Coupaud, S. and McLean, A.N. and Allan, D.B. (2009) *Role of peripheral quantitative computed tomography in identifying disuse osteoporosis in paraplegia.* Skeletal Radiology . ISSN 0364-2348

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Deposited on: 11 June 2009

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Role of peripheral Quantitative Computed Tomography in identifying disuse osteoporosis in paraplegia.

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ABSTRACT

Objective: Disuse osteoporosis is a major long-term health consequence of spinal cord injury (SCI) that still needs to be addressed. Its management in SCI should begin with accurate diagnosis, followed by targeted treatments in the most vulnerable subgroups. We present data quantifying disuse osteoporosis in a cross-section of the Scottish paraplegic population to identify subgroups with lowest bone mineral density (BMD).

Materials & Methods: Forty-seven people with chronic SCI at levels T2-L2 were scanned using peripheral Quantitative Computed Tomography (pQCT) at four tibial sites and two femoral sites, at the Queen Elizabeth National Spinal Injuries Unit, Glasgow (U.K.). At the distal epiphyses, trabecular BMD (BMDtrab), total BMD, total bone cross-sectional area (CSA), and bone mineral content (BMC) were determined. In the diaphyses, cortical BMD, total bone CSA, cortical CSA, and BMC were calculated. Bone, muscle and fat CSAs were estimated in the lower leg and thigh.

Results: BMDtrab decreased exponentially with time since injury, at different rates in the tibia and femur. At most sites, female paraplegics had significantly lower BMC, total bone CSA and muscle CSA than male paraplegics. Subjects with lumbar SCI tended to have lower bone values and smaller muscle CSAs than in thoracic SCI.

Conclusion: At the distal epiphyses of the tibia and femur, there is generally a rapid and extensive reduction in BMDtrab after SCI. Female subjects, and those with lumbar SCI, tend to have lower bone values than males or those with thoracic SCI, respectively.

Keywords: Bone loss, osteoporosis, paraplegia, peripheral Quantitative Computed Tomography, spinal cord injury

LIST OF ABBREVIATIONS

BMC: bone mineral content

BMD: bone mineral density

BMDtrab: trabecular bone mineral density

CSA: cross-sectional area

DXA: dual-energy X-ray absorptiometry

pQCT: peripheral Quantitative Computed Tomography

SCI: spinal cord injury

INTRODUCTION

One of the major secondary complications of spinal cord injury (SCI) is extensive bone loss below the level of injury [1,2]. In paraplegia, bone loss occurs in the lower but not the upper limbs; such localised rather than systemic loss of bone is well-documented [3,4], and is associated with an elevated risk of fragility fracture in the paralysed limbs. Fracture rates in SCI are at least twice those in the general population [5,6] and fractures often occur as a result of minor trauma such as falling out of a wheelchair. Common fracture sites following SCI are the distal epiphyses of the femur and tibia, and the proximal epiphysis of the tibia [7].

General treatments for reduced bone integrity in SCI include exercise (standing, exercise using electrical stimulation of paralysed muscle) and prescription of bisphosphonates, vitamin D and calcium [8]. However, there is only equivocal evidence for any of these increasing bone mineral density (BMD) in SCI, with some treatments seemingly able to slow its decline [9-13]. It would be valuable to identify those groups of individuals most at risk of fracture in the SCI population. We may then prevent fractures through training and education of the subgroups at highest risk, and direct any new treatments that become available to attenuate or reverse bone loss towards these subgroups.

Dual-energy X-ray absorptiometry (DXA) is currently used for routine clinical bone investigations in other patient groups in the UK, and for diagnosing osteoporosis and osteopoenia in the general population [14]. However, the sites commonly scanned using DXA (radius, lumbar spine, femoral neck) are not common sites of severe bone loss and fracture in paraplegia. In contrast, peripheral Quantitative Computed Tomography (pQCT) enables bone parameters of the peripheral skeleton (e.g. tibia and femur) to be investigated in detail. Furthermore, pQCT provides more quantitative information about the bone than DXA, at low radiation doses, and enables calculation of volumetric BMD, instead of projected areal BMD. [15] Using pQCT, trabecular and cortical bone parameters can be analysed separately, thus enabling investigations of bone distribution, architecture and geometry at fracture-prone sites.

