Original article

Lean body mass and leptin, but not fat mass are independent predictors of bone mass in postmenopausal women

Masa slabă şi leptina, însă nu şi masa de țesut adipos, sunt factori predictivi independenți ai masei osoase la femeile aflate în perioada postmenopauzală

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Abstract

Body weight is positively correlated to bone mass. While gravity represents a stimulatory stress for bone turnover, endocrine function of adipocytes may also influence bone. We investigated the relative influence of weight, body composition and leptin upon lumbar bone mass in pre- and postmenopausal women. Materials and methods: This cross-sectional study included six groups varying from 8 to 15 pre- / postmenopausal volunteers with different weights (BMI < 25 kg/m^2, overweight: BMI 25-30 kg/m^2, and obese: BMI > 30 kg/m^2). Lumbar bone mineral density (BMD) and body composition (BC) were evaluated by dual X ray absorptiometry (DXA), while serum leptin was evaluated by ELISA. Results: Lean and overweight postmenopausal women had lower lumbar BMD than premenopausal women (p < 0.05). Bone mass of obese postmenopausal women did not differ from that of premenopausal women. Body weight and compartments were positively correlated with bone mineral content. The best correlation was observed for lean mass (r^2 = 0.47 for the whole group), which was an independent predictor of bone mass, irrespective of age (p < 0.05). Leptin was an independent predictor for bone mass only for postmenopausal women (p < 0.05). Conclusion: Increased body weight is associated with decreased bone loss after menopause. Lean mass predicts bone mass independently of body weight, irrespective of age. The beneficial role of fat mass and total body weight on bone mass through gravitational stress seems to be supplemented by possible direct effects of leptin on bone in postmenopausal women.

Keywords: *bone, body composition, leptin,menopause, osteoporosis*

Rezumat

Greutatea corporală este cunoscută a fi corelată pozitiv cu masa osoasă. Forța gravitațională stimulează turnover-ul osos, dar funcția endocrină adipocitară ar putea influența independent osul. Am investigat așadar influența relativă asupra masei osoase lombare a femeilor pre- şi postmenopauzale exercitată

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de către greutate, compoziție corporală şi leptină. Material şi metodă: Acest studiu transversal a inclus şase grupuri de 8-15 voluntare pre- / postmenopauză, care au fost împărțite funcție de greutate în: normoponderale (BMI < 25 kg/m^2), supraponderale (BMI 25-30 kg/m^2) şi obeze (BMI > 30 kg/m^2). Densitatea minerală osoasa lombară (BMD) şi compoziția corporală au fost evaluate prin absorbțiometrie dual cu raze X. Leptina serică a fost evaluată prin ELISA. Rezultate: Femeile postmenopauzale normo- şi supraponderale au avut BMD inferior femeilor premenopauzale (p < 0.05). Masa osoasă a obezelor postmenopauzale nu a diferit de cea a femeilor premenopauzale. Greutatea corporală şi compartimentele organismului au fost corelate cu conținutul mineral osos, masa slabă având corelația cea mai puternică (r2 = 0.47 pentru tot grupul) şi fiind un predictor independent al masei osoase indiferent de vârstă (p < 0.05). Leptina a fost un predictor independent pentru masa osoasă doar la femeile postmenopauzale (p < 0.05). Concluzii : Greutatea corporală crescută este asociată cu diminuarea pierderii de masă osoasă după menopauză. Masa slabă prezice masa osoasă independent de greutatea corporală la orice vârstă. Rolul benefic al masei de țesut adipos şi al greutății corporale prin stress gravitațional pare a fi suplimentat de posibilele efecte directe ale leptinei asupra osului la femeile postmenopauzale.

Cuvinte cheie: *os, compoziție corporală, leptină,menopauză, osteoporoză*

Introduction

Bone is a living tissue, exposed to continuous remodeling that is essential for the adaptation of skeleton to mechanical stress. Peak bone mass is achieved in the first 25-30 years of age. Osteolysis dominates osteoformation with age, leading to bone demineralization, and therefore to a decrease in bone quality and increased risk of fractures, a phenomenon known as "osteoporosis" (1,2). Women face an increased risk of osteoporosis (2,3). However, the risk of osteoporosis varies greatly among individuals, suggesting that gender and menopause are not the only factors influencing bone loss (4).

