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Bone Fragility after Spinal Cord Injury: Reductions in Stiffness and Bone Mineral at the Distal Femur and Proximal Tibia as a Function of Time

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Abstract

INTRODUCTION: Spinal Cord Injury (SCI) is associated with bone fragility and an increased risk of fracture around the knee. The purpose of this study was to investigate bone stiffness and mineral content at the distal femur and proximal tibia, using finite element (FE) and computed tomography (CT) measures.; A cross-sectional design was used to compare differences between non-ambulatory individuals with SCI as a function of time after injury (0–50 years).

METHODS: CT scans of the knee were obtained from 101 individuals who experienced an SCI 30 days to 50 years prior to participation. Subject-specific FE models were used to estimate stiffness under axial compression and torsional loading, and CT data was analyzed to assess volumetric bone mineral density (vBMD) and bone mineral content (BMC) for integral, cortical, and trabecular compartments of the epiphyseal, metaphyseal, and diaphyseal regions of the distal femur and proximal tibia. **RESULTS:** Bone degradation was well described as an exponential decay over time ($R^2 = 0.33 - 0.83$), reaching steady-state levels within 3.5 years of SCI. Individuals at steady-state had 40% to 85% lower FE derived bone stiffness, and robust decreases in CT mineral measures, compared to individuals who were recently injured ($t = 47$ days). Temporal and spatial patterns of bone loss were similar between the distal femur and proximal tibia.

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CONCLUSIONS: After SCI, individuals experienced rapid and profound reductions in bone stiffness and bone mineral at the knee. FE models predicted similar reductions to axial and torsional stiffness, suggesting both failure modes may be clinically relevant. Importantly, CT derived measures of bone mineral alone under-predicted the impacts of SCI, compared to FE derived measures of stiffness.

SUMMARY

Computed tomography and finite element modelling were used to assess bone structure at the knee as a function of time after spinal cord injury. Analyzed regions experienced degradation in stiffness, mineral density, and content. Changes were well described as an exponential decay over time, reaching steady-state 3.5 years after injury.

Keywords

Osteoporosis; Finite Element Modelling; Spinal Cord Injury; CT Imaging

INTRODUCTION

Spinal cord injury (SCI) is associated with severe, rapid bone loss at sublesional locations [1–4]. Mechanical disuse, potentially combined with post-injury neurogenic, circulatory, and hormonal changes [1, 5], results in an imbalance of the natural resorption and formation of bone. The losses in bone are most significant around the knee, and previous studies have reported reductions in cortical and trabecular bone mineral content at the distal femur and proximal tibia of up to 50% within the first five years after injury [6–8]. These changes have important clinical implications as SCI patients are more than twice as likely to suffer a lower limb fracture in their lifetime compared to able-bodied controls [9]. These fractures often occur from relatively minimal trauma experienced from routine events such as rolling in bed or transferring from a wheelchair [10]. Spiral fracture patterns are commonly reported, implicating torsional loading as the cause of failure [11]. The rate of secondary complications associated with fracture after SCI is high, and these injuries have significant consequences for patient morbidity and mortality [12–14].

Pharmaceutical interventions to reduce fracture risk after SCI may be most effective if administered soon after injury, before bone loss becomes critical. Knowledge of the temporal patterns of bone loss after SCI may help to establish timelines for treatment and assessment. To this end, a number of previous studies have reported changes to bone mineral after SCI as measured by dual-energy x-ray absorptiometry (DXA) or computed tomography (CT) [6, 7, 15, 16]. These studies have reported that magnitude and rate of bone loss vary by region and type of bone measured [7], but it is difficult to interpret how these changes act in concert to reduce the overall mechanical competence of the bone. Subject-specific finite element (FE) modelling is a powerful, non-invasive, tool that can be used to answer this question. Indeed, studies of able-bodied patients have demonstrated FE modelling is a better predictor of bone fragility [17, 18] and osteoporotic fracture risk [19, 20] compared to radiographic measurement alone. This is likely because FE modelling is better able to assess the mechanical consequence of bone loss, which is a complex, multifactorial phenomenon

that depends on both the changing properties of bone tissue as well as the geometric distribution of that tissue and the type of loading experienced.

With this in mind, our research group has used a combination of FE and CT measures to study bone loss after SCI [3, 4, 8, 21, 22]. We originally quantified regional changes in the distal femur and proximal tibia in the acute phase of bone loss, i.e., less than eight months after SCI [3]. A subsequent cross-sectional study quantified whole bone temporal changes in the proximal tibia over a longer duration, 0–50 years after SCI [8]. However, that study did not analyze the distal femur, nor did it explore regional changes to bone stiffness. FE models were used to explore changes to torsional stiffness over time, but axial stiffness was not computed. In this study, we expand on our previous investigations. Our purpose was to examine a cross section of individuals with SCI and thoroughly quantify changes to bone at the distal femur and proximal tibia, as a function of time since injury.. We used subject-specific FE models to predict mechanical stiffness (axial and torsional) at three separate regions (epiphysis, metaphysis, and diaphysis) of each bone. We also performed CT mineral analyses of integral, cortical, and trabecular compartments at epiphyseal, metaphyseal and diaphyseal locations, in order to better understand the source of any FE predicted changes. It is hoped that a more complete understanding of bone loss following SCI may help inform the future development of effective intervention strategies.

