Predicting patient-specific rates of bone loss at fracture-prone sites after spinal cord injury

S. Coupaud[1,2,*] ,* A.N. McLean[2], S. Lloyd[3], and D.B. Allan[2]

[1] Biomedical Engineering Research Division, School of Engineering, School of Engineering, University of Glasgow, Glasgow G12 8QQ.
[2] Scottish Centre for Innovation in Spinal Cord Injury, Queen Elizabeth National Spinal Injuries Unit, Southern General Hospital, 1345 Govan Road, Glasgow G51 4TF.

[3] Robertson Centre for Biostatistics, University of Glasgow, Glasgow G12 8QQ.

Abstract

Purpose: People with spinal cord injury (SCI) experience bone loss and have an elevated rate of fracture in the paralysed limbs. The literature suggests an exponential time course of bone loss after SCI, but true rates may vary between patients. We propose systematic evaluation of bone status in the early stages of SCI to identify fast bone losers.
Method: A case series of six patients with complete SCI were scanned using peripheral Quantitative Computed Tomography within five weeks and at four, eight and twelve months post-injury. Bone mineral density (BMD) and content (BMC) were measured at fracture-prone sites in the tibia and femur. Patient-specific-predictions (PSP) of expected rates of bone loss were produced by individualising published model equations according to each patient's measured values at baseline. Wilcoxon Signed-Rank tests were used to identify changes between time-points; chi-squared tests for differences between measured and PSP values.
Results: In the lower limbs, mean values decreased significantly between baseline and eight months post-injury, by 19–31% for trabecular BMD, 21–32% for total BMD, and 9–29% for BMC. Most subjects showed no significant differences between PSP and measured values, but individuals with significantly faster rates of bone loss than predicted should be investigated further.
Conclusions: There was considerable intersubject variability in rates of bone loss after SCI. Patients showing fastest bone loss could benefit from continued follow-up and possibly treatment.

Keywords: osteoporosis, paraplegia, pQCT, spinal cord injury, tetraplegia

Abbreviations

BMDtrab: Trabecular Bone Mineral Density
BMDtot: Total Bone Mineral Density
BMC: Bone mineral content
HA: Hydroxyapatite
PSP: Patient-Specific Prediction
SCI: Spinal Cord Injury

**Corresponding Author: Dr Sylvie Coupaud, Biomedical Engineering Research Division, School of Engineering, University of Glasgow, Glasgow G12 8QQ, Tel: +44 141 330 2867, Fax: +44 141 330 4343, Email: Sylvie.Coupaud@Glasgow.ac.uk

1 Introduction

One of the consequences of spinal cord injury (SCI) is disuse osteoporosis in the paralysed limbs. The extent of bone loss following SCI is widely documented [1, 2, 3, 4, 5, 6]. There is also low bone integrity and an elevated incidence of fractures in SCI, at a rate at least twice that of the general population [7, 8]. The most common fracture locations in SCI are the proximal and distal tibia and the distal femur, with fewer fractures recorded in the tibial and femoral shafts [9]. At present, there is no consensus on a systematic approach to the management of sublesional bone loss and fracture after SCI. Spinal injuries physicians typically have a reactive response to fracture, rather than implementing proactive management [10]. Early identification of individuals at highest risk of fracture may allow targeted preventative treatment, which would ideally begin during their inpatient stay in their primary care or rehabilitation unit.

Although bone mineral density (BMD) cannot be the sole criterion for assessing fracture risk, it may be used as an indicator. Based on this principle, Eser *et al.* [11] have suggested SCI fracture thresholds for the tibia and femur based on trabecular BMD values derived from peripheral Quantitative Computed Tomography (pQCT) scans at the distal epiphyses. The pQCT technique has been validated for use in SCI [12]. Dual-Energy X-ray Absorptiometry (DXA) is the bone densitometry technique currently more widely used in a clinical setting, but for SCI investigations the benefits of using pQCT over DXA include: (i) targeted measurements at the sites in the peripheral skeleton most prone to fracture in SCI (distal and proximal tibia, distal femur) [11, 12]; (ii) true volumetric BMD measurements rather than projected areal BMD [13, 14]; (iii) the ability to analyse trabecular and cortical bone compartments separately [13, 14, 15].

Cross-sectional studies previously carried out in the chronic SCI population [12, 16] have led to estimates of the time course of decline in trabecular BMD and other key bone density and geometry parameters in motor-complete SCI. Although data are also available from longitudinal DXA studies [17, 1], the measurement artefacts [14] caused by soft-tissue changes that inevitably occur [18] in parallel with loss of bone mineral in the paralysed limbs, and to varying extents in different subgroups of the population (e.g. flaccid versus spastic SCI) [16] limit the potential for extrapolation of the results to the wider SCI population. To date, only a small number of longitudinal studies have been performed in SCI using the pQCT technique [19, 20], but the measurements were carried out either after the first year of SCI [21] or with large time intervals between repeat scans [19, 20]. As interventions are likely to be most effective in the initial stages of SCI, changes within the bones should be determined from as soon as possible after injury, and followed up at higher temporal resolution to describe the time courses of decline quantitatively in key bone parameters in the paralysed limbs.

We present longitudinal pQCT data from six patients in the first year of SCI to address two objectives, which are: (i) to identify the timepoint(s) at which BMD and other bone parameters fall below the normal range at fracture-prone sites in the absence of any intervention; and (ii) to investigate the potential for patient-specific predictive modelling of bone loss by adjusting the best-fit equations from the literature according to each patient's baseline values obtained from pQCT scans carried out as soon as possible after SCI.

2 Methods

2.1 Subjects

We recruited inpatients of the Queen Elizabeth National Spinal Injuries Unit with a motor-complete (grade A or B on the American Spinal Injuries Association Impairment Scale (AIS) [22]) traumatic SCI at neurological levels C4 and below. Exclusion criteria were: (i) metal implants at scan sites, (ii) recent fracture in the bone(s) to be scanned, (iii) inability to provide informed consent, (iv) previously diagnosed metabolic bone disease. The study was approved by the South Glasgow & Clyde Research

Ethics Committee. All subjects provided their informed consent prior to participation in the study, in line with the Declaration of Helsinki.