Body weight, another factor that influences bone mass, is positively correlated to bone mineral density (BMD) (5). This can be explained by the stimulating effect of gravity upon bone formation (5,6). Body weight represents the sum of lean mass and fat tissue mass. Generally, heavy individuals gain weight mainly through the accumulation of adipose tissue, but there are exceptions, such as athletes, where muscular mass dominates (6).

In recent clinical studies the connection between body mass and composition, hormonal and bone mass parameters is discussed. Their common conclusion is that body weight plays an important predictive role on bone mass. The results of these studies differ however, when parameters other than body weight are taken into consideration (7,8). Body composition and fat tissue-related parameters might play different roles in the acquisition, maintainance or loss of bone mass in certain population subgroups and in certain life periods (7-11).

Based on the data in the literature, we hypothesized that lean and fat mass may have different roles on bone mass acquisition in Caucasian women, which might not depend on gravity alone. We checked whether the influence of adipokines on bone mass of Caucasian women differs with age. The aim of our study was therefore to investigate the relative influence of body mass, body composition and adipose tissue-synthesized leptin upon bone mass in pre- and postmenopausal women.

Materials and methods

Subjects

Our cross-sectional study included 6 groups of at least 8 female volunteers each (total number - 68), divided based on age and body mass index (BMI) as follows:

- Age groups: premenopausal: 31 volunteers / postmenopausal (defined as more than two years since arrest of ovarian function): 37 volunteers

Table 1. Characteristics of the groups of volunteers (values are expressed as means +/- SD for age and means +/- SEM for BMI and leptin)

	Groups	nr	Age(years)	BMI(kg/m^2)	Leptin (ng/ml)
Pre-menopausal	Lean	14	36.6 ± 8	19.6 ± 2.1	2.4 ± 0.4
	Overweight	9	38 ± 9.4	27.3 ± 2.3	10.2 ± 3.8
	Obese	8	39.7 ± 9.6	36 ± 4.7	20.1 ± 4.23
Post-menopausal	Lean	10	58.9 ± 4.9	21.9 ± 2.5	5.5 ± 2.4
	Overweight	11	59.2 ± 8.1	26.9 ± 1.5	12.7 ± 4.4
	Obese	15	57.9 ± 6.1	34.9 ± 5.2	24.2 ± 11.3

- BMI groups: lean (BMI < 25 kg/m^2), overweight (BMI between 25-30 kg/m^2) and obese (BMI > 30 kg/m^2) (*Table 1*).

The study was approved by the Ethical Committee of the University of Medicine and Pharmacy "Gr.T.Popa", Iasi. Volunteers were recruited from perimenopausal patients admitted for a routine checkup, students and hospital personnel, after signing an informed consent.

Exclusion criteria were: diabetes mellitus under medication, osteoporosis under therapy (other than calcium and vitamin D supplementation) for longer than 5 years, severe bone trauma, women submitted to hormonal replacement therapy, severe liver or kidney diseases, hyperthyroidism, antecedents of postmenopausal hyperthyroidism, iatrogenic hyperthyroidism (suppressive therapy after total thyroidectomy for thyroid cancer), primary hyperparathyroidism, childhood onset GH deficiency, childhood onset hypogonadism, Cushing syndrome, corticoid therapy for longer than one year, severe rheumatismal diseases, severe malabsorption, anorexia nervosa, genetic syndromes, non Caucasian.

Methods

A morning fasting blood sample was drawn on schedule, centrifuged and serum was stocked in a freezer (-30°C) until biological assessment of serum leptin.

Volunteers were measured and weighed after sampling, and then submitted to DXA investigation (body composition and lumbar bone mineral density). A certified technician evaluated body composition and lumbar bone mineral density (BMD) by DXA (Dual X-ray Absorptiometry, Hologic). Total fat mass and lean mass were expressed in grams, while lumbar BMD was expressed in g/cm^2. Serum leptin (ng/ml) was assessed using a commercial ELISA kit (Diagnostic Automation Inc, Calabasas, CA). Leptin (ng/ml) was further normalized by division to fat mass expressed in kg (leptin/fat mass), obtaining leptin secretion per kilogram of adipose tissue.

