Osteoporosis in Individuals with Spinal Cord Injury

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The pathophysiology, clinical considerations, and relevant experimental findings with regard to osteoporosis in individuals with spinal cord injury (SCI) will be discussed. The bone loss that occurs acutely after more neurologically motor complete SCI is unique for its sublesional skeletal distribution and rate, at certain skeletal sites approaching 1% of bone mineral density per week, and its resistance to currently available treatments. The areas of high bone loss include the distal femur, proximal tibia, and more distal boney sites. Evidence from a study performed in monozygotic twins discordant for SCI indicates that sublesional bone loss in the twin with SCI increases for several decades, strongly suggesting that the heightened net bone loss after SCI may persist for an extended period of time. The increased frequency of fragility fracture after paralysis will be discussed, and a few risk factors for such fractures after SCI will be examined. Because vitamin D deficiency, regardless of disability, is a relevant consideration for bone health, as well as an easily reversible condition, the increased prevalence of and treatment target values for vitamin D in this deficiency state in the SCI population will be reviewed. Pharmacological and mechanical approaches to preserving bone integrity in persons with acute and chronic SCI will be reviewed, with emphasis placed on efficacy and practicality. Emerging osteoanabolic agents that improve functioning of WNT/β-catenin signaling after paralysis will be introduced as therapeutic interventions that may hold promise.

Bone Loss After Acute and Chronic Spinal Cord Injury

Bone loss after more neurologically motor complete forms of spinal cord injury (SCI) is unique for its rate, distribution, and resistance to currently available treatments. In individuals with neurologically motor complete SCI, regional bone loss may occur at rates approaching 1% of bone mineral density (BMD) per week at specific regional sites for the first several months after injury [1-3]. Long bone is lost at varying rates, depending on the particular bone and region [4] (Figure 1). The increased rate of bone loss continues beyond the first 12 months of injury for at least the next 3 to 8 years, albeit at a slower rate than that at which it had initially occurred [5]. The rate of bone loss after SCI is substantially greater than that observed with other types of immobilization that are not associated with muscle paralysis (ie, microgravity [0.25% per week] or bed rest [0.1% per week]) or in postmenopausal women who are not taking antiresorptive medications (3%-5% per year) [6-8]. The mechanisms responsible for the more accelerated rate of bone loss after sustaining a motor complete SCI compared to that of immobilization have not been identified, but this dramatic phenomenon may be related to any number of factors. Because bone is richly innervated by sensory and sympathetic nerves, and the former has been suggested to have osteoanabolic influences, the loss of positive central and peripheral neural influences to the sublesional skeleton may be a prime contributor to the rapidity and magnitude of bone loss [9]. Other possible mechanisms that may be speculated to be, at least in part, responsible for this phenomenon include the severity of immobilization, loss of anabolic factors (eg, circulating testosterone and/or growth hormone), factors in the local bone milieu (ie, paracrine influences from atrophying muscle), and the presence of catabolic factors at the time of injury (ie, administration of methylprednisolone at high doses within hours of the acute event, and/or the systemic and/or local production of inflammatory mediators or cytokines).

The areas of high bone loss include the distal femur and proximal tibia, and fractures predominantly occur at these bony sites. In a cross-sectional study of 31 patients with SCI for more than 1 year, Dauty et al [10] demonstrated a demineralization of −52% for the distal femur and −70% for the proximal tibia, bone losses at the knee that are in agreement with the findings of several other investigators [4,11-13]. In a cross-sectional study of men with motor complete SCI,
Figure 1. Percentage of normal bone loss of regions of interest against time since spinal cord injury. Percentage of normal bone loss of femoral neck (top panel), femoral shaft (middle panel), and proximal tibia (lower panel) months after motor complete SCI (lesions: C7 to L1). The median duration of injury for the baseline determination was 43 days (range: 9-167 days), and subjects were followed up for a median of 41 months (range: 31-53 months). A median of 8 DXA measurements (range: 3-13) were performed on each of the 8 subjects (6 men and 2 women). Note that the percentage of normal bone mineral content for each region is dependent on the specific bone, region of bone, and duration of injury [4, reproduced with permission].
which used peripheral quantitative computed tomography in individuals with SCI to describe trabecular and cortical bone compartments until steady state levels were achieved, loss of epiphyseal bone was 50% at the femur and 60% at the tibia (Figure 2); in the diaphysis, which is predominantly cortical bone, losses were 35% in the femur and 25% in the tibia, and involved erosion of the thickness of cortical bone by 0.25 mm/y over the initial 5 to 7 years after SCI [13]. Zehndler et al reported that BMD of the legs decreased markedly over time, with the femoral neck and distal tibial epiphyseal losses initially being exponential before leveling off at 1 to 3 years after injury, whereas the z scores of the distal tibial diaphysis decreased progressively beyond 10 years after injury [14] (Figure 3). From a study of monozygotic twins discordant for SCI, the difference in sublesional BMD between the twins increased with time after SCI for several decades, suggesting that the heightened net bone loss may continue for an extended period of time in individuals with SCI [15] (Figure 4), possibly because of a chronically depressed bone formation rate at cortical bone sites. This level of bony depletion places the knee in particular, but also the entire lower extremity, at greatly increased risk for fracture.

