Proximal Femur Mechanical Adaptation to Weight Gain in Late Adolescence: A Six-Year Longitudinal Study

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ABSTRACT: The effect of weight gain in late adolescence on bone is not clear. Young women who consistently gained weight ($n = 23$) from 17 to 22 yr of age had increased BMD but a lack of subperiosteal expansion compared with stable weight peers ($n = 48$). Bone strength increased appropriately for lean mass in both groups but decreased relative to body weight in weight gainers, suggesting increased bone fragility in weight gainers.

Introduction: Weight gain leading to obesity often starts in adolescence, yet little is known about its effects on bone. We used longitudinal data to examine the effects of weight gain in late adolescence (from 17 to 22 yr of age) on proximal femur BMD, geometry, and estimates of bending strength.

Materials and Methods: Participants were classified as either weight gainers (WG, $n = 23$) or stable weight (SW, $n = 48$) using a random coefficients model. Weight gainers had positive increases in weight ($p < 0.05$) at each clinic visit from age 17 onward. Proximal femur DXA scans (Hologic QDR 2000) taken annually from 17 to 22 yr of age were analyzed for areal BMD (g/cm^2), subperiosteal width (cm), and bone cross-sectional area (CSA) at the proximal femoral shaft. Cortical thickness was measured, and section modulus (Z , cm^3) was calculated as a measure of bone bending strength. Total body lean (g) and fat (g) mass were measured from DXA total body scans.

Results: Over ages 17–22, height remained stable in both groups. Weight remained static in the SW group but increased 14% on average in the WG group ($p < 0.05$). After controlling for age 17 baseline values, WG had higher BMD (+2.6%), thicker cortices (+3.6%), and greater bone CSA (+2.3%). Increased BMD did not translate to greater increases in bone bending strength (Z). The SW group achieved similar gains in Z by greater subperiosteal expansion. Bone strength index ($\text{SI} = Z/\text{height}$) normalized for body weight remained constant in the SW group but decreased significantly in the WG group. In contrast, SI normalized to lean mass did not change over time in either group. Other variables including physical activity, nutrition, and hormone levels (estradiol, testosterone, cortisol) did not differ significantly between groups.

Conclusions: These data suggest that weight gain in late adolescence may inhibit the periosteal expansion known to normally occur throughout life in long bones, resulting in decreased bone strength relative to body weight.

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Key words: adolescence, obesity, mechanostat, bone strength, bone geometry

INTRODUCTION

UNDERSTANDING HOW BONES adapt in mass, geometry, and strength to weight gain in late adolescence is of interest from both a public health perspective and for understanding basic bone biology. From a public health standpoint, chronic weight gain that leads to adult obesity often begins in adolescence. Although high body weight is

thought to be protective against osteoporotic fractures, obese adults have increased risk of lower limb fractures,^(1,2) and obese children may have a higher incidence of forearm fractures.^(3,4) Weight loss is associated with significant decreases in areal BMD (aBMD) and increased fracture risk in adults⁽⁵⁾ and with inadequate bone gain in children.⁽⁶⁾ However, little is known about the effects of weight gain in late adolescence on bone geometry or estimated bone strength, because studies to date have exclusively used aBMD (g/cm^2) or BMC as outcomes.

It is often implied in the literature that a higher aBMD associated with body weight coincides with an increased bone mechanical strength. However, bone can, and does,

Dr Beck's Institution, the Johns Hopkins University, has licensed the HSA methodology to Hologic and Dr Beck will share in potential royalties. All other authors state that they have no conflicts of interest.

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adapt its geometry in ways that may not be apparent in aBMD outcomes.⁽⁷⁾ Furthermore, increases in aBMD do not necessarily translate to a reduced fracture risk.⁽⁸⁾ From a functional standpoint, bone should adapt its strength (but not necessarily its mass or “density”) to the customary stimulus from peak voluntary loads.

