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Ethnic and sex differences in bone marrow adipose tissue and bone mineral density relationship

W. Shen,

New York Obesity Nutrition Research Center, St. Luke's-Roosevelt Hospital, New York, NY, USA.
Institute of Human Nutrition, Columbia University, 1090 Amsterdam Avenue, 14H, New York, NY 10025, USA

J. Chen,

New York Obesity Nutrition Research Center, St. Luke's-Roosevelt Hospital, New York, NY, USA.
Institute of Human Nutrition, Columbia University, 1090 Amsterdam Avenue, 14H, New York, NY 10025, USA

M. Gantz,

New York Obesity Nutrition Research Center, St. Luke's-Roosevelt Hospital, New York, NY, USA.
Institute of Human Nutrition, Columbia University, 1090 Amsterdam Avenue, 14H, New York, NY 10025, USA

M. Punyanitya,

New York Obesity Nutrition Research Center, St. Luke's-Roosevelt Hospital, New York, NY, USA.
Institute of Human Nutrition, Columbia University, 1090 Amsterdam Avenue, 14H, New York, NY 10025, USA

S. B. Heymsfield,

Pennington Biomedical Research Center, Baton Rouge, LA, USA

D. Gallagher,

New York Obesity Nutrition Research Center, St. Luke's-Roosevelt Hospital, New York, NY, USA.
Institute of Human Nutrition, Columbia University, 1090 Amsterdam Avenue, 14H, New York, NY 10025, USA

J. Albu,

New York Obesity Nutrition Research Center, St. Luke's-Roosevelt Hospital, New York, NY, USA.
Institute of Human Nutrition, Columbia University, 1090 Amsterdam Avenue, 14H, New York, NY 10025, USA

E. Engelson,

New York Obesity Nutrition Research Center, St. Luke's-Roosevelt Hospital, New York, NY, USA.
Institute of Human Nutrition, Columbia University, 1090 Amsterdam Avenue, 14H, New York, NY 10025, USA

D. Kotler,

New York Obesity Nutrition Research Center, St. Luke's-Roosevelt Hospital, New York, NY, USA.
Institute of Human Nutrition, Columbia University, 1090 Amsterdam Avenue, 14H, New York, NY 10025, USA

X. Pi-Sunyer, and

Correspondence to: W. Shen, WS2003@Columbia.edu.

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New York Obesity Nutrition Research Center, St. Luke's-Roosevelt Hospital, New York, NY, USA.
Institute of Human Nutrition, Columbia University, 1090 Amsterdam Avenue, 14H, New York, NY
10025, USA

S. Shapses

Department of Nutritional Sciences, Rutgers University, New Brunswick, NJ, USA

W. Shen: WS2003@Columbia.edu

Abstract

Summary—The relationship between bone marrow adipose tissue and bone mineral density is different between African Americans and Caucasians as well as between men and women. This suggests that the mechanisms that regulate the differentiation and proliferation of bone marrow stromal cells may differ in these populations.

Introduction—It has long been established that there are ethnic and sex differences in bone mineral density (BMD) and fracture risk. Recent studies suggest that bone marrow adipose tissue (BMAT) may play a role in the pathogenesis of osteoporosis. It is unknown whether ethnic and sex differences exist in the relationship between BMAT and BMD.

Methods—Pelvic BMAT was evaluated in 455 healthy African American and Caucasian men and women (age 18–88 years) using whole-body T1-weighted magnetic resonance imaging. BMD was measured using whole-body dual-energy X-ray absorptiometry.

Results—A negative correlation was observed between pelvic BMAT and total body BMD or pelvic BMD ($r=-0.533$, -0.576 , respectively; $P<0.001$). In multiple regression analyses with BMD as the dependent variable, ethnicity significantly entered the regression models as either an individual term or an interaction with BMAT. Menopausal status significantly entered the regression model with total body BMD as the dependent variable. African Americans had higher total body BMD than Caucasians for the same amount of BMAT, and the ethnic difference for pelvic BMD was greater in those participants with a higher BMAT. Men and premeno-pausal women had higher total body BMD levels than postmenopausal women for the same amount of BMAT.

Conclusions—An inverse relationship exists between BMAT and BMD in African American and Caucasian men and women. The observed ethnic and sex differences between BMAT and BMD in the present study suggest the possibility that the mechanisms regulating the differentiation and proliferation of bone marrow stromal cells may differ in these populations.

