Measurement of Bone: Diagnosis of SCI-Induced Osteoporosis and Fracture Risk Prediction

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Background: Spinal cord injury (SCI) is associated with a rapid loss of bone mass, resulting in severe osteoporosis and a 5- to 23-fold increase in fracture risk. Despite the seriousness of fractures in SCI, there are multiple barriers to osteoporosis diagnosis and wide variations in treatment practices for SCI-induced osteoporosis. Methods: We review the biological and structural changes that are known to occur in bone after SCI in the context of promoting future research to prevent or reduce risk of fracture in this population. We also review the most commonly used methods for assessing bone after SCI and discuss the strengths, limitations, and clinical applications of each method. Conclusions: Although dual-energy x-ray absorptiometry assessments of bone mineral density may be used clinically to detect changes in bone after SCI, 3-dimensional methods such as quantitative CT analysis are recommended for research applications and are explained in detail. Key words: bone density, finite element analysis, fracture, osteoporosis, QCT, rehabilitation medicine, spinal cord injury

Acute spinal cord injury (SCI) is associated with rapid loss of bone mass, resulting in severe osteoporosis and eventual fracture in up to 50% of all affected individuals. Fractures after SCI are associated with high rates of complications, prolonged hospital stay, and diminished quality of life. Given the already high rate of secondary conditions in this population, preventing fractures is an important clinical goal. However, there is currently no standard of care for preventing or treating bone loss after SCI, and there are no validated fracture prediction tools available for assessing risk. This article will review the biological and structural changes that are known to occur in bone after SCI in the context of promoting future research to prevent or reduce risk of fracture in this population. We will also review the most commonly used methods for assessing bone after SCI and discuss the strengths, limitations, and clinical applications of each method.

Fracture Incidence and Consequences

SCI resulting in partial or complete paralysis initiates a cascade of physiologic changes within the bone. In healthy adults, bone adapts to its habitual loading environment, with higher-than-usual bone loading resulting in net bone apposition and less-than-usual bone loading resulting in net bone resorption. SCI causes an immediate and permanent reduction in the bone loading experienced by the lower extremities. This, along with endocrine, neural, and vascular changes, is a primary cause of bone loss after SCI. Consequently, individuals with SCI have reported fracture risks 5- to 23-fold higher than able-bodied individuals of similar age. Incidence of fracture has been reported as 2.2% to 2.8% per year, although more recently incidence has been reported as high as 7.4%. Fracture incidence is known to increase as a function of time since injury, with around 1% incidence in persons injured fewer than 10 years but 3.4% to 4.6% fractures per year in persons more than 10 years from injury. The net result is a cumulative fracture rate of over 40%. Fractures tend to be localized to the lower limbs, with the knee (proximal tibia or distal femur) being a common fracture site. Both the femur and the lower leg (tibia and fibula) appear to fracture at about the same rate. Causes of fracture include...
wheelchair transfers, falls, bumping unseen objects, and other low-impact activities such as rolling over in bed.

Fractures in people with SCI are associated with a high rate of complications. Fractures often require prolonged hospitalization\textsuperscript{10} and commonly result in serious medical complications, including pressure ulcer formation, increased pain, spasticity, fracture non-union, lower limb amputation,\textsuperscript{10,11} and increased mortality.\textsuperscript{3} A recent report found that over 80\% of fractures were managed operatively and 13.5\% had complications.\textsuperscript{9} Other studies have reported complication rates as high as 53\% to 54\%,\textsuperscript{3,10} with the most common complications being pressure ulcers, respiratory illness, urinary tract infections (UTIs), and delirium. Despite the seriousness of fractures after SCI, there are multiple barriers to osteoporosis diagnosis and wide variations in treatment practices for SCI-induced osteoporosis.

