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Spinal Cord Injury-Induced Osteoporosis: Pathogenesis and Emerging Therapies

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Abstract

Spinal cord injury causes rapid, severe osteoporosis with increased fracture risk. Mechanical unloading after paralysis results in increased osteocyte expression of sclerostin, suppressed bone formation, and indirect stimulation of bone resorption. At this time there are no clinical guidelines to prevent bone loss after SCI and fractures are common. More research is required to define the pathophysiology and epidemiology of SCI-induced osteoporosis. This review summarizes emerging therapeutics including anti-sclerostin antibodies, mechanical loading of the lower extremity with electrical stimulation, and mechanical stimulation via vibration therapy.

Keywords

Osteoporosis; Sclerostin; Bone Mineral Density; Spinal Cord Injury; Mechanical unloading

Introduction

An estimated 12,000 new cases of spinal cord injury (SCI) occur in the United States each year. The prevalence has increased from 207,000 cases in 1994 to roughly 270,000 cases in

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2012 due to improvements in medical care and greater survival [1]. Low bone mass and deterioration of the skeletal architecture is a well-known consequence of SCI. Long-term follow-up data suggest that as many as 50% of people with SCI will sustain a low-impact or an osteoporotic fracture at some point following their injury [2]. These low-impact fractures often occur spontaneously and in the absence of trauma. Fractures have serious health implications in SCI since they severely reduce independence and mobility and result in significant medical complications. Most fractures are treated non-operatively. Within the Veterans Affairs Health Care system, fracture hospitalizations result in lengths of stay 7 times longer than non-fracture related hospitalizations [3]. During fracture-healing, concurrent skin pressure ulcers can develop that sometimes result in lower extremity amputation [4]. Reduced range of motion and contractures of the hip and knee are another common long-term fracture consequence [5]. In addition to limiting mobility and compromising skin integrity, osteomyelitis at the fracture site can occur and manipulation of a fracture site can trigger severe hypertensive crisis due to autonomic dysreflexia. Despite these serious health implications, there is currently no standard of care or well-accepted clinical guidelines for the diagnosis, prevention, or treatment of SCI-induced osteoporosis. Diagnosis of osteoporosis is difficult in SCI since no standardized clinical screening recommendations exist to identify those at greatest risk for fracture. This clinical void is due in part to limited information regarding the natural course of SCI-induced bone loss. In this article we will review recent advances in the epidemiology and pathophysiology of SCI-induced osteoporosis and highlight emerging therapeutics as they relate to these advances.

Physiologic Changes in Bone after SCI

Normally, bone formation is tightly coupled to bone remodeling with the amount of new bone formed equivalent to the old bone that is removed. In SCI, bone remodeling becomes uncoupled with an initial decrease in bone formation and steadily increasing bone resorption [6]. Bone formation rates normalize after 2 weeks post-injury, however this immediate uncoupling leads to a 4% per month reduction in sublesional (below the neurologic level of injury) trabecular bone mineral content with a 40% reduction of sublesional BMD by 2 years post-injury [7]. There is controversy in the literature regarding the extent of ongoing, chronic bone loss in SCI. Some studies suggest that bone loss plateaus at 3–5 years post-injury [8, 9]. Other studies have demonstrated ongoing bone loss beyond this initial rapid phase in both the cortical and trabecular compartments of bone. These latter findings are supported by quantitative computed tomography studies demonstrating deterioration of trabecular bone microarchitecture at the distal femur and proximal tibia in men with chronic SCI compared to uninjured controls [10]. There was a positive correlation between time since injury and tibial trabecular number and spacing, suggesting that trabecular deterioration progresses for years after injury. Similarly, trabecular deterioration in post-menopausal women with complete SCI is greater than in ambulatory post-menopausal women [11]. Cortical thinning also occurs in the long bones of the lower extremity following SCI [12, 13]. It has been suggested that cortical thinning is slower and steadier than trabecular loss following SCI [14, 15]. This steady rate of cortical bone loss may account for the finding that the mean time to first fracture is 9 years post-injury in SCI [16, 17].

The implications of continued bone loss are not typically addressed in the clinical setting until a fracture occurs. An improved understanding of the natural history and risk factors for chronic bone loss following SCI is essential to designing therapies to reduce the rate of bone loss, define fracture risk, and ultimately prevent osteoporotic fractures and their associated morbidity.