2.2 Procedure

Within 5 weeks of their injury (baseline), subjects underwent peripheral Quantitative Computed Tomography (pQCT) scans (XCT 3000, Stratec Medizintechnik, Germany) at the Queen Elizabeth National Spinal Injuries Unit (Southern General Hospital, Glasgow, UK). Scans were performed unilaterally in the non-dominant arm and the opposite leg, unless there was recent history of fracture (less than 10 years) in which case the other limb was scanned. The pQCT scans were repeated at 4, 8 and 12 months post-injury.

Prior to each patient scan, quality assurance scans were performed using the manufacturer's phantom. Patients were transferred onto a height-adjustable patient couch. A measuring tape was used to measure the length of the tibia, from the distal end of the medial malleolus to the medial joint cleft. The femur length was taken to be equivalent to tibial length for practical reasons. The length of the radius was measured from the humero-radial joint cleft to the styloid process. The lower-leg was placed through the gantry, with the foot resting on the footrest. The opposite leg rested on a height-adjustable holder alongside the scanner. A scout view was performed at the ankle, to enable positioning of the reference line on the distal endplate of the tibia. The tibia was scanned at 4% of total bone length, starting from the distal end. The patient was repositioned with the thigh through the gantry. From the distal femur scout view, the reference line was placed on the lateral femoral condyle; the distal femur was scanned at 4% from the distal end. From the proximal tibia scout view, the reference line was placed on the medial aspect of the tibial plateau; the proximal tibia was scanned at 4% from the proximal end. The patient was repositioned for the upper limb scan. With the hand secured to the handrest, a scoutview was performed at the wrist to place the reference line on the distal radial endplate. The radius was scanned at 4% of total bone length, from the distal end. Slice thickness was set at 2mm and voxel size at 0.5 mm in the tibia and radius and 0.3 mm in the femur. As in the cross-sectional pQCT studies in SCI by Eser, Frotzler *et al.* [11, 12, 21], the choice of the smaller voxel size for femoral slices was due to the typically thin cortical shell at the distal femur epiphysis in this patient group.

2.3 Outcome measures

The manufacturer's software (XCT550, Stratec Medinzintechnik, Germany) was used for analysis of the scans. With pQCT absorption values are linearly transformed into hydroxyapatite (HA) equivalent densities, and HA density measurements are calibrated with respect to fat, set at 0 mg HA cm^{-3}, and resulting in water being at 60 mg HA cm^{-3} [23]. At all 4% scan sites (epiphyses), we calculated trabecular bone mineral density (BMDtrab), total bone mineral density (BMDtot) and bone mineral content (BMC). A contour algorithm was used with thresholds of 180 $mg.cm^{-3}$ in the distal tibia, 150 $mg.cm^{-3}$ in the proximal tibia, 130 $mg.cm^{-3}$ in the distal femur and 150 $mg.cm^{-3}$ in the distal radius to find the periosteal surface of the epiphysis for calculation of BMC, total bone CSA and BMDtrab. For BMDtrab calculations, concentric pixel layers were automatically peeled off from the perimeter until the central 45% area remained. Reproducibility of pQCT in SCI is described by Eser et al. based on duplicate measurements in seven subjects with chronic SCI. This resulted in coefficients of variation ranging from 0.96% (BMC) to 2.04% (BMDtot) in the distal femur epiphysis, and from 0.46% (BMDtot) to 2.23% (BMDtrab) in the distal tibia epiphysis [12].

2.4 Individualised predictive models

Exponential models previously fitted to cross-sectional data by Eser *et al.* (2004) [12], to describe the best-fit pattern of decline in a chronic SCI population, are given for bone parameters of the distal epiphyses for the tibia and femur in Eq. 1 to 6.

$$BMDtrab_{tib} = 190.8e^{-0.41t} + 65.2 \quad (1)$$

$$BMDtrab_{fem} = 139.2e^{-0.56t} + 112.3 \quad (2)$$

$$BMDtot_{tib} = 193.6e^{-0.47t} + 133.2 \quad (3)$$

$$BMDtot_{fem} = 128.8e^{-0.66t} + 144.7 \quad (4)$$

$$BMC_{distaltib} = 2.56e^{-0.57t} + 1.80 \quad (5)$$

$$BMC_{distalfem} = 5.58e^{-0.74t} + 5.82 \quad (6)$$

These model equations were used in combination with pQCT-derived bone parameters measured in our study at baseline to predict each subject's individualised pattern of decline, for key bone parameters in the distal epiphyses of the tibia and femur. The basic model was corrected according to each individual's baseline value for each relevant parameter by introducing an additive "shift" term. The assumption behind this is that the rate of loss is fixed and that the starting value at baseline is the only factor that alters the actual values at subsequent time points. For each parameter (BMDtrab, BMDtot and BMC) at the distal epiphyses (tibia, femur), we calculated these predicted values at 4-, 8- and 12-months as follows.

The absolute difference between the actual value at baseline (as determined from pQCT scans) and the predicted value calculated from the Eser model at baseline provided the shift term to be added for subsequent time-points (4, 8 and 12 months post-SCI). An example of the computation of this *additive* prediction is given in equations 7 and 8, for BMDtrab at the distal tibia.

$$BMDtrab_S = BMDtrab_A - BMDtrab_M \quad (7)$$

$$BMDtrab_{Pa} = 190.8e^{-0.41t} + 65.2 + BMDtrab_S \quad (8)$$

Where t is 'time' in years, and:

$BMDtrab_A$ = value as measured at baseline, in mg.cm^{-3}

$BMDtrab_M$ = uncorrected model-predicted value at baseline, in mg.cm^{-3}

$BMDtrab_S$ = patient-specific shift term for additive-model prediction, in mg.cm^{-3}

$BMDtrab_{Pa}$ = patient-specific additive model-predicted value at time t, in mg.cm^{-3}

No models were available for the proximal tibia or distal radius. Predicted values were not calculated for these sites.