METHODS

Participants

101 individuals with SCI (ages 18–72 yrs; 80 males and 21 females) were recruited from the Northwestern University Feinberg School of Medicine, the Rehabilitation Institute of Chicago (now known as the Shirley Ryan AbilityLab), and the Schwab Rehabilitation Hospital (Table 1) for participation in one of two clinical research studies conducted between June 2011 and February 2018. All participants had sustained SCI between one month and fifty years prior to participation. All participants were non-ambulatory at the time of participation and experienced a range of neurological impairment, evaluated using the American Spinal Injury Association (ASIA) impairment scale (AIS A through D). Individuals were excluded from this study based on the following major criteria: (1) a history of Paget's disease, bone metastasis or skeletal malignancies, (2) taking Dilantin and/or phenobarbital, as these drugs are known to affect bone health, (3) current or recent use of any bone-active agents, (4) individuals who are pregnant, lactating, or planning to become pregnant, (5) known endocrinopathies excluding diabetes and treated thyroid conditions, (6) abnormal TSH levels and T4 levels. Both clinical trials were conducted in accordance with Good Clinical Practice Guidelines; study protocols were approved by the institutional review board (IRB) of each participating site and by the Department of Defense Human Research Protection Office. All participants provided informed consent prior to participation. The clinical trials are registered with [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT01225055, NCT02325414).

CT Image Acquisition

Ninety-one of 101 participants were CT scanned using a Sensation 64 Cardiac Scanner (Siemens Medical Systems, Forchheim, Germany). During the study, the Rehabilitation Institute of Chicago (now known as the Shirley Ryan AbilityLab) moved to a new building and this scanner became unavailable. Thus, the remaining 10 participants were scanned using a SOMATOM Perspective (Siemens Medical Systems, Forchheim, Germany). Regardless of machine, all CT scans were acquired with settings of 120 kVp and 280 mA. Images were reconstructed with an in-plane resolution of $0.352 \text{ mm} \times 0.352 \text{ mm}$, and a slice thickness of 1 mm (voxel size: $0.352 \text{ mm} \times 0.352 \text{ mm} \times 1 \text{ mm}$). A hydroxyapatite calibration phantom (QRM, Moehrendorf, Germany) was placed in the field of view. The phantom had three regions with known mineral densities of 0.0, 0.4, and 0.8 g/cm^3 . It served as a tool for inter-scan calibration, allowing us compute a linear regression relationship between CT absorption (HU) and equivalent mineral density (g/cm^3). A single 30 cm long scan was used to capture approximately 15 cm each of the distal femur and proximal tibia. During the scan, participants lay with the superior-inferior axis of the leg approximately parallel to the axial direction of the CT scanner. As discussed in greater detail below, images were later realigned in order to minimize errors due to positioning. Scans were taken of the individuals' non-dominant knee, unless they had implants and/or a history of fracture on this knee. In these cases, the dominant knee was imaged instead. All image analysis was performed using a combination of Mimics (Materialise, Leuven, Belgium) and Matlab (MathWorks, Natick, MA, USA) software. The workflow was similar to our previously reported protocol [3, 18], but with some changes to the alignment procedure which allowed for better automation.

CT Analysis

CT image voxel intensities, or Hounsfield units (HU), were converted to hydroxyapatite equivalent density (ρ_{ha} ; g/cm^3) using a linear fit of the mean HU values from the calibration phantom against known densities provided by the phantom manufacturer's certificate. Using Mimics (Materialise, Leuven, Belgium) software, each bone was segmented from the CT image semi-automatically. A 0.15 g/cm^3 threshold was used to identify the periosteal surface of each bone. This threshold value was used in our previous investigations of bone density of individuals with SCI, and was found to discriminate between background and bone for the majority of image slices [3, 4, 8, 23]. However, some manual clean-up was still required to isolate each bone and fill in any gaps which occurred at low density regions, i.e., locations where the cortical shell was very thin (Figure A1 in the online Appendix). All image analysis tasks were performed by two trained operators with 1–2 years of experience, and reviewed by a researcher with six years of experience analyzing medical images of bone.

Following segmentation, alignment and registration was performed separately for femora and tibiae creating two image series per scan. For each segmented bone, we used a standard operation available in Mimics to generate a stereolithography (STL) model of the periosteal surface, and images were aligned by comparing this STL to a template. The template was generated from one randomly selected tibia and femur (male; 64 days after SCI; left bone), which had been manually re-aligned along the longitudinal axis of the bone. An iterative closest point algorithm (Open-source Matlab implementation, URL: <https://>

www.mathworks.com/matlabcentral/fileexchange/24301-finite-iterative-closest-point) was used to transform each individual's CT image data to match the template's orientation. This automatic alignment procedure generated final measurements of bone volume and mineral that were, on average, within 3% of measurements made using manual alignment procedures reported previously [3].

