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Marrow adipose tissue composition in adults with morbid obesity

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Abstract

Patients with type 2 diabetes mellitus (T2DM) have increased fracture risk despite normal or increased bone mineral density (BMD). Elevations in marrow adipose tissue (MAT) and declines in MAT unsaturation are both associated with increased skeletal fragility. The objective of our study was to characterize the quantity and composition of MAT in adults with morbid obesity and T2DM, and to evaluate determinants of MAT. We studied 21 adults with morbid obesity prior to bariatric surgery, 8 of whom had T2DM. All subjects underwent 1H-MR spectroscopy of the lumbar spine and femur for assessment of MAT and dual-energy x-ray absorptiometry (DXA) and quantitative computed tomography (QCT) of the lumbar spine and hip for assessment of areal BMD (aBMD) and volumetric BMD (vBMD). Visceral (VAT) and subcutaneous adipose tissue (SAT) were quantified by CT at L1-2. Subjects with T2DM had higher vBMD of the femoral neck and higher total MAT at the lumbar spine and femoral metaphysis compared to non-diabetic controls ($p \leq 0.04$). Lipid unsaturation index (UI) was significantly lower at the femoral diaphysis in T2DM ($p=0.03$). Within the entire cohort, HbA1c was positively associated with MAT ($p \leq 0.03$), and age was associated with higher MAT and lower MAT unsaturation ($p \leq 0.05$). Lumbar spine vBMD was inversely associated with lumbar spine MAT ($p=0.04$). There was an inverse association between SAT and diaphyseal MAT ($p<0.05$) while there were no associations with VAT. Subjects with morbid obesity and T2DM have higher MAT with a lower proportion of unsaturated lipids, despite higher femoral neck vBMD. MAT is positively associated with age and HbA1c, and inversely associated with vBMD, suggesting that MAT may serve as an imaging biomarker of skeletal health and metabolic risk.

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Keywords

marrow adipose tissue (MAT); marrow adipose tissue composition; proton MR spectroscopy, bone mineral density; quantitative computed tomography (QCT); dual-energy x-ray absorptiometry (DXA); type 2 diabetes mellitus (T2DM); morbid obesity

1. INTRODUCTION

Type 2 diabetes mellitus (T2DM) is characterized by chronic hyperglycemia and insulin resistance, and is frequently accompanied by obesity [1]. Patients with T2DM often have normal or increased bone mineral density (BMD), but a paradoxical increase in fracture risk [2-6]. Recent studies have revealed the potential impact of marrow adipose tissue (MAT) in the pathogenesis of bone loss. Bone strength is affected not only by BMD and bone microarchitecture but also its micro-environment [7]. Many osteoporotic states, including old age, glucocorticoid use, immobility and anorexia nervosa are associated with increased marrow adiposity [8-10], suggesting that MAT may contribute to decreased bone strength and increased fracture risk. In fact, increased MAT content could play a role in the detrimental effects of obesity on bone. Studies have shown higher MAT content in subjects with obesity compared to normal-weight controls and positive associations with visceral adipose tissue (VAT) and MAT [11, 12].

MAT can be quantified *non-invasively* using proton magnetic resonance spectroscopy (1H-MRS) which correlates closely with bone biopsies [13]. Moreover, MAT content measured by 1H-MRS in combination with BMD may be more valuable than either parameter alone in evaluating skeletal integrity [7, 14]. We have previously demonstrated inverse associations between MAT and BMD in adults with obesity and low body weight [8, 12, 15].

Moreover, recent studies have used 1H-MRS to also assess the composition of MAT, such as unsaturated and saturated lipids, as a biomarker of skeletal integrity [16-19]. Elevations in MAT content and declines in MAT unsaturation of the lumbar spine were associated with osteoporosis [19] and fragility fractures [18]. Furthermore, lower vertebral MAT unsaturation was found in women with T2DM compared to healthy controls, suggesting that it may also serve as a biomarker for metabolic risk, such as insulin resistance [16, 18].

In addition to impacting skeletal integrity, MAT has been postulated to have extraskeletal effects on energy metabolism. Bone marrow adipocytes express the insulin receptor and are known to produce adipokines [20, 21]. MAT expansion has been observed in the setting of metabolic stress, including anorexia nervosa, high fat feeding, and leptin deficiency [8, 22-24]. Therefore, it is possible that bone marrow adiposity is a contributing player in the pathogenesis of T2DM.