Keywords

Body composition; Bone marrow; Bone mineral density; Dual-energy X-ray absorptiometry; Ethnicity; Magnetic resonance imaging; Sex

Introduction

It has long been known that there are ethnic and sex differences in bone mineral density (BMD) and fracture risk [1–3]. African Americans have higher BMD and lower fracture risk than Caucasians [3, 4], and men have higher BMD and lower fracture risk than women [5]. Recent reports suggest that bone marrow adipose tissue (BMAT) may play a role in the pathogenesis of osteoporosis [6–8]. Our group and others have reported an inverse relationship between BMAT and BMD [7, 9–11]. Most previous studies included a single ethnic group or gender, and some studies did not explicitly report participant ethnicity. To our knowledge, no studies have systematically examined possible ethnic and sex differences in the relationship between BMAT and BMD.

Previous studies suggest that bone marrow adipocytes and osteoblasts share the same precursor: mesenchymal stem cells (MSC) [12–14]. The relationship between bone and fat is complex and not yet fully understood [15, 16]. In vivo studies report that bisphosphonates reduce marrow fat [17] and in vitro studies report that mechanical influences enhance osteoblastogenesis through the inhibition of adipogenesis [18, 19]. A clearer understanding of potential ethnic and sex differences in the relationship between BMD and BMAT is important for guiding future studies aimed at developing prevention and treatment strategies for bone loss (i.e., possibly through enhancing the osteogenic differentiation of progenitor cells).

The aim of the present study was to investigate the effects of ethnicity and sex on the relationship between BMAT and BMD with adjustment of body composition measured by whole-body MRI and dual-energy X-ray absorptiometry (DXA). Because the distribution of marrow fat in the cavity of one bone or across bones is nonhomogeneous [20], magnetic resonance spectroscopy (MRS) is limited in its ability to sample marrow fat within a small region. To overcome this limitation, the present study employed T1-weighted magnetic resonance imaging (MRI) to quantify regional and whole-body BMAT [11, 21]. T1-weighted MRI has not only been validated for quantifying regional adipose tissue volume [22, 23] but has also been widely applied to adipose tissue measurement and serves as a reference method for adipose tissue quantification [24–30]. We used a T1-weighted signal intensity value to determine marrow fat content based on the fact that T1-weighted signal intensity has been validated for quantifying adipose depots such as subcutaneous and visceral adipose tissues [22, 23]. However, it should be noted that the T1-weighted signal intensity of bone marrow fat has not been validated against a reference method such as chemical analysis of cadaver bone marrow fat. Although recently optimized water-fat imaging methods [31–33] combine the merits of both MRS and volumetric MRI methods, there is no large-scale marrow fat dataset measured by water-fat imaging available, to the best of our knowledge. Our unique large-scale whole-body MRI dataset of African American and Caucasian men and women ($n=455$) enables us to provide timely evidence of the potential ethnic and sex differences in the relationship between marrow fat and bone at the human macroscopic imaging level. The pelvic region was selected for the evaluation of BMAT because of its large quantifiable cancellous bone volume and its high correlation with BMD as shown in our previous studies [11].

Methods

Protocol and design

The present study analyzed existing data of healthy subjects archived at the New York Obesity Nutrition Research Center, St. Luke's-Roosevelt Hospital. Participants were a sample of healthy African American and Caucasian men and women over 18 years, and all completed a medical history screening, physical examination and blood studies. Ethnicity was established for each participant by self-report. Athletes, women within 6 months of delivery or breastfeeding and subjects with a history of anorexia nervosa or any other disease conditions were excluded by medical history review. Subjects weighing more than 136.2 kg (300 lbs) were excluded from the study due to the weight limits of MRI and DXA systems. Weight, height, and body composition were evaluated on the same day as the screening examination. There are a total of 486 subjects who meet the above criteria and are, therefore, included in the present study.

The exempt status of the present study was reviewed and approved by the Institutional Review Board of St. Luke's-Roosevelt Hospital. The original study was approved by the Institutional Review Board of St. Luke's-Roosevelt Hospital and each subject gave written consent to participate.

