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Variation in Cortical Density Within the Cortical Shell of Individuals Across a Range in Densities and Ages

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Original Article

Variation in cortical density within the cortical shell of individuals across a range in densities and ages

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Abstract

Objectives: The purpose of this study was to determine variability in cortical volumetric bone density (vBMD) from a single slice tibia image over a range of vBMD readings and ages. **Methods:** Males and females (N=80; aged 6-80) were randomly selected from a previous study. Cortical vBMD at the anterior, posterior, medial, and lateral regions as well as the endocortical, mid-cortical, and pericortical regions of the cortical shell were determined using pQCT. **Results:** Mean anterior ROI cortical vBMD (1111 ± 11 mg/cm^3) was lower than the posterior and lateral ROIs (1169 ± 7 mg/cm^3 and 1151 ± 9 mg/cm^3, respectively), ($p<0.05$). Individuals with lower overall cortical vBMD and younger individuals had greater vBMD variability within the shell ($r=0.37$, $p=0.004$). Difference between anterior and posterior regions was inversely associated with cortical vBMD and jump power ($r=0.46$, $p=0.001$). Endocortical vBMD (1080 ± 6 mg/cm^3) was lower than the mid-cortical and pericortical regions (1152 ± 5 mg/cm^3 and 1147 ± 5 mg/cm^3, respectively). **Conclusions:** Variability in cortical vBMD was higher among young individuals and those with lower overall cortical vBMD, while lowest in older individuals and men. The anterior ROI had lower mean cortical vBMD than posterior or lateral regions, and endocortical vBMD was lower than the mid- and pericortical regions.

Keywords: Bone, Jump-power, Children, pQCT, vBMD

Introduction

Physical activity and bone loading stimulates bone remodeling. Increased rates of intra-cortical remodeling increases porosity and decreases the overall density of cortical bone[1], so that newly remodeled bone has a lower cortical volumetric density (vBMD) than older cortical bone tissue. Variation in cortical vBMD readings from the same slice image of the tibia using pQCT have been reported in postmenopausal women and adolescent girls and boys[2,3] with an increased variability reported with aging[4]. Additionally, endocortical radial vBMD has been reported to be higher in younger men, while pericortical radial vBMD was higher in older men[5]. Endocortical bone loss due to remodeling appears to be significant and has been reported

to comprise as much as 47 percent of all cortical bone loss[6].

Site-specific skeletal response to loading has been reported previously[7-14], however, evidence suggests that only minor load-specific differences in the distribution of cortical bone throughout the tibial shell exist[15]. Bone geometry adaptations also appear to be load pattern specific[15,16], however, greater amounts of non-specific physical activity has been reported to be related to greater measures of bone strength in children regardless of loading pattern[17,18]. Similarly, older individuals who participate in volleyball have been reported to have greater mid-tibia cross-sectional area than age matched referents[19]. Variability of vBMD within the cortical shell may be important in fracture risk and therefore findings from this study may help to improve the understanding of how vBMD within the cortical shell varies within individuals.

The purpose of this study was to determine variation in cortical vBMD from a single slice tibia image over a wide range of vBMD readings and across several decades of life in a healthy population. An awareness of the patterns of variation in cortical vBMD in the tibia of a healthy population may be helpful in understanding patterns seen in other conditions, such as fractures and stress-fractures. Additionally, we hoped to determine whether there was an association between jump power, as a proxy for physical activity and muscle strength, and cortical vBMD.

The authors have no conflict of interest.

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We hypothesized that variation in cortical vBMD readings at four specific regions within a tibia image slice would be greater in participants with lower overall cortical vBMD and that the vBMD variability would be associated with, or predicted by, strength measures or body composition, indicators of physical activity and loading. Additionally, we hypothesized that vBMD in the endocortical region will be lower in older individuals than the mid or pericortical regions.

