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Original Article

Hylonome

Age comparisons of bone density and geometry in men

V.D. Sherk[1], M. Karabulut[2], M.G. Bemben[1], D.A. Bemben[1]

[1]Bone Density Research Laboratory, Department of Health and Exercise Science, University of Oklahoma, Norman Oklahoma, 73019, USA; [2]Department of Health and Human Performance, University of Texas at Brownsville/Texas Southmost College, TX, 78520, USA

Abstract

Objectives: The purposes of this study were to examine tibia bone density and geometry in young and middle aged men, and to explore relationships between pQCT- and DXA-derived body composition variables. **Methods:** Healthy males (18-30 years old, n=31; 50-64 years old, n=37) had their total body areal bone mineral density (aBMD) and body composition measured with Dual Energy X-ray Absorptiometry (DXA). Volumetric bone characteristics, muscle cross-sectional area (MCSA) and fat cross-sectional area (FCSA) of the leg were measured with peripheral Quantitative Computed Tomography (pQCT). **Results:** Young men were significantly ($p<0.05$) lighter and had less fat mass than older men. Total volumetric BMD (vBMD) at 66% of the tibia length was significantly lower ($p<0.05$) in older men. Bone-free lean body mass values were useful predictors of total and cortical area and content (R^2=0.338-0.467). MCSA was more predictive of leg BFLBM than total body BFLBM, and those relationships were stronger in older men. **Conclusions:** Differences in tibial bone area and density existed between young and middle-aged men, and relationships between pQCT- and DXA-derived body composition variables were age-dependent.

Keywords: pQCT, Aging, Bone Free Lean Body Mass, Muscle Cross-Sectional Area, DXA

Introduction

Muscular contractions and age affect bone density and geometry[1]. It is unclear, however, if age-related bone changes are primarily due to decreased mechanical stresses induced by smaller muscles, or primarily due to bona fide aging of the bone. Research on the muscle-bone unit in women has suggested that training, age, and menstrual status affect the relationships between body composition, strength and areal bone mineral density (aBMD)[2-4], as rates of bone loss do not always coincide with rates of muscle loss. Previous reports on muscle and bone changes with aging in men have shown no significant differences in aBMD and lean body mass (LBM) between young and middle-aged men, but significant declines in aBMD and LBM have been reported in older men[5]. Despite a lack of significant differences in LBM and aBMD between young and middle-aged men, muscle mass and age often predict aBMD throughout the lifespan in men[5-7]. There may be changes in bone geometry and trabecular and cortical bone parameters between young and middle-aged men that are detectable with pQCT. Bone-free LBM (BFLBM) variables may also predict these additional bone characteristics, but prediction may be affected by changes in muscle mass distribution with age, resulting in altered bone loading.

Peripheral Quantitative Computed Tomography (pQCT) compliments DXA for bone health assessment by providing information about cortical and trabecular bone content, volumetric density and area, but it is possible that pQCT-derived bone variables could also be useful predictors of osteoporosis or fracture risk. pQCT also provides estimates of torsional bone strength as a strength strain index (SSI), which is affected by bone geometry and bone mineral content. The current position stand of the International Society of Clinical Densitometry supports the use of pQCT measurement of the distal radius for predicting hip fragility fractures in postmenopausal women and monitoring age-related changes in BMD[8]. Since bone loss is site specific[9], the forearm may not be representative of the skeletal sites where mechanical integrity is most needed for daily living and quality of life[10-12]. Intuitively, mechanical and impact loading of the lower leg and mid thigh are more representative of the loading that occurs at the proximal femur than forearm loading. Since measurement of the mid thigh may be difficult for individuals with very large thighs, the muscle-bone

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Corresponding author: Debra A. Bemben, Ph.D., Professor, Department of Health and Exercise Science, University of Oklahoma, Norman, 1401 Asp Avenue, Norman, OK 73109, USA
E-mail: dbemben@ou.edu

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unit of the lower leg may be the optimal pQCT site for estimating hip fracture and fall risk.