Role of Sclerostin in SCI-Induced Bone Loss

Elucidation of the Wnt signaling pathways in bone homeostasis has radically transformed our understanding of the cellular and molecular mechanisms governing bone adaptations to mechanical loading and unloading [18, 19]. The currently accepted paradigm states that Wnt binds to a co-receptor complex involving Frizzled receptor and low-density lipoprotein receptor-related protein (LRP)-5 or LRP-6, both present on osteoblasts. This binding stabilizes cytoplasmic β-catenin causing it to translocate to the nucleus. Translocation of β-catenin, in turn, activates the transcription of genes that promote osteoblast proliferation, differentiation and function, ultimately resulting in new bone formation. Several antagonists have been described that can inhibit this signaling pathway. For instance, molecules such as secreted frizzled-related proteins, Wif (Wnt inhibitor factor), and Cerberus, can bind Wnt and functionally block the pathway. Sclerostin and Dickkopf-related protein 1 (Dkk1), on the other hand, inhibit the Wnt pathway by preventing the formation of the Wnt-Frizzled-LRP5 complex by promoting the internalization of the LRP5/6 co-receptor (Dkk1) or by competitive binding to LRP5 (sclerostin) [20, 21].

Recent studies suggest that sclerostin is a key mediator of SCI-induced bone loss. Sclerostin, encoded by the *sost* gene, is produced primarily by osteocytes and is a potent inhibitor of bone formation and growth [22–24]. Mechanical unloading causes up-regulation of sclerostin, leading to reduced Wnt/β-catenin signaling in osteoblasts. While the anti-anabolic role of sclerostin has been well characterized, recent evidence [25] indicates that sclerostin also has catabolic activity. In fact, sclerostin causes up-regulation of RANKL and down-regulation of OPG expression by osteocytes, increasing osteoclast differentiation and activity, ultimately leading to bone resorption. Several elegant animal studies have shown that sclerostin levels are inversely proportional to bone mass [23, 26] and mechanical loading in rats and mice dramatically reduces that production of sclerostin by osteocytes [27–29]. These studies have defined the central role of sclerostin in the pathogenesis of disuse osteoporosis. They provide an explanation for the regulation of bone responses to unloading via a mechanism that permits enhanced or reduced Wnt signaling upon mechanical stimulation or unloading, respectively.

In humans, mechanical unloading of bone occurs in diseases that cause paralysis, or the inability to walk. Therefore, the association between sclerostin and bone loss is expected to be strongest in disease conditions like spinal cord injury. Stroke can also cause paralysis, and sclerostin levels are increased in subjects with mobility impairments studied a mean of 10 months after stroke [30]. Similarly, we recently analyzed circulating sclerostin in 155 men with varying degrees of SCI who were 1 year or more post-injury [31]. Sclerostin levels were *greatest* in subjects with SCI who were injured less than 5 years and decreased significantly as a function of time during this period. In contrast, there was no association between sclerostin and injury duration in subjects with chronic SCI (more than 5 years post-injury). In another study, we evaluated 49 subjects with varying degrees of chronic SCI and found that sclerostin was significantly *lower* during the *chronic* phase of SCI that is characterized by severe osteoporosis [32]. Lower extremity bone mineral density (BMD) was lowest in persons with the lowest circulating sclerostin. These results would seem paradoxical considering the proposed mechanism of sclerostin-induced bone loss in acute SCI. However, in chronic SCI circulating sclerostin is more a *biomarker* of osteoporosis severity because it reflects the reduced bone mass in the paralyzed lower extremity. We assessed the relationship between bone density and several circulating bone-related proteins including sclerostin, DKK-1, sRANKL, osteoprotegerin, osteocalcin, and c-telopeptide in 39 men with chronic SCI and 10 men with no SCI (In Press, Osteoporosis International). We found that only sclerostin was associated with bone density and is therefore a candidate biomarker of osteoporosis severity in chronic SCI. Taken together, these data suggest that

sclerostin levels are initially increased after SCI in response to mechanical unloading and then decrease over time as rapid bone loss progresses. Collectively these findings support a dual role for sclerostin after SCI: a potential therapeutic target in acute SCI to prevent rapid immobility-induced bone loss, and a biomarker of osteoporosis severity in chronic SCI. These findings require confirmation in people with acute SCI followed longitudinally.

