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Longitudinal relationships between whole body and central adiposity on weight-bearing bone geometry, density, and bone strength: a pQCT study in young girls

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Abstract

Summary—Longitudinal relationships between adiposity (total body and central) and bone development were assessed in young girls. Total body and android fat masses were positively associated with bone strength and density parameters of the femur and tibia. These results suggest adiposity may have site-specific stimulating effects on the developing bone.

Introduction—Childhood obesity may impair bone development, but the relationships between adiposity and bone remain unclear. Failure to account for fat pattern may explain the conflicting results.

Purpose—Longitudinal associations of total body fat mass (TBFM) and android fat mass (AFM) with 2-year changes in weight-bearing bone parameters were examined in 260 girls aged 8–13 years at baseline. Peripheral quantitative computed tomography was used to measure bone strength index (BSI, square milligrams per quartic millimeter), strength–strain index (SSI, cubic millimeters), and volumetric bone mineral density (vBMD, milligrams per cubic centimeter) at distal metaphyseal and diaphyseal regions of the femur and tibia. TBFM and AFM were assessed by dual-energy x-ray absorptiometry.

Results—Baseline TBFM and AFM were positively associated with the change in femur BSI ($r = 0.20$, $r = 0.17$, respectively) and femur trabecular vBMD ($r = 0.19$, $r = 0.19$, respectively). Similarly, positive associations were found between TBFM and change in tibia BSI and SSI ($r = 0.16$, $r = 0.15$, respectively), and femur total and trabecular vBMD ($r = 0.12$, $r = 0.14$, respectively). Analysis of covariance showed that girls in the middle thirds of AFM had significantly lower femur trabecular vBMD and significantly higher tibia cortical vBMD than girls in the highest thirds of AFM. All results were significant at $p < 0.05$.

Conclusions—Whereas baseline levels of TBFM and AFM are positive predictors of bone strength and density at the femur and tibia, higher levels of AFM above a certain level may impair cortical vBMD growth at weight-bearing sites. Future studies in obese children will be needed to test this possibility. NIH/NICHD #HD-050775.

Keywords

Regional adiposity; Bone development; Girls; Volumetric bone mineral density (vBMD); Peripheral quantitative computed tomography (pQCT)

Introduction

Puberty is a critical period of development, marked by increases in bone and lean and fat masses. Obesity during this period is associated with increased risk for metabolic comorbidities, such as type 2 diabetes mellitus (T2DM) and cardiovascular disease [1–3]. Overweight and obese children at a given age are also overrepresented in the number of fracture cases [1, 2, 4]. Whether this is due to a link between childhood obesity and bone growth or some other factor, e.g., less agility, greater falls, and greater impact forces from a fall, is unclear [5–7]. Peak bone mass and bone strength achieved in adolescence or early adulthood are primary determinants of fracture risk [8, 9], and both indices are dependent on maximizing bone density and strength during growth. Optimal bone development during puberty is critical and disturbances that disrupt normal bone development during this time can lead to suboptimal bone strength and possibly increased risk for osteoporotic fractures later in life.

The relationship between excess adiposity and bone in children is complex, and data are conflicting, suggesting a positive [10, 11], negative [2, 12], or null effect [13] of fat mass on bone mass and density. The relationship is multifactorial; one reason for the conflicting

findings may be variability in fat distribution, as different fat depots and ectopic fat likely have different consequences for bone [14]. Indeed, recent studies suggest that increased visceral fat in childhood may impair skeletal growth [15, 16]. In support of this notion, some studies have shown that fractures occurring in childhood are linked to alterations in metabolic parameters associated with deposition of visceral fat mass, which may serve as an early sign of future skeletal insufficiency [17] and osteoporosis [18]. Some studies have shown that children with excess adiposity experience dissociation between weight gain and bone mineral accrual [11], suggesting a mismatch between gains in body mass and skeletal adaptations during growth [4]. Body composition, as opposed to weight per se, may be the strongest determinant of bone throughout life, as lean mass is a well-established determinant of bone mineral content, geometry, and architecture [4]. The mismatch of bone strength and mineral accrual to body weight may explain, in part, why the incidence of fractures during puberty is higher in obese children compared to their normal-weight peers [4, 14, 19]. In children, skeletal adaptations may depend on appropriate gains in lean mass [20, 21] while fat mass may have no additive or even a negative effect on bone mass [19, 22].

