Metabolic Syndrome and Bone Mineral Density in Post Menopausal Women: Is There Any Link?

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Abstract

Introduction: Metabolic Syndrome (MetS) may have a protective or a negative effect on bone. The predominance of different components in individual patients may contribute to inconsistent results regarding its relationship with bone mineral density. Thus, we analyzed the link between MetS and each of its components, and Bone Mineral Density (BMD) in post menopausal women.

Methods: We conducted a cross-sectional study including post menopausal women with and without MetS according to the National Cholesterol Education Program Adult Treatment Panel III criteria. The two groups were compared for BMD after adjusting for covariates that affected BMD significantly. A stepwise multiple linear regression analysis was used to identify independent predictors of BMD.

Results: We included 170 women, 81 with MetS and 89 without MetS. The prevalence of MetS was 48%. In women with MetS, the mean BMD was 0.915 ± 0.159 g/cm² in lumbar spine and 0.865 ± 0.143 g/cm² in total hip. No significant statistical difference was found in comparison with the MetS-free group (0.928 ± 0.160 g/cm²; p=0.61 in lumbar spine, and 0.845 ± 0.143 g/cm²; p=0.29 in total hip). Multiple regression analyses showed that waist circumference was associated with bone loss in lumbar spine (p=0.003), while triglycerides was non-associated with bone loss on total hip (p=0.05).

Conclusion: It seems that BMD is not associated to MetS in post menopausal women. Abdominal obesity might be associated with bone loss underlying the possible effect of inflammation in pathophysiology of osteoporosis and bone loss.

Keywords: Bone mineral density; Metabolic Syndrome; Post menopausal Women;

Background

Metabolic syndrome (MetS) is a heterogeneous and multi-factorial human disorder associated with increased cardiovascular risk [1]. It is a very common medical problem and its prevalence is rapidly increasing in industrialized countries.

Osteoporosis (OP) is a skeletal disorder characterized by compromised bone strength that predisposes affected persons to an increased risk of fracture and consequently to high morbidity and mortality [2]. In our context, 46% of post menopausal women develop at least one vertebral fracture [3].

Although the relationship between cardiovascular disease and osteoporosis has been widely studied, the association between metabolic syndrome, a strong risk factor for vascular disease, and bone loss has not been extensively addressed, and studies are controversial. A study conducted in the USA has found, after adjusting for age, gender, and other covariates, that femur neck BMD was higher in subjects with MetS [4]. In the Camargo Cohort Study, women with MetS had higher age-adjusted BMD at the total hip, femur neck, and lumbar spine than MetS-free women [5]. On the other hand, men with MetS had a lower BMD at the femur neck in the Rancho Bernardo Study after adjusting for Body Mass Index (BMI) [6]. In addition, a recent Korean study has reported that women with MetS also have a lower BMD at the lumbar spine [7].

The joint occurrence of the two diseases is thought to result from the common risk factors and pathophysiological mechanisms, such as smoking, a sedentary lifestyle, sex hormone deficiency, low-grade inflammation, and increased oxidative stress [8–11]. Cumulative evidence has demonstrated that increased bone loss and a lower bone mass are associated with cardiovascular mortality [12, 13] and that an increased risk of cardiovascular events is proportional to osteoporosis severity at the time of diagnosis [14]. MetS is characterized by a proinflammatory state that negatively affects cardiovascular risk [15], and OP is linked to inflammation [16, 17]. Proinflammatory cytokines up-regulate...
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Metabolic Syndrome was defined according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP/ATP III) criteria [26]. Women were classified as having MetS when any three or more of the following items were present: abdominal obesity (waist circumference ≥ 80 cm); serum triglyceride levels ≥ 150 mg/dL (1.7 mmol/L) or High Density Lipoprotein (HDL) cholesterol levels < 50 mg/dL (1.3 mmol/L); blood pressure ≥ 130/85 mm Hg; and fasting glucose level ≥ 100 mg/dL (5.6 mmol/L). Receiving specific treatment for one criterion is counted as fulfilling the criterion.

