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Regional and temporal variation in bone loss during the first year following spinal cord injury

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Abstract

Osteoporosis is a consequence of spinal cord injury (SCI) that leads to fragility fractures. Visual assessment of bone scans suggests regional variation in bone loss, but this has not been objectively characterised. In addition, substantial inter-individual variation in bone loss following SCI has been reported but it is unclear how to identify fast bone losers.

Therefore, to examine regional bone loss, tibial bone parameters were assessed in 13 individuals with SCI (aged 16-76 years). Peripheral quantitative computed tomography scans at 4% and 66% tibia length were acquired within 5 weeks, 4 months and 12 months postinjury. Changes in total bone mineral content (BMC), and bone mineral density (BMD) were assessed in ten concentric sectors at the 4% site. Regional changes in BMC and cortical BMD were analysed in thirty-six polar sectors at the 66% site using linear mixed effects models. Relationships between regional and total loss at 4 months and 12 months timepoints were assessed using Pearson correlation.

At the 4% site, total BMC ($P = 0.001$) decreased with time. Relative losses were equal across the sectors (all $P > 0.1$). At the 66% site, BMC and cortical BMD absolute losses were similar (all $P > 0.3$ and $P > 0.05$, respectively) across polar sectors, but relative loss was greatest in the posterior region (all $P < 0.01$). At both sites, total BMC loss at 4 months was strongly positively associated with the total loss at 12 months ($r=0.84$ and $r=0.82$ respectively, both $P < 0.001$). This correlation was stronger than those observed with 4-month BMD loss in several radial and polar sectors ($r=0.56$-0.77, $P < 0.05$).

These results confirm that SCI-induced bone loss varies regionally in the tibial diaphysis. Moreover, bone loss at 4 months is a strong predictor of total loss 12 months postinjury. More studies on larger populations are required to confirm these findings.

Keywords: Disuse Osteoporosis, tibia, Spinal Cord Injury, pQCT, Unloading, Mechanoadaptation

Introduction

People with complete spinal cord injury (SCI) experience extensive and rapid bone loss in their paralysed limbs[1]. The distal femur and proximal tibia lose up to 52% and 70% of BMD after only one year following injury[2]. This dramatic decline in bone density and quality leads to fragility fractures which occur mostly at the knee and ankle joints[3][4], putting these individuals at risk of developing secondary medical complications[5]. People with SCI are at 23-fold higher risk of experiencing femur fractures compared to the uninjured population[6]. Studies have shown that bone loss continues throughout the first years following SCI[7][8], until it reaches a steady state around 3-8 years postinjury[9]. Whilst there are mixed results regarding the effectiveness of physical interventions in mitigating bone loss[1], anti-resorptive drugs provide positive effects on BMD in people with acute SCI[10]. Administering bisphosphonates early after SCI decreases bone loss in the hip[10][11] and lumbar spine at 12 months[11].Thus, detecting and targeting bone loss during the early months following SCI could potentially lead to more targeted interventions to prevent further loss.

Bone loss after SCI is characterised by substantial inter-individual and regional variation. The rate and magnitude of bone loss has been shown to vary widely among individuals with SCI, with trabecular BMD loss at the distal tibial varying between 1-65% one year postinjury [12]. Bone loss has been shown to be more pronounced at the epiphyseal compared to the diaphyseal sites[7][13] and bone scan images appear to show regions with greater bone loss compared to others within the same bone cross-section[13]. However, this intra-site variation in bone loss has not been objectively characterised before. If regional variation is confirmed, regions with higher rate of bone loss could be assessed and used to predict fast bone losers. An ImageJ plugin[14][15] has been developed which allows regional analysis of bone parameters in concentric or radial sectors. Previous studies have also shown region-specific bone gains in the tibia and femur following electrical stimulation interventions recruiting specific muscles[16][17]. Future strategies could therefore be developed to target those bone regions at greatest risk of loss.

Therefore, we aimed to characterise regional bone loss in the first year following SCI. In addition, to assess the relationships between early stage (four months postinjury) regional and total bone changes and those observed at twelve months postinjury. We hypothesised that bone loss following SCI would vary regionally. In addition, that regions with rapid early-stage bone loss would be predictive of total bone loss at one-year postinjury.

Materials and Methods

Twenty-six inpatients (aged 16-76 years) with motor-complete SCI (grades A or B on the American Spinal Injuries Association Impairment Scale (AIS), 12 with paraplegia, 14 with tetraplegia) at the

Queen Elizabeth National Spinal Injuries Unit (UK), were recruited for this study. Longitudinal changes in the tibia in these individuals have been published in a previous report[7]. The main exclusion criteria were age <16 years, recent bone fracture and continued ventilator dependency at week 5 post-injury. Ethical approval for the study was obtained from the NHS Research Ethics Committee. Further details on patient recruitment and scanning protocols for that study have been described previously[7].