MATERIALS & METHODS

Subjects

Outpatients attending the Queen Elizabeth National Spinal Injuries Unit for their annual review were invited to take part. Inclusion criteria were: (i) SCI at neurological level T2 to L2, (ii) grade A to C on the American Spinal Injuries Association impairment scale. Exclusion criteria included: (i) extensive spasticity, (ii) diagnosed metabolic bone disease, (iii) bilateral fractures in the tibia and/or femur within the past ten years, (iv) bilateral metal implants in the lower leg and/or thigh, (v) age below 18 years or above 65 years.

The study was approved by the South Glasgow Research Ethics Committee. Written informed consent was obtained prior to participation.

Bone measurements

A pQCT scanner (XCT 3000, Stratec Medizintechnik, Germany) was used to scan the lower leg and thigh unilaterally. The pQCT system measures the attenuation of X-rays, which is linearly transformed into hydroxyapatite densities. The scanner is calibrated with respect to water (set at 60 mg hydroxyapatite), with fat at 0 mg hydroxyapatite. Quality assurance scans were performed prior to each scanning session using the manufacturer's phantom.

The length of the tibia was measured from the distal end of the medial malleolus to the medial joint cleft. The subjects transferred from their wheelchair to a height-adjustable patient couch and lay supine, as shown in Figure 1. A scout view was carried out, and the reference line was placed on the distal endplate of the tibia. Tibial scans were performed at 4%, 14%, 38% and 66% of total tibia length. A scout view was then performed to place the reference line at the distal femur, to scan at 4% and 25% of total femur length from the distal end. The femur length was approximated to be equal to tibial length. Slice thickness was set at 2 mm. Voxel size was 0.5 mm in the tibia, and 0.3 mm in the femur.

The pQCT technique enables bone geometry and bone mineral density of trabecular and cortical bone compartments to be investigated separately. The manufacturer's software (XCT 550, Stratec Medizintechnik, Germany) was used for analysis. Bone parameters obtained from the epiphyseal slices (4% scan sites) were: total bone cross-sectional area (CSA), bone mineral content (BMC), trabecular BMD (BMDtrab) and total BMD. A contour algorithm was used with thresholds of 180 $mg.cm^{-3}$ in the distal tibia and 130 $mg.cm^{-3}$ in the distal femur to find the periosteal surface of the epiphysis [4] 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. Bone parameters obtained from the diaphyseal slices (14%, 25% and 38% sites) were: total bone CSA, cortical bone CSA, cortical thickness, cortical BMD and polar strength-strain index. A contour algorithm with a threshold of 280 $mg.cm^{-3}$ identified the periosteal surface of the diaphysis, for calculation of BMC, total bone CSA and polar strength-strain index. Cortical bone was identified using the standard manufacturer's threshold of 710 $mg.cm^{-3}$, to determine cortical BMD, cortical bone CSA and cortical thickness. Cortical thickness was calculated by assuming that the bone shaft is a cylinder, and subtracting the radius of the medullary cavity from the total radius of the bone. To minimise the artefacts caused by the partial volume effect [4], cortical BMD data from diaphyseal scans were excluded from the analysis if cortical thickness was <1.6mm.

Figure 1: Set-up for lower limb bone scans using the pQCT scanner (XCT 3000, Stratec Medizintechnik, Germany).

Muscle measurements

Muscle CSA and subcutaneous fat CSA were estimated at the 66% tibial pQCT scan site and the 25% femoral scan site. Combined muscle and subcutaneous fat CSA was automatically calculated by subtracting total bone CSA from the total CSA of the lower leg or thigh. For the remaining area, the manufacturer's threshold of 36 $mg.cm^{-3}$ was used to separate the subcutaneous fat from the muscle, to provide separate estimates of muscle CSA and fat CSA.

Statistical analysis

All statistical analyses were carried out using SPSS v15.0.