The purpose of this pilot study study was to characterize the quantity and composition of MAT in adults with morbid obesity and T2DM, and to evaluate determinants of MAT at the lumbar spine and hip. We hypothesized that subjects with obesity and T2DM would have higher MAT content but lower unsaturation compared to non-diabetic controls of similar weight.

2. MATERIALS AND METHODS

Our study was IRB approved and Health Insurance Portability and Accountability Act compliant. Written informed consent was obtained from all subjects prior to performance of any study procedures.

2.1. Subjects

Subjects with morbid obesity who were scheduled to undergo bariatric surgery were recruited from the MGH Weight Center. Inclusion criteria were age ≥ 18 years. Exclusion criteria were history of medical disorders known to affect bone metabolism, use of bone-active medication including thiazolidinediones, pregnancy, weight >182 kg (due to limitations of the MRI scanner) and contraindications to MRI, such as the presence of a pacemaker or metallic implant. The following blood tests were obtained after an overnight fast: serum glucose, insulin, hemoglobin A1c (HbA1c), calcium, 25-hydroxyvitamin D, and parathyroid hormone (PTH), triglycerides, total, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) cholesterol. Diabetes status was assessed by self-report of diabetes and/or use of diabetic medications, and confirmed by review of medical records.

2.2 Marrow adipose tissue assessment

Subjects underwent 1H-MRS of the 1st and 2nd lumbar vertebrae (L1-L2) and the left proximal femoral metaphysis and mid femoral diaphysis. All studies were performed on a 3.0-T MR imaging system (Siemens Trio; Siemens Medical Systems, Erlangen, Germany) after an overnight fast. Single-voxel 1H-MRS data were acquired with a point-resolved spatially localized spectroscopy pulse sequence (TR/TE 3000/30, eight acquisitions, 1024 data points, and receiver bandwidth of 1000 Hz). For lumbar spine MAT assessment, a voxel measuring 15 × 15 × 15 mm (3.4 ml) was placed within the anterior L1 and the L2 vertebral bodies avoiding cortical bone and posterior venous plexus. For femoral MAT assessment, a voxel measuring 12 × 12 × 12 mm (1.7 ml) was positioned within the in the proximal femoral metaphysis at the intertrochanteric region and the mid-diaphysis, equidistant to femoral head and medial femoral condyle **(**Figure 1**).** Spectral data were acquired with and without frequency selective water signal suppression. For each voxel placement, automated optimization of gradient shimming was performed [8, 11, 17].

Fitting of all 1H-MRS data was performed using LCModel (version 6.3-0K, Stephen Provencher, Oakville, Canada). Data were transferred from the scanner to a Linux workstation and metabolite quantification was performed using eddy current correction and water scaling. A customized fitting algorithm for bone marrow analysis provided estimates for 5 lipid peaks: olefinic protons at 5.2 and 5.3 ppm (-CH=CH-), an estimate of fatty acid unsaturated bonds; methylene protons at 1.3 ppm [(-CH_2-)n], an estimate of fatty acids saturated bonds; allylic methylene protons at 2.0 ppm (-CH=CH-CH2-); methyl protons at 0.9 ppm (-CH3); and methylene protons β to carbonyl at 1.6 ppm (-CH2-O-CO-CH2-CH2-). Total marrow lipid content was determined from the unsuppressed spectra by combining all lipid peaks (0.9, 1.3, 1.6, 2.0, 5.2 and 5.3 ppm). Average MAT content of L1-L2 was assessed. Lipid resonances were scaled to unsuppressed water peak (4.7 ppm) and expressed in lipid-to-water ratios. Unsaturated lipid estimates were obtained from water suppressed

spectra (Figure 2). The unsaturation index (UI) was determined by obtaining a ratio between the olefinic resonance at 5.2 and 5.3 ppm and total lipid content as previously described [18, 19]. Coefficient of variation for MAT quantification (total and unsaturated lipids) at our institution is 5% [25].

2.3. Bone mineral density assessment

2.3.1. Dual-energy x-ray absorptiometry (DXA)—Areal bone mineral density (aBMD, g/cm^2) of the lumbar spine (L1-L4), total hip and femoral neck was assessed by DXA (QDR Discovery, Hologic, Inc, Bedford, MA). If necessary, manual retraction of pannus overlying the proximal femur was performed during hip measurements.

