Bone Size and Bone Strength Are Increased in Obese Male Adolescents


Departments of Endocrinology (S.V., Y.T., G.R., E.V.C., J.-M.K., J.D.S.), Pediatric Endocrinology (S.V., J.D.S.), and Radiology (N.H.) and Unit for Osteoporosis and Metabolic Bone Diseases (S.V., Y.T., G.R., E.V.C., J.-M.K.), Ghent University Hospital, 9000 Ghent, Belgium; Departments of Pediatric Endocrinology (I.R., J.D.S.) and Radiology (C.E., F.V.), Brussels University Hospital, 1090 Brussels, Belgium; and Zeepreventorium (M.V.H., P.D.), 8420 De Haan, Belgium

Context: Controversy exists on the effect of obesity on bone development during puberty.

Objective: Our objective was to determine differences in volumetric bone mineral density (vBMD) and bone geometry in male obese adolescents (ObAs) in overlap with changes in bone maturation, muscle mass and force development, and circulating sex steroids and IGF-I. We hypothesized that changes in bone parameters are more evident at the weight-bearing site and that changes in serum estradiol are most prominent.

Design, Setting, and Participants: We recruited 51 male ObAs (10–19 years) at the entry of a residential weight-loss program and 51 healthy age-matched and 51 bone-age–matched controls.

Main Outcome Measures: vBMD and geometric bone parameters, as well as muscle and fat area were studied at the forearm and lower leg by peripheral quantitative computed tomography. Muscle force was studied by jumping mechanography.

Results: In addition to an advanced bone maturation, differences in trabecular bone parameters (higher vBMD and larger trabecular area) and cortical bone geometry (larger cortical area and periosteal and endosteal circumference) were observed in ObAs both at the radius and tibia at different pubertal stages. After matching for bone age, all differences at the tibia, but only the difference in trabecular vBMD at the radius, remained significant. Larger muscle area and higher maximal force were found in ObAs compared with controls, as well as higher circulating free estrogen, but similar free testosterone and IGF-I levels.

Conclusions: ObAs have larger and stronger bones at both the forearm and lower leg. The observed differences in bone parameters can be explained by a combination of advanced bone maturation, higher estrogen exposure, and greater mechanical loading resulting from a higher muscle mass and strength. (J Clin Endocrinol Metab 98: 3019–3028, 2013)

Childhood and adolescence are critical periods in the development of optimal bone strength because a low peak bone mass achieved in early adulthood is a risk for osteoporosis later in life. The most crucial stage in bone mass acquisition is puberty; skeletal mass approximately doubles between the start and the end of adolescence (1, 2). Conditions that alter bone development during this particular maturational period may lead to suboptimal bone strength and higher fracture risk (2).

Given the rising prevalence and severity of obesity in adolescence and the increasing evidence that overweight in adolescence may contribute to skeletal fractures (3–5), it
is essential to understand the effects of obesity on bone development. Some studies report higher areal bone mineral density (aBMD) in overweight children (6), whereas others conclude that obesity is linked to a lower aBMD (7). An important limitation of these dual-energy x-ray absorptiometry studies is the size dependence of the aBMD and the lack of data on bone geometry. Prediction of bone strength requires knowledge of both the material (eg, volumetric BMD [vBMD]) and geometric properties of bone (eg, size and shape) (8). Therefore, peripheral quantitative computed tomography (pQCT) is a useful approach in bone strength analysis because it can provide 3-dimensional information about BMD, size, and shape (9).

Literature on the effects of adiposity and obesity on vBMD and bone size in children is scarce (10–12) with conflicting results. In prepubertal children, there is some evidence that fat mass may have a positive effect on bone, whereas fat mass has a negative effect on bone during puberty and immediately after puberty (13–16).

