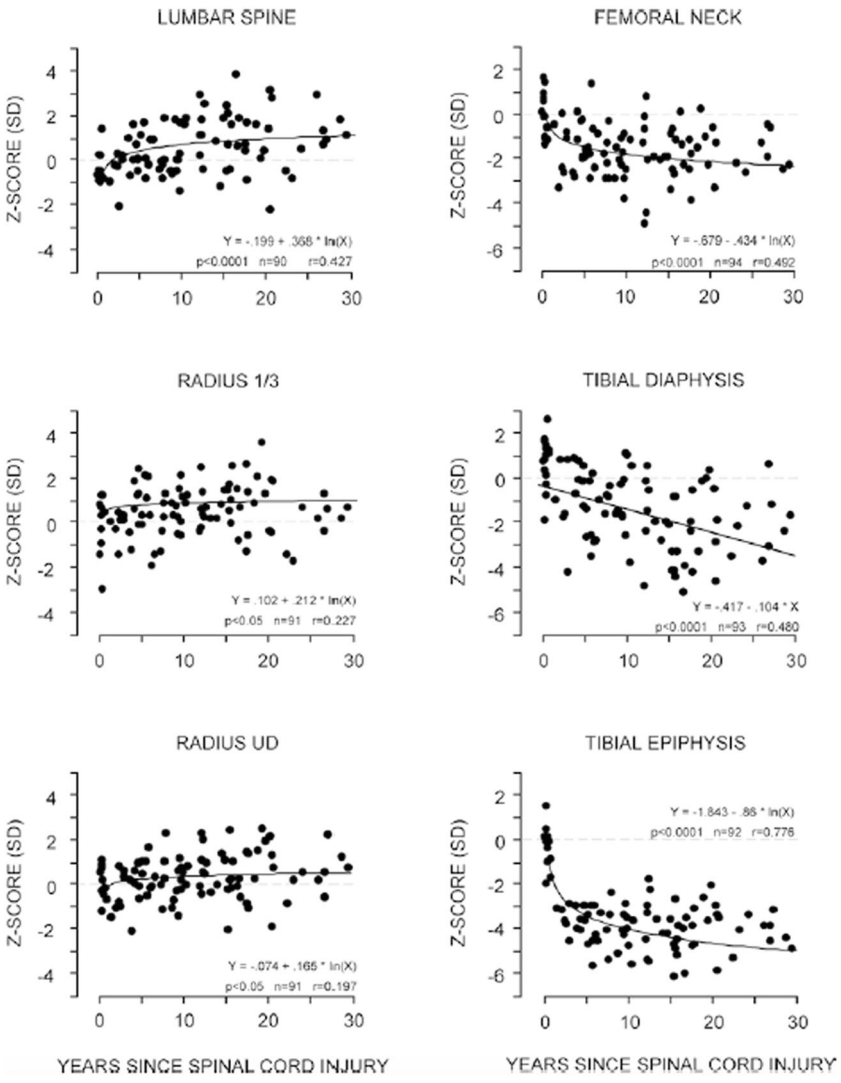

Fig. 1 BMD Z scores (SD) at various skeletal sites as a function of time since spinal cord injury in 98 paraplegic men [13] (reprinted with permission)

C-telopeptide (CTx_s and CTx_u) peak around 10–16 weeks [12, 14, 15, 19] with values reaching as high as 2.5 and 5 times control values, respectively. CTx_s and CTx_u remain elevated for 24 to 71 weeks showing continual long-term resorption [12, 20].

Trabecular bone loss occurs at a rate of 4% per month in the first year while cortical bone loss occurs at 2% per month, with fatty marrow replacing trabecular bone [21, 22]. Histomorphometry exams of iliac crest biopsies confirm the predominate loss of trabecular bone in the first 4–6 weeks after SCI, while less invasive radiographs show decline in BMD as early as 6 weeks post-injury [23–25]. Regional bone loss can approach 1% of BMD loss per week at DF and PT for the first several months [26]. Meanwhile, the trabecular bone of the LS is spared. While age-related changes in bone are well established in AB persons, the impact of age at the time of injury on bone resorption patterns (time course and severity) is undefined and needs further exploration.

Bone Formation

Less data is available on markers of osteoblast activity, which appears to be less significantly altered post-SCI. Osteocalcin (OC) levels have been consistently found to be normal 1-month post-SCI but elevated at 12–24 weeks after injury [6, 12, 13, 27]. Then, from 24 to 48 weeks OC decrease significantly, followed by normalization at 48 weeks [15]. Procollagen type I N-terminal propeptide (PINP) levels rise above normal values suggesting some attempt at bone repair [10]. Alkaline phosphatase has most consistently been shown to be within or slightly higher than normal reference ranges within the first year post-SCI [12, 13, 28, 29]. Despite normal levels of serum markers for osteoblast activity, histopathology from iliac crest of persons with acute SCI reveals decrease in bone formation. This disparity suggests that these serum markers may be less sensitive for osteoblast activity changes resulting from SCI, and normal values may reflect local bone repair processes at the site of a concomitant limb fracture, vertebral body injury [30], immobilization [31], and/or other changes.

Chronic (> 1 Year) Bone Changes After SCI

Increased rate of bone resorption continues for 1–2 years before reaching a steady state, although some sites continue to decline in BMD for up to 30 years (Fig. 1) [6, 12, 13]. However, one study of monozygotic twins discordant for SCI did demonstrate sublesional bone loss for several decades, suggesting that heightened net bone loss after SCI may persist for an extended period of time [7]. Quantitative CT evaluations of the lower extremity in untreated patients 3–8 years post-SCI found that the DF and PT epiphyses (i.e., trabecular bone) had decreased by 50% and 60%, respectively, while the femoral and tibial shafts (i.e., cortical bone) had decreased by 35% and 25%, respectively [32]. Dauty et al. studied 31 SCI patients more than 1 year post-injury and found similar degrees of bone loss with 52% loss at the DF and 70% at PT [33]. Few studies have longitudinally measured biochemical bone turnover markers; however, Zehnder followed 100 paraplegics for up to 30 years and found that deoxypyridoinoline/creatinine (DPD/Cr) remained elevated in 30% of paraplegics over 10 years post-injury [13]. Dionyssiotis also compared bone area relative to time since injury and found a negative correlation between the two in persons with paraplegia [34]. In summary, there is no well-defined time at which resorption stops; however, the continual bone loss over time leads to BMD values well below clinically acceptable fracture thresholds in the able-bodied population. Based on BMD values from LS and proximal femur, approximately 60% of persons with chronic SCI meet World Health Organization (WHO) criteria for osteoporosis, 19.5% for osteopenia and the remaining 20% have normal values [35].

Neurological and Hormonal Mechanisms of Bone Resorption

As previously mentioned, BMD decline immediately post-SCI (1% per week) is more severe than that observed with anti-gravity (0.25% per week), immobility (0.1% per week), or in post-menopausal women (3–5% per year) [36, 37]. While unloading is the most frequently cited cause of rapid BMD loss in SCI, loss of neurological control and hormonal changes are likely also implicated, but often overlooked, as contributing factors in this rapid and severe bone resorption [8, 24, 34, 37] (Fig. 2).