Bone scans were obtained by a single operator using pQCT (XCT3000, Stratec Medizintechnik GmbH, Germany) from these 29 participants within the first 5 weeks (baseline) and at 4,8 and 12 months postinjury and were analysed for longitudinal changes in bone parameters at the tibia throughout the first year of injury[7]. Of these, a subgroup of 13 individuals with complete sets of baseline, 4 months and 12 months scans, were included in this study. Two, four and seven participants were excluded from the analysis for not having their bone scans at baseline, four months and twelve months, respectively.

Scans were taken at 4% and 66% distal-proximal tibial length. These scans were analysed using the pQCT plugin on ImageJ (National Institutes of Health, Maryland, USA)[14][15]. Epiphyseal parameters calculated at the 4% site were the total bone mineral content (BMC), total cross-sectional area (CSA) and bone mineral density (BMD). BMC was also calculated at 10 anatomical concentric sectors, starting from the centre of the bone (Sector 1) and moving toward the cortex of the bone (Sector 10). The parameters calculated at 66% diaphyseal site were total BMC, periosteal circumference, endocortical circumference and cortical BMD. Mean periosteal and endocortical circumferences (Circumference $_{mean}$) were calculated for each subject using the formula:

$$\text{Circumference}_{mean} = 2 * \pi * R_{mean}$$

R_{mean} is the mean periosteal/endocortical radius calculated by averaging the 36 radii values (which were calculated by the plugin for the 36 polar sectors). BMD and cortical BMC were also calculated for the 36 polar sectors. The selection of 10 concentric sectors for epiphyseal sites and 36 polar sectors for diaphyseal sites does not have an particular physiological meaning. The numbers were chosen as a pragmatic compromise between the level of detail provided, and the accuracy of assessment ensuring that sectors were composed of a large enough area to permit repeatable analyses.

Voxel edge length was 0.4mm and average bone CSAs were ~1,250mm^2 and ~550mm^2 at the distal and proximal tibia respectively. Therefore each of the 10 distal tibia sectors and 36 radial sectors would contain ~800 and ~100 voxels respectively. That the sample size was still quite large may explain why coefficients of variation were similar to that of whole-bone measures even in the smaller tibia shaft sectors, being 2.4%, 3.4%, and 1.5% for BMD values, endocortical radii and pericortical radii respectively[14].

Given the thin cortex in individuals with SCI at epiphyseal sites, thresholds of 120 mg.mm^{-3} and 150 mg.mm^{-3} were used to separate bone and soft tissue at the 4% and 66% sites, respectively as in previous studies[18][13]. Coefficient of variation was previously reported to be from 0.46 to 2.23% for BMD in the distal tibia[12], which is similar to values in uninjured individuals.

Normality was assessed using Shapiro-Wilk tests. Linear mixed effects models with time and sector (10 concentric sectors for 4% site bone variables, and 36 radial sectors for 66% site variables) as fixed factors and participant as a random factor were constructed. Site-by-time interactions were also examined, indicating differences in bone change between baseline and follow-up between the sectors. Where interactions terms were not evident ($P > 0.1$), the interaction term was removed. To account for baseline differences in bone parameters between sectors, analyses were also repeated with data normalised for baseline values. The relationships between individual sector losses and total bone losses at 4 months with total loss at 12 months was also examined at both sites using Pearson correlation. Data are presented as mean (SD), except when not normally distributed when median (IQR) is presented.

Results

Descriptive statistics of bone parameters at baseline, 4 months and 12 months post-injury at 4% and 66% of tibial length are summarised in Table 1. All values were normally distributed except the 4% site total BMD at 4 months and 12 months. One scan at the 4% site was removed from the analysis due to movement artefacts. An estimate of the bone cross-sectional shape/circumference was drawn by plotting all the mean periosteal radii for the 36 sectors at the 4% site. This was repeated for periosteal and endocortical radii to draw the cortical bone of the diaphyseal 66% site (Figure 1(upper), Figure 2(a)).

To identify to what extent differences in total BMC at the distal tibia post-injury were attributable to altered density or area, analyses were also performed on total CSA and total BMD. At the 4% site, total BMC ($P = 0.001$) but not total CSA ($P = 0.28$) decreased with time. Total BMD decreased with time across all sites, and values in the most peripheral sector were greater than all other sectors (all $P < 0.001$). There was also a site-by-time interaction for total BMC such that absolute losses in the outermost sector were greater than in other sectors (all $P < 0.05$) except sector 9 ($P = 0.074$). However, when adjusted for baseline values relative losses were similar across all sectors (Figure 2, all $P > 0.1$).