Materials and methods

Eighty subjects were randomly selected from an existing dataset (N=307) to represent males and females over a wide range of cortical vBMD readings (1095-1308 mg/cm^3) and ages (6-80 years of age). The original dataset had 170 females (96 adults) and 137 males (55 adults) and was obtained to investigate muscle-bone relationships in healthy individuals. Peripheral quantitative computed tomography (pQCT) images were ranked by cortical vBMD from low to high and random numbers were generated in order to randomly select 80 subjects with cortical vBMD ranging from 1113-1307 mg/cm^3. The original images were not analyzed for regional or radial vBMD as described below. The original study was approved by the South Dakota State University Human Subjects Committee and written informed consent was obtained on all adult participants and from the legal guardian of minors, along with signed assent by the minor.

Anthropometric measures, jump power, and body composition (lean and fat mass) were considered as potential covariates in the statistical models. Height without shoes was measured to the nearest 0.5 cm (Seca Model 225, Hanover, MD) and weight in light clothing was measured by digital scale to the nearest 0.1 kg (Seca Model 770, Hanover, MD). Maximum jump power in watts was obtained from a two-footed counter movement jump using a ground reaction force platform and software (Novotec Medical, Pforzheim, Germany). Participants were instructed to jump as high as possible in a similar manner to previous studies using jumping mechanography[20,21]. Power was reported as watts per kilogram body weight. Body composition was obtained using whole body DXA (Hologic, Inc., Bedford, MA). Images were analyzed using Discovery Software version 12.3 provided by the manufacturer. Pediatric versions of the software were used for participants under 20 years of age.

The leg measured was the one the participant indicated they would use to kick a ball. Images of the 20% distal tibia site were obtained using the XCT2000 with a voxel size of 0.4 mm and a slice thickness of 2 mm (Orthometrix, White Plains, NY). Procedures for measurement and location of this site have been reported previously[22]. Cortical vBMD of the 20% slice image was analyzed using manufacturer's software version 6.00B with settings for cortical bone at Cort mode 1 and threshold of 710 mg/cm^3. Cortical vBMD was adjusted for partial volume effects using Rittweger's method[23]. Our coefficient of variation (CV) for cortical vBMD at the 20% distal tibia site is less than 1%.
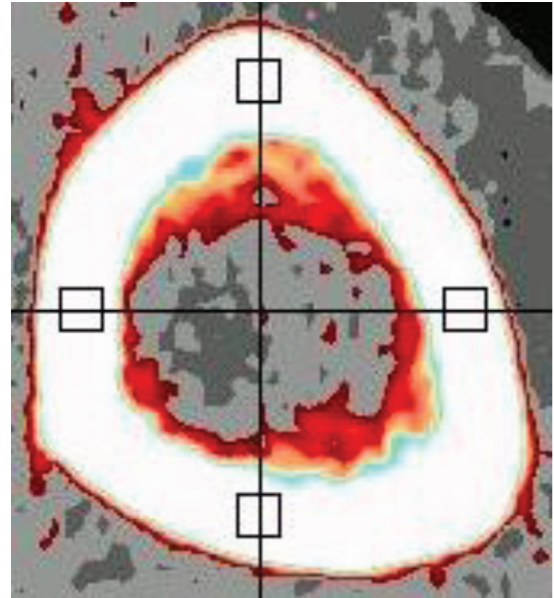

Figure 1. Positioning of four 1.4 mm^2 Regions of Interest (ROI) midway between the inner and outer edges of the cortical shell using a cross-hair to aide in positioning at anterior (ANT), posterior (POST), medial (MED), and lateral (LAT) locations.