Two Phases of SCI-Induced Bone Loss: Acute Versus Chronic

The accepted paradigm for SCI-induced bone loss involves 2 phases: (1) rapid, acute bone loss that plateaus approximately 2 years after injury, and (2) chronic ongoing bone loss that is slower but may proceed for decades after injury.\textsuperscript{12-16} In the acute phase, immediately following SCI, markers of bone turnover indicate that bone formation is suppressed with steadily increasing bone resorption.\textsuperscript{17} Immediate osteocyte and osteoblast apoptosis have been reported in rodents during hind limb unloading, providing a cellular mechanism for the suppressed bone formation and rapid bone loss.\textsuperscript{18} The acute phase of bone loss after SCI includes rapid changes to cortical and cancellous compartments of the femur and tibia. Multiple investigators have used dual-energy x-ray absorptiometry (DXA), peripheral quantitative computed tomography (pQCT), and quantitative computed tomography (QCT) to document changes to bone mass and bone structure following SCI. In a series of 31 patients with acute SCI, bone mineral content (BMC) of the legs decreased linearly at a rate of 0.59\% per week (2.5\% per month) over a 60-week period, with lower rates of bone loss observed in individuals who recovered walking.\textsuperscript{19} Similarly, in 15 men studied within 6 months of injury, quantitative ultrasound and DXA documented decreases in proximal tibia bone measures of 5.3\% to 8.5\% over a 6-week period.\textsuperscript{20} A staggering 40\% loss of lower extremity bone density has been reported by 2 years after injury.\textsuperscript{21} Bone loss during the acute period after SCI stems from 2 primary sources: decreased bone mineral density (BMD) within cancellous compartments, and cortical thinning within cortical compartments. Reports based on pQCT and QCT measurements have documented bone loss from cancellous sites at the epiphysis at rates of 5\% to 35\% per year for the first 3 years following injury.\textsuperscript{22} At the distal femur, a primarily cancellous site, BMC and volumetric BMD (vBMD) decrease rapidly, plateauing at values 46\% to 52\% below a reference group by 2.9 to 4.1 years following injury.\textsuperscript{23,24} In a longitudinal study following 6 men with acute SCI for 12 months, distal femur and proximal tibia BMC decreased by 30\% and 37\% respectively.\textsuperscript{25} Similarly, a recent longitudinal study following 13 individuals with acute SCI documented loss in vBMD of 2.0\% to 4.4\% per month in cancellous compartments of the proximal femur, distal femur, and proximal tibia.\textsuperscript{26,27} Reports based on QCT measurements demonstrate that cortical bone loss occurs primarily due to thinning from the endosteal surface. In acute injury, the cortical compartments of the proximal femur, distal femur, and proximal tibia showed low rates of vBMD loss (0.5\% to 1.0\% per month), high rates of BMC loss (1.0\% to 5.8\% per month, with higher rates at the epiphyses), loss of cortical volume (0.5\% to 5.3\% per month), and no significant change in overall (integral) bone volume.\textsuperscript{26,27} Overall, acute changes to bone structure were associated with estimated 6.9\% per month and 4.1\% per month reductions in proximal femur and proximal tibia fracture strength, respectively.\textsuperscript{28,29} Similarly, cross-sectional pQCT measures documented a 30\% reduction in mid-diaphyseal femur cortical cross-sectional area but no change in femur outer diameter in individuals with long-term SCI compared to a reference group.\textsuperscript{24} Collectively, these reports indicate that a reduction in the volume
of the cortical compartment, primarily through resorption at the endosteal surface, is responsible for much of the observed bone loss after SCI and has severe mechanical consequences.

**Chronic Bone Loss and Changes in Bone Structure**

The chronic phase of bone loss (more than 2 to 3 years after injury) is poorly defined. However, it is known that the mean time to first fracture is 9 years after SCI. The implications of chronic, ongoing bone loss are not typically addressed in the clinical setting until a fracture occurs. Slow rates (0.45% per month) of bone loss have been documented at the tibial epiphysis as late as 10 years from injury. Notable in all published longitudinal studies is the considerable amount of variation in rates of bone loss among participants. Some individuals experienced few detectable changes, whereas others experienced rapid and profound loss. This may be due to small studies with large subject heterogeneity.

Long-term SCI is associated with significant reductions in BMD, bone strength, and muscle mass in the lower limbs. Reductions in femoral neck BMD of 27% to 40%, knee BMD of 37% to 70%, and tibia cortical diaphysis BMC of 7% to 25% are typical. Peripheral QCT measures have documented cortical tibia and femur site BMC as low as 33% below an age-matched reference group. QCT measures show as much as 80% to 90% reductions in epiphyseal tibial BMC, with a corresponding 69% reduction in (finite element-predicted) fracture strength. Indeed, distal femur trabecular BMD below 110 mg/cm² and distal tibia trabecular BMD below 70 mg/cm² by pQCT have been shown to discriminate between individuals with and without fracture. Twenty to 30% reductions in bone moments of inertia and BMD at the mid-femur and mid-tibia and 50% to 60% reductions in BMD at the knee have been documented in injured versus non-injured twins. Trabecular micro-architectural measures such as appBV/TV and appTb.N at the distal femur and proximal tibia are reduced by 20% to 27% compared to healthy control subjects.