There is some confusion over what constitutes a “load” on bone. Body weight is often used as a covariate with the rationale that weight is a dominant osteogenic load on bone. Although it is true that weight induces a load on bone, that load is fairly static unless that weight is moved. Static strains are no more osteogenic to bone than no load.⁽⁹⁾ On the other hand, muscle forces move limbs through the mechanical disadvantage of “short-arm” levers, so the resulting strains are several times larger than those of body weight alone and those strains are dynamic. With this rationale, some researchers suggest correcting bone strength (either bone cross-sectional area [CSA], BMC, or section modulus) for surrogates of muscle force (either muscle CSA by pQCT or total body lean mass by DXA).^(10,11) Although it remains unclear how best to scale bone geometry, these relative bone strength (RBS) or bone muscle-strength indices (BMSI) have been useful for distinguishing healthy from sick children⁽¹²⁾ and for understanding bone adaptation to loading.⁽¹³⁾

However, the idea that body weight is the dominant osteogenic load prevails in the literature. The findings that BMC or BMD are altered with weight change are nearly always explained as an effect of decreasing or increasing body weight—without consideration for the composition of that weight. If muscle forces dominate as an osteogenic stimulus, increased body weight in the form of fat mass should lead to reduced bone strength relative to weight. If weight gain is entirely in the form of lean mass, bone should adapt to that increased load. We recently showed that overweight children had high bone strength—but that strength was adequately adapted to their higher lean mass.⁽¹⁴⁾ No studies, to our knowledge, have explored the change in bone geometry and structural strength that occur with weight gain in late adolescence in a longitudinal study. We therefore used data from the longitudinal Penn State Young Women’s Health Study to examine changes in proximal femur bone geometry with weight gain in late adolescence (17–22 yr of age). We hypothesized that individuals who gained weight in late adolescence would have greater gains in BMD but that bending strength would adapt to changes in lean mass (rather than body weight).

MATERIALS AND METHODS

Participants

The Penn State Young Women’s Health Study is a prospective epidemiological study that was started in 1990 with the enrollment of 112 healthy, premenarcheal girls, 11.9 ± 0.5 yr of age at entry. The study population is representative of white adolescent girls attending public school in central Pennsylvania. Details of the recruitment, baseline measurements, the effects of the calcium supplementation on bone gain, and changes in bone geometry overall have been re-

ported.^(15–19) The study was approved by the Pennsylvania State University College of Medicine Institutional Review Board. Participants and their parents provided informed consent. Proximal femur scans were introduced in the last 6 yr of the study when participants were 17–22 yr. We used data from a total of 71 participants who remained in the study until at least age 21 and had more than three visits since age 17. No differences in baseline age, height or weight, or bone measurements were observed between participants who dropped out and those who remained in the cohort. The same two clinical research coordinators saw all participants throughout the study.

Weight groups

None of the participants in this cohort lost weight from 17 to 22 yr of age; all remained stable weight or gained weight. Using a random effects model for longitudinal data,⁽²⁰⁾ participants were partitioned into two groups, based on whether the age trend in weight slope was significantly positive ($p < 0.05$), into either weight gainers (WG; $n = 23$) or stable weight (SW; $n = 48$) groups.

Body composition and bone measurements

The same Hologic QDR-2000W DXA bone densitometer was used throughout this study. The manufacturer’s lumbar spine phantom was scanned daily for quality control and to correct for any instrument drift. In our laboratory, the CV was $<0.7\%$ for the day-to-day quality control scans. Total body scans were made in the pencil beam mode in the presence of the manufacturer’s three-step acrylic and aluminum tissue phantom. Scans were analyzed for total body bone and lean and fat mass. Bilateral proximal femur scans were made in the array mode, using an Osteodyne hip positioner (Osteodyne, Research Triangle Park, NC, USA). Average values from the left and right proximal femur scans are reported.

Hip structure analysis

The Hip Structure Analysis (HSA) program uses a principle first described by Martin and Burr^(21,22) to derive cross-sectional geometry from images acquired from bone mineral scanners. The HSA software version (v2.1) used in this study averages geometry measurements for a series of five parallel pixel mass profiles spaced ~ 1 mm apart along the bone axis. We report analysis from the narrow neck (NN) region across the narrowest point of the femoral neck and the proximal femoral shaft region located at a distance of 1.5 times the width of the femoral neck distal to the intersection of the NN and femoral shaft axes as described previously.^(23–26)

The main structural parameters derived by HSA are the bone cross-sectional area (bone CSA) and the section modulus (Z , cm^3), which are inversely related to stresses caused by axial and bending loads, respectively.^(27,28) Loading forces on bones are distributed over the surface of bone material in cross-sections; the soft tissues within bony spaces do not contribute significantly to the strength of bone. Therefore, the bone CSA measured by HSA includes only the surface material and not the soft tissue spaces