Using a method we have used previously[24], a 1.4 mm^2 Region of Interest (ROI) was created and positioned midway between the inner and outer edges of the cortical shell of the image using a cross-hair to aide in positioning at anterior, posterior, medial, and lateral locations (Figure 1). The center point was determined as the point within the marrow cavity that was an equal distance from the anterior, posterior, medial, and lateral endosteal surfaces. The intersection of the cross hair was placed at this point and the anterior line was positioned to bisect the thickest point of the anterior cortex. Additionally, 30 scans from the previous study were analyzed twice to determine the reliability of this method and the coefficient of variation between analyses was less than 1 percent. Cortical vBMD of these ROIs were analyzed similar to cortical vBMD of the overall slice image using Cort mode 1 and threshold of 710 mg/cm^3. The variation in the four ROI cortical vBMD readings was calculated as the standard deviation (SD) of the four measurements.

Analysis of radial cortical vBMD in the endocortical, mid-cortical, and pericortical regions was performed on the pQCT images using ImageJ version 1.46 [25], an open source image processing program, and BoneJ version 1.3.7 [26], an open source plug-in for the program. BoneJ allows the determination of pericortical, mid-cortical, and endocortical vBMD.

Statistical Analysis

Repeated measures analysis of variance was used to determine differences among ROIs and radial regions. Post-hoc comparisons were performed using Tukey's HSD. The SD of

	Males (n=29)		Females (n=51)	
	Children	**Adults**	**Children**	**Adults**
Age (years)	10 [7-13]	46 [19-80]	9 [6-17]	43 [13-63]
Height (cm)	140±14	180±7	137±19	164±5*
Weight (kg)	36±10	81±12	39±18	72±11*
Body Fat (%)	20±5	20±7	27±8*	33±7*
Jump Power (W/kg)	39±6	45±14	36±8	34±8*

Children are individuals with a Tanner score of less than 4
Age is given as mean and range
All other data are mean ± SD
*Different than males in the same age category p<0.05

Table 1. Participant characteristics.

	Dependent Variables					
	Anterior vBMD	**Posterior vBMD**	**Lateral vBMD**	**Medial vBMD**	**ROI vBMD SD**	**Post-Ant vBMD Difference**
Age	*NS	*NS	*NS	*NS	*NS	*NS
Sex	-	*p<0.05	*NS	-	*NS	-
Age-By-Sex	*NS	*NS	*NS	*NS	*NS	-
Height	-	*NS	*p<0.001	*NS	*NS	*NS
Lean Mass	*NS	*NS	*p<0.01	*NS	*NS	*NS
Fat Mass	*NS	*NS	*NS	*NS	-	-
Jump Power	*p<0.05	-	-	-	-	*p<0.05
Overall Cort vBMD	*p<0.01	*p<0.001	-	*p<0.01	*p<0.01	*p<0.05

* Variable is significant in univariate model
NS = Not significant when controlling for other covariates
p-values represent significance in the model containing all other covariates
'-' = not included in analyses

Table 2. Contributions of covariates to ROI statistical models.

the four ROIs was tested for associations with cortical vBMD and tested in regression models containing jump power, height, lean mass, fat mass, age, sex, and age-by-sex interaction. Ordinary least squares regression was used to determine which variables added to the prediction in cortical vBMD and variation in cortical vBMD. A p-value of 0.05 was considered significant for all statistical tests.

Results

Participant characteristics are given in Table 1. Table 2 lists covariate contributions to models predicting regional vBMD, variability in regional vBMD, and posterior-anterior difference in vBMD. Mean (±SD) anterior ROI cortical vBMD reading (1111±11 mg/cm^3) was significantly lower than the posterior and lateral ROI vBMD (1169±7 mg/cm^3 and 1151±9 mg/cm^3, respectively) (p<0.05), but not different from the medial vBMD (1143±9 mg/cm^3).

Least square means adjusting for height, lean mass, fat mass, age, and sex for models predicting cortical vBMD in each bone region are shown in Figure 2A. Overall cortical vBMD was associated with vBMD at the anterior (β=1.45), posterior (β=0.89), and medial regions (β=1.0). When overall cortical vBMD and relative jump power were added to the anterior ROI model, all other covariates became non-significant. Jump power was only associated with cortical vBMD at the anterior ROI site (β=-0.71).

