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Comparison of the Relationship between Bone Marrow Adipose Tissue and Volumetric Bone Mineral Density in Children and Adults

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Introduction

An inverse relationship between bone mineral density (BMD) and bone marrow adipocyte levels has been documented in animal and human studies (1–7). This relationship has been attributed to the ability of mesenchymal stem cells (MSCs) to differentiate into either adipocytes or osteoblasts (8–9). Preferential differentiation into a given lineage is dependent upon the extracellular environment of the MSC and the presence of osteoblast or adipocyte stimulatory factors (9–10).

This cellular relationship is supported by recent studies analyzing BMD and BMAT in large cohorts of young and old adult populations (7, 11–15). A recent study by Shen et al. (2012) in young adults who had reached peak bone mass and older adults undergoing potential bone loss, a similar inverse relationship was shown between BMD and BMAT (13). These data support the presence of a competitive relationship between osteoblasts and adipocytes even before the beginning of bone loss. This inverse relationship has not been established in childhood, a stage during which bone mass is accrued.

Dual-energy x-ray absorptiometry (DXA) is commonly used to measure BMD in adults. The output measure of areal BMD (aBMD) produced by DXA, although accurate for adults, is error-prone when being used for the assessment of BMD in children (16). Since bone size and bone thickness increases substantially during childhood development, it is necessary to use volumetric BMD measures (16). Current studies commonly use quantitative computed tomography (QCT) to obtain vBMD; however, caution is required when using QCT extensively in children because of the potential adverse health effects related to CT scans (17).

The aim of this study was to determine if an inverse relationship exists between BMD and BMAT in children. To perform this analysis, vBMD was calculated using DXA measured bone mineral content and MRI measured bone volume. Furthermore, the results of this

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analysis were compared to adult populations to determine the vBMD and BMAT relationship present throughout the lifespan. Since the areal BMD and BMAT relationship in the adult population has been previously reported (13, 18), this paper focuses on comparing this relationship in children and adults.

Methods and Materials

Protocol and Design

The primary study cohort consisted of 181 children, aged 5–17 years. Analysis was also performed on an adult cohort that consisted of 495 study subjects, aged 18 years or older. All subjects were deemed healthy after completion of a medical history, physical examination, and blood test screening. All subjects underwent a standardized whole body MRI and DXA scan. Furthermore, the following measures were obtained for each subject: weight, height, age, pubertal or menopausal status, and self-reported ethnicity.

The current study is an analysis of pre-existing data. The Institutional Review Board of reviewed and approved the exempt status of the present study. All subjects provided written consent to participate in the original study, which was approved by the Institutional Review Board.

Magnetic resonance imaging

Whole-body magnetic resonance imaging (MRI) was carried out using a 1.5 Tesla scanner (General Electric, 6X Horizon, Milwaukee, WI) as previously described (19–20). 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.

The BMAT, bone volume, subcutaneous adipose tissue (SAT), visceral adipose tissue (VAT), and skeletal muscle of each individual were segmented by trained technicians using image analysis software (SliceOmatic, Tomovision Inc., Montreal, QC, Canada). The technicians were blinded to patient demographic and test results. Semi-automated methods (i.e., a combination of threshold method and manual correction) were used to segment BMAT, SAT, VAT, and skeletal muscle as previously described (12–13, 18). Bone regions were manually traced and quality controlled to ensure that non-osseous tissue was omitted from the analysis. Pelvic BMAT and pelvic bone volumes were calculated using the following bones within the region: ilium, sacrum, ischium, pubis, coccyx, and femoral heads. The following equation was used to calculate compartment volumes:

$$V = (t + h) \sum_{i=1}^N A_i$$

Where V is volume, A_i is each scan's cross-sectional area, h is the between slice interval, t is the thickness of each slice, and N is the total number of slices. The intra-class correlation coefficient for volume rendering of skeletal muscle, BMAT, bone volume, SAT and VAT for the same scan by different analysts are 0.99, 0.99, 0.99, 0.99, and 0.95, respectively.