Conceptual Model for Sclerostin Mediated SCI-induced Bone Loss

Figure 1 shows a conceptual model for SCI-induced bone loss. Mechanical unloading (paralysis) in acute SCI subjects causes *greater* sclerostin levels than those observed in the able-bodied. This increase is associated with accelerated bone loss and inhibited bone formation during the acute phase of SCI. In the chronic phase, bone-wasting results in *lower* sclerostin levels than those observed in the able bodied due to the reduction of sclerostin-producing osteocytes in the osteoporotic bone.

Sclerostin has potential as a therapeutic target to improve bone in both the general population and in SCI. Preclinical work demonstrated increases in bone formation, bone mineral density, and bone strength in animals treated with an antibody to sclerostin [33–35]. These results supported the development of anti-sclerostin drugs. AMG 785, a sclerostin monoclonal antibody developed by AMGEN, is the most promising candidate. Well tolerated in phase 1 clinical studies [36], AMG 785 is currently being tested in phase 2 trials examining dosing and efficacy. In addition to antibodies that target sclerostin *activity*, sclerostin pathway can be inhibited by PTH and/or mechanical reloading, which inhibit sclerostin *expression* [28, 37].

PTH, Bone, and Sclerostin

Vitamin D deficiency and abnormal parathyroid hormone (PTH) levels are common in both acute and chronic SCI [38]. Acute SCI suppresses PTH levels due to the hypercalcemia that accompanies increased bone resorption [2, 38, 39]. Low PTH may contribute to SCI-induced bone loss. In fact, PTH may mediate its anabolic bone effects in part via suppression of sclerostin expression [40, 41]. Animal studies have demonstrated that PTH suppresses sclerostin production [37] and intermittent PTH treatment has been clinically demonstrated to stimulate bone formation in humans [42, 43]. Moreover, interventions that have the potential to increase bone density in humans, such as functional electrical stimulation and stationary biking, increase PTH levels [44]. If PTH were a negative feedback regulator of sclerostin, suppressed PTH in acute SCI would exacerbate sclerostin-mediated bone loss. On the other hand, variations in PTH levels may modulate the sclerostin response to acute unloading. However, these important relationships remain unstudied in those with acute SCI. PTH levels normalize or are elevated with time [45], and associations between PTH and sclerostin are also uncharacterized in chronic SCI.

Role of Fat-Bone Interactions in SCI-induced Osteoporosis

Obesity is widely considered to be osteoprotective, i.e., persons with a greater BMI are less likely to have osteoporotic fractures [46–48]. However, the relationship between obesity and bone loss in SCI is not known. There is an increase in central (visceral) fat, an increase in fat in the limbs below the level of injury, and some studies have even demonstrated an increase in fat in non-paralyzed limbs above the level of injury. Although BMI is also increased in SCI, the true increase in body fat is and, compared to the able-bodied, persons with SCI have a greater percentage of body fat [49]. Most studies assessing body fat distribution in SCI using DXA scans have demonstrated an 8 to 18% increase in fat mass compared to the able-bodied, but have included relatively few SCI subjects (8 to 20 per study) [50]. In the largest study, the SCI group was 13% fatter per unit of BMI compared to age and sex

matched controls. Advancing age was strongly associated with greater adiposity and decreased lean mass, and the effect of age on adiposity was greater than in the able-bodied [51]. While these data demonstrate that obesity is more common in SCI than the general population, obesity and high fracture rates co-exist in SCI. This suggests that greater fat mass may result in greater loss of BMD in the years following SCI. Some reports in the literature also suggest increased fractures in obese able-bodied adults [52] and obese able-bodied children. Furthermore, obesity in adolescence causes decreased bone strength relative to body weight [53]. The impact of obesity on bone is multi-factorial, and may involve multiple pathways that influence both bone formation and resorption with competing effects on the skeleton. One such pathway involves increased mechanical loading that stimulates bone formation. The protective effect of obesity on bone in the able-bodied may be attributable to the increased mechanical loading of bones during ambulation. Although persons with SCI have greater body fat compared to the able-bodied, muscle paralysis does not permit mechanical loading of the long bones in the lower extremity.