(note that this is different than the total CSA given by pQCT and QCT, which includes the nonsupporting soft tissue spaces within the periosteal envelope). In a purely cortical bone, the CSA by HSA would be equivalent to cortical CSA reported by QCT; however, in a bone incorporating trabeculae, it also includes the bone surface area due to trabeculae. Because DXA is a 2D technique, bending geometry is measured in the image of the plane only. A single DXA pixel value sums all mineral mass (hydroxyapatite in g/cm^2) along a linear path through the patient excluding all soft tissue voids within the bone as well as above and below it. Conventional DXA BMD is simply the average pixel mass thickness in a region. An equivalent linear thickness of solid bone (with all soft tissue voids collapsed out) is obtained by dividing pixel mass thickness (g/cm^2) by average mineral density of bone tissue (1.051 g/cm^3).⁽²¹⁾ Once the pixels in the mass profile are converted to thickness, the integral is the bone surface area in the cross-section (bone CSA). After determining the center of mass, the cross-sectional moment of inertia (CSMI) can be calculated as the integral of area times the distance from the center of mass. Section modulus (Z , cm^3) is calculated as $\text{CSMI}/d_{\text{max}}$, where d_{max} is the maximum distance from the center of mass to the medial or lateral cortical margin. The HSA program also measures bone outer diameter (cm) directly from the blur-corrected width of the bone mass profile and conventional BMD (g/cm^2 , the average raw pixel value). Finally, an estimate of cortical thickness was calculated by modeling cortices of femoral shaft cross-sections as concentric circles. Models assume 100% of the measured mass is in the cortex for the femoral shaft.⁽²³⁾ Version 2.1 of the HSA program has been adjusted to correct for the fan beam error.⁽¹⁴⁾

Relative bone strength

We wanted to evaluate how bone strength scales with weight and with lean mass, but bone geometry cannot be compared between dissimilar individuals without adjusting for size differences. The ideal scaling method has not been established, and in retrospective analyses, one is constrained to use parameters that were collected. We used a biomechanical observation that over a large range in animal body size, the strength of a long bone generally scales as the section modulus over bone length.⁽²⁹⁾ Bone lengths were not recorded in this study; therefore, we calculated a bone strength index (SI) using height as a surrogate for lever arm [strength index (SI) = Z/height]. To express strength relative to load, we further created a relative bone strength (RBS) as SI/load , where load was either lean mass (as a surrogate for muscle force) or body weight termed RBS_{lean} and $\text{RBS}_{\text{weight}}$, respectively. The purpose of these ratios were not to derive a denominator free variable but rather to express bone morphology based on known relationships.⁽²⁹⁾ In principle, skeletal loads should keep bone tissue strains at a relatively constant level independent of body size. If loads are proportional to body weight, we would expect that $\text{RBS}_{\text{weight}}$ remains constant with body size. If, on the other hand, loads are proportionate to lean mass, RBS_{lean} should remain constant but not $\text{RBS}_{\text{weight}}$.

Nutrient intake and physical activity

Prospective 3-day diet records were completed annually from 17 to 21 yr of age. The records were analyzed with Nutritionist III, Version 7.0, and Nutritionist IV, Version 3.0 software (FirstDataBank, San Bruno, CA, USA). We calculated time-averaged daily calcium intake and total calorie intake for each participant using five 3-day diet records obtained at regular intervals between 17 and 21 yr of age (nutrient intake data were not collected at visit 15, the final measurement date). The cumulative daily average calcium and total calorie intake of each participant is reported with an average of 13.6 records per participant.

Physical activity was assessed between 12 and 18 yr of age (which reflects grades 6–12) with a sports exercise questionnaire based on existing instruments.^(30,31) Details on this questionnaire have been published.⁽³²⁾ We report the cumulative sports exercise score, which was the arithmetic sum, in arbitrary units, for the 7 yr covered by the questionnaires. Physical fitness was estimated from graded exercise cycling test performed annually from 17 to 22 yr of age. Standard protocols were used to estimate $\text{VO}_{2\text{max}}$ from heart rate and power output data.