At the 66% site, total BMC decreased with time across all sites, and values in sector 30 were lower than those in sectors 1-9 and 16-24 (all $P < 0.001$) and 25-28 (all $P < 0.05$), and lower than sectors 11-14 (all $P < 0.001$). There was no evidence of a site-by-time interaction suggesting that absolute BMC losses across all sectors were similar (all $P > 0.3$). However, analysis of baseline adjusted values

showed that relative losses were greater in sector 30 than sectors 1-27 and 35-36 (Figure 3, all $P < 0.01$ except sector 27 where $P = 0.04$).

Table1: Descriptive statistics (Mean, standard deviation (SD), median, interquartile range (IQR)) of bone parameters at baseline, 4 months and 12 months post-injury at 4% and 66% of tibial length

Time point / Scan site and Parameter	Baseline				4 months				12 months			
	Mean	SD	Median	IQR	Mean	SD	Median	IQR	Mean	SD	Median	IQR
4% Distal-proximal												
BMC (mg/mm)	418.1	50.1	420.9	50.3	398.0	57.6	402.7	75.1	356.9	72.1	378.5	106.6
BMD (mg/cm^3)	328.9	19.1	334.3	31.6	-	-	331.7	38.0	-	-	301.0	60.9
Total CSA (mm^2)	1268.4	137.6	1290.8	167.1	1256.1	154.7	1274.8	222	1263.6	149.1	1257.5	170.4
66% Distal-proximal												
BMC (mg/mm)	480.0	57.5	474.2	75.8	477.0	58.5	473.3	79.0	459.3	59.4	449.1	84.8
Cortical BMD (mg/cm3)	834.9	49.1	839.6	66.0	833.1	54.2	837.3	61.8	811.8	57.9	801.4	62.6
Total CSA (mm^2)	763.8	100.1	765.0	158.8	755.6	96.4	754.3	153.6	760.7	96.9	775.9	168.6
Cortical CSA (mm^2)	564.3	66.2	560.3	100.8	562.2	67.2	550.8	102.6	553.4	60.7	538.6	89.6
periosteal circumference	96.2	6.6	95.7	10.0	96.0	6.4	95.9	9.9	96.3	6.6	98.2	11.2
endocortical circumference	47.7	6.3	48.7	9.1	48.2	6.0	48.9	9.9	48.7	7.3	48.1	9.5