Statistical analysis

Results were expressed as mean +/- SD for BMD, and mean +/- SEM for BMI and leptin. The Shapiro-Wilk regression test was performed for attesting the normality of sample distribution. Lumbar BMD was compared between age / body weight groups using the student t test. T and Z scores (defined as the number of standard deviations of one individual from mean lumbar BMD for 25 year old or age matched Caucasian females, respectively) were also evaluated by DXA. In order to eliminate the influence of age upon bone, Z scores were used for whole group correlations. Statistical analysis was performed with NCSS 2007. Pearson's simple correlation was applied to parameter pairs from age groups or the whole group of volunteers. Correlation was considered significant at $p < 0.05$. Multivariate regression (ANOVA) was used to exclude systematical

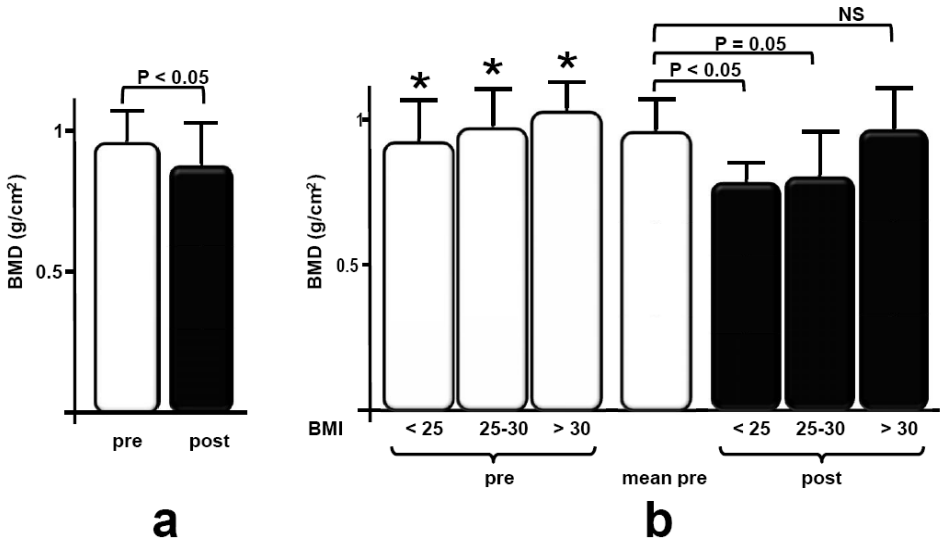

Figure 1. a. Mean lumbar bone mineral density of premenopausal ("pre", white bar) and postmenopausal ("post", black bar) volunteers. **b.** Mean lumbar bone mineral density of lean (BMI < 25 kg/m^2), overweight (BMI between 25 and 30 kg/m^2), and obese (BMI >30 kg/m^2) premenopausal ("pre", white bars) and postmenopausal ("post", black bars) volunteers compared with mean lumbar BMD of all premenopausal women.

* p < 0,05 compared to mean BMD of corresponding postmenopausal group.

distortions. Covariate relations were compared between groups by using covariate multiple regressions (ANCOVA).

Correlations of various factors were rechecked after blockage of the influence of other factors (hierarchical regression). Differences were considered significant at p <0.05.

Results

Several volunteers were either underweight (BMI < 19 kg/m^2) or extremely obese (BMI > 40 kg/m^2), but normality of distribution was confirmed with the Shapiro-Wilk regression test (p = 0.18). Mean lumbar BMD was significantly lower in the whole group of postmenopausal women irrespective of body weight, when compared to premenopausal volunteers (0.9 ± 0.17 g/cm^2 vs 0.99 ± 0.12 g/cm^2, p<0.05, *Figure 1a*). While obese postmenopausal women had a mean lumbar BMD similar to that of premenopausal women, lean and overweight postmenopausal women had a significantly lower (p < 0.05) mean BMD when compared to premenopausal women (*Figure 1b*).

Body weight expressed as BMI (kg/m^2) was positively correlated with lumbar BMD, T score and Z score (*Figure 2*). The best correlation was attained from the Z score since this parameter excludes the influence of age on bone density (r = 0.54 for the whole group, p = 1x10^{-6}).