Hormonal data and age of menarche

Age of menarche was based on interview questions administered by the research nurse. Serum measurements were taken annually from 17 to 22 yr of age and analyzed for total estradiol, testosterone, and cortisol, independent of menstrual cycle day. Hormone serum assays were performed in the Hershey Medical Center Core Endocrine Laboratory using standard radioimmunoassay techniques as previously reported.⁽³³⁾ Data points were excluded from analyses if participants reported oral contraceptive use before that visit.

Statistical analyses

All data were managed by the Division of Data Management in the Department of Health Evaluation Sciences and checked for outliers as described previously.^(15,16) We used 6 yr of longitudinal data from a total of 71 participants who remained in the study until at least age 21 and had more than three visits since age 17. To describe the population, basic descriptive statistics including means, SD, 95% CIs, and percent change in bone structure variables were calculated. In the analysis, the last weight and bone observation for each individual is the average of the value at 21 and 22 yr of age. This was done to optimize the number of participants included in the analysis and to use all available data.

Baseline differences in bone and anthropometric characteristics were compared by *t*-test. To determine whether change in bone structure variables differed between groups over time, we used a random effects/growth curve model. A model was fit to determine the trajectory of each of the bone variables between 17 and 22 yr of age for each group. The model first specified a curvilinear time-trend for each subject with random intercept, slope, and quadratic term between subjects. If the quadratic term of the entire group was not significant, the model was reduced to a linear model with random intercept and slope for each subject. A

TABLE 1. DESCRIPTIVE CHARACTERISTICS AT BASELINE (AGE 17) AND FINAL (21 + 22 YR) FOR STABLE WEIGHT AND WEIGHT GAIN GROUPS

	Stable weight (<i>N</i> = 48)		Weight gain (<i>N</i> = 23)	
	Baseline (17 yr)	Final (21 + 22 yr)	Baseline (17 yr)	Final (21 + 22 yr)
Age (yr)	17.1 (16.9, 17.2)	21.2 (21.1, 21.4)	17.1 (16.8, 17.3)	21.3 (21.0, 21.5)
Height (cm)	165.0 (163.3, 166.7)	165.7 (163.9, 167.5)	167.3 (164.8, 169.7)	167.7 (165.3, 170.2)
Weight (kg)	56.9 (54.9, 59.0)	57.5 (55.7, 59.4)	61.9 (59.2, 64.7)	70.3 (67.3, 73.4)
Lean mass (kg)	39.3 (38.0, 40.6)	38.9 (37.6, 40.1)	43.3 (41.2, 45.5)	43.4 (40.9, 45.9)
Fat mass (kg)	13.9 (12.7, 15.1)	15.9 (14.8, 17.0)	15.7 (13.9, 17.5)	24.3 (21.5, 27.1)
Fat (%)	25.0 (23.5, 26.5)	27.7 (26.3, 29.0)	25.3 (22.8, 27.7)	34.6 (31.4, 37.9)

Values are mean (95% CI).

slope that differed from zero ($p < 0.05$) was considered a significant change. Models were tested for age, group (stable weight versus weight gainers), and age $\times$ group interactions. Age changes in bone geometry in the YWHS population as a group have been previously reported.⁽¹⁹⁾ The group estimate represents the absolute average difference between the WG and SW groups where a positive value means a higher value, whereas the age $\times$ group estimate represents the average annual increase in the WG versus SW group with a positive value equals a greater increase in the WG group. Age estimate is the average annual increase in the SW group where the change in the WG group can be calculated as the age estimate + the age $\times$ group estimate. For simplicity and ease of interpretation, we also report the baseline, final bone geometry values (adjusted for baseline), and percent difference between groups.

RESULTS

Descriptive characteristics

Baseline (age 17 yr) characteristics and bone values of the WG and SW groups are reported in Table 1. Age, height, and percent fat were not different at baseline. However, those who subsequently gained weight (WG) were already heavier (+5 kg, $p = 0.005$) and had significantly more lean mass (+4 kg, $p = 0.003$). Over the 6-yr period, the SW group had no change in body weight (Fig. 1) and no significant changes in lean mass or fat mass on average. In contrast, the WG group increased body weight by 8.4 kg on average, caused entirely by an increase in fat mass (+8.6 kg), with no change in lean mass. Percent fat also increased significantly (+9.3%) in the WG group.