Few studies have prospectively analyzed the effects of soft tissue composition on bone development and bone strength in children [15, 18, 19, 22, 23]. The purpose of this study was to determine the relationships of total body and central adiposity with changes in volumetric bone mineral density (vBMD) and indices of bone strength in young girls. Past studies of bone development in children have been limited by the use of dual-energy x-ray absorptiometry (DXA) [2, 12, 22], which is confounded by changes in bone dimensions during growth and cannot assess bone geometry, an important component of bone strength and fracture risk. A unique feature of this study was the use of peripheral quantitative computed tomography (pQCT), which provides estimates of volumetric BMD and bone structural features and can therefore capture modeling adaptations leading to architectural changes during growth [20]. To our knowledge, no studies have assessed the longitudinal relationship between total and regional (abdominal) body fat and indices of bone strength from pQCT in peri-pubertal girls, a critical phase of bone development. Given that metabolic derangements associated with obesity are closely related with a central (abdominal) fat pattern [16], and because cross-sectional analyses have shown inverse associations between fat mass and bone strength in young girls [24] and adults [25], we hypothesized that higher levels of total body fat and android fat would be inversely associated with gains in bone strength at weight-bearing bone sites in young girls.

Methods

Participants

The study was approved by the University of Arizona Human Subjects Protection Committee and was conducted in accordance with the Helsinki Declaration. All guardians and participating girls ($n=509$) provided written informed consent. Details regarding recruitment and the baseline characteristics of the sample have been published [26]. Individuals taking medications known to affect bone metabolism or who had been diagnosed with a medical condition, or disability that limited participation in physical exercise as defined by the Committee on Sports Medicine and Fitness, were excluded [27]. Sample

ethnicity was 23 % Hispanic and 77 % non-Hispanic, and sample race was 89 % white, 7 % Asian, 2 % black or African American, 0.3 % Latino, 0.7 % Native Hawaiian or other Pacific Islander, and 0.3 % other. Bone and soft tissue composition measures were available on 444 girls [26] at baseline, after elimination of 65 pQCT scans due to motion artifact. Of those girls, 260 girls had 2-year assessments of soft tissue composition and pQCT bone parameters and were included in the present analysis.

Anthropometry

Measures of body mass, standing height, sitting height, and bone lengths were obtained following standardized protocols [28]. Body mass was measured (nearest 0.1 kg) using a calibrated scale (Seca, Model 881, Hamburg, Germany). Standing and sitting heights were measured at full inhalation (nearest millimeter) using a calibrated stadiometer (Shorr Height Measuring Board, Olney, MD). Femur and tibia lengths (nearest millimeter) were measured on the nondominant leg. Femur length was measured from the proximal aspect of the patella to the inguinal crease. Tibia length was measured from the proximal end of the medial border of the tibial plateau to the distal edge of the medial malleolus. Baseline coefficients of variation (CVs) for femur and tibia lengths ($n=444$ girls) are 0.34 and 0.51 %, respectively [26]. For each anthropometric variable, two measurements were taken and averaged.

Physical maturation

Maturation was assessed using maturity offset over the more conventional method of Tanner staging due to its reliance on objective anthropometric measurements of linear growth. Maturity offset is based on estimated years from peak height velocity (PHV) using Mirwald's equation [29] which includes interactions among anthropometric measures (i.e., height, weight, sitting height, leg length) and chronologic age to derive a maturity offset value. Positive maturity offset represents years after PHV while a negative maturity offset represents years before PHV. In Mirwald's sample, the maturity offset equation for girls explained 89 % of the variance in years from PHV [29]. Data regarding menarcheal status was obtained via self-report.

Dietary assessment

As previously described [30], dietary fat and total caloric intake were assessed at baseline and 24-months using the Harvard Youth/Adolescent Questionnaire (YAQ) [31]. The YAQ is a self-administered food-frequency questionnaire (FFQ) designed to assess usual dietary intake and dietary supplement use during the previous year. Acceptable validity and reproducibility of the YAQ have been established [31]. Participants completed the YAQ with assistance available. YAQs were reviewed and coded by trained study staff following standard coding procedures [31]. Nutrient analysis was completed by Channing Laboratories (Boston, MA).

Physical activity

Physical activity (PA) was assessed by the Past Year Physical Activity Questionnaire (PYPAQ) [32], a survey of all sport and leisure-time physical activity in which the

respondent engaged at least ten times in the past year outside of physical education class. The PYPAQ was slightly modified to include a more comprehensive list of 41 activities common to youth [33]. The modified questionnaire was administered in an interview with the participant and guardian. Total PYPAQ score was computed using a modified equation from Shedd and colleagues [34], which incorporated weight-bearing load, frequency, and duration of each activity [33].