2.5 Statistical methods

Bone parameters were summarised for each time-point (baseline, +4 months, +8 months and +12 months) by means and standard deviations. Due to the small sample size, Wilcoxon Signed Rank Tests were used to identify significant differences in key bone parameters in the distal tibia, proximal tibia, distal femur and distal radius between baseline, 4, 8 and 12 months post-injury. In order to asses how well the baseline adjusted models predicted values at later time-points, standardised residuals were calculated and summed for each subject and compared to a chi-squared distribution with three degrees of freedom. Analysis was carried out in SPSS (version 15.0) and SAS (version 9.1).

3 Results

3.1 Subjects

Subject details are given in table 1; all had motor-complete traumatic SCI. Subject S2 did not return for repeat scans at 8 and 12 months post-injury.

Subject	SCI level	Age	Sex
S1	C4	17	M
S2	T9	18	M
S3	C4/5	72	M
S4	T3	17	M
S5	T4	29	M
S6	T6	18	M

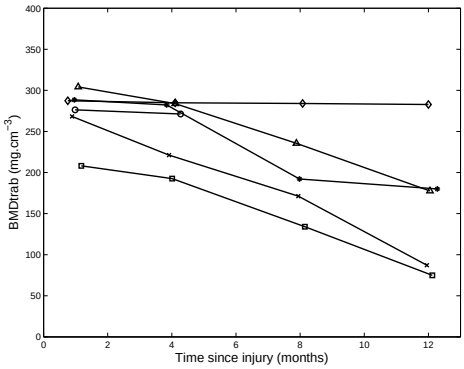
Table 1: Subject details. 'Age': in years, at the start of participation.

3.2 Measured values — Lower Limb

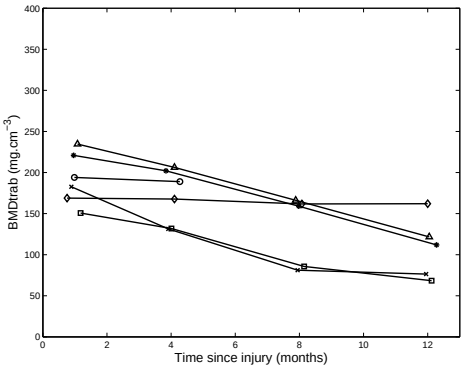
Each subject's BMDtrab values as measured at baseline, 4 months post-SCI, 8 months post-SCI and 12 months post-SCI are shown graphically for each subject for the distal tibia, proximal tibia and distal femur in figure 1. Mean values for BMDtrab, BMDtot and BMC calculated at each time point are given for the distal and proximal tibia, and the distal femur in table 2. Comparing values between scan time-points, statistically-significant changes were recorded in trabecular and total BMD, and BMC in the epiphyses of the bones of the paralysed limbs. At the distal tibia, all changes between the different scan time-points were statistically significant (with p-values ranging from p=0.028 to p=0.043). At the proximal tibia there were statistically significant changes between most time-points for all parameters, except between 8 and 12 months post-injury for BMDtrab and BMDtot (p=0.080). At the distal femur, there were statistically significant changes between most time-points for most parameters, except BMDtrab between 4 and 8 months post-injury (p=0.080), BMDtot between 8 and 12 months post-injury (p=0.080), and BMC between 8 and 12 months post-injury (p=0.080).

The mean values of key bone parameters in the distal epiphyses of the tibia and femur obtained at each scan time-point can be compared to pQCT reference values from the literature [12] for able-bodied subjects and people with long-term SCI who have reached their steady-state levels. No reference data are available for the proximal tibia. At the distal epiphyses of the tibia and femur, the group mean fell below the normal range by 8-months post-injury only. Even at 12-months post-injury, however, these values remained substantially higher than steady-state values recorded in people with long-term motor-complete SCI [12, 16]. Although the mean values for bone parameters at the fracture-prone sites at each of the four time-points post-SCI remain above the mean values reported for long-established SCI, the large intersubject variability at the 8- and 12-month time-points (as indicated by the SD) shows that some patients fell to much lower BMD and BMC levels than others in this time frame.

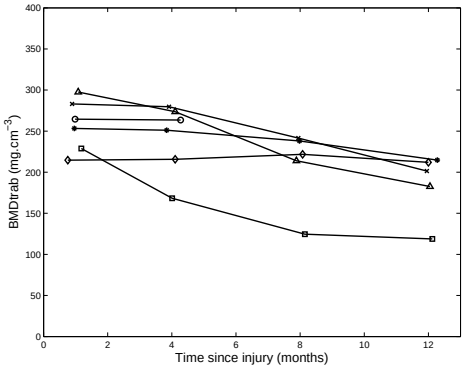
There were some clear differences in patterns of bone loss between subjects and between sites. Subject S4 showed consistently highest percentage loss in the first year of SCI in the tibial epiphyses, ranging from 46% decrease in BMC in the proximal tibia to 67% decrease in BMDtrab in the distal tibia. By 12 months post-SCI, with a measured BMDtrab value of 87.20 mg.cm^{-3} at the distal tibia, subject S4 was already approaching the distal tibia fracture threshold proposed by Eser *et al.* [11] of around 70 mg.cm^{-3}. In contrast, the decline in bone values in the distal femur in this subject was less severe, and his final distal femur BMDtrab at 12 months was only slightly below the normal range at 201.40 mg.cm^{-3}. Subject S5 showed the largest percentage decreases at the distal femur, and had a more consistent pattern of bone loss at the three epiphyseal sites investigated in the lower limbs, reaching low values in all the fracture-prone sites. Subject S5 reached a BMDtrab of 118.80 mg.cm^{-3} that was close to the distal



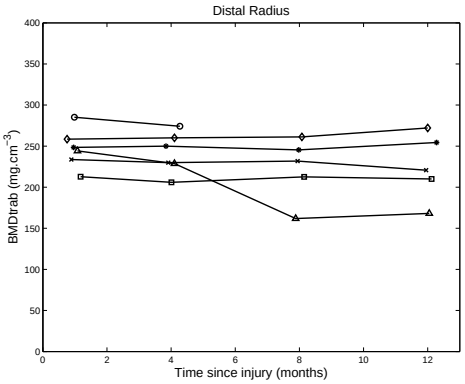
(a) Distal Tibia



(b) Proximal Tibia



(c) Distal Femur



(d) Distal Radius

Figure 1: Each subject's measured trabecular BMD values at at baseline, 4, 8 & 12 months post-SCI.