2.3.2 Quantitative Computed Tomography (QCT)—As DXA is less precise in obesity compared to QCT [26] volumetric bone mineral density (vBMD, g/cm^3) of the lumbar spine (L1-L2) and proximal femur was assessed using a 16-multidetector-row CT scanner (LightSpeed Pro, GE Healthcare, Waukesha, WI, USA). Subjects were placed supine on the CT scanner on a calibration phantom (Mindways Software, Inc., Austin, TX, USA), and helical scanning of L1-L2 and from the proximal articular surface of the femoral head to 1 cm below the lesser trochanter, was performed using the following parameters: 120kV, 100mA (L1-2), 120 KV, 200 mA (proximal femur), slice thickness of 2.5 mm and table height of 144 mm.

Analysis of vBMD of L1-L2, total hip, and femoral neck was performed with QCTPro software (Mindways Software, Inc., Austin, TX) as previously described [27].

2.4. Abdominal fat assessment

Visceral adipose tissue (VAT) and abdominal subcutaneous adipose tissue (SAT) compartments were quantified using a single-slice at the level of L1-L2 using the CT performed for BMD assessment. This level has been found to correlate strongly with adipose tissue volumes [28]. Fat attenuation coefficients were set at −50 to −250 Hounsfield unit as described by Borkan et al. [29] and VAT and SAT cross sectional areas (CSA) (cm^2) were assessed based on offline analysis of tracings obtained utilizing commercial software (Alice version 4.3.9; Parexel, Waltham, MA).

2.5. Statistical Analysis

Statistical analyses were performed using SAS 9.3 (SAS Institute, Cary, NC). Differences between subjects with and without T2DM were assessed by the Wilcoxon signed-rank test or the Fisher's exact test. Correlation analyses between MAT and clinical characteristics, body composition, and BMD were performed and nonparametric Spearman rank correlation coefficients are reported. $P < 0.05$ was used to denote significance. Data are presented as mean ± SD.

3. RESULTS

3.1. Clinical characteristics

Clinical and body composition characteristics are summarized in Table 1. The study group included 21 subjects (mean age 49 ± 11 years, range 25 to 66 years), 18 women, 3 men, with morbid obesity (mean BMI 43.9 ± 5.4 kg/m^2). Eight subjects had T2DM. Diabetes medication included metformin (n=7), insulin (n=3), sulfonylurea (n=1), and GLP-1 agonist (n=1). No subjects reported use of thiazolidinedioines. Subjects with and without T2DM were well-matched for age and gender, and had similar levels of serum calcium, 25-hydroxyvitamin D, and parathyroid hormone. There were a higher number of African American subjects in the T2DM group. As expected, subjects with T2DM had higher HbA1c, insulin, homeostasis model assessment of insulin resistance (HOMA-IR), serum total cholesterol, and serum LDL levels compared to subjects with morbid obesity without T2DM. Although subjects with T2DM tended to weigh less than non T2DM controls, which may reflect referral bias for bariatric surgery, this difference was not statistically significant. Furthermore, VAT and SAT CSA were similar between the groups.

3.2. Bone mineral density (BMD)

There were no differences in aBMD at any site by DXA between obese adults with and without T2DM. Subjects with T2DM had higher vBMD by QCT at the femoral neck compared to non-T2DM controls, while there were no differences in lumbar spine and total hip vBMD **(**Table 2**).**

3.3. Marrow adipose tissue (MAT)

Subjects with T2DM had higher total MAT at the lumbar spine and the femoral metaphysis compared to non-T2DM controls. There were no differences in lipid UI of the lumbar spine and femoral metaphysis, whereas the UI of the femoral diaphysis was significantly lower in subjects with T2DM **(**Table 2**)**.

3.4. Associations between clinical characteristics, body composition, bone mineral density and marrow adipose tissue

Within the entire cohort there was a positive correlation between HbA1C and MAT of the lumbar spine (r=0.61, p=0.004) (Figure 3) and femoral metaphysis (r=0.47, p=0.03). HOMA-IR was not significantly associated with MAT or MAT UI. Increasing age was associated with higher lumbar MAT (r=0.55, p=0.01) and lower lumbar unsaturation index (r= −0.52, p= 0.045). Diaphyseal MAT was inversely associated with SAT (r= −0.48, p=0.049) while there were no associations between VAT and MAT (p≥0.2). Lumbar vBMD was inversely associated with lumbar MAT (r= −0.46, p=0.04). There were no associations between hip vBMD or aBMD and femoral MAT (p≥0.3).