Older individuals had lower regional variability and the slope for cortical vBMD regressed on regional variability was more pronounced in males than in females (age-by-sex interaction, p=0.04) (Figure 3A). In models controlling for height, lean mass, fat mass, age and sex, cortical vBMD predicted variability in vBMD among ROIs (p<0.01): lower cortical vBMD was associated with higher variability in regional vBMD (Figure 3B). Cortical vBMD was lower in pubertal than post-pubertal individuals (1018±6 mg/cm^3 and 1154±5, re-
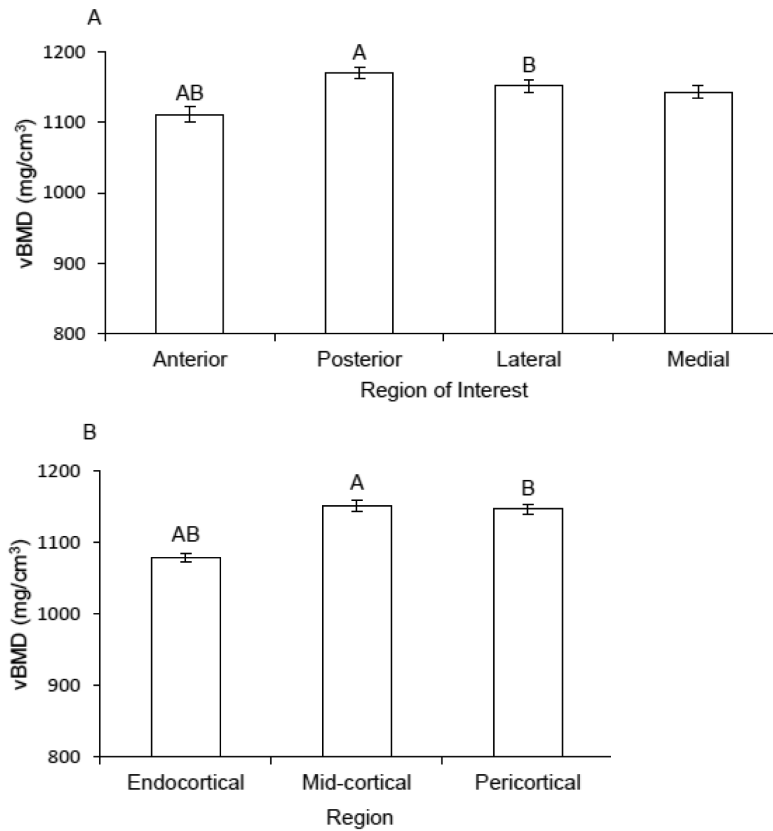
Figure 2. A: Cortical vBMD among ROI locations. Data are least square means±SE after adjusting for age, sex, lean mass, fat mass, and height. Bars with the same letter are significantly different from each other at p<0.05. **B:** Cortical vBMD among endocortical, mid-cortical, and pericortical regions. Data are least square means±SE after adjusting for age, sex, lean mass, fat mass, and height. Bars with the same letter are significantly different from each other at p<0.05.
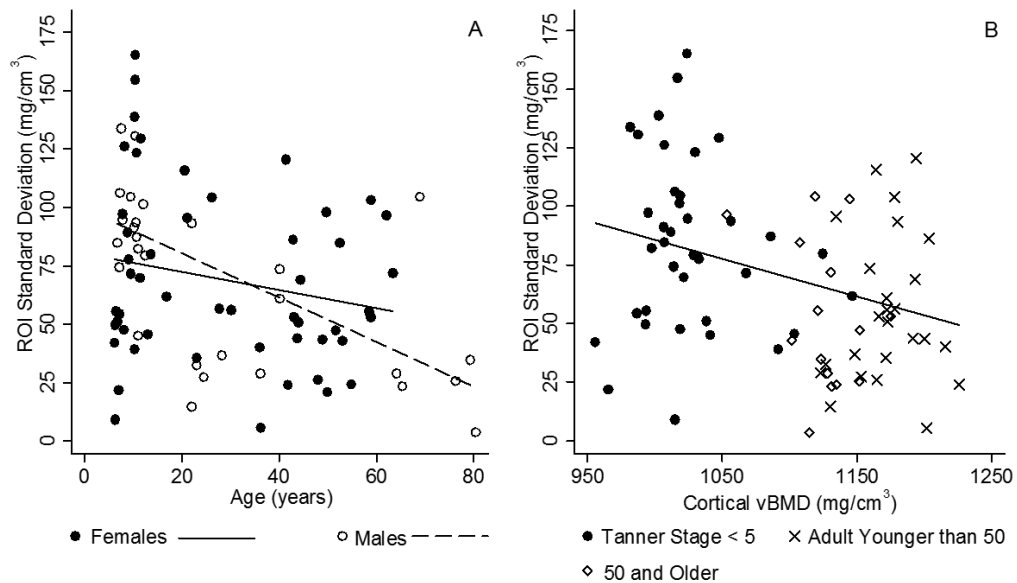