The aim of this study was to evaluate the effect of MetS on BMD in post menopausal women, and to assess the relationship between each component of MetS and BMD.

Materials and methods

Study design and participants

We conducted a cross sectional study. The study population consisted of consecutive post Menopausal women who had undergone a medical visit in the rheumatology department of Hassan II University Hospital. Postmenopausal status was defined as cessation of menses for at least 1 year. Each subject was asked to complete a questionnaire to determine age, age at menarche, age at menopause, history of previous medical or surgical disease, personal and familial history of osteoporotic fracture, medication history, tobacco and alcohol use, and physical exercise (More or less than three times per week).

All subjects underwent a medical interview and a thorough physical examination. The height and weight of each patient were obtained with them wearing indoor clothing and without shoes. Body Mass Index (BMI) was then calculated as weight (kg) divided by square of height (m). Waist circumference (in centimeter) was measured on bare skin between the tenth rib and the iliac crest at the end of a normal expiration. Blood Pressure (BP, in millimeter of mercury), with systolic and diastolic measures, using a calibrated aneroid sphygmomanometer was recorded twice after resting for more than 15 min. The average of two measurements was used.

Exclusion criteria were: (1) personal history of early menopause (<40 years), (2) missing information about menopausal history or if the subject had undergone a hysterectomy prior to natural menopause, (3) nulliparity, (4) use of alcohol, (5) use of drug that can affect bone metabolism such as hormone therapy, anticonvulsivants or corticosteroids, (6) taking medication for osteoporosis, diabetes hypertension or hypercholesterolemia, (7) malignancy, (8) thyroid disease or thyroid function abnormality, (9) inactive life style with limited physical activity (paraplegia, stroke, dementia...), and (10) acute infection or chronic inflammatory disease.

The study was approved by the local ethics committee of the Faculty of Medicine; Sidi Mohammed Ben Abdellah University. All women gave written informed consent.

Metabolic syndrome

Metabolic syndrome was defined according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP/ATP III) criteria [26]. Women were classified as having MetS when any three or more of the following items were present: abdominal obesity (waist circumference ≥ 80 cm); serum triglyceride levels ≥ 150 mg/dL (1.7 mmol/L) or High Density Lipoprotein (HDL) cholesterol levels < 50 mg/dL (1.3 mmol/L); blood pressure ≥ 130/85 mm Hg; and fasting glucose level ≥ 100 mg/dL (5.6 mmol/L). Receiving specific treatment for one criterion is counted as fulfilling the criterion.

BMD measurements

The BMD was measured by dual energy X-ray absorptiometry using a Lunar Prodigy (GE Medical, Madison, WI, USA), calibrated daily using a standard phantom provided by the manufacturer. BMD was measured at the lumbar spine and total hip, and was expressed in absolute values (g/cm²).

Statistical analysis

The statistical analysis was performed with SPSS Version 18.0. All data are presented as the mean ± Standard Deviation (SD) for quantitative variables, and as percentages for qualitative variables. Demographic characteristics of subjects with and without MetS were compared using Student’s t-test or Mann-Whitney U test for continuous variables, and the chi-square test for categorical variables.

Analysis of Covariance (ANCOVA) was used to compare the BMD levels of women with and without MetS after adjusting for significant BMD covariates including age, BMI, and physical exercise.

A stepwise multiple linear regression analysis was used to identify independent predictors of BMD of the lumbar spine and total hip.

The Statistical significance was set as p ≤ 0.05.