After alignment, we performed CT mineral analysis, using previously published protocols [3]. Using published proportionality constants [24], segment lengths (SL) were estimated from the individual's stature. As it is challenging to obtain a precise measure of stature in non-ambulatory individuals with SCI, we chose to use self-reported stature as a reasonable best-estimate. Segment lengths were then used to separate each bone into three regions: the epiphysis at 0–10% SL, the metaphysis at 10–20% SL, and the diaphysis at 20–30% SL. Volumetric bone mineral density (vBMD; g/cm³) and bone mineral content (BMC; g) were computed for integral, trabecular, and cortical compartments. The integral compartment represented all bone within the periosteal surface, as determined by our segmentation method described above. Next, the trabecular compartment was defined by performing a 4.9 mm (14 pixel) in-plane erosion of the integral region, using the erosion function available in Mimics. We selected this value because it ensured that the trabecular region was free of cortical bone, regardless of the individual's size or image slice location. Finally, the cortical compartment was defined by Boolean subtraction of the trabecular region from the integral region, followed by a thresholding of 0.35 g/cm³ to remove any remaining trabecular bone. We computed vBMD and BMC for all three compartments at the epiphysis and metaphysis, but omitted the trabecular compartment at the diaphysis. We also computed a cortical thickness index (cTI) for the metaphyseal region [25]:

$$cTI = \frac{1}{2} \cdot \left(\sqrt{\frac{iBV_{met}}{0.1 \cdot SL}} - \sqrt{\frac{iBV_{met} - cBV_{met}}{0.1 \cdot SL}} \right) \quad (\text{Eq. 1})$$

Where iBV_{met} is the volume of the integral region of the metaphysis, cBV_{met} is the volume of the cortical region of the metaphysis, and SL is the bone segment length estimated from the individual's stature, as described above.

FE Analysis

FE modelling was performed using our previously reported methodology [3], which has been experimentally validated using cadaveric proximal tibia loaded in torsion [18]. In this study, we used the same technique to make separate models of the epiphyseal, metaphyseal, and diaphyseal regions of each bone (101 tibia, 101 femurs), and computed structural stiffness in torsion (K_t) and axial compression (K_c) for each region. Models were subject specific, i.e., generated from the acquired CT images. Images were first resampled to isotropic voxels (1.5 mm edge length), and an FE mesh was generated by direct conversion of segmented bone voxels into first-order hexahedral elements. Element size was selected based on a convergence analysis, where it was found that decreasing edge length from 1.5 to 1.0 mm changed FE predicted stiffness by less than 2%. Thus, the final models had up to

40,000 hexahedral elements. Bone was modeled as an inhomogeneous, linear elastic, orthotropic material. Elastic moduli in the axial direction, E_3 , was computed from CT derived ρ_{ha} using equation 2 [26]:

$$E_3 = 6570 \cdot \rho_{app}^{1.37} \quad (\text{Eq. 2})$$

where E_3 is the elastic modulus (MPa) in the axial direction and ρ_{app} is the apparent density of bone ($\rho_{app} = \rho_{hu}/0.626$; g/cm³) [27]. The other elastic constants were computed assuming constant anisotropy throughout: $E_1=0.574 E_3$, $E_2=0.577 E_3$, $G_{12}=0.195E_3$, $G_{23}=0.265 E_3$, $G_{31}=0.216E_3$, $\nu_{12}=0.427$, $\nu_{23}=0.234$, and $\nu_{31}=0.405$ [28], with subscripts 1, 2 and 3 denoting the medial, anterior, and proximal directions, respectively.

Each model was subject to axial loading, in compression, and torsional loading, in internal rotation. A fixed displacement of 1 mm or rotation of 1° was applied, respectively. As shown in Figure A1, surface nodes were fully fixed at one end of the bone, while a displacement/rotation-type load was applied to the opposite end. This load was applied at a reference node located at the geometric center of the cross section, which was kinematically coupled to the other nodes of the corresponding bony surface. All other degrees of freedom of the reference node were constrained and the reaction force, or torque, was monitored and used to calculate stiffness.

Curve Fitting and Statistical Analysis

Similar to previous work [7, 8], we first fit CT and FE measures as a function of time since injury, using a single decaying exponential function:

$$y = A \cdot \exp(-B \cdot t) + C \quad (\text{Eq. 3})$$

where y is the CT or FE parameter to be estimated, t is the time since injury (years) and A , B , and C are unknown parameters determined by the fitting algorithm. The form of this equation forces the predictor to asymptotically approach a steady-state value of C as time becomes large with respect to the loss rate parameter B . Thus, we computed additional parameters to quantify the behavior at steady-state. First, for each curve fit, the time to achieve 95% of the total change (t_{95}) was first determined using equation 3:

$$t_{95} = -\ln(0.05)/B. \quad (\text{Eq. 4})$$

Where B is the decay parameter computed using equation 2. Means and standard deviations (SD) for each parameter were then quantified for those with an SCI duration greater than t_{95} , i.e., the individuals who had reached the new steady-state after SCI. To account for variance among individuals, the actual time to reach the new steady-state (t_{ss}) was reported as the mean $\pm$ 0.5 SD of the data for those individuals with a SCI duration greater than t_{95} :

$$t_{ss} = -\ln\left(\frac{SD}{2A}\right)/B. \quad (\text{Eq. 5})$$

CT and FE parameters were computed for all individuals with SCI who had an injury duration greater than t_{ss} . A reference group of uninjured controls against which to compare individuals with $t > t_{ss}$ was not available. Instead, they were compared to recently injured individuals, with a SCI injury 47 days before participation in this study. These recently injured individuals had mean integral vBMD at the tibia that was within 3% of the values previously reported for uninjured controls [8], across all three regions of the bone.

