How Does Bone Quality Differ Between Healthy-weight and Overweight Adolescents and Young Adults?

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Abstract

Background Overweight youth have greater bone mass than their healthy-weight peers but sustain more fractures. However, it is unclear whether and how excess body fat influences bone quality in youth.

Questions/purposes We determined whether overweight status correlated with three-dimensional aspects of bone quality influencing bone strength in adolescent and young adult females and males.

Methods We categorized males ($n = 103$; mean age, 17 years) and females ($n = 85$; mean age, 18 years) into

healthy-weight and overweight groups. We measured lean mass (LM) and fat mass (FM) with dual-energy x-ray absorptiometry (DXA). We used high-resolution peripheral quantitative CT to assess the distal radius (7% site) and distal tibia (8% site). Bone quality measures included total bone mineral density (Tt.BMD), total area (Tt.Ar), trabecular bone volume fraction (BV/TV), trabecular number (Tb.N), separation (Tb.Sp), and thickness (Tb.Th). We used multiple regression to compare bone quality between healthy-weight and overweight adolescents adjusting for age, ethnicity, limb length, LM, and FM.

Results Overweight males had higher (10%–21%) Tt.BMD, BV/TV, and Tb.N and lower Tb.Sp at the tibia and lower Tt.Ar at the radius than healthy-weight males. No differences were observed between overweight and healthy-weight females. LM attenuated the differences in bone quality between groups in males while FM negatively predicted Tt.BMD, BV/TV, Tb.N, and Tb.Th.

Conclusions Our data suggest overweight males have enhanced bone quality compared with healthy-weight males; however, when group differences are interpreted in the context of the mechanostat theory, it appears bone quality of overweight adolescents adapts to LM and not to greater FM.

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Introduction

The prevalence of childhood and adolescent obesity has risen dramatically in recent years and is cause for concern [5]. With a propensity to excess adiposity at a population level, the relation of adipose tissue to musculoskeletal health deserves attention [13]. Overweight children sustain more fractures [23, 47] and are at greater risk for forearm fracture than their healthy-weight peers [21]. Further, adolescence is key for skeletal development, as more than 1/4 of adult bone mass is accrued during this crucial period [3]. Consequently, it seems essential to investigate any condition (ie, excess adiposity) that may negatively impact development of a healthy skeleton so we may better understand how to minimize fracture risk during growth and into adulthood.

To date, our knowledge of the fat-bone relationship during growth comes primarily from studies that used dual-energy x-ray absorptiometry (DXA) to assess bone mineral content (BMC) and areal bone mineral density (aBMD) in children and adolescents [1, 11, 13, 15, 16, 22, 26, 37, 42, 48]. Data from the many cross-sectional [1, 13, 15, 16, 22, 26, 37, 42, 48] and relatively few longitudinal studies [11] are equivocal and conflicting, as many DXA-based studies [13, 16, 49] failed to account for the influence of muscle force on bone mass. The mechanostat theory suggests muscle forces impose the primary load on the skeleton [41]. Thus, it is important to consider the fat-bone relationship in the context of muscle force to avoid spurious results.

Previous DXA studies of the fat-bone relationship [1, 11, 13, 15, 16, 22, 26, 37, 42, 48] were also limited by the inability of planar DXA technology to capture aspects of bone quality such as bone geometry and microstructure and the independent contribution of cortical and trabecular parameters to bone strength [35]. With peripheral quantitative CT (pQCT), one is able to assess associations between excess body fat and bone cross-sectional structure, volumetric BMD, and estimates of bone strength at the radius and tibia in children and adolescents [14, 17, 18, 39, 43, 50, 51]. Before adjusting for muscle force (or surrogates), several studies reported a positive association between body fat and pQCT-derived BMD, structure, and strength in females and males [14, 17, 25, 43, 50]. Importantly, after adjusting for lean mass (LM) or muscle cross-sectional area, this association weakened [29], became nonsignificant [14, 17], or negative [25, 39, 40]. This implies the fat-bone relationship in the bones of children who carry excess adiposity is mediated by LM.

We do not yet know how excess body fat influences elements of bone microstructure that contribute to bone strength. However, with technologic advances such as high-resolution pQCT (HR-pQCT) (82- μ m voxel size), we

are able to evaluate trabecular and cortical bone microstructure at the distal radius and tibia in vivo [7, 9] and, specifically, the association between adiposity and bone microstructure in adolescents.

We therefore determined using HR-pQCT whether there were differences in bone quality (ie, bone geometry, density, and microstructure) between healthy-weight and overweight adolescent and young adult females and males at the distal tibia and distal radius. We then determined the independent contribution of LM and fat mass (FM) to bone geometry, density, and microstructure in healthy-weight and overweight youth.