In addition to the bone variables, pQCT provides information about muscle cross-sectional area and fat tissue area, which is useful for quantifying hypertrophy with training or maturation. The ability of the pQCT soft tissue variables to correlate with and predict DXA-derived whole limb and total body soft tissue variables has not been investigated. Similar to skinfolds, in order for pQCT tissue analyses to be useful in predicting fat mass and fat free mass, theoretically, the amounts and proportions of muscle and fat at the chosen slice(s) need to be representative of those in the rest of the limb, as well as the rest of the body. The ability of a single cross-sectional slice to predict whole limb or total body fat or fat free mass is likely to be age-related, as older individuals tend to store less fat subcutaneously, and fat tends to centralize[13]. Thus, relationships between pQCT soft tissue analysis and DXA soft tissue analysis in different age groups warrant exploration. The purposes of this study were to compare bone density and geometry in young and middle aged men, to determine predictors of tibia bone characteristics, and to explore relationships between pQCT- and DXA-derived body composition variables.

Methods

Subjects

Sixty-eight healthy adult males (18-30 years old, n=31; 50-64 years old, n=37) participated in this study. Physically active men were included as long as they had not engaged in a regular resistance training program for at least 4 months prior to this study. Participants were excluded from the study if they had a BMI greater than 40 kg/m^2, and had any conditions or were taking any medications known to affect bone density. The study was approved by the University of Oklahoma Institutional Review Board. All participants were informed of the experimental risks and signed an informed consent document before participation in the study.

Muscle and fat size and bone characteristics

All participants had their volumetric BMD and bone characteristics (bone mineral content (BMC), area, cortical thickness (CTh), strength strain index (SSI) assessed at 4%, and 66% of the limb length proximal to the bony endplate of the right tibia using a peripheral Quantitative Computed Tomography (pQCT) scanner XCT 3000 with software version 6.00 (Stratec Medizintechnik GmbH, Pforzheim, Germany) by a trained pQCT technician. Muscle cross-sectional area (MCSA) and fat cross-sectional area (FCSA) were determined at the 66% tibia site. Scans were acquired with a voxel size of 0.4 mm, a slice thickness of 2.2 mm, and a scan speed of 20 mm/sec. The 4% tibia total and trabecular bone analysis was performed with the following parameters: Contmode 3, Peelmode 4, trabecular thresholds of 169 mg/cm^3 and 650 mg/cm^3. Contmode 3 uses automated contour detection with a user defined threshold. Peelmode 4 is a threshold driven peel that also utilizes a filter. After the initial peel to define cortical and trabecular bone is completed, Peelmode 4 then peels a set percentage (10%) of the total bone area from the endosteal edge found by the initial peel. This method separates trabecular bone from the cortical + subcortical bone, to prevent higher density voxels from being included in the trabecular analysis. The total bone analysis at the 66% site was performed using threshold driven modes Contour Mode 1 and Peel Mode 2 with a threshold of 710 mg/cm^3. The cortical bone analysis was performed using Cortical Mode 2, a threshold driven separation mode with a filter, with a threshold of 710 mg/cm^3. When determining SSI, a threshold of 480 mg/cm^3 was used. MCSA and FSCA analyses were performed as a combination of two analyses. The first trabecular parameters were Contour Mode 3 with Peel Mode 2, using thresholds of -100 mg/cm^3 and 40 mg/cm^3. The second trabecular parameters were Contour Mode 1 and Peel Mode 2, using thresholds of 710 mg/cm^3 and 40 mg/cm^3. Cortical parameters were only utilized for the first analysis, and was Cortical Mode 2 using a threshold of 710 mg/cm^3. Smoothing filter F03F05 was used. MCSA was defined with the following equation: Subcortical area (Analysis 1) – Subcortical area (Analysis 2) – Cortical Area (Analysis 1). FSCA was defined as Trabecular Area (Analysis 1) – Trabecular Area (Analysis 2). Technician precision (CV%) for the total and cortical bone variables at the 66% site ranged from 0.27%-1.21%. Precision for MCSA was 1.42%, and FCSA was 1.61%. At the 4% site, total and trabecular bone variables precision ranged from 0.45%-1.12%.