There is growing evidence for a significant neurological component to loss of BMD in persons with SCI [8, 38, 39]. Bone is richly innervated by sympathetic and sensory nerves and the former have been suggested to have anabolic influences on bone, while the later can have catabolic effects [8]. Studies conducted in SCI mice have shown that upregulation of the sympathetic nervous system via beta 2 receptor activation leads to increased resorptive activity [37, 40]. Catecholamines upregulate the expression of receptor activator of nuclear factor-beta ligand (RANKL), an osteoclast activator, which results in increased bone resorptive activity by osteoclasts [8, 37]. Interestingly, those with spinal cord lesions of T5 and below have higher resting catecholamines than non-injured persons, which may partially explain a "neurologic" role in such rapid and extensive bone loss [41]. The role of the parasympathetic nervous system in maintaining bone mass is less clear, requiring further studies. Human SCI studies have found that the extent of neurological impairment (by ISNCSCI exam) to be a greater predictor of sublesional bone loss than ambulatory/mechanical loading status [33, 39].

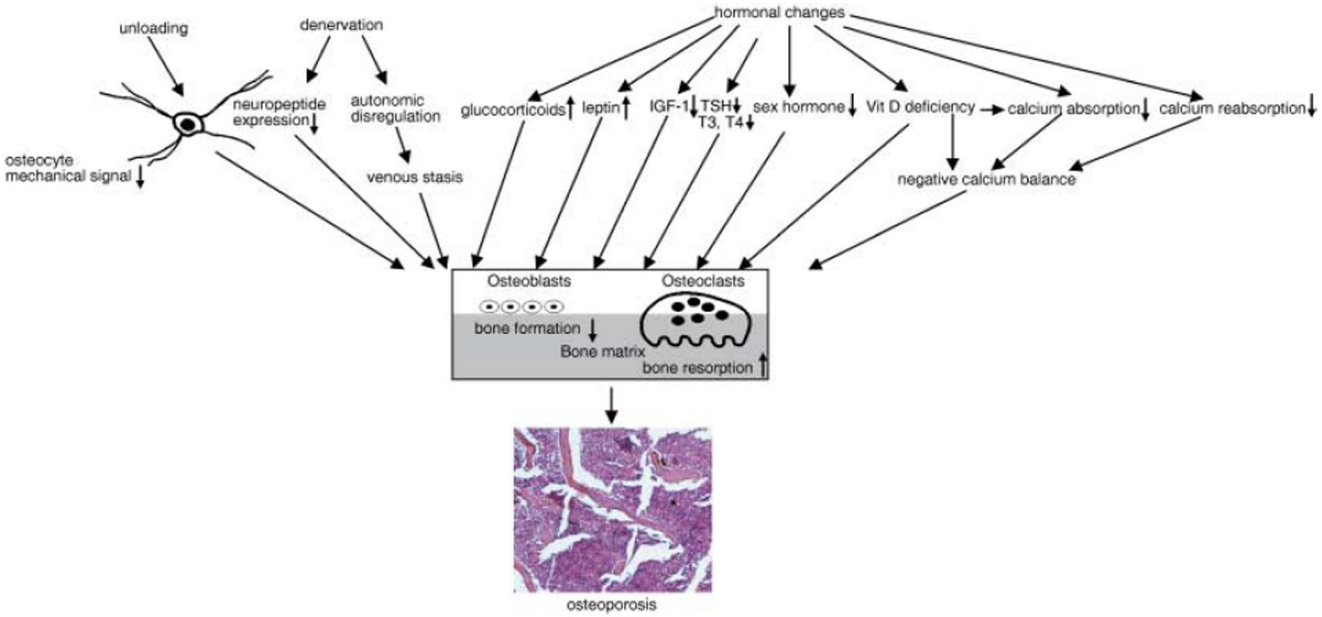

Fig. 2 A schema outlining the pathways implicated in pathogenesis of osteoporosis after SCI [11] (reprinted with permission)

Furthermore, persistent sublesional reduction in bone mineral content has also been seen in SCI persons who have regained near normal mobility 1-year post-injury [22]. It is clear that a disrupted neuronal-bone interaction contributes to bone loss through an independent mechanism that is distinct from loss of mechanical stress on bone [39].

Interestingly, while most bone loss occurs below the lesion, bone loss also occurs (albeit to a lesser degree) in the normally loaded and innervated upper extremities of those with paraplegia [42–44]. For such persons, hormonal perturbations including hypogonadism, vitamin D deficiency, secondary hyperparathyroidism, thyroid disorders, decreased growth hormone, and increased serum leptin levels may also contribute to osteoporosis after SCI. An estimated one in three persons with SCI have at least one identifiable secondary cause of OP [11, 45]. While studies investigating the roles of growth hormone and vitamin D deficiency after SCI report conflicting results, hypogonadism does contribute to bone resorption in SCI patients. Extensive review of secondary causes of osteoporosis in persons with SCI is beyond the scope of this article but has been described elsewhere [11].

Role of Level, Completeness, and Ambulation in Bone Resorption

The degree of sensorimotor impairment after SCI is significantly correlated with degree of loss of BMD and fracture risk. The International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) is a well-validated exam tool/algorithm and classifies injuries as motor complete (AIS A or B) whereby there is complete lack of motor function below the level of injury and motor incomplete (AIS C or D) with varying degrees of partial motor impairment [46]. Figure 3 defines the four standardized classifications (AIS A, B, C, or D) of neurological loss after SCI as established by ISNCSCI [46].

Persons with motor complete SCI (AIS A or B) are the least likely to ambulate (A = < 10% vs. B ~ 50%) [47] and lose 1% BMD per week for the first 6–12 months following injury [48, 49]. Meanwhile, those with motor incomplete SCI (AIS C and D) are more likely ambulatory (~ 75–95%) [47] as they have residual strength in muscles below the injury level, and suffer less bone resorption [35, 50, 51]. In addition, the neurological *level* of SCI determines the extent of bone loss, with greater bone loss being observed in higher cervical (i.e., tetraplegia) injuries with loss of strength to upper and lower extremity vs. lower thoracic and lumbar (i.e., paraplegia) spinal cord lesions, where upper extremity motor control is intact while lower limbs are weak [12, 52, 53].