The pelvic bone mineral content (BMC) obtained by the DXA scan was divided by the pelvic bone volume (BV) determined by MRI analysis to calculate pelvic vBMD:

$$vBMD = \frac{BMC}{BV}$$

Dual-energy x-ray absorptiometry

Dual-energy x-ray absorptiometry [GE Lunar, Madison, WI; adults, DPX software version 4.7e; children, Prodigy software version 6.7) was used to estimate areal bone mineral content (BMC) from the whole-body scan. Acquisition and analysis of the scans was performed by trained technologists. Values for pelvic BMC (a region contained within the whole-body scan) were used in the current analyses. The estimated precision level for BMD is 1.28% (21). Routine DXA calibration and quality control measures have been previously reported (22).

Statistics

Pearson's correlation coefficients among pelvic BMAT, pelvic vBMD, age, weight, BMI percentile, total body fat (TBF), VAT, SAT, and skeletal muscle were calculated for children.

Regression models were established using pelvic vBMD as the dependent variable and pelvic BMAT, weight, TBF, SAT, VAT, skeletal muscle as the independent variables, with adjustment for demographic factors (age, sex, race, and pubertal or menopausal status) and biologically plausible two-way interactions (i.e. puberty and BMAT interaction). Multivariable regression models were built using stepwise regression, with $P=0.05$ for entry and retention.

Equality of variance was assessed using Levene's test and normality of the residual distributions was determined using the Shapiro-Wilk test. Variable values 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.

The SAS 9.2 program package (SAS Institute. Inc., Cary, NC, USA) was used to carry out all statistical tests. Two-tailed ($\alpha=0.05$) significance tests were used.

Results

Descriptive Statistics

The subjects' characteristics are reported in Table 1. The child cohort consisted of 106 boys and 75 girls. Girls had a significantly lower mean skeletal muscle volume (12.80 L vs. 16.37 L, $p<0.05$) than boys. The adult cohort consisted of 150 men and 345 women. Women had a higher mean total body fat (26.6 kg vs. 17.8 kg, $p<0.05$) and a lower mean skeletal muscle volume (20.27 L vs. 30.72 L, $p<0.05$) than men. In addition, women had a higher mean pelvic vBMD (0.374 g/cm³ vs. 0.335 g/cm³, $p<0.05$) and a lower pelvic BMAT (0.136 L vs. 0.166 L, $p<0.05$) than men.

Relationship between vBMD and BMAT in children

An inverse correlation was seen between the Box-Cox transformed pelvic BMAT and the log transformed pelvic vBMD ($r=-0.374$, $p<0.001$) in children. Pelvic vBMD, but not pelvic BMAT, is significantly correlated to weight, BMI percentile, TBF, VAT, SAT, and skeletal muscle (Table 2).

In regression models 1–4 (Table 3), weight and TBF were omitted from model 4 due to collinearity. A significant inverse relationship is present between pelvic vBMD and pelvic BMAT with adjustment for weight ($\beta=-0.319$, $p<0.001$), for TBF ($\beta=-0.348$, $p<0.001$), and for SAT, VAT and skeletal muscle ($\beta=-0.323$, $p<0.001$) (Table 3). The R^2 was the highest for the model that adjusted for SAT, VAT, and skeletal muscle ($R^2=0.581$) (Table 3). Results remained the same when regression analyses were performed in the sub-cohort 153 children with pubertal status available ($\beta=-0.351$ to -0.384 , $p<0.001$, $R^2=0.576$ to 0.603) (Data not shown).