Figure 3. A: The relationship between regional variability of vBMD the 4 ROIs and overall cortical vBMD stratified by age. This relationship remained significant after controlling for age, sex, and the age-by-sex interaction. **B:** The relationship between regional variability of vBMD for the 4 ROIs and age stratified by sex. This relationship remained significant after controlling for age, sex, and the age-by-sex interaction.
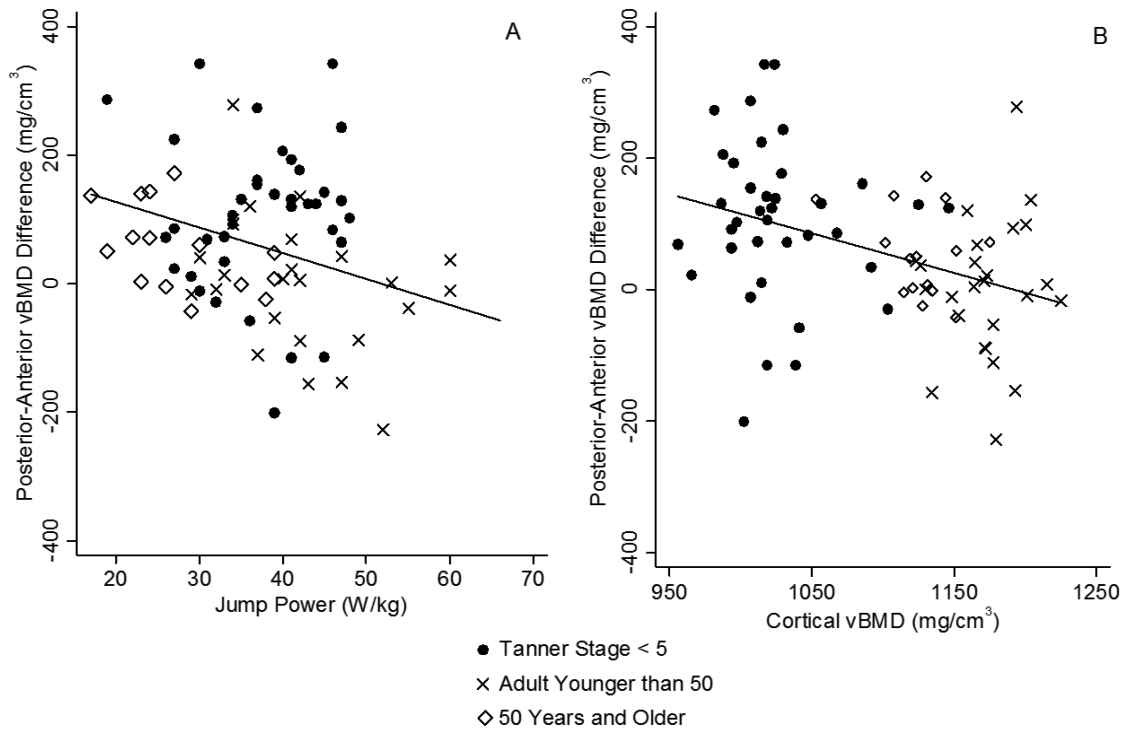
Figure 4. A: The relationship between posterior-anterior vBMD difference and jump power. **B:** The relationship between posterior-anterior vBMD difference and overall vBMD of the cortical shell. Jump power and cortical vBMD were both significantly associated with the anterior-posterior difference in models by themselves and together.
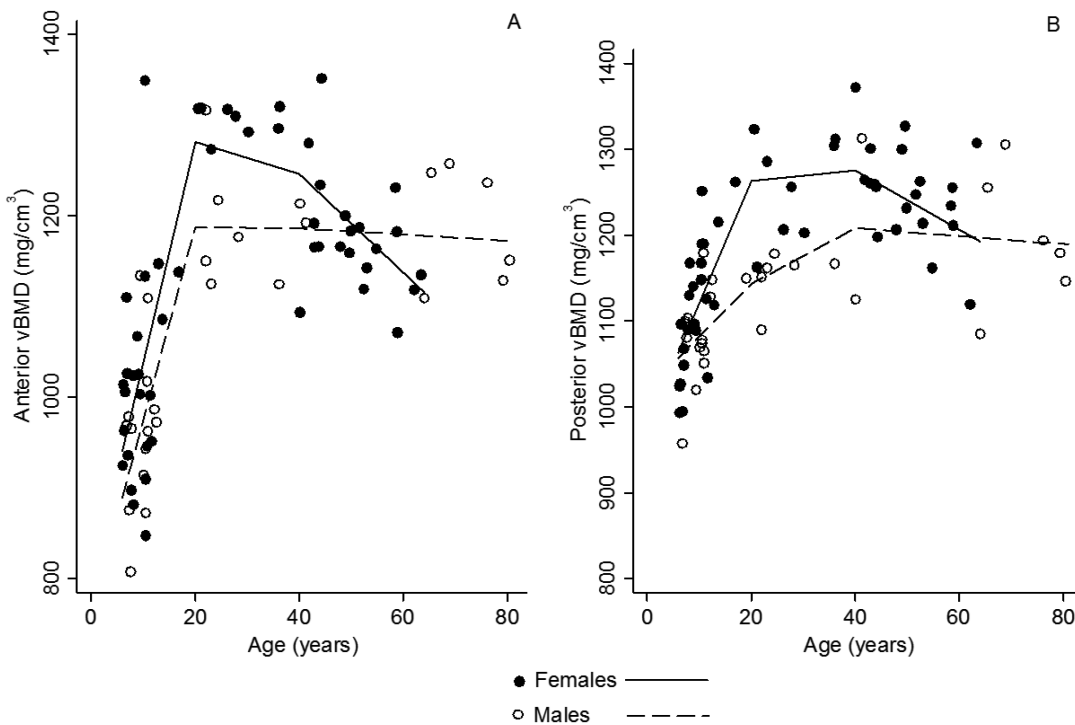

