

Influence of Obesity on Bone Density in Postmenopausal Women

ABSTRACT

Objective: To evaluate the influence of obesity, age, and years since menopause on bone density. **Methods:** A retrospective analysis of bone mineral density (BMD) obtained from 588 women, 41 to 60 years, previously menopausal (1–10 years before). **Results:** Positive influence of obesity was confirmed by the significant differences in BMD at lumbar spine, femoral neck (FN), and trochanter (TR) between the groups ($p < 0.01$). Age and years since menopause (YSM) were negatively correlated with BMD at all sites ($p = 0.000$). Comparing patients within 1 to < 6 YSM versus 6 to 10 YSM, BMD was higher in the former at LS and FN ($p < 0.005$), despite the higher BMI in the older group ($p = 0.01$). Obese patients had a lower prevalence of osteoporosis at LS and FN ($p = 0.009$). Regression analysis identified BMI as the strongest determinant of FN and TR BMD, while YSM was the strongest determinant of LS BMD. **Conclusion:** The protective effect of obesity is overtaken by age and estradiol deficiency. We recommend that even obese postmenopausal women should be screened for osteoporosis. (*Arq Bras Endocrinol Metab* 2007;51/6:943-949)

Keywords: Menopause; Estrogens; Obesity; Bone density; Osteoporosis

RESUMO

Influência da Obesidade na Densidade Óssea em Mulheres na Pós-Menopausa.

Objetivo: Avaliar a influência de obesidade, idade e anos de menopausa sobre a densidade óssea. **Métodos:** Análise retrospectiva da densidade mineral óssea (DMO) obtida em 588 mulheres de 41 a 60 anos, já menopausadas (1–10 anos antes). **Resultados:** A influência positiva da obesidade foi confirmada através de diferenças significativas da DMO entre os grupos na coluna lombar (CL), colo de fêmur (CF) e trocânter (TR) ($p < 0,01$). Idade e anos desde a menopausa (ADM) foram correlacionados negativamente com DMO em todos os sítios ($p = 0,000$). Comparando-se pacientes entre 1 e < 6 ADM vs 6 e 10 AMD, a DMO foi maior no primeiro grupo na CL e CF ($p < 0,005$), apesar de maior DMO no grupo de mais idade ($p = 0,01$). Pacientes obesas tiveram uma prevalência mais baixa de osteoporose na CL e CF ($p = 0,009$). Análise de regressão identificou o IMC como o determinante mais forte da DMO de CF e trocânter, enquanto a ADM foi o determinante mais forte da DMO na CL. **Conclusão:** O efeito protetor da obesidade é sobrepujado pela deficiência de estradiol. Recomendamos que mesmo mulheres obesas na pós-menopausa devam ser examinadas para osteoporose. (*Arq Bras Endocrinol Metab* 2007;51/6:943-949)

Descritores: Menopausa; Estrógenos; Obesidade; Densidade óssea; Osteoporose

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OSTEOPOROSIS IS A SYSTEMIC skeletal disease in which the amount of normally mineralized bone is reduced and the microarchitectural bone tissue, mainly trabecular elements, deteriorated. This disturbance leads to an increase in fracture risk, even with minimum trauma (1). The clinical significance of osteoporosis is currently expressed by the frequency of hip fracture, implying great morbidity and high cost for health services.

It is estimated that osteoporosis fracture cost, in the USA, is about US\$ 10 billion annually for a population of 250 million people (2,3). According to the American National Osteoporosis Foundation (NOF), based on 2000 census data, osteoporosis and low bone mass affect 44 million people that represent 55% of people aged 50 and older. From this total 80% are women. They estimated that in 2020 this number will raise to more than 60 million (4).

Bone density is the major measurable determinant of the risk for osteoporotic fracture. Bone mass increases during childhood and adolescence, peaks in the third or fourth decade of life, remains stable for some years during menopause and declines progressively thereafter, with a sharp acceleration of bone loss during the five to ten years after menopause, ranging from less than 1% to more than 5% per year (1,5-12).

Obesity, defined as body mass index (BMI) between 25 and 39.9 Kg/m², has a protective effect on bone (13,14). Several mechanisms seem to be involved, such as the mechanical effect of increased weight bearing on muscle that stimulates bone formation (15), increased aromatization of androgen to estrogen in adipose tissue (16,17), decreased sex-hormone binding globulin with an increase in free sex steroids (14), increased serum leptin (18,19), increased synthesis of insulin-like growth factors in the liver and the skeleton, and also hyperinsulinemia and insulin resistance (20).

The purpose of this study was to evaluate the relationship between bone density and obesity in postmenopausal women.

