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Sex differences in trabecular bone microarchitecture are not detected in pre and early pubertal children using magnetic resonance imaging

Christopher M. Modlesky^a, Deepti Bajaj^a, Joshua T. Kirby^a, Brianne M. Mulrooney^a, David A. Rowe^b, and Freeman Miller^c

^aDepartment of Kinesiology and Applied Physiology, University of Delaware, Newark, DE, USA 19716

^bSchool of Psychological Sciences and Health, University of Strathclyde, Glasgow, UK

^cDepartment of Orthopedics, Al duPont Hospital for Children, Wilmington, DE. USA

Abstract

Introduction—Sex differences in trabecular bone microarchitecture have been reported in adults and adolescents, but studies in children are lacking. The primary aim of this study was to determine if there are sex differences in magnetic resonance imaging (MRI)-based measures of trabecular bone microarchitecture at the distal femur of children.

Materials and methods—Pre and early pubertal boys ($n = 23$) and girls ($n = 20$) between the 5th and 95th percentiles for height, body mass and BMI were studied. Apparent trabecular bone volume to total volume (appBV/TV), trabecular number (appTb.N), trabecular thickness (appTb.Th), trabecular separation (appTb.Sp) and a composite measure of trabecular bone microarchitecture (TBMcom) were assessed at the lateral aspect of the distal femur using MRI. Areal bone mineral density (aBMD), bone mineral content (BMC) and bone area were assessed at the distal femur using dual-energy X-ray absorptiometry (DXA). Tanner staging was used to assess pubertal development. Physical activity was assessed using an accelerometry-based activity monitor. Calcium intake was assessed using diet records.

Results—There were no sex differences in age, height, femur length, body mass, physical activity or calcium intake (all $P > 0.05$). There were no sex differences in any MRI-based measure of trabecular bone microarchitecture. Consistent with the MRI-based measures, there were no differences in aBMD, BMC or bone area at the distal femur ($P > 0.05$). appBV/TV, appTb.N, appTb.Th, appTb.Sp and TBMcom were also moderately to strongly related to aBMD ($r = 0.73, 0.63, 0.51, -0.74$ and 0.61 , respectively, $p < 0.001$) and BMC ($r = 0.84, 0.63, 0.66, -0.80$ and 0.77 , respectively, $P < 0.001$).

Conclusions—The findings suggest that there are no differences in measures of trabecular bone microarchitecture at the distal femur of pre and early pubertal boys and girls who are similar in size, physical activity and calcium intake. Future studies with larger sample sizes that cover all

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Address of correspondence and reprint requests: Christopher M. Modlesky, PhD, Department of Kinesiology and Applied Physiology, University of Delaware, Newark, DE 19716, Telephone: (302) 831 4185, Fax: (302) 831 43693, modlesky@udel.edu.

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pubertal stages are needed to determine if sex differences in trabecular bone microarchitecture emerge at the distal femur and other weight bearing bone sites.

Keywords

magnetic resonance imaging; sex; bone microarchitecture; children; dual-energy X-ray absorptiometry

1.1 Introduction

It is well established that osteoporosis-related fractures are more prevalent in women than men [1]. This sex-related disparity in skeletal fragility is related to lower areal bone mineral density (aBMD) and bone mineral content (BMC) assessed by dual-energy X-ray absorptiometry (DXA), and less sound bone architecture [6]. The differences in bone mass and bone size emerge largely during puberty when there is a surge in growth factors and sex-specific hormones. Sex-specific differences in cortical bone architecture also emerge largely during puberty. While there is a greater rate of cortical thickening and periosteal expansion in pubertal boys [2], there is a greater consolidation of cortical bone in pubertal girls leading to an increase in cortical volumetric bone mineral density [3, 4].

Trabecular bone microarchitecture is a skeletal feature that is strongly related to bone strength. Although there is evidence of lower apparent trabecular bone volume to total volume (appBV/TV) and apparent trabecular thickness (appTb.Th) in younger [5] and older women [6] than in younger and older men, the presence of sex differences in trabecular bone microarchitecture is poorly studied in children. If sex differences in trabecular bone microarchitecture do not emerge until adolescence, it would suggest that the time between childhood and adolescence may be the most opportune time to stimulate increased development of trabecular bone. Until recently, studies of trabecular bone microarchitecture were lacking due to the inability to discern the small architectural features of trabecular bone. Fortunately, advances in computed tomography and magnetic resonance imaging (MRI) now make it feasible for *in vivo* assessment of trabecular bone microarchitecture in humans [5, 7, 8]. Magnetic resonance imaging is particularly attractive for studies of children because it does not expose them to ionizing radiation. The primary aim of this study was to determine if there are sex differences in measures of trabecular bone microarchitecture in the distal femur of children. Although there is concern about the use of DXA alone in the assessment of osteoporosis in growing bone, it is the most widely used method for assessing bone in children [9]. Furthermore, there is evidence that aBMD from DXA can predict fractures in children [10, 11]. A secondary aim was to determine if MRI-based measures of trabecular bone microarchitecture are related to DXA-based measures of aBMD and BMC in children.