Patients and Methods

Participants in this cross-sectional analysis were part of the ongoing longitudinal Healthy Bones III study at the University of British Columbia, described in detail elsewhere [8, 33, 38]. Participants were healthy adolescent and young adult females ($n = 101$) and males ($n = 119$) aged 15 to 21 years who were measured in 2009. No participants were taking medication known to affect bone metabolism. Parents or guardians previously completed a health history questionnaire for their child from which we determined each participant's ethnicity. We considered participants as white ($n = 101$) if both parents or all four grandparents were born in North America or Europe and Asian ($n = 95$) if both parents or all four grandparents were born in China, India, Philippines, Vietnam, Korea, Taiwan, or other Asian countries. We also considered parental self-report of ethnicity to ensure we correctly classified each participant. Due to the small number of participants of other ethnicities (eg, black, $n = 1$) and the variability in ethnicity represented by participants of mixed ethnicity ($n = 23$), we excluded these individuals from our analysis. We also excluded participants if they were missing DXA ($n = 8$) or Tanner stage data ($n = 1$). After exclusions, 85 females and 103 males were included in the present analysis (Table 1). We acquired HR-pQCT scans from 84 females and 103 males at the distal tibia and from 84 females and 99 males at the distal radius (Fig. 1). All participants and parents provided written informed consent and the University of British Columbia Clinical Research Ethics Board approved all procedures.

Our methods are described in detail elsewhere [9, 33, 38]. Briefly, we measured height and weight to the nearest 0.1 cm and 0.1 kg, respectively, using standard procedures. Tibial length was measured from the medial edge of the tibial plateau to the distal edge of the tibial medial malleolus. Ulnar length was measured as the distance from the proximal edge of the olecranon process to the distal and medial edge of the ulnar styloid process. We assessed

Table 1. Descriptive and anthropometric characteristics of healthy-weight and overweight males and females

Characteristic	Males (n = 103)			Females (n = 85)		
	Healthy weight (n = 85)	Overweight (n = 18)	p value	Healthy weight (n = 68)	Overweight (n = 17)	p value
Age (years)*	17.3 (1.6)	17.5 (1.8)	0.927	17.8 (1.7)	18.0 (2.0)	0.432
Ethnicity (number of Asian/white)	44/41	10/8	0.770	34/34	7/10	0.515
Tanner stage (number at Stage 3/4/5)	0/38/47	0/2/16	0.008			
Age at menarche (years)*				12.5 (1.3)	12.4 (1.3)	0.957
Height (cm)*	175.1 (7.0)	176.1 (9.3)	0.460	162.4 (6.7)	163.7 (8.7)	0.891
Weight (kg)*	63.4 (9.4)	89.5 (17.0)	< 0.001	54.5 (7.0)	76.0 (11.3)	< 0.001
BMI (kg/m ²)*	20.6 (2.2)	28.9 (5.0)	< 0.001	20.6 (1.9)	28.4 (3.6)	< 0.001
Radius length (mm)*	285.0 (15.1)	291.4 (14.6)	0.030	256.5 (12.8)	260.7 (15.1)	0.563
Tibia length (mm)*	420.7 (24.8)	427.7 (36.6)	0.279	380.6 (23.6)	391.0 (27.5)	0.453
Fat mass (kg)*	8.8 (3.4)	23.0 (11.8)	< 0.001	14.4 (3.7)	26.9 (6.9)	< 0.001
% body fat*	14.1 (4.6)	25.2 (8.6)	< 0.001	26.8 (4.6)	35.8 (5.1)	< 0.001
Lean mass (kg)*	50.5 (7.6)	61.5 (7.4)	< 0.001	36.8 (4.2)	45.2 (5.9)	< 0.001

* Data are presented as mean, with SD in parentheses.

Fig. 1 A flowchart shows the number of participants with scans at the distal tibia and distal radius.

maturity as per the method of Tanner (self-reported pubic hair stage for males [46]) and as age at menarche for females. Males were Tanner 4 or 5 (postpubertal) and all females were postmenarchal.

We determined total-body bone-free LM and FM from DXA (Hologic® QDR® 4500 W; Hologic, Inc, Waltham, MA, USA) total-body scans. DXA measures of LM were validated against chemical analysis [24] and DXA measures of FM were validated against the criterion four-compartment model [45]. One trained and qualified technologist conducted all measures and one technologist analyzed all scans using standard manufacturer protocols

(Hologic, Inc). To maintain quality assurance of the QDR® 4500 W, spine and anthropomorphic phantoms were scanned daily.