Main determinants of pubertal bone mass accumulation and changes in bone geometry are sex steroids, the GH–IGF-I axis, and muscle mass and strength. Sex steroids and the GH–IGF-I axis have a role not only in stimulating bone growth but also in muscle mass accrual in adolescents (1). Muscle strength strongly stimulates the acquisition of bone mass by exerting strain on the bone surface (9). The interactions of loading, IGF-I and sex steroids are held responsible for the development of skeletal gender dimorphism, leading to greater bone size, periosteal expansion, and bone strength in adolescent boys (17, 18). There is some evidence from studies in prepubertal children and adolescents that obese subjects have a higher muscle mass (11) and disturbed sex steroid and IGF-I levels (19, 20).

Because mechanical and hormonal determinants (especially estradiol [E2]) are important in bone mass acquisition in male adolescents by their effects on bone expansion and bone mineralization, this study aims to determine the changes in vBMD as well as geometry of long bones by pQCT in male obese adolescents (ObAs) by studying non-weight-bearing (radius) as well as a weight-bearing (tibia) sites. Moreover, it also aims to investigate potential disturbances in muscle strength and specific hormonal parameters, such as sex steroids and IGF-I, known to influence bone mineralization and bone expansion during adolescence. We hypothesized that in ObAs, changes in bone parameters would be more evident at the weight-bearing site and that changes in serum E2 would be most prominent.

Subjects and Methods

Subjects

Fifty-one male ObAs (body mass index [BMI] SD score [SDS] > 2) aged 10 to 19 years were investigated at the entry of a residential weight-loss program in July 2011 at the Zeepreventorium in De Haan, Belgium. Fifty-one age-matched (maximal difference of 6 months) and body height-matched (maximal difference of 5 cm) as well as 51 bone age-matched (maximal difference of 6 months) and body height-matched (maximal difference of 5 cm) healthy normal-weight controls were selected blindly from an ongoing longitudinal study evaluating changes in bone geometry and muscle strength in relation to sex steroids in childhood and adolescence. These healthy children were recruited by letters distributed in several schools within the Ghent area. Obese and control subjects were not related to each other. Neither was there any relatedness between the control subjects. Obese and control children were excluded if they were taking medication known to influence bone or mineral metabolism in the past year or if they had a metabolic bone disease, thyroid disorder, or diabetes. Both study protocols were approved by the Ethical Committee of the Ghent University Hospital. Informed consent was obtained from the parents, and all participants gave their assent.

Methods

Anthropometry

Information about medical history, lifestyle, physical activity, and socioeconomic background was collected through a questionnaire. Standing height was measured to the nearest 0.1 cm using a Harpenden stadiometer (Holtain Ltd, Crymurch, United Kingdom). Body weight was measured in light indoor clothing without shoes to the nearest 0.5 kg. Waist circumference, defined as the smallest abdominal circumference if present or otherwise measured halfway between the iliac crest and the rib cage, was determined to the nearest 0.1 cm. All anthropometric measurements were performed by the same trained physician. The SDS for body height, weight, and BMI was computed using the reference data of the 2004 Flemish growth study (21). Pubertal status of the subjects was assessed by the same trained physician according to the method established by Tanner (Tanner genital staging: stage 1, prepuberty; stage 5, postpuberty).

Bone age determination

Bone age reading of an x-ray of the left hand and wrist was done by 2 independent readers (2 pediatric radiologists), both blinded for the chronological age, using the Greulich and Pyle method (22), and the mean of both readings was taken. If the difference was more than 1 year, a third independent reading (by a trained pediatrician) was performed and the 2 closest estimates were retained. Skeletal age differences (SAD) were calculated by subtracting the chronological age (CA) from the skeletal age (SA) (SAD = SA − CA), with positive differences reflecting an accelerated skeletal maturation and negative differences a delayed bone maturation.