Based on preliminary analyses, the natural logarithmic transform of time since injury, ln_{TSI}, was used for subsequent linear model analyses (general linear model and linear regression) of the following bone parameters: BMDtrab, total BMD, BMC, cortical CSA, and cortical thickness. Time since injury was used for linear model analyses of all other bone parameters (total bone CSA, cortical BMD and polar strength-strain index). These models were used to determine the possible effects on the main bone parameters of gender, lesion category (lumbar or thoracic), age at time of scan, and age at time of injury. The level of statistical significance was set at $p \leq 0.05$.

In the lower leg (at 66% site) and the thigh (at 25% site), total bone CSA was plotted against muscle CSA to determine the relationship between bone and muscle, quantified by the Pearson correlation coefficient (R). Analysis of variance was used to investigate potential differences in bone, muscle and subcutaneous fat composition between subgroups (men versus women; thoracic versus lumbar SCI).

STATEMENT OF ETHICS

We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers/animals were followed during the course of this research.

RESULTS

Forty-seven subjects took part in the study and attended a single scanning session at the Queen Elizabeth National Spinal Injuries Unit at the Southern General Hospital in Glasgow. Thirty-eight were male and 9 were female. One female subject was post-menopausal. The summary of the subjects' details is provided in Table 1.

	Lesion category	N	Age [years]	Time since injury [years]	Body mass [kg]
Women	Thoracic	6	37.3 (11.0)	5.5 (6.1)	64.2 (13.5)
	Lumbar (flaccid)	3	35.0 (17.3)	4.9 (4.9)	62.0 (25.5) n=2
Men	Thoracic	32	41.2 (12.6)	10.2 (11.4)	84.3 (20.8) n=27
	Lumbar (flaccid)	6	35.5 (11.2)	2.9 (2.4)	69.3 (3.2)

Table 1: Summary of subject characteristics, shown as Mean (SD).

In total, 159/188 tibia scan images and 71/94 femur scan images could be used for analysis. The full scan series (4 tibia images and 2 femur images) was aborted with one male subject who had extreme tonus in the lower limbs, preventing us from achieving the required limb positioning. Insufficient hip abduction caused difficulties in limb placement for the 25% femur scan in 5 other subjects. Reasons for excluding scan images from the analysis were: (i) extreme tonus or insufficient hip abduction, preventing us from achieving the required limb positioning, (ii) movement artefacts (usually from spasms), or (iii) evidence of heterotopic ossification, as detected by visual inspection.

Bone Parameters

Plots of BMDtrab against time since injury are shown for the tibia and femur in Figure 2a and 2b, respectively. The rates of decline in BMDtrab at the distal epiphyses are described by the following 1st order exponential equations, for the tibia (equation (1)) and femur (equation (2)):

Distal tibia: $\boldsymbol{BMDtrab} = 151.2\boldsymbol{e}(-0.54\boldsymbol{t}) + 96.1$, $r^2 = 0.24$ (1)

Distal femur: $\boldsymbol{BMDtrab} = 228.5\boldsymbol{e}(-1.32\boldsymbol{t}) + 127.8$, $r^2 = 0.39$ (2)

where t = time since injury (in years).

General linear model analyses were used to investigate the effects of time since injury, age at the time of SCI, age at the time of the scan, gender and lesion category (thoracic or lumbar SCI) on each bone parameter.