We calculated BMI as weight/height² and categorized males and females into BMI groups using the International Obesity Task Force sex-specific BMI cut points for children 2 to 18 years of age [12]. Participants were considered healthy-weight if their BMI for age was less than the curve passing through a BMI of 25 kg/m² at age 18 years, overweight if their BMI for age was greater than the curve passing through a BMI of 25 kg/m² but less than the curve passing through a BMI of 30 kg/m² at age 18 years, or

obese if their BMI for age was greater than the curve passing through a BMI of 30 kg/m² at age 18 years. For participants older than 18 years, we used adult BMI cut points (BMI > 25 kg/m² classified as overweight) [12]. Due to a small number of obese participants (six males, five females), we collapsed the overweight and obese participants into one overweight group.

As in our previous studies [9, 27], participants were scanned using HR-pQCT (XtremeCT[®]; Scanco Medical AG, Brüttisellen, Switzerland) at the nondominant radius and tibia. In the case of a prior fracture, the opposite limb was scanned (*n* = 13). One highly trained technician positioned the participants and performed and analyzed the scans according to manufacturer protocol.

The technologist acquired a two-dimensional scout view image for the tibia and radius before the three-dimensional scanning. The region of interest was 8% and 7% of the tibial and ulnar length, respectively. The reference lines were placed at the tibial plafond and radial notch (Fig. 2). These sites were selected because they capture both cortical and trabecular bone regions, ensure tibial and radial growth plates would not be scanned, and allowed the same relative site to be located at followup [7, 9]. We scanned participants using the manufacturer's standard protocol (60 kVp, 900 μ A, and 100-millisecond integration time) and acquired 110 slices at the tibia and radius at an 82- μ m nominal isotropic resolution (approximately 9.02 mm). The effective radiation dose for each HR-pQCT scan was 3 μ Sv.

We segmented and evaluated all images with system software as per manufacturer's threshold-based algorithms. To differentiate cortical from trabecular bone, the system software uses a threshold that is $\frac{1}{3}$ of the apparent cortical BMD. Standard measures included total bone area (Tt.Ar [mm²]), total BMD (Tt.BMD [mg hydroxyapatite/cm³]), trabecular bone volume ratio (BV/TV), trabecular number (Tb.N [1/mm]), trabecular separation (Tb.Sp [mm]), and trabecular thickness (Tb.Th [mm]) [27]. We define these

variables as measures of bone quality [35]. Reproducibility in our laboratory was 0.2% to 3.8% for all HR-pQCT-acquired bone measures at the tibia and radius [University of British Columbia Bone Health Research Group, unpublished data].

Descriptive data are presented as mean $\pm$ SD. We used bivariate correlations to determine the association between LM, FM, and all bone variables (Tt.BMD, Tt.Ar, BV/TV, Tb.N, Tb.Sp, Tb.Th). We used simple univariable linear regression to compare descriptive variables (age, age at menarche, height, weight, BMI, radius length, tibia length, FM, LM) and bone variables between healthy-weight and overweight groups. Chi-square tests were used to compare categorical variables (Tanner stage, ethnicity) between groups. We analyzed females and males separately in all regression models due to known sex differences in bone accrual [3, 32]. Multivariable linear regression was used to compare measures of bone quality between overweight and healthy-weight females and males. Similar to previous studies [31, 37], we built our regression models in three steps. In Model 1, we compared bone quality of overweight and healthy-weight participants after adjusting for age, ethnicity (Asian or white), and limb length (tibia or ulna). Since all participants were postpubertal (males) or postmenarchal (females), we adjusted for chronologic age and not maturity status. We included ethnicity in our models due to known differences in bone measures, particularly lower BMC in Asian children than in white children [6, 36]. As in previous studies [31, 32], we included limb length as an estimate of moment arm. In Model 2, we added LM as a surrogate of muscle force to the covariates in Model 1. In Model 3, we added FM to Model 2 covariates to determine whether FM independently predicted bone quality. We used histograms and quartile-quartile plots to check assumptions and normal distribution of variables. All analyses were performed using Stata[®] Version 10 (StataCorp, College Station, TX, USA).

Results

As expected, overweight participants had greater weight (39%–41%), BMI (38%–40%), LM (22%–23%), % body fat (34%–79%), and FM (87%–161%) than healthy-weight participants (Table 1). Additionally, overweight males had greater Tt.BMD (10%–21%), BV/TV (9%–14%), and Tb.N (9%–15%) and smaller Tb.Sp (12%–16%) at both the tibia and radius than healthy-weight males (Table 2). Overweight females had greater Tt.Ar at both sites (12%–13%) and greater Tb.N (10%) and smaller Tb.Sp (2%) at the tibia than healthy-weight females (Table 2).