1.2 Materials and methods

1.2.1 Protocol

Children 6 to 12 years of age, between the 5th and 95th age-based percentiles for height and weight, not taking medications known to affect bone and without a prior fracture in the region of interest (i.e. distal femur) were recruited from the Newark, DE community and the AI duPont Hospital for Children in Wilmington, DE to participate in the study. To minimize the potential for outliers in physical activity, children participating in more than 3 hours of organized physical activity per week were excluded from the study. The Institutional Review Boards at the University of Delaware and the AI duPont Hospital for Children approved the study. Written consent was given by parents and written assent was given by children before any testing was initiated. Children completed two different test sessions on

separate days within two weeks apart during the Spring season. During the first session, anthropometrics were assessed and dual-energy X-ray absorptiometry scans of the total body and the nondominant distal femur were collected. During the second test session, magnetic resonance images of the nondominant distal femur were collected.

1.2.2 Anthropometrics

Anthropometrics were assessed without shoes and with minimal clothing. Height was measured to the nearest 0.1 cm using a stadiometer. Body mass was assessed using a digital scale to the nearest 0.2 kg. Height, body mass and BMI percentiles were determined using normative graphs published by the Center for Disease Control [12].

1.2.3 Tanner Staging

A physician assistant used the Tanner staging technique to assess sexual maturity [13]. Signs of pubic hair growth and testicular/penis development were assessed in boys and signs of pubic hair and breast development were assessed in girls. The rating system ranges from 1 to 5, with 1 indicating no signs of sexual development, 2 indicating early sexual development, and 5 indicating full development.

1.2.4 Magnetic Resonance Imaging

The procedure for assessing trabecular bone microarchitecture in the distal femur in children is a modification of a procedure developed for adults [14] and has been described previously [15]. Magnetic resonance images of the nondominant distal femur were collected with a GE 1.5 T MRI (Milwaukee, WI). Prior to imaging, one of two connected phased array coils (USA Instruments; Aurora, OH) was secured to the lateral portion of the nondominant distal femur using a VacFIX system (PAR Scientific A/S; Sivlandvaenge, Denmark). Similar to a procedure described by Krug et al. [16] for the proximal femur, we used only one coil and focused on the lateral aspect of the bone to reduce scan time and to reduce noise created by the opposing coil. To limit motion during the MRI scan, children were immobilized from the waist down using the BodyFIX (Medical Intelligence, Inc., Schwabmünchen, GER), as previously described [15]. After participants were immobilized, the distal femur was identified using a three-plane localizer. Then 26 high resolution axial images were collected in the metaphysis immediately above the growth plate using a 3D fast gradient echo sequence with a partial echo acquisition (echo time = 4.5 ms; repetition time = 30 ms; 30° flip angle; 13.89 kHz bandwidth), a 9 cm field of view and an imaging matrix of 512×384 , corresponding to a reconstructed voxel size of $175 \times 175 \times 700 \mu\text{m}^3$. Image collection lasted approximately 7 minutes.

Measures of trabecular bone microarchitecture were estimated in the lateral half of the 20 most central images of the distal femur using custom software created with Interactive Data Language (IDL; Research Systems, Inc, Boulder, CO). The analysis focused on the lateral half of the bone because of its greater signal to noise ratio than on the medial half which resulted from the coil placement on the lateral aspect of the bone. The analysis also focused on the 20 most central images because the radio frequency excitations of the first three and last three images were different from the more central images. The analysis software was patterned after the procedure described by Majumdar et al. [7] and has been used previously [15]. A visual depiction of the collection and analysis procedures is described in Figure 1. The reproducibility of the trabecular bone microarchitecture assessment in children using this procedure ranges from 2-3 % [15].

1.2.5 Dual-energy X-ray Absorptiometry

Dual-energy X-ray absorptiometry (Delphi W; Hologic, Inc, Bedford, MA) was used to determine aBMD, BMC and bone area in the nondominant distal femur. The 240 mm region beginning at the most distal end of the femur and continuing to the shaft was scanned at a high resolution using the forearm protocol and while the participant was their nondominant side, as previously described [17]. A subregion that began 2 mm above the growth plate and matched the distal end of the femur analyzed for trabecular bone microarchitecture using MRI was identified and analyzed using the DXA Global Region of Interest Analysis software. Quality control was checked daily by scanning a lumbar spine phantom consisting of calcium hydroxyapatite embedded in a cube of thermoplastic resin (model DPA/QDR-1; Hologic x-caliber anthropometric spine phantom). Scans were performed by one trained X-ray technician and analyzed by one investigator. The reproducibility of aBMD, BMC and bone area at the distal femur was determined in children with cerebral palsy (n = 8) with coefficients of variation equal to 3.6, 4.0 and 1.9 %, respectively, and intraclass correlation coefficients > 0.98 [15].