Total body composition

Total and appendicular body composition [body fat %, fat mass (FM), bone free lean body mass (BFLBM)] and total body aBMD were assessed using Dual Energy X-Ray Absorptiometry (DXA) (GE Medical Systems, Lunar Prodigy enCORE software version 10.50.086, Madison, WI) by a single trained technician. Subjects with an abdominal thickness at the umbilicus of ≤25 cm were scanned at the Standard speed and subjects with an abdominal thickness of >25 cm were scanned at the slower Thick speed. A relative skeletal muscle mass index (RSMI) was calculated as the sum of arm and leg BFLBM divided by height squared (kg/m^2)[14]. Technician precision (CV%) for the total body aBMD scan was 0.9%, and body composition values was 1.39%, 2.50%, and 2.74% for BFLBM, body fat %, and FM, respectively.

Data analysis

Statistical analyses were performed using SPSS for Windows version 15.0 (Chicago, IL). Data are represented as mean ±SE. One-way ANOVA was used to compare bone characteristics and body composition variables between the young and middle-aged groups. Linear stepwise regression analyses were used to determine how well body composition measures from pQCT or DXA predicted pQCT bone variables (vBMD, area, BMC, SSI). For predicting pQCT bone variables, we followed a minimum of 20 subjects per predictor variable[15]. Because of the relationships between lean mass measures and the relationships between fat mass variables, various regression models were utilized. All models included age, a fat mass variable, and a bone free lean body mass variable.

	Young (n=31)	Older (n=37)	p-value
Age (yrs)	26.3±0.9	56.8±0.6[b]	0.000
Height (cm)	176.7±1.3	177.0±1.1	0.864
Weight (kg)	77.5±2.7	84.8±2.4[a]	0.048
Total BFLBM (kg)	58.6±1.7	56.9±1.2	0.411
Total fat mass (kg)	17.3±1.8	24.4±1.5[b]	0.003
Leg BFLBM (kg)	19.7±0.5	19.1±0.5	0.398
Leg fat mass (kg)	5.7±0.6	6.7±0.4	0.174
Body fat %	21.1±1.7	28.2±1.2[b]	0.001
Total aBMD (g/cm^2)	1.258±0.015	1.236±0.020	0.410
Total BMC (kg)	3.26±0.09	3.22±0.09	0.756
RSMI (kg/m^2)	8.7±0.1	8.3±0.1	0.090

[a]p<0.05, [b]p<0.01 Significant group difference.
BFLBM: Bone-Free Lean Body Mass; aBMD: Areal Bone Mineral Density; BMC: Bone Mineral Content; RSMI: Relative Skeletal Muscle Index.

Table 1. DXA derived bone and body composition variables.

The tested models were:
1. Age, FSCA, MCSA
2. Age, leg fat mass, leg BFLBM
3. Age, total fat mass, total BFLBM
4. Age, total fat mass, RSMI

Coefficients of determination were calculated between MCSA and leg and total BFLBM and between FCSA and leg and total FM. The level of significance was set at p<0.05.

Results

Subject characteristics are shown in Table 1. Men in this study ranged in age from 18.9 to 35.8 years for the younger group and from 50.8 to 64.2 years for the older group. aBMD and BMC values were not significantly different between groups. Younger men weighed less (p<0.05) than older men, and they had significantly (p<0.01) lower fat mass values. RSMI tended to be lower in the older group (p=0.09).