Two interventional studies for treatment of OP have stratified participants by completeness of injury. Nance et al. stratified participants by completeness and ambulation. Pamidronate 30 mg IV was administered every week for 6 weeks within 6 weeks of the injury to 12 persons with SCI (AIS A = 8 vs. AIS D = 4). BMD was measured by dual energy x-ray absorptiometry (DXA) at the lumbar spine (LS), proximal femur, DF, and PT and was compared to 7 untreated controls with SCI (AIS = 3 vs. AIS D = 4). After 1 year, regardless of treatment, ambulatory, motor incomplete AIS D subjects had an average of 4.6% bone less compared to 15.7% bone loss in the AIS A group ($F = 20$, $p < 0.00$ l). The most

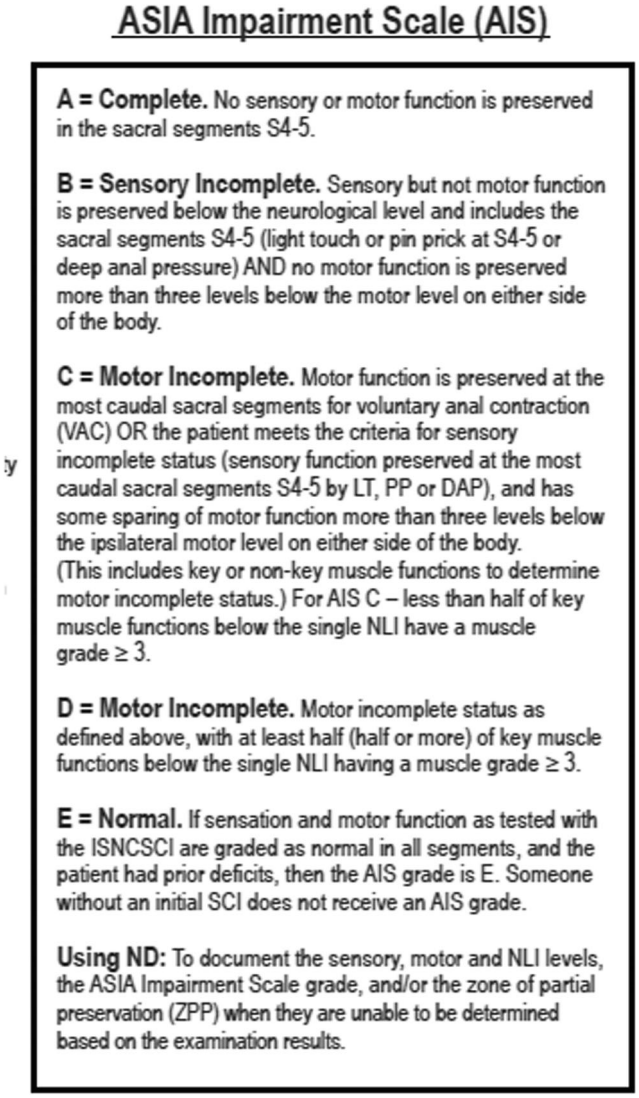

Fig. 3 American Spinal Injury Association (ASIA) impairment scale defining completeness of SCI, as defined by the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) exam [46]

significant changes were seen at the DF and PT. The percent change at the DF for AIS A compared to AIS D was 12.5% vs. 3% ($p = 0.00$ l) and for PT 14.3% vs. 3.25% respectively ($p < 0.00$ l) [54] (Fig. 4).

This study also demonstrated a significant effect of completeness of SCI on NTX excretion ($p = 0.02$); patients with AIS A injuries secreted more NTX than AIS D injuries up to 12 weeks post-treatment. Pamidronate did significantly decrease bone loss at the proximal femur and DF in all subjects; however, when BMD changes at all sites were averaged and analyzed by ambulatory status (i.e., AIS A vs. D), *ambulatory status* (AIS A vs. D) > *treatment* (pamidronate vs. control) had the most profound effects on the high-percentage trabecular bone regions about the knee, the DF, and PT (i.e., where most fractures in SCI occur) and relatively less effect on the proximal femur [54] (Fig. 5).

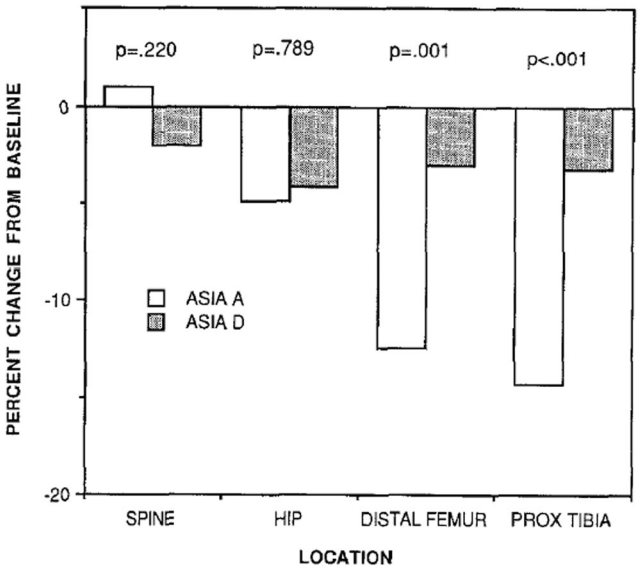

Fig. 4 Ambulatory status and bone location showed a significant interaction on the percent change in bone density from baseline assessment ($p < 0.0001$) such that ambulatory subjects maintained bone density about the knee (distal femur and proximal tibia) compared to non-ambulatory subjects [54] (reprinted with permission)

In another study, Pearson et al. administered etidronate 800 mg daily for 2 weeks over 2 cycles separated by 13 weeks to patients with acute SCI (< 6 weeks post-injury) and compared results to an untreated control group. BMD was

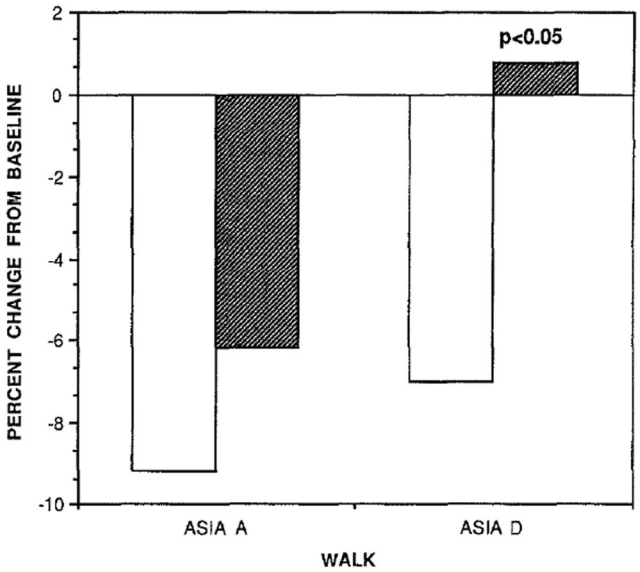

Fig. 5 Percent change in bone density (ANOVA) for all locations for pamidronate-treated subjects (black bars) and controls who did not receive pamidronate (white bars). Data are stratified by functional status within the AIS grade A (complete SCI) compared to the AIS grade D (motor incomplete with most key muscles below the level of injury at least grade 3 strength). Both between-group comparisons—group treatment and ambulatory status—had significant effects, but no additional interaction was observed. By pairwise comparison, the ambulatory, pamidronate-treated subjects had significantly better bone density than the other groups ($p < 0.05$) [54] (reprinted with permission)

measured at LS and femoral neck (FN) using standard protocol, and a locally developed DXA protocol and software was used to measure BMD at the DF and PT [55]. Similar to Nance et al., participants were separated by ambulatory and completeness status (AIS A vs. D). Non-ambulators (AIS A) lost significantly more ($F = 15.38$, $p = 0.0003$) bone density compared to ambulators (AIS D), regardless of treatment group. Meanwhile, the etidronate-treated wheelchair-dependent (i.e., non-ambulators) patients lost bone density at the FN, DF, and PT as did the control patients regardless of ambulatory status. The interaction of etidronate treatment and ambulatory status over time was significant ($p = .0157$); thus, a follow-up analysis was conducted to localize the interaction. It demonstrated bone density *was only preserved* in the etidronate-treated walking patients over time ($p = 0.03$) (Fig. 6) [55].