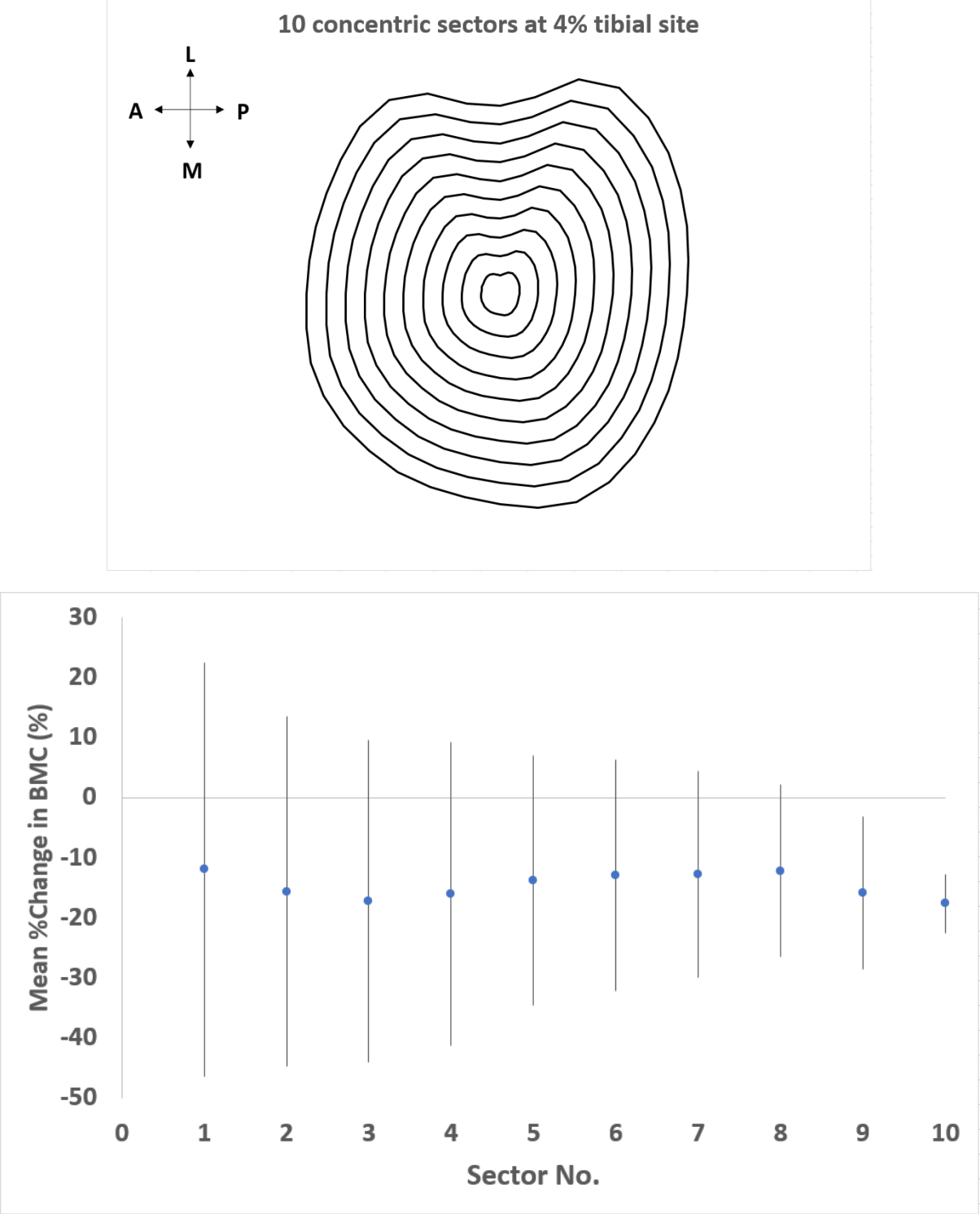
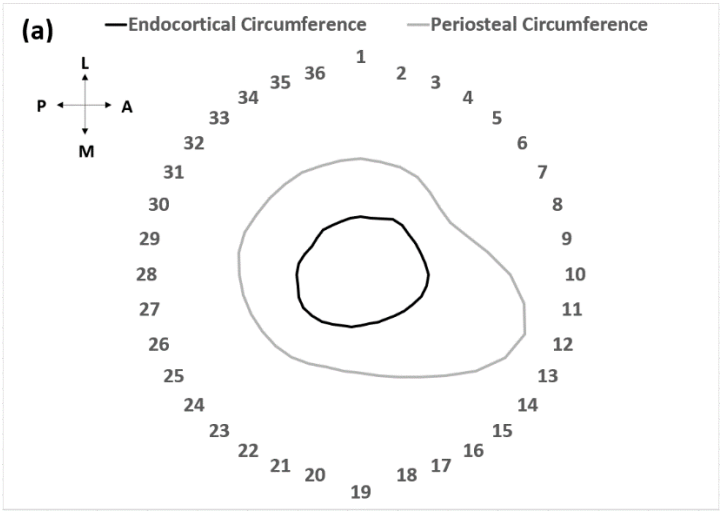
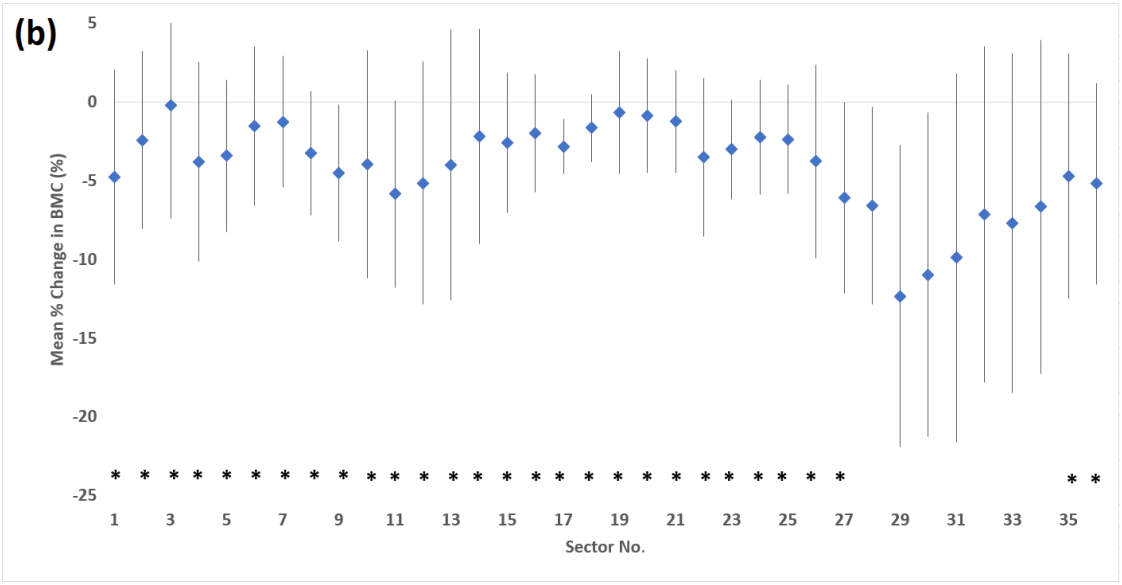


Figure 1: (Upper) A representation of the bone cross section shape at the 4% site in baseline scans, showing the 10 concentric sectors (sector 1 is innermost sector, sector 10 is outermost sector) (lower) Mean percentage change in BMC at the 10 anatomical concentric sectors at 4% distal tibia at 12 months postinjury. Error bars indicate ±SD.

