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MRI-Measured Bone Marrow Adipose Tissue is Inversely Related to Cortical Bone Area in Children and Adolescents 5– 18 Year Old

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Introduction

Recent studies suggest that osteoporosis is not only related to body weight and total body fat, but also to bone marrow fat (1–3). One theory explaining the inverse association between marrow fat and bone is that an increase in the differentiation of MSCs to adipocytes will lead to a decrease in the differentiation of MSCs to osteoblasts, as adipocytes and osteoblasts share the same progenitor, the bone marrow mesenchymal stem cells (MSCs) (4–6). The differentiation of MSCs into either fat or bone is influenced by hormones, adipokines, PPAR γ , as well as mechanical stimuli (5, 7, 8). Mechanisms that promote the adipogenic fate of MSCs actively suppress intracellular osteogenic signals(6).

Consistent with previous findings for cancellous bone (1–3, 9), our group reported an inverse correlation between bone marrow adipose tissue and bone mineral density in the pelvis, spine, and hip regions in adults and in children, independent of gender and ethnicity (10–14). On the other hand, the relationship between marrow fat and bone at cortical bone sites has been reported in very few studies (15–17). Cortical bone strength is critical in weight-bearing and physical performance (18). Cortical bone plays an important role with

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regard to bone strength in both children and adults. Throughout the life span, the cortical envelope constitutes the outer part of all skeletal structures and comprises 80% of skeletal mass. Children, however, are more likely to fracture the cortical-rich appendicular skeleton as compared to adults (19). Specific pediatric metabolic bone disorders, such as X-linked hypophosphatemic rickets and chronic kidney disease (CKD), illustrate the importance of cortical bone parameters in pediatric populations (20). Children with CKD have decreased cortical volumetric bone mineral density as measured by peripheral quantitative computed tomography (21). Importantly, low cortical density in childhood CKD has been associated with a 4-fold higher incidence of fracture (22) than that reported in a large population-based study of fracture epidemiology in children and adolescents (23). Taken together, these reports substantiate the critical role of cortical bone in pediatric populations.

The present study used whole-body magnetic resonance imaging (MRI) technology to explore the relationship between bone marrow adipose tissue area (BMA) and cortical bone area (CBA) in children and adolescents, with adjustment for body weight, fat distribution and body composition. Confirmation of an inverse relationship between BMA and CBA in children and adolescents would suggest that a competitive relationship between marrow fat and bone may exist during the bone accruing stage of life.

Methods and Materials

Protocol and Design

The present study is an analysis of pre-existing data as previously reported (14, 24, 25). The participants were 185 healthy children and adolescents, aged 5–18 years. These subjects were recruited through local advertisement for two studies that were originally designed to collect body composition data in healthy children and adolescents (14, 24, 25). Candidates for this study underwent screening of medical history, physical examination, and blood tests. Those who had a diagnosis of any underlying disease or chronic illness were excluded. A standardized whole-body MRI and dual-energy X-ray absorptiometry (DXA) scans were acquired from all subjects. Weight and height were obtained for each subject. Pubertal status was available in a sub-cohort 155 subjects. Ethnicity was self-reported by each participant.

The Institutional Review Board reviewed and approved the exempt status of the present study. All subjects provided written consent to participate in the original studies, which were approved by the Institutional Review Board.

Magnetic resonance imaging (MRI)

Whole-body MRI was carried out using a 1.5 Tesla scanner (General Electric, 6X Horizon, Milwaukee, WI) as previously described (26). All subjects were scanned with T1-weighted, spin-echo sequence with 210-ms repetition time and a 17-ms echo time. During the scan, subjects remained in a supine position with their arms extended over their heads. The L4-L5 inter-vertebral disk was used as the point of origin, as 10-mm-thick axial slice images were obtained from fingers-to-toes with a 40 mm inter-slice gap.