Based on these studies, ambulation and incompleteness of lesion are associated with better maintenance of bone density and this *may be enhanced* by anti-osteoclastic pharmacological intervention. Bauman supported this hypothesis stating that "a pharmacologic intervention … that is given *in conjunction with* a mechanical stimulation (i.e., dynamic loading) may eventually prove to be the therapeutic approach of choice" [56].

Further studies are needed to better understand the effects of completeness of injury and ambulatory status on bone resorption, and to clarify the role of mechanical stimulation and pharmacologic therapies in managing SCI patients with complete lesions who are non-ambulatory.

Drug Induced Bone Loss Post-SCI

In addition to the intrinsic factors of immobility and denervation to the bone, the extrinsic factor of drug induced bone resorption should not be overlooked in persons with SCI. Multiple SCI-induced comorbidities (e.g., pain, depression, gastro-esophageal reflux, gastritis) require pharmacologic treatments with medications known to impact bone remodeling. While utilization of short course of glucocorticoids in the acute spinal cord injury is still a contested subject [57], they remain commonly used in scenarios of acute worsening neurological compromise. In addition, vagal hyperactivity after acute SCI results in stress gastritis that is commonly treated with proton pump inhibitors for the first few weeks after SCI [58, 59]. While proton pump inhibitors are only recommended in the setting of gastro-intestinal bleeding, persons with SCI impairment after SCI often continue to use proton pump inhibitors long term for gastro-esophageal reflux (prevalence of ~22%) [60], especially when under conditions of impaired diaphragm motility and prolonged recumbent positioning. In addition, deep venous thrombosis prophylaxis in persons with SCI is recommended with low molecular weight heparin for 8–12 weeks immediately after injury [61] which has an association with BMD loss [62]. Other issues commonly associated to the SCI population such as depression (prevalence of 9.8–63.9% prevalence) [63] and metabolic syndrome (prevalence of 57% in SCI veterans) [64] must consider drug induced osteoporosis especially if considering selective serotonin reuptake inhibitors and thiazolidinediones respectively for treatment of these conditions.

BMD Measurements at Distal Femur and Proximal Tibia

Fractures in the SCI population primarily occur in the DF and PT. Standard BMD measurements by DXA EXAMINE the lumbar spine (LS), proximal femur, and radius and do not measure DF or PT. Furthermore, commonly used DXA software is specific to bony configurations of the LS, proximal femur, and radius. This leads clinicians to ask, to what degree can conventional standardized DXA measurements of BMD at the LS, proximal femur or radius be used to predict fracture risk of DF and PT in persons with SCI?

To answer this question, we must first consider the accuracy of LS BMD measurements in the SCI population. While BMD of LS in SCI persons when measured by antero-posterior DXA orientation is commonly found to be no different than that of AB controls [65], degenerative joint disease (premorbid or acquired due to increased LS mechanical loading after becoming

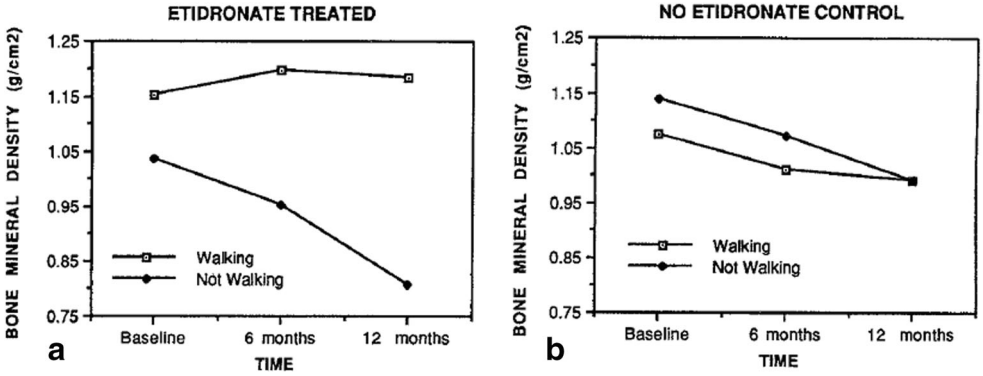

Fig. 6 The effect of etidronate treatment on average BMD (LS, FN, DF, and PT) relative to walking status is shown in ($N = 5$) (**a**) compared with the no-etidronate control group ($n = 6$) (**b**) [55] (reprinted with permission)

wheelchair dependent),or heterotopic ossification in the LS spine often falsely elevates BMD values [66]. Bauman et al. later further investigated this hypothesis by demonstrating that BMD measurements via antero-posterior DXA underestimate LS bone loss when compared to lateral DXA imaging, which is the most accurate measurement method (although less commonly used) for bone loss that is SCI related [67]. Therefore, conventional BMD measurements of LS often underestimate the degree of bone loss at baseline.

That said, when comparing LS BMD to lower extremity BMD after SCI, a few studies have demonstrated significantly less bone loss at the LS compared to the lower leg (DF, PT) [68]. Furthermore, Henderson et al. showed that DXA measures of BMD in the LS were not predictive of subsequent lower extremity fracture and recommended BMD measurement by DXA in the DF as the technique of choice to predict fractures at DF [69, 70].

Regarding standard hip BMD measurements predicting BMD in the peri-knee regions in SCI persons, Lazo et al. demonstrated a correlation between proximal femur BMD and lower extremity fractures, while Shields et al. showed that proximal femur BMD correlates with DF BMD but only marginally correlates with PT BMD [35, 65]. In summary, it is clear that (1) standard DXA measurement of BMD at the LS underestimates bone loss, (2) LS BMD is not an accurate marker of peri-knee region BMD or lower extremity fracture risk, and (3) there is conflicting evidence regarding whether proximal femur BMD can be used to predict lower extremity fractures [67].

Since the standard measurement sites for osteoporosis screening do not predict BMD or fractures at the DF and PT, it is clear that protocols that accurately and reliably calculate BMD at the DF and PT are needed. While there is currently no widely used standardized clinical DXA protocol for measuring BMD above and below the knee, several independent protocols (seen in Fig. 7) have been developed and used for research purposes over the past 15–20 years. Given knee flexion contractures and spasticity (causing motion artifact) that are common in persons with SCI, positioning is more problematic than the AB population. Restraining the hips from external rotation is required to keep the beam in line with the PT and DF regions and some persons with SCI may be unable to tolerate this if significant contractures or spasticity are present (Fig. 8). Furthermore, the proximity of the fibula and patella creates complexities in developing regions of interest (ROI) that ensure these bones to not confound the BMD measurements of DF and PT. Commonly used lumbar spine and forearm software has been used to measure peri-knee region of interest (distal 30% of femur and proximal 30% tibia) on both Hologic [74] and GE Lunar [75] machines. More recently, a commercially available orthopedic knee software developed by GE has been utilized given its improved ability to avoid the patella and fibula in DF and PT BMD measurements [71, 76, 77].