Results

The study included 170 women. The mean age was 58.98 ± 6.58 [44-78] years, and the mean BMI was 29.72 ± 4.09 [18.4-42.7] kg/m². According to NCEP/ATP II definition, the prevalence of metabolic syndrome was 48%. Table 1 shows the clinical characteristics and laboratory parameters of the participants studied according to the presence or absence of MetS. Women with MetS were older with higher BMI. They also had greater values of waist circumference, fasting glucose, triglycerides, and systolic blood pressure, and lower serum HDL cholesterol concentration. No significant difference was found in either serum 25 (OH) vitamin D or total alkaline phosphatase levels in women with and without MetS.

We performed correlation analyses between lumbar spine and total hip BMD, and the known BMD covariates (Table 2). Age showed a negative correlation, and weights a positive correlation with BMD in both sites. Height and BMI had a positive correlation with respectively lumbar spine and total hip BMD.

We analyzed BMD values in lumbar spine and total hip in women with and without MetS (Table 3). It does not seem that BMD is associated to MetS. These findings remained unchanged after adjusting for age, BMI and exercise.

To identify the independent factors affecting the BMD of
Multiple regression analyses were performed to examine the effect of each component of MetS on BMD in lumbar spine and total hip after adjusting for confounding variables (Table 5). In lumbar spine, waist circumference had a negative effect on BMD after adjusting for covariates, while triglycerides had a positive effect on BMD in the base, but this finding disappeared after adjusting for covariates. In total hip, only triglycerides had a positive effect on BMD. This effect remained unchanged after adjusting for all covariates.

Linear regression analyses between 25 (OH) vitamin D, total alkaline phosphatase, and the five single components of MetS were performed. No significant association was found between each of the five MetS components and the two biologic parameters.

**Discussion**

In this study, we did not find any difference in lumbar and total hip BMD in post menopausal women according to the presence or absence of MetS. The literature data about this association is inconclusive. Higher [4-6] and lower [7, 27-
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Concerning the discordant results of the studies analyzing the association between MetS and BMD may reflect the heterogeneous character of MetS and partly depend on the different rates of prevalence of individual components of MetS in various cohorts. Some of MetS components have been studied according to NCEP/ATP III criteria [31], which agrees with our results. These controversial findings may be explained by the fact that MetS is composed from several components, and each one could have a negative or a protective effect on BMD. The concept of MetS is not meaningful in the context of bone mineral density, and the analysis of BMD variation according to the global criterion MetS may obscure pathophysiologic links of BMD with its individual components. Thus, the discordant results of the studies analyzing the association between MetS and BMD may reflect the heterogeneous character of MetS and partly depend on the different rates of prevalence of individual components of MetS in various cohorts. Some of MetS components have been studied such as obesity and diabetes. Despite the high risk of fracture in type 2 diabetic women, hyperinsulinemia accompanied by MetS increases Bone Mineral Density (BMD) [21]. Concerning abdominal obesity, the balance between the possible protection afforded by increased body weight and the damage caused by the inflammatory state has led to controversial results in clinical studies assessing Bone Mineral Density (BMD) [22-25].