Bone	Parameter	Measured values				Reference values *	
		Baseline	+4 months	+8 months	+12 months	Chronic SCI	Able-bodied
Distal Tibia	BMDtrab [mg.cm^{-3}]	272.11 (33.62)	256.03 (39.39)	203.43 (58.11)	160.53 (84.18)	66.1 (23.4)	245.8 (45.0)
	BMDtot [mg.cm^{-3}]	331.75 (24.49)	308.28 (40.16)	254.65 (46.94)	215.40 (68.03)	135.0 (26.9)	312.7 (49.1)
	BMC [g.cm^{-2}]	4.39 (0.60)	3.96 (0.58)	3.29 (0.67)	2.78 (0.78)	1.80 (0.34)	4.31 (0.64)
Proximal Tibia	BMDtrab [mg.cm^{-3}]	191.97 (31.57)	171.37 (33.57)	130.77 (43.35)	108.09 (37.73)	no data	no data
	BMDtot [mg.cm^{-3}]	250.46 (29.13)	214.98 (26.41)	169.65 (32.09)	151.93 (33.32)	no data	no data
	BMC [g.cm^{-2}]	7.57 (1.16)	6.51 (1.10)	5.31 (0.91)	4.78 (0.78)	no data	no data
Distal Femur	BMDtrab [mg.cm^{-3}]	256.99 (31.55)	241.98 (42.62)	207.97 (47.97)	185.91 (39.58)	112.8 (28.3)	243.7 (30.5)
	BMDtot [mg.cm^{-3}]	277.75 (23.41)	253.85 (32.10)	219.50 (36.12)	202.44 (27.34)	146.5 (29.1)	267.6 (32.9)
	BMC [g.cm^{-2}]	11.41 (1.23)	10.20 (1.17)	8.52 (1.10)	8.02 (0.95)	5.86 (1.30)	11.30 (1.56)

Table 2: Key bone parameters, determined using pQCT, at the distal tibia, proximal tibia and distal femur; data are shown as mean (SD). (*Taken from Eser *et al.* 2004 [12]; there are no reference values for the proximal tibia.)

femur fracture threshold proposed by Eser *et al.* [11] of around 110 mg.cm^{-3}, and a distal tibia BMDtrab of 74.91 mg.cm^{-3}, once again very close to the fracture threshold (70 mg.cm^{-3}). His BMDtrab at the proximal tibia decreased to 68.41 mg.cm^{-3}, which is also low, but fracture thresholds for this site in SCI are not available for reference. In contrast, subject S3 showed negligible loss of bone at all measured sites, ranging from 1% decrease in BMDtrab at the distal femur to 13% decrease in BMDtot at the proximal tibia.

3.3 Measured values — Upper Limb

Measured values for BMDtrab at the distal radius are shown graphically for all subjects in figure 1. When comparing key bone parameters at the distal radius at different time-points, only BMDtot differed significantly between baseline and 4-months post-SCI (p=0.046) and between 8-months and 12-months post-SCI (p=0.043). Any other differences were not statistically significant. In table 3, mean values (for paraplegic subjects only) are shown for each time point for BMDtrab, BMDtot and BMC, and are compared to pQCT reference values from the literature [12] for able-bodied subjects and people with paraplegia with long-term SCI. For the radius, the mean values for the paraplegic subject group (n=4) remained above or within the normal range at all four scan time points post-SCI.

Insert table 3 around here.

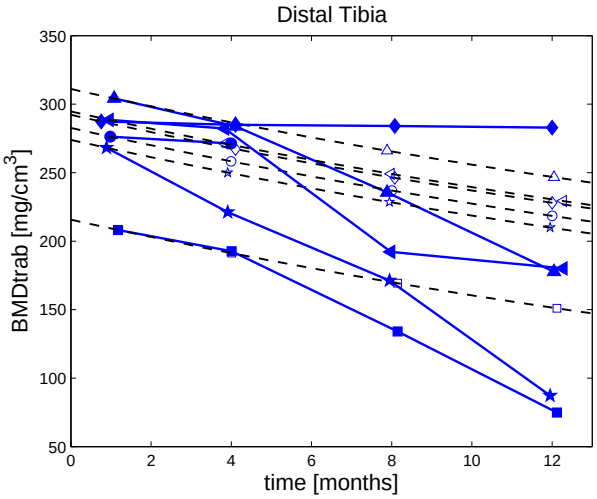
Parameter	Measured values				Reference values *	
	Baseline	+4 months	+8 months	+12 months	Chronic SCI	Able-bodied
BMDtrab [mg.cm^{-3}]	245.03 SD 30.48	239.98 (29.03)	229.94 (16.52)	228.37 (23.17)	202.3 (32.5)	219.7 (46.1)
BMDtot [mg.cm^{-3}]	349.71 (22.73)	331.87 (25.90)	348.41 (15.24)	325.07 (28.17)	352.9 (48.4)	354.0 (50.8)
BMC [g.cm^{-2}]	1.55 (0.18)	1.58 (0.14)	1.52 (0.14)	1.59 (0.08)	1.66 (0.26)	1.69 (0.27)

Table 3: Key bone parameters, determined using pQCT, at the distal radius, for paraplegic subjects only (n=4); data are shown as mean (SD). (* Taken from Eser *et al.* 2004 [12].)