For bone geometry, overweight males had a smaller Tt.Ar than healthy-weight males at the tibia in Model 3

Fig. 2A–B HR-pQCT scout view images of the (A) distal tibia and (B) distal radius illustrate the 8% and 7% respective measurement sites and reference lines.

Table 2. High-resolution peripheral quantitative CT measures of bone quality in healthy-weight and overweight males and females

Measure	Males			Females		
	Healthy weight	Overweight	p value	Healthy weight	Overweight	p value
Tibia	n = 85	n = 18		n = 67	n = 17	
Tt.BMD (mg HA/cm ³)	316.2 (47.6)	349.2 (59.2)	0.012	322.2 (45.7)	330.4 (35.8)	0.495
Tt.Ar (mm ²)	770.8 (117.3)	828.4 (127.5)	0.065	613.4 (74.8)	696.0 (105.4)	< 0.001
BV/TV	0.170 (0.024)	0.186 (0.027)	0.011	0.160 (0.029)	0.167 (0.018)	0.356
Tb.N (1/mm)	1.85 (0.30)	2.12 (0.23)	0.001	1.74 (0.25)	1.91 (0.25)	0.013
Tb.Sp (mm)	0.462 (0.085)	0.389 (0.043)	0.001	0.493 (0.078)	0.444 (0.073)	0.021
Tb.Th (mm)	0.093 (0.011)	0.089 (0.015)	0.239	0.093 (0.014)	0.088 (0.010)	0.231
Radius	n = 81	n = 18		n = 67	n = 17	
Tt.BMD (mg HA/cm ³)	332.0 (65.7)	402.2 (75.6)	< 0.001	355.1 (64.1)	342.3 (39.6)	0.435
Tt.Ar (mm ²)	287.4 (47.3)	263.8 (48.7)	0.060	215.7 (30.1)	241.0 (35.7)	0.004
BV/TV	0.160 (0.029)	0.183 (0.032)	0.003	0.139 (0.033)	0.136 (0.020)	0.639
Tb.N (1/mm)	1.91 (0.24)	2.09 (0.23)	0.005	1.87 (0.27)	1.86 (0.18)	0.884
Tb.Sp (mm)	0.448 (0.072)	0.395 (0.050)	0.004	0.473 (0.085)	0.471 (0.056)	0.936
Tb.Th (mm)	0.084 (0.013)	0.089 (0.019)	0.182	0.074 (0.013)	0.073 (0.009)	0.715

Data are presented as unadjusted means, with SD in parentheses; HA = hydroxyapatite; Tt.BMD = total bone mineral density; Tt.Ar = total area; BV/TV = trabecular bone volume ratio; Tb.N = trabecular number; Tb.Sp = trabecular separation; Tb.Th = trabecular thickness.

(10%) (Table 3) and at the radius in Models 1 (10%), 2 (20%), and 3 (16%) (Table 4). Overweight females had a greater Tt.Ar than the healthy-weight group at the tibia (10%) and radius (9%) in Model 1. In Models 2 and 3, there were no longer differences in Tt.Ar between healthy-weight and overweight females. In terms of bone density, in Model 1, Tt.BMD was greater in overweight males than in healthy-weight males at the tibia (10%) and radius (21%). In Model 2, Tt.BMD at the radius remained greater (14%) in overweight males whereas Tt.BMD at the tibia did not differ between groups. In Model 3, Tt.BMD was greater in overweight males than in healthy-weight males at both sites (15% tibia; 18% radius). Tt.BMD was not different between overweight and healthy-weight females at either site. In terms of bone microstructure, BV/TV and Tb.N were greater in overweight males than in healthy-weight males at the tibia (10% and 13%, respectively) and radius (16% and 8%, respectively) in Model 1. Conversely, Tb.Sp was smaller in overweight males than in healthy-weight males at the tibia (15%) and radius (12%) in Model 1. In Model 2, these relationships were attenuated by LM and no longer significant. In Model 3, BV/TV was greater in overweight males than in healthy-weight males at both the tibia (12%) and radius (17%). In Model 1, Tb.N was greater and Tb.Sp was smaller in overweight females than in healthy-weight females at the tibia only (9% and 10%, respectively). Other bone microstructure variables (BV/TV, Tb.N, Tb.Sp, Tb.Th) were not different between overweight and healthy-weight females at either site in any model.