Dual-energy X-ray absorptiometry

DXA (DPX GE Lunar, software version 4.7e, Madison, WI) was used to estimate BMD, total body fat and %fat using the whole-body scan mode. All scans were acquired and read by trained technologists. In addition to total body BMD, we report pelvic BMD since this site approximates the pelvic region used to measure BMAT by MRI. Our estimated precision for BMD and %fat is 1.28% and 3.3%, respectively [34]. The system was routinely calibrated and quality control measures were followed as recommended by the manufacturer [35].

Magnetic resonance imaging

Whole-body MRI scans were acquired as previously reported by our group [36, 37] using the body coil of a 1.5 T General Electric system (6X Horizon, Milwaukee, WI). The MRI data were obtained using a T1-weighted, spin-echo sequence with 200-ms repetition time and a 17-ms echo time. A 26-s breath hold was required during abdominal slice imaging. The field of view is 48 cm by 48 cm with a matrix of 256 by 256. The protocol involved acquisition of approximately 40 10-mm thick axial images at 40 mm intervals from ringers to toes. The participant rested in either a prone or supine position during the procedure with the L₄–L₅ intervertebral disk as the point of origin. The total scanning time for whole body is ~20 min. Following acquisition, the bone marrow, visceral and subcutaneous adipose tissue compartments and skeletal muscle were segmented at the New York Image Reading Center by trained, quality controlled, and cross-validated technicians using an image analysis software (SliceOmatic, Tomovision, Inc., Montreal, Canada). Technicians were blind to patient demographic information and test results. From a total of 486 subjects, 31 were excluded because of severe inhomogeneity of the MRI adipose tissue signal. The remaining 455 participants were included in the study. The threshold for BMAT segmentation was set at the same level as it was for SAT on the gray scale [11]. A threshold-based paintbrush was used to paint adipose tissue in bone regions first. We then used an “eraser” to carefully manually erase any non-BMAT signals including adjacent intramuscular or subcutaneous adipose tissue and blood flow artifacts. BMAT in the ribs and skull were not included due to difficulty in differentiating this component from adjacent intramuscular or subcutaneous adipose tissue. The intraclass correlation coefficient for volume rendering of BMAT, subcutaneous adipose tissue, visceral adipose tissue and skeletal muscle for the same scan by different analysts are 0.99, 0.99, 0.95 and 0.99, respectively. Tissue compartment volume was calculated as:

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

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 number of total slices [38]. Pelvic BMAT volumes were calculated from the region that matches the pelvic region of DXA and included ilium, sacrum, ischium, pubis, coccyx and femoral heads. The pelvic region was selected for evaluation because of its large quantifiable cancellous bone volume and its high correlation with BMD as shown in our previous studies [11].

Statistical methods

Data are presented as mean $\pm$ SD (Table 1). Analysis of variance (ANOVA) was used to compare means among groups. Posthoc analysis using least significant difference (LSD) method was performed to compare means between each pair of groups. Pearson correlation coefficients among pelvic BMAT, total body BMD, pelvic BMD, age, weight, body mass

index (BMI), skeletal muscle, visceral adipose tissue, subcutaneous adipose tissue and total body fat were calculated. Due to the retrospective nature of the study and the small number of participants for whom spine BMD data was available, spine BMD was not included in the data analysis.

Regression models were established with total body BMD or pelvic BMD as the dependent variable and pelvic BMAT, age, weight, total body fat, skeletal muscle, menopausal status, sex, ethnicity and biological plausible two-way interactions as potential independent variables. Variables and interactions with significant contributions to the model were retained in the regression equation.

Levene's test was used to evaluate the equality of variance among groups and the Shapiro-Wilk test was applied to test the normality of the residual distributions. When necessary, variables were mathematically transformed to normalize the residual distributions and to equalize the residual variance across centers or laboratories. Log transformations were applied initially and followed by Box-Cox transformations if necessary [39].

The intraclass correlation coefficient was calculated with participants as a random effect and analysts as a fixed effect. All statistical analyses were carried out using SAS 9.2 package (SAS Institute, Inc., Cary, NC, USA). Two-tailed ($\alpha = 0.05$) tests of significance were used.

Results

Descriptive statistics

Participant characteristics are presented in Table 1. The participants ranged in age from 18 to 88 years with a mean age of 45.1 years. Body weight ranged from 42.3 to 126.8 kg (mean weight 74.3 kg). Body mass index ranged from 15.9 to 44.4 kg/m² (mean BMI 26.9 kg/m²).

