Bone 129 (2019) 115103

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Full length article

Marrow adipose tissue in adolescent girls with obesity

Vibha Singhal[a,b,c,1], Amita Bose[a,1], Yini Liang[a], Gitanjali Srivastava[d,e,f], Susan Goode[g], Fatima Cody Stanford[a,b,c], Madhusmita Misra[a,b], Miriam A. Bredella[h,*]

[a] Neuroendocrine Unit, Massachusetts General Hospital and Harvard Medical School, United States
[b] Division of Pediatric Endocrinology, Massachusetts General Hospital for Children and Harvard Medical School, United States
[c] Massachusetts General Hospital Weight Center, United States
[d] Department of Medicine, Section on Endocrinology, Diabetes, Nutrition & Weight Management, Boston Medical Center, United States
[e] Department of Medicine, Division of Diabetes, Endocrinology & Metabolism, Vanderbilt University School of Medicine, United States
[f] Department of Pediatrics, Vanderbilt University School of Medicine, United States
[g] Division of Pediatric Gastroenterology, Massachusetts General Hospital for Children and Harvard Medical School, United States
[h] Department of Radiology, Massachusetts General Hospital and Harvard Medical School, United States

ARTICLE INFO

Keywords:
Obesity
Marrow adipose tissue (MAT)
1H-MRS
Bone mineral density (BMD)
Trabecular microarchitecture
Finite element analysis
Adolescents

ABSTRACT

Background: Marrow adipose tissue (MAT) is increasingly recognized as an active and dynamic endocrine organ that responds to changes in nutrition and environmental milieu. Compared to normal weight controls, adolescent girls with anorexia nervosa have higher MAT content, which is associated with impaired skeletal integrity, but data are limited regarding MAT content in adolescents with obesity and how this interacts with bone endpoints.
Objective: To evaluate (i) MAT content in adolescents with obesity compared to normal-weight controls, (ii) the association of MAT with bone endpoints, and (iii) whether these associations of MAT are affected by body weight.
Methods: We assessed MAT, bone endpoints, and body composition in 60 adolescent girls 14–21 years old: 45 with obesity (OB) and 15 normal-weight controls (NW-C). We used (i) DXA to assess areal bone mineral density (aBMD) at the lumbar spine and total hip, and total body fat and lean mass, (ii) proton magnetic resonance spectroscopy (1H-MRS) to assess MAT at the 4th lumbar vertebra and femur, and MRI to assess visceral (VAT) and subcutaneous adipose tissue (SAT), (iii) high resolution peripheral quantitative CT (HR-pQCT) to assess volumetric BMD (vBMD), (iv) individual trabeculae segmentation to evaluate trabecular bone (plate-rod morphology), and (v) finite element analysis to assess stiffness (a strength estimate) at the distal radius and tibia.
Results: Groups did not differ for age or height. Weight, BMI, and areal BMD Z-scores at all sites were higher in the OB group ($p < 0.0001$). MAT was lower in OB at the femoral diaphysis ($p = < 0.0001$) and the lumbar spine ($p = 0.0039$). For the whole group, MAT at the lumbar spine and femoral diaphysis was inversely associated with BMI, total fat mass, lean mass, and VAT. Even after controlling for body weight, independent inverse associations were observed of femoral diaphyseal and lumbar MAT with total tibial vBMD, and of lumbar MAT with radial trabecular vBMD.
Conclusion: Adolescent girls with obesity have lower MAT than normal-weight controls despite having an excess of total body fat. These findings confirm that MAT is regulated uniquely from other adipose depots in obesity. MAT was inversely associated with vBMD, emphasizing an inverse relationship between MAT and bone even in adolescent girls with obesity.

1. Introduction

Recent studies have recognized bone marrow adipose tissue (MAT) as an active endocrine organ involved in skeletal health. Marrow adipocytes originate as mesenchymal stem cells (MSCs), which are the common progenitor stem cells for adipocytes and osteoblasts [1]. Studies have demonstrated an inverse relationship between MAT and bone mineral density (BMD) due to the shared stem cell origins of adipocytes and osteoblasts. Consistent with this, MAT is inversely associated with areal and volumetric BMD in female adolescents with anorexia nervosa

* Corresponding author at: Harvard Medical School, Massachusetts General Hospital, Yawkey 6E, 55 Fruit Street, Boston, MA 02114, United States.
E-mail address: mbredella@mgh.harvard.edu (M.A. Bredella).
[1] The authors have contributed equally as first authors.

https://doi.org/10.1016/j.bone.2019.115103
Received 9 August 2019; Received in revised form 26 September 2019; Accepted 6 October 2019
Available online 14 October 2019
8756-3282/

and women with obesity and type 2 diabetes [2–6].