In both sexes, LM was an independent, positive predictor of Tt.Ar at the tibia (Table 3, Fig. 3) and radius (Table 4, Fig. 4) and explained 6% to 17% of the variance. FM was an independent positive predictor of Tt.Ar at the tibia for males only and accounted for 3% of the variance. In males, FM was an independent negative predictor of Tt.BMD at the tibia and accounted for 10% of the variance. In both sexes, LM was a positive predictor of Tt.BMD at both sites and explained 4% to 7% of the variance. In males, LM was a positive predictor of BV/TV and Tb.N at both sites and was a positive predictor of Tb.Sp at the tibia and negative predictor of Tb.Sp at the radius accounting for 4% to 17% of the variance (Model 2). Also in males, FM was an independent negative predictor of BV/TV and explained 9% to 10% of the variance. Additionally, males' FM was a negative predictor of Tb.Th at both sites and of Tb.N at the tibia and explained 1% to 5% of the variance. In females, LM was a positive predictor of tibial BV/TV and Tb.Th (4%–10% of variance) while LM was a negative predictor of tibial Tb.Sp (6% of variance) in Models 2 and 3.

Discussion

Recent evidence highlighted increased fracture risk among overweight children and adolescents [21]. Thus, we investigated differences in bone quality between healthy-weight and overweight youth using a novel imaging tool, HR-pQCT. In addition, we evaluated the independent

Table 3. Multivariable regression models for high-resolution peripheral quantitative CT measures of bone quality at the distal tibia in males and females

Measure	Model 1	p value	Model 2	p value	Model 3	p value
Males						
Tt.BMD						
Group	31.9 (12.2)	0.010	11.7 (13.9)	0.401	47.0 (16.1)	0.004
Lean mass			2.1 (0.7)	0.007	2.5 (0.7)	0.001
Fat mass					−2.9 (0.8)	< 0.001
Adjusted R ²	0.165		0.219		0.312	
Tt.Ar						
Group	44.8 (29.2)	0.129	−35.9 (30.8)	0.246	−80.7 (37.4)	0.033
Lean mass			8.5 (1.7)	< 0.001	8.0 (1.7)	< 0.001
Fat mass					3.6 (1.8)	0.043
Adjusted R ²	0.142		0.310		0.332	
BV/TV						
Group	0.017 (0.006)	0.010	0.004 (0.007)	0.555	0.020 (0.008)	0.023
Lean mass			0.001 (3.97·10 ^{−4})	0.001	0.002 (3.85·10 ^{−4})	< 0.001
Fat mass					−0.001 (4.01·10 ^{−4})	0.003
Adjusted R ²	0.067		0.156		0.225	
Tb.N						
Group	0.24 (0.08)	0.001	0.07 (0.08)	0.402	0.13 (0.10)	0.195
Lean mass			0.02 (4.37·10 ^{−3})	< 0.001	0.02 (4.42·10 ^{−3})	< 0.001
Fat mass					−4.89·10 ^{−3} (4.60·10 ^{−3})	0.290
Adjusted R ²	0.158		0.280		0.281	
Tb.Sp						
Group	−0.068 (0.021)	0.001	−0.012 (0.022)	0.577	−0.033 (0.027)	0.219
Lean mass			0.006 (0.001)	< 0.001	−0.006 (0.001)	< 0.001
Fat mass					0.002 (0.001)	0.184
Adjusted R ²	0.119		0.288		0.294	
Tb.Th						
Group	−0.003 (0.003)	0.390	−2.901·10 ^{−4} (0.003)	0.932	0.005 (0.004)	0.256
Lean mass			−2.35·10 ^{−4} (1.89·10 ^{−4})	0.218	−1.75·10 ^{−4} (1.88·10 ^{−4})	0.355
Fat mass					−4.07·10 ^{−4} (1.96·10 ^{−4})	0.040
Adjusted R ²	0.136		0.141		0.169	
Females						
Tt.BMD						
Group	12.8 (11.5)	0.267	−13.4 (14.8)	0.365	−9.7 (17.4)	0.579
Lean mass			3.6 (1.3)	0.009	3.8 (1.5)	0.011
Fat mass					−0.5 (1.1)	0.684
Adjusted R ²	0.101		0.166		0.157	
Tt.Ar						
Group	63.9 (19.3)	0.001	−4.9 (23.1)	0.831	−15.5 (27.2)	0.571
Lean mass			9.4 (2.1)	< 0.001	8.7 (2.3)	< 0.001
Fat mass					1.3 (1.8)	0.463
Adjusted R ²	0.367		0.490		0.487	
BV/TV						
Group	0.010 (0.007)	0.139	−0.009 (0.009)	0.296	−0.005 (0.010)	0.596
Lean mass			0.003 (8.58·10 ^{−4})	0.001	2.87·10 ^{−3} (8.58·10 ^{−4})	0.001
Fat mass					−4.52·10 ^{−4} (6.59·10 ^{−4})	0.495
Adjusted R ²	0.178		0.274		0.269	