Total body BMAT ranged from 0.51 to 3.28 l with a mean of 1.64 l. The BMAT percentage of total adipose tissue ranged from 1.1% to 43.2% with a mean of 7.7%. Of the 325 total women, 213 were premenopausal and 104 were postmenopausal. The menopausal status of eight women were not collected.

Ethnicity and sex differences in the relationship between BMAT and BMD

A negative correlation was observed between logarithm-or Box-Cox transformed pelvic BMAT and BMD (total body BMD, $r = -0.533$, $p < 0.001$; pelvic BMD, $r = -0.576$, $p < 0.001$) (Fig. 1) (Table 2).

Regression models were developed with total body BMD or pelvic BMD as the dependent variable, and pelvic BMAT, age, weight, skeletal muscle, total body fat, menopausal status, ethnicity, sex and their biologically plausible two-way interactions as independent variables. The regression models are presented in Table 3. BMAT, age, weight, skeletal muscle and total fat were selected to enter the regression models because of their relatively high correlations with BMD. Ethnicity significantly entered both models with either total body BMD or pelvic BMD as the dependent variable. The interaction between ethnicity and BMAT was also significant ($p = 0.01$) for the pelvic BMD model. African Americans had higher total body BMD than Caucasians for the same amount of BMAT, and the ethnic difference for pelvic BMD was higher in those participants with greater BMAT. Sex only significantly entered the total body BMD model. Men and premenopausal women have higher total body BMD for the same amount of BMAT compared to postmenopausal women.

Discussion

The present study is the first to systematically examine the relationship between BMAT and BMD for potential sex and ethnic differences within a relatively large sample using both DXA and whole-body MRI data. An inverse relationship was found between BMAT and BMD in African American and Caucasian men and women. The inverse association exists even after adjustment of demographics, body composition and menopausal status. The results of the present study are consistent with our previous findings in Caucasian women [11] and other groups' studies of Asian men and women [7, 9]. An inverse association between marrow fat and BMD has also been found in studies of men and women without ethnicity explicitly reported [8, 10].

Although the inverse relationship between BMAT and BMD exists independent of ethnicity, we found that African Americans have higher BMD for the same amount of BMAT compared to Caucasians. Similarly, men and premenopausal women have higher total body BMD for the same amount of BMAT compared to postmenopausal women. These ethnic and sex differences in the relationship between BMAT and BMD remained even after adjusting for age, weight, skeletal muscle and total body fat. Therefore, the differences in weight and body composition across sex and ethnicity cannot fully explain the ethnic and sex differences in the relationship between BMAT and BMD. Recent findings suggest that preferential differentiation of stromal cells from osteoblasts to adipocytes is linked to bone loss [40]. If this notion is validated by in vivo human studies, then the observed ethnic and sex differences between BMAT and BMD in the present study suggest the possibility that the mechanisms regulating the differentiation and proliferation of bone marrow stromal cells differ between these populations. Otherwise, high BMAT may reflect a passive compensation for trabecular bone loss, whereby the fat helps to strengthen mineral-depleted bone [41, 42]. However, there is evidence that replacement of less compressible hemopoietic marrow with the more compressible fatty marrow may cause vertebral weakening [41]. Future studies may exam the ethnic and sex differences regarding the influence of BMAT on bone strength.

Since the present study is limited by its cross-sectional nature, we cannot draw any conclusions regarding whether the relationship between BMAT and BMD described here is causal or whether the associations are the result of other unmeasured factors. Future longitudinal studies need to clarify the potential ethnic and sex differences in the relationship between changes of BMAT and BMD over time. Nonetheless, the present study highlights that the potential role of BMAT as it relates to BMD differs between sexes and ethnicities. In addition, future studies evaluating drugs or other interventions that target the reduction of adipogenesis and increase of osteohistogenesis can use the results of the current study to provide information on the racial and gender differences of the endpoints BMAT and BMD.