1.2.6 Physical Activity

To assess physical activity, an accelerometer-based activity monitor (Actical; MiniMitter Co., Sunriver, OR) was worn continuously around the waist on the nondominant side for four days (1 weekend day and 3 week days). Sedentary, light, moderate and vigorous physical activity was quantified based on activity counts registered every 15 seconds (sedentary < 0.01, light = 0.01 to 0.04, moderate = 0.04 to 0.10 and vigorous > 0.10 kcal/min/kg) [18]. The number of counts in each activity category (counts/d) and the time spent in each category (min/d) are reported. The Actical activity monitor has been validated using a broad range of gross and fine motor physical activities [18]. Four days of data collection was chosen because it is tolerable and has been shown to have good reliability and validity [19].

1.2.7 Diet

The procedure for collecting the dietary information was explained to each child participant and a parent by a research assistant. The parents, with the aid of child, recorded the child's dietary intake for two weekdays and one weekend day. To facilitate accurate quantification of foods, each participant and their parent received a list of serving size estimates based on comparisons to everyday objects (e.g. 3 oz of meat or poultry is approximately the size of a deck of cards)[20]. Parents were contacted to clarify any uncertain foods or quantities. Calcium intake was estimated from the diet records using the USDA Food and Nutrient Database for Dietary Studies, 1.0 [21]. All diet records were analyzed by a single research assistant.

1.2.8 Statistical analysis

Data were analyzed using SPSS (Version 17.0, Chicago, IL). Z-scores for each trabecular bone microarchitecture parameter were calculated and the average was used to represent a composite measure of trabecular bone microarchitecture (TBMcom). Descriptive statistics for all variables were conducted to screen for outliers and to assess normality. Sex differences were assessed using independent t-tests. To statistically control for variation in femur length, sex differences in MRI-based and DXA-based bone measures were also tested using analysis of covariance with femur length as a covariate. Height, body mass and BMI percentiles were compared to their respective 50th age-based percentile for each sex using a one-sample t-test. Pearson correlation analysis was used to assess the relationship between DXA-derived measures of aBMD and BMC and MRI-derived measures of trabecular bone

microarchitecture. Alpha level was set at 0.05. Cohen's d (d) is reported to indicate small ($d = 0.2$), medium ($d = 0.5$) and large ($d > 0.8$) effect sizes for sex comparisons [22].

1.3 Results

Fifty children (25 boys and 25 girls) enrolled in the study. All subjects were Caucasian except for one girl who was Asian. One boy withdrew from the study before testing was completed due to illness. One boy was excluded because he did not complete DXA testing. One girl was excluded because she could not complete MRI testing. Four girls were excluded because they had Tanner stages > 2 . Of the 23 boys and 20 girls included in the final analysis, most children were Tanner stage 1 for pubic hair ($n = 22$ boys and $n = 16$ girls), penis/testicular development ($n = 22$ boys) and breast development ($n = 15$ girls). Three boys did not complete diet records; however, they were included in the final analysis.

Physical characteristics are reported in Table 1. There were no sex differences in age, pubic hair Tanner stage, breast/testicular Tanner stage, height, femur length, body mass and BMI. Additionally, height, body mass, and BMI percentiles were not different from the 50th age-based percentiles in either sex. Because total, sedentary and vigorous physical activity counts were not normally distributed, they were log transformed. There were no sex differences in any measures of physical activity or calcium intake.

No statistically significant sex differences were detected for appBV/TV ($d = 0.038$, $P = 0.843$), appTb.N ($d = 0.298$, $P = 0.354$), appTb.Th ($d = 0.083$, $P = 0.723$) or appTb.Sp ($d = 0.203$, $P = 0.551$) in the distal femur, as shown in Figure 2. There were no sex differences in TBMcom ($d = 0.235$, $P = 0.462$), aBMD ($d = 0.022$, $P = 0.944$), BMC ($d = 0.127$, $P = 0.690$) or bone area ($d = 0.279$, $P = 0.382$) in the distal femur, as shown in Figure 3. The lack of sex differences in MRI-based and DXA-based bone measures remained when the sex comparisons were covaried for femur length.

Relationships between MRI-derived measures of trabecular bone microarchitecture and DXA-derived measures of aBMD and BMC are presented in Table 2. All relationships were moderate to strong. A scatter plot of appBV/TV vs. aBMD is presented in Figure 4.