To examine density and geometrical changes underlying these total BMC results at the 66% site, we repeated the analyses for cortical BMD, periosteal circumference and endocortical circumference. For cortical BMD, similar results to BMC were observed as values decreased with time across all sites ($P = 0.013$) and were higher in sector 30 than sectors 8-17, and lower than values in sectors 1-6, 21-26 and 32-36 (all $P < 0.05$) but no site-by-time interaction was observed ($P > 0.9$). However, baseline-adjusted relative losses were greater in sector 30 than sectors 1-9, 17, 25-26, 34 and 36 (Figure 3, all $P < 0.05$).





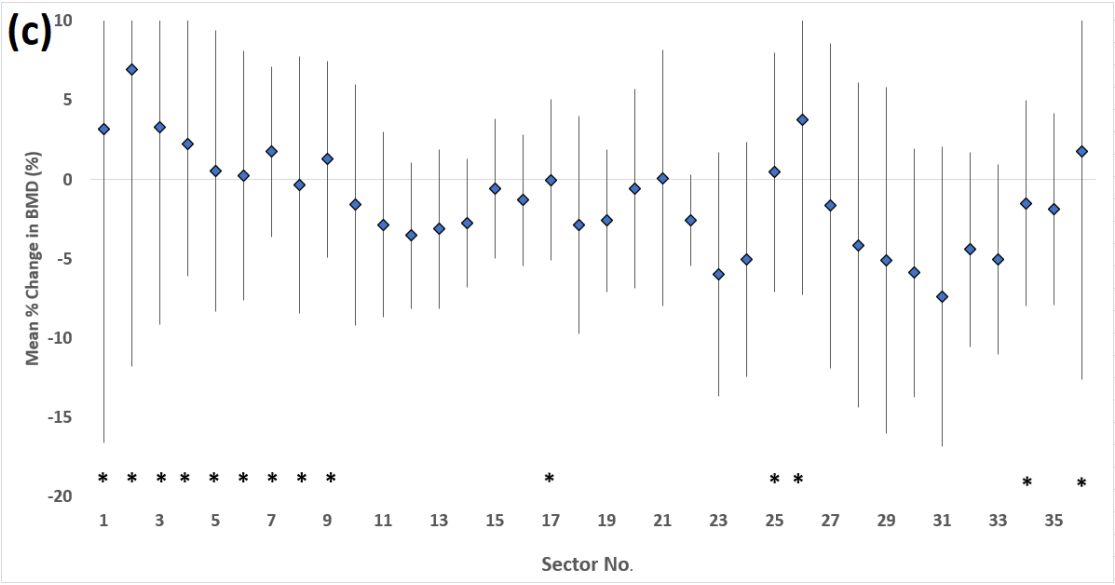


Figure 2: (a) An estimate of the bone cross section shape at 66% site, showing the 36 polar sectors,(b) Mean percentage change in BMC and (c) BMD (lower) at 12 months postinjury at the 36 polar sectors at the 66% diaphyseal site. (*) indicates the sectors that have less loss compared to sector 30. Error bars indicate ±SD

The uneven bone loss across the bone cross section can be seen in some of the bone scans shown in Figure 3, with bone loss being more pronounced not only at the posterior region but also in the anterior region. The loss can be seen across the bone cross section from periosteal to endocortical surfaces.

Cortical CSA did not change with time ($P = 0.45$) nor was there a sector-by-time interaction ($P > 0.9$), but values in sector 30 were greater than in sectors 1-8, 17-27 and 33 to 36 and lower than those in sectors 10 to 14 ($P = 0.05$). There was no effect of time on periosteal circumference ($P = 0.914$) but absolute values in sector 30 were greater than sectors 1-8, 17-26 and 32-36 and lower than 10-15 (all $P < 0.05$). There was no evidence of a sector-by-time interaction (all $P > 0.05$). $P > 0.2$. Endocortical circumference increased with time ($P = 0.003$), and values in sectors 5 and 8-13, were higher and 16-22 and 25-29 lower (all P 0.05) than in sector 30. There was no evidence of a sector-by-time interaction ($P = 0.55$).