All images were segmented and analyzed at the Image Analysis Laboratory of the New York Obesity Nutrition Research Center using SliceOmatic imaging analysis software

(Tomovision Inc., Montreal, QC, Canada). Right mid-femur BMA, right mid-femur CBA, subcutaneous adipose tissue (SAT), visceral adipose tissue (VAT), and skeletal muscle of each subject were semi-automatically (i.e., a combination of manual analysis and threshold method) analyzed by trained technicians (11–13). The examiners were blind to subject clinical history, image interpretation and test results.

Dual-energy x-ray absorptiometry

Total body fat of each subject was assessed by DXA (GE Lunar, Madison, WI) with the whole-body mode. All scans were analyzed by trained technologist using Prodigy software version 6.7. Routine DXA calibration and quality control measures have been previously reported (27).

Statistical analysis

Mean and standard deviations (SD) were used as descriptive statistics. Pearson's correlation coefficients were calculated among CBA, BMA, weight, BMI percentile, age, SAT, VAT, and skeletal muscle.

Four regression models were established with CBA as dependent variable and BMA as independent variable (Table 3). Adjustment for demographic factors (age, sex, pubertal status and ethnicity) was applied in all 4 models. Additional variables included body weight (Model 1), total body fat (Model 2), and SAT, VAT and skeletal muscle (Model 3). Model 4 included all variables including body weight, total body fat, SAT, VAT, and skeletal muscle. Because of multicollinearity, weight and total body fat were excluded from model 4 in the final analysis. Stepwise regression was used to build the multivariable regression models, with a P value of 0.05 for entry and retention.

Shapiro-Wilk test was used to test normality of the residual distributions, and Levene's test was used to evaluate homogeneity of variance. Variables that did not have a normal distribution were log transformed initially. If the log transformation did not normalize the residual values, the Box-Cox transformations were applied.

All statistic tests and data analysis were performed by SAS 9.2 program package (SAS Institute. Inc., Cary, NC, USA). Two-tailed ($\alpha=0.05$) significance tests were used.

Results

Descriptive Statistics

The characteristics of participants are reported in Table 1. The study included 109 boys and 76 girls. The cohort consisted of 14% Caucasian, 37% African American, 34% Hispanic, 8% Asian, and 7% other ethnic groups.

Relationship between CBA and BMA

Pearson correlation coefficients among CBA, BMA, weight, BMI percentile, age, total body fat, SAT, VAT, and skeletal muscle are shown in Table 2. A positive association between log-transformed BMA and log-transformed CBA ($r = 0.313$, $p < 0.001$) was observed in

unadjusted analyses. After adjustment for demographic factors (age, sex, and ethnicity), body weight, total body fat, SAT, VAT, and skeletal muscle, a negative relationship was observed between BMA and CBA ($\beta = -0.201$ to -0.272 , $P < 0.001$, Table 3).

Relationship between CBA, BMA and body composition

In unadjusted analyses, both BMA and CBA were significantly correlated with weight, BMI percentile, total body fat, SAT, VAT, and skeletal muscle (Table 2). Skeletal muscle was strongly correlated with CBA ($r = 0.891$, $P < 0.001$; Table 2). In regression Model 1 that controlled for weight and body composition, weight was positively associated with CBA after adjusting for BMA (Table 3). In Model 2 that replaced total body fat for weight, total body fat showed a weaker positive association with CBA, but remained statistically significant (Table 3). In Model 3, SAT and skeletal muscle were positively related to CBA (skeletal muscle was more strongly associated with CBA than SAT), and VAT was negatively related to CBA after adjusting for BMA (Table 3). For Model 3, the R^2 was the highest for the model that adjusted for SAT, VAT, and skeletal muscle (R^2 improvement, 0.095–0.155; Table 3). Finally, when weight, total body fat, VAT, SAT and skeletal muscle were all included in Model 4, weight and total body fat were excluded due to multicollinearity. Therefore, the final Model 4 was identical to Model 3 (Table 3).

Results remained the same when regression analyses were performed in the sub-cohort 155 subjects with pubertal status available ($\beta = -0.201$ to -0.272 , $p < 0.001$, $R^2 = 0.717$ to 0.854) (Data not shown).