The distal tibia (4%) is typically used for assessing trabecular bone, and the diaphysis (66%) is used for assessing cortical bone. Thus, the total bone results are reported for both sites, trabecular bone results are reported for the 4% site, and cortical bone results are reported for the 66% site. Table 2 shows that the younger group had significantly greater (p<0.05) trabecular density (TrD) at the 4% tibia site, and greater (p<0.05) total density (ToD) at the 66% site than the older men. Total density tended (p=0.057) to also be greater in the young men at the 4% site. Total area (ToA) tended (p=0.092) to be greater in the older group at the 66% site. There were no significant age group differences in cortical bone measures, SSI, MSCA or FCSA.

Predictors of pQCT-derived bone variables

Table 3 shows the best fit regression models for pQCT-derived bone area and content variables at the 4% and 66% tibia site.

	Young (n=31)	Older (n=37)	p-value
TIBIA 4%			
ToC (g/mm)	404.33±9.29	381.74±11.17	0.134
ToA (mm^2)	1198.99±24.81	1229.05±36.30	0.513
ToD (g/cm^3)	337.583±6.485	318.084±7.458	0.057
TrC (g/mm)	288.42±7.57	271.39±7.99	0.131
TrA (mm^2)	1010.55±23.17	992.75±32.09	0.666
TrD (g/cm^3)	286.374±5.747	268.011±6.193[a]	0.036
TIBIA 66%			
ToC (g/mm)	448.56±10.68	445.22±10.89	0.829
ToA (mm^2)	626.05±14.43	661.22±14.44	0.092
ToD (g/cm^3)	718.194±10.414	676.108±12.116[a]	0.012
CoC (g/mm)	406.20±9.75	403.24±10.41	0.838
CoA (mm^2)	361.03±8.64	360.05±8.74	0.937
CoD (g/cm^3)	1125.316±4.309	1118.784±5.614	0.374
CTh (mm)	4.95±0.11	4.74±0.10	0.162
SSI (mm^3)	2995.08±97.98	3114.60±100.39	0.402
MCSA (mm^2)	6399.1±114.4	6552.5±153.8	0.279
FCSA (mm^2)	3967.1±197.7	4265.9±196.6	0.291

[a]p<0.05 Significant group difference.
ToC: Total Content; ToA: Total Area; ToD: Total volumetric Density; TrC: Trabecular Content; TrA: Trabecular Area; TrD: Trabecular volumetric Density; CoC: Cortical Content; CoA: Cortical Area; CoD: Cortical volumetric Density; CTh: Cortical Thickness; SSI: Strength-Strain Index; MCSA: Muscle Cross-Sectional Area; FCSA: Fat Cross-Sectional Area.

Table 2. pQCT derived bone quality and soft tissue composition.

DV	Best Significant Predictor Variable	β	SEE	R^2
4% Tibia				
ToC	Leg BFLBM	0.500	53.839	0.250
ToA	Leg BFLBM	0.372	174.904	0.138
TrC	Leg BFLBM	0.432	42.021	0.187
TrA	MCSA	0.547	156.322	0.153
	FCSA	-0.330		
66% Tibia				
ToC	Leg BFLBM	0.644	48.44	0.414
ToA	Leg BFLBM	0.582	68.22	0.385
	Age	0.311		
CoC	Leg BFLBM	0.635	45.87	0.403
CoA	Leg BFLBM	0.683	37.19	0.467
SSI	Leg BFLBM	0.654	433.93	0.433
	Age	0.210		

β: Standardized Coefficient; SEE: Standard Error of the Estimate; ToC: Total Content; ToA: Total Area; ToD: Total volumetric Density; TrA: Trabecular Area; TrD: Trabecular volumetric Density; CoC: Cortical Content; CoA: Cortical Area; BFLBM: Bone-Free Lean Body Mass; MCSA: Muscle Cross-Sectional Area; FCSA: Fat Cross-Sectional Area.

Table 3. Predictors of pQCT-derived bone characteristics at the 4% and 66% tibia using age and body composition variables.

