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Original Article

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Bone mass and density response to a 12-month trial of calcium and vitamin D supplement in preadolescent girls

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Abstract

Background: Maximal bone acquisition in adolescent girls through dietary and lifestyle practices is advocated to prevent or minimize the development of osteoporosis and its associated complications in later life. Longitudinal investigations of bone acquisition in children and adolescents have utilized areal bone mineral density (BMD, mg/cm^2) as a measure of bone mass and strength. Peripheral quantitative computed tomography (pQCT), which provides a three-dimensional display of data, separate analyses of bone compartments, and bone mass in terms of volumetric BMD (vBMD, mg/cm^3), has recently been introduced for clinical use. Objective: To assess the impact of a 12-month daily calcium supplement on total and trabecular bone acquisition as measured by pQCT in preadolescent girls. Design: Early adolescent Caucasian girls (aged 12 years, Tanner Stage 2) were enrolled in a randomized trial of daily calcium supplement (TX, 800 mg calcium carbonate and 400 IU vitamin D) or placebo (C). Body weight, height, and distal tibia measurements by pQCT were obtained at enrollment, 6 and 12 months. Pubertal status and physical activity records were assessed at baseline and 12 months. Three-day food intake records were completed every three months. Results: Seventy-one girls completed the 12-month trial (TX=35, C=36). No differences were found for age, weight, height, body mass index, pubertal maturation, or reported physical activity at enrollment or during the study. Average intakes during the study were 1524 mg calcium and 496 IU vitamin D (TX) versus 865 mg calcium and 160 IU vitamin D (C) per day. Baseline total bone values were similar, however, trabecular values were greater in TX girls despite randomization. Percent changes were calculated to adjust for baseline differences. Because of the small cortical thickness at the 10% site (mean values < 1.6 mm), cortical mass and density were not analyzed. The percent changes for trabecular bone mineral content (BMC, mg) and vBMD were significantly greater in TX girls (+4.1% BMC and +1.0% vBMD TX versus –1.6% BMC and –2.0% vBMD C, $p<0.006$; ANCOVA) after 12 months of supplement. Trabecular bone area (BA, cm^2) and total bone change, however, did not differ between groups. Conclusions: Daily calcium and vitamin D supplementation promotes greater trabecular BMC and vBMD acquisition in preadolescent girls. The single site selected for pQCT evaluation in this study did not allow evaluation of the cortical bone compartment. Future studies that utilize the pQCT technique need to incorporate multiple measurement sites to better assess total, cortical, and trabecular bone.

Keywords: Bone Mineralization, Calcium, Preadolescent Girls, Peripheral Quantitative Computed Tomography (pQCT)

Introduction

Osteoporosis is a skeletal disorder characterized by low bone mass and deterioration of the microarchitectural structure of bone tissue, which predisposes bone to fracture[1]. Primary prevention of osteoporosis consists of maximizing peak bone mass during childhood, adolescence and young adulthood, and minimizing bone loss later in life, especially after menopause for women[2].

A significant, positive effect of calcium intake on bone mineralization has been suggested by a number of cross-sectional[3,4] and prospective studies[5-12], however, other cross-sectional studies have not demonstrated the same effect[13,14]. The current recommended daily calcium intake for preadolescent and adolescent girls is 1200 mg/day[15]. Unfortunately, dietary calcium intake for adolescent girls begins to decline at the time when their requirements are the highest to maximize bone accretion. Data from the NHANES III survey estimate that dietary calcium intake is <65% of the RDI for females aged 12 to 15 years[16]. Strategies to increase dietary

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calcium intake in children and adolescents include education[17,18], increased milk and dairy product consumption[9,10,12], calcium fortification of non-dairy foods[11], and calcium supplementation[5-8].

In the past decade, considerable progress has been made in the development of methods for non-invasive bone mass measurement. The capability now exists to precisely evaluate the peripheral, axial, or total body bone status, which in turn determine bone strength and predict fracture risk. Traditionally, bone mass in terms of bone mineral density (BMD) has been assessed with single photon absorptiometry (SPA), dual photon absorptiometry (DPA), or dual energy X-ray absorptiometry (DEXA). These methods provide a measurement of "areal density" expressed as g/cm^2. Peripheral quantitative computed tomography (pQCT) has been recently introduced to clinical users and investigators. The pQCT provides a three-dimensional display of the data and an integrated measurement of combined cortical and trabecular bone, as well as a separate measurement for cortical and trabecular bone[19]. The pQCT analysis accounts for bone architecture and depth and provides a measurement of bone mass as volumetric BMD (vBMD, mg/cm^3).