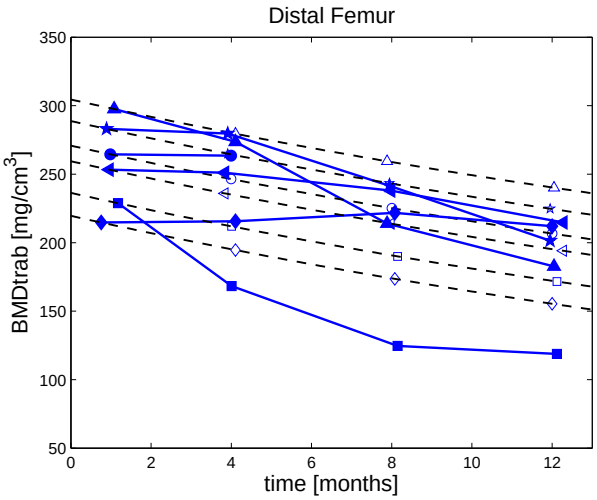
3.4 Predicted versus Measured Values — Lower Limb

For most subjects, there was no indication that the measured rates of bone loss were slowing during the last post-injury time window investigated (8–12 months post-SCI) compared to the earlier time windows. Previous studies have shown that an exponential decay provides the best description of the long-term relationship between BMD and time since injury. We modified the equations of best fit from the literature [12] to individualise each patient's temporal pattern of bone loss according to their own starting values at baseline. These patient-specific predicted (PSP) patterns of decline in BMDtrab at the epiphyses of the tibia and the femur are shown in relation to their measured patterns of decline, in figure 2. The results of the analysis of goodness-of-fit between the patient-specific predicted and the measured rates of decline in BMDtrab, BMDtot and BMC are given for each subject for the distal epiphyses of the tibia and the femur in table 4.

Subject S4 showed statistically significant deviation from the predicted curve for BMD at the distal tibia (p=0.010 for BMDtrab; p=0.021 for BMDtot), as confirmed in figure 2, with increasing deviation between the measured and prediction curves with time post-SCI. Subject S5 showed consistently significant deviation from the prediction model at the distal femur (p=0.029 for BMDtrab; p=0.050 for BMDtot; p=0.012 for BMC). In the distal tibia, values for S5 did not differ significantly between predicted and measured models. For subject S1, predicted and measured BMC values differed significantly, but BMD measures did not. For all other subjects, no statistically significant differences were detected between the predicted and measured models.



(a)



(b)

Figure 2: Predicted & measured changes in trabecular BMD at distal epiphyses over the first year of SCI. For each subject, the dashed line represents the patient-specific prediction (PSP) curve and the solid line follows the measured time course.

Subject	Distal Tibia Chi-square test p-value			Distal Femur Chi-square test p-value		
	BMDtrab	BMDtot	BMC	BMDtrab	BMDtot	BMC
1	0.339	0.080	0.007*	0.129	0.075	0.288
2	0.752	0.942	0.915	0.619	0.757	0.846
3	0.424	0.377	0.333	0.185	0.209	0.182
4	0.010*	0.021*	0.084	0.823	0.232	0.437
5	0.246	0.436	0.362	0.029*	0.050*	0.012*
6	0.332	0.291	0.890	0.831	0.982	0.909

Table 4: Goodness-of-fit analysis results, comparing the individualised patient-predicted models, and the measured values at the distal tibia and distal femur. * Statistically significant differences between models of predicted and measured values ($p \leq 0.05$).

4 Discussion

We characterised bone loss during the first year of SCI through a case series of six SCI patients, enabling us to investigate the predictive potential of early pQCT bone scans and to identify the first 8 months of SCI as a key therapeutic window during which early preventative intervention should be implemented in patients exhibiting high rates of bone loss. In this longitudinal study of six acute patients with motor-complete SCI, a sequence of pQCT scans was performed within 5 weeks of injury and again at 4-, 8- and 12-months post-SCI, to quantify the changes in key bone parameters in the first year after injury. The focus here is on the trabecular-rich epiphyses, which typically are the first to show changes in response to altered loading of the bones [1, 12, 24]. The mean responses of our study group suggest that values of key bone parameters at fracture-prone sites (distal femur, and proximal and distal tibia) only start to fall below the normal range at 8 months post-injury. However, the intersubject variability increases at each successive scan time-point, with some patients showing fast rates of bone loss but others showing little change in bone parameters over the same time period. Although mean responses are useful in describing the overall patient population's bone status relative to normal, detailed investigations of the individual patients' own rates and magnitudes of bone loss are likely to be more informative in a proactive approach to management of sublesional bone loss in SCI, to enable clinicians to target treatments towards those patients showing the most extensive and/or rapid bone loss. There was large intersubject variability in the rates of bone loss in the paralysed limbs in the first year of SCI, but less intrasubject variability: those patients showing bone loss tended to have similar rates of decline in BMD and BMC at all fracture-prone sites. Based on our initial findings, we propose a densitometric method of screening SCI patients in the first few months of their injury to identify those with high rates of bone loss at fracture-prone sites early on.

We produced patient-specific-predictions (PSP) of the time course of bone loss at the distal epiphyses of the tibia and femur. The underlying assumptions of these individualised models were that: (i) all patients experience the same rate of bone loss (described by an exponential decay equation); and (ii) any differences in bone values between patients at any particular time point are explained by differences in their starting values at baseline, i.e. their initial bone status. We compared PSP curves with the actual measured values at those time-points to determine the validity of these assumptions. A goodness-of-fit (chi-squared test) analysis showed that, for most patients, there were no statistically significant differences between predicted values and measured values of BMC, BMDtrab and BMDtot at the distal epiphyses of the tibia and femur. For BMD values, the exceptions were subjects S4 (for the distal tibia) and S5 (for the distal femur), whose deviations from the PSP curves became greater with time post-injury. This analysis showed them to be losing bone in the first 12 months at faster rates and more extensively than predicted. To achieve fracture-risk diagnosis based on pQCT densitometry, these statistically significant deviations could be used as a "red flag". For example, for the two patients showing much lower BMD values than expected at one year post-SCI, one could postulate an increased fracture risk, as they both approached the BMDtrab-based fracture thresholds proposed by Eser*et al.* [11] of 70 mg.cm^{-3} for the distal tibia and 110 mg.cm^{-3} for the distal femur by the end of the period of investigation. Thus, there may be potential for implementing patient-specific predictions of bone loss at key sites in the paralysed limbs to identify individuals at highest risk of fracture. However, it is clear that there are other factors that may need to be considered when analysing fracture risk. Additional fracture risk factors are not explored in this paper.