Bone and body composition assessment

pQCT-bone measures—Changes in bone geometry, strength, and volumetric bone mineral density (vBMD) were assessed using pQCT (XCT 3000, Stratec Medizintechnik GmbH, Pforzheim, Germany, Division of Orthometrix; White Plains, NY, USA) at the 4 and 20 % femur and 4 and 66 % tibia sites relative to the respective distal growth plates on the nondominant limb. Bone parameters measured at distal metaphyseal regions of the femur and tibia included trabecular vBMD (milligrams per cubic centimeter) and bone strength index (BSI, square milligrams per quartic millimeter); parameters measured at diaphyseal regions included cortical vBMD (milligrams per cubic centimeter) and strength-strain index (SSI, cubic millimeters). BSI, calculated as the total area $\times$ total vBMD² [35], provides an estimate of the bone's ability to withstand compression, and SSI is used to estimate the bone's ability to resist torsion and bending forces. SSI is the integrated product of the geometric properties (i.e., section modulus) with the material properties of bone: SSI (mm^3)= $\sum_{i=1}^n [(r_i^2 \times a)/r_{\max}] \times (\text{cortical vBMD}/\text{ND})$; section modulus is calculated as $(r_i^2 \times a)/r_{\max}$, where a is the area of a voxel (square millimeters), r is the distance of a voxel from the center of gravity (millimeters), and $r_{\max}$ is the maximum distance of a voxel from the center of gravity (millimeters). The material properties of bone are calculated as the quotient of measured cortical density (cortical vBMD, milligrams per cubic centimeter) and normal physiologic cortical density (ND, 1,200 mg/cm³).

Scout scans were performed to locate the distal growth plates, with the scanner programmed to find the sites of interest based on skeletal lengths. Additional details regarding image processing, calculations, and analysis are published elsewhere [36, 37]. CVs previously reported from our laboratory [36] were <1.1 % for vBMD, bone geometry, and indices of bone strength (i.e., BSI and SSI). pQCT data acquisition and analyses followed guidelines provided by Bone Diagnostics, Inc. (Fort Atkinson, WI, USA). All scans were performed by a single technician, while a separate investigator analyzed all scans (STRATEC software; version 6.0). The pQCT instrument was calibrated, and quality assurance procedures were completed daily in order to ensure precision of measurements.

Dual-energy x-ray absorptiometry

Total body lean mass (TBLM), total body fat mass (TBFM), and abdominal (android) fat mass (AFM) were obtained from whole body DXA scans using the GE Lunar Prodigy (software version 5.60.003) fan-beam densitometer (GE Lunar Corp, Madison, WI, USA). AFM is defined as the area enclosed between a demarcation immediately above the iliac crest to a second mark at 20 % of the total distance between the iliac crest and the base of the skull. Subjects were positioned following the standard manufacturer protocols. All participants were scanned by a certified technician, and all analyses were performed by a

single technician. The unit was calibrated daily. DXA CVs for precision in measuring soft tissue composition in our laboratory have been previously reported [38].

Statistical analysis

Data were checked for outliers and normality using histograms, and skewness and kurtosis were calculated for all variables. Changes in covariates (i.e., maturity offset, height, and TBLM), vBMD, and bone strength were defined as the difference between baseline and 24-month measurements. All changes in bone variables were normally distributed; thus, transformations were not performed. Descriptive statistics were calculated for the entire sample. Since no significant changes in intakes of calories or fat, or physical activity, were observed, the average dietary intake values and physical activity (average PYPAQ score) were used as covariates. Associations were estimated from bivariate correlations using Pearson's r for continuous variables in order to determine simple relationships between bone outcome variables and covariates. Multiple linear regression analysis was used to regress changes in bone variables on baseline measures of TBFM and AFM after controlling for baseline and the 2-year change in maturity offset, height, and TBLM, as well as average physical activity and calorie and fat intakes. All regressions included maturity offset rather than age as previous reports from our laboratory have shown it to have a stronger relationship with bone parameters [36]. Maturation has been previously assessed in our laboratory using two methods: Tanner staging [39] and maturity offset [29]. Separate analyses were conducted with Tanner stage and maturity offset as measures of maturation. In addition, we repeated analyses substituting maturity offset with menarcheal status. Results were similar (data not shown); thus, we report analyses with maturity offset over the more conventional method of Tanner staging and menarche due to its stronger association with bone parameters in this sample [36]. Linearity, normality, and homoscedasticity of residuals were assessed. Collinearity between covariates (criteria= $VIF \leq 10$) was also evaluated, and covariates with the lowest VIF were included in the model. All models were initially run with ethnicity and race in all models; however, since these variables did not contribute to the variance explained by the model, they were not included in the final analyses. The effect of baseline TBFM and AFM on bone outcomes was evaluated as separate models to determine whether the relationships between bone parameters and abdominal soft tissue composition differed from their relationships with TBFM. All models were repeated with the 2-year change in TBFM or AFM included. Because inclusion of change in adiposity did not significantly improve explained variance, the models presented herein include only baseline measures of TBFM and AFM.