1.4 Discussion

The main finding in the present study was that sex differences in measures of trabecular bone microarchitecture were not detected in the distal femur of pre and early pubertal children using magnetic resonance imaging. To our knowledge, this is the first study to assess whether there are sex differences in trabecular bone microarchitecture in the femur of children. The finding is supported by Kirmani et al. [5] who studied the pattern of trabecular bone microarchitecture in the distal radius of 6 to 21 year-old males ($n = 61$) and females ($n = 66$) using high resolution peripheral quantitative computed tomography. No sex differences were observed in any measure of trabecular bone microarchitecture in pre and early pubertal children. However, appBV/TV and appTb.Th were higher and appTb.Sp was lower in males and females at late and post puberty. Therefore, it is plausible that sex differences in trabecular bone microarchitecture will emerge in the distal femur as the children mature. This notion is consistent with the observation that trabecular bone microarchitecture is more developed in the distal tibia, another weight bearing bone, of adolescent boys than adolescent girls [23]. It is also possible that sex differences emerge during puberty but then realign after puberty. Gilsanz et al. [24] reported no sex difference in trabecular volumetric BMD in the spine between 5-9 years of age, followed by an increase in both sexes. Although the increase occurred earlier in girls (10 y) than boys (12 y), there was no difference between sexes by 17 years of age. Larger cross-sectional studies that include children from prepuberty through early adulthood or longitudinal studies that

follow children through puberty and into adulthood are needed to determine if sex differences in trabecular bone microarchitecture emerge and when they emerge in the distal femur.

If changes in trabecular bone microarchitecture emerge in the distal femur of boys during the later stages of puberty, these changes may be driven by surges in testosterone and IGF-1 levels. In the study of trabecular bone microarchitecture in the distal radius of 6 – 21 year-old males and females by Kirmani et al. [5], BV/TV and Tb.Th were positively associated with serum testosterone, Tb.N was positively associated with serum IGF-1 and Tb.Sp was negatively associated with serum IGF-1 [5] in males. On the other hand, no relationships were observed in females (n = 66). Longitudinal studies that simultaneously track changes in testosterone, IGF-1, other hormones and growth factors and trabecular bone microarchitecture through puberty are needed to determine the factors that underlie bone development in children and adolescents.

Another factor that may contribute to sex differences in trabecular bone microarchitecture is physical activity. There is evidence that high-impact, or vigorous, physical activity during childhood and adolescence fosters greater accretion of bone mineral [25-28]. There is also evidence that boys have greater participation in vigorous physical activity than girls, even during the prepubertal years [29]. Furthermore, vigorous physical activity is positively associated with BMC, cross-sectional area of bone and section modulus in prepubertal children [29, 30] and higher appBV/TV and appTb.N and lower appTb.Sp have been reported in elite athletes [31, 32]. Moreover, extremely low levels of physical activity are associated with deteriorated trabecular bone microarchitecture in adults [33, 34] and underdeveloped trabecular bone microarchitecture in children [15]. In the present study, there were no sex differences in the number of total, sedentary, moderate or vigorous physical activity counts and the amount of time spent in each activity category. The lack of difference in physical activity may be due to the exclusion of children who participated in more than 3 hours of organized physical activity each week, which minimized the potential effect of physical activity on bone. Therefore, it is possible that trabecular bone microarchitecture is more robust in boys than girls in the general population; however, additional studies are needed to determine the potential influence of physical activity on trabecular bone microarchitecture in children.

Another interesting observation in the present study was the moderate-to-strong relationships between the MRI-based measures of trabecular bone microarchitecture and DXA-based measures of aBMD and BMC. Previous studies have reported relationships that ranged from weak to strong ($r = 0.12$ to 0.82) in adults [34-36]. The relationship between the MRI- and DXA-based measurements that are most similar, appBV/TV and aBMD, respectively, was moderately strong in the present study. The strength of the relationship is notable considering their differences. appBV/TV is the bone fraction in trabecular bone calculated from a three dimensional information, whereas aBMD includes trabecular and cortical bone and is calculated from two dimensional information (i.e., bone area rather than bone volume). Although there is concern about the use of DXA-based measures alone in the assessment of growing bone [9], DXA is the most widely used method to assess skeletal health in children. Furthermore, aBMD has been shown to predict fracture in children [10, 11]. Therefore, the moderate-to-strong relationship between the MRI-based measures and the DXA-based measures provides some validation for the assessment of trabecular bone in children using MRI.