This study found that for any given level of BMAT, postmenopausal women tend to have lower BMD than men and premenopausal women. The BMD difference between pre-and postmenopausal women has been well-documented and may be largely attributed to hormone and fat distribution changes [43–45]. The higher incidence of osteoporosis in women than in men can be partially attributed to the larger bone mass and bone size of men [5]. In addition, men do not experience a significant drop in circulating estradiol levels with menopause like women do [46, 47]. The dramatic hormonal changes associated with menopause in women is believed to be the major cause of rapid bone loss in women during this period (i.e., $-1.2 \pm 1.5\%$ loss per year vs. physiologically age-related bone loss rate of $-0.8 \pm 1.5\%$ per year) [44, 45]. Physical activity and weight are important mediators of bone strength as high weight-bearing activity induces an osteogenic response [18, 19, 48]. It

seems plausible that the BMD differences seen between men and women could be partly explained by the greater weight bearing associated with higher body weight and skeletal muscle of men compared to women [49]. In the present study, body weight did not enter any regression model once skeletal muscle and total body fat were included. This is consistent with our previous findings [11] and suggests that previously reported relationships between weight and BMD may actually reflect the relationship between BMD and individual body composition components such as skeletal muscle and fat. We did not have physical activity level information for the current study cohort. However, the fact that skeletal muscle was a significant predictor of BMD is consistent with the notion that physical activity may prevent bone loss.

The present study finds that African Americans have greater total body BMD than Caucasians for the same amount of BMAT and that the ethnic difference for pelvic BMD is larger in those participants with greater BMAT. This is consistent with findings that African Americans have higher peak bone mass than Caucasians [50, 51] and that Caucasian men have almost twice the rate of bone loss than African American men of 60–75 years of age [51, 52]. However, one study reported no difference in the rate of bone loss with aging between African American and Caucasian men [53]. Since this ethnic interaction was only observed in pelvic BMD and not total body BMD, there is a need for future studies to investigate the potential anatomical differences in bone loss related to BMAT increase.

A previous study reported a positive association between subcutaneous adipose tissue and bone strength and a negative association between visceral adipose tissue and bone strength [54]. A recent large-scale study found that both visceral and subcutaneous adipose tissues are negatively associated with BMD [55]. This is consistent with a DXA study which showed both percent body fat and percent trunk fat are negatively associated with BMD [56]. In the present study, a weak but significant positive correlation exists between total body BMD or pelvic BMD and subcutaneous adipose tissue; however, neither total body BMD nor pelvic BMD correlates with visceral adipose tissue in our study. We did find that BMAT is positively correlated to visceral adipose tissue, which is consistent with Bredella et al.'s finding [57]. However, we also found BMAT to be negatively correlated to subcutaneous adipose tissue, which was not found in Bredella et al.'s study [57]. The fact that we used whole-body MRI rather than single slice MRI may partially explain the inconsistency of the results between the present study and previous studies. In addition, the inconsistency may also be attributed to differences in subject composition, anatomical location of BMAT measurement or DXA and computed tomography BMD measurement. The relationship between adipose tissue distribution and BMD warrants further investigation.

Limitations and future directions

One important question is whether the observed inverse relationship between BMAT and BMD is an artifact since DXA BMD readings can be underestimated when BMAT is present. Previous studies reported that a 50% increase in marrow fat content can only cause a 5–6% underestimation of the apparent areal bone density [58] and this underestimation is only severe in osteoporosis when a small amount of extraosseous fat is present [59]. In addition, the same change in soft tissue fat content (not in the path of the beam traversing the bone) causes overestimation of bone density [8, 58, 59]. A recent study has also shown that the changes in BMAT are not related to changes in BMD during weight loss [21]. Considering that subjects in the present study had a mean BMD -1.13 g/cm^2 and a mean subcutaneous fat of -6.9 L , it is unlikely that there was a major underestimation of BMD, if at all. A more detailed discussion of this concern regarding DXA methodology can be found in our previous study [11].

The present study used a threshold-based method to quantify BMAT. However, the semiquantitative nature of the utilized MRI method should not detract from the overall study conclusions. From a statistical point of view, if a method is less accurate, the observed correlations will be reduced from their potential maximum. It is likely that application of even more accurate BMAT measurement methods such as IDEAL would strengthen the observed associations between BMD and BMAT [32]. In addition, the use of 10-mm skip 40-mm MRI acquisition protocol can induce ~6% error comparing to contiguous protocol (unpublished data, $n=27$, $r=0.97$, $P<0.001$). We expect that future studies that use contiguous MRI acquisition protocol will strengthen the observed association between BMD and BMAT.