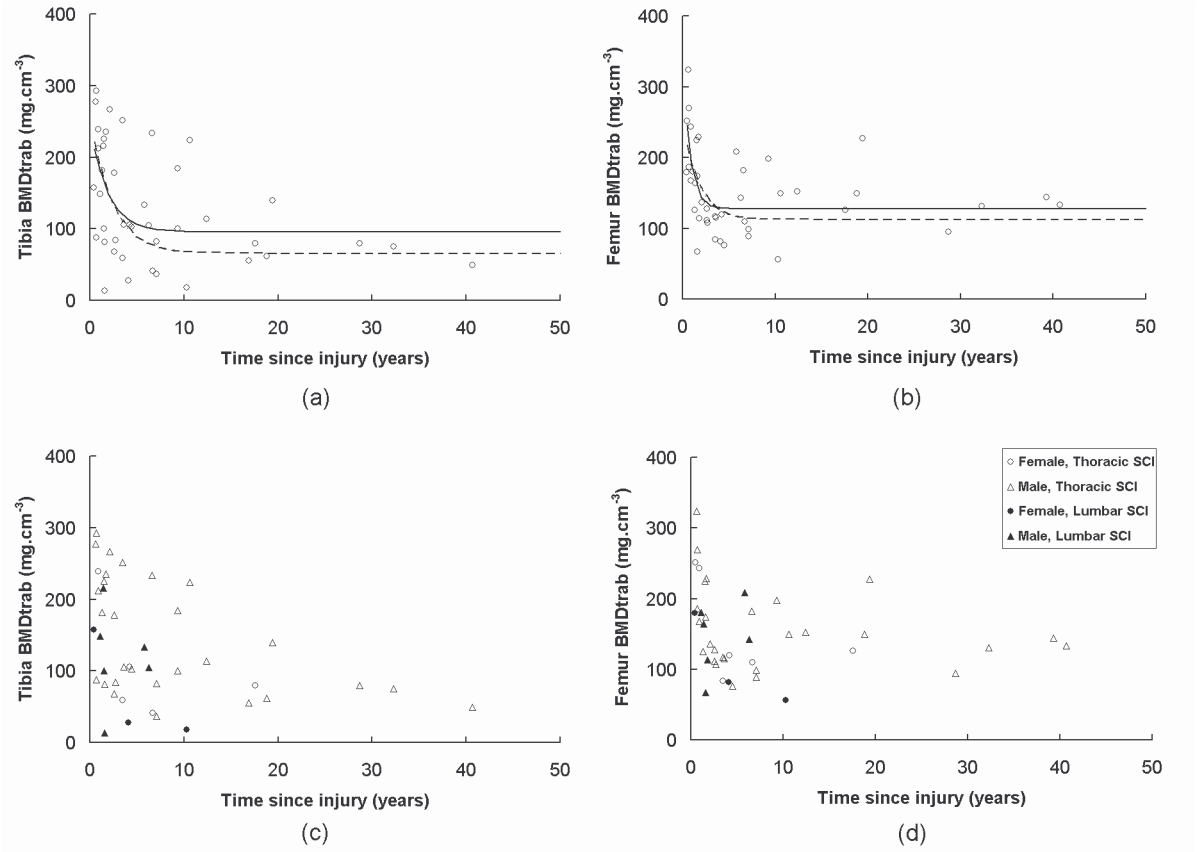

Figure 2 – BMDtrab at the distal epiphyses of the tibia and femur in a cross-section of the Scottish paraplegic population, in relation to time since injury. The best fit exponential lines for the data from this study (solid line), and those published by Eser *et al.* [4] for the Swiss SCI population (dashed line) for comparison, are superimposed for the tibia (a) and the femur (b). The data are then grouped according to gender and lesion category for the tibia (c) and the femur (d).

Time since injury was a consistently significant factor affecting bone parameters in the distal epiphyses of the tibia and femur (all p-values <0.05), except for total bone CSA at the distal tibia (p=0.171); and a significant factor affecting some parameters in the diaphysis (25% site) of the femur with p=0.007, p=0.006 and p=0.012 for cortical CSA, cortical thickness and BMC, respectively.

Significant differences in BMC were detected between the male and female subjects at most scan sites except in the distal femur (p=0.088), and in total bone CSA (except at 14% in the tibia and 25% in the femur, with p=0.198 and p=0.073, respectively). There were suggestions of effects of age at the time of SCI and age at the time of the scan on some bone parameters, but these were not consistent between the tibia and femur nor between different sites within the same bone. The possible effect of lesion category is of a tendency (although not significant at the 5% level) for the thoracic and lumbar SCI groups to differ in BMDtrab at the distal epiphyses (p=0.068 and p=0.067 in the tibia and femur, respectively).