MAT accumulation is closely related to aging. At birth, red or hematopoietic bone marrow consists of multipotent MSCs. As we age, red marrow gradually transitions into yellow or fatty marrow from increased differentiation of MSCs into adipocytes. The adult distribution of MAT in the skeletal system is typically reached by 25 years [7]. Two different types of MAT have been described. Regulated MAT (rMAT) is responsive to environmental cues including nutritional, hormonal, and weight changes, and is found in proximal skeletal sites, and constitutive MAT (cMAT), which is comparatively more inert, and is found at distal skeletal sites [8].

While MAT levels are higher in some conditions of bone loss, such as aging, osteoporosis, and anorexia nervosa, [2,9,10], there are limited data regarding the quantity of MAT in adolescents with obesity. Children and young adults with obesity have higher bone mineral content (BMC) and BMD compared to children and young adults of normal weight [11]. However, studies have revealed a higher incidence of fractures in adolescents with obesity despite this higher BMC and BMD [12]. We have recently shown that trabecular microarchitecture in adolescents and adults with obesity may be affected adversely and may not compensate adequately for the increased mechanical loading associated with obesity [13,14]. Moreover, we have shown inverse associations of MAT with trabecular vBMD at the distal tibia in a small cohort of adolescents with obesity [15]. However, there are no data regarding associations of MAT with rod and plate trabecular parameters, which confer differential strength to long bones, and no data in adolescents with obesity. Moreover, associations of MAT with bone endpoints at the non-weight-bearing distal radius, a common site of fracture in adolescents with obesity, have not been examined.

The purpose of this study was to examine MAT content of the lumbar spine and femoral diaphysis in adolescents with obesity (OB) compared to normal-weight controls (NW-C). We hypothesized that OB participants, who are known to have higher areal BMD, would have lower MAT than NW-C, based on the known inverse relationship between BMD and MAT. We additionally characterized associations of MAT and bone endpoints, particularly plate and rod trabecular parameters, and evaluated how these relationships are affected by body weight. We hypothesized that MAT would be inversely associated with bone trabecular parameters in adolescents with obesity.

2. Methods

2.1. Participants

We evaluated 60 female adolescents and young adults between the ages of 14–21 years, 45 with obesity (OB) and 15 normal-weight controls (NW−C). Data for OB and NW−C groups were obtained between 2014–2018 from baseline visits of three ongoing studies assessing MAT and body composition in our institution. The Partners HealthCare Institutional Review Board (IRB) approved all three studies. Informed consent was obtained from all participants ≥18 years and parents of participants younger than 18 years old. Assent was obtained from participants < 18 years old.

Participants within the OB group had a body mass index (BMI) above the 95th percentile for age and gender. NW−C were required to have a BMI between the 10th and 90th percentiles for age and gender and at least 9 menstrual cycles in the preceding 12 months.

2.2. Experimental protocol

This was a cross sectional study where all subjects completed a medical history, physical examination and anthropometric measurements (weight and height) at our institution. BMI was calculated as (weight [kilograms]) / (height [m]) ^{2}. Participants' BMI z-scores were determined via CDC databases. The Paffenberger questionnaire was used to evaluate physical activity.

2.3. Assessment of bone and body composition endpoints

All participants were evaluated on the same DXA and HR-pQCT instruments, and scans were analyzed with the same software. Areal BMD Z-scores of the lumbar spine and total hip were determined using DXA (Hologic 4500 A, Waltham, MA). Areal BMD was adjusted for age and race and Z-scores reported using a standardized database [16]. DXA was also used to assess total body lean and fat mass.

Bone volumetric BMD (vBMD)- total, cortical, and trabecular- of the distal radius and tibia were assessed using HR-pQCT (XtremeCT; Scanco Medical AG, Bassersdorf, Switzerland). The non-dominant wrist and leg were analyzed unless there was a previous acute fracture at these sites, in which case the non-fractured side was assessed. Distal CT slices at 9.5 mm and 22.5 mm from the radius and tibia endplates, respectively, were obtained. All participants had a bone age of at least 15 years. We used fixed sites as linear growth is mostly complete in girls by this age.

Characterization of rod-plate trabecular morphology was performed using individual trabecula segmentation. [17]. Trabeculae microarchitecture of cancellous bone can be plate-like or rod-like. Plate-like trabeculae provide greater strength to bone than rod-like trabeculae. Therefore, relative proportions of plate-like vs. rod-like trabeculae can have an impact on bone strength [18].

Finite element analysis (FEA) was performed to estimate biomechanical properties of bone in the setting of simulated axial compression. Of note, strength estimates from FEA correlate strongly with bone strength assessed using cadaveric bone [19,20]. Failure load was estimated by scaling the resultant load from a 1% apparent compressive strain until 2% of all elements reached an effective strain > 7000μ strain [21].