The pQCT technique has not been used in previous studies to assess the effect of a calcium supplement on bone mass acquisition in pediatric populations. The purpose of this 12-month randomized trial was to assess the impact of a daily calcium and vitamin D supplement on total and trabecular bone mineral content (BMC; mg) and volumetric BMD measured by pQCT in preadolescent girls.

Subjects and methods

Study sample

One hundred healthy, preadolescent girls entering the 7th grade were recruited to participate in a 12-month double blind, placebo-controlled study. The Institutional Review Board for Human Subjects, University of Utah approved the protocol, and written informed consent was obtained from each girl and parent. Participants were selected based on the evaluation of a questionnaire-reported medical history, medication use, and menstrual history. The inclusion criteria included: generally healthy as determined by the medical history; absence of diseases or medications that might affect calcium metabolism or bone growth; no tobacco or alcohol consumption; and no known eating disorder.

Anthropometric measures and pubertal assessment

Body weight and height were measured on the day that bone scans were obtained. At baseline, 6 and 12 months, the girls, in light clothing without footwear, were weighed on a digital scale (kg), standing height (cm) was measured with a stadiometer, and body mass index (BMI, kg/cm^2) was calculated. A trained research nurse determined pubertal status by Tanner Stage[20] and presence of menarche at baseline and 12 months.

Calcium and vitamin D supplement

A two-group design was used with participants randomized at study enrollment. Girls randomized to treatment (TX) received 800 mg calcium carbonate and 400 IU vitamin D in four orange-flavored, chewable tablets (USANA, Inc., Salt Lake City, UT). Girls randomized to placebo (C) received tablets that were identical in color, texture, and taste. All girls were instructed to take two tablets at home with their morning and evening meals for a total of four tablets each day. A postcard with a reminder to take study tablets was mailed monthly to each participant. Tablet compliance was assessed by tablet count at 6 and 12 months.

Dietary intake estimation

A three-day food intake record of all foods and beverages consumed over two weekdays and one weekend day was collected at baseline, 3, 6, 9, and 12 months. All participants were provided with detailed instructions on how to complete the record and were given specially prepared sheets on portion sizes and how to record food intake. The computer program Food Processor (Version 7.3, ESHA Research, Salem, OR) was used to analyze the food records and calculate average daily energy and macro- and micro-nutrient intake. Percentage of recommended daily intake (RDA) was calculated according to current recommendations[15].

Physical activity assessment

A modified past year leisure-time activity questionnaire[21,22] was completed at baseline and 12 months. From a list of physical activities, girls indicated the frequency and duration of each activity in which they participated during the past year. Subjects also completed an open-ended question about participation in activities not included on the list. Activities such as cycling and swimming were considered non-weight bearing or not supported by body mass. Only weight-bearing physical activities (WPA) such as walking, running, and skiing were used in the analysis. Total leisure WPA was determined as the summed product of the frequency and duration of WPA. The hours per week of each WPA were multiplied by an estimated MET value and expressed as MET-hours per week to determine metabolic cost. A MET is a multiple of the resting metabolic rate and represents the milliliters of oxygen consumed per kilogram of body mass per minute (ml/kg/min)[21].

Bone mineral measurement

The non-dominant leg was measured by pQCT (XCT 2000, Norland Medical Systems, Inc., Fort Atkinson, WI) at baseline, 6 and 12 months for all participants. To obtain a cross-sectional measurement of the distal tibia metaphysis, which is composed predominantly of trabecular bone, the 10% distal site was selected. Tibia length (cm) was deter-