Analysis of covariance (ANCOVA) was used to compare bone outcomes among tertiles of baseline TBFM and baseline AFM after adjusting for baseline and the 2-year change in maturity offset and height, TBLM, plus average physical activity, calorie and fat intakes. Because of the differences in units for pQCT bone outcome variables, data presented were normalized to the highest tertile by setting the highest tertile to 1.0. Bonferroni post hoc tests were used to adjust for multiple comparisons among tertiles of baseline TBFM and AFM. The level of significance was set at $p < 0.05$ (two-tailed). All analyses were performed using the Statistical Package for the Social Sciences for Windows, version 20.0 (SPSS, Chicago, IL, USA).

Results

Descriptive characteristics

Descriptive results for baseline and 2-year variables are provided in Table 1. Based on baseline BMI, 3.5 % of the sample was underweight (BMI<5th percentile), 75 % of the sample had healthy weight (BMI 5th to 85th percentile), 13.5 % of the sample was overweight (BMI 85th to 95th percentile), and 7.7 % of the sample was obese (BMI>95th percentile) [40]. At baseline, the average percent fat for the entire sample was 27.6 % (range 8.5–50.9 %), and for each BMI category (underweight, normal weight, overweight, and obese) was 18 % (range 8.5–22.4 %), 24.6 % (range 11.1–41.3 %), 36.8 % (range 29.2–44.0 %), and 45 % (range 36.6–50.9 %), respectively. On average, at baseline, girls were 1.2 years prior to PHV and ranged from 3.2 years before PHV to 1.04 years post PHV. Average caloric ($1,711 \pm 541$ kcal) and fat ($31 \% \pm 4.0$ %) intakes met the dietary recommendations for girls of this age established by the 2010 Dietary Guidelines for Americans [41]. As expected in healthy growing girls, height, body weight, body mass index (BMI), femur length, tibia length, total body lean mass, total body and android fat and lean masses, percent fat, calf and thigh muscle densities, and femur and tibia bone strength and density indices all increased significantly ($p < 0.0001$) from baseline to 2 years.

Associations between body composition and bone change outcomes

As evident in Table 2, baseline TBFM and AFM were both positively correlated with changes in BSI and SSI at metaphyseal and diaphyseal regions of the femur and tibia. Baseline TBFM was positively correlated with change in cortical vBMD at the femur and tibia and trabecular vBMD at the tibia. Baseline AFM was positively correlated with the change in cortical vBMD of the femur.

Results from the multiple linear regression analyses are provided in Table 2, which shows the individual contribution (partial r) of TBFM and AFM with changes in bone parameters after controlling for covariates in comparison to the simple correlation (Pearson's r). Baseline measures of TBFM and AFM were both significantly and positively associated with changes in trabecular vBMD (all $p < 0.002$) at metaphyseal regions of the femur. Positive associations were found between TBFM and changes in cortical vBMD of the femur and changes in BSI of the femur and tibia. Similar trends were noted for change in SSI at diaphyseal regions of the tibia. By contrast, no significant associations were observed between baseline AFM and change in BSI of the tibia or changes in SSI of the femur or tibia. For all regression analyses, substitution of TBFM by percent body fat gave similar results (data not shown).

Comparison of bone parameters across tertiles of body composition

Estimated means ($\pm$ SE) for the *change* in bone outcome parameters were compared across tertiles of baseline TBFM and AFM using ANCOVA, after adjusting for baseline and 2-year change in maturity offset, height, total body lean mass, plus average diet (calorie; fat intake) and physical activity. No significant differences in bone parameters were observed among tertiles of TBFM (all $p > 0.05$).