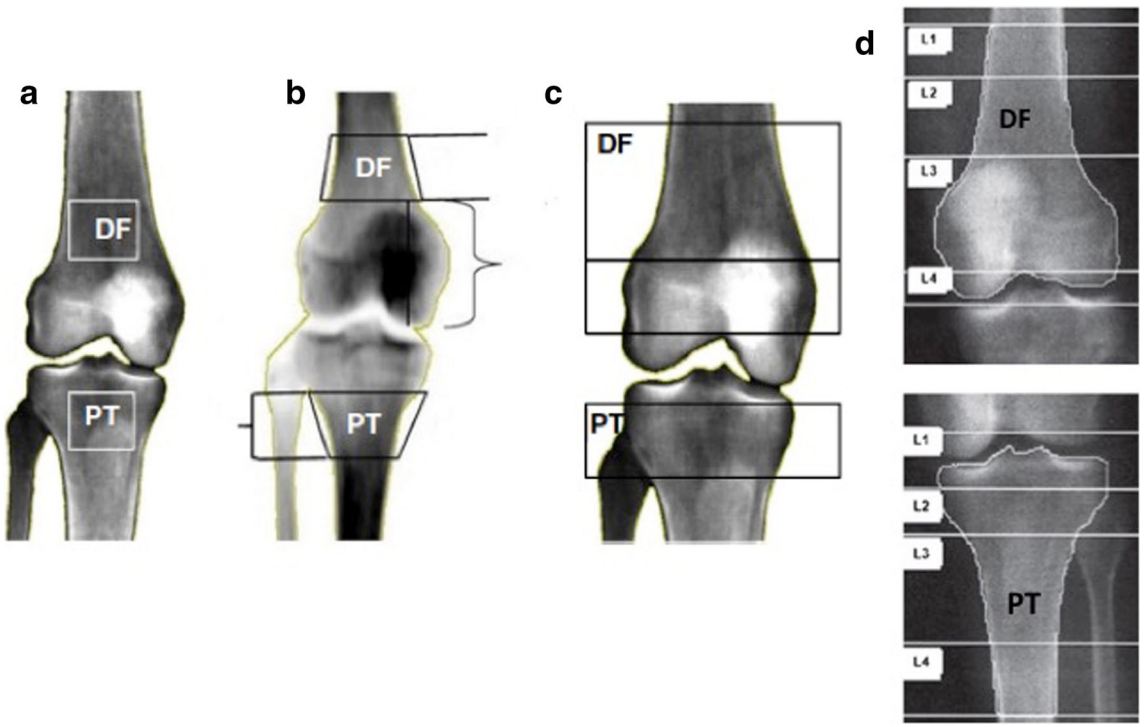

Fig. 7 Commonly used methods using a custom region of interest to capture the DF and PT of the knee using DXA adapted from (a) Morse et al. [71], (b) Shields et al. [65], (c) McPherson et al. and Edwards et al. [72, 73], and (d) Lala et al. (Hologic) and Lobos et al. (GE Lunar) [74, 75] (all reprinted with permission)

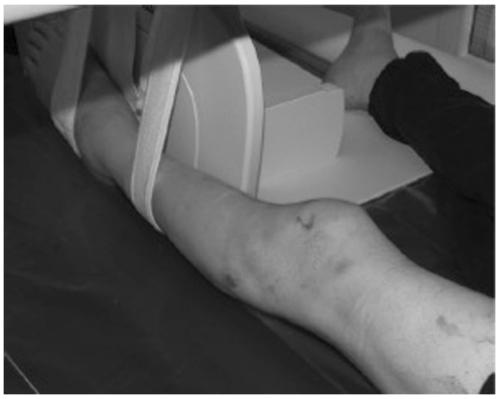

Fig. 8 Photo illustration of a patient on the GE Lunar Prodigy DXA scanner showing positioning for scanning of the knee [71] (reprinted with permission)

The protocols using LS and forearm software measure variable regions of interest (ROI) at the DF and PT. Lala et al. and Lobos et al. utilized LS software (Fig. 7d) proposed the most comprehensive protocol, measuring the diaphysis, metaphysis, and epiphysis of both the DF and PT [74, 75]. Lala ($n = 110$) obtained an LSC of 2% at the DF and 3% at PT [74] while Lobos ($n = 18$) obtained LSC values of 4.3–5.5% at DF and 2.7–2.8% at PT [75]. While these protocols capture the BMD of the epiphyses of both DF and PT, which are most prone to fracture, they are criticized as it is technically complex to subtract the BMD of the patella and fibula within the ROI areas, thus potentially compromising repeatability and accuracy. The protocol used by Shields (Fig. 7b) utilized the same LS software to capture the ROI of metaphyses of DF and PT [65], while McPherson (Fig. 7c) developed the only validated protocol using forearm software (Hologic) to capture the ROI of the distal femoral epiphysis and metaphysis and the proximal tibial epiphysis [72].

Fewer studies have utilized a newer commercially available orthopedic knee software program, which measures the metaphyses of the DF and PT and also avoids the patella and fibula regions [55, 65, 71, 72]. One such protocol outlined by Morse et al. (Fig. 7a) demonstrated that the precision of measurements at DF (3.01%), but not PF (5.91%), were consistent with those reported at traditional DXA scan sites (precision of 1.5–3.0% for the LS and 1.4–2.3% for the proximal femur) in 20 able-bodied individuals, and therefore recommends DF as the site of choice for longitudinal assessment of BMD in chronic SCI [71, 78]. The International Society for Clinical Densitometry (ISCD) requires 30 scans to calculate the least significant change (LSC), a value used to determine whether an intervention has a significant change [79]. To date, no studies have reported the precision error from 30 repeat scans using the orthopedic software to calculate the LSC at a 95% confidence interval [80].

Furthermore, well-validated BMD values that predict fracture risk threshold have not have been clearly defined. Three studies (total $n \sim 200$) have independently measured and compared areal (g/cm^2) mean BMD (aBMD) in persons with SCI with and without a recent lower extremity (LE) fracture. The aBMD of persons with fracture history was ~ 0.6 g/cm^2, so authors thus suggested this value as the "fracture threshold" which is still used in some clinical and research protocols [52, 74, 81] [71, 82, 83]. Later the aBMD data of the SCI persons with fracture was reanalyzed using methods to define fracture thresholds in AB persons and the SCI fracture threshold (i.e., below which fragility fractures occur) was re-defined as 0.78 g/cm^2 while fracture breakpoint (i.e., values at which the majority of fragility fractures occur) defined as 0.49 g/cm^2 [80, 84]. In conclusion, the fracture threshold is variable and dependent on the method used to determine cutoff values [81]. Furthermore, no longitudinal study has assessed baseline BMD at the DF or PT at the exact time of fracture, which could be helpful in interpreting fracture threshold values.