Strengths of the present study should be highlighted. First, the potential confounding of race was controlled by including primarily Caucasian children. Although one Asian girl was included in the study, her measures of trabecular bone microarchitecture, physical activity

and calcium intake were within the range of the sample. Furthermore, the same results were observed when she was removed from the statistical analysis. Second, height, body mass and BMI were not different between groups and they were not different from their age-based 50th percentile suggesting that the sample was representative of the general population of Caucasian children. Third, the effect of physical activity and calcium intake were controlled as sex differences were not detected. Fourth, the potential effect of sexual maturity was minimized by only including children with a Tanner stage of 1 or 2 in the final analyses. Fifth, physical activity was assessed using an objective method (i.e. activity monitors) and during the same period of the year (i.e. Spring) for all subjects. This is important because physical activity is influenced by season [21, 37]. Sixth, a composite measure of trabecular bone microarchitecture was calculated and its relationship to factors that are typically associated with bone mass was determined. In theory, the composite measure should better reflect trabecular bone microarchitecture for each group. Lastly, trabecular bone microarchitecture was assessed using an *in vivo* method. Few studies have evaluated trabecular bone microarchitecture *in vivo* in children [5, 15, 38]. In addition, to our knowledge, only one other study has evaluated trabecular bone microarchitecture in children using MRI [15].

One limitation of the study is that the resolution of the magnetic resonance images used to assess trabecular bone microarchitecture can result in partial volume effects. Glorieux et al. reported that the trabeculae in the iliac crest range in thickness from 96 to 193 micrometers in 7 to 13.9 year-old children, which is smaller than the resolution of our imaging protocol. However, the effect is minimized by having the lower resolution of the slice (700 μm^3 in this study) along the primary direction of the trabecular structures [39]. In addition, to distinguish the MRI estimates of trabecular bone microarchitecture from the actual measurements, the MRI estimates are referred to as 'apparent' [40]. A second limitation of the study is that the general procedure for assessing trabecular bone microarchitecture from MRI was developed using adults [7]. Although it is possible that the procedure is less accurate for children, it was modified to account for the smaller bones of children [15]. Furthermore, the same procedure was used on all children; visual inspection of the raw and binarized images suggests the bone and marrow phases were appropriately separated; and all measures of trabecular bone microarchitecture were moderately-to-strongly related to aBMD and BMC from DXA (Table 2). Moreover, the same procedure has been shown to detect the expected underdevelopment of trabecular bone microarchitecture in nonambulatory children with cerebral palsy [15]. In addition, the lack of a sex difference in measures of trabecular bone microarchitecture in the distal femur is consistent with the observation that sex differences in distal radius trabecular bone microarchitecture are not present until Tanner stages 4 and 5 [5]. Another limitation of the study is the inability of the activity monitors to discriminate between high-impact and low-impact activity. Although activity monitor data can be separated into sedentary, light, moderate and vigorous intensities, these categories do not necessarily reflect differences in impact levels. Janz et al. [41] found that accelerometry-based activity counts and ground reaction forces adjusted for body weight were moderately-to-strongly related during walking and running (r range = 0.38 to 0.59, $p < 0.05$) but poorly related during jumping ($r = -0.15$) in children. This is a notable flaw because jumping has been shown to stimulate bone accretion in children [25, 26]. Some may view the exclusion of children with more than three hours of organized physical activity per week as a limitation because the sample may not accurately represent the general population of children. However, this approach allowed us to examine the potential effect of sex on trabecular bone microarchitecture in children without the influence of a physical activity difference that has been reported in boys vs. girls [29].

In conclusion, the present study suggests that sex differences in trabecular bone microarchitecture are not present in the distal femur of pre and early pubertal children who

are similar in size and have a similar level of physical activity and calcium intake. MRI-based measures of trabecular bone microarchitecture are moderately-to-strongly related to aBMD and BMC from DXA in the distal femur of children. Future studies with larger sample sizes that cover all pubertal stages are needed to determine if sex differences in trabecular bone microarchitecture emerge at the distal femur and other weight bearing bone sites.