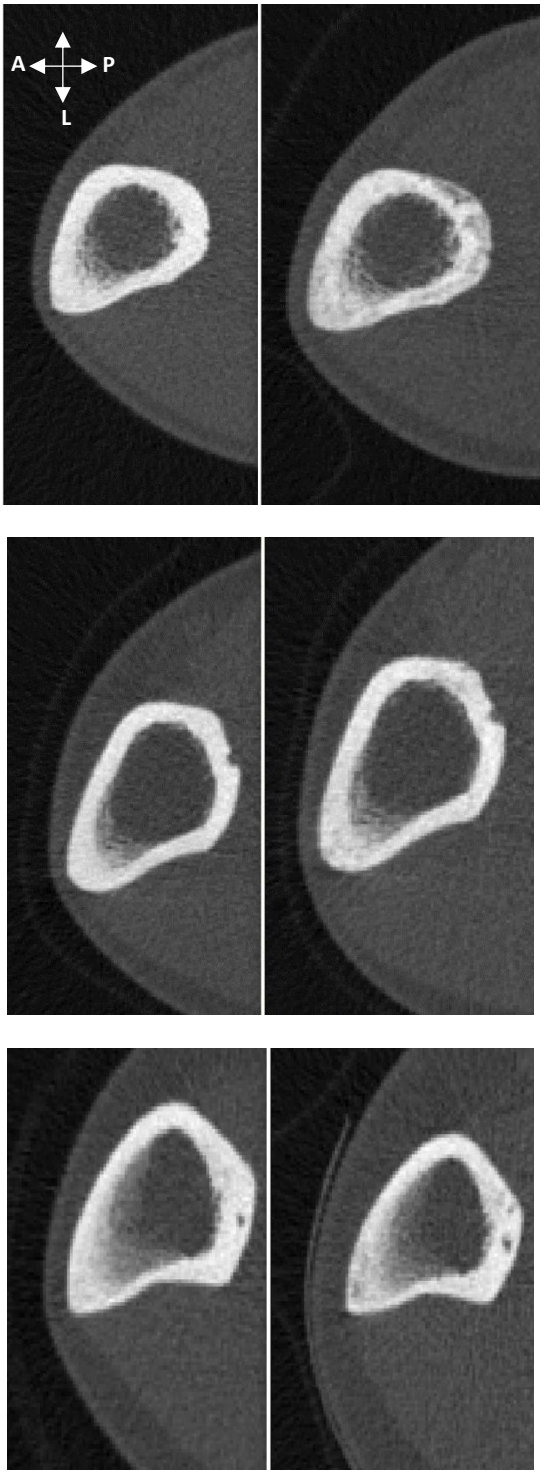


Figure 3: pQCT scans of tibial shaft (at 66%) from three individuals with SCI obtained at baseline (left column) and at twelve months postinjury. Scans show more pronounced bone loss at the posterior and anterior sites of tibia cross-section.

BMC loss in concentric sectors 3-10 at 4 months was positively associated with total BMC loss at 12 months (r=0.62-0.77, $P < 0.05$) but not at sectors 1 and 2 ($P > 0.2$). These relationships were slightly weaker than those observed between total BMC loss at 4 months and at 12 months (r=0.84, $P < 0.001$) (Figure 4).

BMC loss at 4 months in sectors 1, 3, 12-14, 30 and 36 was positively correlated with total BMC loss at 12 months (r=0.56-0.67, $P = 0.05$) but not at other sites. The strength of the correlation was weakly positively associated with the bone loss *i.e.* those regions in which greater losses were observed had closer relationships with total losses at 12 months (r=0.35, $P = 0.037$). As with the 4% site, the relationships between 4 months sector losses and 12 months total losses were weaker than those observed between total BMC losses at 4 and 12 months (r=0.84, $P < 0.001$) (Figure 4).

