

Bone Marrow Adipose Tissue in Adolescence- Protective or Pathogenic

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Abstract

Background: Pathogenic attributes of bone marrow adipose tissue (BMAT) described in the older population could explain the prominent sequela in osteoporosis and even type 2 diabetes in adults. However, its rapid appearance in long bones during arguably the most critical period in skeletal and metabolic programming, challenge this notion. The timing of a substantial proportion of BMAT accrual in long bones during the linear growth spurt suggest an evolutionarily conserved protective effect in which the growing skeleton must benefit from its appearance in some way. Thus, if BMAT is protective, how does induced disruption of the conversion influence differentiation at the cellular level between osteogenesis and adipogenesis and subsequently affect bone strength-structure properties. The objective of this study was to test the hypothesis that obesity accelerates the size of the marrow compartment at the expense of quality components of bone, ultimately compromising bone material properties and structural design. Further, as muscle and bone adapt in parallel we also aimed to evaluate qualitative and quantitative aspects of skeletal muscle and the relationship between bone and muscle.

Methods: Subjects were 46 overweight/obese girls age 7-12 years. Magnetic resonance imaging (MRI) was used to assess femoral BMAT and marrow area and density were assessed by peripheral quantitative computed tomography (pQCT). Bone and muscle parameters were evaluated by MRI, pQCT and dual-energy X-ray absorptiometry (DXA). Partial correlation was used to assess the degree of association between BMAT and bone parameters as well as BMAT and muscle parameters after controlling for race and age.

Results: BMAT was positively associated with quantitative aspects of bone and muscle. However, marrow density, a qualitative attribute of the marrow compartment representative of hematopoietic capacity was inversely associated with cortical density and marginally inversely associated with cortical area. Further, muscle density, reflective of muscle health was positively associated with quantitative aspects of bone and muscle, yet an association with quality was not detected.

Conclusion: Early in the life course, at a critical period for bone health, obesity may negatively influence muscle and skeletal development. Though speculative, our results support a potential mechanism by which obesity impairs bone integrity via effects on the marrow compartment. Future studies are warranted to evaluate how the protective effect of BMAT on bone and muscle health may be conserved.

Keywords: Bone marrow adipose tissue; Puberty; obesity; Bone muscle

Abbreviations: BMC: Bone Mineral Content; BMAT: Bone Marrow Adipose Tissue; CA: Tibial Cortical Area; CD: Tibial Cortical Density; CSMA: Cross-Sectional Muscle Area; DXA: Dual-Energy X-Ray Absorptiometry; fBMAT: Bone Marrow Adipose Tissue; MRI: Magnetic Resonance Imaging; MSC: Mesenchymal Stem Cell; pQCT: Peripheral Quantitative Computed Tomography

Introduction

Whereas obesity in childhood has been associated with greater quantitative parameters of bone (i.e., mineral content and density) [1], fracture is overrepresented among obese youth [2-5] suggesting impairments in bone quality [6]. The association between increased fracture and obesity has been attributed to greater rate of falls due to poor balance, increased impact during falls due to excess weight, abnormal loading of the bones and joints and decreased physical activity impeding growth of skeletal muscle among obese children [7-9]. While these factors warrant consideration, evaluation of the relationship largely focused on bone mineral content and/or density estimated from assessment of the outer surface of the bone, have failed to delineate a potential causal mechanism. The strength of bone is dependent upon size and structure as well as qualitative aspects, suggesting a need for evaluation of the inner surface of the bone, including the marrow compartment. The marrow compartment is largely comprised of red, hematopoietic marrow and yellow fatty marrow. In aging, the fatty

elements in the marrow increase as does the composition of the marrow. A change in composition leads to a change in function. Importantly, the variety of secretory factors synthesized and released by adipocytes within the bone marrow adipose tissue (BMAT), change with aging and in disease states [10-15]. Thus the marrow compartment represents an auspicious area of investigation underlying long-term bone health.