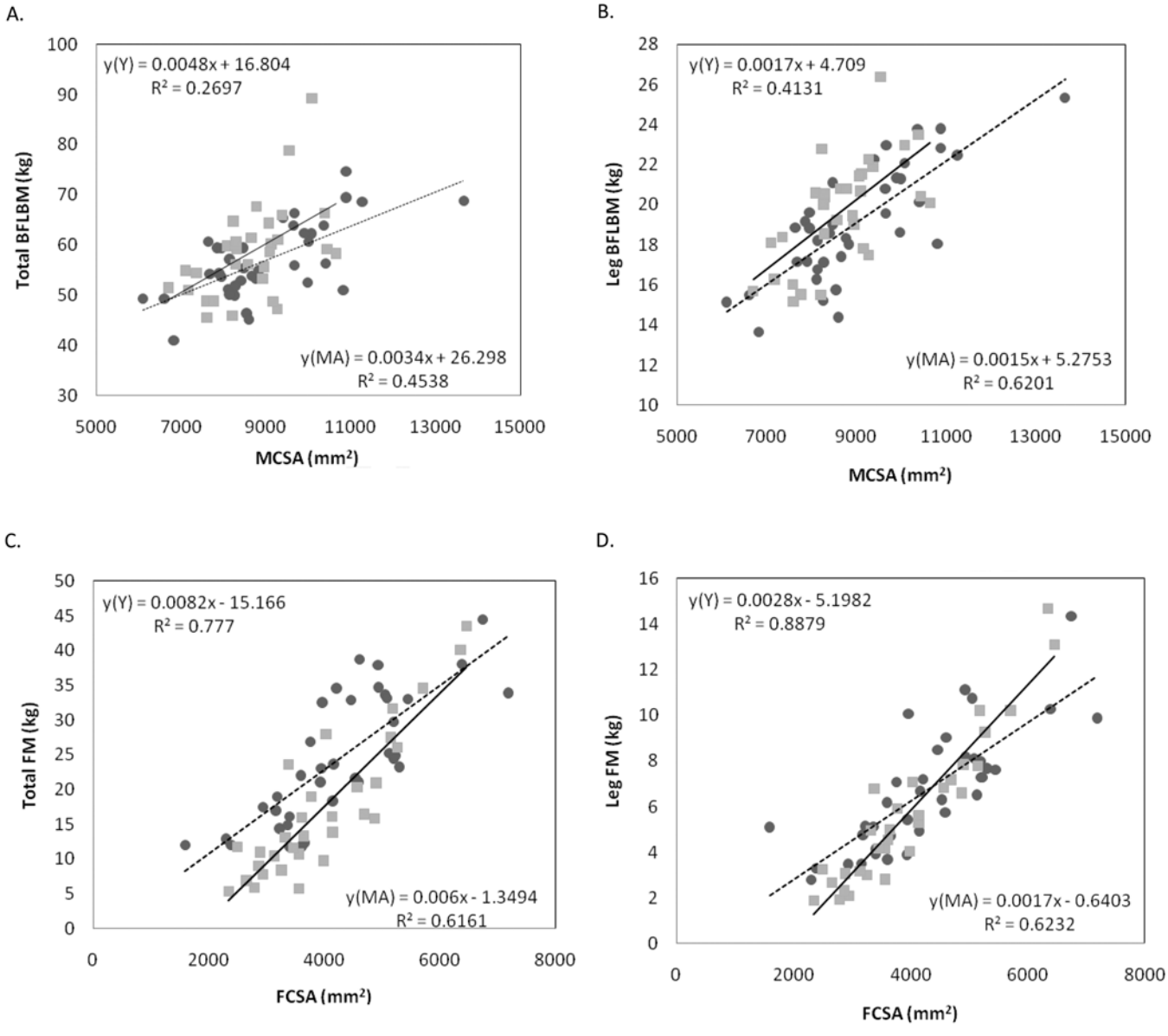

Figure 1. Relationships between pQCT-derived calf muscle cross-sectional area (MCSA) and fat cross-sectional area (FCSA) and DXA-derived total body and leg bone free lean body mass (BFLBM) and fat mass (FM). R^2 is the coefficient of determination. Circles and dashed trend lines represent middle-aged (MA) men. Squares and solid trend lines represent young (Y) men. A. Total BFLBM vs. calf MCSA; B. Leg BFLBM vs. calf MCSA; C. Total FM vs. calf FCSA; D. Leg FM vs. calf FCSA.