Fracture After SCI

Fracture of the extremities below the level of lesion is a well-appreciated complication of the development of osteoporosis after SCI [14] (Figure 5). Fractures most often involve the tibia or fibula [14,16-20] (Table 1), but upper extremity fractures also occur, most commonly in those with higher cord lesions. Falls from a wheelchair and transfers are the most common causes of fracture, although fractures can also result from low-impact activities, such as performing range-of-motion activities. One recent longitudinal study reported that 15 of 98 persons with SCI sustained 39 fragility fractures of the legs over 1,010 years of combined observation; the mean time to first fracture was about 9 years, with a 1% fracture rate within the first 12 months and 4.6%/y fracture rate if the duration of injury was more than 20 years [14]. Increasing risk for fracture was associated with motor complete SCI, lower level of lesion (eg, individuals with paraplegia tend to be more active than those with tetraplegia), longer duration of injury, greater alcohol consumption [14,17], and use of anti-convulsant medications [21]. The risk of fractures has been found to be closely related to the BMD of epiphyseal trabecular bone [22]. Since persons with SCI may often lack awareness of the acute occurrence of fracture because of the lack of pain secondary to interruption of somatic afferent nerves, they may seek medical attention only for resultant symptoms of swelling at the fracture site, fever, increased muscle spasticity, and/or inexplicable and more frequent occurrence of autonomic dysreflexia. Fractures of the lower extremities can result in the development of joint stiffness, reduced range of motion, skin breakdown, greater pain, and heightened spasticity [23].

Bone Metabolism After SCI

As a consequence of acute SCI, abrupt skeletal unloading results in uncoupling of the functional relationship of the osteoblasts and osteoclasts. Of note, immediately after injury, an increase in the function of both osteoclasts and osteoblasts appears to occur [24]. Eventually, over the ensuing months, a profound depression in osteoblastic bone formation and a marked increase in trabecular osteoclastic resorptive surfaces is observed [25], which is reflected in preclinical studies by the increased numbers of osteocytes from ex vivo cultures of bone marrow cells, and clinical studies with the onset of hypercalcuiar and elevated markers of bone resorption [25-29]. Although not reported, one would assume that bone turnover rate would be markedly depressed in individuals with long-standing SCI.

Vitamin D and Calcium

Serum ionized calcium levels are often elevated after acute SCI because of rapid bone resorption, and these elevated levels are reflected in a markedly increased renal clearance of calcium [30]. Parathyroid hormone (PTH) levels are suppressed in the presence of elevated ionized serum calcium levels (Figure 6), which serves to reduce PTH-mediated tubular absorption of calcium and contributes to increased calciuria. Another previously unrecognized consequence of suppression of serum PTH levels is that low or absent levels would be anticipated to contribute to increased levels of sclerostin, a known potent inhibitor of WNT/β-catenin signaling in osteocytes, with potentially adverse effects on bone health [31,32], which will be discussed subsequently in greater detail.

Persons with severe chronic conditions have long been recognized to be at heightened risk for the development of vitamin D deficiency because of reduced sunlight exposure secondary to lifestyle changes, institutionalization, and/or medications (eg, anti-convulsants and psychotropic agents) that may increase renal clearance of vitamin D [33,34]. Possibly because of the risk of hypercalcemia and/or hypercalciuria, and the associated heightened risk of calcium renal stones early after SCI due to high bone turnover, misguided dietary counseling has encouraged avoidance of dairy products even in persons with chronic SCI (Note: Even in the setting of acute SCI, there is no need to reduce calcium intake because PTH is suppressed, resulting in low gut calcium absorption) [30,35]; this dietary advice has often resulted in lower calcium intake than that in the general population, including
vitamin D—fortified milk, which is the major dietary source of vitamin D [36].