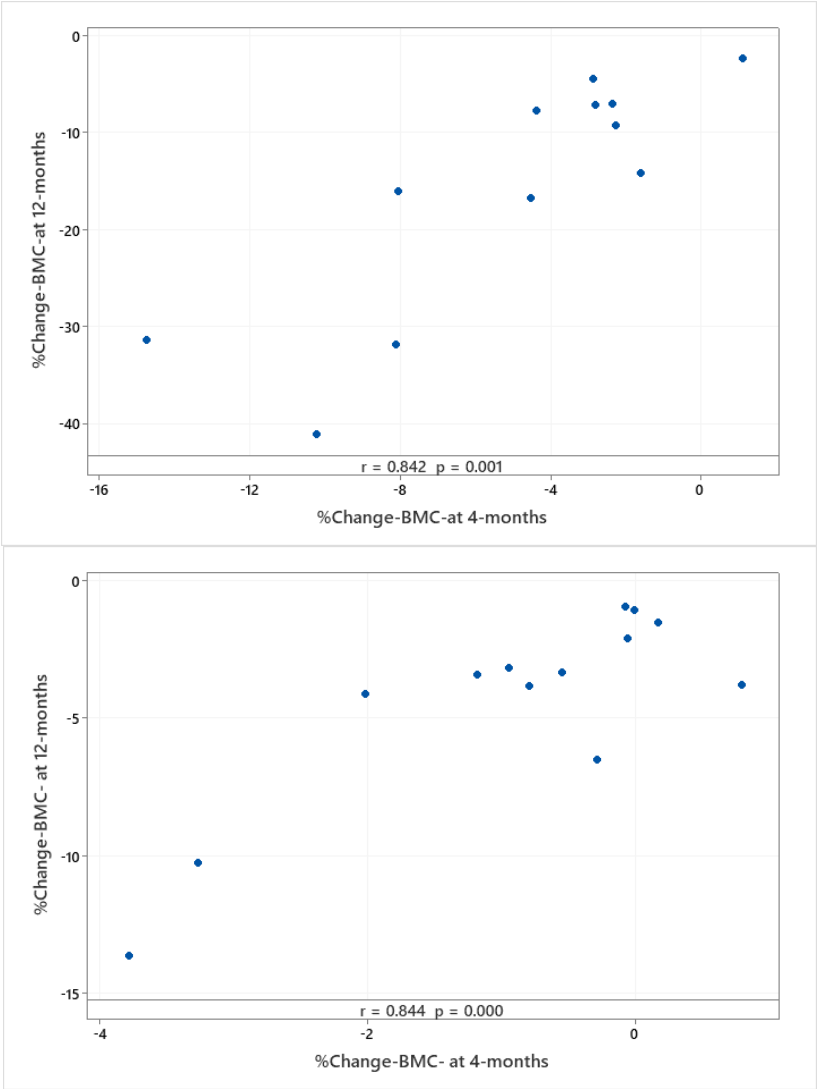


Figure 4: Correlations between total BMC losses at 4 months and 12 months total BMC losses for 4% (upper) and 66% (lower) sites.

Discussions and Conclusions

The aim of this study was to investigate whether bone losses following SCI vary regionally within the tibia. In addition, to assess whether total and regional bone loss at the 4 months postinjury are associated with total loss at 12 months postinjury.

Whilst absolute losses in BMD were greater in the outermost region of the distal tibia cross-section, relative (*i.e.* percentage) losses were equal across the bone. In contrast, both total BMC and cortical BMD decreased equally in absolute terms in all sectors at 66% site, but relative loss was greatest in the posterior region compared to other sectors across the bone. In addition, total BMC loss at 4 months postinjury was highly correlated with loss at twelve months postinjury, whereas associations with regional loss were weaker.

Greater absolute losses in BMD at the outermost sector in the distal tibia can be explained by the predominantly cortical bone component of that region which has higher density compared to the predominant trabecular component in other sites. Even when adjusted for this discrepancy, losses in the outer sector were similar to those in other sectors, which contradicts the assumption that trabecular loss is faster and greater than cortical losses[19]. This finding corroborates the results of a recent HR-pQCT-based study which reported similar deficits in bone mass in trabecular and cortical bone at distal tibia following long-term spinal cord injury[20]. A comparable relative bone loss across different regions at this site may be due to the similar mechanical stresses (that are mostly compressive) experienced at this site.

As previously reported, the 4.3% loss in total BMC at the diaphyseal 66% was largely due to a 2.8% cortical BMD loss[7]. Whilst cortical CSA values were ~2% lower at 12 months, there was not strong statistical evidence to support this change perhaps in part because of a larger degree of inter-individual variation in CSA compared to BMD. Longer-term studies suggest that bone mass loss is mostly due to the reduction in cortical wall thickness[9]. Bone loss appears to be more pronounced in the posterior and anterior regions compared to other parts of the bone[13], similar to the regional variation reported in age-related bone loss in uninjured individuals[21]. This outcome is not well understood but could be explained by difference in habitual loading regimes experienced across different regions of the bone.