2.4. Assessment of marrow adipose tissue

Subjects underwent single voxel proton magnetic resonance spectroscopy (1H-MRS) of the L4 vertebra (proximal skeleton) and mid femoral diaphysis (distal skeleton) to determine MAT content utilizing a 3.0 T MR imaging system (Siemens Trio, Siemens Medical Systems, Erlangen, Germany).

For lumbar 1H-MRS, a 15 × 15 x 15 mm (3.4 ml) voxel was placed in the L4 vertebral body. Similarly, for femoral 1H-MRS, a 12 × 12 x 12 mm (1.7 ml) voxel was placed in the femoral diaphysis. At both sites, point-resolved spatially located spectroscopy (PRESS) pulse sequence without water suppression was used to obtain data for single-voxel 1H MRS (TE:30 ms, TR: 3000 ms, 8 acquisitions, 1024 data points, receiver bandwidth:2000 Hz). We used automated procedures for gradient shimming and transmit and receive gain optimization. MAT quantification at our institution has a coefficient of variation of 3% [22].

LC Model software (version 6.1-4A; Stephen Provencher, Oakville, ON, Canada) was used for 1H-MRS data fitting as previously described [2]. LC Model bone marrow lipid estimates were expressed as a lipid to water ratio (LWR) once automatically scaled to unsuppressed water peak (4.7 ppm).

2.5. Assessment of visceral and subcutaneous adipose tissue

At the mid-portion of the L4 level, we obtained a single axial T1-weighted MR image (Siemens Trio, 3 T, Siemens Medical Systems, Erlangen, Germany) through the abdomen (10 mm slice thickness, 40 cm field of view, TR: 300 msec, TE: 12 msec, echo train:4, 512 × 512 matrix). Abdominal subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) cross sectional areas (cm^2) were determined based on offline analysis of tracings via commercial software (VITRAK; Merge/eFilm, Milwaukee, WI).

Table 1
Clinical characteristics of adolescents and young women of normal-weight and with obesity.

	Normal-weight controls (NW-C) (n = 15)	Obesity (OB)(n = 45)	P-value
Age (years)	18.4 ± 2.3	18.1 ± 2.0	0.71
Weight (kg)	59.6 ± 6.6	120.3 ± 18.0	< .0001
Height (cm)	166.2 ± 3.3	165.4 ± 6.5	0.62
BMI (kg/m^2)	21.6 ± 2.3	43.9 ± 5.7	< .0001
BMI Z-Score	0.2 ± 0.8	2.4 ± 0.2	< .0001
Age at Menarche (Years)	12.9 ± 0.8	11.9 ± 1.5	0.01
Gynecologic Age (years)	5.5 ± 2.7	6.3 ± 2.1	0.21
% with Amenorrhea	0 (0/15)	17.8 (8/45)	0.18
Activity (hrs/week)	4.2 ± 5.8	3.6 ± 3.9	0.63
Race			
White	66.7	55.6	0.0002
Black	0	20.0	
Asian	33.3	2.2	
Unknown	0	22.2	

2.6. Statistical analysis

JMP Statistical Discovery Software (Version 13, SAS Institute, Carey, NC) was used for data analysis. Clinical characteristics of OB and NW−C groups were compared with either t-tests or Wilcoxon tests, depending on data distribution. We controlled the results for race. We used Spearman correlations to study relationships between MAT and other covariates. If there were significant associations, we ran regression models controlling for weight to determine whether the covariates had independent relationships with MAT. A significant p-value was represented by a value < 0.05.

3. Results

3.1. Clinical characteristics

Clinical characteristics of the participants are shown in Table 1. Groups were similar in age and height. As per the design of the study, weight and BMI were higher in OB than NW−C. Activity level was similar in both groups. Race differed between the two groups with a higher representation of blacks in the OB group and Asians in the NW−C group.

Menarchal age was younger in OB than NW−C, consistent with obesity being associated with an earlier age of menarche, but the gynecological age (duration since menarche) did not differ between groups. This suggests similar chronic estrogen exposure between groups. The NW−C group did not include any participants with amenorrhea (per study design). The percentage of OB who had amenorrhea for more than 6 months was 17.8% (8/45). Amenorrhea in OB group was likely consequent to polycystic ovarian syndrome (PCOS), which is associated with normal estrogen exposure despite oligo-amenorrhea. Two of the 15 NW−C and 16 of the 45 OB were using oral contraceptives ($p = 0.08$). None of the OB participants had diabetes.

3.2. Marrow adipose tissue, body composition, and bone parameters

MAT at the lumbar spine **(**Fig. 1**)** and femoral diaphysis was lower in the OB group compared to the NW−C group (Table 2). These differences persisted after controlling for age, gynecologic age (to control for chronic estrogen exposure) and activity hours (as exercise is known to affect MAT). After controlling for race, MAT remained lower in OB vs. NW−C at the femoral diaphysis ($p = 0.0005$), but the statistical significance was attenuated to a trend level at the lumbar spine ($p = 0.08$). As expected, total lean and fat mass, VAT and SAT were higher in OB than NW−C (Table 2).