Since body weight and fat mass were correlated to lumbar Z score in a comparable fashion (r = 0.51 for correlation with fat mass for the whole group), we found that lean mass showed a better correlation with bone mass than with the other two parameters (r = 0.69, *Figure 3*). Similar correlations were found when assessed on age subgroups (pre- and postmenopausal, *Table 2*). Covariate multiple regressions emphasized that lean body mass was an independent predictive factor for bone mass in the whole group, as well as in premenopausal and postmenopausal groups (*Table 3*, p < 0.05). Leptin was correlated positively both with fat mass and Z score (*Figure 4a and b*). When nor-

Table 2. Bivariate regression analysis of body mass, body composition and serum leptin as predictor factors for lumbar bone mineral density expressed by the Z score

	Total R	Pre R	Post R
BMI (kg/m^2)	0.54*	0.51*	0.582*
Fat mass (g)	0.489*	0.491*	0.507*
Lean mass(g)	0.683*	0.680*	0.681*
Leptin (ng/ml)	0603*	0.250	0.715*

R – bivariate standardized linear regression coefficient for the whole group (total), premenopausal (pre) and postmenopausal women. * $p < 0.05$

Table 3. Multivariate regression analyses of body mass, body composition and serum leptin as predictor factors for lumbar bone mineral density expressed by the Z score

	Total R1	Pre R1	Post R1	Total R2	Pre R2	Post R2
BMI (kg/m^2)	-	-	-	-0.201	-0.216	-0.23
Fat mass (g)	0.161	0.112	0.157	-	-	-
Lean mass(g)	0.294*	0.302*	0.289*	0.260*	0.253**	0.295*
Leptin (ng/ml)	0.507*	0.163	0.620*	0.475*	0.083	0.596*

R1 –multivariate standardized linear regression coefficient adjusted for BMI; R2 - multivariate standardized linear regression coefficient adjusted for fat mass; * $p < 0.05$; ** $p = 0.05$

malized to fat mass, leptin correlation with Z score was still significant ($r^2 = 0.226$ for the whole group of volunteers, $p < 0.05$, *Figure 4c*), suggesting that leptin might have a supplementary effect on bone mass than just being a reflection of fat mass. Covariate multiple regressions proved the role of leptin as an independent predictor for bone mass only in postmenopausal women (*Table 2*).

Discussion

Bone mineral content is strongly influenced by menopause and estrogen depletion. Trabecular bone is characterized by higher turnover. The vertebrae are therefore the first bones where mineral loss becomes significant after menopause (3,12). Within the first 3 years after the menopause onset, women lose on average 5% of their initial mineral content (12). Body mass was also proven to influence bone mineral content (5). Underweight is known to be an independent risk factor for osteoporosis both in pre- and postmenopausal women (13,14). Our obese postmenopausal volunteers had a mean lumbar BMD overlapping that of premenopausal women, while lighter postmenopausal women suffered significant bone loss (*Figure 1*). Our data emphasize, as shown by others, that the risk of osteoporosis in postmenopausal women seems to be, indeed, buffered by increased weight (14).

It is actually less clear how different body compartments influence bone mass in other ways than does gravitational stress. The influence of body composition on bone mass was investigated only in a limited number of studies and results were conflicting. Trying to give further insight into this matter, our study proved that lean mass is a better predictor for bone mass than are fat mass and total body weight, both in premenopausal and postmenopausal women.

