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Age- and gender-related differences in cortical geometry and microstructure: Improved sensitivity by regional analysis

Galateia J. Kazakia [a,*], Jasmine A. Nirody [a], Gregory Bernstein [a,b], Miki Sode [a,c], Andrew J. Burghardt [a], Sharmila Majumdar [a,c]

[a] Musculoskeletal Quantitative Imaging Research Group, Department of Radiology and Biomedical Imaging, University of California, San Francisco, San Francisco, CA, USA
[b] University of California, Berkeley, Berkeley, CA, USA
[c] Joint Graduate Group in Bioengineering, University of California, San Francisco and Berkeley, San Francisco and Berkeley, CA, USA

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ABSTRACT

Objective: While the importance of cortical structure quantification is increasingly underscored by recent literature, conventional analysis techniques obscure potentially important regional variations in cortical structure. The objective of this study was to characterize the spatial variability in cortical geometry and microstructure at the distal radius and tibia using high resolution peripheral quantitative computed tomography (HR-pQCT). We show that spatially-resolved analysis is able to identify cortical sub-regions with increased sensitivity to the effects of gender and aging.

Methods: HR-pQCT scans of 146 volunteers (92 female/54 male) spanning a wide range of ages (20–78 years) were analyzed. For each subject, radius and tibia scans were obtained using a clinical HR-pQCT system. Measures describing geometry (cortical bone thickness (Ct.Th)), microstructure (porosity (Ct.Po), pore diameter (Ct.Po.Dm), and pore size heterogeneity (Ct.Po.Dm SD)), and cortical bone density were calculated from the image data. Biomechanical parameters describing load and stress distribution were calculated using linear finite element analysis. Cortical quadrants were defined based on anatomic axes to quantify regional parameter variation. Subjects were categorized by gender, and age, and menopausal status for analysis.

Results: Significant regional variation was found in all geometric and microstructural parameters in both the radius and tibia. In general, the radius showed more pronounced and significant variations in all parameters as compared with the tibia. At both sites, Ct.Po displayed the greatest regional variations. Correlation coefficients for Ct.Po and Ct.Th with respect to load and stress distribution provided evidence of an association between regional cortical structure and biomechanics in the tibia. Comparing women to men, differences in Ct.Po were most pronounced in the anterior quadrant of the radius (36% lower in women ($p<0.01$)) and the posterior quadrant of the tibia (27% lower in women ($p<0.01$)). Comparing elderly to young women, differences in Ct.Po were most pronounced in the lateral quadrant of the radius (328% higher in elderly women ($p<0.001$)) and the anterior quadrant of the tibia (433% higher in elderly women ($p<0.001$)). Comparing elderly to young men, the most pronounced age differences were found in the anterior radius (205% higher in elderly men, ($p<0.001$)) and the anterior tibia (190% higher in elderly men ($p<0.01$)). All subregional Ct.Po differences provided greater sensitivity to gender and age effects than those based on the global means.

Conclusion: These results show significant regional variation in all geometric and microarchitectural parameters studied in both the radius and tibia. Quantification of region-specific parameters provided increased sensitivity in the analysis of age- and gender-related differences, in many cases providing statistically significant differentiation of groups where conventional global analysis failed to detect differences. These results suggest that regional analysis may be important in studies of disease and therapeutic effects, particularly where microstructural parameters based on global analyses have thus far failed to identify a response in bone quality.

Introduction

Cortical bone strength is critical to skeletal integrity, particularly at appendicular sites where the cortex is responsible for the majority of axial load transfer [1,2]. Both geometry and microstructure of the cortical compartment are important in determining strength and

* Corresponding author at: Musculoskeletal Quantitative Imaging Research Group, Department of Radiology and Biomedical Imaging, University of California, San Francisco, 185 Berry St, Suite 350, San Francisco, CA 94107, USA. Fax: +1 415 353 9423.
E-mail addresses: galateia.kazakia@ucsf.edu (G.J. Kazakia), jnirody@gmail.com (J.A. Nirody), gregb@ucsd.edu (G. Bernstein), msode@mac.com (M. Sode), andrew.burghardt@ucsf.edu (A.J. Burghardt), sharmila.majumdar@ucsf.edu (S. Majumdar).

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fracture resistance [3–7]. Highlighting the importance of cortical geometry, cortical thinning has been shown to result in increased fracture incidence in postmenopausal women [8,9]. Cortical porosity, the main microstructural feature of the cortex, is greater at the femoral neck in hip fracture patients than in age-matched controls, and disruption of the normal spatial distribution of cortical porosity is associated with fracture incidence [10,11]. Further, age-related increases in cortical porosity account for more than 75% of the concomitant reduction in cortical strength [12]. Additionally, cortical bone geometry and microstructure are responsive to disease, therapy, and metabolic alterations. For example, increased cortical porosity is associated with chronic kidney disease [13], parathyroid hormone treatment [14], and reduced weight-bearing [15]. Therefore the investigation of cortical geometry and microstructure is an important aspect of understanding biological, pathoetiological, and biomechanical processes occurring within the skeleton.