We have previously reported aBMD, vBMD and ITS data in a subset of this cohort [13,15]. We report these endpoints in this manuscript to demonstrate associations of bone parameters with MAT. As previously reported, OB had higher areal and volumetric BMD at most sites (except radial and tibial cortical vBMD and tibial plate trabecular bone volume fraction) (Table 2). We only report trabecular parameters here as we have previously shown inadequate adaptation of trabecular parameters to body weight in obesity [13,14]. We now explore the potential role of MAT in the inadequate adaptation of trabecular parameters to increasing body weight in adolescents with obesity.

3.3. Whole group associations of MAT with body composition and bone endpoints

3.3.1. Femoral diaphyseal MAT

No association was found between femoral diaphyseal MAT and age, menarchal age or gynecological age. This did not change after controlling for weight. We did observe an inverse association of femoral diaphyseal MAT with weight, BMI, total fat and lean mass, VAT and SAT. This inverse association with total fat and lean mass persisted after controlling for body weight ($p = 0.01$ and 0.03 respectively). However, associations with VAT and SAT lost significance. ($p = 0.29$ and 0.44 respectively).

MAT at the femoral diaphysis was inversely associated with aBMD at the lumbar spine and hip, vBMD at the distal radius and tibia, and trabecular parameters as shown in Table 3, most of which seem to be driven by body weight (as associations were attenuated after controlling for weight). Only total tibial vBMD remained independently inversely associated with MAT after controlling for weight ($p = 0.01$) **(**Fig. 2**).**

3.3.2. Lumbar MAT

No association was found between lumbar MAT and age, menarchal age or gynecological age. We found an inverse association of lumbar MAT with weight, BMI, total fat and lean mass, and VAT. However, associations with fat mass, lean mass and VAT were lost after controlling for body weight ($p = 0.37$; $p = 0.29$ and $p = 0.17$ respectively).

Lumbar MAT was inversely associated with hip aBMD, total and trabecular vBMD at the distal radius and tibia, and trabecular parameters at the distal radius as shown in Table 3. We found an inverse association between lumbar MAT and plate and axial bone volume fraction at the radius, and a positive association with the rod bone volume fraction ($p \leq 0.04$). Most of these associations were drive by body-weight, and only total vBMD at the distal radius and tibia remained independently inversely associated with MAT after controlling for weight ($p = 0.04$ and $p = 0.02$, respectively) **(**Fig. 2**).**

4. Discussion

To our knowledge, this is the first study to focus on the quantitative assessments of marrow adipose tissue (MAT) in adolescents with obesity, compared no normal weight controls (NW-C), and to evaluate its association with trabecular bone and body composition endpoints. We found that adolescent girls with obesity had lower MAT at both the femoral diaphysis (DIA), an appendicular inert MAT depot, and the lumbar spine (L4), an axial dynamic MAT depot, compared to NW-C. This suggests that obesity during adolescence counters the normal physiologic increase in MAT seen with normal pubertal development. Higher MAT content has been demonstrated in adolescents with anorexia nervosa at the opposite end of the weight spectrum [10], and weight recovery in young women with anorexia nervosa has been shown to normalize MAT [22]. This further suggests that MAT development is responsive to weight changes, including weight gain, during adolescence. While high fat diets lead to MAT expansion in preclinical studies [23], the factors leading to decreases in MAT in adolescents with obesity are still unknown and merit further research.