Vitamin D deficiency has been reported to be far more prevalent in SCI cohorts than in the general population [37,38]. About one third of a veteran SCI population in the early 1990s had an absolute deficiency of 25-hydroxyvitamin D (25(OH)D <16 ng/mL) [37]. In a report by Oleson and Wuermser in subjects with chronic SCI, 81% had 25(OH)D levels that were defined as insufficient (<32 ng/mL) in the summer, which increased to 96% in winter, with 54% of these SCI subjects having an absolute deficiency of 25(OH)D levels (<13 ng/dL) [38]. The prevalence of relative or absolute 25(OH)D deficiency was 93%, with a mean level of 16.3 ± 7.7 ng/mL, in a retrospective study of 100 SCI patients who were consecutively admitted to an acute inpatient rehabilitation facility [39].

If 25(OH)D levels are insufficient to provide adequate gut absorption of calcium when potent suppression of bone resorption occurs with the use of antiresorptive agents, such as bisphosphonates or denosumab, profound iatrogenic hypocalcemia may quickly develop. Thus, before initiating such therapies, vitamin D levels should be determined, and when low, vitamin D replacement should be initiated before starting antiresorptive therapy.

Vitamin D supplementation, if at appropriate doses, is effective in restoring vitamin D levels in individuals...
with SCI. In a study evaluating the efficacy of supplemental vitamin D in this population, cholecalciferol (vitamin D3) 2000 IU/d was administered to vitamin D–deficient subjects with SCI for 3 months, which raised the level of vitamin D into the normal range in 85% of subjects, and the mean level of vitamin D after supplementation for the total group was well above the lower limit of the normal range [25(OH)D >30 ng/mL] [40] (Figure 7), a cutoff level for 25(OH)D that would be anticipated to optimize gastrointestinal absorption of calcium [41]. The Endocrine Society, an organization concerned with patients with metabolic bone diseases, has recommended a goal for replacement of 25(OH)D of >30 ng/mL because of the belief that higher values correlate with increased bone density and increased antifracture efficacy; their reasoning also posits that values should be raised above 30 ng/mL because of the variability in vitamin D determination and the relative absence of toxicity with moderately higher values (eg, values <50 ng/mL) [42]. The recommendation of the Institute of Medicine for the general population of North America is to maintain vitamin D levels >20 ng/mL [43], which, in the absence of more compelling evidence, may certainly be appropriate for the vast majority of healthy adults and would serve to reduce the risk of potential adverse events.

Potential Pharmacological Therapies to Prevent or Reduce Bone Loss

Bisphosphonates have been used in an effort to prevent or reduce bone resorption associated with acute SCI. This class of drugs has a strong affinity for bone and inhibits osteoclast bone resorption. The potent amino-bisphosphonates, such as alendronate or zoledronate, act by inhibiting farnesyl pyrophosphate synthase, which interferes with isoprenylation of GTPases at the ruffled border of osteoclasts and prevents attachment.
of osteoclasts to the bone surface, thus halting resorption and initiating cell death [44]. Although there is some evidence that bisphosphonates are efficacious in reducing bone loss in individuals with motor incomplete lesions permitting weight bearing activity [45,46], our experience with the use of bisphosphonates has raised troubling questions concerning the efficacy of this class of medications in persons with SCI who are unable to weight bear or to ambulate (ie, those with more complete motor deficits). This will be discussed subsequently in greater detail.

Bisphosphonate administration was not effective at preventing bone loss or maintaining cortical bone strength in preclinical models of disuse osteoporosis [47,48], which appears to differentiate disuse osteoporosis from other postmenopausal models of osteoporosis in which bisphosphonates have been shown to be efficacious.

In persons with incomplete motor SCI who are able to bear weight and to ambulate, 2 small case series have demonstrated the benefit of bisphosphonate treatment [45,46]; this work does support the administration of bisphosphonates to patients with SCI who weight bear or ambulate. Several encouraging reports on the effect of bisphosphonates on BMD after acute SCI have studied a range of patients with varying degrees of completeness of motor lesions and ability to weight bear [49,50]. These studies provide an important insight that must be considered when evaluating studies of bisphosphonates or other bone-active agents in which the study cohort comprised patients with varying degrees of motor impairment who have vastly different abilities to weight bear and to ambulate. Specifically (as will be discussed shortly), in our experience, bisphosphonates do not positively influence bone loss at the knee after SCI in persons with motor complete SCI, or those in those cannot weight bear. Thus, interpretation of such reports should be made with caution, and conclusions are possible only when the study design and data analysis take motor completeness and weight bearing into consideration. As the field moves forward, it is imperative that investigators prospectively address varying degrees of motor impairment and associated functional capacity in their experimental designs.