Peripheral quantitative computed tomography

Bone variables, estimates of bone strength, and regional body composition of the forearm and the lower leg were measured using pQCT (Stratec XCT-2000, version 6; Stratec Medizintechn.
The scanner was positioned on the nondominant forearm (radius) and lower leg (tibia). Two 2.0-mm slices (voxel size 0.5 mm) were measured at the 4% and 66% sites proximally from the distal end of the radius and 2 slices at the 4% and 38% site proximally from the end of the tibia. The cross-sectional area (CSA) of the radius/tibia was determined after detecting the outer bone contour at a threshold of 280 mg/cm³. For determining cortical vBMD, the threshold was set at 710 mg/cm³, whereas for trabecular bone, it was set at 180 mg/cm³. The cortical vBMD (mg/cm³), cortical CSA (mm²), muscle and fat CSA, endosteal and periosteal circumferences (mm), and cortical thickness (mm) were measured at the midradius (66% of bone length from the distal end) and midshaft tibia (38% of bone length from the distal end). The combined CSA of muscle and bone (fibula and tibia or radius and ulna) was determined at a threshold of 40 mg/cm³, and the bone CSA was determined with the threshold set at 280 mg/cm³. Muscle CSA was calculated by subtracting the bone CSA from the combined muscle and bone CSA. Fat CSA was calculated by subtracting the combined muscle and bone CSA from the total CSA. The strength-strain index (SSI) of the radius 66% and the tibia 38% was calculated (23). To assess the SSI, a threshold of 480 mg/cm³ was used. Trabecular vBMD (mg/cm³) and area were measured using a scan through the distal metaphysis at the radius and the tibia (at 4% of bone length). The CSA of the radius/tibia was determined after detecting the outer margin; 55% of this cross-sectional bone area was peeled off to separate trabecular bone from the cortical shell. The coefficient of variation (CV) for the calibration phantom was <1% as calculated form daily phantom measurements.

Jumping mechanography

All measurements were recorded with the Leonardo Mechanography Ground Reaction Force Platform (Novotec Medical GmbH, Pforzheim, Germany). Both the multiple 1-legged hopping and the single 2-legged jump were analyzed using the Leonardo Mechanography GRFP Research Edition software version 4.2-b0546d. The multiple 1-legged hopping represents 1-legged hopping on the forefoot with the aim to achieve a maximal ground reaction force. It evaluates the maximal force to which the tibia is exposed and thus can serve to evaluate the muscle-bone unit. The maximal force and the maximal force relative to body mass of the left and the right leg were analyzed for this hop. The single 2-legged jump is a vertical countermovement jump to achieve maximum jump height. Parameters of this particular analysis were jump height, peak velocity, maximal force, maximal force/body mass, maximal peak power, and maximal peak power/body mass (24).

Each subject performed 3 single 2-legged jumps, and the recording with the highest jump height was selected. For the multiple 1-legged hopping, a minimum of 10 accurate jumps had to be performed on each leg. All tests were performed between 10:00 AM and 3:00 PM by the same observer using the same device. All subjects were fed and had exerted normal daily activity before the test.

Hormonal measurements

Venous blood samples in the obese group were obtained between 8:00 and 10:00 AM after overnight fasting. Blood samples in the age- and height-matched control group were collected between 8:00 and 10:00 AM after a small breakfast (25). All samples were stored at −80°C until batch analysis. Commercial immunoassays were used to measure serum IGF-I (Diagnostic
Systems Laboratories, Webster, Texas), leptin (Linco Research Inc, St Charles, Missouri), and SHBG (Modular, Roche Diagnostics, Mannheim, Germany). The intra- and interassay CV for all assays were less than 10%. Estradiol (E2), estrone (E1), and testosterone were determined by liquid chromatography tandem mass spectrometry (AB Sciex 5500 triple-quadrupole mass spectrometer; AB Sciex, Toronto Canada). Serum limit of quantification was <0.5 pg/mL (1.9 pmol/L) for E2 and E1, and the interassay CV were 4.0% at 21 pg/mL (77 pmol/L) for E2 and 7.6% at 25 pg/mL (93 pmol/L) for E1 (26). Serum limit of quantification was 1.2 ng/dL for testosterone, and the interassay CV were 8.3% at 36.7 ng/dL and 3.1% at 307.8 ng/dL. Free testosterone was determined by equilibrium dialysis (27), and free estradiol was calculated from total E2, SHBG, and albumin concentrations using a previously validated equation derived from the mass action law (28).