Discussion

Relationship between CBA and BMA

The present study examined for the first time CBA and BMA relationships in a healthy pediatric sample, in which bone mass was accruing with growth and bone loss only occurs rarely. The present study utilized MRI, which does not involve radiation and has advantages over CT technology in children due to the potential adverse health effects related to CT scans. Our study demonstrated that healthy children and adolescents with higher BMA had lower CBA after adjustment for demographic factors (i.e., age, sex, pubertal status, and ethnicity), body weight or body composition. The positive correlation between BMA and CBA observed in unadjusted analyses could be due to the inclusion of subjects of a wide age range (i.e., 5 to 18 years old). During the period of active bone growth in the childhood years, the medullary cavity enlarges as bone gets larger in diameter (28). Although body weight variation in children and adolescents of the same age may also relate to bone size variation, we assume the large age range of children and adolescents in this study would explain a much larger variation in bone size than weight range of the same age. Our finding is consistent with a recent study in 4–10 year old girls showing older children have more femoral bone marrow adipose tissue and more bone mineral content than younger children (29). Conversely, in young adults when bone size depends less on age, a negative correlation between CBA and BMA was observed (15, 16).

Osteoblasts and adipocytes share a common precursor (i.e., the MSCs in bone marrow) (4–6); and increased adipogenesis may impair bone integrity through reducing osteoblastogenesis (6). Previous studies reported an inverse association between bone and marrow fat in the elderly, young adults, and children (1–3, 9–14). These results support the notion that competition exists between adipogenesis and osteoblastogenesis during the bone loss stage, the peak bone mass stage, and the bone accruing stage (13, 14). Previous studies have reported the relationship between bone and marrow fat in cancellous bone rich sites such as the pelvis, lumbar spine, and femoral neck (1–3, 9–14). The present study, on the other hand, examined the bone and marrow fat in mid-femur, which is a cortical bone region. Cancellous bone is filled with hematopoietically active red marrow. The mid-femur region, on the other hand, is filled with yellow marrow. Bone marrow is converted from red to yellow (adipose, non-hematopoietically active) in a progressive manner. After 5 years of age, the femoral diaphysis contains homogeneous yellow marrow (30). The findings from the present study could be interpreted to suggest that competition between osteogenesis and adipogenesis exists in cortical bone, the non-hematopoietic cellular environment. Moreover, the negative association in cortical bone between bone and marrow fat after adjustment appeared weaker than that in cancellous bone as previously reported by our group (10, 11, 14). These observations are consistent with Di Iorgi et al.'s study that reported a stronger inverse association between bone and marrow fat in the axial than in the appendicular skeleton (15). The regulation of MSCs differentiation may be different in the hematopoietic and non-hematopoietic marrow environment.

Our findings agree with previous studies investigating marrow fat and cortical bone relationship (15–17). Di Iorgi et al. reported a similar inverse relationship between bone acquisition and marrow adiposity in appendicular skeleton of young adults using computed tomography (CT) (15, 16). Another study reported an inverse correlation between cortical bone and marrow adiposity at multiple sites along the diaphysis of the long bones using MRI (17). By studying cortical bone in children and adolescents, the present study fills an important age gap in the literature on the cortical bone and marrow fat relationship. Future researches investigating pediatric bone disorders which specifically affect the cortical compartment, such as CKD, may clarify the role of bone marrow adipose tissue in this pathological condition.

Relationship between BMA, CBA and body composition

Both BMA and CBA were significantly correlated with body weight, BMI percentile, total body fat, SAT, VAT and skeletal muscle in unadjusted analyses. In the cancellous bone study in the same cohort of children and adolescents (14), pelvic bone mineral density, but not pelvic bone marrow fat, was significantly correlated to weight, BMI percentile, total body fat, SAT, VAT and skeletal muscle. The regulation of weight and body composition on cortical bone marrow (yellow marrow) may be different from that on cancellous bone marrow (red marrow).