A second pathway linking bone to fat involves adipocyte production of hormones that are known regulators of bone metabolism. Leptin is one example of a bone-regulating hormone produced primarily by adipocytes. Circulating leptin levels are elevated in SCI compared to able-bodied controls, and circulating leptin correlates better with other measurements of adiposity than with BMI [54–56]. Leptin was originally described as the product of the obesity gene. It is known to regulate energy expenditure and appetite via binding to its receptor in the arcuate nucleus of the hypothalamus. This binding triggers sympathetic regulation of energy expenditure in the periphery. The observed link between obesity and bone mass led to the investigation of leptin's role in bone metabolism. Several lines of evidence suggest leptin signals via central and local pathways to regulate both bone formation and bone resorption. The mechanism of central control of bone is similar to but distinct from the hypothalamic relay controlling appetite [57]. The downstream target of this pathway is the beta 2-adrenergic receptor expressed on the surface of osteoblasts. Signaling via this pathway results in leptin-induced suppression of bone formation by sympathetic inhibition of osteoblast activity [58]. Within the bone microenvironment, the leptin receptor is expressed on osteoblasts [59] and has been shown to promote osteoblast over adipocyte differentiation in bone marrow stromal cells [60]. Leptin has also been shown to inhibit *in vitro* differentiation of human peripheral blood mononuclear cells (PBMC) into mature, functional osteoclasts. Leptin may suppress osteoclast differentiation via a target cell within the PBMC population. Therefore, leptin can itself have competing effects on bone metabolism depending upon the signaling pathway. Similarly, adiponectin is a polypeptide hormone produced by osteoblasts and by adipocytes in both visceral and marrow fat depots. Active adiponectin receptors are expressed on bone cells [61] and, although adiponectin levels are typically inversely related to the degree of adiposity, elevated levels of adiponectin have been associated with bone loss in both men and women as well as in rodent studies [62–65]. Elevated serum levels of both leptin and adiponectin have been associated with accelerated bone loss. Each one, acting alone or in conjunction with the other, may contribute to ongoing bone loss in SCI.

Treatment of SCI-induced Osteoporosis: Limitations of Anti-resorptive Agents

The use of osteoporosis medications, including the anti-resorptive bisphosphonates, has been studied in SCI. Bisphosphonates have been shown to slow bone loss in both acute and chronic SCI [66, 67] but none has demonstrated new bone formation. In one study, a 2-year course of treatment with the anti-resorptive medication alendronate was shown to prevent further bone loss in 55 subjects with chronic SCI but did not seem to increase BMD at any skeletal site tested. These results fell surprisingly short of those reported in able-bodied post-

menopausal women where alendronate treatment usually results in increased BMD [68]. Given the extreme skeletal wasting that occurs following SCI, an effective therapeutic intervention should reduce the rate of bone loss and promote normal bone formation. Potential anabolic therapies include mechanical loading and vibration therapy and recent advances in both are discussed below.

Treatment of SCI-induced Osteoporosis: Mechanical Loading

The most profound stimulus to bone formation and, in some cases, for reversal of osteoporosis, is exercise that actively loads the bone. Bone is a dynamic organ that modulates the rate of new bone formation via osteocyte expression of sclerostin in response to varying levels of mechanical strain. In complete spinal cord injury the long bones of the lower extremity adapt to minimal mechanical strain by atrophying as described above. However, reintroduction of mechanical loading may reverse these changes. The skeleton is known to respond to mechanical loading by increasing cortical bone at the site of greatest mechanical strain [69]. However, strain patterns must be atypical, and be delivered with sufficient force and with sufficient frequency to stimulate new bone formation [70]. Bone cells rapidly become desensitized to prolonged loading and therefore periods of rest are required between sessions to maximize osteogenic potential [71, 72]. Based on these findings, the optimal weight-bearing exercise rapidly delivers a high loading force in an unusual distribution with sufficient rest between training sessions. Weight bearing exercises have been shown to increase bone density, cortical thickness, and bone strength in the general population. While weight-bearing is difficult to achieve after lower extremity paralysis, this is now possible with electrical stimulation (ES) and functional electrical stimulation (FES). For this reason, ES and FES training programs are attractive exercise models for the SCI population. Several animal and human studies have shown new bone formation in response to electrical stimulation [73–75]. In a small study of 8 men with acute thoracic motor complete SCI, a single session of electrical stimulation reduced c-telopeptide levels indicating reduced bone resorption 48 hours after treatment [76]. Electrical stimulation of the quadriceps muscle in upright stance reduced bone loss and preserved trabecular bone micro-architecture at the distal femur in seven subjects with SCI compared to 5 subjects who stood without stimulation and 15 subjects with SCI who received no standing or stimulation [77]. Similarly, in a study of 26 subjects with acute (less than 12 weeks post-injury) motor complete SCI, electrical stimulation delivered 1 hour a day, 5 days a week for 6 weeks reduced bone resorption (indicated by n-telopeptide levels) and bone loss at the distal femur [78]. Improvements in bone have also been reported in response to FES-cycling [79]. A recent case-report demonstrated feasibility of a home-based FES-cycling program for people with SCI [80]. The one participant completed 25 of the 27 recommended exercise sessions over a 9 week training period. While these reports are encouraging, the long-term effects of ES and FES on bone and ultimately fracture risk after SCI are unknown. Larger longitudinal studies are required to definitively establish the efficacy of these therapies and to translate of the findings to clinical care.