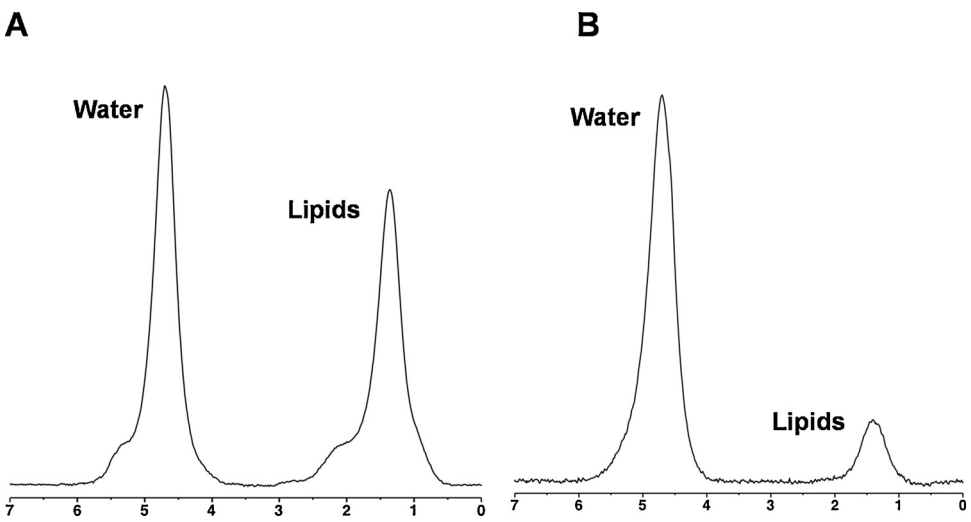

Fig. 1. 1H-MR spectroscopy (1H-MRS) of L4 in an 18-year-old female of normal weight (BMI: 24.8 kg/m^2 (A) and an age-matched female with obesity (B). Marrow adipose tissue (MAT) content by 1H-MRS is lower in the subject with obesity compared to the normal-weight control (lipid-to-water ratio 0.92 vs 0.27). For purposes of visual comparison, the amplitudes of unsuppressed water are scaled identically.

As mesenchymal stem cells differentiate into osteocytes and adipocytes during the transition of red marrow into yellow marrow, a commensurate increase in MAT is expected during adolescence. We did not find associations between MAT and age despite literature reporting positive associations between these variables [24,25]. This may be due to the narrow age range of our cohort.

As observed in other conditions that span the nutritional spectrum, such as anorexia nervosa, athletic amenorrhea, and type 2 diabetes [2,4,6,10], we found inverse associations of MAT with (i) areal BMD at the lumbar spine and hip, and (ii) total and trabecular vBMD at the radius and tibia. In obesity, which is characterized by higher BMD, we show lower MAT, but persistence of the inverse relationship between MAT and BMD. Furthermore, we report an independent inverse association of both axial (lumbar) and appendicular (femoral diaphysis) MAT with total vBMD at the weight bearing tibia after controlling for weight. This suggests that paracrine and autocrine factors from MAT may impact vBMD and require further investigation.

More specifically, for the first time, we report an inverse association of lumbar MAT with plate and axial bone volume fraction at the radius, and a positive association with the rod bone volume fraction. Recent studies have highlighted that plate-like and axially aligned trabeculae provide greater strength to bone than rod-like trabeculae [26]. This

Table 2
Measures of Body Composition, marrow adipose tissue, bone density and microarchitecture in adolescents and young women of normal-weight and with obesity.

	Normal-weight controls (NW-C) (n = 15)	Obesity (OB) (n = 45)	P-value
Body Composition Measures (DXA and MRI)			
Total Fat Mass (kg)	20.7 ± 4.7	60.9 ± 12.4	< .0001*
Total Lean Mass (kg)	39.1 ± 3.6	61.2 ± 8.3	< .0001*
Visceral Adipose Tissue (cm^2)	36.1 ± 19.5	109.1 ± 50.0	< .0001*
Subcutaneous Adipose Tissue (cm^2)	162.3 ± 83.5	700.8 ± 144.4	< .0001*
Marrow Adipose Tissue Measures (1H-MRS)			
Femoral Diaphysis MAT (Lipid/Water Ratio)	6.10 ± 1.69	3.27 ± 2.41	< .0001*
L4 vertebral MAT (Lipid/Water Ratio)	0.59 ± 0.25	0.39 ± 0.19	0.0039
Areal BMD (DXA)			
Total Hip Z-Score	−0.31 ± 0.88	2.0 ± 1.01	< .0001*
Lumbar Spine Z-Score	−0.66 ± 1.01	1.3 ± 0.95	< .0001*
Volumetric BMD Measures (HR-pQCT) - Radius			
Radius Total Density (mgHA/cm^3)	302.3 ± 50.9	357.1 ± 68.3	0.0087*
Radius Cortical vBMD (mgHA/cm^3)	809.9 ± 81.5	841.3 ± 55.2	0.117
Radius Trabecular vBMD (mgHA/cm^3))	156.2 ± 21.1	200.6 ± 36.9	< .0001*
Individual Trabecular Segmentation (ITS)- Radius			
Radius BV/TV	0.258 ± 0.031	0.318 ± 0.044	< .0001*
Radius Axial BV/TV	0.10 ± 0.02	0.123 ± 0.03	0.03
Radius Plate BV/TV	0.085 ± 0.03	0.12 ± 0.04	0.0049
Radius Rod BV/TV	0.17 ± 0.02	0.19 ± 0.03	0.03
Strength Estimates (FEA) - Radius			
Radius Stiffness (kN/mm)	70.1 ± 14.48	89.54 ± 15.27	< .0001*
Volumetric BMD Measures (HR-pQCT) - Tibia			
Tibia Total Density (mgHA/cm^3)	284.1 ± 33.8	358.6 ± 49.3	< .0001*
Tibia Cortical vBMD (mgHA/cm^3)	854.1 ± 40.4	875.4 ± 32.8	0.06
Tibia Trabecular vBMD (mgHA/cm^3))	176.4 ± 21.6	225.5 ± 30.2	< .0001*
Individual Trabecular Segmentation (ITS)- Tibia			
Tibia BV/TV	0.287 ± 0.028	0.359 ± 0.038	< .0001*
Tibia Axial BV/TV	0.142 ± 0.03	0.136 ± 0.03	0.47
Tibia Plate BV/TV	0.145 ± 0.04	0.153 ± 0.04	0.5**
Tibia Rod BV/TV	0.142 ± 0. 03	0.21 ± 0.05	0.0002*
Strength Estimates (FEA) - Tibia			
Tibia Stiffness (kN/mm)	196.88 ± 27.18	25.61 ± 31.27	< .0001*

