

Bone marrow adiposity is inversely associated with bone mineral density in postmenopausal females

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ABSTRACT

Aim To evaluate vertebral bone marrow adiposity (BMA) using magnetic resonance spectroscopy (MRS) in postmenopausal women and to determine an association of bone density with bone marrow fat content.

Methods This cross-sectional study included 120 postmenopausal women referred for osteoporosis screening. All women underwent assessment of bone mineral density by dual X-ray absorptiometry (DXA), who were divided based on T scores into osteoporosis (OST; n=60) and control group (CG; n=60). MRS was used to measure fat fraction (FF), lipid/water ratio (LWR) and fat content (FC) at vertebral spine (L1-L4).

Results Mean age, menopause or reproductive period duration was not significantly different between women in OST and control group. Median LWR in OST group was significantly higher compared to CG, 31.5 (22.9-38.8) vs. 28.7 (13.7-37.3) (p=0.039). Median FC was significantly higher in OST compared to the control group, 47.0 (46.3-78.8) and 46.4 (44.3-48.6), respectively (p=0.011). FC was significantly negatively associated with BMD at lumbar spine (Rho=-0.042; p<0.001) and with BMD at hip (Rho=-0.64; p<0.001). In logistic regression model, FC remained independently associated with osteoporosis after controlling for confounders (age, menopause duration, reproductive period duration and body mass index) (OR=1.3; 95% CI 1.1-1.6).

Conclusion Bone marrow adiposity is an independent predictor of low bone mass in postmenopausal women suggesting its role as a therapeutic target in postmenopausal osteoporosis management.

Key words: adiposity, magnetic resonance spectroscopy, osteoporosis

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INTRODUCTION

Bone marrow adiposity (BMA) is defined as the volume of bone marrow populated by the adipocytes within the stromal compartment (1). An increase in BMA can be caused by increasing the size and number of adipocytes (1). It is known that BMA increases with aging at specific predilection sites of skeleton. During the early years bone marrow is mostly haematopoietic (red), but it is transformed into fatty (yellow) bone marrow later in life (2). Within bone marrow, osteoblasts and adipocytes arise from a common mesenchymal stem cell and many conditions associated with osteoporosis such as old age, medication use, immobility and anorexia nervosa are associated with increased marrow adiposity (3).

Recent interest in the role of BMA and its relationship to bone lineage and skeletal fragility has led to the development of non-invasive imaging techniques to assess the quantity and composition of BMA, such as magnetic resonance spectroscopy (MRS). Single-voxel proton magnetic resonance spectroscopy (1H-MRS) is regarded as the gold standard for the quantification of BMA. It can provide both quantitative (fat fraction, FF) and qualitative (BMA composition) information (4). Using 1H-MRS, the signal within a voxel is divided into two major peaks, a lipid and a water peak and, using software the area under the curve of the lipid and water peaks can be determined and FC and FF can be calculated (4).

Studies by Shen et al. (5,6), who used magnetic resonance imaging (MRI) to assess BMA in healthy adult populations observed a significant negative association between BMA and bone mineral density (BMD) in anatomically related and non-anatomically related sites. A significant negative correlation between the lumbar spine BMD and BMA was also observed in premenopausal women and men aging less than 50 years, although the association lost its significance after adjustment for age, body mass index (BMI), fat, and lean mass (7). Increased BMA, as measured by the MRS, was found in patients with osteoporosis compared to patients with osteopenia and subjects with preserved bone mass. These results were significant for both men and women aged 55 and older (8). A recent study involving 51 postmenopausal women (54-73 years) showed that the BMA content measured by MRS was signifi-

cantly higher in patients with osteoporosis/osteopenia compared to controls, which remained significant even after controlling for age and BMI (9). Similar results were also found in a study involving 78 postmenopausal women (55-81 years) (10). However, all these results were obtained in studies involving patients of Asian origin, while data on the Caucasian populations are scarce.

A clearer understanding of the relationship between bone mineral and marrow fat is a critical first step toward the development of prevention and treatment strategies for bone loss, possibly through enhancing the oestrogenic differentiation of progenitor cells. Assessment of bone marrow adiposity by MRS is still an experimental method and is not a part of routine practice in MRI units. However, MRS provides *in vivo* insight into the quality of the bone structure, it is non-invasive, and it is not a time consuming method, and can simply be introduced into routine practice, which is why we decided to do this research.