Another consideration is that high-dose glucocorticoids may have been administered in an attempt to...
preserve neurological function in prior studies [50-52], but potential effects of glucocorticoids were not controlled for, or even captured, in the experimental design, potentially confounding interpretation of the findings. Shapiro et al administered zoledronic acid to neurologically motor complete patients with acute SCI, and observed apparent benefit at the hip at 6 months (eg, endpoints determined were BMD, cross-sectional area, and measures of bone strength), but these early beneficial effects were almost completely absent at 12 months [52]. Bubbear et al also treated patients with acute SCI and varying degrees of completeness of lesion with zoledronic acid, and demonstrated a more sustained beneficial effect of drug at the total hip, trochanter, and lumbar spine at 12 months; no mention was made of glucocorticoid administration at the time of presentation for acute injury in the study cohort [50]. It should be appreciated that patients with chronic SCI tend to fracture the distal femur and proximal tibia, unlike those in the general population, who tend to fracture at the hip. The knee and more distal lower extremity were not studied in these prior reports [49,50,52]. In a study that determined the BMD of the total leg and knee, pamidronate was repetitively administered over the course of the year after acute SCI, with measurements failing to find a significant effect of drug administration at 1 and 2 years [53]. In recent work, Bauman et al showed that zolendronic acid successfully preserved BMD at the hip 6 and 12 months after acute SCI compared to no treatment, but this agent appeared to result in the increased loss of BMD at the knee [54]. An obvious, but profound, shortcoming of all prior studies with bisphosphonate prescription in the SCI population is the lack of data
receptor activator of nuclear factor-
remodeling. Denosamub (XGEVA
unloading, menopause, or other stimuli for bone
should assess fracture outcomes[55]."
address specific populations (acute or chronic SCI) and
improve reliability of outcomes. Future studies should
control and compliance monitoring are needed to
bone density measurement sites with rigorous quality
patient populations and outcome measures. Uniform
tients. Current studies are limited by heterogeneity of
bisphosphonates for fracture prevention in these pa-
were insufficient to recommend routine use of
in patients with acute SCI concluded the following: "Data
increase BMD in a phase I clinical trial in healthy men
due to disuse[63,64]. Anti-sclerostin antibodies
and osteocytes. The net accrual of bone substance
resonance imaging at the knee at 3 months but not 6 or
subjects; trabecular thickness increased by magnetic
evaluated in 12 chronically injured nonambulatory
combination with robotically assisted gait training were
iparatide on bone mass or metabolism after SCI are
increase osteoclastic activity and reduced osteoblastic
function.

A potent inducer of bone resorption is the cytokine
stimulates both osteoclastogenesis and function.
RANKL is produced primarily in bone in response to
unloading, menopause, or other stimuli for bone
remodeling. Denosamub (XGEVA®) is a human mono-
clonal antibody to RANKL that represents a novel
immunological/pharmacological Food and Drug
Administration (FDA)—approved approach to the
treatment of osteoporosis. The mechanism of action of
denosamub is distinctly different from that of
bisphosphonates, although both agents inhibit the
osteoclast. Analyses of bone density and bone turnover
rate demonstrated that the effects of denosumab on
bone remodeling appear to be more potent than those
of bisphosphonates [56,57]; denosumab dramatically
reduced eroded bone surfaces compared to the effect of
bisphosphonates, which may be requisite for drug
efficacy after acute SCI because of the robust
osteoclastosis/bone resorption that develops shortly
after the acute immobilization of paralysis.