* P < 0.05 after controlling for race.
** P < 0.05 after controlling for race and changes directionality.

Table 3
Correlation analysis of femoral diaphyseal and lumbar marrow adipose tissue with clinical characteristics, body composition, bone density and micro-architecture in adolescents and young women of normal-weight, and with obesity.

	DIA MAT		L4 MAT	
	r	p	r	p
Clinical Characteristics				
Age	−0.13	0.34	−0.11	0.41
Menarchal Age	0.03	0.81	−0.02	0.99
Gynecologic Age	−0.1	0.46	−0.07	0.61
Body Composition				
Weight	−0.42	0.001	−0.35	0.006
BMI	−0.50	< 0.0001	−0.44	0.0004
Total Fat	−0.48	0.0001*	−0.36	0.005
Total Lean Mass	−0.35	0.006*	−0.31	0.016
Visceral Adipose Tissue (cm^2)	−0.44	0.0005	−0.43	0.0006
Subcutaneous Adipose Tissue (cm^2)	−0.42	0.001	−0.25	0.05
Areal BMD (DXA)				
Total Lumbar Z Score	−0.31	0.02	−0.26	0.05
Total Hip Z Score	−0.41	0.001	−0.33	0.01
(HR-pQCT) - Radius				
Radius Total vBMD (mgHA/cm^3)	−0.39	0.004	−0.36	0.009
Radius Cortical vBMD(mgHA/cm^3)	−0.32	0.02	−0.21	0.14
Radius Trabecular vBMD(mgHA/cm^3)	−0.34	0.01	−0.42	0.002*
Radius Axial Bone Volume Fraction	−0.14	0.32	−0.38	0.006
Radius Plate Bone Volume Fraction	−0.17	0.22	−0.28	0.04
Radius Rod Bone Volume Fraction	−0.35	0.01	0.28	0.04
Radius Failure Load (N)	−0.12	0.39	−0.28	0.04
(HR-pQCT) - Tibia				
Tibia Total vBMD (mgHA/cm^3)	−0.50	0.0001*	−0.42	0.0016*
Tibia Cortical vBMD (mgHA/cm^3)	−0.31	0.02	−0.14	0.31
Tibia Trabecular vBMD (mgHA/cm^3)	−0.39	0.004	−0.36	0.007
Tibia Axial Bone Volume Fraction	00.13	0.34	0.06	0.66
Tibia Plate Bone Volume Fraction	0.006	0.96	0.15	0.29
Tibia Rod Bone Volume Fraction	−0.41	0.002	−0.15	0.29
Tibia Failure Load (N)	−0.26	0.06	−0.24	0.09

* P < 0.05 after controlling for weight.

may be particularly relevant in obesity because we have recently shown that although adolescents with obesity have higher BMD, they have altered bone adaptation with deficits in plate trabecular bone fraction [13]. However, similar associations of MAT were not observed at the weight bearing tibia. These differences may be due to the unique relationships of appendicular MAT (diaphyseal MAT) versus axial MAT (lumbar MAT) with appendicular skeleton structure and need further exploration.

We also investigated associations between MAT and body composition, including total fat and lean mass, VAT, and SAT. MAT is one of many adipose depots throughout the body and accounts for 10% of total body fat. The regulation of MAT seems to differ from that of other fat depots [27,28], although studies of the relationships of MAT with SAT, VAT, and total body fat have not been conclusive. We found inverse associations of diaphyseal and lumbar MAT with VAT and SAT, which were lost after controlling for weight, though diaphyseal MAT remained inversely associated with total fat and total lean mass. These results indicate that bone marrow does not accumulate fat in adolescents with obesity to the same degree as other fat depots, suggesting that MAT is a unique fat depot, which is regulated differently from VAT or SAT. Our observed inverse association between MAT and VAT is unlike studies in adults, which have found a positive correlation between lumbar MAT and VAT in premenopausal women with obesity [5] and between lumbar MAT and total and subcutaneous adipose tissue in women with diabetes [29], while a study in adult women with obesity both with and without type 2 diabetes could not demonstrate an association between MAT and VAT [30].