Given the lack of normative BMD DXA values at the DF and PT and insufficient resolution to calculate volumetric changes in bone mineral content, some experts have suggested peripheral Quantitative CT (pQCT) be the first line diagnostic tool to measure improvement in BMD in any clinical trial [85]. Despite greater sensitivity, pQCT it is not widely available, so is of limited clinical use. A recent review by Cirnigliaro argues that since pQCT is not readily available, normative DXA data of BMD at DF and PT is lacking, so it is not a tenable diagnostic tool to accurately diagnose OP in the SCI population. Cirnigliaro concludes that "the future of routine densitometry in the SCI population is dependent on the development of normative databases and improved cutoff values for fracture at the DF and PT using *both* DXA and advanced imaging methods" [80]. Until well-validated values for fracture thresholds are available, it is recommended that SCI clinicians utilize the previously referenced DF and PT DXA protocols (Fig. 7) in the SCI population with an aBMD of 0.6 to 0.78 g/cm^2 in addition to known fracture risk factors to predict patients at greatest risk (see subsequent section on "Fractures after SCI") [71].

Fractures after SCI

Seventy percent of persons of SCI will sustain a long bone fracture during their lifetime [42]. As previously mentioned, fractures occur in the lower extremities with PT being the most common site, followed by the DF [86]. Upper extremity fractures are less frequent and are mainly seen in persons with tetraplegia. The femur and tibia reach fracture thresholds at 1 to 5 years post-SCI, with a mean time to the first fracture of 9 years, a 1% fracture rate within the first 12 months and a cumulative 4.6% fracture rate per year for injuries over 20 years post-injury (Fig. 9) [48, 87].

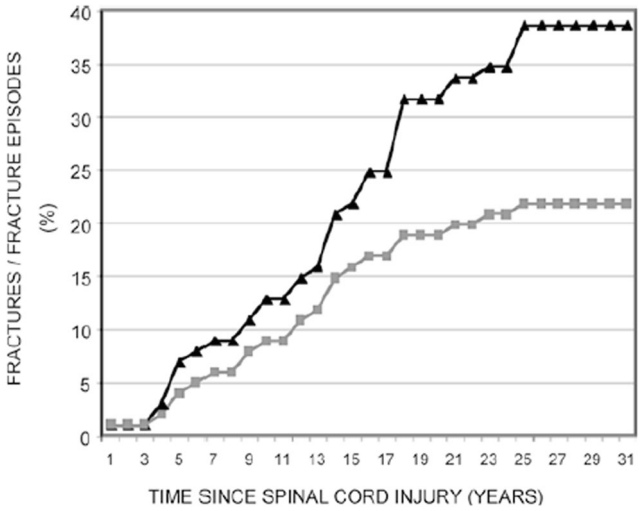

Fig. 9 Cumulative fracture rate (triangles) and fracture incidence (rectangles) observed in 1,010 patient-years among 98 paraplegic men 0–30 years after spinal cord injury [13] (reprinted with permission)

A cross-sectional study of 98 men with paraplegia reported 15 persons with 39 fragility fractures over 1,010 years of observation [13]. All fractures were exclusively in the lower extremities; however, none occurred in the proximal femur or LS. Similarly, a 7-year longitudinal study of hospitalizations due to fracture reported 39 of 1,487 hospitalizations were due to lower extremity fractures of the tibia/fibula (47.5%), distal femoral metaphysis (20%), proximal femur (15%) metatarsal (5%), and phalanx (7.5%) [86]. The remaining 5% occurred in the humerus and, notably, none occurred in the LS.

Causes of fractures include falls from a wheelchair (51%) or during transfers (14%) but can also occur as a result of minor trauma, such as range of motion activities [86, 88]. In addition to accelerated BMD loss, other fracture risk factors include motor complete SCI (AIS A or B), paraplegia, body mass index below 19, previous fragility fracture, longer duration of injury (> 10 years), and more than 5 servings of alcohol per day [13, 35, 80, 82, 86]. Risk factors are closely related to BMD of DF and PT trabecular bone [87]. Craven et al. proposed an evidence-based algorithm to predict fracture risk based on BMD and aforementioned risk factors [45]. Prospective validation of this algorithm would be helpful to clinicians caring for persons with SCI. Fracture comorbidities include pain, deep venous thrombosis, joint contractures, spasticity, pressure ulcers, lengthy immobilization, prolonged hospitalizations, increased health care costs, increased risk of autonomic dysreflexia, and increased disability to an already physically disabled person [48, 89, 90]. Unfortunately, while the incidence and risk factors of fractures are known, no studies have evaluated long-term fracture incidence > 2 years after OP treatment and no treatments have been proven to reduce fracture risk. Considering the compound effects of fractures on quality of life for individuals with SCI, further studies are warranted to prevent this functionally debilitating outcome.

Treatments of Bone Loss in SCI

Non-pharmacologic Interventions

Non-pharmacological interventions include therapies to mitigate "immobilization" in persons with SCI, primarily with multiple static and dynamic loading/mechanical stimulation. Such interventions include static standing, tilt table, reciprocating gait orthoses, functional electrical stimulation (FES), body weight supported treadmill training (BWSTT), and lower body and whole-body vibration.

Static standing vs. standing with treadmill walking 5 h per week in a heterogenous (levels C4-T12, complete and incomplete) group of 13 persons < 4 weeks post-SCI demonstrated minimal bone density loss at the tibia compared to immobilized controls [91]. No difference in static vs. dynamic loading was seen. Kunkel and others have consistently shown dynamic physical activity (e.g., FES BWSTT) to be insufficient in prevention of bone loss unless the activity is frequent (30–60 min, 2.3–5 days/week); even among subjects engaged in frequent dynamic activity the modest (~ 10%) improvement in BMD is not sustained once exercise stops [28, 92–94]. Whole or partial body vibration, or mechanical stimulation at low intensity, has shown some positive effect on BMD in post-menopausal women and other adults with osteoporosis [95]. The application in the SCI population has mixed results, however. In one study of 42 motor complete patients with 12 months of low intensity vibration therapy [96], there were no BMD or trabecular micro-architecture adaptations noted in the DF or tibia. Other studies of animal models show some change in bone turnover markers and a reduction in osteoclast genesis with vibration therapy but failed to demonstrate preservation of BMD [97, 98].

These aforementioned studies also confirm older findings, that while exercise shortens the duration of hypercalciuria after SCI, there is no effect on the peak excretion, and calcium excretion in immobilized SCI patients is much greater than in immobilized persons without SCI [20, 99]. A systematic review of all non-pharmacologic interventions noted that clinical designs varied widely and the level of evidence for attenuating BMD loss was low for some, but no intervention resulted in sustained increases in BMD at the hip, DF, or PT [93]. Such findings suggest multifactorial etiologies contribute to the phenomena of dramatic bone resorption following SCI.

Pharmacologic Interventions

Evidence for efficacy of various pharmacologic interventions administered during the acute phase of SCI is variable. Pharmacologic treatment has been based on agents studied in females with post-menopausal osteoporosis, consisting of anti-resorptives (calcitonin, bisphosphonates, and denosumab) and anabolics such as teriparitide and anti-sclerostin antibodies.