Information on lifestyle factors such as physical activity level, dietary calcium or vitamin D levels, breastfeeding history and smoking were not available in the present study. This served as a limitation since these factors are known to be related to peak bone mass and bone loss. For example, a recent animal study showed that vitamin D is linked with low marrow fat [60]. In addition to the observed paradox linking low vitamin D levels with high bone mass in African Americans [3, 61], a recent case-control study also found lower fracture risk in Black women [62]. The role of BMAT in the connection between vitamin D and fracture risks warrants further study. Another limitation is that total body and pelvic BMD may not reflect BMD in the femoral neck or spine, which are the anatomical regions used for the clinical diagnosis of fracture risk and osteoporosis [63]. In addition, studies using quantitative computed tomography (QCT) are advantageous since this method allows for the differentiation of cortical and cancellous bone [64]. Future studies should, therefore, include QCT methods as a means to expand our findings to locations such as the vertebrae, femoral neck and wrist which are particularly vulnerable to fracture and to marrow fat infiltration with aging, and it would be especially interesting to look at an osteoporotic population. Future studies need to establish whether there are ethnic and sex differences regarding the mechanism of marrow fat infiltration—either the differentiation of MSCs in bone marrow or the passive accumulation of fat when bone is lost. In vivo studies have recently found that bisphosphonates reduce marrow fat [17] and in vitro studies have found that mechanical influences enhance osteoblastogenesis by inhibiting adipogenesis [18, 19]. Future longitudinal studies should test whether there are ethnic and sex differences in the prevention and treatment of osteoporosis through inhibiting adipogenesis in the bone marrow.

Conclusions

There is an inverse relationship between BMAT and BMD in 18- to 88-year-old African American and Caucasian men and women. African Americans have higher total body BMD than Caucasians for the same amount of BMAT, and the ethnic difference for pelvic BMD is greater in those participants with higher BMAT. Men and premenopausal women have higher total body BMD compared to postmenopausal women for the same amount of BMAT. The observed ethnic and sex differences between BMAT and BMD in the present study suggest the possibility that the mechanisms regulating the differentiation and proliferation of bone marrow stromal cells may differ in these populations.

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Fig 1. Correlation between bone mineral density (BMD) [**a** total body BMD; **b** pelvic BMD] and pelvic BMAT in African American (AA) and Caucasian (C) men and women. BMD and BMAT were either log-or Box-Cox transformed to normalize the distribution of the residuals and to equalize the residual variance among groups

Table 1

Participant characteristics for total study group

Group	Men		Women	
	Caucasian	African American	Caucasian	African American
Sample size	79	51	158	167
Age (years)	46.1 ± 16.4(31.0,44.0, 59.0)	44.2 ± 19.8 (30.0, 37.0, 68.0)	42.4 ± 15.4 (31.0,39.0,54.0)	47.5 ± 18.7 (32.0, 43.0, 63.0)
Weight (kg)	79.5 ± 12.3(71.6,80.1, 87.5)	86.2 ± 11.8 (72.4, 79.9, 88.6)	69.6 ± 16.5 ^{*,**} (55.4, 66.8, 29.7)	74.6 ± 16.1 ^{*,**,*} (64.0, 72.3, 85.6)
BMI (kg/m ²)	25.7 ± 3.7 (23.0, 25.3, 27.5)	25.8 ± 3.8 (23.4, 25.2, 29.1)	26.1 ± 5.8 (21.5, 24.9, 29.7)	28.4 ± 5.7 ^{*,**,*} (23.7,28.1,32.6)
Total body BMD (g/cm ²)	1.23 ± 0.09 (1.17, 1.23, 1.30)	1.29 ± 0.09 [*] (1.24, 1.28, 1.34)	1.17 ± 0.12 ^{*,**} (1.09, 1.17, 1.25)	1.21 ± 0.11 ^{*,**,*} (1.14, 1.23, 1.29)
Pelvic BMD (g/cm ²)	1.17 ± 0.16 (1.09, 1.14, 1.25)	1.23 ± 0.14 (1.11, 1.20, 1.30)	1.13 ± 0.15 ^{**} (1.00, 1.10, 1.24)	1.18 ± 0.14 ^{***} (1.08, 1.20, 1.28)
Pelvic bone BMAT (l)	0.17 ± 0.11 (0.09,0.15,0.22)	0.15 ± 0.14 (0.02, 0.12, 0.23)	0.14 ± 0.13 (0.03,0.11,0.21)	0.12 ± 0.12 [*] (0.03,0.08,0.18)
Subcutaneous adipose tissue (l)	18.1 ± 7.6(12.0, 16.7,22.8)	16.9 ± 6.6 (12.1, 17.6,20.1)	25.4 ± 13.0 ^{*,**} (16.3, 22.0, 34.3)	30.3 ± 12.2 ^{*,**,*} (21.3,27.2,39.4)
Visceral adipose tissue (l)	3.0 ± 2.0 (1.3, 2.6, 3.9)	1.8 ± 1.6 [*] (0.7, 1.7,2.6)	1.5 ± 1.3 [*] (0.6, 1.1,2.1)	1.78 ± 1.17 [*] (0.84, 1.53,2.50)
Total body fat (kg)	18.2 ± 9.4 (11.0, 16.8,24.1)	17.3 ± 8.4 (12.7, 17.2, 20.7)	24.4 ± 12.4 ^{*,**} (13.8,21.2,35.4)	29.6 ± 12.1 ^{*,**,*} (20.7,28.2,38.1)