Comparison of children and adult populations

In the adult population, an inverse correlation between the Box-Cox transformed pelvic BMAT and the log transformed pelvic vBMD ($r=-0.650$, $p<0.001$) was observed. Using similar regression models as those used in children (model 1, 2, 3 and 4), we observed an inverse relationship between pelvic vBMD and pelvic BMAT in the adult population in all of the models created ($\beta=-0.501$ to -0.509 , $p<0.001$, $R^2=0.471$ to 0.475) (Data not shown). The children and adult populations show a similar inverse trend between pelvic vBMD and pelvic BMAT (Figure 1). In the pooled dataset including both adult and children, a regression model was created that included child or adult status as an independent variable. The inverse relationship between pelvic vBMD and pelvic BMAT remained ($\beta=-0.323$, $p<0.001$). Additionally, being a child or adult did not significantly contribute to the pelvic BMD ($p=0.995$) and no significant interaction was found between child status and pelvic BMAT ($p=0.415$).

Discussion

The current study found that an inverse relationship exists between pelvic vBMD and pelvic BMAT in 5–17 year old children. Several studies have shown that BMD and BMAT are reciprocally related throughout adulthood (>18 years of age) (13). However, to our knowledge, this is the first study to examine the BMD and BMAT relationship in children (<18 years of age). Furthermore, this study compares vBMD with BMAT, replacing the more commonly used aBMD measures of previous studies. These findings confirm the presence of an inverse relationship between vBMD and BMAT throughout the lifespan, even during periods of bone acquisition. A recent study shows that physical activity intervention decreases femoral BMAT in young children (23), suggesting that possibility of using BMAT as a biomarker for bone quality in children.

A similar inverse relationship between vBMD and BMAT was found in both childhood and adult populations. This inverse relationship between vBMD and BMAT apparent across the lifespan can be explained by the intricate relationship that exists between osteoblasts and bone adipocytes. Both of these cell types share a common precursor cell: the mesenchymal stem cell (8–9). MSCs have been found to preferentially differentiate into adipocytes (9–10). Therefore, in a cellular environment not conducive to osteoblast formation, a higher level of adipocytes will be present. Fat has been shown to inhibit osteoblast formation, so a high level of bone marrow fat can significantly reduce the amount of functional osteoblast cells present (24). The paucity of osteoblast cells results in decreased bone mineral deposition. Another hypothesis is that the inverse relationship between bone and BMAT can be simply explained by the space-filling role of adipocytes during bone loss (10). However, since this inverse relationship is also evident in childhood when bone loss is rare, support for the latter hypothesis is less.

Previous studies have used MRI and DXA in adult populations to determine if an inverse relationship exists between BMD and BMAT. The novelty of this study lies in its choice of bone density measure and body region. Two-dimensional DXA measures of bone mineral

density are reliable in adults, but are error-prone when used with child populations (16). Therefore, the three-dimensional measure of vBMD is preferred because it accounts for the factors that reduce the accuracy of two-dimensional measures (e.g. the size of the bone along the axis parallel to the X-ray beam) (16, 25). Previous studies have used QCT, volumetric calculations from lateral DXA scans, and a combination of lateral and anteroposterior DXA scans to obtain the vBMD (25–27).

Studies performed with adult populations have confirmed that an inverse relationship exists between pelvic aBMD measures and total body BMAT (13, 28). Furthermore, pelvic aBMD has been shown to be inversely related to BMAT levels in body regions such as the vertebrae and pelvis (13, 29). The present study is the first to use the pelvic vBMD in children and adults.

In children, vBMD was found to be positively correlated to skeletal muscle but not related to VAT or SAT. Previous studies have found similar relationships in children, albeit with different bone mineral measures. In a study performed by Faulkner *et al.*, BMD and body composition of 224 boys and girls aged 8–16 were analyzed. They found that in both boys and girls, bone free lean tissue mass was positively correlated to increasing total BMD, while fat mass was not (30). Although the study uses two dimensional DXA measurements, the findings corroborate those found in the current study.