4. DISCUSSION

Our pilot study shows that subjects with morbid obesity and T2DM have higher MAT with a lower proportion of unsaturated lipids compared to non-diabetic obese controls, despite higher vBMD. In addition, MAT is positively associated with HbA1c. Lumbar MAT is

positively associated and unsaturation index is negatively associated with age. Lumbar vBMD is inversely associated with lumbar MAT content whereas no such associations are present in the hip.

Multiple studies have demonstrated the clinical paradox that patients with T2DM have impaired skeletal integrity and increased fracture risk, despite normal or increased BMD [2-6]. Meta-analyses have indicated that especially hip fracture risk is increased in T2DM [3, 30] and fractures occur at a higher femoral neck BMD T-score than in non-diabetics [31]. We therefore focused our study of bone density and marrow fat comparisons at both the lumbar spine and femur. In our study subjects with T2DM had higher vBMD at the femoral neck and higher metaphyseal and lumbar MAT compared to non-T2DM controls, while there was no significant difference in lumbar spine areal or volumetric BMD. Our findings are consistent with animal models of T1DM and T2DM which also demonstrate increased MAT quantity [32-34].

It is possible that our observation of increased MAT content at the lumbar spine and hip among subjects with T2DM may contribute to the skeletal fragility of this population. Indeed, recent studies have highlighted the role of MAT in skeletal health and metabolism [35, 36]. MAT is distinct from white or brown adipose tissue with unique gene expression and the ability to respond to nutritional status [25, 35]. The non-invasive assessment of MAT using 1H-MRS allows assessment of different skeletal sites and has been proposed as an imaging biomarker for fracture risk [18, 37]. Furthermore, several studies in humans have revealed inverse associations between MAT and BMD, as well as elevations of MAT content in subjects with impaired bone microarchitecture and fragility fractures [12, 15, 37]. Consistent with these results, we found an inverse association between lumbar MAT and vBMD.

It is possible that MAT also plays a role in the metabolic phenotype of T2DM. We have previously shown that MAT secretes adiponectin and can function as an endocrine organ [20]. Elevations in MAT content have been found in chronic undernutrition [8, 17] but also in obesity [11, 12]. In our current study, lumbar and femoral MAT were positively associated with HbA1c, suggesting that it might serve as a marker of skeletal integrity and metabolic risk in T2DM. These results are in line with the study by Baum et al that also found positive correlations between lumbar MAT and HbA1c [16]. Abdominal SAT was inversely associated with femoral MAT whereas there were no associations between MAT and VAT. Elevations in VAT are associated with inflammation and decreased BMD and bone microarchitecture [12, 15, 38], while SAT has been found to be protective against bone loss [39, 40].

Moreover, not just the amount of MAT but also its composition might affect skeletal health and metabolism. In particular, the ratio of saturated and unsaturated lipids may differ depending on anatomic site. Only a few studies in humans have assessed the composition of MAT using 1H-MRS and have found that increased saturated and decreased unsaturated lipids are associated with impaired skeletal integrity [16-19]. We found a decrease in UI of the lumbar spine with age, consistent with a study by Yeung et al that showed a higher UI in young women compared to postmenopausal women over 60 years [19]. Two studies have

assessed MAT composition of the lumbar spine in subjects with T2DM using 1H-MRS. Both studies showed that postmenopausal women with T2DM had similar lumbar total MAT content but lower UI compared to non-diabetic controls [16, 18] and women with T2DM and fragility fractures had the lowest UI [18]. Our results confirm the findings of lower MAT UI content at the lumbar spine in T2DM but differ in that we also found that total lumbar MAT content was high. Furthermore, we provide new data demonstrating parallel findings in the femur with lower MAT UI and higher MAT content in T2DM compared to non-diabetic controls. Our observed higher total MAT content in subjects with T2DM might reflect differences in age and BMI of our subjects that were younger and more obese than in other reported studies.

Our study has the following limitations. The cross-sectional study design limits our ability to ascertain causality. Another limitation is our small sample size. However, in this pilot study even with a limited number of subjects in each group, we were able to detect a difference in MAT content and composition between T2DM and non-diabetic controls. There was more racial diversity within the T2DM patients, and it is therefore possible that racial/ethnic components contributed to the observed differences in MAT. Strengths of our study include the detailed assessments of MAT content and composition at the lumbar spine, the femoral metaphysis, and diaphysis, as well as the assessment of BMD by DXA and QCT.