While leg BFLBM was typically the best predictor of content and area variables at both tibia sites, total BFLBM also significantly predicted ToC (R^2=0.205, $p<0.01$) and ToA (R^2=0.110, $p<0.01$) at the 4% site, and ToC, ToA, CoC, and CoA at the 66% site (R^2=0.338-0.434, $p<0.01$). Total BFLBM also predicted SSI (R^2=0.398). R^2 values were consistently lower when using RSMI and MCSA as the predictors. Age was the only significant predictor (R^2=0.071-0.089, $p<0.05$) of 4% TrD and ToD, regardless of which body composition variables were used, and contributed to predicting variance in ToA and SSI of the 66% site. Age and RSMI predicted 16.8% of the variance in ToD at the 66% site.

Interestingly, the coefficients of determination between MCSA and leg and total body BFLBM seemed to differ between age groups. As shown in Figure 1, MCSA tended to be more related to leg and total BFLBM in the older group than the young group, while FCSA tended to be more closely related to leg FM and total FM in the young group.

Discussion

We found age group differences in bone characteristics of the tibia that were not explained by total bone free lean body mass,

leg lean mass, or fat mass variables. Cortical bone tissue characteristics were similar between age groups. Therefore, nearly six percent lower total vBMD in the older men at the tibia 66% site, a trend for lower total vBMD at the 4% site, and an upward trend in total bone area at the 66% site were due to differences found in non-cortical tissues. We expected that cortical thickness would be lower in the older group since there were no age group differences in cortical bone content and area, and the 66% total area tended to be higher in older men. However, this result did not occur perhaps due to partial volume effects within the pQCT analysis. The density value given to a voxel is an average of the different densities within the voxel. Since the pQCT analysis is threshold driven, as long as the average density is greater than the threshold, the voxel would still be defined as cortical bone. Thus, use of different thresholds may have given different results in terms of values and significance. However, we utilized thresholds and analysis modes that are common for our tibia sites and these thresholds gave an adequate analysis of bone characteristics for both age groups.

Age group differences at the tibia bone sites in our study are less than those previously reported for the radius and hip using pQCT, however, we focused on cohorts that were closer in age[16,17]. Khosla et al. (2006) reported that trabecular thickness in the wrist decreased 24%, and cortical thickness and vBMD decreased 38% and 16%, respectively, between the ages of 20 and 90 years in men[16]. Riggs et al. (2004) reported total and trabecular vBMD losses ranging from 34-47% in the lumbar spine and femoral neck for the same age span[17]. Distal radius and tibia vBMD losses ranged from 21-28%. Age 50 seemed to be a critical time point for accelerated vBMD losses at the wrist. However, both of these studies only reported values for the 20-29 year-old cohort, so it is unclear if bone variables were significantly different between young and middle-aged participants. Total and trabecular bone area of the wrist and femoral neck significantly increased with age, as did total and trabecular area of the distal tibia after adjusting for height[17]. It is notable that these large changes over a very long period of time translate into a generally slow progression of bone loss that may make tracking difficult in healthier male populations. Even in older men, Schiessl et al. (2006) found that bone loss in the distal tibia was typically less than 10 mg/cm^3 over a 4 year period[18].