There are limitations to our study. One limitation is the use of the pelvic region to assess the relationship between BMD and BMAT. Bone mineral accrual and bone marrow fat accumulation varies depending on body region and age (31–33). An assessment of the bone mineral-bone marrow relationship in other regions, such as the spine and femoral neck, would be important because these regions are used for diagnosis of osteoporosis. A previous study has reported the inverse relationship between BMD and BMAT in the hip and spine regions in an adult population, but this relationship needs to be shown in future studies in children (13).

Another limitation is that the data used is cross-sectional. As such, it is difficult to determine whether bone mineral loss precedes bone marrow fat accumulation, or vice versa.

The interslice distance (i.e., 5 cm) may also be inducing error when calculating tissue volume. Although a previous study has shown that a 5 cm image acquisition protocol is comparable in accuracy to the contiguous protocol for group comparisons in 5–17 year old children (19), for future studies with young children it may increase accuracy to use a contiguous MRI protocol for the quantification of pelvic vBMD. Future studies may also use the recently advanced water-fat imaging technique to quantify BMAT, especially in children.

Previous studies have found that BMAT presence can cause an underestimation of BMD(34). A BMAT increase of 50% is needed to underestimate BMD by 5–6%, with the underestimation being severe in some osteoporotic individuals (34–35). Given the low levels of BMAT in children (Table 1), the error caused by underestimating BMD may be minimal. The influence of BMAT on BMD may partially affect the relationship observed, but it is unlikely that there was a major underestimation of BMD. More detailed discussion on this issue can be found in a previous study (36).

Conclusion

The current study found an inverse relationship between BMD and BMAT in children. This extends previous findings showing an inverse relationship in both young and older adults. The findings call for further study of the mechanisms that affect BMD- BMAT relationship.

Given that BMD accrual may be dependent on BMAT levels –and vice versa- at all stages of life, targeting and reducing BMAT through lifestyle or drug therapies may promote the attainment of peak bone mass.

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Figure 1.
The relationship between pelvic BMAT and pelvic vBMD in children (N=181) and adults (N=495).

Table 1

Subject Characteristics

	Children (5–17 years old)		Adult (18 years old)	
	Males	Females	Males	Females
Total Subjects	106	75	150	345
Caucasian	15	9	65	138
African American	34	34	47	156
Hispanic	39	23	18	26
Asian	7	7	19	24
Other	11	2	1	1
Age (yrs)	11.5 ± 3.6 (10.0, 8.0, 14.0)	10.9 ± 3.5 (9.0, 8.0, 14.0)	43.1 ± 18.0 (38.0, 28.0, 57.0)	44.7 ± 17.3 (41.0, 31.0, 56.0)
Weight (kg)	49.1 ± 21.1 (44.5, 31.2, 63.9)	44.5 ± 18.5 (41.3, 27.3, 54.9)	79.1 ± 13.1 (79.7, 70.4, 87.8)	71.3 ± 16.6 (68.2, 58.2, 82.8)
BMI (kg/m²)	N/A	N/A	25.5 ± 4.1 (25.2, 22.4, 28.0)	27.0 ± 5.9 (26.0, 22.2, 31.4)
BMI Percentile	67.4 ± 27.1 (72.1, 50.0, 91.2)	65.1 ± 28.0 (70.0, 45.6, 93.0)	N/A	N/A
Pelvic vBMD (g/cm³)	0.354 ± 0.091 (0.332, 0.295, 0.395)	0.376 ± 0.096 (0.383, 0.318, 0.434)	0.335 ± 0.081 (0.280, 0.320, 0.389)	0.374 ± 0.115* (0.299, 0.364, 0.436)
Pelvic BMAT (L)	0.043 ± 0.038 (0.035, 0.013, 0.064)	0.052 ± 0.053 (0.034, 0.015, 0.064)	0.166 ± 0.127 (0.142, 0.064, 0.227)	0.136 ± 0.130* (0.098, 0.030, 0.198)
Total body fat (kg)	11.4 ± 9.2 (8.8, 4.8, 15.8)	14.0 ± 10.2 (11.6, 6.0, 20.4)	17.8 ± 8.9 (16.9, 11.0, 22.6)	26.6 ± 12.2* (24.7, 16.6, 36.3)
VAT (L)	0.6 ± 0.7 (0.4, 0.2, 0.9)	0.5 ± 0.4 (0.4, 0.2, 0.8)	2.5 ± 1.9 (2.1, 1.1, 3.5)	1.7 ± 1.2 (1.3, 0.7, 2.3)
SAT (L)	12.0 ± 8.0 (9.3, 6.3, 15.6)	14.3 ± 9.4 (11.6, 7.1, 18.9)	17.4 ± 7.2 (16.6, 12.0, 20.7)	27.2 ± 12.2 (24.3, 17.2, 36.8)
Skeletal Muscle (L)	16.4 ± 8.5 (13.5, 9.6, 23.5)	12.8 ± 5.2* (12.0, 8.2, 16.5)	30.7 ± 5.4 (30.3, 27.2, 34.3)	20.3 ± 3.7* (20.0, 17.8, 22.6)