Calcium ($p = 0.674$) and calorie ($p = 0.482$) intakes were similar between groups and within the normal range for young adults. Age of menarche was also similar between groups ($p = 0.279$), averaging 13.4 ± 1.0 yr and ranging from 11.6 to 17.5 yr. All but two of the girls had achieved menarche by 15 yr of age, and 90% had achieved menarche between 12 and 14 yr of age. There were no differences between the groups in other measurements averaged from 17 to 22 yr including serum estradiol, testosterone, cortisol, physical activity, or aerobic fitness (Table 2).

BMD and bone geometry

Baseline: Femoral shaft BMD (+5.8%, $p = 0.018$), bone CSA (+8.8%, $p = 0.006$), cortical thickness (+5.8%, $p =$

FIG. 1. Change in body weight in young women who gained weight (Gainer, $n = 23$) and those with stable weight (Stable, $n = 48$) from 17 to 22 yr of age. Values are mean (SE). * $p < 0.05$ for significant difference in slopes between groups.

TABLE 2. AVERAGE NUTRITION, HORMONE, AND MENSTRUAL CHARACTERISTICS FOR STABLE WEIGHT AND WEIGHT GAIN GROUPS

	Stable weight (<i>N</i> = 48)	Weight gain (<i>N</i> = 23)
Age of menarche (yr)	13.5 (13.2, 13.8)	13.2 (12.8, 13.6)
Kilocalories*	1749 (1643, 1856)	1682 (1530, 1836)
Calcium (mg/d)*	914 (803, 1025)	872 (705, 1039)
Sports score (grades 6–12)	83 (69, 98)	110 (81, 138)
Serum estradiol*	67.3 (57.0, 77.6)	58.9 (43.3, 74.6)
Serum testosterone*	35.7 (31.2, 40.1)	36.3 (29.5, 43.1)
Cortisol*	23.4 (19.2, 27.7)	23.4 (21.4, 25.4)
Estimated $\dot{V}O_2$ max (ml/kg/min)	36.6 (34.7, 38.5)	36.5 (32.9, 40.2)

Values are mean (95% CI).

* Values are averaged from six measurements taken annually from 17 to 22 yr of age.

0.054), and section modulus (+9.6%, $p = 0.026$) values were higher in the WG group at baseline (Table 3). Differences disappeared after controlling for baseline body weight or lean mass ($p > 0.25$ for all, data not shown). Femoral strength index ($SI = Z/\text{height}$) values were also higher at baseline in the WG group; however, SI relative to weight and lean mass was similar between groups at baseline ($p > 0.21$). Average values from 17 to 22 yr of age for

TABLE 3. BONE GEOMETRY AT THE PROXIMAL FEMORAL SHAFT AT BASELINE (AGE 17) AND FINAL (ADJUSTED FOR BASELINE VALUES) FOR STABLE WEIGHT AND WEIGHT GAIN GROUPS

	Baseline—age 17		Change (% change)	
	Stable weight (n = 48)	Weight gain (n = 23)	Stable weight (n = 48)	Weight gain (n = 23)
BMD (g)	1.33 (0.137)	1.41 (0.115)*	0.012 (0.060) 1.0%	0.049 (0.066) 3.5%
Cort. Th. (cm)	0.505 (0.068)	0.537 (0.061)	0.005 (0.030) 1.1%	0.025 (0.037)* 4.8%
Outer diameter (cm)	2.60 (0.165)	2.67 (0.130)	0.029 (0.036) 1.1%	0.003 (0.068)* 0.2%
CSA (cm ²)	3.31 (0.427)	3.59 (0.363)*	0.065 (0.160) 2.1%	0.126 (0.170) 3.6%
Endocortical diameter (cm)	1.60 (0.179)	1.59 (0.218)	0.020 (0.069) 1.2%	−0.048 (0.118)* −2.8%
Section modulus (cm ³)	1.56 (0.281)	1.71 (0.231)*	0.048 (0.075) 3.4%	0.055 (0.104) 3.5%
Strength index (Z/height)	0.094 (0.014)	0.102 (0.013)*	0.002 (0.004) 2.8%	0.003 (0.006) 3.2%
Strength index/weight	0.166 (0.018)	0.166 (0.021)	0.003 (0.011) 1.9%	−0.014 (0.012)* −8.2%
Strength index/lean	0.238 (0.023)	0.239 (0.032)	NS	NS

Values are mean (SD).