Paralysis, casting of limbs, prolonged bed rest, or
weightlessness in preclinical trials of immobilization
resulted in substantial bone loss due to uncoupling of
the osteoclast from the osteoblast, with an observed
initial phase of accelerated bone resorption and a pro-
longed phase of decreased formation [58,59]. In several
animal models of disuse (eg, spaceflight, tail suspen-
sion, and sciatic nerve injury), appropriate manipula-
tion of the OPG/RANKL system was highly efficacious at
preserving cortical bone mass [60]. Findings in an animal
model of acute SCI suggest that a several-fold increase
in RANKL expression after acute SCI occurs together
with an almost 2-fold increase in osteoclast differenti-
markers in ex vivo cell cultures [61]. Because of
excessive RANKL expression after acute SCI in a rodent
model of acute SCI, it may be postulated that an
appropriate agent in human clinical trials would be one
that directly and effectively antagonizes RANKL to
markedly reduce function of the osteoclast. It should be
appreciated that, as yet, there is no report on the
efficacy of denosumab administration in mitigating
the high bone turnover state of acute SCI. In contrast
to the marked osteoclastosis, osteoblast differentiation
markers were found to be profoundly depressed [61]. As
such, there appears to be the dual challenge in SCI to
preserve bone integrity in the presence of both
increased osteoclastic activity and reduced osteoblastic
function.

Teriparatide (recombinant PTH 1-34) is the only
agent available at present with the ability to stimulate
osteoblast activity and function. The effects of ter-
paratide on bone mass or metabolism after SCI are
unclear. In one small case series, effects of teriparatide
combined with robotically assisted gait training were
evaluated in 12 chronically injured nonambulatory
subjects; trabecular thickness increased by magnetic
resonance imaging at the knee at 3 months but not 6 or
12 months; BMD measurements after treatment at the
spine and hips were not statistically significant [62].
Teriparatide administration activates both osteoblasts
and osteocytes. The net accrual of bone substance
observed with teriparatide administration in able-
body populations is lost after about 2 years of
starting its administration, and drug holidays or dis-
continuation of treatment are recommended for this
reason. If teriparatide is prescribed acutely after SCI,
when hypercalcemia and/or hypercalciuria are often
present, close monitoring of serum calcium levels is
suggested.

Sclerostin, one of the inhibitors of the conical Wnt
signaling pathway in bone, has recently been demon-
strated to be a crucial regulator of bone cells that is a
critical molecule in the pathogenesis of osteoporosis
due to disuse [63,64]. Anti-sclerostin antibodies
increased BMD in a phase I clinical trial in healthy men

Figure 7. Serum vitamin D [25(OH)D] levels after supplementation
with 2000 IU/d. Values are displayed for 7 subjects after months 1 and
3 of replacement vitamin administration. Note that 6 of 7 subjects had
25(OH)D levels >30 ng/mL by month 3; the only subject who did not
normalize the 25(OH)D level by month 3 approached the lower limit of
normal (ie, 28 ng/mL) from a baseline value of 17 ng/mL [40, repro-
duced with permission].
and postmenopausal women [65]. In a phase II trial of romosozumab, a monoclonal anti-sclerostin antibody, was administered monthly to postmenopausal women with low BMD, and this approach was reported to be more potent than alendronate or teriparatide at increasing the percentage of BMD from baseline at the lumbar spine, total hip, or femoral neck [66]. This agent is currently in phase 3 clinical trials in postmenopausal osteoporosis. In a preclinical trial, reduction in sclerostin, either by the administration of antiscerostin antibody or by use of a sclerostin knockout mouse model, almost completely prevented the SCI-induced reduction of BMD at the femur and tibia, as well as at several other regions of interest; reducing sclerostin decreased the production of osteoclasts and increased the number of osteoblasts in ex vivo cultured bone marrow stem cells [67]. Therefore, the prescription of antisclerostin antibody may be a highly efficacious antcatabolic, as well as an anabolic, therapy to prevent, reduce, and/or possibly reverse bone loss after acute and chronic SCI.

Effects of Mechanical Loading and Electromagnetic Fields on Bone

Appropriate and sufficient mechanical loading of the skeleton is obligate for maintenance of bone health. Mechanical stress and strain is sensed sensed by the osteocyte by the osteocyte to induce a coordinated, regional response by osteoclasts and osteoblasts [64,68]. Loading forces to bone must be delivered with sufficient intensity and frequency to stimulate bone formation and to inhibit bone resorption. For a discussion of this topic that addresses the variety and efficacy of various mechanical interventions on preserving bone after acute injury or reversing bone loss after chronic injury, the reader is referred to a review by Biering-Sørensen et al [69]. Microgravity, or space-flight, results in significant bone loss, but 1 year of gravitational loading by returning to earth generally leads to significant reversal of these bony changes in most astronauts [70]. Thus, it may also be possible to prevent or reverse loss of bone mass and strength, even after complete motor lesions, by devising an approach that will appropriately and consistently restore mechanical forces to the sublesional skeleton.