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References

1. Foundation NO. America's Bone Health: The State of Osteoporosis and Low Bone Mass in Our Nation. 2003.
2. Hogler W, Blimkie CJ, Cowell CT, Inglis D, Rauch F, Kemp AF, Wiebe P, Duncan CS, Farpour-Lambert N, Woodhead HJ. Sex-specific developmental changes in muscle size and bone geometry at the femoral shaft. *Bone*. 2008; 42:982–9. [PubMed: 18337201]
3. Schoenau E, Neu CM, Rauch F, Manz F. Gender-specific pubertal changes in volumetric cortical bone mineral density at the proximal radius. *Bone*. 2002; 31:110–3. [PubMed: 12110422]
4. Leonard MB, Elmi A, Mostoufi-Moab S, Shults J, Burnham JM, Thayu M, Kibe L, Wetzsteon RJ, Zemel BS. Effects of sex, race, and puberty on cortical bone and the functional muscle bone unit in children, adolescents, and young adults. *J Clin Endocrinol Metab*. 2010; 95:1681–9. [PubMed: 20157194]
5. Kirmani S, Christen D, van Lenthe GH, Fischer PR, Bouxsein ML, McCready LK, Melton LJ 3rd, Riggs BL, Amin S, Muller R, Khosla S. Bone structure at the distal radius during adolescent growth. *J Bone Miner Res*. 2009; 24:1033–42. [PubMed: 19113916]
6. Hudelmaier M, Kollstedt A, Lochmuller EM, Kuhn V, Eckstein F, Link TM. Gender differences in trabecular bone architecture of the distal radius assessed with magnetic resonance imaging and implications for mechanical competence. *Osteoporosis International*. 2005; 16:1124–1133. [PubMed: 15744451]
7. Majumdar S, Genant HK, Grampp S, Newitt DC, Truong VH, Lin JC, Mathur A. Correlation of trabecular bone structure with age, bone mineral density, and osteoporotic status: in vivo studies in the distal radius using high resolution magnetic resonance imaging. *J Bone Miner Res*. 1997; 12:111–8. [PubMed: 9240733]
8. Wehrli FW, Hwang SN, Ma J, Song HK, Ford JC, Haddad JG. Cancellous bone volume and structure in the forearm: noninvasive assessment with MR microimaging and image processing. *Radiology*. 1998; 206:347–57. [PubMed: 9457185]
9. Bianchi ML, Baim S, Bishop NJ, Gordon CM, Hans DB, Langman CB, Leonard MB, Kalkwarf HJ. Official positions of the International Society for Clinical Densitometry (ISCD) on DXA evaluation in children and adolescents. *Pediatr Nephrol*. 2010; 25:37–47. [PubMed: 19603190]
10. Goulding A, Jones IE, Taylor RW, Manning PJ, Williams SM. More broken bones: a 4-year double cohort study of young girls with and without distal forearm fractures. *J Bone Miner Res*. 2000; 15:2011–8. [PubMed: 11028455]
11. Henderson RC, Berglund LM, May R, Zemel BS, Grossberg RI, Johnson J, Plotkin H, Stevenson RD, Szalay E, Wong B, Kecskemethy HH, Harcke HT. The relationship between fractures and DXA measures of BMD in the distal femur of children and adolescents with cerebral palsy or muscular dystrophy. *J Bone Miner Res*. 2010; 25:520–6. [PubMed: 19821773]
12. Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, Flegal KM, Guo SS, Wei R, Mei Z, Curtin LR, Roche AF, Johnson CL. CDC growth charts: United States. *Adv Data*. 2000; 314:1–27. [PubMed: 11183293]
13. Tanner, J. Growth and Adolescence. 2nd. Oxford: Blackwell Scientific Publications; 1962.