The historical view of bone marrow adipose tissue (BMAT) as simply a “filler” void of function has been reconsidered, with more recent implications suggesting that appearance of adipose within the marrow is a pathogenic consequence of suppressed (inner) bone formation. As the greatest rate of the natural course of conversion from hematopoietic marrow to BMAT in long bones occurs at the same time bone growth peaks, converging metabolic pathways to optimize skeletal integrity may have the greatest impact on long-term bone

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health [16-18]. Pathogenic attributes of BMAT described in the older population could explain the prominent sequelae in osteoporosis and even type 2 diabetes in adults, although its rapid appearance in long bones during arguably the most critical period in skeletal and metabolic programming challenge this notion. However, the timing of a substantial proportion of BMAT accrual in long bones during the linear growth spurt indicates a conferred benefit to the growing skeleton. While BMAT represents a "fat-storage" depot supporting hematopoiesis, a fine-tuned homeostatic balance tolerating very little disruption has led to a conserved selective priority in storing energy for supporting bone development and metabolic regulation. Accordingly, the delicate balance of the multi-potency of marrow-derived mesenchymal stem cells (MSC) during normal developmental processes, which underlies the conversion of red marrow to BMAT were adapted for a system which imparts mechanotransduction to bone maintaining MSC multipotency, promoting osteogenesis and limiting adipogenesis within the marrow cavity [13,19]. Speculatively, obesity-induced disruption of normative conversion of hematopoietic to adipose constituents within the marrow represents consequential differentiation at the cellular level between osteogenesis and adipogenesis. Subsequently, altered marrow conversion may result in a maturational switch perturbing mitogenic signaling, growth factor synthesis and release and feedback systems controlling developmental aspects of bone development.

The objective of this study was to test the hypothesis that obesity accelerates the size of the marrow compartment at the expense of quality components of bone, ultimately compromising bone material properties and structural design. Further, as muscle and bone adapt in parallel we also aimed to evaluate qualitative and quantitative aspects of skeletal muscle and the relationship between bone and muscle.

Subjects and Methods

Subjects

This evaluation represents an ongoing cohort comprised of overweight/obese but otherwise healthy participants enrolled in clinical studies, including dietary and physical activity interventions, and observational studies aimed at investigating body composition during the pubertal transition conducted at the University of Alabama at Birmingham (UAB). Subjects were recruited through newspaper advertisements, flyers posted at various community partnerships and by word-of-mouth. Irrespective of study enrollment, the present investigation is limited to cross-sectional analyses of baseline data for participants who underwent DXA, pQCT and MRI scans. The total sample included 46 girls ages 7-12 years (78% non-Hispanic black). All the procedures were approved by the UAB Institutional Review Board and informed consent and assent (where appropriate) were obtained.

Anthropometric assessment

Weight was measured using a digital scale to the nearest 0.1 kg in minimal clothing without shoes. Height was also recorded without shoes using a digital stadiometer.

Scanning

Bone, muscle and fat parameters were assessed using magnetic resonance imaging (MRI of the femur), whole body dual-energy x-ray absorptiometry (DXA) and peripheral quantitative computed tomography (pQCT) of the tibia.

DXA

Total body composition (percent body fat mass, lean body mass

and bone mineral content) was measured by DXA using a GE Lunar Prodigy densitometer (GE LUNAR Radiation Corp., Madison, WI). Subjects were scanned in light clothing, while lying flat on their backs with arms at their sides. DXA scans were performed and analyzed using pediatric software (enCORE 2002 Version 6.10.029). In our laboratory, the coefficient of variation (CV) for repeated measures of total body fat mass is 6.55%.