Previous studies have reported that a steady-state is reached 1.7–7.6 years after injury, depending on the location and bone measure, when using equation 2 to model bone loss [7, 8]. However, there is some evidence that bone loss after SCI may slowly progress for much longer durations, up to 25 years after injury [29]. This behavior may not be adequately described by a single exponential decay, which asymptotes quickly for all $t > t_{ss}$. With this in mind, we also fit our data to a double exponential decay function:

$$y = A_d \cdot \exp(-B_d \cdot t) + C_d \cdot \exp(-D_d \cdot t) \quad (\text{Eq. 6})$$

where y and t are, again, the parameter to be estimated and the time since SCI, respectively. A_d , B_d , C_d and D_d are four new unknown parameters determined by the curve fit. The form of equation 5 allows the data to be described as the superposition of two processes, a fast process causing rapid bone loss soon after injury, and a slower process which allows for slow steady bone loss many years after injury.

Equations 2 and 5 were fit to CT and FE data using the Matlab Curve Fitting Toolbox (MathWorks, Natick, MA, USA). An F-statistic was computed from regression results [30] and used to test the null hypothesis that the more complex double exponential decay model (Eq. 6) provides no additional information compared to the simpler single exponential decay model (Eq. 3); this hypothesis test was evaluated at a criterion alpha level of 0.05. We also performed independent samples t-tests, at the same criterion alpha level, comparing FE and CT measures from recently injured individuals ($t = 47$ days) relative to individuals with SCI who reached steady-state ($t > t_{ss}$).

RESULTS

From the 101 individuals with SCI participating in this study, scans of three bones from three different individuals were omitted because they did not pass quality control standards. Two tibia scans were omitted, one due to extreme motion artifact and the second due to metal artifact from a recent fracture fixation surgery. One femur scan was also omitted because the knee was not sufficiently centered in the field of view, and we were unable to image the entire diaphyseal region (20–30% SL). All reported analyses were computed using the remaining 99 scans of the femur and 100 scans of the tibia.

Most CT-derived measures of bone mineral and all FE derived measures of stiffness, were well described as exponential decays as a function of time. As shown in Figures 1 and 2, the single and double decay functions, Eq. 3 and Eq. 6 respectively, behaved similarly before reaching steady-state (t_{ss}) in the first few years after SCI ($t \leq 3.5$ years). However, the two models often predicted very different behavior many years after the injury ($t > 3.5$ years); Eq. 6 often predicted continuous, slower, bone loss, while Eq. 3 asymptotes quickly to a steady-state value. For most measures, both models explained a nearly identical percentage of the total variation in the dataset with differences in R^2 less than 0.02. In 2 of the 56 measures, however, Eq. 6 fit the data very poorly compared to Eq. 3, with R^2 values lower by 0.17–0.34 (Tables 2 and 3). In all cases, the more complex Eq. 6 model failed to provide a statistically significant increase in the percentage of variation explained, compared to the simpler Eq. 3 model ($p = 0.67$).

The FE derived axial and torsional stiffness, in all three regions of both bones, reached new steady-state values within 3 years after injury (Tables 2 and 3). After this duration, bone stiffness was 40% to 85% lower ($p < 0.005$), compared to equivalent bone stiffness measured from individuals with recent SCI ($t = 47$ days). The magnitude and pattern of stiffness reduction was similar between both bones, with both axial and torsional stiffness varying based on bone region (Figure 3). Stiffness losses were greatest at the epiphysis where we observed an 85% reduction in axial stiffness and 79% reduction in torsional stiffness ($p < 0.005$). These losses became somewhat attenuated moving away from the epiphysis. At the metaphysis, we observed 60–66% ($p < 0.005$) and 61–65% ($p < 0.005$) reductions in axial and torsional stiffness, respectively, while the diaphysis illustrated reductions of 49–50% ($p < 0.005$) and 44–51% ($p < 0.005$) for axial and torsional stiffness, respectively.

All CT derived measures of bone mineral reached steady-state within 3.5 years (Tables 2 and 3). Individuals with a SCI injury duration $> t_{ss}$ illustrated significant reductions in cortical BMC, cortical BV, trabecular BMC, and trabecular vBMD in all regions, with measures that were 23–107% lower than those who recently experienced SCI ($p < 0.005$). Reductions greater than 100% were observed at the trabecular compartment of the metaphysis, where negative mean values were observed at steady-state (Table 3), suggesting a region with little remaining hydroxyapatite. Changes to cortical vBMD were somewhat more modest by comparison, with reductions between 12% and 26% ($p < 0.005$). In contrast to all other measures observed in this study, variation in integral BV was not well-modelled as a function of time ($R^2 < 0.02$), and the value of this measure was not significantly different between the baseline individuals with recent SCI ($t = 47$ days) compared to the rest of the cohort ($p = 0.30$).

DISCUSSION

The purpose of this investigation was to thoroughly quantify regional changes to stiffness and bone mineral at the distal femur and proximal tibia as a function of time since SCI. We compared CT derived measures of bone mineral and FE derived measures of axial and torsional stiffness at three locations of each bone (epiphyseal, metaphyseal, and diaphyseal). The study demonstrated that bone degradation after SCI was well described as an exponential decay over time which, consistent with previous findings, reached steady-state

levels within 3.5 years after injury [6–8]. The observed and robust decreases to CT measured bone mineral had important mechanical consequences, with FE models predicting that steady-state values in axial and torsional stiffness were 40% to 85% lower than those who recently experienced SCI ($t = 47$ days). Moreover, individuals with recent SCI were not statistically different in age compared to those with $t > t_{ss}$, ($p=0.67$) suggesting that these observations were not significantly confounded by age-related bone loss.