SUBJECTS AND METHODS

Study group

A retrospective analysis of bone density data obtained from 588 postmenopausal women examined at a densitometric Clinic in Rio de Janeiro (Osteolab). Inclusion criteria were to be Caucasian, healthy, 41 to 60 years old and within 1 to 10 years after spontaneous menopause. The exclusion criteria were BMI \geq 40 (severe obesity), history of chronic diseases, such as

renal, hepatic, cardiac, rheumatic diseases, use of drugs that could interfere with bone mass, such as corticosteroids and antireabsorptive drugs, hormonal replacement therapy or to smoke more than 10 units/day or alcohol user. All these statements were obtained by a questionnaire applied before the exam was done and answered by the patients themselves.

As it was a retrospective study, we based it on the World Medical Association Declaration of Helsinki, with Ethical Principles for Medical Research Involving Human Subjects.

Data collection

Anthropometric measures included weight (W), height (H), and body mass index (BMI) calculated as W/H^2 (21,22). Patients were divided in normal weighted ($18.5 \leq \text{BMI} < 24.9 \text{ Kg/m}^2$) and overweight or obese women ($25 \leq \text{BMI} < 40 \text{ Kg/m}^2$). We considered that any grade of excessive weight could be a protective factor for bone density. Patients were also divided according to the number of years since natural menopause (YSM) in two groups: 1 to 5 YSM and 6 to 10 YSM. This division was done because we have just a 10-year period after menopause. Smaller divisions seem not to improve our data.

Bone densitometry

Bone mineral density (BMD) was assessed by dual energy X-ray absorptiometry at the lumbar spine (LS) and hip (femoral neck and trochanter), using a Lunar DPX-L, Madison, Wisconsin, USA. The coefficient of variation (CV) was 0.5% with Phantom and 2% in vivo evaluation. Accuracy and precision were, respectively, 1% and 2.5% (23).

Medical ethics

As a retrospective study, it was in accordance with the Helsinki Declaration.

Statistics

Statistical analysis was performed with SPSS software (version 10.0). Data were expressed as mean \pm SD. Groups were compared by Student's *t* test. Chi square was used to analyze the frequency of osteopenia or osteoporosis in normal weighted and obese patients. Pearson simple linear regression and correlation analysis were used to evaluate the interrelationship between parameters. In addition, regression linear analysis was used to assess the association between bone density (dependent variable) and age, body mass index and years since menopause (independent variables). The correlation analysis was carried out in two stages. In

the first stage, each explanatory variable was tested using the Pearson coefficient. Then, those variables that reached a significant association at the 5% level were included in a multiple linear regression model. A p-value less than 0.05 was accepted as significant for all analyses in the study.

RESULTS

Anthropometric data, time elapsed since menopause and bone density are shown in table 1. Age and years since menopause (YSM) were not significantly different between normal weighted and obese patients, but bone density was higher in obese patients in all sites evaluated.

Patients within 1 and ≤ 5 years since menopause were younger, had a lower BMI but a higher BMD at

the LS and FN than the group within ≥ 6 to 10 YSM, as seen in table 2.

Assuming lumbar spine and femoral neck as the most important areas of fracture risk, we compared normal weighted and obese patients according to the prevalence of normal bone density, osteopenia, and osteoporosis at both sites. Osteoporosis was significantly less frequent in obese women, as shown in figure 1.

Correlation analysis confirmed the positive influence of obesity on bone mass and also showed a significant and negative influence of age and YSM, as shown in table 3.

Regression analysis identified BMI as the most important determinant of bone density at femoral neck, while the time elapsed since menopause was the most important determinant of lumbar spine BMD.

Table 1. Comparisons of normal weighted and obese postmenopausal women according to anthropometric and densitometric data.

Characteristics	Normal weight n = 289	Obese n = 299	p value
Age (years)	53.9 ± 4.0	54.5 ± 3.7	0.071
Weight (Kg)	56.5 ± 5.2	69.9 ± 8.4	0.000
Height (cm)	157.8 ± 5.8	157.7 ± 5.3	0.841
Body mass index (Kg/m ²)	22.7 ± 1.5	28.1 ± 2.8	0.000
Years since menopause	4.8 ± 2.7	5.2 ± 2.8	0.070
Lumbar spine BMD (g/cm ²)	0.992 ± 0.178	1.031 ± 0.168	0.006
Femoral neck BMD (g/cm ²)	0.798 ± 0.113	0.853 ± 0.110	0.000

Data are expressed as means ± SD. BMD: bone mineral density.

Table 2. Differences in bone mineral density according to the time elapsed since menopause: 1 to ≤ 5 years and ≥ 6 to 10 years since menopause (YSM).

