Bone 74 (2015) 69–75

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Original Full Length Article

Decreases in bone mineral density at cortical and trabecular sites in the tibia and femur during the first year of spinal cord injury

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ARTICLE INFO

Article history:
Received 29 September 2014
Revised 5 January 2015
Accepted 8 January 2015
Available online 14 January 2015

Edited by: Kristine Ensrud

Keywords:
Bone mineral density (BMD)
Cortical
Osteoporosis
Peripheral Quantitative Computed Tomography (pQCT)
Spinal cord injury (SCI)
Trabecular

ABSTRACT

Background: Disuse osteoporosis occurs in response to long-term immobilization. Spinal cord injury (SCI) leads to a form of disuse osteoporosis that only affects the paralyzed limbs. High rates of bone resorption after injury are evident from decreases in bone mineral content (BMC), which in the past have been attributed in the main to loss of trabecular bone in the epiphyses and cortical thinning in the shaft through endocortical resorption.
Methods: Patients with motor-complete SCI recruited from the Queen Elizabeth National Spinal Injuries Unit (Glasgow, UK) were scanned within 5 weeks of injury (baseline) using peripheral Quantitative Computed Tomography (pQCT). Unilateral scans of the tibia, femur and radius provided separate estimates of trabecular and cortical bone parameters in the epiphyses and diaphyses, respectively. Using repeat pQCT scans at 4, 8 and 12 months post-injury, changes in BMC, bone mineral density (BMD) and cross-sectional area (CSA) of the bone were quantified.
Results: Twenty-six subjects (5 female, 21 male) with SCI (12 paraplegic, 14 tetraplegic), ranging from 16 to 76 years old, were enrolled onto the study. Repeated-measures analyses showed a significant effect of time since injury on key bone parameters at the epiphyses of the tibia and femur (BMC, total BMD, trabecular BMD) and their diaphyses (BMC, cortical BMD, cortical CSA). There was no significant effect of gender or age on key outcome measures, but there was a tendency for the female subjects to experience greater decreases in cortical BMD. The decreases in cortical BMD in the tibia and femur were found to be statistically significant in both men and women.
Conclusions: By carrying out repeat pQCT scans at four-monthly intervals, this study provides a uniquely detailed description of the cortical bone changes that occur alongside trabecular bone changes in the first year of complete SCI. Significant decreases in BMD were recorded in both the cortical and trabecular bone compartments of the tibia and femur throughout the first year of injury. This study provides evidence for the need for targeted early intervention to preserve bone mass within this patient group.

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1. Introduction

There has been mounting evidence of fragility fractures or "osteoporotic fractures" being more common after spinal cord injury (SCI) than in the general population [1–3]. This is one of the long-term health complications of SCI that remains to be resolved, since the establishment of SCI care units has led to an increase in life expectancy in this patient group. The elevated fracture risk has been attributed to the extensive paralysis of muscles of the lower limbs (in paraplegia) or of all four limbs (in tetraplegia) leading to disuse osteoporosis below the level of injury [4,5]. Higher rates of bone resorption, compared to bone formation, in the long bones cause an imbalance in bone turnover in the early phases of SCI [6]. Bone resorption reaches up to 10 times normal levels at peak activity (at 10–16 weeks post-SCI), and the net bone loss eventually manifests itself through densitometric imaging as a decrease in the bone mineral content (BMC) in the lower limbs [6,7].

Studies involving measurements of calcium excretion and activity levels of biochemical markers of bone formation and resorption have provided valuable detailed descriptions of bone turnover activity following immobilization (e.g. SCI) or bedrest [6,8]. These biochemical studies have quantified overall rates of bone loss accurately in the acute phases of SCI, much earlier than can be achieved with bone densitometry. Some studies have identified gender effects, and variations in the rate of bone turnover (between different age groups and/or in tetraplegia versus paraplegia) through the use of blood and urine samples taken weekly in newly-injured patients. Maynard et al. showed that young men with tetraplegia suffered from hypercalcemia more frequently than other SCI subgroups [9]. Marked increases in bone

Abbreviations: SCI, Spinal cord injury; pQCT, Peripheral Quantitative Computed Tomography; TSI, Time since injury

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http://dx.doi.org/10.1016/j.bone.2015.01.005
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resorption with only modest changes in bone formation were recorded, with greater bone resorption in tetraplegia compared to paraplegia during the first 6 months of SCI [6]. This may be explained by the greater extent of paralysis in tetraplegia, affecting both the upper and lower limbs [4]. Higher levels of biochemical markers of bone resorption would result from concurrent bone losses in the radius, ulna, and humerus, as well as in the long bones of the legs (femur, tibia and fibula), compared to bone loss occurring only in the latter in paraplegia.

One of the limitations of bone turnover studies is that the source of the measured bone loss is difficult to localize, as the blood and urine samples represent cumulative bone turnover activity for the whole body. To achieve some level of localization of the bone loss, densitometry techniques such as the clinical-standard dual energy X-ray absorptiometry (DXA) can be used to image different sections of the body: forearm, spine, hip, and lower limb. Repeat DXA scans allow a gross quantification of changes in BMC and projected areal bone mineral density (BMD) to highlight differences between the healthy upper limbs and the paralyzed lower limbs in paraplegia [10]. Even so, the standard clinical DXA technique is inadequate for localizing changes in the bone further. As a two-dimensional imaging modality, it does not allow quantification of volumetric bone density in the different bone compartments [11] and tends to underestimate bone loss in SCI [12].