Our study has some limitations. First, this was a cross-sectional study, so we cannot determine causation. Second, the use of a single TE without applying T2 correction might affect the age-dependent changes of MAT in our adolescent population, as it was shown in adults [31]. Third, race differed between the two groups with a higher representation of Blacks in the OB group and Asians in the NW−C group. We therefore controlled our analyses for race. Additionally, we did not investigate vitamins or hormones involved in MAT regulation to evaluate the biochemical regulation of this fat depot versus other fat depots and bone endpoints. Future studies should assess longitudinal outcomes and incorporate hormonal evaluations to investigate the micro-environment involved in MAT and bone health.

In conclusion, MAT in the lumbar spine and femoral diaphysis is lower in adolescent girls with obesity compared to normal-weight controls. Also, MAT at the femoral diaphysis is inversely associated with total volumetric BMD at the tibia and plate trabecular BMD at the radius. These findings demonstrate that the inverse association between MAT and BMD is maintained in adolescents with obesity.

Authorship

All authors should have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

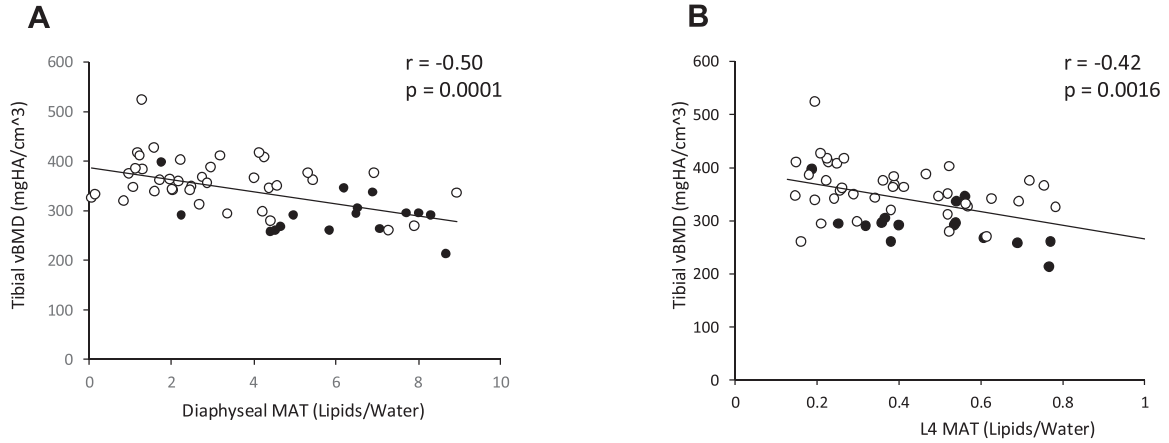

Fig. 2. Correlation analysis between femoral diaphyseal (A) and lumbar (B) marrow adipose tissue with tibial volumetric BMD in females with obesity (open circles) and normal weight controls (closed circles). There is an inverse association between femoral and lumbar marrow adipose tissue and tibial volumetric BMD, which remained significant after controlling for weight.

Declaration of Competing Interest

The authors have no conflicts of interest to disclose relevant to this paper

Grant support

This work was supported by the NIH R01 DK103946MM, MAB, NIH K23DK110419VS,P30-DK040561VS, FCS,K24DK109940MAB,K24 HD071843MM,L30 DK118710FCS