MRI imaging and analysis

Measures for femoral bone marrow adipose tissue were acquired using MRI. MRI which involves no ionizing radiation is emerging as a comprehensive tool for fat quantification. For MRI, children were scanned using a Philips 3T system in the UAB Division of Cardiology. A series of T1-weighted slices (allowing for rapid scans with strong fat-water tissue contrast) were acquired at the upper-leg regions with data acquisition beginning at the iliac crest and continuing to the knee (superior border of the patella). Scans were analyzed off-site in the laboratory at the University of Southern California using Sliceomatic (Tomovision, Inc.) software. The technique used for analysis has been described elsewhere [20,21]. Briefly, the procedure involves the transfer of images to an offline workstation, followed by the use of Sliceomatic software that requires manual intervention.

pQCT

For the pQCT scan, the Stratec 3000XCT (White Plains, NY) was used. The tibial length was measured from the prominence of the medial malleolus to the medial condyle (mm). One slice was taken at 66% of the total length using the TIBIA Muscle mask and then analyzed using the macro software to quantify marrow area, marrow density, cortical area, cortical density, bone area, cross-sectional muscle area and muscle density.

Statistical Analysis

Subject characteristics (Table 1) were determined by univariate analysis. Partial correlation coefficients were determined between variables of interests with adjustment for age and race. Statistical

Variable	Mean+SEM
Age (yrs)	9.9 + 0.2
Height (in)	56.9 + 0.5
Weight (lbs)	131.9 + 4.3
BMI%	97.6 + 0.4
BMC (g)	1577.1 + 49.9
Lean Mass (kg)	31.6 + 10.0
Total Body Fat (kg)	25.9 + 10.5
% Fat	43.5 + 0.7
fBMAT (mm ³)	140.1 + 10.8
Marrow Area (mm ²)	116.4 + 8.9
Marrow Density (mg/cm ³)	29.6 + 1.7
CA (mm ²)	209.6 + 10.9
CD (mg/cm ³)	950.7 + 6.4
BA (g/cm)	3.6 + 0.1
CSMA (mm ²)	4984.4 + 206.8
Muscle Density (mg/cm ³)	71.0 + 1.2

BMI%= Body mass index percentile based on age- and sex-specific charts (CDC); BMC= Whole body bone mineral content (assessed by DXA); fBMAT=Femoral bone marrow adipose tissue (assessed via MRI); CA=Tibial cortical area (assessed by pQCT); CD = Tibial cortical density (pQCT); CSMA= cross-sectional muscle area (pQCT); BA= Bone area (pQCT)

Table 1: Study Subjects (n=46) Characteristics.

significance was set at $p < 0.05$. All data were analyzed using SAS 9.1 software (SAS institute Inc. Cary, NC).

Results

Subjects were 46 overweight/obese but otherwise healthy peri-pubertal girls (9.9 ± 1.8 yrs; range 7-12 years) with BMI percentile ranging from (90-98th).

Quantitative assessment of bone was similar irrespective of method of measurement. Bone mineral content (BMC) assessed by DXA and bone mass area assessed by pQCT strongly correlated ($r=0.83$; $p < 0.001$). Similarly, fBMAT by MRI and pQCT were highly associated ($r=0.73$; $p < 0.01$). Finally, muscle area by pQCT and lean mass by DXA were associated ($r=0.89$, $p < 0.001$). However, neither BMC and cortical density nor marrow area and density were correlated. Further, muscle area and muscle density were marginally inversely associated ($r=-0.24$, $p=0.09$). fBMAT assessed by MRI or pQCT was positively associated with BMC (DXA, $p < 0.001$; pQCT, $p < 0.001$), bone area (pQCT, $p < 0.001$) and muscle area/mass (DXA, $p < 0.001$, pQCT $p < 0.01$) but not cortical density. Conversely, fBMAT was inversely associated with marrow density ($r=-0.46$, $p=0.05$).

Figure 1 presents the correlation coefficients for the relationship between weight or total fat and bone and muscle quantity and quality measures. Weight and total fat were positively associated with measures reflecting bone and muscle size. However, qualitative aspects of bone and muscle were inversely associated with obesity measures.