Figure 2c and 2d shows the BMDtrab data against time since injury for the distal tibia and distal femur, respectively, this time highlighting different subgroups of the cross-section of the paraplegic population studied here (male, female, lumbar SCI and thoracic SCI).

Muscle Parameters

Total bone CSA is plotted against muscle CSA in Figure 3 for the lower leg and thigh in Figure 3a and 3b, respectively. The Pearson correlation coefficient, R, was 0.568 in the lower leg ($p<0.001$) and 0.479 in the thigh ($p=0.003$).

Cortical bone CSA is also plotted against muscle CSA in Figure 3 for the lower leg and thigh in Figure 3c and 3d, respectively. R was 0.542 in the lower leg ($p<0.001$) and 0.648 in the thigh ($p<0.001$).

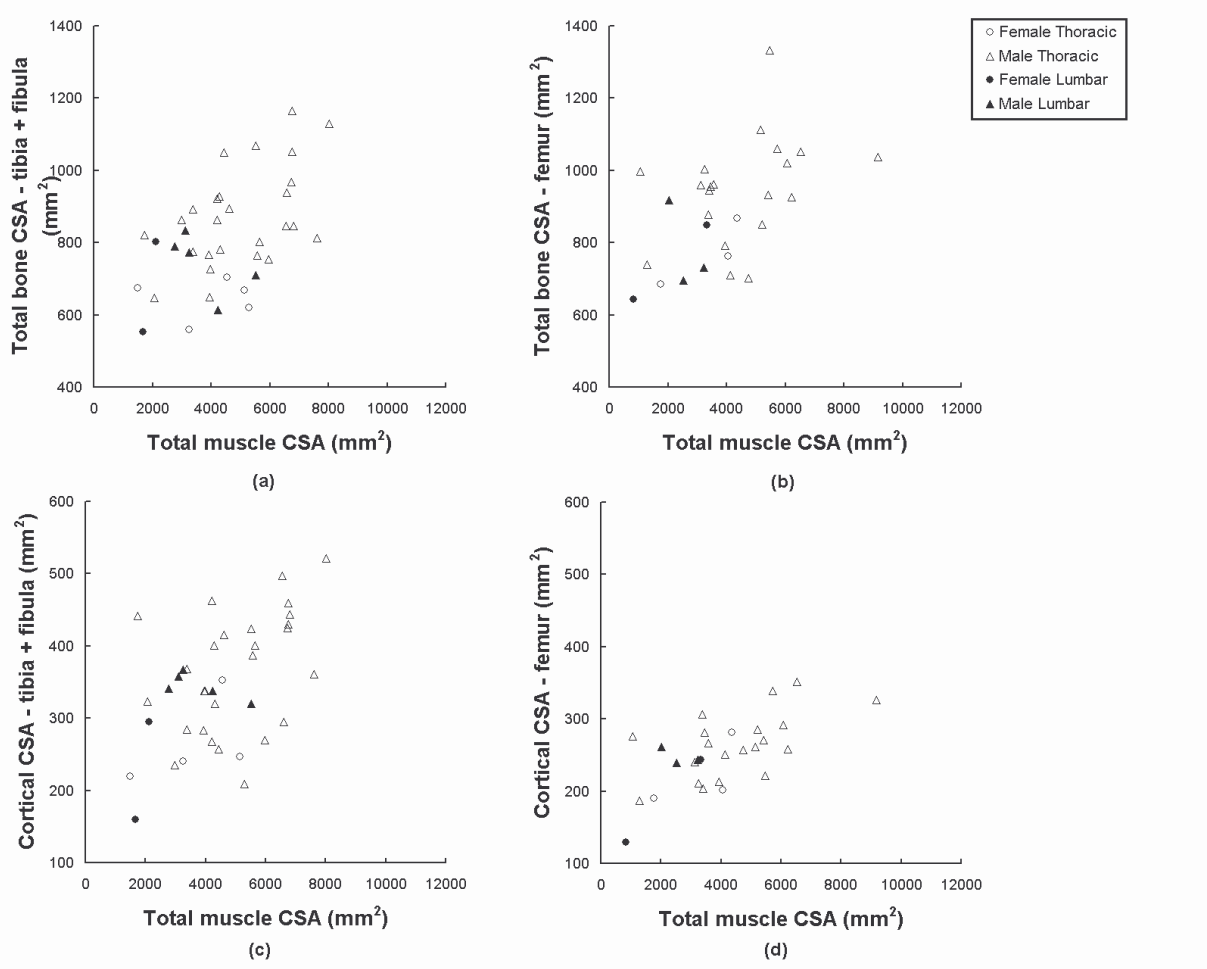

Figure 3 – Total bone CSA in the diaphysis against total muscle CSA for the lower leg (a) and the thigh (b); and cortical CSA in the diaphysis against total muscle CSA for the lower leg (c) and the thigh (d). These were calculated at the 66% scan site in the lower leg and at the 25% scan site in the thigh. The data are grouped according to gender and lesion category.

DISCUSSION

We identified specific subgroups that may be at even greater risk of fracture in comparison to the rest of the SCI population, based solely on a bone integrity criterion from pQCT scans. These subgroups may be the highest priority in targeting treatment against bone loss. Female subjects have significantly lower BMC values at the distal tibia and femur, compared to their male counterparts. Subjects with lumbar SCI, resulting in extreme muscle atrophy and flaccid paralysis, tend to have lower BMDtrab values than those with thoracic SCI. However, the numbers of women and numbers with lumbar (flaccid) SCI in this study were low. A larger cross-section of these subgroups would need to be measured to determine if they consistently have lower bone mineral density and content values than the rest of the SCI population. In addition, the relative incidence of fracture in these subgroups should be investigated further to determine whether or not this more extensive bone loss translates into an inflated risk of fracture. The use of pQCT, which allows separate determination of trabecular and cortical bone parameters, is recommended for densitometric identification of patients with SCI most at risk of fracture. There is evidence that pQCT bone integrity measurements (BMDtrab, BMC) at the distal epiphyses of the tibia and the femur, which are fracture-prone sites in the paraplegic population, can be used as indicators of fracture risk in this patient group [7].

