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Bone loss in the lower leg during 35 days of bed rest is predominantly from the cortical compartment

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ABSTRACT

Immobilization-induced bone loss is usually greater in the epiphyses than in the diaphyses. The larger fraction of trabecular bone in the epiphyses than in the diaphyses offers an intuitive explanation to account for this phenomenon. However, recent evidence contradicts this notion and suggests that immobilization-induced bone loss from the distal tibia epiphysis is mainly from the cortical compartment. The aim of this study was to establish whether this pattern of bone loss was a general rule during immobilization. We monitored various skeletal sites with different tissue composition during 5 weeks of immobilization.

Ten healthy male volunteers with mean age of 24.3 years (SD 2.6 years) underwent strict horizontal bed rest. Bone scans were obtained during baseline data collection, at the end of bed rest and after 14 days of recovery by peripheral Quantitative Computed Tomography (pQCT). Sectional images were obtained from the distal tibia epiphysis (at 4% of the tibia's length), from the diaphysis (at 38%), from the proximal metaphysis (at 93%) and from the proximal epiphysis (at 98%), as well as from the distal femur epiphysis (at 4% of the femur's length) and from the patella.

Relative bone losses were largest at the patella, where they amounted to −3.2% (SD 1.8%, $p<0.001$) of the baseline values, and smallest at the tibia diaphysis, where they amounted to −0.7% (SD 1.0%, $p=0.019$). The relative losses were generally larger from cortical than from trabecular compartments ($p=0.004$), and whilst all skeletal sites depicted such cortical losses, substantial trabecular losses were found only from the proximal tibia epiphysis.

Results confirm that the differential losses from the various skeletal sites cannot be explained on the basis of trabecular vs. cortical tissue composition differences, but that endocortical circumference can account for the different amounts of bone loss in the tibia. The present study therefore supports the suggestion of the subendocortical layer as a transitional zone, which can readily be transformed into trabecular bone in response to immobilization. The latter will lead to cortical thinning, a factor that has been associated with the risk of fracture and with osteoarthritis.

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Introduction

Bone loss from immobilized limbs can be observed as a result of prolonged experimental bed rest [1–3] and space flight [4–6], as well as in clinical cases such as stroke [7] or spinal cord injury [8,9]. It is commonly held that mechanical stimuli, in particular strains, are important for adaptive processes in bone [10], and that the largest forces causing these strains arise from muscle contractions [11]. Bones can therefore be theorized to be adapted to these muscular forces [12,13].

Quite consistently, immobilization-induced bone losses are found to be larger in regions rich in trabecular bone (e.g. epiphyses) than from regions rich in compact or cortical bone (e.g. diaphyses). Two years or more after spinal cord injury, for example, epiphyseal bone mass in the tibia is reduced by 50%, whilst diaphyseal losses amount to only 30% [9,14]. In seeming agreement, bed rest-induced bone losses seem to be three or four times larger from the epiphysis than from the tibia shaft [2], and very similar figures seem to apply to tibial bone losses incurred during space flight [5].

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It is obvious that trabecular bone has a greater surface-to-volume ratio than compact bone, and it might be that the different tissue composition between trabecular and compact bone is responsible for the discrepancy between epiphyseal and diaphyseal losses described above. Indeed, it is suggested that 'trabecular bone is […] more metabolically active than cortical bone' [15], and thus one is intuitively inclined to associate the alleged high trabecular remodelling activity with the larger epiphyseal bone losses during immobilization.

However, as Parfitt has pointed out, biological and geometrical factors have to be taken into account, and trabecular turnover is therefore not always greater than cortical turnover [16]. For example, in the iliac bone, turnover is generally largest at the endocortical envelope [16,17]. Moreover, we have recently reported that bone loss incurred during unilateral lower limb suspension was larger from the peripheral (i.e. mixed trabecular and cortical) area than from the central region (i.e. purely trabecular bone) [18]. Furthermore, and in strong support of this, data from the Berlin Bed Rest study demonstrated that bed rest-induced bone loss in the distal tibia epiphysis is almost exclusively from the cortical bone compartment [19], and data from astronauts show that bone loss from the hip is predominantly from the cortical compartment [20].

Clearly, understanding the dynamics of immobilization-induced bone losses is paramount to our understanding of bone adaptive processes. Therefore, in order to assess whether cortical bone loss exceeds trabecular bone loss during bed rest as a general rule, we monitored various measurement sites, distinguished by their different tissue compositions. Based upon the available evidence, we hypothesized that (i) relative bone losses are larger from epiphyseal than from diaphyseal sites, but (ii) comparable between different epiphyseal sites of the same bone. Moreover, we hypothesized that (iii), irrespective of the bone sites, relative bone losses would generally be larger from the cortical bone compartment as compared to the trabecular portion.