14. Beuf O, Ghosh S, Newitt DC, Link TM, Steinbach L, Ries M, Lane N, Majumdar S. Magnetic resonance imaging of normal and osteoarthritic trabecular bone structure in the human knee. *Arthritis Rheum.* 2002; 46:385–93. [PubMed: 11840441]
15. Modlesky CM, Subramanian P, Miller F. Underdeveloped trabecular bone microarchitecture is detected in children with cerebral palsy using high-resolution magnetic resonance imaging. *Osteoporos Int.* 2008; 19:169–76. [PubMed: 17962918]
16. Krug R, Banerjee S, Han ET, Newitt DC, Link TM, Majumdar S. Feasibility of in vivo structural analysis of high-resolution magnetic resonance images of the proximal femur. *Osteoporos Int.* 2005; 16:1307–14. [PubMed: 15999292]
17. Harcke HT, Taylor A, Bachrach S, Miller F, Henderson RC. Lateral femoral scan: an alternative method for assessing bone mineral density in children with cerebral palsy. *Pediatr Radiol.* 1998; 28:241–6. [PubMed: 9545479]
18. Puyau MR, Adolph AL, Vohra FA, Zakeri I, Butte NF. Prediction of activity energy expenditure using accelerometers in children. *Med Sci Sports Exerc.* 2004; 36:1625–1631. [PubMed: 15354047]
19. Trost SG, Pate RR, Freedson PS, Sallis JF, Taylor WC. Using objective physical activity measures with youth: how many days of monitoring are needed? *Med Sci Sports Exerc.* 2000; 32:426–31. [PubMed: 10694127]
20. Just Enough for You. National Institutes of Health (NIH). Publication No. 03-5287; Updated August 2006.
21. Rowlands AV, Hughes DR. Variability of physical activity patterns by type of day and season in 8-10-year-old boys. *Res Q Exerc Sport.* 2006; 77:391–5. [PubMed: 17020083]
22. Cohen, J. *Statistical Power Analysis for the Behavioral Sciences*. 2nd. Hillsdale, NJ: Lawrence Erlbaum Associates; 1988.
23. Burrows M, Liu D, Moore S, McKay H. Bone microstructure at the distal tibia provides a strength advantage to males in late puberty: an HR-pQCT study. *J Bone Miner Res.* 2010; 25:1423–32. [PubMed: 19874197]
24. Gilsanz V, Perez FJ, Campbell PP, Dorey FJ, Lee DC, Wren TA. Quantitative CT reference values for vertebral trabecular bone density in children and young adults. *Radiology.* 2009; 250:222–7. [PubMed: 19001149]
25. Fuchs RK, Bauer JJ, Snow CM. Jumping improves hip and lumbar spine bone mass in prepubescent children: a randomized controlled trial. *J Bone Miner Res.* 2001; 16:148–56. [PubMed: 11149479]
26. Petit MA, McKay HA, MacKelvie KJ, Heinonen A, Khan KM, Beck TJ. A randomized school-based jumping intervention confers site and maturity-specific benefits on bone structural properties in girls: a hip structural analysis study. *J Bone Miner Res.* 2002; 17:363–72. [PubMed: 11874228]
27. Kannus P, Haapasalo H, Sankelo M, Sievanen H, Pasanen M, Heinonen A, Oja P, Vuori I. Effect of starting age of physical activity on bone mass in the dominant arm of tennis and squash players. *Ann Intern Med.* 1995; 123:27–31. [PubMed: 7762910]
28. Modlesky CM, Lewis RD. Does exercise during growth have a long-term effect on bone health? *Exerc Sport Sci Rev.* 2002; 30:171–6. [PubMed: 12398114]
29. Janz KF, Burns TL, Torner JC, Levy SM, Paulos R, Willing MC, Warren JJ. Physical activity and bone measures in young children: the iowa bone development study. *Pediatrics.* 2001; 107:1387–93. [PubMed: 11389262]
30. Janz KF, Burns TL, Levy SM, Torner JC, Willing MC, Beck TJ, Gilmore JM, Marshall TA. Everyday activity predicts bone geometry in children: the iowa bone development study. *Med Sci Sports Exerc.* 2004; 36:1124–31. [PubMed: 15235315]
31. Modlesky CM, Majumdar S, Dudley GA. Trabecular bone microarchitecture in female collegiate gymnasts. *Osteoporos Int.* 2008; 19:1011–8. [PubMed: 18074110]
32. Chang G, Pakin SK, Schweitzer ME, Saha PK, Regatte RR. Adaptations in trabecular bone microarchitecture in Olympic athletes determined by 7T MRI. *J Magn Reson Imaging.* 2008; 27:1089–95. [PubMed: 18425824]

33. Slade JM, Bickel CS, Modlesky CM, Majumdar S, Dudley GA. Trabecular bone is more deteriorated in spinal cord injured versus estrogen-free postmenopausal women. *Osteoporos Int.* 2005; 16:263–72. [PubMed: 15338112]
34. Modlesky CM, Majumdar S, Narasimhan A, Dudley GA. Trabecular bone microarchitecture is deteriorated in men with spinal cord injury. *J Bone Miner Res.* 2004; 19:48–55. [PubMed: 14753736]
35. Link TM, Majumdar S, Augat P, Lin JC, Newitt D, Lu Y, Lane NE, Genant HK. In vivo high resolution MRI of the calcaneus: differences in trabecular structure in osteoporosis patients. *J Bone Miner Res.* 1998; 13:1175–82. [PubMed: 9661082]
36. Link TM, Vieth V, Langenberg R, Meier N, Lotter A, Newitt D, Majumdar S. Structure analysis of high resolution magnetic resonance imaging of the proximal femur: in vitro correlation with biomechanical strength and BMD. *Calcif Tissue Int.* 2003; 72:156–65. [PubMed: 12370799]
37. Fields DA, Goran MI, McCrory MA. Body-composition assessment via air-displacement plethysmography in adults and children: a review. *Am J Clin Nutr.* 2002; 75:453–67. [PubMed: 11864850]
38. Liu D, Burrows M, Egeli D, McKay H. Site Specificity of Bone Architecture Between the Distal Radius and Distal Tibia in Children and Adolescents: An HR-pQCT Study. *Calcif Tissue Int.* 2010
39. Kothari M, Keaveny TM, Lin JC, Newitt DC, Genant HK, Majumdar S. Impact of spatial resolution on the prediction of trabecular architecture parameters. *Bone.* 1998; 22:437–43. [PubMed: 9600776]
40. Kazakia GJ, Majumdar S. New imaging technologies in the diagnosis of osteoporosis. *Rev Endocr Metab Disord.* 2006; 7:67–74. [PubMed: 17043763]
41. Janz KF, Rao S, Bauman HJ, Schultz JL. Measuring children's vertical ground reaction forces with accelerometer during walking, running, and jumping: the iowa bone development study. *Pediatr Exerc Sci.* 2003; 15:34–43.