Figures 1 and 2 show the normalized adjusted means ($\pm$ standard errors) for change in vBMD (Fig. 1) and bone strength (Fig. 2) across tertiles of AFM. Change in cortical vBMD of the tibia (66 % site) was significantly higher for girls in the middle versus highest third of baseline AFM ($p < 0.05$). By contrast, girls in the highest compared to the middle third of AFM gained significantly more trabecular vBMD at the femur ($p < 0.01$). No significant differences were observed among tertiles of AFM and changes in bone strength indices (all $p > 0.05$).

Discussion

In this longitudinal analysis, we investigated the effects of total body and abdominal fat mass (android fat) on bone development in young girls, aged 8–13 years. The results show that during a period of rapid mineral accrual, total and android adiposity are significant determinants of bone development although their effects may be different. Whereas higher total body fat promotes gains in weight-bearing bone strength, at higher levels, android fat may be detrimental to gains in vBMD, particularly at diaphyseal regions of weight-bearing bones where cortical bone predominates. Previous cross-sectional findings from this laboratory [36] showed evidence of a positive, albeit weak, association between TBFM and indices of bone strength and vBMD at the diaphyseal femur and tibia. The results from the present longitudinal study support these earlier findings, as simple Pearson's correlations indicated that both TBFM and AFM were positively correlated with change in nearly all bone strength and bone density parameters assessed at metaphyseal and diaphyseal sites of the femur and tibia. Indeed, the positive associations between TBFM and bone outcomes remained significant after adjusting for influential covariates in multiple regression analysis, whereas relationships with AFM were modified after adjusting for these covariates. For example, relationships between baseline TBFM and femur BSI, tibia BSI and SSI, and femur total, cortical, and trabecular vBMD remained positive and significant. While associations between AFM and femur BSI and femur trabecular vBMD (4 % site) were also significant and positive, a negative association between AFM and cortical vBMD at the tibia (66 % tibia) approached significance ($p = 0.06$). Comparisons across tertiles of baseline AFM showed that girls in the highest versus middle third of AFM had significantly greater gains (by 49 %) in femur trabecular vBMD. In contrast, girls in the middle third of AFM had higher cortical vBMD (by 49 %) than girls in the highest third of AFM. These results suggest a curvilinear effect of regional fat mass on bone development; while moderate levels of adiposity may augment bone development, excessive levels of abdominal adiposity may impair cortical bone development in young girls. These results are consistent with cross-sectional findings from Clark et al. [22] and Wang et al. [42] who found positive associations between fat mass and areal BMD and BMC measured by DXA at various skeletal sites in young adult women (aged 20–25 years). In a longitudinal pQCT study, Wey and colleagues [23] showed that positive correlations between fat mass and bone strength and bone geometry observed in a cross-sectional analysis in children and adolescents were attenuated and subsequently reversed in participants who gained excess fat mass when examined at follow-up [14, 23]. Despite our results suggesting a positive effect of increased mechanical loading imposed by higher body weight on bone, girls with higher levels of android fat mass experienced smaller gains in cortical vBMD at the tibia, compared to girls

with lower levels of android fat mass ($p < 0.05$). These results suggest that higher levels of central adiposity may counteract the stimulatory effects of whole body fat mass on bone and compromise skeletal adaptations in vBMD and bone structural parameters during growth [36] independent of the weight-bearing effects of total adiposity on bone. Consequently, abdominal adiposity above a certain, as yet undetermined, level may predict suboptimal cortical bone development beginning in pre- and early pubertal girls.