Both SAT and skeletal muscle were significant predictors of CBA after adjustment for BMA, weight, total body fat, and VAT. These findings agree with the longtime belief that body weight enhances bone mass through mechanical loading. Skeletal muscle has a much

stronger correlation with CBA than SAT, indicating a larger contribution from skeletal muscle to cortical bone mass. It has been found that strengthening muscle increases bone formation rates and bone mass (31), whereas a decrease of mechanical tension on the bone reduces both trabecular and cortical bone mass (32). Mechanical tension also has been shown to influence the differentiation of MSCs. When low gravity was applied to cell culture, MSCs preferentially developed into fat-accumulating cells instead of bone-forming cells (33). Mechanical loading leads to osteoblastogenesis by down-regulating PPAR γ in adipogenesis. Our study also found that the effect of skeletal muscle on cortical bone ($\beta=1.024$, $P<0.001$) is greater than that on cancellous bone ($\beta=0.264-0.614$, $p<0.05$) (11, 14).

In the present study we found that VAT was negatively correlated with CBA after adjustment for BMA, SAT and skeletal muscle. We previously found that VAT was not related to cancellous bone mineral density (11, 14). A recent study by Bredella et al. reported that VAT was positively related to vertebral bone marrow fat, but not vertebral trabecular bone mineral density (9). We speculate that the observed difference in the relationships between cortical and cancellous bones and VAT could be that there are differences in how growth hormone and IGF-1 increase cortical bone mass and cancellous bone density. Growth hormone stimulates the proliferation of osteoblastic cell lineage through increasing IGF-1, which enhances the differentiation of MSCs towards bone formation (7). Growth hormone and IGF-1 are inversely associated with VAT (34), and specifically increase the cortical thickness along with endosteal growth (35). Since VAT accounts for approximately 1/50 of body weight (10), the negative contribution of VAT to CBA is likely a hormonal effect of VAT, rather than weight-bearing effect of VAT.

Limitation

This cross-sectional study is not able to answer whether there is a causal relationship between CBA and BMA. Another limitation is that we only examined mid-femur, a weight-bearing site. Our results may not represent the relationship between cortical bone and bone marrow adipose tissue in non-weight bearing bones. In addition, fracture history and measurement of areal BMD by DXA were not obtained, as these were not part of the aims of the original study. Further studies need to evaluate the difference between non-weight-bearing and weight-bearing sites in the CBA-BMA relationship.

Although the inverse CBA and BMA relationship was statistically significant, the correlation was not strong. Therefore, the present study does not suggest any immediate clinical significance of BMA in bone disease. Rather, our results suggest potential future studies to clarify the role of BMA in bone disease, and to clarify the fat-bone regulation differences between cortical and cancellous bone.

Conclusion

There is a negative relationship between MRI-measured femoral CBA and BMA after adjustment for weight, total body fat, SAT, VAT and skeletal muscle in children and adolescents. Skeletal muscle has the strongest correlation with CBA after adjusting for BMA. A novel finding is that VAT is inversely associated with CBA but not cancellous

bone. Our results contribute to the growing evidence supporting a competitive relationship between marrow fat and bone.

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Table 1

Subject Characteristics (n=185)