Abbreviations

appBV/TV	apparent bone volume to total volume
appTb.N	apparent trabecular number
appTb.Th	apparent trabecular thickness
appTb.Sp	apparent trabecular separation
TBMcomp	composite measure of trabecular bone microarchitecture

Highlights

- We assessed sex differences in MRI-based measures of trabecular bone microarchitecture at the distal femur of children.
- There were no sex differences in any measure of trabecular bone microarchitecture of pre and early pubertal children.
- Measures of trabecular bone microarchitecture from MRI were moderately-to-strongly related to areal bone mineral density and bone mineral content from DXA.

Figure 1.

A visual description of the procedure used to determine measures of apparent trabecular bone microarchitecture in the lateral aspect of the distal using magnetic resonance images is depicted. Twenty six images were collected immediately above the growth plate in the distal femur as demonstrated by a coronal image of the distal femur (A). The 20 most central raw images (B) were filtered using a low-pass filter-based correction algorithm and then reversed in gray scale to facilitate visualization (C). The lateral half of the bone was manually identified by first separating the medial and lateral aspects of the distal femur beginning at the trochlear groove (large arrow) and extending perpendicular to the posterior portion of the bone (medium arrow) and then separating the trabecular bone from the cortical shell (small arrows). Eight samples were taken from the cortical shell in each image (D). The three cortical bone samples with the highest signal intensity were then used to separate the region of interest into bone and marrow phases (binarized; E). Measures of trabecular bone microarchitecture were calculated for each of the twenty binarized images, as described by Majumdar et al. [7], and the averages are reported.

Figure 2. A comparison of trabecular bone microarchitecture measures from MRI in the distal femur of 6 to 12 year-old boys and girls. Values are means $\pm$ SD.

Figure 3.

A comparison of a composite measure of trabecular bone microarchitecture from MRI (TBMcom) presented as a Z-score and areal bone mineral density (aBMD), bone mineral content (BMC) and bone area from DXA in the distal femur of 6 to 12 year-old boys and girls. Values are means $\pm$ SD.

Figure 4. Scatter plot of aBMD from DXA vs. appBV/TV from MRI at the distal femur ($r^2 = 0.527$, $p < 0.001$). The solid line represents the regression line for the combined sample of boys and girls.

Table 1
Physical characteristics of 6 to 12 year-old boys and girls

	Boys (n = 23)	Girls (n = 20)	P	d
Age (y)	9.8 ± 1.7	10.1 ± 1.8	0.591	0.167
Tanner stage				
Pubic hair	1.13 ± 0.3	1.20 ± 0.4	0.549	0.131
Breast/testicular	1.13 ± 0.3	1.25 ± 0.4	0.327	0.250
Height (m)	1.38 ± 13	1.40 ± 12	0.654	0.178
Height (%)	51 ± 30	47 ± 21	0.636	0.154
Femur length (cm)	37.9 ± 4.0	38.5 ± 3.7	0.510	0.214
Body mass (kg)	33.8 ± 8.7	33.8 ± 7.9	0.888	0.080
Body mass (%)	54 ± 28	46 ± 23	0.339	0.308
BMI (kg/m ²)	17.2 ± 1.9	17.3 ± 2.3	0.909	0.049
BMI (%)	52 ± 28	47 ± 27	0.560	0.179
Physical activity (counts/d)				
Sedentary	5423 ± 3140	4433 ± 999	0.185	0.462
Light	53,223 ± 20,632	52,014 ± 10,613	0.818	0.141
Moderate	306,612 ± 127,780	337,433 ± 127,816	0.435	0.241
Vigorous	49,607 ± 62,622	52,939 ± 96,730	0.888	0.042
Total	414,690 ± 176,618	446,820 ± 204,968	0.584	0.164
Physical activity (min/d)				
Sedentary	873 ± 133	828 ± 110	0.239	0.370
Light	344 ± 81	348 ± 43	0.831	0.065
Moderate	214 ± 77	250 ± 77	0.129	0.467
Vigorous	10 ± 13	14 ± 22	0.443	0.229
Total	1440	1440		
Calcium intake (mg) *	992 ± 310	921 ± 240	0.421	0.256

Values are means ± SD. BMI = body mass index; height % = height relative to age-based norms; body mass % = body mass relative to age-based norms; BMI % = BMI relative to age-based norms;

*
n = 20 for boys.

Table 2
Zero-order correlations between measures of trabecular bone microarchitecture from MRI and aBMD and BMC from DXA in the distal femur of 6 to 12 year-old children (n = 43)

	aBMD (g/cm ²)	BMC (g)
appBV/TV	0.73 *	0.85 *
appTb.N (1/mm)	0.63 *	0.63 *
appTb.Th (mm)	0.51 *	0.66 *
appTb.Sp (mm)	-0.74 *	-0.80 *
TBMcomp	0.61 *	0.77 *

* Significant correlation, P < 0.001.