Some (potentially significant) amount of bone loss may have occurred prior to the baseline scans. Ideally, the baseline scans would be carried out within days of injury, but the earliest that we were able to perform them was 3 weeks post-SCI due to the acute effects of SCI on the patients. On average, baseline scans were performed at 4.2 SD 0.6 weeks post-injury. The extent of any bone loss prior to this is unknown. We can only base patient-specific predictions on the earliest timepoint at which we can achieve the bone imaging safely, once the patient is neurologically stable. By applying the model to the time period preceding the baseline scan, we can then infer by interpolation the starting BMD and other bone values at the time of injury. A factor that could contribute to differential rates of bone loss in the

first few weeks post-SCI is the length of the "spinal shock" phase. Others may be the length of time on bedrest and immobilisation. From bedrest studies [25], used to simulate conditions experienced by astronauts in space flight, immobilisation-related bone resorption has been shown to occur as early as day 7 of bed rest, and to peak at around 92–102 days of bed rest. After SCI, as the length of time of spinal shock, immobilisation and bedrest varies from patient to patient, this may also explain some of the intersubject variability in bone parameters at baseline and 4 months post-injury. However, postulating an effect of the length of spinal shock and immobilisation periods on the rate of bone loss during the acute stages of SCI would be speculative at this stage.

We suggest that some patients follow a close-to-predicted pattern of bone loss whilst others deviate substantially from it. This provides some support for the hypothesis proposed by other authors [26, 3] that persons with osteoporosis can be classed into "fast" and "slow" bone losers. Dambacher *et al.* [26] proposed this distinction for postmenopausal women with osteoporosis, and identified trabecular BMD as an appropriate parameter to distinguish between the two subgroups. deBruin *et al.* [3] suggested an equivalent pattern in patients with disuse osteoporosis as a result of SCI, based on their results from a longitudinal pQCT study in ten SCI patients involving an initial scan in the acute phase and a repeat scan at around 3 years post-injury. From these data, the investigators observed that some subjects lost much less bone than others over the investigation period. These "slow" bone losers showed no sign of reaching a steady-state, continuing to lose bone at a slow rate. In contrast, other subjects showed a much higher rate of decline in bone density over the same period. Based on only six subjects in our study, it is not possible to identify a single source of any apparent difference between "fast" and "slow" bone losers, but this warrants further investigation. Regardless of the possible cause(s) of these differences, if a clear bimodality in bone responses to SCI could be determined by continuing to collect longitudinal data from additional acute SCI subjects, we may be able to produce separate predictive equations for these two subgroups. If we do not make the distinction, the basic model (or mean response) fitted to data from a mixed cross-section of the chronic SCI population would underestimate the rate and magnitude of bone loss in "fast" losers and overestimate the bone loss in "slow" bone losers, and would reduce the applicability and validity of the predictive equations. In an extension to the study, we propose that patients should be followed up until they show a plateau in their bone values — chronic steady-state values. Based on the literature, this is expected to occur at 3–7 years post-SCI [12], but we would see this occurring earlier in some subjects ("fast" bone losers) and later in others ("slow" bone losers) if there is indeed a distinction in rates of bone loss between them.

The focus of this paper is on changes in bone at fracture-prone sites in SCI, and so PSPs were only determined for these. However, we also carried out pQCT scans at the distal radius. Fragility fractures of the radius are not common in SCI, and we expect no or minimal bone loss in the non-paralysed upper limbs of paraplegic subjects. This was confirmed with paraplegic subjects showing little change in the radius, remaining in the normal range over the 12-month period. In tetraplegic patients, epiphyseal data from the distal radius allowed us to investigate whether or not bone loss occurs in the radius to a similar extent as in the tibia and femur in subjects with cervical level SCI. Some bone loss would be expected in the radius in tetraplegia, where there is paralysis of upper limb muscles as well as the lower limb ones, albeit to varying extents depending on the exact level of injury. Both subjects with tetraplegia included in this study had motor-complete high-level cervical injuries, resulting in paralysis of elbow, wrist and finger flexors and extensors. One subject with tetraplegia (S1) showed clear bone loss in the radius, as well as in the tibia and femur, whereas the other (S3) showed only minimal changes at all scan sites. This might suggest that at least in high tetraplegia those who experience bone loss in the lower extremities also experience bone loss in the upper extremities.

The elderly subject (S3) with complete tetraplegia showed much less decline in bone parameters than expected at all scan sites. Comparing this response with the extensive bone loss in a teenager (S1) with complete tetraplegia who showed extensive bone loss in the paralysed limbs, we might be led to speculate that age may play a role in determining rates of bone loss after SCI. (Age-related differences in bone

density and geometry have been documented for the young [27, 28] and the elderly [29] in the general population.) However, larger numbers of patients would need to be included in the study to ascertain possible effects of age on the bones' responses to SCI.

By starting the longitudinal investigation as soon as possible after the injury, we were able to develop uniquely accurate and detailed documentation of the rates and extents of bone loss in a in a case series of six patients with SCI, and to investigate the potential for individualised predictive modelling for this patient group. These data would allow us to propose a practical tool that could be implemented as part of a management plan in SCI, and to inform future interventional study design. Possible interventions may be pharmacological agents or bone-strengthening rehabilitation programmes (or a combination of the two), but there is currently no single treatment that has been shown conclusively to attenuate or reverse bone loss in SCI. Interventions aimed at retarding bone loss in these early stages of SCI are expected to yield greater success rates than those introduced at a later stage and aimed at reversing bone loss once it is already established, in chronic SCI [21, 5].

In a clinical implementation of these findings, we would propose that patients are scanned using pQCT as soon as possible after SCI (e.g. within 5 weeks) and predictions made as to the individuals' expected rates of bone loss, to identify the time point at which they would be expected to start to fall below the normal range. Ideally, repeat scans would be performed at around eight months post-SCI, as this is the time-point at which statistically significant changes were first identified in our study. For each patient, clinicians could determine whether or not the rate of bone loss within the first eight months deviates significantly from the predicted rate, and whether values at that time-point have already fallen below the normal range. This could inform the clinical decision of whether to manage those patients through education on bone loss and fracture risk in SCI alone, to initiate treatment against further bone loss, or a combination of the two. Follow-up scans thereafter would determine the effectiveness of any chosen intervention. We will be able to extend the clinical application after collecting data to represent other subgroups of the SCI population, including women (pre- and post-menopausal separately) and motor-incomplete SCI. Increasing the numbers of patients investigated within each subgroup would also enable us to determine any effect of age on the response of the musculoskeletal system to SCI. This longer-term study is underway. With larger numbers, we plan to prepare nomograms (similar to those currently available for DXA, with T- and Z-scores) to provide an easy-reference tool for SCI physicians.