Treatment of SCI-induced Osteoporosis: Vibration Therapy

Mechanical stimulation via low magnitude mechanical signals (LMMS), has great therapeutic potential in SCI. LMMS have been shown in both human and rodent models to promote new bone formation as well as decrease dietary induced obesity [81]. Limited information exists on vibration therapy for bone in SCI. A case report suggested 10 weeks of whole body vibration therapy combined with standing increased bone density in the trunk and spine for a single subject [82]. Similarly, low-intensity vibration was investigated as a potential therapy for bone loss in SCI. A stimulation applied to the feet was transmissible to

the axial skeleton in 7 subjects with SCI, suggesting this treatment has potential to modulate bone metabolism [83].

Emerging Anti-Osteoporosis Agents: Potential Areas of SCI-induced Osteoporosis Research

Activins are transforming growth factor-β (TGFβ) family and are highly expressed in bone. Blocking the type II activin receptor (ActRIIA) prevents activin A ligand signaling and increases bone formation, bone mass, and bone strength in both normal and ovariectomized mice [84]. Activin blockade may also be beneficial in SCI-induced osteoporosis, but there is no literature to date on this topic. Similarly, cathepsin-K inhibitors have demonstrated early success in clinical studies for treatment of post-menopausal osteoporosis [85], but there is no information in the literature in subjects with SCI-induced osteoporosis.

Conclusion

Osteoporosis is an important complication of SCI. Mechanical unloading after paralysis results in increased osteocyte expression of sclerostin, suppressed bone formation, and indirect stimulation of bone resorption. At this time there are no standard clinical guidelines to prevent the consequences of bone loss after SCI. Sclerostin is both a mediator of acute bone loss in SCI and a biomarker of osteoporosis severity in chronic SCI. Bone-fat interactions may also play a role in SCI-induced osteoporosis, though more research is required to establish this association. Emerging therapeutics to prevent or treat SCI-induced osteoporosis may include anti-sclerostin antibodies, mechanical loading of the lower extremity using ES or FES, and mechanical stimulation via vibration therapy.

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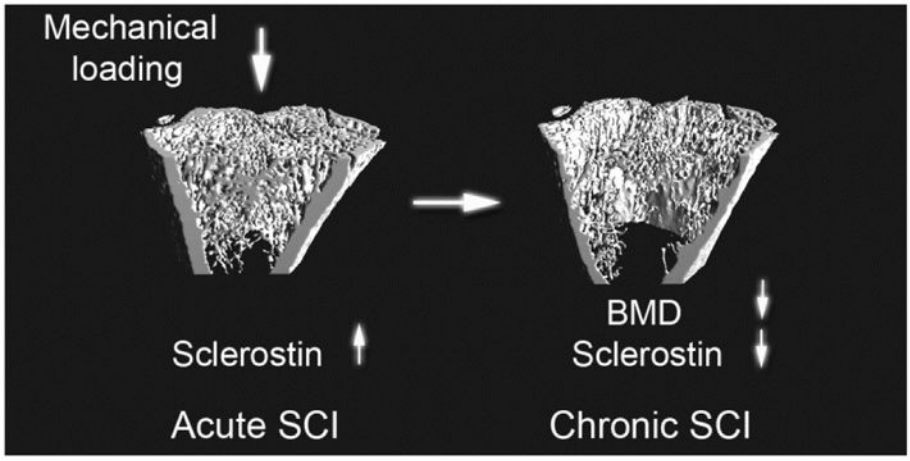

Figure 1.
A possible mechanism to explain a decrease of bone mass and increase fragility in chronic SCI. Immediately after SCI sclerostin levels increase preceding bone loss. In chronic SCI bone wasting is associated with lower sclerostin levels due fewer sclerostin-producing osteocytes in the osteoporotic bone.