**Statistics**

Normality was checked using quantile-quantile plots and Shapiro-Wilk tests. Data are presented as mean ± SD or as medians (25th–75th percentile) in case of a non-normal distribution. Comparisons between obese and control groups were performed using parametric independent \( t \) tests or ANOVA, when criteria for normality were met. In other cases, Mann-Whitney \( U \) tests were used. Between-group differences of categorical variables were calculated using \( \chi^2 \) tests.

**Table 1. Comparison of Anthropometric Data and Measures of Regional Body Composition Between Obese Boys and Age and Bone-Age–Matched Control Boys**

<table>
<thead>
<tr>
<th>Anthropometry</th>
<th>Obese boys (mean ± SD)</th>
<th>Age-matched Controls (mean ± SD)</th>
<th>Bone age-matched Controls (mean ± SD)</th>
<th>Significance Age-matched (p)</th>
<th>Significance Bone-age matched (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anthropometry</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>14.4 ± 2.3</td>
<td>14.4 ± 2.3</td>
<td>15.0 ± 2.0</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Bone age (y)</td>
<td>15.5 ± 2.3</td>
<td>14.6 ± 2.7</td>
<td>15.4 ± 2.5</td>
<td>.07</td>
<td>NS</td>
</tr>
<tr>
<td>Difference bone age - age (y)</td>
<td>1.12 ± 0.90</td>
<td>0.18 ± 0.90</td>
<td>-0.36 ±1.0</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>167.6 ± 11</td>
<td>166.3 ± 11.3</td>
<td>168.7 ± 10.5</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Height sds</td>
<td>0.29 ± 1.25</td>
<td>0.17± 0.89</td>
<td>-0.04 ± 0.9</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>99.4 ± 24.0</td>
<td>53.4 ± 12.4</td>
<td>57.7 ± 11.9</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Weight sds</td>
<td>2.74 ± 0.59</td>
<td>-0.05 ± 0.77</td>
<td>0.06 ± 0.8</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>35.0 ± 5.7</td>
<td>19.0 ± 2.5</td>
<td>19.5 ± 2.5</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BMI sds</td>
<td>2.55 ± 0.37</td>
<td>-0.18 ± 0.89</td>
<td>-0.36 ± 1.0</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>102 ± 11</td>
<td>68 ± 6</td>
<td>71 ± 6</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

| Body Composition | | |
|------------------|| |
| **Proximal forearm** | | |
| Fat CSA (cm²)     | 2660 ± 817              | 683 ± 380                       | 709 ± 388                           | <.001                       | <.001                         |
| Muscle CSA (cm²)  | 3106 ± 840              | 2673 ± 799                      | 2969 ± 799                          | <.01                        | NS                            |
| Fat/Muscle ratio  | 91 ± 31.9               | 29 ± 20.8                       | 27 ± 19.2                           | <.001                       | NS                            |

| **Proximal tibia** | | |
| Fat CSA (cm²) | 4402 ± 1426  | 1574 ± 498  | 1656 ± 580  | <.001  | <.001  |
| Muscle CSA (cm²) | 3737 ± 776  | 3213 ± 850  | 3429 ± 735  | <.01  | <.05  |
| Fat/Muscle ratio | 121 ± 41  | 51 ± 21  | 51 ± 22  | <.001  | <.001  |

<table>
<thead>
<tr>
<th><strong>Tanner genital stage</strong></th>
<th>Obese boys (frequency)</th>
<th>Age-Matched Controls (frequency)</th>
<th>Bone-age matched Controls (frequency)</th>
<th>Significance (chi-square test)</th>
<th>NS (chi-square test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>11.8%</td>
<td>9.8%</td>
<td>3.9%</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>G2</td>
<td>17.6%</td>
<td>15.7%</td>
<td>7.8%</td>
<td>17.6%</td>
<td></td>
</tr>
<tr>
<td>G3</td>
<td>11.7%</td>
<td>15.7%</td>
<td>17.6%</td>
<td>17.6%</td>
<td></td>
</tr>
<tr>
<td>G4</td>
<td>33.3%</td>
<td>33.3%</td>
<td>37.3%</td>
<td>37.3%</td>
<td></td>
</tr>
<tr>
<td>G5</td>
<td>25.5%</td>
<td>25.5%</td>
<td>33.3%</td>
<td>33.3%</td>
<td></td>
</tr>
</tbody>
</table>