There are a number of limitations to this study. Although we focus on bone parameters in the epiphyses of the bones in this paper, a longer period of investigation of changes in bone parameters in the shaft of the tibia, femur and radius would provide additional key information about any differences in the rates of bone loss at different sites along the bone (i.e. the spatial distribution of bone loss) and the effects of differential bone loss along the bone on the bone's geometry and strength. This would provide a more complete pQCT-based evaluation of fracture risk in this patient population. By extending the period of investigation through regular repeat scans until each subject's BMD values level off to a new, lower "steady-state" would be the way to confirm the validity of our individualised predictions of patterns of bone loss. A second issue is that the question of whether differences in measured rates of bone loss are real or not depends on the repeatability and reliability of the pQCT scans. We do not present repeatability or reliability in this paper, as these have been cited elsewhere in the validation of use of pQCT in SCI [12]. There are issues of repositioning to obtain the same orientation of the bone during repeat scans, which are often more pronounced for the proximal tibia and distal femur than for the distal tibia. This is likely due to the different shapes of the condyles of the bones at each site, and the ease of patient limb positioning at different times post-injury, depending on the differences in spasticity, tone or increased/decreased fat and muscle atrophy in the paralysed limbs over time. Bone densitometry is not the only tool for predicting bone loss in SCI. Blood and urine samples could be collected at regular intervals post-injury for analysis of biochemical markers of bone resorption and formation. These data may complement BMD and other bone architecture measurements, and may even enable characterisation of rates of bone loss at earlier timepoints post-injury than bone densitometry. Analysis of biochemical

markers of turnover, and the investigation of clinical factors alongside bone densitometric evaluations would produce a more complete description of bone loss after SCI. The applicability of this work may, in time, extend to other patient groups that exhibit high rates of bone loss following trauma or disease, including stroke and multiple sclerosis. Further work would be needed to validate the nomograms that will result from this ongoing longitudinal SCI study, for use in these other patient groups.

5 Conclusions

In this longitudinal study of six acute patients with motor-complete SCI (4 paraplegia, 2 tetraplegia), we used a sequence of pQCT scans performed within 5 weeks of injury and again at 4-, 8-months and 12-months post-SCI, to quantify the decline in key bone parameters in the early phases of injury. The temporal and spatial pattern of bone loss shown during the first year of SCI varied between subjects, with some showing consistent loss at all measured epiphyseal sites in the paralysed limbs, others showing more loss at some sites compared to others, and yet others showing minimal loss at all sites. This makes a strong case for implementing a clinical tool that would enable clinicians to identify those patients (during their stay in the spinal unit) who are showing rapid and extensive loss of bone during the initial phases of SCI, and target them for treatment and follow-up. We propose that one method to achieve this would be to use patient-specific predictions of bone loss based on an initial pQCT scan performed as soon as possible after injury. Results from repeat scans at eight-months post-injury could then be compared to predicted values, and used in parallel with reference values for the general population and proposed BMD fracture thresholds at fracture-prone sites, to flag up those high-risk patients. The first 8-months after SCI may prove to be the key therapeutic window during which early intervention should be implemented in this patient group. A longer-term study, characterising the bone loss in larger numbers of SCI patients should confirm this, and enable us to produce nomograms for the SCI physicians as a reference guide to assist in decision-making regarding therapeutic intervention.

6 Implications for Rehabilitation

- Spinal cord injury (SCI) leads to extensive muscle paralysis, and is often accompanied by significant bone loss and increased fracture risk.
- Repeat bone scans within months of injury can be used to "red-flag" patients who are losing bone faster than predicted.
- A patient-specific approach to osteoporosis management will facilitate targeted treatment aimed at those who need it most, in SCI and other patient groups.

Acknowledgments

We should like to thank all subjects who have taken part in this study, and nursing staff in Edenhall and Philipshill wards at the Queen Elizabeth National Spinal Injuries Unit for their assistance. Thanks also to Andrew Dunne and other colleagues from the Centre for Rehabilitation Engineering at the University of Glasgow for their help during scanning sessions. We gratefully acknowledge Dr Angela Frotzler and Dr Prisca Eser for their thoughts on study design, Prof. Kenneth Hunt for his initial input on predictive modelling, and Dr Alex McConnachie for statistical advice.

Declarations of Interest

The authors report no declarations of interest.The first author (SC) gratefully acknowledges the Glasgow Research Partnership in Engineering for funding her research post. The NHS Greater Glasgow & Clyde R&D department provides invaluable support for this research.

References

[1] F. Biering-Sørensen, H. Bohr, and O. Shaadt, "Longitudinal study of bone mineral content in the lumbar spine, the forearm and the lower extremities after spinal cord injury," *Eur. J. Clin. Investig.*, vol. 20, pp. 330–335, 1990.

[2] B. Chen and A. Stein, "Osteoporosis in acute spinal cord injury," *Top. Spinal Cord Inj. Rehabil.*, vol. 9, no. 1, pp. 26–35, 2003.

[3] E. de Bruin, B. Vanwanseele, M. Dambacher, V. Dietz, and E. Stüssi, "Long-term changes in the tibia and radius bone mineral density following spinal cord injury," *Spinal Cord*, vol. 43, pp. 96–101, 2005.

[4] G. Demirel, H. Yilmaz, N. Paker, and S. Önel, "Osteoporosis after spinal cord injury," *Spinal Cord*, vol. 36, pp. 822–825, 1998.

[5] L. Maïmoun, C. Fattal, J.-P. Micallef, E. Peruchon, and P. Rabischong, "Bone loss in spinal cord-injured patients: from physiopathology to therapy," *Spinal Cord*, vol. 44, pp. 203–210, 2006.

[6] S. Szollar, E. Martin, J. Parthemore, D. Sartoris, and L. Deftos, "Densitometric patterns of spinal cord injury associated bone loss," *Spinal Cord*, vol. 35, pp. 374–382, 1997.