The aim of this study was to use MRI spectroscopy to evaluate vertebral BMA in postmenopausal women, to compare BMA between postmenopausal women with osteoporosis and those with preserved bone mass and to determine whether bone density is associated with bone marrow fat content.

PATIENTS AND METHODS

Patients and study design

The study was designed as observational, cross-sectional, controlled study, which enrolled 120 postmenopausal women referred to the Clinical Centre of the University of Sarajevo (CCUS) for osteoporosis screening by their primary health care practitioner. All participants were interviewed regarding the data on menstrual cycles/the last menstrual cycle. Postmenopausal status was initially defined as absence of menstruation for at least 12 months. Participants were excluded if they reported taking medications known to affect the skeleton (such as corticosteroids), if they were on calcium and vitamin D supplements, using bisphosphonate therapy or hormone replacement therapy. Women who self-reported having diabetes mellitus, breast cancer or any other disease affecting skeleton, were excluded from the study too.

The patient's demographic details i.e. date of birth, sex, weight and height were obtained. After

initial assessment, females were further referred to bone mineral density measurement by dual X-ray absorptiometry (DXA) and MRI spectroscopy for BMA assessment. All imaging procedures were performed at Clinics for Radiology at Clinical Centre University of Sarajevo.

All participants signed an informed written consent after the explanation of the study procedure. All procedures were conducted in accordance with the guidelines of The Declaration of Helsinki. The study was approved by the Ethics Committee at School of Medicine, University of Sarajevo and by the Research Ethics Committee at the CCUS.

Methods

Bone mineral density was measured with Hologic QDR 4500 DXA equipment (Hologic Inc., Waltham, MD, USA) at the Clinics for Radiology at Clinical Centre of the University of Sarajevo. Values of bone mineral density were expressed as BMC (g) and areal BMD (g/cm²) and then converted into T-scores and Z-scores. The bone mineral density was measured at the lumbar spine (L1–L4), and all regions of the hip including total hip, femoral neck, trochanter and intertrochanteric shaft.

For the lumbar spine measurement, the patient was positioned supine on the scanner table with arms resting on the tabletop with the knees flexed over 90° and placed on a support pad. Hip measurements were always performed on the left side, unless there was a previous fracture or joint replacement. For the hip measurements the dedicated angled foot support was placed between the patient's legs, abducting the leg to be scanned approximately 15° away from the midline. The whole leg was then internally rotated through 25°.

T-scores are used for the densitometric diagnosis of osteoporosis: preserved bone mineral density: T-score in the range -1 and +1; osteopenia: T-score < -1 and > -2.5; osteoporosis: T-score < -2.5.

BMA was measured with a Trio Tim 3T and AVANTO 1.5-T scanner (Siemens) with a spine coil. The imaging protocol included a standard clinical sagittal T2-weighted fast spin echo (FSE) sequence, repetition (TR)/echo time (TE) 4540/97 msec, slice thickness of 3 mm between slice distance 0.3 mm with basal resolution 384, which was used for visual assessment of lumbar vertebrae and for prescription of the spectral acquisition box.

Single-voxel spectroscopy was performed SVS SE 30 with voxel size 20x20x20 mm, which was positioned in the middle of vertebral bodies from L1 to L4 with the total number of acquisitions 80, flip angle 90 degrees, sweep width 30 Hz and acquisition time 853 ms. The spectral data were analysed using software. After phase, baseline, and frequency shift correction, 2 peaks were fitted using Marquardt Fit: water peak at 4.65 ppm and fat peak at 1.3 ppm. The area under each peak was calculated, and the lipid water ratio (LWR) was calculated as fat peak/water peak, fat fraction (FF) as LWR divided by (LWR+1), and fat content (FC) was calculated as fat/(fat + water) x 100%. The mean BMA of all 4 levels was used in data analyses.

Statistical analysis

Data was checked for skewness by Kolmogorov Smirnov tests of normality. For normally distributed data means were compared using student's paired t-test. The correlations variables were investigated using the Pearson correlation test for normally distributed variables. Logistic regression analysis was performed to evaluate independent association between BMA and BMD controlling for the effects of age, body mass index, menopause and reproductive period duration. All statistical tests were two-sided and performed at a significant level of p=.05.

RESULTS

Mean age of women in OST group was 60.4±8.6 and in control group (CG) 57.7±8.6 years (p=0.09). Mean menopause or reproductive period duration was not significantly different between two groups (Table 1).