Participants and methods

Study protocol and participants

Data were collected between June and August 2007 in a bed rest study organized in the Valoltra Orthopaedic Hospital in Ankaran, Slovenia. The study details have been reported elsewhere [21]. In brief, ten healthy men (devoid of any musculoskeletal disorder) underwent 35 days of horizontal bed rest. The participants' mean age was 24.3 years (SD 2.6), their weight was 77.5 kg (SD 11.0), their height 179.5 cm (SD 7.6), and their body mass index was 24.0 $kg \cdot m^{-2}$ (SD 2.9).

Adherence to the protocol was ascertained by continuous medical supervision, and also by closed-circuit television (CCTV), i.e. by continuous video surveillance. Physical activity was not permitted at any time during the period of bed rest. Development of contractures, however, was prevented by passive joint mobilization, which was performed three times weekly by a qualified physiotherapist who was briefed regarding the principle aims of the study.

Body mass of participants was stable for at least 3 months before the study. The bed rest period was preceded by 1 week of ambulatory adaptation period, in which each participant received a weight-maintaining diet containing 1.4 times their resting energy expenditure calculated according to the FAO/WHO equations [22]. The diet contained approximately 60% of energy as carbohydrate, 25% as fat, and 15% as protein. Six meals were administered daily, i.e., three main meals (breakfast, lunch and dinner) and three snacks. During the 35-day bed rest period, each participant received an activity-adjusted diet containing 1.2 times their resting energy expenditure [22] with the same meal frequency and relative macronutrient content of that planned in the pre-bed rest period. Subjects were required to consume all served food.

The study was approved by the Slovenian National Committee for Medical Ethics at the Ministry of Health (Republic of Slovenia) and conformed to the Declaration of Helsinki. Participants were included only after they had given their informed consent. Participants were aware that they could discontinue their participation at any time.

Peripheral quantitative computed tomography

Bone scans were obtained by peripheral Quantitative Computed Tomography (pQCT) with an XCT (Stratec Medizintechnik, Pforzheim, Germany). All scans were obtained from the right leg, and no participant reported a history of fracture in that leg. As in past studies, we chose the distal tibia epiphysis at 4% of its length (from its distal end) and the diaphysis at 38% of its length as measurement sites (Tibia_04 and Tibia_38, respectively) [2,13]. In addition to that, measurements were taken of the proximal tibia metaphysis (at 93%=Tibia_93) and of the proximal epiphysis (at 98%,=Tibia_98), the former being just distal and the latter being just proximal from the patella tendon's insertion into the tibial tuberosity. We also obtained a patella scan at 70% of its length from its distal end, and a scan of the distal femur epiphysis at 4% of the femur's length (Femur_04). An overview of the different skeletal sites with their specific bone tissue composition is given in Table 1.

Tibia length was measured by palpation as the distance between the most prominent point of the medial malleolus and the medial knee joint cleft, and femur length was defined as the distance between the lateral knee joint cleft and the greater trochanter. Patella length, by contrast was defined during the scout view procedure (see below). Reproducibility of pQCT scans depends to a large extent on exact repositioning. In an attempt to achieve exact repositioning we aligned the participants in their beds in supine position in the same way during all scans. To this effect the left foot, the left shoulder and the right pelvis were all placed approximately 5 cm from the mattress rim. Both legs were kept straight and the trunk was aligned so that hip abduction was identical for the left and right side. Next, it was ascertained that the vertical heights of the pQCT scanner's foot holder and of the mattress were identical, and the knee holder was set to the same position for a given participant throughout the study. Hip rotation was controlled for by asking participants to align their foot vertically without twisting the ankle. Importantly, all measurements, including the measurements after re-ambulation were performed in the same bed.

Two different scanning procedures were performed to obtain all six scans. First, the Tibia_04 and Tibia_38 scans were taken as described previously [2]. Next, the remaining scans were obtained following scout viewing of the knee in the sagittal plane, starting with the proximal patella end and continuing just beyond the insertion of the patella tendon into the tibial tuberosity. Reference lines were positioned to the proximal tibia plateau (for Tibia_93 and Tibia_98) as well as to the femur condyles (for Femur_04). For the patella scan, the patella length was manually assessed from the scout view (using the 'change reference line position' option and reading the position co-ordinates with the integrated XCT software), and the measurement line was then positioned at 70% of the patella length (from the distal end).

Bone scans were obtained during baseline data collection 2 days before the onset of bed rest (BDC-2), in the morning of the first day of bed rest (BR1), on the last day of bed rest (BR35), and 14 days after re-ambulation (R+14). Two complete sets of scans were obtained on each operational day, and values were averaged. Importantly, participants took their leg out of the gantry after the first of these two scans, rolled over in their bed and were positioned again, in order to produce comparable repositioning errors within days and across the entire study.

Data processing

The cross-sectional images were further analysed with the integrated XCT version 5.50D software (Stratec Medizintechnik,

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