[7] P. Vestergaard, K. Krogh, L. Rejnmark, and L. Mosekilde, "Fracture rates and risk factors for fractures in patients with spinal cord injury," *Spinal Cord*, vol. 36, pp. 790–796, 1998.

[8] M. Lazo, P. Shirazi, M. Sam, A. Giobbie-Hurder, M. Blacconiere, and M. Muppidi, "Osteoporosis and risk of fracture in men with spinal cord injury," *Spinal Cord*, vol. 39, pp. 208–214, 2001.

[9] A. Comarr, R. Hutchinson, and E. Bors, "Extremity fractures of patients with spinal cord injuries," *Am. J. Surgery*, vol. 103, pp. 732–739, 1962.

[10] M. Ashe, J. Eng, and A. Krassioukov, "Physiatrist's opinions and practice patterns for bone health after SCI," *Spinal Cord*, vol. 47, no. 3, pp. 242–248, 2009.

[11] P. Eser, A. Frotzler, Y. Zehnder, and J. Denoth, "Fracture threshold in the femur and tibia of people with spinal cord injury as determined by peripheral Quantitative Computed Tomography," *Arch. Phys. Med. Rehabil.*, vol. 86, pp. 498–504, 2005.

[12] P. Eser, A. Frotzler, Y. Zehnder, L. Wick, H. Knecht, J. Denoth, and H. Schiessl, "Relationship between the duration of paralysis and bone structure: a pQCT study of spinal cord injured individuals," *Bone*, vol. 34, no. 5, pp. 869–880, 2004.

[13] T. Fujita, "Volumetric and projective bone mineral density," *J. Musculoskel. Neuron. Interact.*, vol. 2, no. 4, pp. 302–305, 2002.

[14] H. Bolotin, "Inaccuracies inherent in dual-energy x-ray absorptiometry in vivo bone mineral densitometry may flaw osteopenic/osteoporotic interpretations and mislead assessment of antiresorptive therapy effectiveness," *Bone*, vol. 28, no. 5, pp. 548–555, 2001.

[15] J. Ferretti, "Noninvasive assessment of bone architecture and biomechanical properties in animals and humans employing pQCT technology," *J. Jpm Soc. Bone Morphom.*, vol. 7, pp. 115–125, 1997.

[16] S. Coupaud, A. McLean, and D. Allan, "Role of peripheral quantitative computed tomography in identifying disuse osteoporosis in paraplegia," *Skeletal Radiology*, vol. 38, no. 10, pp. 989–995, 2009.

[17] D. Garland, R. Adkins, and C. Stewart, "Five-year longitudinal bone evaluations in individuals with chronic complete spinal cord injury," *J. Spinal Cord Med.*, vol. 31, pp. 543–550, 2008.

[18] A. Gorgey and G. Dudley, "Skeletal muscle atrophy and increased intramuscular fat after incomplete spinal cord injury," *Spinal Cord*, vol. 45, pp. 304–309, 2007.

[19] E. de Bruin, P. Frey-Rindova, R. Herzog, V. Dietz, M. Dambacher, and E. Stussi, "Changes of tibia bone properties after spinal cord injury: effects of early intervention," *Arch. Phys. Med. Rehabil.*, vol. 80, pp. 214–220, 1999.

[20] P. Frey-Rindova, E. de Bruin, E. Stüssi, M. Dambacher, and V. Dietz, "Bone mineral density in upper and lower extremities during 12 months after spinal cord injury measured by peripheral quantitative computed tomography," *Spinal Cord*, vol. 38, pp. 26–32, 2000.

[21] A. Frotzler, M. Berger, H. Knecht, and P. Eser, "Bone steady-state is established at reduced bone strength after spinal cord injury: a longitudinal study using peripheral quantitative computed tomography (pQCT)," *Bone*, vol. 43, no. 3, pp. 549–555, 2008.

[22] F. Maynard, M. Bracken, G. Creasey, J. D. (Jr), W. Donovan, T. Ducker, S. Garber, R. Marino, S. Stover, C. Tator, R. Waters, J. Wilberger, and W. Young, "International Standards for Neurological and Functional Classification of Spinal Cord Injury," *Spinal Cord*, vol. 35, pp. 266–274, 1997.

[23] P. Augat, C. Gordon, T. Lang, H. Iida, and H. Genant, "Accuracy of cortical and trabecular bone measurements with peripheral quantitative computed tomography pQCT," *Phys. Med. Biol.*, vol. 43, pp. 2873–2883, 1998.

[24] J. Rittweger, H. Frost, H. Schiessl, H. Ohshima, B. Alkner, P. Tesch, and D. Felsenberg, "Muscle atrophy and bone loss after 90 days' bed rest and the effects of flywheel resistive exercise and pamidronate: results from the LTBR study," *Bone*, vol. 36, pp. 1019–1029, 2005.

[25] M. Inoue, H. Tanaka, T. Moriwake, M. Oka, C. Sekiguchi, and Y. Seino, "Altered biochemical markers of bone turnover in humans during 120 days of bed rest," *Bone*, vol. 26, no. 3, pp. 281–286, 2000.

[26] M. Dambacher, M. Neff, R. Kissling, and L. Qin, "Highly precise peripheral quantitative computed tomography for the evaluation of bone density, loss of bone density and structures," *Drugs Aging*, vol. 12, no. Suppl 1, pp. 15–24, 1998.

[27] F. Rauch and E. Schoenau, "Peripheral quantitative computed tomography of the proximal radius in young subjects - new reference data and interpretation of results," *J. Musculoskeletal Neuronal Interact*, vol. 8, no. 3, pp. 217–226, 2008.

[28] F. Rauch and E. Schoenau, "Peripheral quantitative computed tomography of the distal radius in young subjects - new reference data and interpretation of results," *J. Musculoskeletal Neuronal Interact*, vol. 5, no. 2, pp. 119–126, 2005.

[29] C. Russo, F. Lauretani, E. Seeman, B. Bartali, S. Bandinelli, A. D. Iorio, J. Guralnik, and L. Ferrucci, "Structural adaptations to bone loss in aging men and women," *Bone*, pp. 112–118, 2006.