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Spatial distribution of intracortical porosity varies across age and sex

Jasmine A. Nirody [a], Karen P. Cheng [b,c], Robin M. Parrish [b], Andrew J. Burghardt [b], Sharmila Majumdar [b], Thomas M. Link [b], Galateia J. Kazakia [b,*]

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

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ABSTRACT

Cortical bone porosity is a major determinant of strength, stiffness, and fracture toughness of cortical tissue. The goal of this work was to investigate changes in spatial distribution and microstructure of cortical porosity associated with aging in men and women. The specific aims were to: 1) develop an automated technique for spatial analysis of cortical microstructure based on HR-pQCT data, and; 2) apply this technique to explore sex- and age-specific spatial distribution and microstructure of porosity within the cortex. We evaluated HR-pQCT images of the distal tibia from a cross-sectional cohort of 145 individuals, characterizing detectable pores as being in the endosteal, midcortical, or periosteal layers of the cortex. Metrics describing porosity, pore number, and pore size were quantified within each layer and compared across sexes, age groups, and cortical layers. The elderly cohort (65–78 years, $n = 22$) displayed higher values than the young cohort (20–29 years, $n = 29$) for all parameters both globally and within each layer. While all three layers displayed significant age-related porosity increases, the greatest difference in porosity between the young and elderly cohort was in the midcortical layer ($+344\%$, $p < 0.001$). Similarly, the midcortical layer reflected the greatest differences between young and elderly cohorts in both pore number ($+243\%$, $p < 0.001$) and size ($+28\%$, $p < 0.001$). Females displayed greater age-related changes in porosity and pore number than males. Females and males displayed comparable small to non-significant changes with age in pore size. In summary, considerable variability exists in the spatial distribution of detectable cortical porosity at the distal tibia, and this variability is dependent on age and sex. Intracortical pore distribution analysis may ultimately provide insight into both mechanisms of pore network expansion and biomechanical consequences of pore distribution.

Introduction

Cortical bone microstructure is vital to the mechanical competence and fracture resistance of long bones. Cortical bone porosity, in particular, is a major determinant of strength, stiffness, and fracture toughness of cortical tissue [1–3]. One recent study using HR-pQCT identified significant differences in cortical porosity in the ultradistal radius between young and elderly subjects matched for areal bone mineral density (aBMD) [4], suggesting that porosity contributes to the aBMD-independent effect of age on bone fragility and fracture risk [5]. This is supported by a second recent HR-pQCT study at the ultradistal radius in which cortical porosity predicted prevalent fractures independent of aBMD [6]. In addition to porosity, measures of pore structure including size, shape, orientation, and distribution may be critical in understanding fracture incidence [7,8].

Early studies of cortical pore distribution showed that porosity is not spatially uniform [9,10]; however, a lack of automated tools has limited the widespread implementation of spatial distribution analysis. More recent studies have used semi-automated techniques to analyze porosity distribution from microradiograph [11–14] and synchrotron [15] data of cadaveric bone specimens. In vivo quantification of cortical bone microstructure is now possible using high-resolution peripheral quantitative computed tomography (HR-pQCT). This technology permits, for the first time, visualization and quantification of longitudinal changes in cortical porosity. While the resolution of HR-pQCT does not allow for the depiction of cortical porosity at the level of the smallest canals, pores on the order of 100 μm in diameter and larger are detectable [16]. HR-pQCT data provide reproducible and accurate bone microstructure and strength data [16–19]. While cortical microstructure parameters derived from HR-pQCT images have primarily been reported as values averaged over the entire cortical compartment, recent HR-pQCT studies have confirmed that cortical bone microstructure is heterogeneous

* 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: jnirody@berkeley.edu (J.A. Nirody), kcheng329@berkeley.edu (K.P. Cheng), rmparrish@berkeley.edu (R.M. Parrish), andrew.burghardt@ucsf.edu (A.J. Burghardt), sharmila.majumdar@ucsf.edu (S. Majumdar), thomas.link@ucsf.edu (T.M. Link), galateia.kazakia@ucsf.edu (G.J. Kazakia).

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[20–22] and that regional analysis of cortical bone microstructure increases sensitivity in detecting age-related changes [22].

Characterization of cortical microstructure within concentric layers, or laminar regions, may provide important information about the processes accompanying aging. Identification of microstructural changes at the endosteal border would clarify longitudinal shifts in trabecular and cortical compartment boundaries [23]. Identification of changes near the periosteal border may detect altered mechanical resistance to bending loads [10,24]. Further, determination of microstructure distributions – and longitudinal changes in distributions – could help to elucidate mechanisms of pore network expansion. For example, a longitudinal increase in porosity concentrated near the endosteal border could indicate a process driven by expansion of the marrow space and 'trabecularization' of the cortical compartment, while an increase in porosity that is uniform throughout the cortical compartment could indicate a process driven by expansion of the vascular network. Moreover, determining microstructure distribution may prove helpful in assessing fracture risk and providing personalized pharmacologic interventions.

