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Regional variations of gender-specific and age-related differences in trabecular bone structure of the distal radius and tibia

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ABSTRACT

Regional variation in trabecular structure across axial sections is often obscured by the conventional global analysis, which takes an average value for the entire trabecular compartment. The objective of this study is to characterize spatial variability in trabecular structure within a cross-section at the distal radius and tibia, and gender and age effects using *in vivo* high-resolution peripheral quantitative computed tomography (HR-pQCT). HR-pQCT images of the distal radius and tibia were acquired from 146 healthy individuals aged 20–78 years. Trabecular bone volume fraction (BV/TV), number (Tb.N), thickness (Tb.Th), separation (Tb.Sp), and heterogeneity (Tb.1/N.SD) were obtained in a total of 11 regions—the entire trabecular compartment (the global means), inner, outer, and eight defined subregions. Regional variations were examined with respect to the global means, and compared between women and men, and between young (20–29 years old) and elderly (65–79 years old) adults.

Substantial regional variations in trabecular bone structure at the distal radius and tibia were revealed (e.g. BV/TV varied −40% to +57% and −59% to +100% of the global means, respectively, for elderly women). The inner-lateral (IL) subregion had low BV/TV, Tb.N, and Tb.Th, and low Tb.Sp and Tb.1/N.SD at both sites; the opposite was true in the outer-anterior (OA) subregion at the distal radius and the outer-medial (OM) and -posterior (OP) subregions at the distal tibia. Gender differences were most pronounced in the inner-anterior (IA) subregion compared to the other regions or the global mean differences at both sites. Trabecular structure associated with age and differed between young and elderly adults predominantly in the inner-posterior (IP) subregion at the distal radius and in the IL and IA subregions at the distal tibia; on the other hand, it remained unchanged in the OA subregion at the distal radius and in the OM subregion at the distal tibia for both women and men.

This study demonstrated that not only the conventional global analysis can obscure regional differences, but also assuming bone status from that of smaller subregion may introduce a confounding sampling error. Therefore, a combined approach of investigating the entire region, each subregion, and the cortical compartment may offer more complete information.

Introduction

Bone quality is a key component for fracture risk assessment and is determined by complex features such as mineralization, architecture, turnover, collagen cross-link and damage accumulation [1]. Bone strength is determined by the quality and quantity of the mineralized skeletal bone tissue. As bone mineral density (BMD) reflects both bone volume and the degree of mineralization, it has been regarded as a surrogate measure for bone strength. Areal BMD measured using dual X-ray energy absorptiometry (DXA) is primarily used for the routine diagnosis of osteoporosis. However, BMD only explains up to 70% of bone strength [1]. A variety of morphologic parameters have been introduced to quantitatively characterize the structural properties of trabecular bone. These indices include, but not limited to, bone volume-fraction (BV/TV), and metric indices such as trabecular thickness (Tb.Th), number (Tb.N), and separation (Tb.Sp).

With the emergence of high-resolution imaging modalities such as high-resolution peripheral quantitative computed tomography (HR-pQCT), isotropic nominal resolutions of 82 μm can be achieved, enabling *in vivo* assessment of these structural indices for trabecular bone at peripheral sites (specifically at the distal radius and tibia). Their accuracy has been validated against μCT-obtained values [2–4]. Structure indices obtained from HR-pQCT images have also been compared to results of mechanical testing and finite element analysis

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[5]. In addition, the discriminatory power of HR-pQCT-obtained for cortical and trabecular structure indices for disease [6] and fracture [7–9] states has been demonstrated, showing its feasibility as a non-invasive tool for assessing skeletal status.

Density and structural indices of trabecular bone calculated from HR-pQCT images are usually reported as average values for the entire trabecular compartment of interest. However, trabecular density and structure can vary substantially throughout cross-sections of the distal radius and tibia (Fig. 1). In fact, Lai et al. imaged cores of trabecular bone using μCT and found that trabecular bone in the posterior region of the distal tibia exhibits significantly higher BMD, BV/TV, Tb.N, Tb.Th, and degree of anisotropy, as well as lower Tb.Sp and structure model index compared to the anterior region (all $p<0.01$) [10]. This is most likely the result of adaptation to the habitual loading pattern [10] as the posterior part of the distal tibia is subject to substantial compressive and shear forces from the ground reaction and internal muscle forces during gait [11,12]. Such regional differences are obscured by global averaging of the entire trabecular compartment. The standard deviation of trabecular separation (denoted either as Tb.1/N.SD or Tb.Sp.SD) is often regarded as a measure of heterogeneity in trabecular bone distribution. While this indicates the degree to which the structure is heterogeneous across the entire trabecular region, it does not provide spatial information.

By subdividing the HR-pQCT images of the radius and tibia cross-section, regional analysis provides complementary information about the intrinsic structural heterogeneity of trabecular structure that is related to the underlying biomechanical conditions. We hypothesize that trabecular bone structure varies spatially across the trabecular compartment at the distal radius and tibia, and the degree of differences due to gender and age depend on the region. The objective of this study is to use *in vivo* HR-pQCT to investigate regional variations in trabecular structure at the distal radius and tibia and its differences due to gender and age.