Anti-resorptives

Calcitonin Calcitonin, an inhibitor of bone resorption, acts specifically upon osteoclasts and their precursors. Studies have shown that calcitonin temporarily reduces hypercalcemia and hypercalciuria in SCI, but have demonstrated little efficacy in reversing and preventing bone loss [25, 100, 101].

Bisphosphonates Bisphosphonates inhibit osteoclastic activity and while many studies have documented efficacy in women with post-menopausal osteoporosis, efficacy is variable in SCI.

Zoledronic acid (ZA) has been shown to significantly ameliorate BMD loss (5% vs 10% BMD loss in controls) at the proximal femur in patients at 6 months post-injury; however, this effect was not sustained at 12 months [102]. A later study in motor complete subjects showed that ZA failed to *preserve* bone density at the DF and PT [76]. This fact was supported by a similar study suggesting a benefit of ZA treatment in the proximal femur but not at the DF [103]. The largest ($N = 57$) and most recent randomized controlled trial comparing standard treatment to treatment with ZA initiated within 3 months of SCI showed significant reduction in bone loss (BMD at proximal femur) compared to control at 3, 6, and 12 months [104]. However, this study did not measure BMD at the DF or PT, the most common sites for fractures in SCI patients. No ZA studies address the impact of treatment on BMD (i.e., was BMD improvement maintained) 1 year post-SCI or fracture incidence.

Alendronate was studied in a randomized, placebo-controlled study ($N = 31$) of a mixed SCI group (complete and incomplete) who received weekly administration of the drug initiated within 1 week post-SCI for a total of 18 months. After 12 months, there was less bone loss in the treated group with a 5.3% difference ($P < 0.001$) in total body BMD, a 17.6% difference ($P < 0.001$) in the proximal femur BMD, and a 15.2% difference ($p < 0.001$) in the femoral shaft compared to placebo [68]. On the other hand, the LS demonstrated increased BMD in treated persons, but this was not statistically significant ($p = 0.096$) [68]. While these results suggest clear efficacy at some sites, bone loss was not entirely prevented and long-term beneficial effects on BMD and fracture incidence were not reported.

Etidronate has been shown to increase BMD at the DF and PT by 14.3% on average for over 1 year, but *only* in patients who eventually became ambulatory, as previously discussed (Fig. 6) [55]. It should be noted, however, that etidronate is currently not available in the USA.

Two studies on IV pamidronate have conflicting results. In Nance's study of a mixed group of 24 incomplete and complete persons with SCI, with treatment initiated within 6 months of injury, patients treated with IV pamidronate (30 mg/month; $N = 14$) had significant attenuation in bone loss at the proximal femur, 0.9% vs. 8.2%, ($p = .012$) and DF, 4.7% vs 10.8% ($p = 0.033$) when compared with controls ($N = 10$) [54]. However, completeness of lesion was also a significant factor as those with AIS D incomplete lesions had lower BMD loss than those with complete lesions (3.1% in AIS D vs. 7.7% loss in AIS A group). This study illustrates how ambulation in combination with a bisphosphonate (pamidronate) preserved BMD best [54]. Bauman's study of a uniform group of 11 motor complete (AIS A and B) persons who were given IV pamidronate (60 mg) at 1, 2, 3, 6, 9, and 12 months following injury showed treatment prevented hypercalcemia and decreased urinary cross-linked N-telopeptide of type I collagen (NTX) levels (marker of bone resorption) at 1 month but had no significant effect on BMD [105].

In summary, the administration of bisphosphonates to non-weight bearing persons with acute motor complete SCI (i.e., AIS A or AIS B) has not demonstrated an increase in bone density, although some studies indicate preservation of BMD during the treatment phase at some but not all sites. There is less evidence but possibly more potential for bisphosphonates to improve BMD in the ambulatory and/or incomplete cohort that merits further investigation [18]. Additional studies are needed to evaluate the efficacy of pharmacologic therapies on BMD and fracture incidence beyond 2 years of treatment, when most fractures typically occur (i.e., average time to fracture of 9 years post-injury) [32, 35, 86].

Bryson's review in 2009 concluded that data are "insufficient to recommend routine use of bisphosphonates for fracture prevention in these (SCI) patients. Current studies are limited by heterogeneity of patient populations and outcome measures. Uniform bone density measurement sites with rigorous quality control and compliance monitoring are needed to improve reliability of outcomes. Future studies should address specific populations (acute or chronic SCI) and should assess fracture outcomes." [106] A more recent systematic review concluded that there is moderate-quality evidence for the effectiveness of zoledronic acid in prevention of BMD loss in acute SCI and very low-to-low-quality evidence to support effectiveness of other bisphosphonates [107].

Denosumab The biomarker, osteoprotegerin (OPG), has been recently targeted in the treatment of post-menopausal osteoporotic women for its anti-osteoclastic activity, but only recently examined in patients with SCI [108–110]. A study of men with SCI showed a correlation between the severity of neurological injury and level of serum OPG, suggesting OPG as a potential biomarker for osteoporosis in persons with SCI [39]. Lower levels of OPG were found in men with more severe SCI. The levels of OPG were not related to the ability to ambulate, supporting the hypothesis that disrupted neuro-osteogenic signaling interaction may independently suppress OPG in the SCI population.

OPG is part of the RANK/RANKL system and acts as a decoy receptor of RANKL (an osteoclast activator) to limit osteoclast activation and inhibit bone resorption. Manipulation of the OPG/RANKL system in several disuse models in animals has been found highly effective in maintaining cortical bone mass [111]. Denosumab is an anti-RANKL antibody which functions in a similar manner as OPG and hence may have therapeutic potential in persons with SCI [10, 56]. One preliminary study showed treatment with denosumab decreased bone turnover and not only prevented BMD loss at the proximal femur and LS after SCI but also significantly increased BMD after 1 year by approximately 3% at the proximal femur and 8% at the LS [109]. Unfortunately, this study did not measure BMD at the DF or PT, so is of limited utility. An additional study showed strong correlation between serum RANKL and decreased BMD at the femur 6 months post-injury; after 6 months administration of denosumab, a marked decrease in serum RANKL was observed [110]. While there are conflicting results, these studies along with the animal and non-SCI human studies warrant further investigation with human subjects to further delineate therapeutic effects in SCI population [8, 80].

Anabolics

Teriparatide Teriparatide is a recombinant formulation of endogenous parathyroid hormone and the only available agent with the ability to stimulate osteoblast function. The effects of teriparatide on BMD after SCI are not clear. Edwards et al. studied the effects of teriparatide with vibration therapy in acute SCI [112]. Sixty-one patients were randomized into groups receiving teriparatide and sham vibration ($n = 20$), placebo and vibration ($n = 20$), and teriparatide and vibration ($n = 21$) for 12 months. After completion of the study, 25 subjects participated in an open-label extension and received teriparatide 20 mug/day for an additional 12 months with the optional use of vibration (10 min/day). At the end of the initial 12 months, both groups treated with teriparatide demonstrated a significant increase in areal bone mineral density (aBMD) at the spine (4.8 to 5.5%) but showed no treatment effect at the proximal femur and only a small increase in cortical bone at the DF and PT (2.2 to 4.2%) [112]. Due to its effects on blood calcium, close monitoring of serum calcium levels is required for patients treated following acute SCI, as hypercalcemia and hypercalciuria are often present.