Characteristics	1 to ≤ 5 YSM n = 318	≥ 6-10 YSM n = 270	p value
Age (yrs)	52 ± 3.7	56 ± 3.2	0.00001
BMI (kg/m ²)	25 ± 3.5	25.7 ± 3.8	0.01
Lumbar spine BMD (g/cm ²)	1.051 ± 0.151	0.974 ± 0.163	0.0001
Femoral neck BMD (g/cm ²)	0.843 ± 0.121	0.811 ± 0.112	0.004

Data are expressed as means ± SD. BMD: bone mineral density

Table 3. Pearson's coefficient (R) and significance level (p), between body mass index (BMI), age, and years since menopause (YSM) with bone mineral density (BMD) in 588 postmenopausal women.

	Femoral neck BMD		Lumbar spine BMD	
	R	p	R	p
BMI	0.294	0.000	0.151	0.000
Age	-0.158	0.000	-0.201	0.000
YSM	-0.160	0.000	0.278	0.000

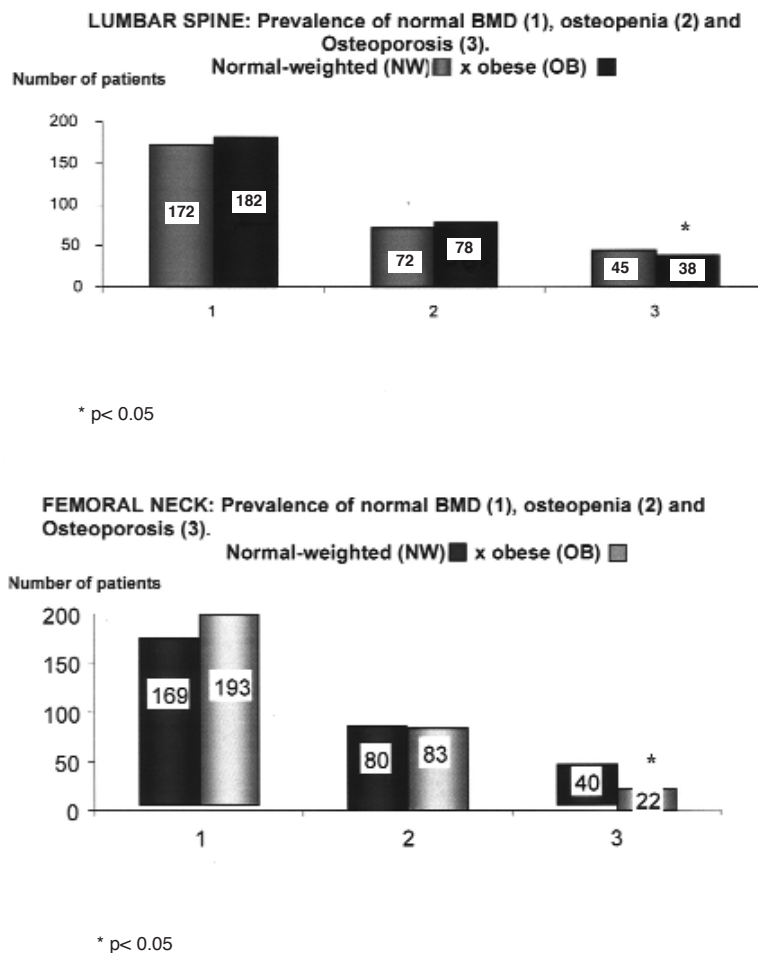


Figure 1. Number of postmenopausal women (absolute values) with normal BMD (1), osteopenia (2), and osteoporosis (3) at the lumbar spine and femoral neck, comparing the normal-weighted and the obese patients.

DISCUSSION

Menopause is associated with an imbalance in bone metabolism, and the first five to ten years after menopause is the period of higher bone turnover and bone loss (24,25). Approximately 35% of postmenopausal women lose significant amounts of bone mineral during this period (“fast losers”) and are at a higher risk for osteoporosis and fragility fractures later in life (26). The decline in ovarian estrogen production is the main determinant of this imbalance, but estradiol serum levels explain only a small proportion of inter individual variance of BMD and bone loss. Therefore, many other factors seem to be involved, such as age, lean and fat mass, exercise, race, smoke, and genetic factors.

Ribot and Albala (27,14) previously described that obese women have higher bone mass after menopause than normal weighted age-matched women, especially at lumbar spine and femoral neck. In our cross-sectional study of 588 postmenopausal patients, we confirmed this influence as body mass index was positively correlated with bone density at all sites and the prevalence of osteoporosis was lower in the obese group.