Consistent with the magnitude of bone loss, the majority of individuals with long-term SCI are osteoporotic based on bone density at the hip. One large cohort-based study reported that 48% of men with SCI for more than 5 years were osteoporotic by DXA. Others have reported osteoporosis prevalence of 21% to 35% in adults with mixed-duration chronic SCI. The prevalence may be greater in individuals with SCI who do not ambulate. Nearly 70% of male wheelchair users with SCI were osteoporotic at the hip compared to 15% of men with SCI who walked.

**Etiology of Bone Loss and Fracture Risk Prediction After SCI**

Loss of lower extremity mechanical loading following paralysis is the primary cause of disuse osteoporosis. Wheelchair users with SCI are more likely to have reduced lower extremity bone density, to have osteoporosis determined by DXA, and are more likely to report a post-SCI osteoporotic fracture than individuals with SCI who retain the ability to walk. Sclerostin, a Wnt signaling antagonist, is thought to mediate the acute bone response to loss of mechanical loading. Bone–fat interactions have been suggested to play a role in ongoing bone loss in chronic SCI. Adiponectin, an adipokine produced by visceral fat, is negatively associated with both bone density and bone strength in male wheelchair users with SCI. This is thought to be due to direct actions of adiponectin on bone cell receptors to regulate osteoblastogenesis and osteoclastogenesis. Few other clinical or demographic factors associated with the severity or rate of SCI-induced bone loss have been identified to date. This may be due to a lack of large, multicenter studies possessing the power to adequately assess and identify such factors.

Disuse osteoporosis is more rapid than postmenopausal or age-related bone loss. Additionally, demineralization after SCI progresses in a distal to proximal fashion, affecting the calcaneus to a much greater degree than the hip. Clinically relevant fracture sites include the distal femur, proximal tibia, ankle, and to a lesser degree the hip following SCI. This is distinct from osteoporosis in the general population where fractures are most common at the hip, radius, and lumbar spine. As a result, protocols for assessing bone health and fracture risk in the
general population have uncertain clinical utility in SCI. In the general population, the World Health Organization (WHO) criteria are used clinically to diagnose osteoporosis based on bone density in men and women over the age of 50. The WHO Fracture Risk Assessment Tool (FRAX) estimates 10-year fracture risk based on bone density and clinical risk factors. However, there is no information on fracture risk based on WHO bone density categories following SCI and FRAX has not been validated in this population. Given this clinical void, fracture thresholds and breakpoints based on bone density in g/cm$^2$ rather than WHO bone density categories have been proposed.\textsuperscript{37,38} Craven et al\textsuperscript{38} have put forth a clinical paradigm based on bone density (BMD) and the following known risk factors for fracture after SCI: age at injury less than 16, female sex, duration of SCI 10 years or more, motor complete SCI, paraplegia, body mass index (BMI) less than 19, alcohol intake greater than 5 servings per day, prior fragility fracture, and family history of fragility fracture.

DXA measurement of BMD is a widely adopted and low-cost method for assessing bone health. However, the most common measurement sites for the diagnosis of age-related osteoporosis, the lumbar spine and proximal femur, are not the most common fracture sites in people with SCI. In this context, several groups have adopted or modified existing analysis protocols for application at the distal femur or proximal tibia. Typically, these involve manually drawing boxes on the image to identify analysis regions of interest. Patient positioning and standardized protocols have been reported by several groups. All show good reproducibility, with RMS coefficients of variation ranging from 2% to 3\%.\textsuperscript{39-41} DXA measurements are also highly correlated with quantitative CT measurements from the same anatomic site.\textsuperscript{40} As a general principal, the larger the analysis region of interest and the less subjectively it is delineated, the more reproducible the measure. Although DXA is low cost and widely available, it has limitations: it is sensitive to poor patient positioning, artifacts from heterotopic ossification, fracture non-union, and instrumentation, and the patella often overlaps with the site of interest. Despite these limitations, DXA remains a useful clinical tool for identifying individuals at elevated risk for fragility fracture and for tracking large changes in bone mass.