Abaloparatide is a newer parathyroid hormone-related protein analog FDA-approved for post-menopausal osteoporosis but has not been studied in persons with SCI.

Anti-sclerostin Antibodies Sclerostin is a circulating osteocyte-derived glycoprotein that negatively regulates Wnt signaling within bone. Induction of the Wnt signaling pathway promotes osteoblast activity while inactivation of the pathway leads to osteopenic states [38] [113]. Unloading after SCI results in high serum sclerostin levels compared to able-bodied persons and is associated with reduced bone formation [38]. Emerging evidence points to sclerostin as a key regulator in SCI-induced bone loss [114–118]. One study in men with varying degrees of SCI found that sclerostin levels were highest in subjects who were injured within 5 years, suggesting that the rapid bone loss early after paralysis due to motor complete SCI could be attributed, at least in part, to elevated sclerostin levels [77]. In addition, a recent study by Invernizzi et al. demonstrated significantly higher values of serum sclerostin in chronic SCI (8 years after injury on average) compared to healthy subjects suggesting this phenomena is not only found in the acute SCI (<1 year post injury) stage [119].

Pharmacologic sclerostin inhibition in mice appears to produce bone anabolic effects after SCI [113, 114, 117, 120]. Zhao et al. studied 33 rats that underwent either complete transection of spinal cord or sham and were treated with sclerostin antibody (Scl-Ab) or vehicle for 8 weeks. At 12 weeks post-treatment, the Scl-Ab group had largely restored BMD, bone structure, and strength [120]. This study was supported by previous studies that demonstrated a preserved morphology and structure of osteocytes and reduction of the severe skeletal deterioration with Scl-Ab treatment after motor complete spinal cord injury in rats [117].

While clinical studies are needed, anti-sclerostin antibodies may represent a promising new therapeutic approach in preserving overall bone structure and function after neurologically complete SCI. Very recently, the FDA-approved romosozumab as the first anti-sclerostin antibody therapy for osteoporosis, so clinical trials are likely forthcoming. It should be noted that romosozumab may increase risks for myocardial infarction, stroke, and cardiovascular (CV) death and should not be taken by patients who experienced a CV event within the previous year. Persons with SCI do have a higher incidence of CV disease so should be monitored closely for any signs/symptoms of CV dysfunction while on the drug.

In summary, there are currently no pharmacologic or non-pharmacologic treatments known that effectively prevent and/or improve BMD once lost. Based on current studies, a therapeutic intervention would likely be most efficacious if given during the acute period following injury and *if combined with* aggressive mechanical loading [10, 56]. Data on efficacy for bisphosphonates is unconvincing to date. Whether this is due to large heterogeneity in methodology, the short time of intervention, and/or incomplete understanding of anti-osteoclastic compound efficacy is not yet known. The evidence for neurological etiology of OP (i.e., sympathetic denervation of bone) and treatment with denosumab or anti-sclerostin antibodies appear potentially promising and warrant clinical studies.

VA SCI Clinician Management

In a survey of about 100 VA physicians, only 54% regularly ordered DXA to screen for OP and 54% routinely prescribed bisphosphonates to treat OP [121]. Twenty-three percent of respondents reported not screening for OP due to barriers including lack of SCI specific scanning protocols (i.e., DF, PT), cost, inaccessible DXA scanning tables and rooms, inability of patients with flexion contractures to lie flat on the scanning table, increased time required to conduct a DXA scan, and lack of effective treatment guidelines once osteoporosis is diagnosed [121]. Recent literature reports a significant decline in the number of prescriptions for OP in SCI veterans from FY 2005 (13.0%) to FY 2015 (2.2%), with receipt of a DXA and enduring a fracture predicting their use [122]. These clinical practice patterns suggest that VA SCI clinicians are merely responding after occurrence of fracture, rather than proactively diagnosing and treating low BMD.

While software that measures BMD at the DF and PT is now commercially available, most VA SCI hub sites do not have technicians trained in its use. As the largest health care system for persons with SCI in the world, the VA hubs are uniquely suitable to establish and test peri-knee protocols to effectively measure and follow BMD in these patients. Availability of this diagnostic data may enhance clinician uptake of screening DXAs, allowing better assessment of fracture risk and provide the groundwork for future intervention research trials. It is likely that paucity of data on effective treatments for acute and long-term prevention of bone loss, lack of widely accessible diagnostic tools to measure BMD at peri-knee fracture sites and lack of clinical practice guidelines for treating OP in SCI patients contribute to less effective screening and treatment by VA SCI clinicians. In response to this, three separate initiatives are underway by the ISCD, the Consortium for Spinal Cord Medicine and Orthopedic Trauma Association who have each assembled experts to establish clinical practice guidelines for SCI-induced OP screening, treatment, and fracture management, respectively, that should be available in the near future.

Future Directions

Future studies should (1) examine OP interventions in a homogenous neurologically impaired population (i.e., motor complete) or stratify by degree of neurological impairment; (2) utilize a consistent (preferably validated) DXA protocol for DF and PT in over 30 persons (to meet ISCD criteria for LSC); (3) include BMD measurements at fracture sites of DF and PF; and (4) assess outcome measures of fracture incidence by following patients for up to a minimum of 10 years (intervention trial), to determine fracture risk reduction [106]. Accumulated normative data for BMD at DF and PF may then permit development of a validated algorithm that accounts for other fracture risk factors (e.g., age post-injury), completeness of injury and time since injury to predict fracture risk [80].

The VA Spinal Cord Injury/Disorder system of care is the largest of its kind in the world providing chronic long-term care to 27,000 SCI veterans. Given the SCI system does maintain an integrated electronic medical record and follows SCI patients lifelong, the VA infrastructure is equipped and well-poised to carry out multi-site investigations. The authors call on clinicians providing care to persons with SCI (e.g., physiatrists and endocrinologists) and VA researchers to collaborate across VA SCI centers nationwide to assist with addressing knowledge gaps and to improve clinical care for this unique population.

Meanwhile, in the absence of strong objective evidence, clinicians typically rely on expert guidelines. Currently, there are no guidelines or consensus statements on screening, prevention, and treatment of OP after SCI. Thankfully, guidelines are on the horizon to be published by the ISCD, Consortium for Spinal Cord Medicine and Orthopedic Trauma Association in the near future.

Acknowledgments The authors acknowledge Dr. Leslie Morse and Christopher Cirnigliaro for their guidance and expertise in clinical screening protocols, Dr. Nancy Kellogg for her assistance with editing, and UT librarian Christine Gaspard for her expertise in literature search.

Compliance with Ethical Standards

This article does not contain any studies with human or animal subjects performed by the any of the authors.

Conflict of Interest The authors declare that they have no conflicts of interest.

Informed Consent Not applicable.

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