*Results are shown as mean ± SD or percent. Comparisons between obese and control groups were performed using parametric independent \( t \) tests. Between-group differences of categorical variables were calculated using \( \chi^2 \) tests.
with $\chi^2$ tests. The independent predictors of the various bone parameters were tested using linear regression analysis including age, BMI, and estrogen levels. The difference was considered statistically significant at $P < 0.05$. In Figure 1A, the following age categories were used: children between 11 and 12 years were categorized as 11 years, children between 12 and 13 years were categorized as 12 years, etc. No rounded ages were used in the other statistical analyses. Data were analyzed using SPSS software version 19.0.

**Results**

**Comparison of anthropometric data and regional body composition analysis by pQCT**

**Groups matched for chronological age and height**

As shown in Table 1, not only chronological age and body height but also pubertal stage were comparable between the 2 groups, whereas body weight (SDS) and BMI (SDS) of the obese group were almost double ($P < 0.001$). Moreover, ObAs had a significantly greater waist circumference ($P < 0.001$). A higher absolute fat CSA, fat to muscle CSA ratio, and muscle CSA at both tibia and forearm ($P < 0.01$) were observed in the obese boys (Table 1). There was no significant difference in mean chronological age and bone age between both groups. However, there was a significantly advanced bone maturation in the obese group ($P < 0.001$).

Figure 1A shows an advanced bone maturation present up to the age of 16 years.

**Groups matched for bone age and height**

Although body weight SDS (+2.69; $P < 0.001$), BMI SDS (+2.47; $P < 0.001$), and waist circumference (+31 cm; $P < 0.001$) were significantly different between obese and control group, no significant difference could be found in bone age (0.1 year; $P = .8$), height SDS (0.29; $P = .13$), chronological age (−0.6 year; $P = .2$), or pubertal stage distribution (P1, 12% vs 4%; P2, 18% vs 8%; P3, 12% vs 18%; P4, 33% vs 37%; P5, 26% vs 33%, $P = .27$).

**Comparison of bone parameters at the upper and lower limb using pQCT radius**

ObAs have a higher trabecular vBMD (+7%) and a larger trabecular area (+10%) at the distal radius. At the proximal site, cortical area (9%), periosteal circumference (+6%), endosteal circumference (+6%), and SSI (+13%) were significantly larger in the obese group (Table 2). However, there was no difference in cortical vBMD and cortical thickness between the groups. Figure 2 shows higher values of trabecular vBMD, trabecular area, periosteal circumference, and cortical area at the different pubertal stages in the obese group.
Groups matched for bone age and height

ObAs still had a higher trabecular vBMD (±6.5%) in comparison with bone-age–matched controls, but there was no difference anymore in trabecular area at the distal end. Moreover, at the proximal site, cortical parameters were comparable (Table 2).

Tibia

Groups matched for chronological age and height

As shown in Table 2, trabecular vBMD (±6%) and area (±15%) at the tibia were significantly higher in the obese group. At the midshaft, tibial cortical area (±12%), periosteal circumference (±10%), and endosteal circumference (±13%) were larger in the obese group (P < .001). There was no significant difference in cortical vBMD and cortical thickness between the 2 groups.