Regional differences in habitual loading across the tibia cross-section in uninjured individuals have previously been reported, with higher compressive strains in the posterior region during high-impact

activities such as sprinting[22]. Accordingly, in young and older adults higher BMD is observed in these regions[14], and the greater change in loading following SCI might explain greater post-injury loss. We investigated the diagnostic potential of these regional variations in early bone loss but did not find early post-injury regional measures to predict 12-month losses as well as whole-bone measures. Whilst regional bone loss has been shown to predict hip fracture risk in uninjured individuals[23], the predictive value of tibia regional measures has not been explored due to the relatively low clinical importance of these fractures in individuals without SCI. Such information may be of limited relevance in SCI given the different mechanisms of tibia fracture in the two populations. Given the high incidence of tibia fractures following SCI, larger longitudinal studies should assess the value of tibia regional measures for fracture risk. Current literature on fracture risk in SCI[24] does not describe the mechanism or region of fracture within each bone, and this knowledge gap should also be addressed.

Our findings of regional bone loss have clinical relevance informing development of rehabilitation strategies. Interventions focused on selective electrical stimulation of the soleus and quadriceps led to preferential sparing of bone in the posterior region of the tibia[16] and femur[17] respectively. Such strategies could effectively target regions at risk of greater loss The greater decline in the posterior region could also be explained by the relatively high endocortical circumference: area ratio at this region than in the thicker-walled anterior region. This ratio was suggested to be associated with greater bone loss following SCI in a cross-sectional study due to the higher turnover in the endocortical border [13]. The low BMD may indicate a higher porosity at this region compared to other regions, which would provide more surface to resorb bone.

In agreement with other reports, endocortical circumference increased post-injury while the periosteal circumference showed no change[25][26]. One study reported decreased periosteal circumference in people with SCI compared to able-bodied controls [13]. However, the SCI group in that study had sustained their injury between 9-32 years ago, which might suggest that this decline in periosteal circumference occurs later in the chronic phase. Alternatively, that group differences reflect a blunting of the usual age-related increase in periosteal circumference observed in uninjured adults[27]. Given that area increases by the square of the radius, relatively large changes in area equate to small changes in circumference. Hence, some minor changes in periosteal circumference and regional variations in both circumferences may not have been detected by our pQCT assessments.

Bone losses 4 months postinjury were strongly correlated with losses at twelve months postinjury. Previous studies have identified huge variation in bone loss following SCI, with trabecular BMD losses of 1-65% observed twelve months after injury[12]. That fracture incidence in SCI, as with uninjured individuals, increases dramatically with degree of BMD loss[28] means that those with rapid bone loss are at high risk of fracture even relatively shortly after injury. However, a recent study

found that 51% of SCI medical professionals would only test for bone loss in the chronic phase, or only after a fragility fracture occurs (43%)[29], which highlights the inconsistency in the detection of bone loss following SCI. It should be noted here that the International Society of Clinical Densitometry (ISCD) recommended testing people with SCI as soon as they are medically stable in its Official Position published in 2019 [30]. Our finding of the importance of the four months bone scans supports this recommendation and emphasises the need for clinical guidelines for early bone scans and probably preventive treatments to reduce fracture risk.

A previous study used statistical shape modelling to predict bone loss in SCI[31], in order that individuals at risk could be identified and early treatment commenced. Whilst these models identified individuals at risk of bone loss, these relationships were less strong (all $r \leq 0.53$) than those observed in the current study ($r = 0.56$-0.84). A previous report of whole-bone tibia changes using the dataset examined in the current study found no effect of either age or gender on bone loss magnitude[7]. Therefore, to the best of our knowledge four-month scan assessments represent the strongest predictor of post-SCI bone loss identified to date. In addition, that the total BMC measures are available from the pQCT manufacturer's software without additional analysis increases their clinical viability. Further assessment of the predictive value of bone assessments in the early postinjury stages should be conducted, and if appropriate, the effects of early-stage interventions in those at risk of rapid bone loss should be assessed. These studies should also consider other regions that are prone to fracture in this group such as the proximal tibia and distal femur.

To our knowledge, this is the first study to assess regional bone loss within tibia cross-sections. A longitudinal assessment in injured individuals represents stronger evidence than that available from cross-sectional comparisons of injured and uninjured individuals. Whilst repeated measures assessments are a powerful statistical technique even with small participant numbers, these assessments were performed in a relatively small cohort. Therefore, we may have been underpowered to detect more modest variations in regional loss, which reinforces our call for these assessments to be replicated in a larger cohort. This may be more evident for variables such as cortical CSA where the relative degree of inter-individual variability is greater than for those such as cortical BMD.

We observed regional variation in tibia bone loss following spinal cord injury. Absolute losses in the distal tibia were greatest in outer region of bone, although relative losses were similar. Conversely, whereas absolute decreases were similar across radial sectors in the tibia shaft, relative losses were greater in the posterior region. We also found that bone losses at four months postinjury were strongly correlated with bone loss twelve months after injury. More studies on larger populations are required to help assess the utility of early-stage bone assessments in identifying rapid bone losers and implementing early treatments to prevent greater bone loss.

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