We performed a multiple regression analyses to examine the effect of each component of MetS on BMD in both sites after adjusting for confounding variables. When we considered each component of MetS as an independent variable, a higher waist circumference was most significantly associated with lower BMD at lumbar spine. This means that subjects with abdominal obesity are more likely to have lower BMD at lumbar spine. No difference related to abdominal obesity was found at total hip. The reason for the difference between the two sites is not definite, but as shown in the stepwise multiple regression analyses, it appears that the stronger positive correlation between BMI and BMD at the total hip ($\beta=0.007; p=0.007$) could have a greater effect on the association between waist circumference and BMD at the total hip. Indeed, general obesity and body weight are the strongest protectors against bone loss by exercising greater load on the lower limbs and trunk [32]. Other mechanisms related to obesity may also explain its protective effect such as higher 17p-estradiol [33-35] and insulin [36] levels, and some adipokines especially lower adiponectin and higher leptin [37-39]. Also, it seems that visceral obesity is influencing mainly trabecular bone [40]. The negative association between waist circumference and BMD has been reported in the literature which is in total accord with our findings [29, 41]. Visceral fat is not only specialized with regard to the storage and mobilization of lipids but also a remarkable endocrine organ that release proinflammatory cytokines stimulating bone resorption such as TNF alpha, interleukin 6, and interleukin 18 [42-44]. Therefore, it is feasible that the resultant low-grade inflammation, which is known to be involved in the pathophysiological mechanisms underlying osteoporosis [10], may lead to bone loss despite the protective effects of general obesity. In other studies, abdominal obesity was found to be a protective factor on BMD at the lumbar spine [5], the total hip [5, 27], and the femoral neck [5]. Currently, the mechanism of the effect of fat on bone is not clear. A number of mechanisms for the fat-bone relationship exist and include the effect of soft tissue mass on skeletal loading, the association of fat mass with the secretion of bone active hormones from the pancreas beta cell (including insulin, amylin, and preptin), and the secretion of bone active hormones (e.g., estrogens and leptin) from the adipocyte. These factors alone probably do not fully explain the observed clinical associations, and study of the actions on bone of novel factors is an important area of further research.

In our study, triglycerides level correlated positively with total hip BMD. Similar data was reported in literature. Indeed, higher triglycerides level was associated with a less bone loss [6, 27, 45], and with a lower risk of vertebral and non-vertebral fractures [41, 46-48]. This relationship was significant when adjusted for BMD confounders. Thus its mechanism remains unclear. Experimental data suggest that apolar lipids, including TG, form a layer between collagen fibers and mineral crystals [49]. Triglycerides may mediate the interaction between protein matrix and bone mineral and contribute to the improvement of qualitative properties of bone [41].

### Table 3: BMD findings by Metabolic Syndrome status.

<table>
<thead>
<tr>
<th>Presence of MetS (n=81)</th>
<th>Absence of MetS (n=89)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lumbar spine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.915 ± 0.159</td>
<td>0.928 ± 0.160</td>
</tr>
<tr>
<td>Age adjusted</td>
<td>0.916 ± 0.135</td>
<td>0.934 ± 0.150</td>
</tr>
<tr>
<td>Age + BMI</td>
<td>0.911 ± 0.153</td>
<td>0.939 ± 0.160</td>
</tr>
<tr>
<td>All covariates</td>
<td>0.912 ± 0.153</td>
<td>0.938 ± 0.150</td>
</tr>
<tr>
<td><strong>Total hip</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.865 ± 0.143</td>
<td>0.845 ± 0.143</td>
</tr>
<tr>
<td>Age adjusted</td>
<td>0.867 ± 0.135</td>
<td>0.836 ± 0.141</td>
</tr>
<tr>
<td>Age + BMI</td>
<td>0.860 ± 0.135</td>
<td>0.843 ± 0.141</td>
</tr>
<tr>
<td>All covariates</td>
<td>0.861 ± 0.135</td>
<td>0.842 ± 0.141</td>
</tr>
</tbody>
</table>

### Table 4: Stepwise multiple linear regression analysis with bone mineral density as a dependent variable, and metabolic syndrome parameters, age, BMI and exercise as independent variables.

<table>
<thead>
<tr>
<th>β</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lumbar spine</strong></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>-0.006</td>
</tr>
<tr>
<td>BMI</td>
<td>0.005</td>
</tr>
<tr>
<td>Exercise</td>
<td>-0.067</td>
</tr>
<tr>
<td><strong>Total hip</strong></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>-0.005</td>
</tr>
<tr>
<td>BMI</td>
<td>0.007</td>
</tr>
<tr>
<td>Exercise</td>
<td>-0.014</td>
</tr>
</tbody>
</table>