Table 1. Baseline characteristics of postmenopausal women in osteoporosis (OST) and control group (CG)

Characteristic	Total (N=120)	OST group (N=60)	CG (N=60)	p
Age (years)	59.0±8.7	60.4±8.6	57.7±8.6	0.09
Age at menopause (years) (mean±SD)	47.5±3.2	47.8±3.4	47.3±3.1	0.37
Menopause duration (years) (mean±SD)	11.5±7.4	12.6±7.4	10.5±7.4	0.12
Reproductive period duration (years) (mean±SD)	35.1±3.0	35.4±3.0	34.9±3.0	0.35
Smoking (No, %)	No 31 (25.8%)	18 (30.0%)	13 (21.7%)	
	Yes 81 (67.5%)	40 (66.7%)	41 (68.3%)	0.24
Alcohol consumption (No, %)	Former 8 (6.7%)	2 (3.3%)	6 (10.0%)	
	No 81 (67.5%)	43 (71.7%)	38 (63.3%)	
	Yes 39 (32.5%)	17 (28.3%)	22 (36.7%)	0.33

Table 2. Bone mineral density (BMD), bone mineral content (BMC) and T-score values of postmenopausal women in osteoporosis (OST) and control group (CG)

Spine level	BMC (g) (mean±SD)		p	BMD (g/cm ²) (mean±SD)		p	T-score		p
	OST (N=60)	CG (N=60)		OST (N=60)	CG (N=60)		OST (N=60)	CG (N=60)	
Total hip	27.3±6.1	31.9±6.7	<0.001	0.82±0.15	0.94±1.13	<0.001	-1.36±0.9	-0.51±0.5	<0.001
Femur	17.5±5.7	18.1±5.7	<0.001	0.99±0.2	1.1±0.18	<0.001	-1.24±0.9	-0.47±1.0	<0.001
Neck	4.0±0.9	4.4±0.8	<0.001	0.78±1.1	0.88±0.13	<0.001	-1.55±0.9	-0.8±0.93	<0.001
Trochanter	8.4±2.9	9.7±2.7	<0.001	8.4±2.9	9.7±2.7	<0.001	-1.28±1.1	-0.37±1.2	<0.001
Total lumbar	44.9±6.9	68.8±4.8	<0.001	0.87±0.13	1.1±0.14	<0.001	-2.34±0.8	-0.14±0.13	<0.001
L1	11.3±2.2	14.8±2.3	<0.001	0.9±0.13	1.16±0.12	<0.001	-2.4±1.1	-0.46±1.1	<0.001
L2	12.5±2.3	13.7±2.1	<0.001	0.9±0.13	1.17±0.14	<0.001	-2.44±0.9	-0.38±1.2	<0.001
L3	13.2±2.5	17.9±2.5	<0.001	0.9±0.13	1.16±0.12	<0.001	-2.3±1.0	0.04±1.0	<0.001
L4	14.9±2.7	19.8±2.8	<0.001	0.9±0.13	1.17±0.14	<0.001	-2.2±1.1	0.05±1.2	<0.001