Table 3. continued

Measure	Model 1	p value	Model 2	p value	Model 3	p value
Tb.N						
Group	0.16 (0.06)	0.014	0.07 (0.08)	0.431	0.057 (0.10)	0.576
Lean mass			0.01 ($7.64 \cdot 10^{-3}$)	0.097	0.01 ($8.43 \cdot 10^{-3}$)	0.152
Fat mass					$1.18 \cdot 10^{-3}$ ($6.48 \cdot 10^{-3}$)	0.856
Adjusted R ²	0.205		0.223		0.213	
Tb.Sp						
Group	−0.047 (0.019)	0.018	−0.005 (0.025)	0.852	−0.006	0.852
Lean mass			−0.005 (0.002)	0.014	−0.006 (0.003)	0.024
Fat mass					$1.06 \cdot 10^{-4}$ ($1.94 \cdot 10^{-3}$)	0.957
Adjusted R ²	0.196		0.246		0.237	
Tb.Th						
Group	−0.002 (0.003)	0.575	−0.008 (0.004)	0.070	−0.006 (0.005)	0.256
Lean mass			$8.47 \cdot 10^{-4}$ ($3.99 \cdot 10^{-4}$)	0.037	$9.91 \cdot 10^{-4}$ ($4.39 \cdot 10^{-4}$)	0.027
Fat mass					$-2.68 \cdot 10^{-4}$ ($3.37 \cdot 10^{-4}$)	0.429
Adjusted R ²	0.178		0.213		0.209	

Model 1 covariates: group (overweight versus healthy weight), age, ethnicity (white versus Asian), limb length (tibia or ulna); Model 2 covariates: all of Model 1 covariates plus lean mass; Model 3 covariates: all of Model 2 covariates plus fat mass; values for group, lean mass, and fat mass are expressed as coefficients, with standard error in parentheses; Tt.BMD = total bone mineral density; Tt.Ar = total area; BV/TV = trabecular bone volume fraction; Tb.N = trabecular number; Tb.Sp trabecular separation; Tb.Th = trabecular thickness.

Table 4. Multivariable regression models for high-resolution peripheral quantitative CT measures of bone quality at the distal radius in males and females

Measure	Model 1	p value	Model 2	p value	Model 3	p value
Males						
Tt.BMD						
Group	69.8 (15.3)	< 0.001	46.9 (17.2)	0.008	61.05	0.005
Lean mass			2.7 (1.0)	0.010	2.9 (1.0)	0.006
Fat mass					−1.2 (1.0)	0.255
Adjusted R ²	0.368		0.405		0.407	
Tt.Ar						
Group	−29.7 (11.5)	0.011	−58.4 (12.0)	< 0.001	−47.94	0.002
Lean mass			3.3 (0.7)	< 0.001	3.5 (0.7)	< 0.001
Fat mass					−0.9 (0.7)	0.230
Adjusted R ²	0.190		0.338		0.341	
BV/TV						
Group	0.026 (0.008)	0.001	0.011 (0.009)	0.190	0.028	0.008
Lean mass			0.002 ($5.03 \cdot 10^{-4}$)	0.001	0.002 ($4.96 \cdot 10^{-4}$)	< 0.001
Fat mass					−0.001 ($4.88 \cdot 10^{-4}$)	0.008
Adjusted R ²	0.087		0.177		0.229	
Tb.N						
Group	0.18 (0.06)	0.004	0.11 (0.07)	0.137	0.13 (0.09)	0.126
Lean mass			0.01 ($4.17 \cdot 10^{-3}$)	0.030	0.01 ($4.27 \cdot 10^{-3}$)	0.026
Fat mass					$-2.37 \cdot 10^{-3}$ ($4.20 \cdot 10^{-3}$)	0.574
Adjusted R ²	0.095		0.131		0.124	
Tb.Sp						
Group	−0.055 (0.018)	0.003	−0.026 (0.020)	0.200	−0.040 (0.024)	0.105
Lean mass			−0.003 (0.001)	0.005	−0.004 (0.001)	0.003
Fat mass					0.001 (0.001)	0.316
Adjusted R ²	0.105		0.169		0.169	