The analysis of bone and soft-tissue composition suggests that the differences in bone parameters identified between men and women, and between those with thoracic versus lumbar SCI, may be explained in part by differences in muscle bulk. The muscles in the paralysed limbs of subjects with lumbar SCI exhibit no activity after injury due to the lower motor neurone damage to the leg muscles (in addition to the main upper motor neurone lesion in the spinal cord), whereas thoracic SCI is often accompanied by involuntary reflex activity, or spasticity, from muscles below the level of injury with intact lower motor neurones. Spasticity has been shown by other groups to have a protective effect on the femur [16]. Although peak muscle forces and muscle activity levels were not recorded here, we can use muscle CSA as a surrogate for muscle activity [17].

From the estimates of bone and soft-tissue CSAs, we see that subjects with flaccid paralysis (lumbar SCI) have smaller muscle CSAs in both the lower leg and the thigh than those with thoracic SCI, as expected. This subgroup also has smaller bone CSAs in the shaft. Overall, there is a linear relationship between bone CSA and muscle CSA ($R=0.568$, $R^2=0.323$ in the lower leg, $R=0.509$, $R^2=0.259$ in the thigh). With the lumbar SCI subgroup lying at the lower end of the scale of this relationship, it seems that the severely reduced muscle bulk (and activity) in flaccid SCI may account for some of the differences in bone properties between the two lesion categories. These data are in keeping with the theory that mechanical unloading of the bones associated with severe muscle paralysis is likely to be the main stimulus for bone loss following SCI. Frost's Mechanostat theory [18] suggests that if muscle activity is reduced to such an extent as to cause strains within the bones to fall below a "bone remodelling" threshold, this adaptive structure will go into "disuse mode" and bone will be resorbed at a faster rate than it is produced. The localisation of the bone loss following SCI, restricted to the bones of the paralysed limbs, conforms to this theory. It should be noted that neurogenic factors may also have an effect [19].