In conclusion, our pilot study shows that subjects with morbid obesity and T2DM have higher MAT with a lower proportion of unsaturated lipids as compared with non-diabetic obese controls, despite higher femoral neck vBMD. MAT increases with age, is positively associated with HbA1c, and inversely associated with vBMD, suggesting that MAT may serve as an imaging biomarker of skeletal health and metabolic risk.

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Highlights

- Subjects with morbid obesity and T2DM have higher marrow adipose tissue (MAT) than non-diabetic controls of similar weight.
- Subjects with morbid obesity and T2DM have a lower proportion of unsaturated lipids within MAT in the femoral diaphysis.
- MAT is positively associated with age, and is inversely associated with volumetric BMD.

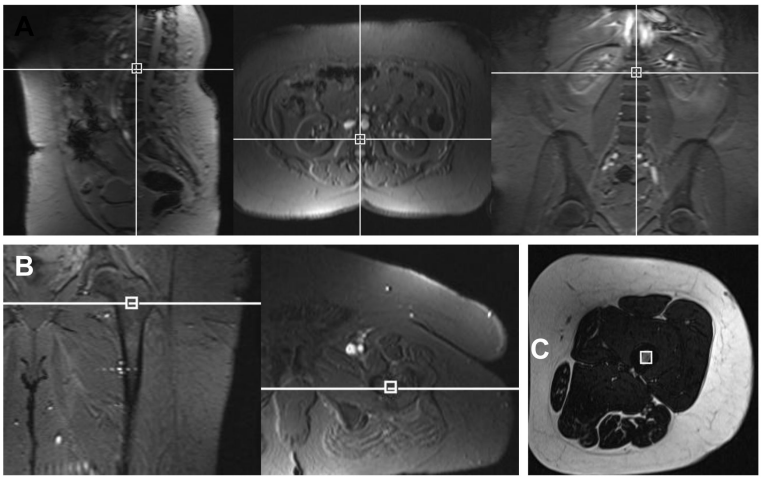

Figure 1.
Voxel placement for lumbar spine (A), femoral metaphysis (B) and femoral diaphysis (C) marrow adipose tissue quantification.

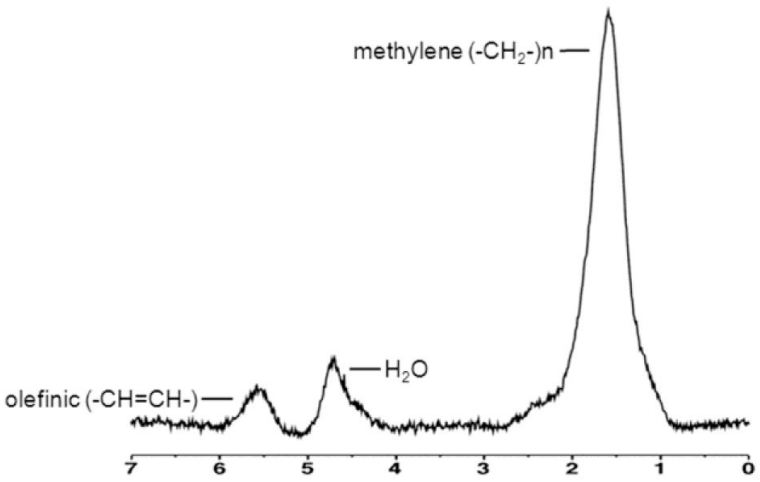

Figure 2.

1H-MR spectroscopy of L2 obtained at 3.0T with water suppression in a 58 year-old woman with obesity and type 2 diabetes mellitus demonstrating combined olefinic protons at 5.2 and 5.3 ppm (-CH=CH-, an estimate of fatty acid unsaturated bonds) and methylene protons at 1.3 ppm [(-CH_2-)n, an estimate of fatty acids saturated bonds]. Residual water (H_2O) is noted at 4.7 ppm.

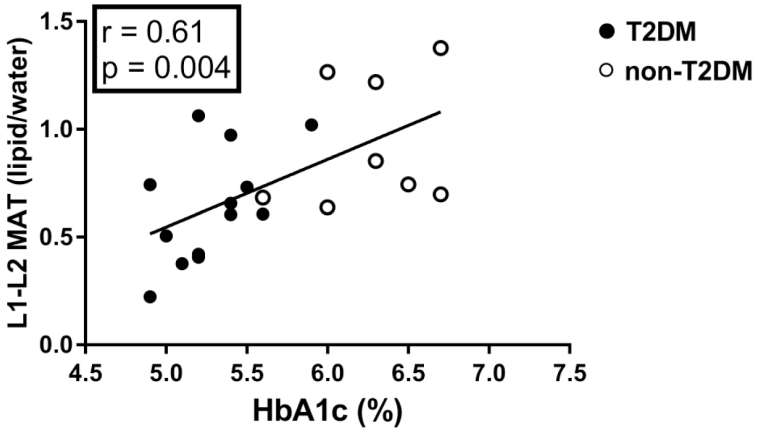

Figure 3.