Change values are change from baseline (age 17) to final (age 21 + 22 average).

* $p < 0.05$ for differences between group.

NS, not significant.

femoral shaft BMD, bone CSA, cortical thickness, Z, and outer diameter were also higher in the WG (group estimates in Table 4 show the average difference between groups).

Final bone values and change over time: After controlling for age 17 baseline values, section modulus values were similar at age 22, but the WG group had thicker cortices (+3.6%, $p = 0.024$), greater bone CSA (+2.0%, $p = 0.057$), and higher BMD (+2.2%, $p = 0.023$). Section modulus values were not different. As shown in Fig. 2A, BMD increased in the WG group but remained stable in the SW group (Fig. 2A; Table 3). In contrast, section modulus values increased similarly (Fig. 2B). The SW group achieved similar section modulus values by a modest subperiosteal expansion that did not occur in the WG group (Fig. 2C), whereas the WG group had increased cortical thickness (Fig. 2D) caused by apparent endocortical contraction (Fig. 2E; Table 3) from 17 to 22 yr of age. When the femoral shaft bone strength index (SI = section modulus/height) was normalized to body weight, the ratio remained stable in the SW group but decreased significantly in the WG group (Fig. 3A). In contrast, the SI normalized to lean mass did not change significantly in either group (Fig. 3B).

DISCUSSION

Our findings are consistent with previous work showing increased BMD with weight gain in adults. In our young adult population, BMD increased significantly in women who gained weight from 17 to 22 yr of age but did not change in those with stable weight. In contrast, both groups had equivalent increases in bone bending strength (section modulus) from 17 to 22 yr of age, but they achieved gains in strength with different geometric adaptations of bone. Gains in bone strength in the stable weight group at the proximal femoral shaft were achieved primarily by increased subperiosteal width, whereas the weight gainers had increased cortical thickness but no change in subperiosteal width (implying endosteal contraction). Both groups had stable bone strength relative to lean mass, whereas the

WG group showed increasingly reduced bone strength relative to body weight. Several aspects of these findings warrant discussion including (1) the discrepancy between bone geometry and BMD outcomes; (2) the bone adaptation to changing skeletal load—why did weight gainers lack periosteal expansion; (3) the role of lean mass and body weight as osteogenic loads on bone; and (4) public health implications.

Discrepancies between bone geometry and BMD outcomes

The limitations of using BMD as a primary bone outcome are now well recognized. A recent meta-analysis showed that BMD changes do not correspond with reductions in fracture risk.⁽³⁴⁾ Our data further show the importance of interpreting DXA data using mechanically meaningful measures of bone geometry. If we had used BMD as the primary (or only) outcome, we would conclude (as is often reported in the literature) that individuals who gain weight also increase BMD and, by inference, that weight gain leads to greater increases in bone strength. In reality, bone bending strength (Z) increased similarly in both individuals who gained weight and those with stable weight, as clearly shown in Fig. 2B. These discrepant findings are because expanding subperiosteal width (as occurred in the weight stable group but not the weight gainers) has opposing effects on BMD and section modulus.⁽³⁵⁾

There are several factors that influence bone strength and fracture risk, including cortical porosity, bone microdamage, and trabecular architecture. These parameters were not measured directly in our study but are unlikely to influence bone strength in otherwise healthy young women. Section modulus is a mechanical term that represents the strength of bone in bending (with DXA, we are only able to measure bending strength in the image plane). Section modulus does not represent bone stability, or lack of, and we do not purport that section modulus is an outcome that could (or should) be used to predict fracture. Rather, we hypothesize (and much of our and others data support) that, in healthy individuals, bone will continually adapt its

TABLE 4. MODELS SHOWING INFLUENCE OF AGE (17–22 YR), WEIGHT GROUP (GAINERS VS. STABLE), AND WEIGHT GROUP BY AGE INTERACTIONS ON BONE GEOMETRY AND STRUCTURAL STRENGTH VARIABLES