The positive effect of body weight on bone is mediated by both lean mass and fat mass. Rico et al. studied the effect of soft tissue mass on skeletal loading in overweight and obese women, and found that this factor is the main determinant of bone mass, regardless of gonadal status (28).

Muscular strength also influences skeletal loading. Physically exercising postmenopausal women have greater lean mass that explains the strong association between increased muscle mass and bone density. According to Blain et al., quadriceps strength explains a great part of the association between lean mass and BMD at the femoral neck, suggesting a specific effect of muscular strength on bone and an age-related decline of muscle strength in age-related bone loss in postmenopausal women (29).

Muscle mass or lean body mass were not evaluated in our study, but there were no athletes in the group. We thus suppose that the increase in body weight was mostly due to increased fat mass, as previously described by Frost et al. (23).

The positive effect of obesity on bone is multifactorial, as it is associated not only with the mechanical load as well as with the secretion of bone-active hormones from the pancreatic beta cell (insulin, amylin, and preptin), and the secretion of bone-active hormones such as estrogens and leptin from the adipocyte (30).

The secretion of bone-active hormones from the pancreatic beta cell is increased in obesity. Insulin and insulin-like growth factor can influence bone turnover as well as peripheral estrogen production in adipose tissue (31). Reid and Haffner (32,33) demonstrated a positive correlation between bone density and fasting insulin level, emphasizing that hyperinsulinemia could be an osteogenic factor. Preptin and amylin are also hormones produced in pancreatic beta-cells. Amylin is a polypeptide that belongs to the family of calcitonin gene-related peptides, stimulates the proliferation of osteoblasts, inhibits bone resorption, and increases bone mass and bone density (34).

Another bone-active hormone linked to bone mass and obesity is an *ob* gene product named Leptin, produced in adipocytes. It regulates feeding behavior and energy homeostasis with both neuroendocrine and reproductive effects (35) and acts on human marrow stromal cells to enhance differentiation to osteoblasts and to inhibit differentiation to adipocytes (18,19). Both bone mass and serum leptin levels are increased in obesity, although the influence of leptin on bone is still a matter of debate. Some authors show a positive correlation (30,31) while others show a negative one, both in female (36) and male patients (37).

Estrogen is another bone active hormone increased in obesity. Fat tissue converts androstenedione to estrone by aromatization and this corresponds to the principal source of estrogen in the postmenopausal female, rather than ovarian or adrenal secretion (16,17). Cleland (38) showed that aromatase activity in adipose

stromal cells increases as a function of age, being higher in postmenopausal than in premenopausal women. Thus, the increased estrogen production in obese postmenopausal women is due to a larger number of adipose cells and enhanced aromatase activity. These findings provide strong support for the view that increased synthesis of estrone in adipose tissue may be a contributing factor to bone mass in women passing through natural menopause. Furthermore, Nawata (16) demonstrated that the adrenal androgen DHEA is converted to estrone in osteoblasts by P450 aromatase, and this could also contribute to the maintenance of bone mass in the 6th to 7th decade of life.

In postmenopausal women, increased bone turnover is associated with an increased risk of osteoporotic fracture independently of BMD (39). This risk is diminished in obese women as they seem to lose bone at a slower rate after menopause (40-42). As a consequence, obese postmenopausal women have less osteoporotic fractures, particularly hip fractures (13,14,24,27).

We didn't forget that obesity can be associated with bone artrosis and that this factor can have a positive effect on BMD (43).

We observed that the prevalence of osteoporosis was lower in obese than in non-obese postmenopausal women, both at the lumbar spine and the femoral neck. This positive correlation between obesity and bone mass could be due to the influence of increased estrone and the mechanical load on skeleton (44).

We also demonstrated the negative effect of age and time elapsed since menopause on bone mass, as previously described by Becker, McClung, Ahlborg, and Szejnfeld (45-48). Our population within 6 to 10 years since menopause had a lower BMD either at the lumbar spine and femoral neck. It must be considered that these women were older and had higher BMI than the group with less hormonal deprivation. Therefore, the age-related decline of muscle strength and ovarian estrogen production should be considered important factors involved in osteoporosis, more important than the eventual increase in estrone production in adipose tissue.

We conclude that the protective effect of obesity is overtaken by age and years of estradiol deficiency. Our data lead us to recommend that all postmenopausal women should be screened for osteoporosis whether obese or not.

Once detected osteopenia or osteoporosis, adequate treatment should be instituted, which includes modifications in lifestyle such as exercise, calcium and vitamin D supplements and fall prevention, as well as anti resorption therapy when necessary.

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