Correlation analysis between glycemic control and marrow adiposity. There was a positive correlation between HbA1c and lumbar marrow adipose tissue.

Table 1
Clinical characteristics and body composition of study subjects

Data are presented as mean ± SD for continuous variables and n for categorical variables

	Non-T2DM (n=13)	T2DM (n=8)	*p*
Age (years)	48.2 ± 10.9	50.3 ± 12.0	0.9
Premenopausal women/Postmenopausal women/Men (n)	8/3/2	3/4/1	0.6
Fracture History (n)	3	3	0.6
Weight (kg)	121 ± 18	109 ± 10	0.1
BMI (kg/m^2)	45.4 ± 5.7	41.5 ± 4.0	0.1
Visceral Adipose Tissue (cm^2)	220 ± 33	185 ± 101	0.5
Subcutaneous Adipose Tissue (cm^2)	483 ± 119	481 ± 114	0.9
Race/Ethnicity			**0.01**
White non-hispanic	11	3	
White hispanic	2	-	
African American non-hispanic	-	4	
African American hispanic	-	1	
Serum fasting glucose (mg/dl)	93 ± 8	101 ± 23	0.3
Serum calcium (mg/dl)	9.6 ± 0.5	9.5 ± 0.5	1.0
Serum 25-hydoxyvitamin D (ng/ml)	25 ± 5	33 ± 14	0.1
Serum PTH (pg/ml)	49 ± 17	69 ± 35	0.2
HbA1c (%)	5.3 ± 0.3	6.3 ± 0.4	**<0.0001**
Insulin (μIU/ml)	13.4 ± 9.8	25.3 ± 15.9	**0.02**
HOMA IR	3.2 ± 2.7	6.0 ± 3.6	**0.02**
Triglycerides (mg/dl)	132 ± 76	97 ± 46	0.3
Total Cholesterol (mg/dl)	194 ± 25	160 ± 28	**0.02**
LDL (mg/dl)	117 ± 23	90 ± 24	**0.02**
HDL (mg/dl)	51 ± 8	51 ± 14	1.0

T2DM: type 2 diabetes mellitus; PTH: parathyroid hormone, HbA1c: hemoglobin A1c, HOMA IR: homeostasis model assessment of insulin resistance, LDL: low-density lipoprotein, HDH: high-density lipoprotein. *P*-values < 0.05 are bolded.

Table 2
Bone mineral density and marrow adipose tissue of study subjects

Data are presented as mean ± SD

	Non-T2DM	T2DM	*p*
DXA (g/cm^2)			
Spine aBMD	1.1 ± 0.1	1.2 ± 0.2	0.3
Total Hip aBMD	1.1 ± 0.1	1.1 ± 0.2	0.8
Femoral Neck aBMD	0.9 ± 0.1	1.0 ± 0.2	0.6
QCT (mg/cm^3)			
Spine vBMD	166 ± 33	172 ± 37	0.7
Total Hip vBMD	360 ± 43	374 ± 45	0.4
Femoral Neck vBMD	357 ± 52	404 ± 55	**0.02**
Marrow Adipose Tissue (lipids/water)			
L1-L2	0.64 ± 0.3	0.93 ± 0.3	**0.03**
Femoral Metaphysis	2.4 ± 0.9	4.0 ± 2.6	**0.04**
Femoral Diaphysis	3.2 ± 1.9	2.7 ± 0.9	1.0
Marrow Adipose Tissue (unsaturation index)			
L1-L2	0.08 ± 0.03	0.1 ± 0.02	0.9
Femoral Metaphysis	0.06 ± 0.01	0.06 ± 0.02	0.9
Femoral Diaphysis	0.07 ± 0.01	0.06 ± 0.001	**0.03**

DXA: dual-energy x-ray absorptiometry; QCT: quantitative computed tomography; aBMD: areal bone mineral density; vBMD: volumetric bone mineral density