High resolution peripheral quantitative computed tomography (HR-pQCT) enables 3D visualization of cortical and trabecular structure at the distal radius and tibia at an isotropic nominal resolution of 82 μm. This resolution permits consideration of indices that quantify densitometric, geometric, and microstructural properties of both compartments. Though HR-pQCT cannot resolve cortical porosity at the level of the smallest Haversian and Volkmann canals, the accuracy [16], reproducibility [17], and discriminatory power [16,18,19] of HR-pQCT cortical indices including thickness and porosity have demonstrated its viability as a tool for evaluation of cortical bone quality. Furthermore, mechanical indices derived from micro-finite element modeling (μFE) based on HR-pQCT data have also shown high reproducibility in previous studies [20].

While the importance of cortical structure quantification is increasingly underscored by recent literature, conventional analysis techniques obscure potentially important regional parameter variations. To address this, regional analysis can be used to explore anatomic distribution of geometric and microstructural features. Analyses focusing on variation along the length of the bone have found considerable variation in geometry and microarchitecture measures [21,22], as well as correlation between these measures and mechanical competence of bone [22]. In site-specific analyses focused on the trabecular compartment, regional analysis has improved sensitivity to morphologic changes associated with age and gender differences [23] as well as those effected by antiresorptive therapy [24]. Regional analysis has also been used to detect a spatial association between cortical area and stress fracture prevalence at the tibia [25].

In this context, the goal of this study is to characterize the spatial variability in cortical geometry and microstructure at the distal radius and tibia using HR-pQCT. We show that spatially-resolved analysis is able to identify cortical sub-regions with increased sensitivity to the effects of gender and aging.

Methods

Subjects

HR-pQCT image data from the baseline examinations of an ongoing longitudinal patient study were evaluated for this study (Table 1). The subjects consisted of 146 volunteers (92 females age 47.8 ± 15.7 years/54 males age 45.5 ± 16.3 years). Of the 92 women, 46 were post-menopausal. The diversity of the San Francisco Bay Area was reflected in the ethnic composition of the subjects: 47% Caucasian, 44% Asian, 6% Hispanic, and 3% African-American. No bone mineral density (BMD) inclusion/exclusion criteria were used. Subjects with a history of or evidence of metabolic bone disease, as well as those receiving chronic treatment that may affect bone metabolism, were excluded from the study. The study protocol was approved by the UCSF Committee on Human Research, and all subjects gave written informed consent prior to participation.

Table 1
Summary of subject numbers by gender, decade, and anatomic site. The subjects consisted of 146 volunteers (92 females/54 males). Subject ages ranged from 20 to 78 years.

Decade								
Sex	Site	20	30	40	50	60	70	Total
Female	Radius	14	14	12	22	17	7	86
	Tibia	16	16	14	21	18	7	92
Male	Radius	11	13	6	13	8	3	54
	Tibia	13	13	5	11	8	3	53

HR-pQCT imaging

All subjects were imaged in a clinical HR-pQCT system (XtremeCT, Scanco Medical AG, Brüttisellen, Switzerland) using the manufacturer's standard in vivo protocol, described in detail in previous publications [8,26,27]. The subject's forearm and ankle were immobilized in a carbon fiber cast that was fixed within the gantry of the scanner to minimize motion during imaging. The scan region, spanning 9.02 mm in length and composed of 110 slices, was defined on a single dorsal–palmar projection image of the distal radius/tibia. This region was fixed starting at 9.5 mm for the radius and 22.5 mm for the tibia proximal from the mid-jointline and extending proximally. For tomography, 750 projections were acquired over 180° with a 100-ms integration time at each angular position. The 12.6-cm field of view (FOV) was reconstructed across a 1536×1536 matrix using a modified Feldkamp algorithm, yielding 82-μm voxels [28]. Total scan time was 2.8 min with an equivalent dose of approximately 3 μSv. Images were inspected for motion-related artifacts, and scans were repeated if necessary. One tibia scan and 6 radius scans were excluded due to excessive motion (quality grading > 2 based on the manufacturer's qualitative grading scheme) and/or subject discomfort.

Segmentation algorithm

Image analysis was performed in a customized version of Image Processing Language (IPL v5.08b, Scanco Medical AG) that includes in-house functionality. In this section a segmentation technique used to delineate periosteal and endosteal cortical boundaries is described briefly. Further details on this extended cortical analysis technique can be found in Burghardt et al. [17]. The automated image processing chain is composed of three stages. First, an autocontouring process demarcates the cortical bone compartment. In this stage, a periosteal contour, which separates mineralized bone from extra-osseal soft tissue, and an endosteal contour, which delineates the endocortical boundary from the trabecular compartment, are generated based on an algorithm applying a series of morphological operations. Qualitative inspection of the automatically generated contours is always performed for quality assurance. If a contour visibly deviated from the apparent periosteal or endosteal boundary, minor adjustments are made to the affected region, leaving the remainder of the contour unaffected. In the next step, resolved intra-cortical porosity is distinguished from other features (e.g. erosions or artefactual surface roughness). Finally, the segmented cortical bone and porosity images are combined to generate a refined image of the cortical compartment.

Quantitative cortical bone analysis

Standard measures describing cortical bone density, geometry, and microarchitecture were derived based on the cortical segmentation described above. Apparent cortical bone mineral density (Ct.BMD) is defined as the mean mineralization value for all voxels in the cortical compartment volume of interest (VOI) following a surface erosion of 2 voxels. Cortical tissue mineral density (Ct.TMD) is calculated