Table 4. continued

Measure	Model 1	p value	Model 2	p value	Model 3	p value
Tb.Th						
Group	0.006 (0.004)	0.094	0.003 (0.004)	0.527	0.009 (0.005)	0.067
Lean mass			$4.05 \cdot 10^{-4}$ ($2.45 \cdot 10^{-4}$)	0.101	$5.15 \cdot 10^{-4}$ ($2.44 \cdot 10^{-4}$)	0.038
Fat mass					$-5.46 \cdot 10^{-4}$ ($2.40 \cdot 10^{-4}$)	0.025
Adjusted R ²	0.053		0.070		0.110	
Females						
Tt.BMD						
Group	-11.9 (16.4)	0.472	-11.3 (22.7)	0.620	-23.4 (26.6)	0.381
Lean mass			-0.1 (2.1)	0.970	-0.1 (2.3)	0.715
Fat mass					1.4 (1.7)	0.382
Adjusted R ²	0.003		-0.009		-0.012	
Tt.Ar						
Group	20.4 (7.5)	0.008	1.2 (9.8)	0.899	7.1 (11.5)	0.543
Lean mass			2.6 (0.09)	0.006	3.0 (1.0)	0.004
Fat mass					-0.7 (0.7)	0.337
Adjusted R ²	0.304		0.361		0.361	
BV/TV						
Group	-0.004 (0.008)	0.666	0.002 (0.011)	0.880	0.006 (0.013)	0.652
Lean mass			$-7.27 \cdot 10^{-3}$ ($8.58 \cdot 10^{-3}$)	0.498	$-4.55 \cdot 10^{-3}$ ($1.16 \cdot 10^{-3}$)	0.695
Fat mass					$-5.27 \cdot 10^{-4}$ ($8.49 \cdot 10^{-4}$)	0.537
Adjusted R ²	0.033		0.027		0.019	
Tb.N						
Group	-0.02 (0.07)	0.796	$1.37 \cdot 10^{-3}$ (0.09)	0.988	0.02 (0.11)	0.874
Lean mass			$-2.55 \cdot 10^{-3}$ ($8.62 \cdot 10^{-3}$)	0.768	$-1.55 \cdot 10^{-3}$ ($9.37 \cdot 10^{-3}$)	0.869
Fat mass					$-1.94 \cdot 10^{-3}$ ($6.87 \cdot 10^{-3}$)	0.779
Adjusted R ²	0.071		0.060		0.049	
Tb.Sp						
Group	$2.02 \cdot 10^{-4}$ (0.021)	0.992	-0.006 (0.029)	0.826	-0.014 (0.034)	0.673
Lean mass			$8.95 \cdot 10^{-4}$ ($2.69 \cdot 10^{-3}$)	0.740	$3.96 \cdot 10^{-4}$ ($2.92 \cdot 10^{-3}$)	0.893
Fat mass					$9.70 \cdot 10^{-4}$ ($2.14 \cdot 10^{-3}$)	0.652
Adjusted R ²	0.075		0.064		0.055	
Tb.Th						
Group	-0.001 (0.003)	0.843	0.001 (0.005)	0.746	0.003 (0.005)	0.637
Lean mass			$-2.91 \cdot 10^{-4}$ ($4.24 \cdot 10^{-4}$)	0.495	$-2.25 \cdot 10^{-4}$ ($4.61 \cdot 10^{-4}$)	0.627
Fat mass					$-1.28 \cdot 10^{-4}$ ($3.38 \cdot 10^{-4}$)	0.706
Adjusted R ²	-0.018		-0.025		-0.037	

Model 1 covariates: group (overweight versus healthy weight), age, ethnicity (white versus Asian), limb length (tibia or ulna); Model 2 covariates: all of Model 1 covariates plus lean mass; Model 3 covariates: all of Model 2 covariates plus fat mass; values for group, lean mass, and fat mass are expressed as coefficients, with standard error in parentheses; Tt.BMD = total bone mineral density; Tt.Ar = total area; BV/TV = trabecular bone volume fraction; Tb.N = trabecular number; Tb.Sp trabecular separation; Tb.Th = trabecular thickness.

contribution of LM and FM to key aspects of bone quality (bone microstructure, geometry, and density) that underpin bone strength [20].

We acknowledge several limitations of our study. First, based on the cross-sectional study design, we cannot infer any causal relationships between weight status, LM or FM, and the parameters of bone quality. Second, due to the small number of overweight participants in our study, we

may have been underpowered to detect differences in some bone measures between healthy-weight and overweight males and females. Additionally, our sample was a convenience sample and we chose to collapse obese and overweight participants into one category. Thus, we cannot generalize our results to the general population. Third, HR-pQCT measures distal, and thus predominantly trabecular, regions of the tibia and radius. Therefore, we cannot

Fig. 3A–D Scatterplots show (A, B) Tt.Ar and (C, D) BV/TV versus (A, C) LM and (B, D) FM at the tibia. Healthy-weight males are represented by solid circles; overweight males are represented by solid triangles; healthy-weight females are represented by open circles; overweight females are represented by open triangles. Correlations are represented by a solid line for males and a dashed line for females.

generalize our results to diaphyseal cortical bone or other skeletal sites. Thus, future studies would benefit from including both trabecular and cortical bone sites. Finally, we did not measure endocrine markers, such as leptin, that are strongly associated with adiposity and independent negative predictors of cortical area and thickness [29]. Thus, we are unable to report their contribution to our findings.