Table 2 presents the relationship between BMAT and bone parameters. Marrow adiposity was positively associated with quantitative aspects of bone, but not cortical density, a qualitative estimate. However, marrow density was inversely associated with cortical density and marginally inversely associated with cortical area.

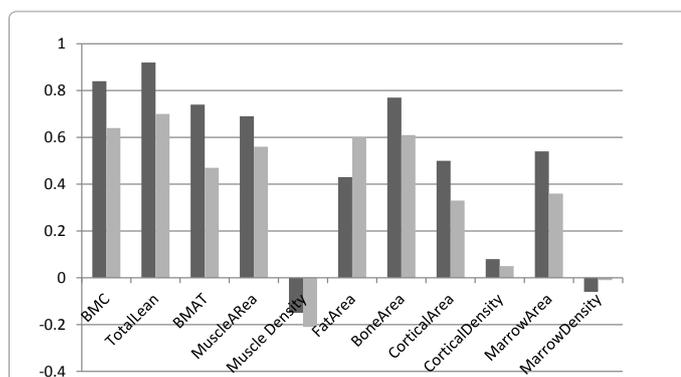


Figure 1: illustrates the correlation coefficients between measures of obesity (weight dark gray bars) and body fat (light gray bars) and bone and muscle parameters. Bars above axis represent positive association, below inverse. Statistical significance was set at $p < 0.05$.

	Bone Area		Cortical Area		Cortical Density		BMC	
	r	p-value	r	p-value	r	p-value	r	p-value
BMAT	0.78	0.0001	0.69	0.0014	0.13	0.62	0.83	<0.001
Marrow Area	0.53	0.02	0.58	0.01	0.03	0.91	0.62	0.006
Marrow Density	-0.33	0.18	-0.41	0.09	-0.52	0.03	-0.38	0.12

BMC= Whole body bone mineral content (assessed by DXA); BMAT=Femoral bone marrow adipose tissue (assessed via MRI)

Table 2 Relationship between bone marrow adipose tissue and bone parameters.

	Muscle Area		Muscle Density		Lean Mass	
	r	p-value	r	p-value	r	p-value
BMAT	0.66	0.0031	0.41	0.09	0.81	<.0001
Marrow Area	0.32	0.19	0.33	0.18	0.56	0.02
Marrow Density	-0.19	0.46	-0.33	0.19	-0.33	0.18

Table 3 Relationship between Bone Marrow Adipose Tissue and Muscle Parameters.

Table 3 presents the relationship between BMAT and muscle parameters. Marrow adiposity was positively associated with quantitative aspects of muscle, but not a qualitative.

Discussion

The bone marrow microenvironment's integral involvement in directing cell lineage represents the crux of integrative physiology, ultimately governing bone marrow stem cell function. The timing of conversion of hematopoietic marrow to BMAT is suggestive of physiologic relevance for linear growth and an evolutionarily conserved physiologic benefit to the bone modeling process. Notwithstanding an accelerated presence of BMAT is associated with impairments in metabolic and skeletal health reminiscent of aging [19]. The objective of this study was to evaluate the relationships between bone marrow adipose tissue and bone and muscle parameters in overweight/obese girls. Our main finding in this cohort of overweight/obese girls was a positive relationship between BMAT and quantitative aspects of bone and muscle that were not translated to greater bone strength or muscle function.