Findings regarding the relationship between whole body and regional fat and skeletal development remain inconsistent. Importantly, the findings of this study demonstrate a positive relationship between bone outcomes and total body fat mass. However, the potential differences in the effects of total body and android fat masses on bone outcomes may contribute to a change in the fat–bone relationship when examining the effects of whole body and regional adiposity during longitudinal transitions from early childhood to adolescence [14, 22]. In the present study, girls in the middle third of android fat mass had significantly greater gains in vBMD, particularly at cortical sites of the diaphyseal tibia, than girls in the highest third of android fat mass. Presumably, children with lower AFM were “metabolically healthy,” whereas children in the highest third of fat mass may have begun to experience metabolic complications (e.g., metabolic syndrome). In a recent study examining the relationship between regional fat deposition and bone in young, prepubertal children, Pollock and colleagues [15] showed that overweight prepubescent children with prediabetes had lower total body BMC, compared to overweight children without prediabetes. Inverse relationships between visceral adiposity (VAT) and indices of bone structure and strength have also been shown in adolescent girls and young women [18]; similar inverse relationships between bone strength and density parameters and VAT may exist in children [26]. Because of the femur's weight-bearing function, it is possible that the extra weight from fat mass contributes to a greater bone strength compared with effects on the non-weight-bearing radius. Mechanistically, fat mass generally has a stimulatory effect on periosteal bone by mechanism of its mechanical loading effects imposed on the skeleton [22]. However, when comparing 2-year bone density measurements among tertiles of android adiposity, after controlling for linear growth, diet, physical activity, and MCSA, girls with lower android fat mass experienced significantly larger gains in cortical vBMD at the diaphyseal tibia, whereas girls in the highest versus lowest third of android fat mass had significantly larger gains in trabecular vBMD of the diaphyseal femur. These findings suggest that high amounts of android adiposity may negatively influence bone development independent of its contribution to weight-bearing effects, and areas consisting predominantly of cortical bone seem to be affected more than trabecular bone. Although additional studies are needed, these findings provide some evidence that bone development may depend on fat distribution independent of total adiposity. Depending on its distribution, an increased fat mass that persists into adulthood may lead to skeletal impairment along with the better-known metabolic abnormalities (i.e., type 2 diabetes).

Past investigations of the fat–bone relationship in youth have been limited by their cross-sectional study designs, as the bone–adiposity relationship at a given age may not accurately reflect what occurs over time [2]. Further, longitudinal studies of the effects of adiposity on bone have been limited by the failure to account for fat pattern, as regional adiposity,

especially abdominal adipose tissue (VAT) and fat within skeletal muscle, is strongly related to metabolic derangements that may impair bone [19, 20, 23]. To our knowledge, this is the first study that investigated the longitudinal relationship between abdominal (android) fat and changes in bone structure and bone strength in children and adolescents.

The associations between body weight and fracture in children remain unclear. Previous findings by Kalkwarf et al. [43] showed no significant relationship between body composition and fracture among cases and controls, and evidence from studies of fracture incidence in children and adolescents supports this finding. In a review of risk factors for fractures, adiposity was associated with a higher incidence of fracture in normal-weight children (16 %) compared to overweight children (33 %) [5]. In contrast, Dimitri et al. [44] observed that obese children had lower total body and regional bone mass relative to body size than nonobese children, and this effect was significantly larger in obese children with prior history of fracture. Similar results from a large observational follow-up study showed a negative association between percent body fat and fracture [45]. The results from the present study suggest that greater abdominal adiposity may offset the positive effects on cortical bone development at proximal weight-bearing bone sites, possibly by increased inflammation, metabolic abnormalities, or other factors that may affect bone (i.e., advanced glycation end products (AGEs)), thereby resulting in a greater risk of fractures later in life.

This study was not without limitations. For example, serum samples were not available, and thus, control for differences in hormone levels (e.g., estrogen, IGF-1, GH) was not possible. While direct assessment of sex hormones would be preferable, we used maturity offset [29] as a practical and objective surrogate measure of maturation. Past studies have shown maturity offset is significantly related to bone parameters [36], and in our own work, maturity offset is more highly related to bone density and bone strength than Tanner stage and menarcheal status. A second limitation was the relatively small number of obese girls in our sample. Thus, it is possible that the fat–bone relationship was underestimated compared to what would be found if a more obese population was included in the study [14, 44]. Nevertheless, even in this sample of primarily normal-weight girls, we clearly showed that higher levels of adiposity (total body and android fat) predicted lower cortical density. Also, our use of DXA measures of android fat as a surrogate for visceral fat was a limitation since DXA android fat includes both subcutaneous and visceral adiposity. Given that visceral adiposity is more strongly related to skeletal fragility and insufficiency in children [16, 18], using a more direct estimate of VAT, such as obtained from magnetic resonance imaging (MRI), may have shown stronger associations between abdominal adiposity and bone strength and other bone development parameters. Previous work in our laboratory showed strong correlations between MRI estimates of VAT and DXA—android fat ($r=0.78$) supports its use as a reasonable surrogate of VAT. Lastly, pQCT measurements were limited to weight-bearing bones (femur and tibia). The relationship between fat mass and bone may be different at weight-bearing versus non-weight-bearing skeletal sites. To our knowledge, no studies have prospectively assessed bone structure at both the radius and tibia in children. Fat mass may be positively associated with femoral and tibial bone size, but not related at the radius or even inversely related. This might explain, in part, why obese children are overrepresented in distal forearm fracture cases [46]. Future prospective studies of both

weight-bearing and non-weight-bearing skeletal sites will be necessary to examine the site-specific differences in the effects of fat on bone and whether the relationships between total body and regional adiposity and bone parameters relate differently to fracture risk at specific skeletal sites.