	Parameter estimates (SE)		
	Age*	Group†	Group × age‡
Section modulus (Z, cm ³)	0.012 (0.002) [¶]	0.162 (0.061) [§]	0.0016 (0.0053)
Cortical thickness (cm)	0.0019 (0.0007) [§]	0.033 (0.016) [§]	0.0040 (0.0017) [§]
Outer diameter (cm)	0.0065 (0.0012) [¶]	0.0774 (0.0350) [§]	−0.0056 (0.0034)
BMD (g/cm ²)	0.0042 (0.0014) [§]	0.0786 (0.0303) [§]	0.0070 (0.0032) [§]
Bone CSA (cm ²)	0.0183 (0.0038) [¶]	0.298 (0.094) [§]	0.0112 (0.0089)
Endocortical diameter (cm)	0.0029 (0.0020)	0.0101 (0.0483)	−0.0134 (0.0055) [§]
SI/lean	0.0003 (0.00005) [¶]	−0.00017 (0.000641)	−0.00004 (0.000105)
SI/weight	0.0324 (0.0371) [¶]	−0.0799 (0.4888)	−0.4096 (0.0681) [¶]
Buckling ratio	0.00184 (0.00477) [§]	−0.1051 (0.0811)	−0.0234 (0.00972) [§]

* Age estimate is the average annual increase in the SW group (the change in the WG group = the age estimate + group × age estimate).

† Group estimate = difference between WG and SW groups (positive value is higher in WG group).

‡ Group × age estimate = average annual increase in WG vs. SW group (positive value is a greater increase in WG group).

§ $p < 0.001$.

¶ $p < 0.05$.

SI, strength index (Z/height).

geometry to a homeostatic level of strength appropriate for the individual that should be apparent in the section modulus (or rather section modulus relative to the load on bone). Other parameters such as the bone buckling ratio in adults (and it is not clear what variable in children) might better represent fracture risk.

Bone adaptation to changing skeletal load—why is there a lack of subperiosteal expansion in weight gainers?

A unique finding from these data was the lack of subperiosteal expansion in the WG group. It has been recently recognized that subperiosteal expansion normally occurs in long bone throughout the lifespan.^(23,35,36) This expansion was apparent in the SW group in our sample at ~0.25%/yr, which is approximately equivalent to the rate of expansion in older women.⁽³⁵⁾ Despite having wider bones overall, there was no expansion in subperiosteal width in the WG group from 17 to 22 yr of age.

One plausible explanation for the lack of subperiosteal expansion is the type of forces imposed on the proximal femoral shaft in this population. Theoretically, an increased body weight from fat would induce a primarily axial (or compressive) force on the proximal femoral shaft. Weight gainers also had higher absolute lean mass, which would help to dissipate bending loads on the bone.⁽³⁷⁾ Thus, overall, their bones seemed well adapted to increased compressive loads—bone was apparently laid down more on the endocortical surface to increase overall bone cross-sectional area (note that bone CSA by HSA is different from ToA by pQCT). A bone with greater CSA caused by increased cortical thickness would also be more resistant to bending. Thus, the normal periosteal expansion known to occur in long bones with age would not be required in the weight gainers. It is possible that these different adaptations could be explained entirely from a mechanical point of view. In this group, the weight gain was caused entirely by an increase in fat mass with no increase in lean mass, suggesting bending loads did not change. However, the SW group

likely maintained normal bending moments at this site as evident in increased periosteal expansion.

It is also possible that different nutritional, genetic, or hormonal factors influence the change in bone geometry. High levels of estradiol seem to inhibit periosteal expansion,⁽³⁸⁾ and estradiol is high in obese individuals. Although these young women gained weight, most remained within a relatively healthy weight for their height. Only one participant had a BMI > 30 kg/m² (obese), and 14 in the gainer group had BMIs between 25 and 30 kg/m² (considered overweight but not obese). Although we found no evidence for higher estradiol levels from 17 to 22 yr of age in the weight gainers in our population, our study was not designed to control for menstrual cycle day, which clearly increases the variability in our hormone data. Thus, we cannot exclude the possibility of a hormonal effect on the periosteal surface or a strong genetic influence. It is extremely likely that hormonal (and genetic) factors interact with the effect of loading on bone. For example, the similar increase in bending strength (Z) in the two groups may show the different ways Z can be increased relative to lean mass in the absence or presence of additional estradiol. However, several aspects of our data support the hypothesis that adaptations were mediated primarily by mechanical effects: (1) bone geometric parameters were similar at baseline after adjusting for body weight, and the cohort were all white from central Pennsylvania (a largely homogenous genetic heritage); (2) we did not detect any differences in hormonal, nutritional, or fitness parameters from six measurements; and (3) as discussed below, bone strength relative to lean mass did not change in either group over time.