The overall goal of this work was to investigate spatial distributions of microstructural changes in the cortical compartment associated with aging in males and females. The specific aims were to: 1) develop an automated technique for laminar analysis of cortical microstructure based on HR-pQCT data, and; 2) apply this technique to explore sex- and age-specific distribution of porosity within the cortex. To address these aims, we evaluated HR-pQCT images of the distal tibia from a cross-sectional cohort of 145 males and females ranging in age from 20 to 78, characterizing detectable pores as being in the endosteal, midcortical, or periosteal layers of the cortical compartment. Metrics describing porosity, pore size, and pore number were quantified within each layer and compared across sexes, age groups, and cortical layers. Laminar analysis of cortical microstructure provides a framework for localizing and characterizing the influence of sex and aging on the cortical pore network.

Methods

Subjects

For this study, baseline examinations from a longitudinal study were considered (Table 1). HR-pQCT image data were acquired from 145 subjects aged 20 to 78 years (92 females, age = 47.8 ± 15.7 years; 53 males, age = 45.5 ± 16.3 years). Of the women aged less than 50, 1 was postmenopausal. This represents 1 of 14 (7%) of the 40–49 year age group. Of the women aged 50 and over, 1 was premenopausal. This represents 1 of 21 (5%) of the 50–59 year age group. The ethnic composition of the subjects reflected the diversity of the San Francisco Bay Area: 47% Caucasian, 44% Asian, 6% Hispanic, and 3% African-American. Ethnic distribution was similar across sexes and age groups. History or evidence of metabolic bone disease, as well as chronic treatment with pharmacological agents affecting bone metabolism were exclusion criteria for this 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 sex and age group. The study consisted of 145 volunteers (92 females/53 males). Subject ages ranged from 20 to 78 years. All subjects were scanned at the tibia.

	Decade						Young	Elderly
Sex	20–29	30–39	40–49	50–59	60–69	70–78	20–29	65–78
Female	16	16	14	21	18	7	16	13
Male	13	13	5	11	8	3	13	9

HR-pQCT imaging

All subjects were imaged using the XtremeCT HR-pQCT system (Scanco Medical AG, Brüttisellen, Switzerland) using the manufacturer's standard in vivo protocol [25,26]. Two operators acquired the scans, using identical procedures and protocols. For each subject, the ankle was immobilized in a carbon fiber cast fixed within the gantry of the scanner to minimize motion during imaging. The scan region was composed of 110 slices, spanned 9.02 mm in length, and was defined on a single dorsal–palmar projection image of the distal tibia. This region started 22.5 mm from the mid-jointline and extended proximally. For tomography, 750 projections were acquired over 180° with a 100-ms integration time at each angular position. 82-μm voxels were obtained from a 12.6-cm field of view (FOV) reconstructed across a 1536 × 1536 matrix using a modified Feldkamp algorithm [27]. The total scan time was 2.8 min with an equivalent dose of approximately 3 μSv for each site scanned. Images were inspected for motion-related artifacts, and subjects were rescanned if necessary. All scans included in this study were of quality grading ≤ 2 based on the manufacturer's qualitative grading scheme [28]. A single operator determined the quality grading and performed image analysis.

Cortical segmentation

Initial contours of the cortical compartment were generated using a three-stage semi-automated image processing chain. A detailed discussion of this algorithm has been presented by Burghardt et al. [17]. In the first stage, an autocontouring process identifies the periosteal and endosteal boundaries. Qualitative inspection of the automatically generated contours is performed for quality assurance, and minor adjustments are made where necessary. In the second stage, resolved intracortical porosity is distinguished from other features (e.g., erosions or artefactual surface roughness). In the final stage, the segmented cortical compartment and porosity masks are combined to generate a refined image of the cortical compartment. All image analysis was performed in a customized Image Processing Language (IPL v.506a-ucsf, Scanco Medical AG) that includes in-house functionality.

Separation into three layers

After the initial segmentation, the refined cortical compartment was divided into three laminar layers of equal thickness: the endosteal, midcortical, and periosteal layers (Fig. 1). For each slice, the inner and outer boundaries of the midcortical layer were generated as follows. First, endosteal and periosteal boundaries were discretized. Starting from an initial point on each boundary, each pixel was iteratively recorded in a clockwise direction. Second, every point (X^k_{endo}, Y^k_{endo}) on the endosteal boundary was paired with the closest point on the periosteal boundary (X^k_{peri}, Y^k_{peri}). Note k enumerates the number of points on the endosteal boundary. Because the number of discretized points on the periosteal boundary is larger than on the endosteal boundary, not all points on the periosteal boundary are matched. Third, points one-third and two-thirds of the distance d^k between points (X^k_{endo}, Y^k_{endo}) and (X^k_{peri}, Y^k_{peri}) mark points on the inner and outer boundaries of the midcortical layer, respectively. That is, a point on the inner midcortical boundary was calculated as $\left(X^k_{endo} + {d^k_x}/{3}, Y^k_{endo} + {d^k_y}/{3}\right)$ and a point on the outer midcortical boundary as $\left(X^k_{endo} + {2d^k_x}/{3}, Y^k_{endo} + {2d^k_y}/{3}\right)$. Finally, continuous midcortical boundaries were generated by performing dilations and erosions to join the discrete midcortical boundary points.

Assignment of pores to layer

Once the cortical compartment was separated into endosteal, midcortical, and periosteal layers, each cortical pore was assigned to a