A significant strength of this study was the use of pQCT for measuring indices of bone strength, volumetric BMD, and structural properties thereby avoiding the confounding of growth [8, 26]. Unlike DXA, with pQCT, the contributions of changes in bone mass, density, and geometry to changes in indices of bone strength can be accurately estimated in young children. Also, our longitudinal design improves upon the limitations of past cross-sectional studies by providing an opportunity to examine prospectively how overall adiposity and specific fat depots commonly associated with metabolic comorbidities may lead to suboptimal bone development. Further, assessment of adiposity from fat mass rather than body mass index (BMI), which is used as a surrogate of adiposity in development studies and clinical practice, provides a more direct assessment of the relationship of adiposity with bone without the confounding of variation in other components of body composition. The control of diet and physical activity, maturation reflected in PHV [29], and whole body lean mass by direct analysis using DXA [2, 22] was another strength of the study.

Conclusion

In conclusion, our results demonstrated that after controlling for growth, maturation, whole body lean mass, diet, and physical activity, baseline measures of total body and android fat masses were positively associated with changes in bone strength and density at weight-bearing bone sites (femur and tibia). However, girls in the highest versus lowest thirds of AFM experienced smaller gains in cortical vBMD growth at weight-bearing sites providing evidence that higher levels of central adiposity may counteract the positive effects of total adiposity, and this effect may vary by skeletal site. The findings suggest that higher levels of abdominal adiposity during the pre- and early pubertal years may not only serve as an important risk factor for metabolic dysfunction but may also contribute to suboptimal cortical bone development in girls. Future studies in obese children will be needed to test this possibility.

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Fig. 1.

Estimated marginal means $\pm$ SE for changes in femur and tibia volumetric bone density across thirds of baseline android fat mass (AFM). Bone outcome values were normalized to the highest group by setting the highest group values to 1.0, while lower values were set to less than 1.0 and higher values set to greater than 1.0. Differences among groups for respective tertiles of baseline AFM were evaluated by ANCOVA using baseline and 2-year change values for maturity offset, height and total body lean mass and average diet (calorie, fat intake) and physical activity score. *Tot. vBMD* =total (average) volumetric bone mineral density (milligrams per cubic centimeter); *Cort vBMD* =cortical volumetric bone mineral density (milligrams per cubic centimeter); *Trab vBMD* =trabecular volumetric bone mineral density (milligrams per cubic centimeter). *a* Significantly different ($p < 0.05$) from *highest* tertile; ANCOVA

Fig. 2.

Estimated marginal means $\pm$ SE for changes in femur and tibia bone strength indices across thirds of baseline android fat mass (AFM). Bone outcome values were normalized to the highest group by setting the highest group values to 1.0, while lower values were set to less than 1.0 and higher values set to greater than 1.0. Differences among groups for respective tertiles of baseline AFM were evaluated by ANCOVA using baseline and 2-year change values for maturity offset, height and total body lean mass and average diet (calorie, fat intake) and physical activity score. *BSI* =bone strength index (square milligrams per quartic millimeter); *SSI* =strength-strain index (cubic millimeters)

Table 1Sample descriptive characteristics ($\bar{x} \pm \text{SD}$)