mined by external measurement of the extreme ends of the tibia using the distal end of the medial malleolus and the internal point of articulation with the knee as landmarks. The participant was then seated on the scanner chair with the extended non-dominant leg resting inside the concentric acrylic cylinder (diameter 14 cm) of the central gantry. A planar scout view over the joint line of interest was performed to determine the anatomic reference line. A tomographic scan was then performed at the 10% site from the distal end plate of the tibia using a constant voxel size of 0.6mm and a speed of 30mm/s, per the manufacturer's guidelines. To analyze trabecular bone, a contour mode with a threshold of 180 mg/cm^3 was used to separate soft tissue and bone. A constant default threshold of 711 mg/cm^3 was used to identify and remove cortical bone from analysis so that trabecular BMC, bone area (BA, mm^2), and vBMD could be calculated. The cortical bone was not analyzed as the cortical thickness at the 10% distal site was <2mm in our subjects, increasing the likelihood of partial volume effect (PVE). PVE is an incomplete filling of voxels at the bone edge leading to an underestimate of cortical vBMD[23]. Cross-sectional measurements were reviewed and those determined to be of poor quality due to artifact (presence of growth plate) or movement were excluded from the final analysis. The short-term coefficient of variation (CV) for repositioning in 15 adult subjects was 1.8% and 2.0% for total and trabecular vBMD, respectively.

Statistical analysis

The mean, standard deviation (SD), and range are given as descriptive statistics. Chi-square was used to assess differences in Tanner Stage and menarche status. Pearson's r correlation was used to determine the associations between each related variable. Analysis of covariance was used to assess longitudinal changes with weight, height, BMI, menarche status, and WPA as cofactors. Initial enrollment of 100 (50 per group) allowed for an anticipated 20% drop out for a sample size of 80 (40 per group) with 80% power based on a 2% difference in BMD[5-8,10-12]. As only 71 girls had pQCT measurements of good quality, post-hoc tests were performed to assure statistical power was maintained. A p-value of less than 0.05 was considered significant for all statistical tests. Data was analyzed using SPSS program version 10.2 (SPSS Inc., Chicago, IL).

Results

Eighty-one girls completed the 12-month study, however, only 71 girls were included in the analyses (TX=35; C=36). Ten girls had one or more pQCT measurements rated as poor quality and nineteen girls withdrew from the trial; twelve withdrew initially due to tablet taste, two moved out-of-state prior to the 6 months visit, and five did not return at 12 months. Subjects' characteristics at baseline and after the 12-month trial are found in Table 1. All girls were of European American descent. There were no differences between groups for age, weight, height, BMI, Tanner Stage, menarche status, or reported physical activity at baseline or at 12 months. Average tablet compliance of 72% was found in both groups and 80% of all girls consumed greater than 65% of assigned tablets. Dietary intake at enrollment, 3, 6, 9, and 12 months was similar for energy and macro- and micronutrients with average daily intake for energy, protein, calcium, magnesium, phosphorus, sodium, and vitamin D presented in Table l. By design, TX girls had greater total daily intakes of calcium and vitamin D ($p<0.001$). The average number of MET hours that the girls spent in physical activities did not differ between groups at baseline or completion.

Total and trabecular cross-sectional bone mass values are presented in Table 2. Baseline cross-section measurements of the distal tibia were similar for total bone; however, despite randomization, trabecular vBMD values were greater in TX girls. Values for trabecular BMC and vBMD were also greater in TX girls at 6 and 12 months of study ($p<0.05$). Tibia length, total bone, periosteal and endosteal circumferences, cortical thickness, and the calculated strength strain index (SSI) did not differ between groups. Tests of correlation between total and trabecular BMC, BA, and vBMD and baseline body weight, height, BMI were significant ($R=0.32$-0.77, $p<0.01$). WPA was also linked to trabecular BMC ($R= -0.35$; $p<0.05$) and BA ($R=0.53$; $p=0.001$), while menstrual status was associated with total BMC and vBMD ($R=0.51$ and 0.58; $p<0.001$). Weight, height, BMI, and WPA at baseline, 6 and 12 months were treated as cofactors for trabecular bone change and total bone change, was adjusted for weight, height, BMI, and menstrual status in the statistical analyses. Bone change, calculated as percent change to adjust for baseline differences, and the 95% confidence intervals for the trabecular bone compartment are provided in Table 3. Percent change from baseline to 12 months was significantly greater for trabecular BMC and vBMD for TX girls ($p <0.03$). Post-hoc tests supported sufficient effect size for trabecular bone changes between treatment groups, despite a 12% decrease in sample size due to poor pQCT measurement quality, to maintain a power of 0.80.