Static mechanical loading of the sublesional skeleton after SCI has been ineffective in reducing loss of BMD [71,72]. Partial body weight–supported treadmill training is associated with cyclical reloading but has also proved to be ineffective in reducing bone loss after acute SCI or increasing bone mass in individuals with chronic paralysis [73,74]. However, functional electrical stimulation (ES) using cyclical muscle contraction has been shown to be beneficial to bone mass. During ES with surface electrodes activates muscular contraction. In one study, the effects of isometric contraction of the soleus muscle over 4 to 6 years and initiated within several months of acute SCI were examined for the tibia as compared to the contralateral tibia. Whereas the untreated leg lost BMD progressively over time, ES partially preserved trabecular bone along the posterior aspect of the tibia (where the forces applied by ES were greatest) [75] (Figure 8); trabecular bone in the tibia from the ES-trained leg was about double that for the untrained leg and was only 25% lower than the corresponding region of interest in able-bodied controls. A separate study suggested that combining ES with standing may have a greater beneficial effect on BMD of the hip and the knee in a subset of subjects with subacute SCI than ES alone, and that standing alone resulted in a decrease in BMD of these regions [76].

FES was less effective in its ability to increase bone mass in individuals with chronic SCI who had long-established and fairly marked bone loss, possibly because of greater antecedent loss of trabecular architecture [77]; however, after ES training, either on a cycle ergometer or with knee extension against resistance, bone mass was increased in those with chronic injury [78,79], demonstrating that even years after SCI it may be possible to stimulate net accrual of bone. Summarizing these findings, ES training administered at the time of acute injury appears to markedly reduce bone loss at the site applied or, if administered to those with chronic SCI, is also efficacious, albeit with a reduced magnitude of effect, at the site to which the load is applied. Translation to clinical care has been fraught with considerable difficulty due to the labor-intensive nature of the present approaches and the appreciation that any effect on bone is rapidly lost when the ES training is either reduced in frequency or terminated. As such, a modality that provides

![Figure 8. Bone mineral density (BMD) of the posterior tibia region. Values are expressed as mean (standard error [SE]) for non–spinal cord injury (SCI) cohort (provided on right side of figure) and chronic SCI cohort (provided on left side of figure). Data from all other subjects are presented longitudinally, with each limb displayed separately [75, reproduced with permission].](image-url)
sufficient skeletal loading which can be successfully incorporated into activities of daily living with initial rehabilitation would be the optimal strategy to maintain bone mass.

Low-intensity, high-frequency vibration has been found to reduce bone loss in children with disuse osteoporosis due to neurological impairments and in postmenopausal women [80,81]. Low-intensity mechanical signals can be feasibly delivered through the lower appendicular and axial skeleton even while supine in subjects with SCI; however, as expected, transmission of mechanical signal is increased with additional load applied by increasingly upright posture [82] (Figure 9). The value of low-intensity vibration as a mechanical intervention has yet to be adequately tested in the prevention or reduction of bone loss in patients with acute or subacute SCI. In a female rat model of moderate severity contusion injury of the mid-thoracic spinal cord, the effect of low intensity vibration initiated 28 days after SCI (15 minutes twice daily for 35 days) was investigated; LIV did not significantly increase BMD or trabecular bone (BV/TV), although the length of stimulation was relatively short for the control group and 0.861 for the SCI group, which are not significantly different (P = .98). There is increased transmission for increased %BWT for control (P < .01) and SCI (P < .05) groups [82]. Of note, LIV increased serum osteocalcin, an indirect measure of bone formation, and reduced the SCI-induced 2-fold elevation of osteocalstogenic potential of marrow precursors by 70% and favorably altered gene expression in osteoblasts, completely reversing the 2-fold elevation in mRNA levels for SOST and the 40% reduction in mRNA for Runx2. However, in a trial in 9 subjects with motor complete SCI with durations of injury of 2 or more years, LIV administered for 20 minutes per day for 5 days per week over 6 months had no effect on BMD or trabecular bone architecture [84]. Additional preclinical models or human studies are needed to establish the potential beneficial effects of LIV on bone in individuals with SCI and the optimal frequency, intensity, and duration of low intensity vibration.