Figure 5. A: The relationship between vBMD at the anterior site and age between sexes. This relationship remained significant controlling for age, sex, and age-by-sex interaction. **B:** The relationship between vBMD at the posterior site and age between sexes. This relationship remained significant after controlling for age, and sex.

	Dependent Variables		
	Endocortical vBMD	Mid-Cortical vBMD	Pericortical vBMD
Age	*p<0.001	*NS	*p<0.001
Sex	*NS	*p<0.001	-
Age-By-Sex	*NS	*NS	*NS
Height	*NS	*NS	*NS
Lean Mass	*p<0.001	*NS	*NS
Fat Mass	*NS	*NS	*NS
Jump Power	-	-	-
Overall Cort vBMD	*p<0.001	*p<0.001	*p<0.001

Variable is significant in univariate model
NS = Not significant when controlling for other covariates
p-values represent significance in the model containing all other covariates
'-' = not included in analyses

Table 3. Contributions of covariates to radial vBMD statistical models.

spectively) while variability (SD) of regional cortical vBMD within the cortical shell was greater in pubertal than non-pubertal individuals (86±6 mg/cm^3 and 59±6 mg/cm^3).

Anterior vBMD was usually less than posterior vBMD, except in 22 subjects (27.5%) who had greater anterior cortical vBMD than posterior cortical vBMD. The posterior-anterior vBMD difference was inversely related with overall cortical vBMD (p<0.05) and jump power (p<0.05) (Figures 4A & 4B).

After 40 years of age, vBMD at the anterior site was lower in females than males but not in younger individuals (Figure 5A). At the posterior site, females had higher ROI cortical vBMD than males throughout all age groups after adjusting for height, lean mass, fat mass, age, and sex (p=0.01) (Figure 5B). Cortical vBMD did not differ between males and females at the lateral or medial sites.

Table 3 lists covariate contributions to models predicting endocortical, mid-cortical, and pericortical regions. Age, height, lean mass, fat mass, and overall cortical vBMD were all significant in univariate models, while sex was significant at the endocortical and mid-cortical sites. After controlling for age and overall cortical vBMD, lean mass was inversely related to endocortical vBMD (β=-0.97, p<0.001) but was not related to mid or pericortical vBMD.

Least square means±SE were calculated for radial vBMD adjusting for height, lean mass, fat mass, age, sex and age-by-sex interaction. Adjusted endocortical vBMD (1080±6 mg/cm^3) was lower than the mid-cortical and pericortical regions (1152±5 mg/cm^3 and 1147±5 mg/cm^3, respectively), but no difference was observed between the mid-cortical and pericortical regions (Figure 2B). After controlling for overall cortical vBMD, endocortical and pericortical vBMD were lower in pubertal than non-pubertal individuals. Additionally, the age-by-radial region interaction was significant (0<0.01): endocortical vBMD was lower with increasing age while mid- and pericortical vBMD did not differ with age. Distribution of vBMD among radii was similar between males and females.

Discussion

Variability of vBMD within the cortical shell was greater among younger individuals and pubertal individuals than older individuals. Variability of vBMD also was greater in individuals with lower overall cortical vBMD. Since new bone tissue is less dense than old bone tissue[1], these results correspond with bone growth in younger individuals and with bone remodeling in older individuals, especially among females. Our results that endocortical and pericortical vBMD is lower during puberty supports previous research which reported that periosteal growth in early life and at puberty is rapid, but after puberty slows significantly[27], so younger individuals in this sample would have higher variability in cortical vBMD and lower cortical vBMD in the endocortical and pericortical regions due to growth. This variability would be expected to be lower at older ages and this is supported by our findings that vBMD in the periosteal region increases early in life and then slowly tapers off after about age 40.

Our findings that cortical vBMD of the anterior region of the tibia is significantly lower than the posterior region are consistent with the findings of Lai et al[3] and Cooper et al[2]. In healthy Chinese post-menopausal women aged 47-60 years, Lai found a 6.5% difference between anterior and posterior regional cortical vBMD. Our difference between the anterior and posterior regions, sampling a broader age range and with a slightly different method also was approximately 5%. Cooper et al[2] used eight regional sectors to analyze mid-tibia regional cortical vBMD from pQCT images in 183 adolescents. They found significant variation (up to 12% difference) across sectors with the highest vBMD found at the medial and lateral margins of the posterior sector and lowest vBMD in the anterior sectors. The lower percentage difference between anterior and posterior regions of interest that we observed in our study may be explained in part by 22 subjects who had anterior vBMD greater than posterior. These subjects ranged in age

from 7-80 years old and were evenly distributed among sexes with 11 males and 11 females. We further investigated the predictors of the difference between anterior and posterior vBMD and found that the posterior-anterior difference was inversely related with jump power and overall cortical vBMD.