Linear regression attributed the variability in trabecular vBMD from baseline to 6 months to TX (10.5%), WPA (6.1%), and BMI change (6.8%); the variability in trabecular BA was accounted for by linear growth (32.8%). From 6 to 12 months WPA accounted for 12.7% of the variability in trabecular vBMD change and the onset of menses accounted for 12.7% and 19.1% of the variability in trabecular BMC and BA, respectively. The variability in trabecular change from 0 to 12 months of study was attributed to TX (10.4%), WPA (7.6%), and BMI change (6.0%) for vBMD; onset of menses (21.6%), linear growth (6.3%), and TX (5.2%) for BMC; and onset of menses (53.2%) and linear growth (23.7%) for BA.

Tibia length, total BMC, BA and vBMD, periosteal and endosteal circumferences, cortical thickness, and SSI per-

	Treatment n=35	Control n=36
Age (y)	11.9 (0.9)	11.7 (0.8)
Weight (kg)		
Baseline	44.5 (12.8)	41.5 (8.7)
12 Months	49.8 (11.4)	46.6 (8.9)
Height (cm)		
Baseline	153.7 (9.1)	153.7 (9.1)
12 Months	157.8 (7.7)	157.0 (7.6)
BMI (kg/cm2)		
Baseline	18.6 (3.8)	17.5 (2.6)
12 Months	19.9 (4.3)	18.8 (2.5)
Tanner Stage (I-V)		
Baseline	2.0 (0.7)	2.1 (0.7)
12 Months	2.7 (0.5)	2.7 (0.5)
Post-Menarche (%Yes)		
Baseline	19%	28%
12 Months	59%	59%
Physical Activity (MET hr/wk)		
Baseline	27.8 (68.0)	32.9 (24.8)
12 Months	31.5 (39.5)	27.8 (37.7)
3-Day Food Intake (per day)		
Energy (kcal)	1807 (466)	1875 (479)
Protein (g)	64 (16)	63 (18)
Calcium (mg)	1524 (353)*	906 (345)
Magnesium (mg)	210 (57)	199 (75)
Phosphorus (mg)	1001 (358)	990 (355)
Sodium (mg)	2783 (934)	2623 (1097)
Vitamin D (IU)	496 (104)*	160 (92)
Mean (SD); *p<0.001		

Table 1. Age, weight, height, BMI, menarche status, activity, and dietary intake of treatment and control groups at baseline and after 12 months of study.

cent gains did not differ between groups from baseline to study completion. Linear regression found that the variability in change from baseline to 12 months for total BA and vBMD and periosteal and endosteal circumferences were attributed to linear growth (13.9-33.1%), onset of menses (3.9-9.6%) and WPA (3.4%). Weight gain accounted for 10.9% of variability observed for total BMC change. The onset of menses contributed 9.2% of the variability found in tibia length change.

Discussion

To our knowledge, this is the first randomized supplement trial in preadolescent girls using the pQCT technique to evaluate bone response. The treatment group in the present trial received 610 mg calcium and 297 IU vitamin D per day from the supplement. The TX girls were found to have greater net percent change in trabecular BMC (+5.7%) and vBMD (+3.0%) relative to the control subjects at the completion of the trial.

Our results suggest that supplementation had the strongest impact on trabecular BMC and vBMD during the first 6 months of study. This finding has also been observed in clinical trials of children, mature adults, and the elderly in which higher calcium intakes cause a remodeling transient, defined as a decrease in bone resorption in the presence of continued or increased bone formation or modeling[24]. Pubertal stage, menarche status, and daily physical activity levels did not differ between the two groups and should not be confounding factors in explaining the variation in bone acquisition between the TX and C groups. Overall, net change in trabecular BMC and vBMD were significantly greater for TX girls for the 12-month study.