Interestingly, although there were differences in bone characteristics between age groups at the tibia 4% site, very few bone variables were predicted by age. This may be due to the relatively narrow age ranges used and the variability of bone characteristics. Also, the prediction of bone characteristics at the 4% site by BLFBM values was much weaker than at the 66% site. Because of the high trabecular content of this site, it is possible that this site is more dependent upon impact loading and hormonal factors for bone content and density maintenance, which were not assessed in this study. The ISCD Position Stand does not currently include information for or against the use of the tibia for assessing fracture risk or monitoring age-related changes[8]. While the ultradistal radius can be used to monitor age-related bone loss with pQCT, the tibia may be a functional site to test, since it may predict fragility fracture risk due to mechanical loading. Future studies are warranted to determine if bone loading history or hormone levels can predict bone variables of the distal tibia, or if the distal tibia can be used to predict hip fractures or age-related changes in the lumbar spine similarly or better than the distal radius.

Leg and total body BFLBM values consistently predicted pQCT content and area variables better than MCSA, RSMI, or any fat mass variables. Having leg BFLBM predict bone characteristics more strongly than total body BFLBM lends support to a notion that the distribution of BFLBM has importance to bone health over simply having more total BFLBM, as the location of BFLBM will partly determine where the strongest muscular contractions occur. Fat mass and fat area values from DXA and pQCT were not consistently or strongly related to pQCT-derived bone variables, but were utilized in regression analyses to help illustrate the importance of body composition on bone characteristics. Age significantly predicted vBMD variables in our study, while Lauretani et al. (2006) found that age was a predictor of total and cortical area and vBMD in old men[19]. Taaffe et al. (2003) found only low correlations between cortical area and MCSA and FCSA, and between polar moment of inertia and MCSA in older men[20].

While it is well known that pQCT can be used to measure MCSA[21], its potential use in predicting whole body composition has not been examined. Since pQCT is a valid tool for estimating bone area and muscle area, pQCT may be a valid tool for estimating fat area. Fat cross-sectional area of the forearm has been compared to total fat mass based on skinfold thickness measures and used to predict bone characteristics in a few studies of children and adolescents[22,23]. Technician precision for estimating FCSA in our lab was good, and relationships between FCSA and leg and total FM were strong. While total body fat mass was significantly greater in the older group, group differences in calf fat were not significant. FCSA seemed to predict DXA FM variables slightly better in young men. Since fat distributions become more centralized with age, fat in the lower leg may be less representative of total body fat[13,24]. An unexpected result was the large divergence in R^2 values for MCSA and BFLBM value between age groups, in that MCSA predicted BFLBM values in the older group far better than in young men. Potential reasons are differences in muscle mass distribution and differences in rates of muscle loss with aging[25], as suggested by Lee et al. (2004) when utilizing MRI images of the mid-thigh to estimate total body skeletal muscle mass[26]. Strong relationships between pQCT-derived data and DXA-derived variables suggest that with proper prediction equations, pQCT may provide a reasonable estimate of whole body composition, but further research is warranted. Future studies may also focus on the merit of developing a criterion for sarcopenia based on pQCT values.

There are several limitations to this study. First, our age-related findings should be interpreted with caution given the cross-sectional design of our study. Muscular strength was not assessed in our subjects. Although total bone-free lean body mass and calf muscle CSA did not differ between groups, ap-

pendicular muscle mass tended to be greater in the younger group, suggesting that the younger men would have greater leg strength. In addition to probable differences in weight distributions between age groups, the older group may not have been able to recruit motor units as well as the younger group, which would affect the amount of force the muscles could exert on bones. Also, we did not assess lifetime bone loading history. Peak bone mass is a determinant of bone mass later in life, and activities with high impact loading during times of rapid growth have been shown to be effective at increasing peak bone mass[27]. Thus, even if total or appendicular bone-free lean body mass or strength were not different between age groups, there may be differences in impact loading histories that may affect outcomes.

Conclusion

Cortical bone content, area, and density of the tibia were similar between age groups, but the trabecular analysis showed greater area and lower density in older men compared to younger men. Muscle cross-sectional area, relative skeletal muscle index, and bone free lean body mass all predicted pQCT bone variables, but associations were strongest with leg bone free lean body mass. More studies are needed to determine if pQCT muscle and fat area values can estimate total body composition variables.

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