We have previously reported greater BMAT in obese girls relative to their leaner counterparts. This study provides a potential explanation for the impaired bone integrity frequently reported among obese children, particularly the lower extremities of obese girls [8]. Though speculative, our results support a potential mechanism by which obesity impairs bone integrity via effects on the marrow compartment. Maintenance of hematopoietic capacity is essential for bone strength-structure by promoting deposition of bone matrix proteins and minerals as well as supporting self-renewal, expansion and activity crucial for the dynamic remodeling of the skeletal system. This is particularly relevant to the development of the appendicular skeleton during the linear growth spurt. While BMAT represents a "fat-storage" depot with hematopoietic properties, a fine-tuned homeostatic balance has led to a conserved selective priority in storing energy for supporting bone development and metabolic regulation. Accordingly, the multi-potency of marrow-derived mesenchymal stem cells (MSC) during normal developmental processes, which underlies the conversion of red marrow to BMAT, were adapted for a system which imparts mechanotransduction to bone maintaining MSC multi-potency, promoting osteogenesis and limiting adipogenesis within the marrow cavity [2,22]. Premature diversion from hematopoietic lineage alters MSC "stemness" and associated properties including cell adhesion, survival and proliferation elicits a toxicity manifested as hypocellular, vascular congestion [2,10,13]. Thus, any evolutionarily conserved protective effect of the timing of conversion would be diminished.

The positive association between weight and quantitative attributes of bone and muscle in the absence of qualitative associations further supports the notion of an attenuation of benefit afforded by the marrow compartment in early life. A correlation between weight and cortical bone density is consistent with studies in animals and adults which support that cortical bone adapts to weight loading by preferentially increasing bone size rather than density. Optimizing the potential of

skeletal function during growth and development involves activities which maintain a healthy bone microenvironment, encompassing both periosteal (outer) and endosteal (inner) surfaces of bone. Periosteal expansion in the contemporary obesogenic/sedentary environment is evidenced by purported greater bone mass and density via two-dimensional imaging techniques. However, endosteal resorptive properties are not captured via the same imaging technology, which likely underlies the paradoxical increase in fracture risk among the same population. Reduced strength-structural properties of bone may be reflective of increased BMAT, particularly as it is associated with increased global adiposity.

While the inverse association between marrow density and cortical density and area was somewhat unexpected, it may actually reflect a conferred benefit. The maintenance of hematopoietic capacity may serve to slow both periosteal expansion and endosteal resorption allowing for optimization of the scaffolding network. Although we were unable to assess bone turnover or signaling from the BMAT, in concordance with our results and others [18,23,24], this is a plausible explanation.

In the context of muscle quality, muscle density has been validated as a reflection of adipose deposition into the muscle such that, greater fat infiltration is an indicator of reduced muscle density [25]. The musculoskeletal system was evolved for locomotion and performance. Beyond the purported adaptations related muscle 'dis-use' in obesity fat infiltration within the muscle interferes with development as well as with musculoskeletal-derived factors that reach circulation. Similar to adipokines from native adipose tissue, paracrine/endocrine hormones produced by muscle and termed myokines and osteokines, interact locally and systemically to influence parallel growth and development. However, identification and specification of linking pathways underlying crosstalk between BMAT and muscle remains to be elucidated and warrant investigation.

Limitations

The use of robust body composition measures and MRI and pQCT assessment of BMAT allowed for greater precision beyond that which has been previously used to assess bone parameters which routinely rely on DXA. Although this study generates valuable insight regarding the relationship between BMAT and bone and muscle, limitations must be taken into consideration. Despite the cross-sectional nature of this study, with modest sample sizes, the interesting findings relating to BMAT lay the groundwork for future studies of longer duration and larger sample size. All of the girls in this study were overweight/obese and normative data is lacking, warranting further research. Although we examined only the appendicular skeleton, specifically the femur and tibia, that of the axial skeleton may also be relevant and warrants investigation. Future studies should include a larger sample size, inclusion of multiple races/ethnicities, as well as inclusion of individuals with a wider range of body habitus.

We hypothesized that during growth and development, obesity induces disturbances within the marrow compartment accelerating BMAT conversion and diminishing the protective value of BMAT. In the context of early puberty, when the foundations of skeletal health are largely established, the impact on preventing the "maturational switch" of BMAT is relevant. If BMAT is protective as would be surmised by the timing of its appearance, a better understanding of how the protective nature can be maintained will guide prevention/intervention efforts and have profound effects on health and disease across the life course.

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