What is the osteogenic “load” on bone? Bone strength relative to body weight versus lean mass

In addition to reporting BMD as the primary outcome, another limitation of standard reporting of surrogates of bone strength is the lack of adjustment for appropriate mechanical load on bone. Rather than asking if a bone is “strong” relative to the average individual, a more appro-

FIG. 2. Change in proximal femoral shaft (A) BMD (g/cm^2), (B) bone bending strength (section modulus, cm^3), (C) subperiosteal width (cm), (D) cortical thickness (cm), and (E) endocortical diameter in young women who gained weight (Gainer, $n = 23$) and those with stable weight (Stable, $n = 48$) from 17 to 22 yr of age. Values show change from baseline and are presented as mean (SE). * $p < 0.05$ for significant difference in slopes between groups.

appropriate question would be “is this bone as strong as needed for the mechanical requirements placed on it?” Body weight is often used as a surrogate for load on bone, and it is widely accepted that a high body weight leads to high bone strength. We would argue that it is the higher lean mass that naturally comes with high body weight that confers higher absolute bone strength.⁽¹⁴⁾

As stated above, had we just measured BMD or even section modulus (Z) alone, we would have stated that weight gain leads to higher bone strength. In reality, bone strength was normally adapted to the size (height) and

muscle mass (lean mass). That is, strength index (Z/ht) was equal in both groups relative to lean mass but low relative to body weight in those who gained weight (WG). Bone strength relative to lean mass remained stable in both groups over time but decreased relative to weight in the weight gain group from 17 to 21 yr of age. Thus, the overall increase in section modulus was adequate for changes in lean body mass in both groups but not adequate for increased body weight in weight gainers. These findings are consistent with our previous findings in overweight children and adolescents⁽¹⁴⁾ and in line with the mechanostat

FIG. 3. Change in relative bone strength (RBS) express as femoral shaft strength index (section modulus/height) relative to lean mass (RBS_LEAN; A) and body weight (RBS_WEIGHT; B) in young women who gained weight (WG, $n = 23$) and those with stable weight (SW, $n = 48$) from 17 to 22 yr of age. Values show change from baseline and are presented as mean (SE). * $p < 0.05$ for significant difference in slopes between groups.

theory.^(39–41) Recent studies suggest that children who fracture have low bone strength relative to their body size, suggesting weight gainers may be at increased fracture risk.^(42,43)

Although our data clearly show the osteogenic load is represented by lean mass rather than body weight, we used crude surrogates of “load” on bone and of the moment arm that the load acts through. Total body lean mass by DXA is predominately muscle, it does correlate with muscle CSA, and muscle CSA correlates with muscle force; however, these relationships are not perfectly linear, and other factors (such as muscle fiber recruitment, direction of the force, frequency of application, etc.) influence the overall magnitude and osteogenic stimulus of any load on bone. Furthermore, we used height as a surrogate for moment arm. Again, height does scale with limb length, which is representative of the moment arm, but these relationships are not perfectly linear. As methodologies are refined, it should be possible to develop more accurate and properly scaled indices of bone geometric strength and of the load that the bone experiences. In the meantime, we argue that it is important to consider the composition of body weight (lean and fat) rather than just weight alone.

Public health implications

We separated our population based on weight gain. Weight gain by itself may not be associated with increased

obesity per se if that gain is in the form of muscle mass rather than fat mass. For girls in our population, weight gain was attributed entirely to gain in fat mass and not lean mass. That said, none of the lifestyle parameters measured differed between the groups—physical activity, physical fitness, and total calorie intake were similar between groups and did not change differently over time. Those individuals who gained weight were already heavier at age 17; therefore, it is possible that some of these characteristics differed earlier in life and contributed to subsequent weight gain and differences in bone characteristics. These data might also suggest a strong genetic component to subsequent weight gain in this population, but our study was not designed to address this issue in depth.

In summary, we showed that the greater increase in aBMD associated with weight gain does not translate to greater increases in bone bending strength. Otherwise, healthy girls who gained weight from 17 to 22 yr of age did not exhibit the normal subperiosteal expansion known to occur in long bones throughout life. Their bone strength was appropriately adapted to their lean mass, but became low for body weight over time, potentially increasing the risk of fracture.

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