**Three-Dimensional Measurement of Bone As an Alternative to DXA**

Whereas the standard of care in the general population is based on bone density measured with DXA, it is well acknowledged that bone density fails to completely explain fracture risk. Bone density provides no information on bone quality or bone strength. Furthermore, DXA scanning can be difficult to perform after SCI due to hip and knee flexion contractures that limit correct positioning, lower extremity amputation, or the presence of heterotopic ossification. For these reasons, bone strength determination by QCT and finite element (FE) analysis based on CT data has been studied to improve fracture risk prediction. QCT analysis is based on the principle that each voxel (3-dimensional pixel) has an associated x-ray attenuation (gray scale, measured in Hounsfield units [HU]) and volume (determined by the scan resolution). The HU value is linearly proportional to the amount of mineral present at that location, or $\rho_{\text{min}}$ (g/cm$^3$), determined with a calibration phantom. By summing the volume of all voxels enclosed within a specific region, bone volume can be calculated. Similarly, bone mineral content may be calculated by multiplying $\rho_{\text{min}}$ (g/cm$^3$) by volume (cm$^3$). This principle can be used to determine bone volume, volumetric bone mineral density (vBMD; g/cm$^3$), and volumetric bone mineral content (vBMC; g) for integral (everything within the periosteal surface), cortical, and trabecular regions of a given bone. Simple structural measures such as moments of inertia and bending indices, which provide insight into bone mechanical behavior based on the distribution of mineral, can also be calculated using this methodology.\textsuperscript{42} QCT has been shown to be highly repeatable at several anatomic sites, and its 3-dimensional nature makes it suitable to detect subtle structural changes that would not be apparent with DXA. The disadvantages of this technique include cost and radiation dose (0.01 to 2.5 mSv for a typical stack of images, depending
the appropriate context. Because of the number of assumptions and simplifications that must be made when creating an FE model of bone, it is ideal that models be validated against cadaveric testing. Fortunately, many validated modeling methods explain 80% to 90% of the variance in fracture strength or stiffness at the distal radius, proximal femur, tibia, and vertebrae. Specific to SCI, subject-specific FE models have been developed to predict proximal tibia torsional stiffness and strength with less than 10% absolute error, a significant improvement compared to DXA or quantitative CT-based statistical models. FE models have also indicated diminished tibial strength in SCI versus able-bodied subjects, and subject-specific models have demonstrated that bone strength is lost at approximately twice the rate of BMC after injury. Generally, CT-based FE models of bone will account for any characteristics of the bone that can be detected by CT. These include structural features of bone loss after SCI such as cortical thinning and changes in cancellous density or mineral distribution. However, changes to bone not detectable with CT, such as collagen cross-linking or fracture toughness, will not be accounted for with FE and probably account for a portion of the unexplained 10% to 20% data scatter.

**Recommended Outcome Measures for Research on Post-SCI Bone**

Clinical trials and other research targeting bone health after SCI require a higher level of detail and precision than clinical care. We believe that DXA is not adequate in terms of sensitivity and specificity to definitively confirm or negate the efficacy of novel osteogenic therapies. DXA may be considered as a secondary outcome in clinical trials designed to establish an osteogenic effect. Additionally, DXA may be an appropriate research outcome for an established intervention known to stimulate large increases in lower extremity bone density. We therefore recommend that quantitative CT measures be adopted as a primary outcome measure for clinical trials. When performed correctly, QCT measures are accurate and repeatable and can be performed at any relevant anatomic site. However,
care must be taken to standardize data acquisition settings such as patient positioning, x-ray intensity, field of view, slice thickness, and CT reconstruction algorithm. It is also critical that objective and repeatable methods be established for aligning the bones to be analyzed to ensure a common analysis region and for defining compartmental boundaries for analysis. A calibration phantom must be included with the scan, but even so, it is important that longitudinal data be collected on a single scanner to avoid systematic error. FE models are another optional and physiologically relevant outcome that directly address the research question of whether an intervention has changed fracture strength. We consider FE outcomes to be important that longitudinal data be collected and that measurements are included with the scan, but even so, it is important that longitudinal data be collected on a single scanner to avoid systematic error. FE models are another optional and physiologically relevant outcome that directly address the research question of whether an intervention has changed fracture strength. We consider FE outcomes to be important that longitudinal data be collected and that measurements are included with the scan, but even so, it is important that longitudinal data be collected on a single scanner to avoid systematic error. FE models are another optional and physiologically relevant outcome that directly address the research question of whether an intervention has changed fracture strength. We consider FE outcomes to be important that longitudinal data be collected and that measurements are included with the scan, but even so, it is important that longitudinal data be collected on a single scanner to avoid systematic error.

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REFERENCES


55. Edwards WB, Schnitzer TJ, Troy KL. Torsional stiffness and strength of the proximal tibia are better predicted by finite element models than DXA or QCT. *J Biomech.* 2013;46:1655-1662.