Eser *et al*. [4] used pQCT to document the patterns of lower-limb bone loss in a cross-section of the Swiss SCI population. These patterns are closely matched in the cross-section of the Scottish SCI population investigated here, as evidenced by comparing the best fit line of the overall time course to steady-state bone values obtained in each study. The mean rates of decline seem to differ only slightly between the two populations, but the final steady-state values appear to be higher in the Scottish paraplegic group for both the tibia and the femur. This may be a result of having fewer subjects beyond 10 years post-injury in our study group,

compared to the Swiss study group. Furthermore, a few possibly “unusual” cases of near-normal BMDtrab beyond 5 years post-SCI may lead to an apparently higher mean response in the cross-section of the Scottish population than would be expected. If, on the other hand, the differences in post-SCI steady-state BMDtrab values between the Scottish and Swiss paraplegic populations are real ones, we would only be speculating about possible reasons for these, without further investigation.

Despite the relatively robust overall trend in bone loss in the SCI population, our data and the data of Eser *et al*. [4] show a large inter-subject variability in BMDtrab at the distal epiphyses at any particular timepoint, and especially in the first 5-10 years post-injury. The variability is clearly not completely explained by gender or lesion category. Through a longitudinal pQCT study following 39 SCI patients for 30 months, Frotzler *et al*. [20] have recently shown that key bone parameters do not change significantly in individual patients after 3 years post-injury.

There are a number of limitations to the study. The first is the small sample group studied, when compared with the previous study by Eser et al. [4], especially when the data are categorised according to subgroups. However, the fact that the differences observed between subgroups for some of the key bone parameters (BMDtrab and BMC) reached significance or close to it at the 5% level despite these small numbers suggests that the differences are real. Rather than extending the cross-sectional study in the chronic population to collect additional data, thus increasing the sample size available for each subgroup, the further work that should be carried out based on these findings is a longitudinal investigation in individual patients to describe true patterns of bone loss over time in each of the subgroups highlighted here. Such a study should be powered to take into account the findings from our work that women and those with flaccid SCI may have accelerated and/or greater magnitudes of bone loss than the rest of the SCI population. The second limitation of the study is the lack of a control group to show that the steady-state bone values reached in chronic SCI lie outside the normal range for the general population. As there are published data providing reference values for the general population, it seemed unjustified to carry out scans involving ionising radiation (albeit at relatively low equivalent doses) on able-bodied volunteers. We can use the able-bodied data from the literature to draw conclusions about the extent to which SCI bone values deviate from the normal range at various time points post-injury, much in the same way as Z- and T-scores are used in DXA-based diagnoses of osteoporosis even though each hospital bone densitometry department may not have collected its own reference data upon which to base diagnostic decisions. Finally, the work presented here may be considered as confirmatory rather than original. By confirming the findings of Eser et al. [4], but placing the emphasis on the clinical implications of the results by identifying those subgroups of the SCI population that may be most vulnerable to bone loss and fracture, we propose that our work reinforces the need for pQCT-based rather than DXA-based diagnosis of disuse osteoporosis in SCI. The supportive evidence that we present here further reinforces the need for targeted treatment intervention studies in the most vulnerable subgroups.

However, in the absence of any clear evidence to date of effective interventions (either medical or physical) to prevent bone loss in this population, we would recommend that all patients with SCI should be educated early on about bone loss and increased risk of fragility fractures.

CONCLUSIONS

Women and those with lumbar SCI show lower bone values (BMDtrab and BMC) than men and those with thoracic SCI, respectively. This may in part be explained by the differences between subgroups in muscle activity, as evidenced by muscle bulk. Those with flaccid SCI, and female paraplegics, may be at higher risk of fracture even within this already vulnerable patient population, and may need to be primary targets for future interventions to tackle bone loss in SCI.

ACKNOWLEDGEMENTS

We thank the subjects who took part in the study, and Sister Karen McCarron and Ms Kathy Craig for their assistance in subject recruitment.

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