A more appropriate densitometry technique is peripheral Quantitative Computed Tomography (pQCT), which is volumetric and provides accurate and separate estimates of trabecular and cortical bone parameters [11,13,14]. Data from a cross-sectional pQCT study describing the differences in trabecular and cortical bone parameters in 99 subjects with SCI at different times post-injury suggest that the shaft undergoes a thinning of the cortex rather than a decrease in cortical BMD. Furthermore, cortical BMD values remain close to the lower limits of the normal range even in chronic SCI [4]. Based on this dataset, the time course of cortical thinning appears to be slower than the rapid fall in trabecular BMD described for the epiphyses of the long bones. Evidence for cortical thinning after SCI, resulting from endocortical resorption, is provided by pQCT measurements of periosteal circumference and endocortical circumference. The former remains unchanged, but the latter appears to increase after SCI [4]. This pattern of cortical thinning and trabecular bone loss is also seen in long periods of bedrest and spaceflight [15].

Sequential pQCT bone scans in newly injured patients would allow a more accurate description of early changes in the different bone compartments in response to SCI, enabling the quantification of any differences in patterns of change in cortical and trabecular bone. Maimoun summarizes our limited understanding of osteoporosis progression after SCI: “It is very difficult to clearly identify the time needed to normalize bone remodelling post-injury because of the lack of long-term longitudinal studies. Most data have been obtained from cross-sectional studies on heterogeneous populations with several confounding factors” [16]. By carrying out repeat pQCT scans at four-monthly intervals, in patients who have not undergone bone-loading interventions or bone-targeting pharmacological treatments, this study provides a uniquely detailed description of cortical bone changes that occur alongside trabecular bone changes in the first year of complete SCI.

2. Methods

2.1. Subject recruitment

Inpatients of the Queen Elizabeth National Spinal Injuries Unit (Southern General Hospital, Glasgow, U.K.) with motor-complete SCI at neurological levels C4 and below were eligible to take part. Twenty-nine subjects diagnosed with motor-complete SCI (grades A or B on the American Spinal Injuries Association Impairment Scale (AIS) [17]) were recruited. Exclusion criteria were: (i) age below 16 years, (ii) ventilator-dependency at 5 weeks post-injury, (iii) recent concurrent bilateral fractures in bone(s) to be scanned (within the previous 10 years), (iv) inability to provide informed consent, and (v) previous diagnosis and/or pharmacological treatment for osteoporosis. Candidates who agreed to take part in the study provided informed consent prior to participation. Ethical approval for the study was obtained from the NHS Research Ethics Committee.

2.2. Scanning protocol

A single operator carried out all peripheral Quantitative Computed Tomography (pQCT) scans (XCT 3000, Stratec Medizintechnik, Pforzheim, Germany). Scans were carried out within 5 weeks post-injury, and repeated at 4, 8 and 12 months post-injury. The dominant leg and contralateral arm were scanned, unless the subject had experienced a recent fracture, in which case the opposite limb was scanned. Bone length was measured using a tape measure, from the medial knee joint cleft to the medial malleolus for the tibia and from the humeroradial joint cleft to the styloid process for the radius. As an approximation, femur length was taken to be equal to the length of the tibia, as described by Eser et al. [4]. Patients were transferred to a height-adjustable couch and positioned with the leg lined up with the central axis of the scanner gantry, with the foot resting on a support in a fixed position. The other leg rested on a custom-made limb support on the side. The lower leg was scanned first, followed by the thigh. The patient was repositioned for the arm scan, with the couch at 90° to the scanner.

A quality control scan was carried out prior to each set of patient scans. Scout views were taken to locate the standard reference positions for the distal tibia (endplate), the proximal tibia (medial aspect of the tibial plateau), the distal femur (lateral condyle) and the distal radius (endplate). Scans were performed unilaterally, (i) at two epiphyseal and two diaphyseal sites in the tibia (at 4%, 38%, 66% and 96%, relative to the distal end); (ii) at one epiphyseal and one diaphyseal site in the femur (4%, 25% from the distal end); and (iii) at one epiphyseal and one diaphyseal site in the radius (4%, 66% from the distal end). Voxel size was set to 0.5 mm for tibia and radius scans, and 0.3 mm for femur scans, in accordance with previous pQCT studies in SCI [4,5,18,19]. A higher resolution was used for the distal femur due to the typically thin cortical bone at this site.

2.3. Image analysis

Scan image analyses were performed using the manufacturer's software (XCT550, Stratec Medizintechnik, Pforzheim, Germany). The epiphyseal parameters calculated (at all 4% sites) were BMC, total BMD, trabecular BMD, and total cross-sectional area (CSA). The diaphyseal parameters calculated (at all other sites) were BMC, cortical BMD, total CSA and cortical bone CSA. In the lower leg, diaphyseal BMC and bone CSA were calculated for the tibia and fibula combined, as the fibula represents an important component of the weight-bearing structure in the healthy loaded limb.

To calculate the outcome measures at the standard 4% scan locations, the manufacturer's guidelines were followed. A contour algorithm was used, with thresholds set at 180 mg/cm^3 for the distal tibia, and 150 mg/cm^3 for the distal femur and radius. As described previously, a threshold of 130 mg/cm^3 was used for the proximal tibia [20]. Imaging of the proximal tibia is less repeatable than at other sites [21], and so is not imaged in many DXA or pQCT studies in SCI [22,5], but due to its clinical relevance in this patient group, the proximal tibia scan site has been included in this and other recent pQCT studies in SCI [23,20].

To calculate the trabecular BMD, a concentric peel was applied until the central 45% area of trabecular bone remained. In cases where the concentric peel did not adequately delineate the periosteal surface of the epiphysis (as determined by visual inspection), the algorithm was re-applied with a lower threshold, reduced by 10 mg/cm^3 increments until the peel was successful. Similar to bedrest studies in which thresholds for detection of the periosteal surface had to be lowered, detection thresholds were kept constant for each time point for any individual

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