Comparison of hormonal parameters between ObAs and age-matched controls

ObAs have significantly higher serum leptin levels (28.3 [17.0–38.9] vs 2.9 [2.1–5.4] ng/mL; P < .001) compared with chronological age-matched controls representative for their higher fat mass. Median serum estrogen levels (E2, 16.2 [3.7–25.7] vs 8.4 [1.7–15.7] ng/L, P < .01; free E2, 0.32 [0.07–0.54] vs 0.14 [0.02–0.30] ng/L, P < .01; and E1, 22.3 [13–35.6] vs 17.0 [7.6–26.5] ng/L, P < .03) were markedly higher in the obese group. Although both testosterone (247 [35–355] vs 407 [81.1–482] ng/dL, P = .05) and SHBG (2.5 [1.9–4.3] vs 5.5 [4.0–8.9] nmol/L, P < .001) levels were lower in the obese group, free testosterone levels (5.6 [0.6–9.0] vs 5.7 [0.7–9.1] ng/dL, NS) were comparable between both groups. There was no difference in IGF-I levels between the 2 groups (288 [217–412] vs 314 [251–399] ng/mL, NS).
As expected, higher sex steroids (E2 and testosterone) levels were found with advancing pubertal development in both groups (Figure 1, C and D). Moreover, ObAs had at each pubertal stage markedly higher serum estrogen levels (E2 and E1) compared with normal-weight controls (Figure 1, B and C). Median testosterone levels tended to be lower in the obese group at different pubertal stages (Figure 1D).

Comparison of muscle force and muscle mass data between ObAs and age-matched controls
As shown in Table 3, peak force and peak power in the single 2-legged jump were, respectively, 43% and 21% higher in the ObAs compared with the controls. However, ObAs jumped on average less high than the controls, and their maximal vertical velocity during the takeoff phase of the jump was lower. Weight-related peak force and power were, respectively, 9% and 32% lower than in the controls. In the multiple 1-legged hopping, peak force on the left and right side were 35% and 32% higher in the obese subjects. However, relative to body weight, these forces were 6% and 11% lower in the obese group than in the control group. Muscle mass as well as muscle force was higher in the obese group at any pubertal stage (data not shown).

The correlation between E2 and free E2 and the bone parameters in the whole population
Both E2 and free E2 (FE2) correlated by linear regression with trabecular vBMD at the radius (E2, $\beta = 0.46$, $P < .001$; FE2, $\beta = 0.47$, $P < .001$) and tibia (E2, $\beta = 0.51$, $P < .001$; FE2, $\beta = 0.53$, $P < .001$) and with cortical area at both sites (radius: E2, $\beta = 0.70$, $P < .001$; FE2, $\beta = 0.50$, $P < .001$; tibia: E2, $\beta = 0.73$, $P < .001$; FE2, $\beta = 0.73$, $P < .001$). Regression models including age and BMI showed that E2 and FE2 were positively associated with trabecular vBMD at the radius (E2, $\beta = 0.38$, $P < .05$; FE2, $\beta = 0.42$, $P < .01$) and tibia (E2, $\beta = 0.35$, $P < .05$; FE2, $\beta = 0.37$, $P < .05$) and with the cortical area at the radius (E2, $\beta = 0.31$, $P < .01$; FE2, $\beta = 0.32$, $P < .01$) and the tibia (E2, $\beta = 0.24$, $P < .05$; FE2, $\beta = 0.23$, $P < .05$). No significant associations were found between (F)E2 and cortical vBMD, endosteal circumference, and trabecular area.

Discussion
The present study was undertaken to investigate the vBMD and bone geometry of the peripheral skeleton in obese children during late childhood and adolescence. Our results demonstrate that ObAs have larger and stronger bones at the lower leg (tibia) and to a lesser degree at
the lower arm (radius) than their normal-weight peers. Moreover, ObAs show a more advanced bone maturation in early and midpuberty, have higher circulating estrogen levels, and develop higher muscle forces at jumping.

As far as we know, only 3 other studies investigated the effects of obesity on vBMD and bone size in male children, but they included principally prepubertal children (10–12). Because our study group consists mainly of adolescents, our data can contribute to a better understanding of the effect of obesity on bone geometry and mineralization in puberty. In contrast, we used both a chronological and bone age-matched control design to explore the impact of increased adiposity. Additionally, changes in hormones involved in bone growth, such as sex steroids and IGF-I, as well as alterations in muscle mass and force were investigated to explore their potential role in bone development during adolescence.