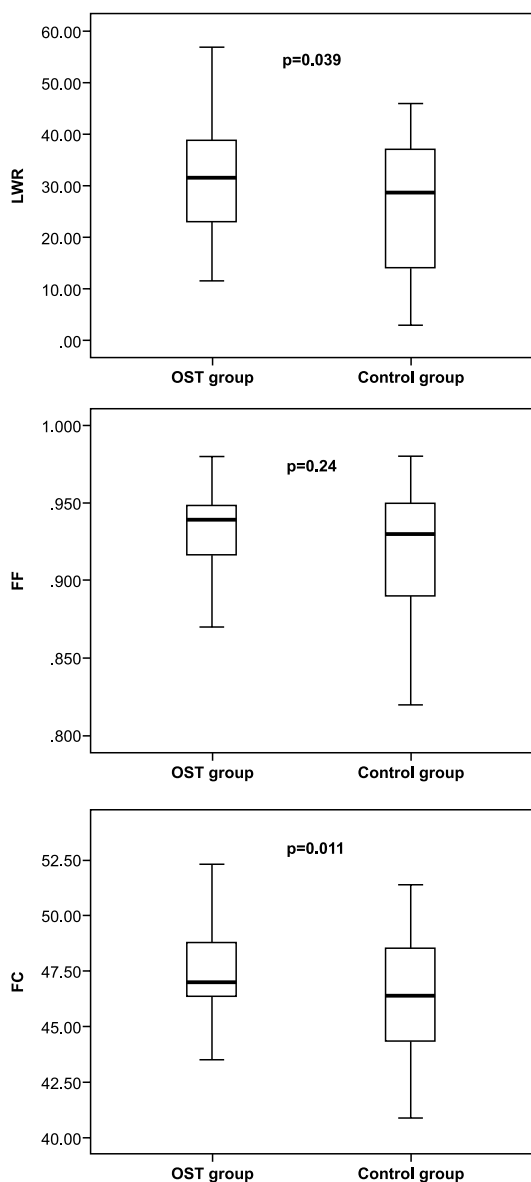


Figure 1. Lipid/water ratio (LWR), fat fraction (FF) and fat content in osteoporosis (OSP) and control group (CG) of postmenopausal females; Data are presented as median and interquartile range

Mean T-score value at hip in OST group was significantly lower compared to CG, $-1.36±0.9$ vs. $-0.51±0.5$ (<0.001), as were T-score values at lumbar spine $-2.34±0.8$ vs. $-0.14±0.13$ (<0.001) (Table 2). Mean BMD and BMC values were also significantly higher in OST compared to CG (Table 2). Mean LWR, FF and FC in postmenopausal women was $29.2±12.6$, $0.92±0.04$ and $46.9±2.3$, respectively. Median LWR in OST group of 31.5 ($22.9-38.8$) was significantly higher compared to CG, 28.7 ($13.7-37.3$) ($p=0.039$). Median FF was not significantly different between OST and CG,

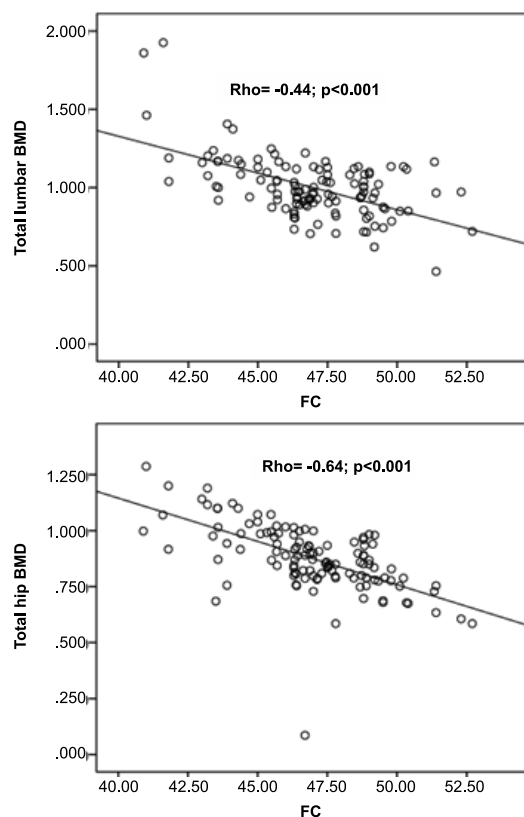


Figure 2. Relationship between fat content (FC), total lumbar spine and total hip bone mineral density (BMD) in postmenopausal women

0.94 (0.92-0.95) vs. 0.93 (0.89-0.95) ($p=0.24$). Median FC was significantly higher in OST group, 47.0 (46.3-78.8) compared to CG, 46.4 (44.3-48.6) ($p=0.011$) (Figure 1).

FC was not significantly associated with age, menopause duration or reproductive period duration. In postmenopausal females FC was significantly negatively associated with BMD at lumbar spine ($Rho=-0.042$; $p<0.001$) and with BMD at hip ($Rho=-0.64$; $p<0.001$) (Figure 2). FF was significantly negatively associated with BMD at lumbar spine and with BMD at hip ($Rho=-0.28$; $p=0.002$ and $Rho=-0.44$; $p<0.001$, respectively).

In logistic regression model, FC remained independently associated with osteoporosis after controlling for confounders: age, body mass index, menopause and reproductive period duration ($OR=1.3$; 95% CI 1.1-1.6). The model was statistically significant ($X^2=32.5$; $p<0.01$) and could explain from 35.6% (R^2 Cox and Snell) and 37.8% (R^2 Nagelkerk) variance and correctly classify 63.3% of cases.

DISCUSSION

Results of this study have shown that BMA was significantly higher in postmenopausal women with osteoporosis compared to that one with preserved bone mass. However, bone marrow FC was not significantly associated with age, menopause duration or reproductive period duration; postmenopausal women FC was significantly negatively associated with BMD at lumbar spine and with BMD at hip, and the association remained significant even after controlling for age, menopause duration, reproductive period duration and body mass index.