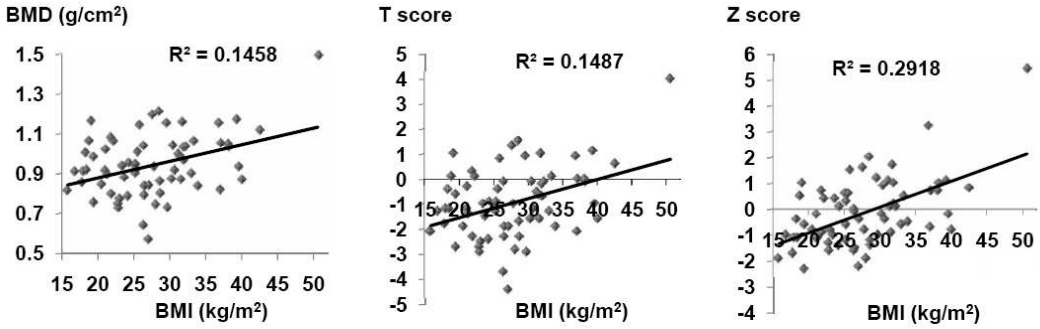

Figure 2. Positive correlation between BMI and lumbar BMD (left panel), T score (mid panel) and Z score, respectively (right panel) for the whole group of volunteers. BMI was best correlated with Z score (r = 0,54), because this parameter eliminates the influence of age on bone.

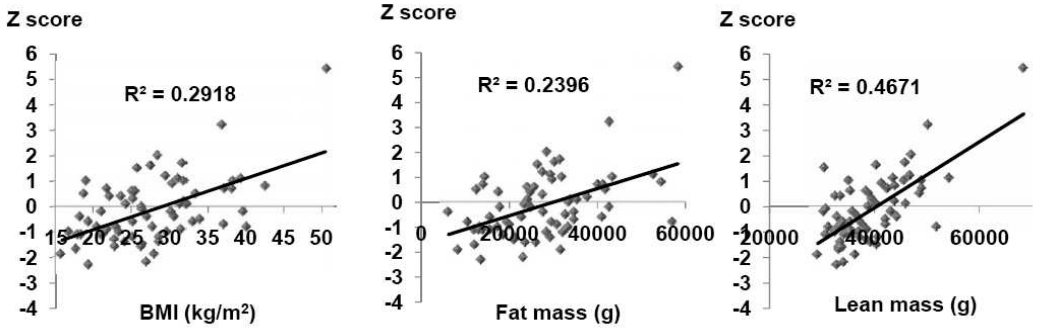

Figure 3. Correlation between lumbar bone mass evaluated by the Z score and BMI (left panel), fat mass (mid panel) and lean mass (right panel) for the whole group of volunteers. Whereas BMI and fat mass were comparably correlated, lean mass showed superior correlation with Z score (r = 0,69).

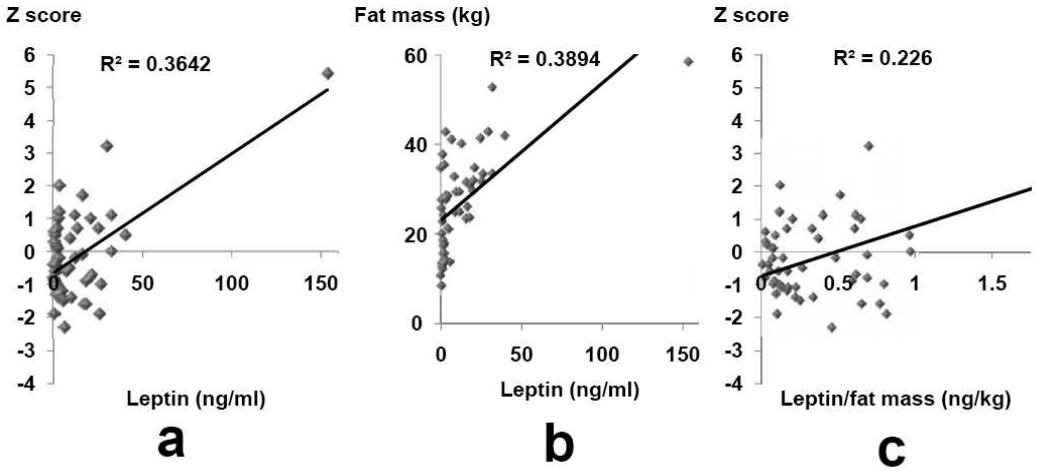

Figure 4. Positive correlation of serum leptin with the Z score (panel a) and fat tissue mass (panel b). When leptin levels were normalized to fat tissue mass, the quantity of leptin secreted by the unit of fat mass was still positively correlated to the Z score (r = 0,475)(**panel c**).