	Treatment n=35	Control n=36
Tibia Length (cm)		
Baseline	34.4 (2.3)	33.2 (2.4)
6 Months	35.6 (2.2)	35.5 (2.2)
12 Months	35.6 (2.3)	35.2 (2.2)
Total BMC (mg/mm)		
Baseline	186.7 (32.3)	174.7 (32.2)
6 Months	194.7 (33.5)	181.2 (33.3)
12 Months	205.7 (37.7)	192.8 (33.6)
Total BA (mm^2)		
Baseline	539.8 (95.3)	525.5 (96.4)
6 Months	541.6 (92.0)	524.0 (93.7)
12 Months	567.5 (99.8)	544.9 (99.9)
Total vBMD (mg/cm^3)		
Baseline	349 9 (55.5)	334.4 (40.3)
6 Months	363.9 (62.1)	348.2 (46.5)
12 Months	367.4 (67.6)	357.0 (48.0)
Trabecular BMC (g)		
Baseline	105.2 (26.6)	96.3 (20.9)
6 Months	102.8 (24.1)*	91.0 (21.3)
12 Months	109.2 (27.1)*	95.0 (25.4)
Trabecular BA (cm^2)		
Baseline	418.9 (97.6)	407.9 (88.9)
6 Months	420.2 (94.8)	409.9 (88.6)
12 Months	431.4 (100.9)	416.1 (99.1)
Trabecular vBMD (mg/cm^3)		
Baseline	251.7 (28.9)*	236.6 (19.9)
6 Months	251.3 (28.0)**	229.6 (22.0)
12 Months	254.0 (29.7)*	231.9 (23.1)
Periosteal Circumference (mm)		
Baseline	80.0 (7.8)	77.8 (6.9)
6 Months	80.2 (7.6)	78.1 (6.9)
12 Months	82.0 (7.8)	79.4 (7.3)
Endosteal Circumference (mm)		
Baseline	67.0 (7.9)	65.2 (7.0)
6 Months	67.2 (7.7)	65.5 (6.8)
12 Months	69.1 (7.9)	66.6 (7.3)
Cortical Thickness (mm)		
Baseline	1.3 (0.7)	1.4 (0.7)
6 Months	1.6 (0.6)	1.5 (0.8)
12 Months	1.6 (0.7)	1.6 (0.7)
Polar SSI (mm^2)		
Baseline	518.7 (231.9)	490.0 (204.4)
6 Months	598.9 (251.0)	586.4 (222.0)
12 Months	643.3 (285.5)	637.4 (240.2)

Mean (SD); *$p<0.05$; **$p=0.001$

Table 2. Total and trabecular bone measurements of treatment and control groups at baseline, 6 and 12 months of study.

	TX	C	p	95% Confidence Intervals
Baseline-6Mo				
BMC	-1.8%	-5.4%	0.007	-3,8, -1.1 TX; -8.2,-3.3 C
BA	0.3%	0.4%	NS	-0.3, 0.5 TX; -0.5, 0.8 C
VBMD	-0.04%	-3.0%	0.03	-1.2, 1.5 TX; -4.5,-1.8 C
6Mo-12Mo				
BMC	6.0%	4.0%	NS	3.1, 8.7 TX; 1.2, 6.8 C
BA	2.7%	1.5%	NS	1.0, 3.8 TX; 0.5, 2.6 C
VBMD	1.1%	1.0%	NS	-0.4, 2.3 TX; -0.2, 2.5 C
Baseline-12Mo				
BMC	4.1%	-1.6%	0.001	0.9, 8.0 TX; -5.5, 1.6 C
BA	3.1%	2.0%	NS	0.8, 5.9 TX; -0.7, 3.4 C
VBMD	1.0%	-2.0%	0.006	-0.5, 2.5 TX; -3.5,-0.5 C
(MANOVA)				

Table 3. Percent change in trabecular BMC, BA, and vBMD from baseline to 6 months, 6 months to 12 months, and baseline to 12 months.

Tablet compliance was similar to compliance reported by other trials in which study participants took tablets at home[6,7]. Average daily intake of calcium and vitamin D in supplemented girls was 113% and 120%, respectively, of the current recommended daily intake, while the control groups met 70% and 45% of the RDI for calcium and vitamin D, respectively. Although the C group's vitamin D intakes did not exceed the current RDI, 15% reported a dietary calcium intake >1200 mg/day.