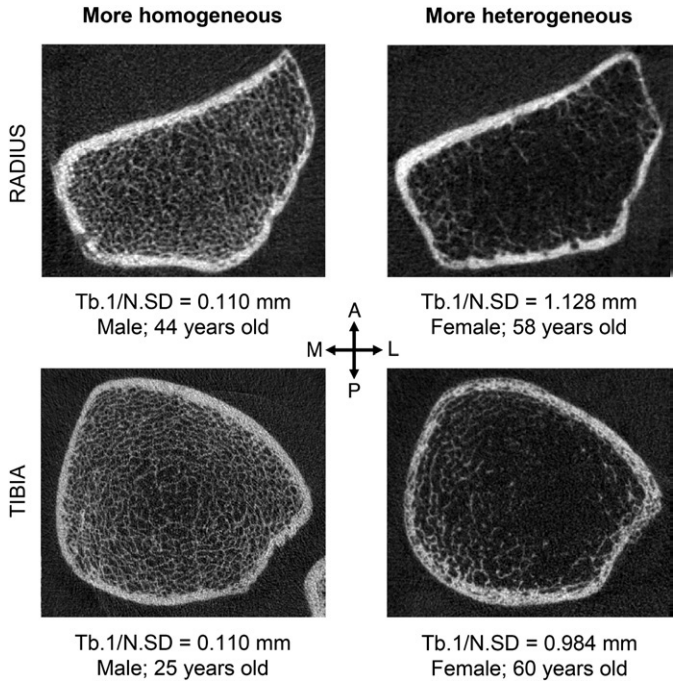

Fig. 1. Representative HR-pQCT images of cross-sections of human distal left radius (top) and tibiae (bottom) with low Tb.1/N.SD (more homogenously distributed) (left) and high Tb.1/N.SD (more heterogeneous distributed) (right). Notice that not only the distribution but also the thickness of trabeculae varies from subregion to subregion.

Materials and methods

Subjects

Healthy volunteers aged between 20 and 78 years—93 women (mean age 48.1 ± 15.8 years) and 53 men (mean age 44.7 ± 16.7 years)—were recruited through public fliers posted locally as a part of ongoing effort to build a normative database. Persons with known disease conditions or receiving chronic treatment that may affect bone metabolism were excluded from the study. All subjects gave written informed consent prior to participation. Out of 93 women, 43 were postmenopausal, who had complete cessation of menses for at least 6 months prior to entrance into the study. Among a total of 79 individuals with DXA measurements (54 women and 25 men), 15 women and 10 men were classified as osteopenic ($-1<T\text{-score}<-2.5$ at either L1–L4 or total femur), and 7 women and 3 men were classified as osteoporotic ($T\text{-score}\leq -2.5$). Subjects were Asian (46%), followed by 46% Caucasian, reflecting the ethnic composition of San Francisco Bay Area. The study protocol was approved by the University of California San Francisco Committee on Human Research.

HR-pQCT image acquisition

The distal radius and tibia of each subject were imaged using an *in vivo* HR-pQCT scanner (XtremeCT, Scanco Medical AG, Brüttisellen, Switzerland). HR-pQCT image acquisitions were performed by a total of five operators over the 3-year course of the study. Each subject's forearm and lower leg were immobilized in corresponding carbon-fiber molds, and fixed to the scanner to minimize motion during acquisition. A 9-mm-long section of the radius and tibia was imaged 9.5 and 22.5 mm proximal to the distal endplate, respectively. The non-dominant side was scanned unless there was a history of fracture, in which case, the contra-lateral side was scanned. The X-ray source potential was 60 kVp with a current of 900 μA. A two-dimensional detector containing 3072 × 256 CCD elements was used to acquire 750 projections at a 100 ms integration time/projection. The 12.6 mm field of view was reconstructed across a 1536 × 1536 matrix, yielding 82 μm isotropic voxels. Image acquisition time was 3 min/scan. Images were immediately reviewed for motion artifacts and repeated if obvious artifacts were detected. Five radius images were excluded due to motion artifacts despite repeated acquisition. The final dataset consisted of 142 radius and 146 tibiae images. The effective dose was <3 μSV/measurement [13].

Attenuation values were converted to equivalent hydroxyapatite density (mg HA/cm^3) using a linear relationship based on a phantom containing cylinders of HA-resin mixtures with five different concentrations (0, 100, 200, 400, and 800 mg HA/cm^3) (QRM, Moehrendorf, Germany). For quality control, the linear attenuation values of the phantom were monitored daily.

Analysis

The images were segmented and processed in accordance to the standard patient-style analysis protocol using Image Processing Language (Scanco Medical AG) as described elsewhere [6,14–20]. First, a semi-automated edge-defining algorithm was applied to the original grayscale image to contour the periosteal surface. The cortical and trabecular regions were segmented automatically by the analysis protocol as described in detail by Laib et al. [17]. The following process for defining subregions was performed on the trabecular mask automatically using Matlab at every slice. The trabecular compartment was first divided into two concentric circular regions (inner and outer subregions), where the area of the inner subregion was 60% of the entire trabecular region. This was consistent with the definition of inner and outer subregions where density measurements were obtained as a part of the standard patient analysis [20,21]. Furthermore,