We showed that its predicting power is independent of total body weight, irrespective of age (*Table 3*). Other authors also describe lean mass to be more predictive for bone mass both in women (7,8,15-18) and in men (7,8). A high muscular mass correlated to physical activity favors the increase of bone mass in young age (6,15). Muscle mass is not only dependent of physical activity, but also of hormones, such as IGF1 or testosterone, which also have a direct effect on bone (19,20).

Data concerning the effects of adipose tissue on bone is even more conflicting. Certain authors suggest that fat tissue mass might be more important in predicting bone mass, especially in postmenopausal women (7,9,21). This effect could be mediated by adipocytokines (22) or by the extragonadal estrogenic reservoir represented by the adipocyte (23). Other authors described that the predictive effect on bone mass disappears (24,25), or becomes negative (26-28), once fat tissue mass is expressed as percentage of the total body weight. We found a similar correlation between fat mass and lumbar bone in pre- and postmenopausal women. When we adjusted fat mass to total body weight, however, the correlation became non-significant (*Table 3*). Our data suggests that fat tissue influences bone mainly by gravitational effect, rather than by other mechanisms, contributing to increased total body mass. Morbid obesity was described by others as having a negative effect on bone mass (29). It should be mentioned though that the physical activity of the participants was not evaluated. It is well known that sedentarism is an important risk factor for both obesity and loss of bone mass (4-6). It is therefore not surprising to observe poor bone quality in obese, sedentary persons. We did not evaluate either the physical activity of the volunteers participating in the study.

There is still much debate concerning the direct effects of fat tissue hormones on bone metabolism. Adipocytes and osteoblasts have common mezenchymal origin. The relationship between adipose tissue and locomotor system might therefore exceed the burden of pure mechanical interference (11,30). Adipocytes secrete specific peptidic hormones, named adipocytokines (31). Adipose tissue represents, indeed, a hormonal reservoir that might directly influence bone metabolism (31-33). These hormones act on specific receptors, localized in many tissues and having multiple, only partially elucidated effects. In this respect, leptin influences eating behavior through a central mechanism, via hypothalamic neuronal connections (31). Leptin is presently considered to be a mediator between adipocyte and bone metabolism (31- 33). Leptin receptors were described on osteoblasts, but in vitro and in vivo effects of leptin on bone metabolism are multiple and frequently antagonistic (34). It is shown that leptin stimulates bone formation through a direct mechanism, but inhibits the recruitment of osteoclastic precursors, thereby decreasing osteolysis (35). However, its central effect of stimulating the sympathetic nervous system causes bone demineralization in animal models (34). The puzzle of leptin effects on bone is further complicated by its central stimulative role on somatotrophic axis (36) and the inhibition of neuropeptide Y (37), both actions favoring bone mass accumulation. These pleiotropic effects exerted by leptin on bone metabolism might partially explain the variety of results in clinical studies (38). Certain effects might become more important in specific subpopulations and in critical moments for bone metabolism, such as puberty or after menopause (7-9).

The beneficial effects of leptin on bone were described in several studies (22,31). Other studies found however a close correlation between leptin and fat mass, without a direct impact of leptin levels normalized to fat mass upon bone, or even a negative correlation of the ratio between leptin and fat mass with bone mineral content (39- 41). A possible answer of the large variability of conclusions from clinical studies is that the populations studied had particular characteristics. Our study is the first to correlate leptin with bone mass in pre-

and postmenopausal weight-matched groups. We found that leptin is a positive predictor of bone mass, independent of fat mass or body weight, only in postmenopausal women (*Table 3*), suggesting a direct effect of the hormone on bone in this category of women at risk for osteoporosis.

Conclusions

Our study confirms that increased body mass is associated with decreased bone loss in postmenopausal women and that fat and lean tissue have distinct impact on bone acquisition. When compared to body weight or fat mass, lean mass is a better independent predictor of bone mineral content, irrespective of age. Increased lean and muscle mass possibly reflect a more intensive physical activity or higher levels of certain anabolic hormones, both leading to a more important bone mass acquisition. Individuals with a higher lean mass and bone mass might also share a common, particular genetic background, without a direct cause-effect relationship.

The present study suggests that fat tissue may also directly influence bone mass, through its hormonal secretion. The observation that leptin is an independent predictor of bone mass in postmenopausal women suggests that this adipokine may become important for bone mass preservation in critical moments such as post menopause.

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