In tissue culture and animal models, electromagnetic stimulation has shown a remarkable effect to modulate human mesenchymal stem cell osteogenesis, favorably alter cytokine profiles during disuse osteoporosis, promote bone formation and repair, regulate proteoglycan and collagen synthesis, and increase bone formation in models of endochondral ossification [85-88]. The effect of pulsed electromagnetic fields applied unilaterally at the knee in subjects who were injured at least 2 years revealed increased BMD of the stimulated knee and decreased BMD of the contralateral knee at 3 months, a return to baseline levels of BMD at 6 months, and a fall in BMD of both knees by 12 months, with generally larger magnitude of changes closer to the site of stimulation; these complex and constantly evolving findings for BMD in this experimental model suggest both local and systemic effects of pulsed electromagnetic field stimulation on bone above and below the knee [89]. It should be evident that additional studies with the application of electromagnetic field stimulation on bone may hold promise, albeit, to date, the direction of effect over time was unpredictable and unsustainable.

**Combined Pharmacological and Mechanical Therapy**

A combination of mechanical and pharmacological interventions would be a logical approach to prevent or reduce bone loss after acute SCI. It may be necessary to begin therapy with drug intervention(s) because of the inherent difficulty of instituting a mechanical intervention immediately after the injury. A pharmacological approach to target and inhibit RANKL in an effort to suppress rampant osteoclastosis may be effective as well as practical even for the acutely ill or bedridden patient. To provide hormone replacement therapy for the frequently encountered hypogonadal state in men after acute or subacute SCI is another approach worth considering [90]; a relative or absolute testosterone deficiency state may occur precipitously after paralysis and may be assumed to worsen bone loss, as it does in men on androgen ablation therapy for prostate cancer [91]. Another reason to consider testosterone replacement therapy in those who may be

![Figure 9. Transmission of vibration. Percentage of transmission (P2P% Transmission) for able-bodied control (solid circles) and spinal cord injury (SCI) (open squares) subjects for the vibrating plate (delivering 0.27 g at 34 Hz). The percentage of transmission is the percentage of the vibration signal detected at the mouth. The percentage of body weight (%BWT) is that which is loaded on the vibrating plate. The slopes of the regression lines associated with transmission are 0.923 for the control group and 0.861 for the SCI group, which are not significantly different (P = .98). There is increased transmission for increased %BWT for control (P < .01) and SCI (P < .05) groups [82], reduced with permission].
hypoestrogenic and hypogonadal shortly after paralysis is that high-dose methylprednisolone is prescribed at time of acute SCI [51], and it is well appreciated that such administration is likely to exacerbate bone loss due to the sudden unweighting of the skeleton after an SCI; studies in both animals and humans have demonstrated that testosterone attenuates the adverse effects of glucocorticoids on muscle and bone [92-94].

An approach combining a mechanical intervention with at least one pharmacological therapy may have synergistic effects, as exemplified by the apparent benefit of bisphosphonates in patients with SCI who can weight bear or ambulate [45,46], the suggestive benefit of parabutamide and gait training [62] and by findings that in preliminary results observed with the combination of teriparatide and gait training [51], and it is well appreciated that such administration is likely to exacerbate bone loss due to the sudden unweighting of the skeleton after an SCI; studies in both animals and humans have demonstrated that testosterone attenuates the adverse effects of glucocorticoids on muscle and bone [92-94].

Emerging Therapies

There are several categories of emerging, mechanism-based pharmaceuticals that may have value in treating bone disorders after SCI. Inhibitors of the action on bone of bone-morphogenic proteins, members of the transforming growth factor—β family, represent an emerging class of osteoanabolic agents [97] that may eventually prove to be efficacious in the preservior of bone mass after paralysis. Inhibitors of cathepsin K, a protease critical to resorption of bone by the osteoclast, are now in clinical trials for postmenopausal osteoporosis and could be beneficial in attenuating bone loss after SCI. Synthetic anabolics that do not stimulate prostate but that retain full anabolic activity toward muscle and bone have been developed by several pharmaceutical companies and are currently in clinical trials. As anabolics mitigate bone loss in animal models of SCI [98,99], these agents are additional promising candidates in the search for safe and effective candidates to preserve bone and to reduce the risk after SCI.

References


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Disclosure

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CME Question

What is the weekly rate of bone loss during the first several months after a spinal cord injury?

a. 0.1%
b. 1.0%
c. 3.0%
d. 0.25%

Answer online at me.aapmr.org