30] BMD values have been reported for women with MetS compared with women without MetS. Yoldemir et al reported that the mean T scores for the lumbar area for women with or without MetS were comparable either according to NCEP/ATP III criteria [31], which agrees with our results. These controversial findings may be explained by the fact that MetS is composed from several components, and each one could have a negative or a protective effect on BMD. The concept of MetS is not meaningful in the context of bone mineral density, and the analysis of BMD variation according to the global criterion MetS may obscure pathophysiologic links of BMD with its individual components. Thus, the discordant results of the studies analyzing the association between MetS and BMD may reflect the heterogeneous character of MetS and partly depend on the different rates of prevalence of individual components of MetS in various cohorts. Some of MetS components have been studied such as obesity and diabetes. Despite the high risk of fracture in type 2 diabetic women, hyperinsulinemia accompanied by MetS increases Bone Mineral Density (BMD) [21]. Concerning abdominal obesity, the balance between the possible protection afforded by increased body weight and the damage caused by
Data on the link between other components of MetS – Blood pressure and serum concentrations of glucose and HDL cholesterol- and BMD are conflicting. Similarly to our data, BMD was not associated with fasting glucose [5, 27-30], with HDLc [5, 7, 27, 29], and with systolic blood pressure [27-29].

Several potential limitations should be considered in the interpretation of our data. First, our recruitment was based on patients who underwent a clinical examination in our university hospital. These subjects may not be representative of the general population. Second, this was a cross sectional study, limiting our ability to determine the cause and effect of MetS and each of its components with the respect to BMD. We could assess only the temporal relationship. Further prospective studies should be performed to determine a causal relationship between these variables. Finally, prevalent fractures and the risk of fractures were not measured in our study. Although MetS do not affect BMD quantitatively, the bone quality could be deteriorated.

**Conclusion**

In summary, our findings reveal that even if the presence of MetS as a global entity has no impact on BMD in post menopausal women, the association between individual component of MetS and low BMD is not excluded. That is because of the characteristics of MetS including both obesity and inflammation. Indeed, abdominal obesity in post menopausal women is the most important factor associated with bone loss, especially in lumbar spine. These results underline the role of inflammation in the pathophysiology of osteoporosis and bone loss.

**Acknowledgment**

Authors’ contributions

FA and FL have drafted the manuscript.

FA, FL, HA, JE, and SR have made substantial contributions to conception and design, acquisition and interpretation of data.

TH and ME supervised the study’s design and planning, and revised the final manuscript.

SK and KR performed the statistical analysis.

All authors read and approved the final manuscript.

**References**


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**Table 5: Multiple regression analysis to determine the independent effects of each specific component for metabolic syndrome on bone mineral density.**

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted</th>
<th>Age adjusted</th>
<th>Age + BMI</th>
<th>All covariates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p</td>
<td>r</td>
<td>p</td>
</tr>
<tr>
<td><strong>Lumbar spine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waist circumference</td>
<td>-0.013</td>
<td>0.740</td>
<td>-0.043</td>
<td>0.137</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>0.026</td>
<td>0.443</td>
<td>0.010</td>
<td>0.686</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.070</td>
<td><strong>0.05</strong></td>
<td>0.008</td>
<td>0.757</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>-0.020</td>
<td>0.607</td>
<td>-0.023</td>
<td>0.340</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>-0.003</td>
<td>0.921</td>
<td>0.013</td>
<td>0.245</td>
</tr>
<tr>
<td><strong>Total hip</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waist circumference</td>
<td>-0.024</td>
<td>0.504</td>
<td>0.003</td>
<td>0.911</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>0.027</td>
<td>0.377</td>
<td>0.024</td>
<td>0.295</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.089</td>
<td><strong>0.007</strong></td>
<td>0.057</td>
<td><strong>0.01</strong></td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>0.017</td>
<td>0.629</td>
<td>0.005</td>
<td>0.815</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>-0.008</td>
<td>0.757</td>
<td>0.011</td>
<td>0.292</td>
</tr>
</tbody>
</table>

All covariates: Age +BMI+ Exercise
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