	Baseline (<i>n</i> =260)	24 months (<i>n</i> =260)	% change [*]
Age (years)	10.6±1.1	12.7±1.1	–
Maturity offset (years)	–1.2±1.0	0.70±1.0	–
Tanner (%; 1/2/3/4/5)	34/34/27/5/0	1/4/13/37/36/8	–
Menarche (%; post)	7	47	–
Height (cm)	144.1±9.8	156.7±9.1	8.7 [*]
Weight (kg)	38.6±9.8	50.0±12.0	29.6 [*]
BMI (kg/cm ²)	18.34±3.2	20.2±3.7	9.9 [*]
Femur length (cm)	34.0±3.0	36.7±2.5	8.1 [*]
Tibia length (cm)	33.1±2.9	36.4±2.5	9.9 [*]
Total energy intake (kcal)	1,719±647	1,703.8±490.4	–0.9
Total fat intake (g)	60.2±25.6	59.7±21.5	–0.9
Physical activity score	5,229.2±4,589.7	5,263.7±5,593.5	0.7
Percent body fat (%)	27.7±8.8	29.6±8.4	6.9 [*]
Total body fat mass (kg)	11.0±6.0	15.2±7.8	38.9 [*]
Total body lean mass (kg)	25.4±4.9	32.0±5.5	26.0 [*]
Android fat mass (kg)	0.8±0.5	1.0±0.7	31.7 [*]
TBLH-BMC (g)	1,032.6±315.0	1,495.5±418.2	0.4 [*]
Thigh muscle density (mg/cm ³)	76.3±1.5	77.5±1.5	1.6 [*]
Calf muscle density (mg/cm ³)	79.0±1.2	80.0±1.2	1.2 [*]
Femur BSI (mg ² /mm ⁴)	94.5±26.8	123.8±36.2	31.0 [*]
Femur SSI (mm ³)	1,315.4±389.7	1,874.8±508.1	42.5 [*]
Femur total density (ave) (mg/cm ³)	275.1±33.4	290.0±40.6	5.4 [*]
20 % Femur cortical density (mg/cm ³)	1,045.8±23.1	1,067.2±32.5	2.0 [*]
4 % Femur trabecular density (mg/cm ³)	236.7±31.9	246.5±36.8	4.2 [*]
Tibia BSI (mg ² /mm ⁴)	50.7±12.8	68.1±19.6	34.4 [*]
Tibia SSI (mm ³)	1,151.8±320.8	1,590.9±408.4	38.1 [*]
Tibia total density (ave) (mg/cm ³)	294.7±34.7	322.4±46.6	9.4 [*]
66 % Tibia cortical density (mg/cm ³)	1,028.2±32.4	1,056.9±37.6	2.8 [*]
4%Tibia trabecular density (mg/cm ³)	222.3±25.5	229.8±30.7	3.4 [*]

Values are presented as mean $\pm$ SD. *p* values represent paired samples *t* test for difference between the baseline and 2-year study visits

TBLH total body less head, *BMC* bone mineral content (grams), *BSI* bone strength index (square milligrams per quartic millimeter), *SSI* strength-strain index (cubic millimeters)

* Significant at *p* <0.0001

Table 2

Bivariate relationships and partial correlations from multiple linear regression of baseline TBFM and AFM on changes in bone parameters

	TBFM		AFM	
	Partial <i>r</i>	Pearson's <i>r</i>	Partial <i>r</i>	Pearson's <i>r</i>
4 % femur BSI	0.20 [*]	0.26 [*]	0.17 ^{**}	0.23 [*]
20 % femur SSI	0.07	0.24 [*]	0.04	0.21 ^{**}
Femur total vBMD	0.12 ^{**}	0.26 [*]	0.08	0.22 [*]
20 % femur cort vBMD	0.14 ^{**}	0.27 [*]	0.07	0.21 ^{**}
4 % femur trab vBMD	0.19 ^{**}	0.08	0.19 ^{**}	0.09
4 % tibia BSI	0.16 ^{**}	0.34 [*]	0.09	0.29 [*]
66 % tibia SSI	0.15 ^{**}	0.22 [*]	0.07	0.18 ^{**}
Tibia total vBMD	0.08	0.31 [*]	0.04	0.27 [*]
66 % tibia cort vBMD	−0.08	0.13 ^{**}	−0.12 ^{**}	0.09
4 % tibia trab vBMD	0.09	0.19 ^{**}	0.08	0.17 ^{**}

All bone outcome variables were calculated as the change occurring from baseline to 24 months. Model covariates include baseline and 2-year change values for maturity offset, height and total body lean mass, and average diet (calorie, fat intake) and physical activity score

TBFM total body fat mass (kilograms), *AFM* android fat mass (kilograms), *BSI* bone strength index (square milligrams per quartic millimeter), *Trab vBMD* trabecular volumetric bone density (milligrams per cubic centimeter), *Cort vBMD* cortical volumetric bone mineral density (milligrams per cubic centimeter), *SSI* strength–strain index (cubic milliliters)

* $p < 0.001$; Pearson's *r* for continuous variables;

** $p < 0.05$; Pearson's *r* for continuous variables