Data are presented as mean ± SD (25th percentile, median, 75th percentile)

BMI body mass index, *BMAT* bone marrow adipose tissue^{*} *P* < 0.05 (statistical significance, different from Caucasian men)^{**} *P* < 0.05 (statistical significance, different from African American men)^{***} *P* < 0.05 (statistical significance, different from Caucasian women)

Table 2

Pearson correlation coefficients among BMD, BMAT, visceral and subcutaneous adipose tissue, total fat, BMI and age ($N=455$)

	Total body BMD	Pelvic BMD ^a	Pelvic BMAT ^a	Age ^a	Weight	BMP ^a
Pelvic BMD ^a	0.896 ^{**}	-	-	-	-	-
Pelvic BMAT ^a	-0.533 ^{**}	-0.576 ^{**}	-	-	-	-
Age ^a	-0.394 ^{**}	-0.428 ^{**}	0.525 ^{**}	-	-	-
Weight	0.353 ^{**}	0.327 ^{**}	-0.167 ^{**}	-0.075	-	-
BMI ^a	0.200 ^{**}	0.224 ^{**}	-0.160 ^{**}	0.064	0.854 ^{**}	-
Skeletal muscle ^a	0.556 ^{**}	0.496 ^{**}	-0.258 ^{**}	-0.255 ^{**}	0.477 ^{**}	**
VAT ^a	-0.021	-0.040	-0.102 ^{**}	0.459 ^{**}	0.412 ^{**}	0.428 ^{**}
SAT	0.110 [*]	0.178 ^{**}	0.194 ^{**}	0.141 [*]	0.454 ^{**}	0.635 ^{**}
Total body fat	0.187 ^{**}	0.239 ^{**}	0.242 ^{**}	0.107 [*]	0.526 ^{**}	0.671 ^{**}

BMD bone mineral density, BMAT bone marrow adipose tissue, BMI body mass index, VAT visceral adipose tissue, SAT subcutaneous adipose tissue

^aEither log- or Box-Cox transformed to normalize the distribution of the residuals and to equalize the residual variance among groups

* $P < 0.05$ (statistically different from 0)

** $P < 0.001$ (statistically different from 0)

Table 3
Regression equation with BMD as dependent variable and pelvic BMAT, weight, demographics and body composition as potential covariates

(a) Dependent variable	(b) Independent variables									
	Pelvic BMAT ^a	Age	Skeletal muscle ^a	Total fat	Sex (F=1, M=0)	Ethnicity (AA=1, C=0)	Menopause status (Post=1, Pre=0)	Ethnicity * pelvic BMAT	Intercept	R ²
Total body BMD	−0.099 ** (0.011)		0.183 ** (0.026)	0.00089 ** (0.00035)	−0.00070 (0.015)	0.025 * (0.0078)	−0.0386 ** (0.011)		0.471 ** (0.085)	0.513
Pelvic BMD ^a	−0.143 ** (0.018)	−0.051 * (0.015)	0.191 ** (0.018)	0.00165 * (0.00039)		0.104 * (0.033)		0.0553 * (0.0221)	−0.510 ** (0.094)	0.518

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

BMATbone marrow adipose tissue, Ffemale, Mmale, AA African-American, C Caucasian

^aEither log- or Box–Cox transformed to normalize the distribution of the residuals and to equalize the residual variance among groups

* P<0.05;

** P<0.001