Percent BMC change in the present study supports the results of previous calcium supplement trials in children and adolescents[6-8]. Lloyd et al.[7] conducted an 18-month randomized, controlled trial of calcium supplementation in 94 twelve-year-old peripubertal girls. The average dietary intake for all subjects was 960 mg/d and supplemented girls received an additional 354 mg/d as calcium citrate malate. Incremental change in lumbar spine BMC and areal BMD as measured by DEXA in the study group were 4.7% and 2.9%, respectively, significantly greater than those of the control group after supplementation. In another controlled trial, by Johnston et al.[6], 45 monozygotic twin pairs, age 6-14 years, were randomized to receive calcium supplement (1000 mg/d calcium citrate malate) or placebo for 3 years. The supplemented group had an average daily intake of 1612 mg Ca vs. 908 mg Ca in the placebo group. In prepubertal children, supplementation plus diet enhanced the rate of increase in lumbar spine BMC (+4.8%) and BMD (+2.8%) at the end of the 3-year study. No benefit was found in the pairs who went through puberty or who were postpubertal during the study. By comparing the results of our study with these earlier studies for the first 12-month duration, the percent BMC change (+4.1%) was greater than that of 12-year-old adolescent girls (+3.1% lumbar spine, n=94) (7) or prepubertal twins (+1.6% lumbar spine, n=44)[6] (p<0.0l). Lee et al.[8] reported another randomized, controlled calcium supplement trial comprising 162 seven-year-old Chinese children with an initial daily intake of 280 mg calcium. Supplementation with 300 mg/d as calcium carbonate for 18 months resulted in distal radius BMC and BMD gains that were greater in the supplement group than the control group (+2.5% and 3.1%, respectively, p<0.02). The authors attributed the positive BMC and BMD response, despite a calcium intake lower than the current US RDI for children, to a documented greater efficiency in calcium absorption in children routinely exposed to low calcium intake[25]. Calcium absorption in Caucasian children in the United States has been found to be <40%[26,27]. Enhanced calcium absorption, however, has been found during early adolescence in US Caucasian and African American subjects[28-30]. Our present investigation and other published controlled trials[5-12] support the hypothesis that an increase in calcium intake in children and adolescents enhances bone acquisition.

Vitamin D intake from diet alone was 45% of the RDI in all subjects; the supplemented girls attained 120% of the RDI for vitamin D during the study. Participants in this study live in a high desert environment with year round sunlight exposure and maintain outdoor activities during the winter months. Vitamin D deficiency in healthy adolescents has not been reported in our region[31]. Biochemical levels of active vitamin D to assess seasonal variation would have added strength to this assumption. We were unable to detect, by correlation or linear regression, whether the positive effect on trabecular BMC and vBMD was due to greater calcium intake, enhanced calcium resorption due to vitamin D, or a direct effect of vitamin D alone.

Differences in percent BMC change from the present study to those reported by others[6-8] may be explained by the instrumentation used to assess bone mass, i.e., DPA, DEXA, and pQCT, and the sites selected for study. As both DPA and DEXA techniques are limited by the inherent planar

nature of the measurement so that a true geometric assessment of a bone is impossible[32,33], we chose to assess bone using the pQCT. While previous investigations using SPA, DPA, or DEXA have selected the ultra-distal radius or lumbar spine to evaluate trabecular bone, we selected the distal tibia for the larger trabecular surface area and the higher rate of bone turnover due to mechanical loading. The isolation of the trabecular bone eliminates the problem of partial volume effect associated with the cortical bone compartment in growing children. The different tempo of skeletal growth reported between axial and appendicular sites in girls may also have contributed to the differences in BMC change between the present study and others. Bass et al. have reported greater appendicular skeletal growth and mineralization before puberty with an acceleration in skeletal growth and mineralization of the lumbar spine in late puberty[34].

Previous to the present study, only cross-sectional data using pQCT or QCT of distal and mid-shaft radius, distal tibia, or the lumbar spine to determine relationships to age, gender, body size, and pubertal stage in children and adolescents have been reported[35-37]. We successfully conducted a longitudinal evaluation of calcium supplementation and vitamin D on bone acquisition at the distal tibia using pQCT.

In conclusion, after a 12-month controlled calcium and vitamin D supplementation trial in preadolescent girls, the treatment group had significant gains in trabecular BMC and vBMD when compared with the control subjects. Our findings are similar to results reported by others that used calcium alone as a treatment. The single site selected for pQCT evaluation in this study did not allow evaluation of the cortical bone compartment. Further studies that utilize the pQCT technique need to incorporate multiple sites for better assessment of total, cortical, and trabecular bone size, mass, and density.

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