To our knowledge, this is the first study to explore changes to FE derived measures of bone stiffness at the distal femur as a function of time. We found that the magnitude and rate of stiffness loss was similar between equivalent regions of the tibia and femur. We also found that torsional and axial stiffness loss was similar in magnitude, suggesting that both failure modes may be clinically relevant. Indeed, previous studies have reported that both spiral [10, 11] and impacted [2] fracture patterns are observed in clinical settings, consistent with torsional and compressive failure modes, respectively. FE results also revealed that losses in torsional stiffness were much more rapid than losses in axial stiffness (1.2–2 years vs. 2.3–2.8 years, respectively). This has important implications for future pharmaceutical trials seeking to attenuate SCI-induced bone loss before it becomes critical. These results suggest the window of opportunity to prevent torsional stiffness degradation is very short; to observe potential benefits, treatment and follow-up assessments should occur well before the first 1.2 years after SCI.

Similar to previous findings [7, 8], we observed that integral BV did not change as a function of time after SCI. However, cortical BV decreased by up to 87%, while cortical vBMD decreased by up to 26%, depending on the region. Together, these results suggest that cortical bone loss after SCI is primarily driven by resorption at the endosteal surface, with some additional losses due to intercoral resorption, and no change to periosteal surface geometry.

We also found that reductions in axial stiffness, torsional stiffness, integral BMC, integral vBMD, and cortical BV were greatest at the epiphysis and progressively decreased moving towards the diaphysis. Similar patterns of bone loss have been reported previously at the proximal femur [22] and proximal tibia [8], though the mechanisms for this regional discrepancy are not well understood. It has been speculated that this may be due to differences in timelines associated with distinct osteoclastogenic events at different locations [2]. A murine disuse model has demonstrated immediate bone loss at the epiphysis, mediated by basal osteoclast activity, followed by losses at the diaphysis, as a consequence of osteoclastogenesis within the marrow space [31], which is consistent with this hypothesis.

In a previous investigation examining the entire proximal tibia (15 cm length), our group observed that integral BMC and torsional stiffness illustrated similar magnitudes of reduction over time after SCI [8]. In this study, however, this was not necessarily the case when comparing bone mineral and stiffness loss at different anatomical regions of bone. Indeed, percent changes in integral BMC were similar in magnitude to percent changes in torsional stiffness at the diaphysis only (Figure 3; Table 3). The stiffer diaphyseal region likely plays a dominate role in the structural behavior of the entire proximal tibia, thereby explaining our previous finding. At the epiphyseal and metaphyseal regions, however, losses

in integral BMC were 6–14 percentage points less than losses in torsional stiffness (Figure 3). Similarly, losses in integral BMC were 5–18 percentage points less than losses in axial stiffness. These findings further demonstrate, as others have suggested [8, 32], that CT derived measures of bone mineral alone tend to underestimate the mechanical consequences of bone loss.

The time to reach steady-state was computed based on a decaying single exponential model (Eq. 3), which has been examined previously [7, 8]. The model predicts rapid bone loss soon after injury, which asymptotically approaches a steady-state level over time. In other words, this model predicts negligible change in bone parameters after t_{ss} , or within 3.5 years after injury. While a number of studies reported that bone loss does indeed cease to change after approximately two years post-injury [6–8], other studies reported that bone degrades steadily for much longer durations [29, 33]. To explore this question further, we also fit data using a double exponential model (Eq. 6), which allowed for an initial period of rapid bone loss, followed by a period of slower bone loss that continues beyond the end of our data record (i.e., 50 years). The double exponential model was not able to explain any additional variation in bone or stiffness loss when compared to the single exponential model ($p = 0.67$; Figures 1 and 2). Although it remains plausible that bone loss after SCI continues following an initial period of exponential decay, the data presented here suggest that the rate of bone loss after the initial period is small with respect to other sources of variation among individuals and could not be detected in this cross-sectional study. Presumably, bone loss many years after SCI may be the result of aging. Indeed, after 3.5 years, Eq. 6 predicts losses in cortical vBMD of approximately 0.12%/decade, which is similar to the rate of bone loss reported in able-bodied males over fifty years old [34].

The study has a number of important strengths. We collected CT data from a large cohort of 101 individuals with SCI across a large range of time since injury (1 month to 50 years). The effects of SCI were evaluated using both CT measures of bone mineral, and state-of-the-art subject specific FE modelling techniques. Moreover, we performed regional FE analyses in order to understand the mechanical implications of bone loss, and how these effects differ, in the epiphysis, metaphysis, and diaphysis of each bone.

Despite these strengths, the study also has some noteworthy limitations. First, we lacked uninjured controls against which to compare individuals with SCI. In lieu of these data, we utilized data from recently injured participants ($t = 47$ days) as a baseline for comparison. While it is extremely likely that these recently injured individuals have already begun to experience bone loss after SCI, data from previous investigations suggest that magnitude of bone loss over such a short duration is relatively small ($< 4\%$) [8, 35] and likely indistinguishable from normal variation among individuals.

Another important limitation is that FE models were used to assess stiffness only; ultimate load, i.e., strength, was not evaluated as we do not have a validated nonlinear model to predict failure at the distal femur. In the past, however, we validated [18] and used [8] more complex non-linear material models in order to study strength of the proximal tibia, and found that decreases in strength were somewhat greater in magnitude than decreases in stiffness.