References

[1] L. Hu, et al., Mesenchymal stem cells: cell fate decision to osteoblast or adipocyte and application in osteoporosis treatment, Int. J. Mol. Sci. 19 (2) (2018).
[2] M.A. Bredella, et al., Increased bone marrow fat in anorexia nervosa, J. Clin. Endocrinol. Metab. 94 (6) (2009) 2129–2136.
[3] N. Abdalrahaman, et al., The relationship between adiposity, bone density and microarchitecture is maintained in young women irrespective of diabetes status, Clin. Endocrinol. (Oxf.) 87 (4) (2017) 327–335.
[4] V. Singhal, et al., Regional fat depots and their relationship to bone density and microarchitecture in young oligo-amenorrheic athletes, Bone 77 (2015) 83–90.
[5] M.A. Bredella, et al., Vertebral bone marrow fat is positively associated with visceral fat and inversely associated with IGF-1 in obese women, Obes. (Silver Spring) 19 (1) (2011) 49–53.
[6] E.W. Yu, et al., Marrow adipose tissue composition in adults with morbid obesity, Bone 97 (2017) 38–42.
[7] S.G. Moore, K.L. Dawson, Red and yellow marrow in the femur: age-related changes in appearance at MR imaging, Radiology 175 (1) (1990) 219–223.
[8] E.L. Scheller, et al., Region-specific variation in the properties of skeletal adipocytes reveals regulated and constitutive marrow adipose tissues, Nat. Commun. 6 (2015) 7808.
[9] J. Justesen, et al., Adipocyte tissue volume in bone marrow is increased with aging and in patients with osteoporosis, Biogerontology 2 (3) (2001) 165–171.
[10] V. Singhal, et al., Impaired bone strength estimates at the distal tibia and its determinants in adolescents with anorexia nervosa, Bone 106 (2018) 61–68.
[11] J. van Leeuwen, et al., Differences in bone mineral density between normal-weight children and children with overweight and obesity: a systematic review and meta-analysis, Obes. Rev. 18 (5) (2017) 526–546.
[12] G. Valerio, et al., Prevalence of overweight in children with bone fractures: a case control study, BMC Pediatr 12 (2012) 166.
[13] V. Singhal, et al., Suboptimal bone microarchitecure in adolescent girls with obesity compared to normal-weight controls and girls with anorexia nervosa, Bone 122 (2019) 246–253.
[14] M. Schorr, et al., Differences in trabecular plate and rod structure in premenopausal women across the weight spectrum, J. Clin. Endocrinol. Metab. (2019).
[15] V. Singhal, et al., Differential associations between appendicular and axial marrow adipose tissue with bone microarchitecture in adolescents and young adults with obesity, Bone 116 (2018) 203–206.
[16] B.S. Zemel, et al., Revised reference curves for bone mineral content and areal bone mineral density according to age and sex for black and non-black children: results of the bone mineral density in childhood study, J. Clin. Endocrinol. Metab. 96 (10) (2011) 3160–3169.
[17] X.S. Liu, et al., Individual trabeculae segmentation (ITS)-based morphological analysis of high-resolution peripheral quantitative computed tomography images detects abnormal trabecular plate and rod microarchitecture in premenopausal women with idiopathic osteoporosis, J. Bone Miner. Res. 25 (7) (2010) 1496–1505.
[18] J. Wang, et al., Trabecular plates and rods determine elastic modulus and yield strength of human trabecular bone, Bone 72 (2015) 71–80.
[19] R.P. Crawford, C.E. Cann, T.M. Keaveny, Finite element models predict in vitro vertebral body compressive strength better than quantitative computed tomography, Bone 33 (4) (2003) 744–750.
[20] A. Kroker, et al., Distal skeletal tibia assessed by HR-pQCT is highly correlated with femoral and lumbar vertebra failure loads, J. Biomech. 59 (2017) 43–49.
[21] W. Pistoia, et al., Estimation of distal radius failure load with micro-finite element analysis models based on three-dimensional peripheral quantitative computed tomography images, Bone 30 (6) (2002) 842–848.
[22] P.K. Fazeli, et al., Marrow fat and preadipocyte factor-1 levels decrease with recovery in women with anorexia nervosa, J. Bone Min. Res. 27 (9) (2012) 1864–1871.
[23] M. Tencerova, et al., High-fat diet-induced obesity promotes expansion of bone marrow adipose tissue and impairs skeletal stem cell functions in mice, J. Bone Min. Res. 33 (6) (2018) 1154–1165.
[24] H. Kugel, et al., Age- and sex-specific differences in the 1H-spectrum of vertebral bone marrow, J. Magn. Reson. Imaging 13 (2) (2001) 263–268.
[25] D. Schellinger, et al., Potential value of vertebral proton MR spectroscopy in determining bone weakness, AJNR Am. J. Neuroradiol. 22 (8) (2001) 1620–1627.
[26] X.S. Liu, X.H. Zhang, X.E. Guo, Contributions of trabecular rods of various orientations in determining the elastic properties of human vertebral trabecular bone, Bone 45 (2) (2009) 158–163.
[27] M.J. Devlin, C.J. Rosen, The bone-fat interface: basic and clinical implications of marrow adiposity, Lancet Diabetes Endocrinol. 3 (2) (2015) 141–147.
[28] J. Paccou, et al., The role of bone marrow fat in skeletal health: usefulness and perspectives for clinicians, J. Clin. Endocrinol. Metab. 100 (10) (2015) 3613–3621.
[29] I.M. de Araujo, et al., Marrow adipose tissue spectrum in obesity and type 2 diabetes mellitus, Eur. J. Endocrinol. 176 (1) (2017) 21–30.
[30] T. Baum, et al., Does vertebral bone marrow fat content correlate with abdominal adipose tissue, lumbar spine bone mineral density, and blood biomarkers in women with type 2 diabetes mellitus? J. Magn. Reson. Imaging 35 (1) (2012) 117–124.
[31] M. Dieckmeyer, et al., The need for T(2) correction on MRS-based vertebral bone marrow fat quantification: implications for bone marrow fat fraction age dependence, NMR Biomed. 28 (4) (2015) 432–439.