Studies have shown that BMA is continuously increasing with aging (11,12). Depending on the MRI method used, BMA at the lumbar spine level is about 20-30% at the age of 20 and increases by about 7% with each subsequent decade of life so that at the age of 50 is about 50%. During these years, men have higher bone marrow than women, but this relationship changes later in life. From 50 years up, women have accelerated accumulation of BMA resulting in 70% of BMA in women at the age of 80 and about 60% in males at the same age (12).

Accelerated accumulation of BMA in women over 50 years coincides with the occurrence of

menopause. Increase in BMA during menopause is most likely associated with hormonal changes (estrogen and progesterone decline, and FSH and LH increase) (11). Estrogen supplementation in women leads to a BMA reduction of 5% (13). Our study did not show that BMA is associated with age or menopause duration. The reason might be due to relative homogeneity of age of females involved. Also, median menopause duration for both osteoporosis and control group were within second decade range (12 and 10 years) suggesting that accumulation of bone marrow fat might reach a certain point where increasing age does not contribute to additional accumulation. This could be due to the fact that both FSH and LH, after rapid increase during early years after menopause, reach a higher level and do not increase further, and possibly do not contribute more to increased BMA. However, there could be other factors having greater influence on BMA accumulation in postmenopausal females during the second decade after menopause. Recent interest in the role of BMA and its relationship to bone lineage and skeletal fragility has led to the development of non-invasive imaging techniques to assess the quantity and composition of BMA. MRI based quantitative techniques, such as water-fat imaging and H-MRS have helped in determining mechanisms of increased skeletal fragility and metabolic risk associated with several clinical conditions, such as aging, anorexia nervosa, the female athlete triad, obesity and T2DM (4). Although MRS is a reference method for quantifying fat in a small volume of tissue, the heterogeneous distribution of fat in the cavity of one bone or across bones limits its utility (14). Employing MRI with spectroscopy in combination with dual energy x-ray absorptiometry (DXA) allows direct evaluation of the effect of BMA on skeletal health (15). Several studies have reported a significant negative association between BMF content and BMD in healthy men and women (5,6). Although studies have shown negative association between BMD and BMA but it is unknown whether this relationship represents preferential differentiation of mesenchymal stem cells (MSC) into adipocytes instead of osteoblasts; or a passive accumulation of BMA as bone is lost and marrow space increases with aging.

In a study by Shen et al. (6) authors found an inverse relationship between BMA and BMD in the

younger group, suggesting that the differentiation of multipotent stem cells to either osteoblasts or adipocytes is competitive even before the onset of bone loss. These results provided *in vivo* human imaging evidence in support of *in vitro* studies showing that osteoblastogenesis and adipogenesis are competing processes. In our study, there was a negative association between bone marrow fat content and BMD in an anatomically matched region (i.e. vertebral BMD and vertebral bone marrow fat) but also in anatomically different regions (hip BMD and vertebral bone marrow fat content) suggesting that both local and systemic factors might have a role in directing differentiation from mesenchymal stem cells to adipocytes.

It has been shown that mesenchymal cell undergo adipogenesis with declining estrogens, and PTH levels, increasing FSH and IL-6 (16-19). It has been suggested that investigation of relationship between marrow fat and other fat depots such as total body, visceral and subcutaneous fat could yield important clinical data (20). Also, there is a possibility that the relationship between BMA and BMD could be better understood by evaluating adipokines levels such as adiponectin and

leptin, which could both act in autocrine and endocrine fashion. Future studies may investigate potential targets to prevent and treat osteoporosis at both the MSC level and hormonal level. Inhibiting bone marrow adipogenesis or blocking fatty acid metabolism could have detrimental effects, if indeed, the bone marrow adipocytes are rescuing metabolically stressed bone or hematopoietic cells (21). However, it could also be a very effective therapy possibly with few systemic side-effects, if indeed, the marrow adipocytes are supporting the pathological response (21).

In conclusion, bone marrow adiposity is increased in postmenopausal women with osteoporosis and inversely associated with bone mineral density in both anatomically and non-anatomically skeletal regions. These data suggest that bone marrow adiposity might be a potential target to prevent and treat postmenopausal osteoporosis.

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TRANSPARENCY DECLARATION

Competing interests: None to declare.

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