Also, only 21 of 101 participants were female. As a result, we were unable to determine if the effects of SCI were dependent on sex. Post-hoc analyses revealed that males and females who reached $t > t_{ss}$ experienced reductions in bone stiffness that were not statistically different ($p = 0.26$), with percent reductions computed relative to a sex-matched group of recently injured individuals ($t = 47$ days). However, only 9 female participants reached steady-state, and it is plausible that this result was due to a lack of statistical power.

Another limitation of this study stems from the fact that a clinical CT-based FE modelling technique was used to assess local bone material properties as a function of average vBMD at element locations. Clinical resolution scans are unable to assess changes to bone microarchitecture (e.g., trabecular architecture, collagen-cross linking, changes to remodeling spaces), and there is some evidence that microarchitecture changes in the context of SCI are more significant compared to other forms of osteoporosis [1]. While the mechanical consequences of these microarchitectural changes are not fully understood, we speculate that our models based on CT derived density alone may underpredict the mechanical consequences of SCI induced bone deterioration.

We are unable to quantify precision errors of the CT and FE analysis, as we do not have repeated scans of the same individual over a short duration. However, a previous study using comparable hardware reported an inter-scan coefficient of variation of only 1.7% [36]. Furthermore, using a similar CT analysis protocol [3], we previously found that inter-operator precision errors resulted in a coefficient of variation less than 0.6%. These findings suggest that precision errors are likely small compared to the magnitude of SCI-induced bone loss observed in this study.

Finally, there are limitations associated with our cross-sectional study design. We are unable to control for the effects of individual variation in bone mineral and stiffness before injury, nor are we able to quantify variability due to differences in patient-specific responses to SCI [6, 22]. Together, these factors may account for some of the unexplained variation in our regression results (Table 2 and 3; $R^2 = 0.34\text{--}0.79$).

CONCLUSION

The results of this study demonstrate that torsional and axial stiffness in the distal femur and proximal tibia decay exponentially as a function of time after SCI. Both bones experienced similar magnitudes and rates of bone loss, with reaching steady-state levels 1.2–3.5 years after injury. Stiffness losses were greatest at the epiphysis and progressively decreased moving towards the diaphysis. Similar patterns were observed in integral BMC and vBMD, though these parameters underestimated the mechanical consequences of bone loss after SCI. Changes over time were well modelled with a single decaying exponential function, which predicted rapid bone loss immediately after injury, and little bone loss after 3.5 years. Data were also modelled using a double exponential decay function, which predicted a secondary period of more moderate bone loss that continued for many years after injury. However, this double decay model did not provide a better fit to the observed data ($p = 0.67$). It is plausible that patients continue to suffer moderate bone loss for many years after SCI, but it is likely that the rate of loss is small, with respect to variation among individuals.

In summary, the findings presented here support the general notion that bone loss at the knee after SCI is rapid and profound, with rates of bone loss that are greatest immediately after injury. We found that CT derived measures of density alone may underestimate the consequences of SCI, compared to patient-specific FE models, which provide a mechanistic assessment of the mechanical consequences of bone loss. Finally, we found that SCI induced bone loss results in significant reductions to both torsional and axial stiffness, suggesting that both failure modes may be clinically relevant.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1:

Model fits at the distal femur for select FE and CT parameters. Both models match the rapid bone loss observed in the acute phase, soon after injury. The single exponent model (Eq.3; LEFT) quickly reaches a steady-state value, while the double exponent model (Eq.6; RIGHT) predicts progressive bone loss up to 50 years after SCI. Both models explained a similar percentage of the total variation in measured data ($R^2 > 0.51$).

Figure 2:

Model fits at the proximal tibia for select FE and CT parameters. As with the distal femur, shown in Figure 1, both models match the rapid bone loss observed in the acute phase, soon after injury. The single exponent model (Eq.3; LEFT) quickly reaches a steady-state value, while the double exponent model (Eq.6; RIGHT) predicts progressive bone loss up to 50 years after SCI. Both models explained a similar percentage of the total variation in measured data ($R^2 > 0.52$).

Figure 3:

%Change in FE derived stiffness and select CT mineral measures, in patients who reached steady state ($t > t_{ss}$) compared to a recently injured reference group ($t = 47$ days). The magnitude and spatial pattern of bone loss was similar between the proximal tibia (WHITE) and distal femur (GRAY). Losses were greatest at the epiphysis and progressively decreased, moving towards the diaphysis.

Table 1:

Participant characteristics.

Parameter	Mean $\pm$ SD
Subjects, n	101
Female, n	21
Age (years)	38.6 $\pm$ 14.6; range 18–72
Height (cm)	175.1 $\pm$ 10.4
Weight (kg)	75.2 $\pm$ 18.0
Time since injury (years)	7.7 $\pm$ 10.8; range 0.2–49.9

Table 2:

FE and CT measures at the epiphyseal, metaphyseal, and diaphyseal regions of the distal femur.