In our study, jump power was associated with cortical vBMD in the anterior ROI, but was not in other regions. The loading environment that the tibia is exposed to may help to explain this relationship. Modeling studies have suggested that during ambulation that axial strain is tensile at the anterior part and compressive at the posterior part[28,29]. This is interesting because the anterior cortex is considered a high-risk site for stress fracture in many sports, with stress fractures of the middle third of the tibia being known to occur in sports involving repetitive jumping[30,31]. Stress fractures would be assumed to occur in areas of bone that have not adapted to sustain the forces applied at the time of fracture[32]. The anterior and posterior portions of the tibia are exposed to the highest strain and thus may be susceptible to stress fractures due to an inability to repair adequately. This would seem logical since anterior tibial stress fractures are common. It is not known whether the limiting factor in a stress fracture is due to geometric or material characteristics, but bone structural adaptations to particular loading patterns have been shown in athletes[7,33]. A study in runners with previous stress fractures concluded that interventions to reduce stress fracture risk might be aimed at improving muscle size and strength[34]. This is logical given findings of a study by Milgrom et al. that reported an increase in tibial strains following a 2 km run and a 30 km desert march[35]. A study by Schaffler et al. reported that while bones lose some stiffness during the initial phases of loading, a failure point when strains are within normal limits is not reached[36]. However, based on the post-fatigue strains reported by Milgrom et al., a bone could reach its failure point rather quickly. Our studies on muscle-bone relationships in children found that jump power was not associated with overall cortical vBMD at the 20% distal tibia, but was associated with bone area[22]. Results from the current study show that higher jump power is associated with higher cortical vBMD in the anterior cortex. Studies that have investigated polar vBMD have reported differences in the variability of vBMD within the cortical shell[24] and differences in vBMD at different sectors within the cortical shell[15] depending on the predominant loading environment. The aforementioned studies[15,24], and other previously published research[37], indicates that muscle pull has a large role in the strains and subsequent adaptations at the tibia.

Analysis of radial density over the course of the lifespan may also aid in developing an understanding of why some fractures may occur. Our findings that vBMD was lower in the endocortical region than the mid-cortical region is in agreement with previous research[5,15]. This may be explained by the findings of Zebaze et al. who reported that endocortical bone loss accounts for up to 47 percent of total bone loss[6]. Our findings support those of Zebaze et al. in that endocortical vBMD is negatively associated with age compared with mid- and pericortical regions. Given that new bone is less dense than old bone[38], we can postulate that the endocortical region is remodeling more frequently than the other regions. This could theoretically be in an effort to support periosteal growth.

This study is limited by the cross-sectional design that does not enable us to determine changes over time. Additionally, we have used jump power and body mass as surrogates for muscle strength and loading. Activity levels were self-reported and therefore are subject to over- or under-reporting. The method we developed to locate the ROIs was done in a non-computerized manner. Although, we have determined this method of analysis to be repeatable, we are uncertain whether or not the differences we observed would be similar using computerized software. Finally, the random sample we obtained for this study yielded slightly unequal age ranges with men ranging in age from 7 to 80 while women ranged in age from 6-63. The lack of elderly women in the study made it difficult to assess the long term relationships between menopause and the distribution of cortical density.

In conclusion, our results indicate a higher variability in cortical vBMD of the tibia among individuals with lower overall cortical vBMD. Variability of vBMD among ROIs was lowest in older individuals and men, while younger individuals had the greatest variability. The anterior region of the bone had lower mean cortical vBMD than the posterior or lateral regions, but was not different from the medial region. However, in some participants the anterior vBMD was greater than the posterior and this was related to greater overall cortical vBMD and jump power. Additionally, endocortical vBMD was lower than mid- and pericortical vBMD and this difference became even greater with aging.

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