Our bone results are in line with the results of Wetzsteon et al (10) and Ducher et al (11) who studied only prepubertal children. Wetzsteon et al (10) described higher vBMD, bone area, and bone strength parameters at the tibia in overweight children. These results were confirmed by Ducher et al (11), who found a significantly larger bone size and trabecular density at the forearm and the lower leg in their overweight group. No difference in cortical density could be found in either study (10, 11). Ehehalt et al (12) studied a group of 84 overweight children and early adolescents (mean age 12 years) and found an altered bone structure compared with normal-weight peers at the radius; bone circumferences were larger, whereas the cortex was thinner.

By studying bone maturation, hormones, and muscle force in parallel, our data give the opportunity to speculate about the different mechanisms that may underlie the observed differences in bone geometry and bone mineralization. First, in accordance with previous studies, we found that up to the age of 16 years, ObAs have a more advanced bone maturation compared with age- and height-matched controls (19, 29–31). The advanced bone development might explain at least part of the observed differences in bone expansion in our study, because after matching for bone age, no differences in cortical parameters were present, at least at the radius. However, most of the geometric differences at the tibia remained, in favor of the obese group. These results indicate that advanced bone maturation is probably not the sole explanation for the observed differences in bone geometry between obese and control boys. We speculate that higher estrogen levels as a consequence of a higher aromatization rate due to excess body fat are likely to contribute to the advanced bone maturation in adolescent obesity (29). However, this might not be the unique explanation because Johnson et al (30) described also a more advanced rate of bone maturation throughout childhood. Some authors suggest that the advanced bone development in obese children is due to an increased IGF-I production (19). However, we did not find significant differences in IGF-I levels between young obese boys and their controls. Our results of normal serum IGF-I levels are in accordance with the more recent studies in obese children and adolescents using similar immunoassays (32, 33), although we cannot exclude that the free IGF-I concentration might be elevated as a consequence of decreased IGF-I–binding proteins 1 and 2 concentrations and an elevated IGF-I–binding protein proteolysis in obesity (33).

Second, a larger muscle size and force might play an important role in a greater bone expansion in adolescent obesity. Strain from muscle force is a known major determinant of bone size during childhood and adolescence (34, 35). Our results confirmed a significantly higher muscle CSA at the tibia and the radius and a higher muscle force

| Table 3. Comparison of Single 2-Legged Jump and Multiple 1-Legged Hopping Between Obese and Normal-Weight Boys (Matched for Age and Height) |
|-----------------|-----------------|-----------------|
| Single 2-legged jump | Obese | Controls | Significance Level (P) |
| Jumping height, m | 0.2 (0.16–0.25) | 0.4 (0.38–0.49) | <.001 |
| Peak force, kN | 2.1 (1.5–2.4) | 1.2 (1.1–1.6) | <.001 |
| Peak power, kW | 2.9 (2.1–3.7) | 2.3 (1.8–3.2) | <.02 |
| Peak velocity, m/s | 2.0 (1.8–2.1) | 2.5 (2.2–2.6) | <.001 |
| Peak force per body weight | 2.4 (2.1–2.6) | 2.5 (2.2–2.6) | .068 |
| Peak power per body weight, W/kg | 34.3 (29.5–40.6) | 45.0 (40.2–52.4) | <.001 |
| Multiple 1-legged hopping | | | |
| Peak force left leg, kN | 2.1 (1.7–2.6) | 1.4 (1.2–1.8) | <.001 |
| Peak force right leg, kN | 2.0 (1.6–2.5) | 1.4 (1.2–1.8) | <.001 |
| Peak force left leg per body weight | 2.5 (2.2–2.7) | 2.7 (2.4–3.1) | <.001 |
| Peak force right leg per body weight | 2.5 (2.3–2.7) | 2.8 (2.4–3.1) | <.001 |