The smaller bone cross-sectional area we report for overweight adolescent males may place them at an increased risk for fracture. Geometric measures such as bone size, cross-sectional area, or moment of inertia reportedly predict up to 70% to 80% of whole-bone strength [2]. In human cadaveric models, bone size made a larger contribution than bone density to failure load [28]. Thus, although overweight males had higher Tt.BMD compared with healthy-weight males, this may be insufficient to compensate for their smaller bone size, on average. Importantly, differences in bone microstructure between overweight and healthy-weight males were attenuated or no longer significant after adjusting for LM. This result is consistent with previous DXA [26, 37, 42] and pQCT [14, 25, 29, 50] studies and suggests enhanced bone microstructure in overweight youth adapts to their greater LM, not FM, consistent with the functional model of bone

development [44]. It is unclear as to why we did not observe the same differences between groups for females. This may, in part, be due to our distal, highly trabecularized, measurement sites. A number of pQCT studies in females found differences in cortical area and density at diaphyseal, primarily cortical, measurement sites [17, 39, 40]. Additionally, females generally have less LM and more FM than males [34] and this was the case for both healthy-weight and overweight groups. However, the distribution of BMI, LM, and FM within sexes was similar, so greater heterogeneity within soft tissue for males does not explain this finding. There was, however, greater heterogeneity within males across bone microstructure variables at the radius and for BV/TV at the tibia, which might contribute to this finding.

The contribution of LM to bone mass, structure, and strength is well established [19]. The functional model of bone development [44] proposes bone adapts its size, structure, and strength to dynamic loads associated with muscle contractions, not static loads associated with body weight. In previous studies of children and adolescents, LM explained a high proportion of variance in bone mass [4, 41] and strength and their accrual [32]. In the present study, LM predicted as much as 17% of the variance in bone

Fig. 4A–D Scatterplots show (A, B) Tt.Ar and (C, D) BV/TV versus (A, C) LM and (B, D) FM at the radius. Healthy-weight males are represented by solid circles; overweight males are represented by solid triangles; healthy-weight females are represented by open circles; overweight females are represented by open triangles. Correlations are represented by a solid line for males and a dashed line for females.

geometry, density, and microstructure variables across sites in males and females. Further, in our study, males' FM was an independent negative predictor of BV/TV, Tb.N, and Tb.Th and was not associated with Tb.Sp (Fig. 3). This finding is in contrast to the positive relationships observed between excess body fat and BV/TV measured with micro-CT at the distal femur in mice fed a high fat diet for 21 weeks [30]. Thus, in adolescent boys and young adult men, some elements of bone microstructure do not appear to adapt to the excess load associated with higher FM. More importantly, excess adiposity may actually compromise bone microstructure in overweight males. Similar negative relationships between FM and pQCT-derived measures of bone area, BMD, and bone strength were observed at metaphyseal and diaphyseal sites of the radius and tibia in males and females [17, 18, 25, 39, 40, 50, 51]. The mechanisms that underpin potential detrimental effects of excess adiposity on bone structure and strength are not well defined. However, elevated adiposity is linked with increased levels of proinflammatory cytokines, which may, in turn, be linked with increased bone resorption [10]. Thus, the skeleton may fall victim to adverse metabolic effects related to excess adiposity.

At first glance, our results suggest overweight youth have a bone microstructural advantage over their

healthy-weight peers. However, on closer examination, our findings for bone microstructure align with the pQCT-based findings of Wetzsteon et al. [50]; that is, bone strength in overweight children appears to adapt to LM but is disproportionate relative to body weight, given the greater proportion of FM. We found the trabecular bone microstructure of overweight males, but not overweight females, adapted to their greater LM. Specifically, excess FM in males may have a detrimental effect on the thickness and number of individual trabeculae. Although bone microstructure appeared adapted to LM in overweight males, this may be insufficient to withstand the greater load from FM, particularly if excess adipose tissue enhances inflammatory response and promotes bone resorption [10]. This may partially explain why overweight adolescents are at greater risk of fracture and supports the need for effective interventions to promote healthy weight across the growing years. As in other studies [14, 17, 25, 29, 39, 43, 50, 51], we highlight the importance of accounting for LM (or other surrogates of muscle force) when examining the body mass or body fat-bone relation. Longitudinal studies with a greater number of overweight and obese participants are essential to further describe the fat-bone relationship across the important period of adolescent growth and into adulthood in females and males.

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