Region	Parameter	Eq.2: Single Exponent Fit (R^2)	Eq.5: Double Exponent Fit (R^2)	Single vs Double (p)	Baseline Group (Mean $\pm$ SD)	Chronic SCI Group (Mean $\pm$ SD)	%Change	T-test (p)	t_{ss} (years)
Epiphysis	K_c [kN/mm]	0.72	0.72	0.99	180.8 $\pm$ 40.36	27.47 $\pm$ 19.96	-84.8	< 0.005	2.6
	K_t [N/Deg]	0.66	0.66	1.00	512.9 $\pm$ 152.0	109.9 $\pm$ 56.07	-78.6	< 0.005	2.1
	iBMC [g]	0.72	0.72	0.98	32.40 $\pm$ 7.990	10.84 $\pm$ 4.480	-66.5	< 0.005	2.3
	iBMD [g/cm^3]	0.80	0.80	0.98	0.260 $\pm$ 0.030	0.080 $\pm$ 0.030	-68.4	< 0.005	2.8
	iBV [cm^3]	0.01	0.01	1.00	124.1 $\pm$ 31.10	126.4 $\pm$ 21.65	1.80	0.763	0.0
	cBMC [g]	0.74	0.74	1.00	9.380 $\pm$ 2.970	1.080 $\pm$ 0.620	-88.4	< 0.005	3.1
	cBMD [g/cm^3]	0.52	0.52	0.67	0.520 $\pm$ 0.026	0.460 $\pm$ 0.030	-12.4	< 0.005	1.5
	cBV [cm^3]	0.69	0.68	0.96	9.733 $\pm$ 3.183	1.958 $\pm$ 1.052	-79.9	< 0.005	2.5
	tBMC [g]	0.83	0.83	1.00	32.40 $\pm$ 7.992	4.350 $\pm$ 3.200	-86.6	< 0.005	2.6
	tBMD [g/cm^3]	0.79	0.79	0.99	0.225 $\pm$ 0.028	0.050 $\pm$ 0.040	-77.7	< 0.005	2.8
Metaphysis	K_c [kN/mm]	0.69	0.69	0.95	85.57 $\pm$ 18.75	28.68 $\pm$ 13.66	-66.5	< 0.005	2.4
	K_t [N/Deg]	0.58	0.59	0.98	111.3 $\pm$ 33.28	38.80 $\pm$ 20.43	-65.2	< 0.005	1.6
	iBMC [g]	0.65	0.65	0.95	21.35 $\pm$ 5.825	9.360 $\pm$ 3.620	-56.2	< 0.005	1.9
	iBMD [g/cm^3]	0.68	0.68	0.94	0.290 $\pm$ 0.051	0.140 $\pm$ 0.050	-53.3	< 0.005	2.8
	iBV [cm^3]	0.00	0.01	0.94	74.45 $\pm$ 20.35	69.16 $\pm$ 14.78	-7.10	0.300	0.0
	cBMC [g]	0.60	0.60	0.95	13.19 $\pm$ 3.763	7.200 $\pm$ 2.390	-45.4	< 0.005	1.7
	cBMD [g/cm^3]	0.64	0.64	0.96	0.765 $\pm$ 0.060	0.650 $\pm$ 0.050	-15.3	< 0.005	1.9
	cBV [cm^3]	0.49	0.50	0.94	17.06 $\pm$ 4.140	11.01 $\pm$ 3.079	-35.5	< 0.005	1.3
	tBMC [g]	0.87	0.53	1.00	21.35 $\pm$ 5.825	-0.020 $\pm$ 2.000	-100.	< 0.005	2.7
	tBMD [g/cm^3]	0.61	0.61	1.00	0.130 $\pm$ 0.036	-0.000 $\pm$ 0.050	-101.	< 0.005	2.4
Diaphysis	cTI [cm]	0.61	0.61	0.91	0.145 $\pm$ 0.021	0.093 $\pm$ 0.021	-35.8	< 0.005	2.1
	K_c [kN/mm]	0.65	0.65	0.93	106.6 $\pm$ 20.23	53.93 $\pm$ 15.89	-49.4	< 0.005	2.6
	K_t [N/Deg]	0.47	0.47	0.95	87.90 $\pm$ 24.27	42.88 $\pm$ 22.52	-51.2	< 0.005	1.5
	iBMC [g]	0.57	0.58	0.91	19.25 $\pm$ 4.824	11.36 $\pm$ 3.620	-41.0	< 0.005	1.9
	iBMD [g/cm^3]	0.63	0.64	0.92	0.461 $\pm$ 0.078	0.280 $\pm$ 0.070	-39.1	< 0.005	3.1
	iBV [cm^3]	0.01	0.01	0.98	41.99 $\pm$ 9.565	40.82 $\pm$ 8.500	-2.80	0.683	0.0

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Region	Parameter	Eq.2: Single Exponent Fit (R^2)	Eq.5: Double Exponent Fit (R^2)	Single vs Double (p)	Baseline Group (Mean ±SD)	Chronic SCI Group (Mean ±SD)	%Change	T-test (p)	t_{∞} (years)
	cBMC [g]	0.54	0.55	0.91	17.37 ± 4.517	11.06 ± 3.280	-36.3	< 0.005	1.8
	cBMD [g/cm^3]	0.67	0.50	1.00	0.997 ± 0.043	0.820 ± 0.070	-17.3	< 0.005	2.2
	cBV [cm^3]	0.32	0.33	0.93	17.33 ± 4.199	13.27 ± 3.370	-23.4	< 0.005	1.2

Table 3:
FE and CT measures at the epiphyseal, metaphyseal, and diaphyseal regions of the proximal tibia.