Results are expressed as mean±SD and (median, 25th and 75th percentile).

BMI, body mass index; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

* Differs from male counterparts, P<0.05;

Table 2

Pearson correlation coefficients among vBMD, BMAT, visceral and subcutaneous adipose tissue, total fat, BMI percentile and age in children.

	Pelvic BMAT [‡]	Pelvic vBMD [‡]	Age	Weight	BMI Percentile	TBF [‡]	VAT [‡]	SAT [‡]
Pelvic vBMD[‡]	-0.374**	-	-	-	-	-	-	-
Age	-0.048	0.593**	-	-	-	-	-	-
Weight	-0.103	0.597**	0.762**	-	-	-	-	-
BMI percentile	-0.038	0.202*	-0.004	0.482**	-	-	-	-
TBF[‡]	0.056	0.424**	0.450**	0.770**	0.724**	-	-	-
VAT[‡]	0.109	0.329**	0.453**	0.728**	0.631**	0.863**	-	-
SAT[‡]	0.107	0.474**	0.489**	0.828**	0.692**	0.978**	0.861**	-
Skeletal Muscle[‡]	-0.122	0.618**	0.849**	0.916**	0.323**	0.588**	0.571**	0.636**

[‡] Either log or Box-Cox transformed to normalize the distribution of the residuals and to equalize the residual variance among groups.

* Differs from 0, P<0.05;

** Differs from 0, P<0.001.

BMI, body mass index; TBF, total body fat; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

Table 3

Regression equation with pelvic vBMD as the dependent 10 variable in children.

Dependent variable	Independent Variables:						
	Model	Pelvic BMAT [‡]	Weight	TBF [‡]	SAT [‡]	VAT [‡]	Skeletal Muscle [‡] R ²
Children Pelvic vBMD [‡]	1	-0.319 ^{**} (0.051)	0.312 ^{**} (0.079)	-	-	-	0.570
	2	-0.348 ^{**} (0.052)	-	0.206 ^{**} (0.058)	-	-	0.562
	3	-0.323 ^{**} (0.052)	-	-	0.180 ^{NS} (0.125)	-0.041 ^{NS} (0.117)	0.581
	4	-0.323 ^{**} (0.052)	§	§	0.180 ^{NS} (0.125)	-0.041 ^{NS} (0.117)	0.581

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

[‡] either log or Box-Cox transformed.

* P<0.05,

** P<0.001,

NS not significant,

§ not included in the model due to multicollinearity.

TBF, total body fat; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

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

Model 1, pelvic vBMD= pelvic BMAT + demographics + weight;

Model 2, pelvic BMD= pelvic BMAT + demographics + TBF;

Model 3, pelvic BMD= pelvic BMAT + demographics + SAT + VAT + skeletal muscle;

Model 4, pelvic BMD= pelvic BMAT + demographics + weight + TBF + SAT + VAT + skeletal muscle.