Children and adolescents (5–18 years old)		
	Boys	Girls
Total Subjects	109 (58.9%)	76 (41.1%)
Caucasian	16 (8.6%)	10 (5.4%)
African American	35 (18.9%)	34 (18.4%)
Hispanic	40 (21.6%)	23 (12.4%)
Asian	7 (3.8%)	7 (3.8%)
Other	11 (5.9%)	2 (1.1%)
Age (yrs)	11.5 ± 3.5 (9.0, 10.0, 14.0)	11.0 ± 3.6 (8.0, 9.5, 14.0)
Weight (kg)	49.5 ± 21.5 (31.2, 44.6, 63.9)	45.5 ± 20.3 (28.3, 41.6, 56.3)
BMI Percentile	67.4 ± 27.1 (50.0, 71.8, 92.2)	65.6 ± 28.1 (46.0, 70.1, 93.4)
CBA (cm²)	2.672 ± 1.191 (1.760, 2.360, 3.340)	2.324 ± 1.046 (1.510, 2.160, 2.880)
BMA (cm²)	1.021±0.556 (0.630, 0.950, 1.270)	0.859±0.391 (0.600, 0.810, 1.050)
Total body fat (kg)	11.5 ± 9.2 (4.8, 8.9, 15.8)	14.0 ± 10.2 (6.0, 11.6, 20.4)
VAT (L)	0.6 ± 0.6 (0.2, 0.4, 0.9)	0.6 ± 0.6 (0.2, 0.4, 0.8)
SAT (L)	12.1 ± 8.0 (6.5, 9.3, 15.8)	14.9 ± 10.9 (7.2, 11.8, 19.0)
Skeletal Muscle (L)	16.5 ± 8.7 (9.6, 13.7, 23.5)	13.0 ± 5.4 (8.3, 12.1, 16.6)

Results are expressed as n (percentage of total n), mean±SD, and as percentiles (25th, 50th, and 75th).

BMI, body mass index; CBA, cortical bone area; BMA, bone marrow adipose tissue area; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

Table 2

Pearson correlation among right femoral CBA, right femoral BMA, weight, BMI Percentile, age, total body fat, subcutaneous adipose tissue, visceral adipose tissue, and skeletal muscle in children and adolescents.

	CBA [‡]	BMA [‡]	Weight [‡]	BMI Percentile	Age	Total body fat [‡]	SAT [‡]	VAT [‡]
BMA [‡]	0.313 [*]	-	-	-	-	-	-	-
Weight [‡]	0.836 [*]	0.564 [*]	-	-	-	-	-	-
BMI Percentile	0.277 [*]	0.306 [*]	0.520 [*]	-	-	-	-	-
Age	0.769 [*]	0.444 [*]	0.796 [*]	0.033	-	-	-	-
Total body fat [‡]	0.527 [*]	0.450 [*]	0.795 [*]	0.731 [*]	0.446 [*]	-	-	-
SAT [‡]	0.565 [*]	0.438 [*]	0.848 [*]	0.707 [*]	0.505 [*]	0.978 [*]	-	-
VAT [‡]	0.456 [*]	0.426 [*]	0.758 [*]	0.645 [*]	0.471 [*]	0.862 [*]	0.867 [*]	-
Skeletal Muscle [‡]	0.891 [*]	0.558 [*]	0.945 [*]	0.353 [*]	0.852 [*]	0.585 [*]	0.643 [*]	0.581 [*]

[‡]Log transformed to normalize the distribution of the residuals and to equalize the residual variance among groups (i.e., gender and ethnical groups).

^{*} Differs from 0, P<0.001.

BMI, body mass index; CBA, cortical bone area; BMA, bone marrow adipose tissue area; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

Table 3

Regression equation with CBA as the dependent variable in children and adolescents.

Dependent variable	Independent Variables:				
	Model	BMA [‡]	Weight	Total body fat [‡]	Skeletal Muscle [‡]
CBA [‡]	1	-0.254* (0.041)	0.732* (0.061)	-	-
	2	-0.178* (0.050)	-	0.338* (0.050)	-
	3	-0.269* (0.035)	-	-	1.024* (0.077)
	4	-0.269* (0.035)	§	§	1.024* (0.077)

Values are estimates of standardized regression coefficients and standard error of estimates (SEE) are in parentheses.

[‡]Log transformed.

* P<0.001,

§ not included in the model due to multicollinearity.

CBA, cortical bone area; BMA, bone marrow adipose tissue area; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

Covariates tested in each model: (Demographics included age, sex, and ethnicity)

Model 1, CBA = BMA + demographics + weight;

Model 2, CBA = BMA + demographics + total body fat;

Model 3, CBA = BMA + demographics + SAT + VAT + skeletal muscle;

Model 4, CBA = BMA + demographics + weight + total body fat + SAT + VAT + skeletal muscle.