Region	Parameter	Eq.2: Single Exponent Fit (R^2)	Eq.5: Double Exponent Fit (R^2)	Single vs Double (p)	Baseline Group (Mean $\pm$ SD)	Chronic SCI Group (Mean $\pm$ SD)	%Change	T-test (p)	t_{ss} (years)
Epiphysis	K_c [kN/mm]	0.61	0.61	0.97	99.97 $\pm$ 34.08	15.90 $\pm$ 11.63	-84.1	< 0.005	2.3
	K_t [N/Deg]	0.63	0.62	0.96	252.9 $\pm$ 107.5	53.51 $\pm$ 30.99	-78.8	< 0.005	1.9
	iBMC [g]	0.68	0.68	0.96	21.67 $\pm$ 6.301	7.170 $\pm$ 3.100	-66.9	< 0.005	2.1
	iBMD [g/cm^3]	0.75	0.75	0.94	0.218 $\pm$ 0.034	0.070 $\pm$ 0.030	-68.4	< 0.005	2.5
	iBV [cm^3]	0.00	0.02	0.91	100.5 $\pm$ 28.31	102.8 $\pm$ 18.29	2.20	0.729	0
	cBMC [g]	0.67	0.67	0.97	5.245 $\pm$ 1.854	0.910 $\pm$ 0.520	-82.7	< 0.005	2.7
	cBMD [g/cm^3]	0.63	0.64	0.89	0.535 $\pm$ 0.028	0.456 $\pm$ 0.029	-14.8	< 0.005	2.5
	cBV [cm^3]	0.69	0.68	0.96	9.733 $\pm$ 3.183	1.958 $\pm$ 1.052	-79.9	< 0.005	2.5
	tBMC [g]	0.68	0.68	0.97	11.91 $\pm$ 4.026	2.431 $\pm$ 2.184	-79.6	< 0.005	2.1
	tBMD [g/cm^3]	0.73	0.73	0.96	0.179 $\pm$ 0.033	0.036 $\pm$ 0.034	-80.1	< 0.005	2.4
Metaphysis	K_c [kN/mm]	0.63	0.63	0.95	83.09 $\pm$ 19.02	32.89 $\pm$ 11.73	-60.4	< 0.005	2.9
	K_t [N/Deg]	0.49	0.49	0.96	89.66 $\pm$ 37.81	34.95 $\pm$ 18.50	-61.0	< 0.005	1.8
	iBMC [g]	0.62	0.63	0.92	19.99 $\pm$ 6.527	8.985 $\pm$ 3.160	-55.1	< 0.005	2.3
	iBMD [g/cm^3]	0.69	0.70	0.90	0.364 $\pm$ 0.044	0.168 $\pm$ 0.053	-54.0	< 0.005	3.3
	iBV [cm^3]	0.00	0.00	0.97	54.84 $\pm$ 16.63	54.56 $\pm$ 11.42	-0.50	0.944	0.0
	cBMC [g]	0.66	0.66	0.92	15.46 $\pm$ 4.423	7.468 $\pm$ 2.375	-51.7	< 0.005	2.3
	cBMD [g/cm^3]	0.79	0.80	0.89	0.886 $\pm$ 0.055	0.655 $\pm$ 0.054	-26.0	< 0.005	2.8
	cBV [cm^3]	0.51	0.52	0.91	17.36 $\pm$ 4.526	11.23 $\pm$ 3.351	-35.3	< 0.005	1.6
	tBMC [g]	0.51	0.51	0.95	3.346 $\pm$ 2.146	-0.260 $\pm$ 1.231	-108.	< 0.005	2.2
	tBMD [g/cm^3]	0.53	0.53	0.97	0.102 $\pm$ 0.041	-0.008 $\pm$ 0.043	-108.	< 0.005	2.6
Diaphysis	cTI [cm]	0.65	0.67	0.88	0.176 $\pm$ 0.015	0.110 $\pm$ 0.025	-38.0	< 0.005	2.7
	K_c [kN/mm]	0.64	0.64	0.94	107.2 $\pm$ 21.58	52.90 $\pm$ 19.45	-50.7	< 0.005	2.7
	K_t [N/Deg]	0.34	0.33	0.97	64.30 $\pm$ 24.87	35.94 $\pm$ 19.88	-44.1	< 0.005	1.2
	iBMC [g]	0.53	0.55	0.90	20.08 $\pm$ 5.907	11.71 $\pm$ 3.655	-41.7	< 0.005	2.0
	iBMD [g/cm^3]	0.69	0.70	0.88	0.586 $\pm$ 0.053	0.340 $\pm$ 0.078	-42.5	< 0.005	3.6
	iBV [cm^3]	0.01	0.00	1.00	34.18 $\pm$ 9.438	34.93 $\pm$ 7.443	2.20	0.766	0.0

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Region	Parameter	Eq.2; Single Exponent Fit (R^2)	Eq.5; Double Exponent Fit (R^2)	Single vs Double (p)	Baseline Group (Mean ±SD)	Chronic SCI Group (Mean ±SD)	%Change	T-test (p)	t_{∞} (years)
	cBMC [g]	0.55	0.56	0.91	19.46 ± 5.655	11.12 ± 3.553	-42.8	< 0.005	2.1
	cBMD [g/cm^3]	0.78	0.78	0.89	1.052 ± 0.050	0.810 ± 0.061	-22.8	< 0.005	3.0
	cBV [cm^3]	0.34	0.35	0.91	18.463 ± 5.261	13.66 ± 3.983	-26.0	< 0.005	1.2