For non-Gaussian distribution, data are presented as median (25th–75th percentile). Comparisons between obese and control group were performed using Mann-Whitney U tests.
and power in ObAs. Because muscle mass and force increase throughout puberty together with increases in bone area, it seems plausible that the larger bones and increased bone strength in ObAs, after correction for bone age, are caused by the higher mechanical load applied to the skeleton, not only through a greater body weight but also by an increased muscle mass and force. This is supported in our study by the observation of more distinct differences in bone geometry at the tibia, a weight-bearing bone, compared with the radius, a non–weight-bearing bone. These features are consistent with the results of some other studies. In obese children, Ducher et al (11) described a higher muscle CSA both at the tibia and at the radius and Rauch et al (36) documented a higher peak muscle force and peak power. More support for this view comes from a recent longitudinal study in overweight children showing that increases in bone size and strength were related to the larger muscle mass but not fat mass (10). These findings support the mechanostat theory of Frost (34) and the concept that bones adapt primarily to dynamic forces produced by muscle contractions (37, 38) and not to static forces imposed by extra fat mass.

Finally, we hypothesized that hormonal changes related to obesity could be involved in a different bone development and bone mass accrual during puberty. Obese adolescents in our study had at the different pubertal stages higher E2 and E1 levels, which were determined using a state-of-the-art liquid chromatography tandem mass spectrometry-based methodology. It can be noted that the difference in serum E2 is even greater when considering FE2 as a consequence of lower SHBG concentrations. Only 1 other study addressed the influence of sex steroids on BMD in obese children. In contrast to our study, no differences in circulating estrogen levels and a similar aBMD were found in this study (29). Both the low number of adolescents studied and the use of an immunoassay known to have a limited reliability for measuring low levels of E2 might be responsible for not finding a difference in circulating estrogens in this particular study. To study the influence of E2 on different bone compartments, well-described determinants of bone mass were assessed using linear regression. We observed a positive association between (F)E2 and trabecular vBMD at the radius and the tibia as well as an association between (F)E2 and cortical area at the radius and tibia.

To our knowledge, this is the first matched-control study to report data on volumetric bone parameters and bone geometry of the tibia and the radius in adolescent obesity. The strength of the present study is the comprehensive evaluation of bone geometry, muscle strength, pubertal development, and hormonal factors (especially estrogens) involved in bone expansion. Although the important role of estrogens in bone homeostasis is generally acknowledged, this study is the first to look for a relationship between circulating total and free estrogens in a mixed obese and lean adolescent population. Moreover, in this study, sex steroids were measured by highly sensitive and accurate mass spectrometry-based methodology as required when studying low androgen and estrogen serum levels in children and adolescents. Our study is limited by the fact that we have assessed only cross-sectional data. To confirm and further unravel underlying mechanisms, prospective longitudinal studies are required, ideally with follow-up from early childhood at onset of obesity until adulthood.

Conclusion

We observed at both forearm and lower leg larger and stronger bones in ObAs compared with normal-weight peers. These differences in bone development can be explained by a combination of advanced bone maturation, higher estrogen exposure, and higher mechanical loading resulting from a greater muscle mass and strength.

Acknowledgments

We are indebted to Dr Hilde Franckx and Mr Rudy Reyntjens to give their permission to perform the study in Zeepreventorium in De Haan and to Eddy Basslé for his excellent technical support during the study in De Haan. We thank Dr Tom Fiers and Eric Vandersyp for the implementation of the liquid chromatography tandem mass spectrometry technique and thank Kaatje Toye and Kathelyne Mertens for their excellent technical assistance.

Address all correspondence and requests for reprints to: Sara Vandewalle, Department of Endocrinology, Ghent University Hospital, De Pintelaan 185 6K12IE, 9000 Ghent, Belgium. E-mail: sara.vandewalle@ugent.be.

This work was supported in part by Grant G.0867.11 from the Research Foundation Flanders (FWO Vlaanderen). S.V. and E.V.C. are holders of a PhD fellowship and Y.T. is holder of a postdoctoral fellowship from the Research Foundation Flanders. I.R. is supported by a grant from the Belgian Study Group for Pediatric Endocrinology.

Disclosure Summary: The authors have nothing to disclose.

References

3. Goulding A, Jones IE, Taylor RW, Williams SM, Manning PJ. Bone mineral density and body composition in boys with distal forearm


