Int J Endocrinol Metab 2006; 4: 70 -77

ORIGINAL ARTICLE

Leptin and Bone Mineral Density in Healthy Postmenopausal Iranian Women: A Population-based Study

Shams M, Homayouni K, Hamidi A, Sadegholvad A, Omrani GR.

Endocrine and Metabolism Research Center, Namazi Hospital, Shiraz University of Medical Sciences, Shiraz, I.R. Iran

Obesity is associated with both higher bone mineral density (BMD) and plasma leptin concentration. Inconsistent data are available about the relationship of leptin concentration and BMD, and the aim of this study was to explore the relationship of plasma leptin concentration with BMD as well as bone-related markers in healthy postmenopausal Iranian women.

Materials and Methods: Two-hundred and ninety-six postmenopausal women from a population-based study on prevalence of osteoporosis in Shiraz participated in this study. The BMD was determined at the lumbar spine (L1-L4) and neck of femur by dual-energy X-ray absorptiometry. Blood samples were taken in the fasting state for plasma leptin, serum parathyroid hormone, creatinin, calcium, albumin, phosphorus and alkaline phosphatase evaluations.

Results: The mean age of the participants was 60.75±7.46 years and the mean body mass index (BMI) was 27.51±5.3 kg/m². Mean leptin concentration was 18.12±9.08 ng/ml. One-hundred and forty-two (48%) individuals were osteoporotic, with mean plasma leptin concentration being significantly lower in these individuals (P<0.0001). BMDs at both the lumbar spine (r=0.25; P<0.0001) and the neck of femur (r=0.29; P<0.0001) had significant positive correlation with plasma leptin. The association between BMD and plasma leptin concentration was no longer significant when adjusted for BMI. There was no correlation between plasma leptin concentration and bone-related markers.

Conclusion: This cross-sectional study suggests that the relationship of plasma leptin concentration with BMD is mediated through obesity and plasma leptin is dependently associated with BMD.

Correspondence: Gholamhossien Ranjbar Omrani, Endocrine and Metabolism Research Center, Namazi Hospital, Shiraz University of Medical Sciences, Shiraz, I.R.Iran

E-mail: hormone@sums.ac.ir

Key Words: Leptin, Bone mineral density, Osteoporosis, Obesity, Epidemiology

Received: 30/12/2005 - **Accepted**: 01/07/2006

Introduction

Obesity is associated with increased bone mineral density (BMD) and a decreased risk of fracture.[1-3] The related mechanisms are incompletely understood, but the hypotheses include muscle-mediated mechanical effects of increased weight bearing,[4] increased aromatization of androgen to estrogen in adipose tissue,[5] decreased sex hormone binding globulin with increased free sex steroids[6] and hyperinsulinemia.[7]

Leptin, the protein product of the obesity (ob) gene, is synthesized and secreted by adipocytes, and serum concentrations are highly

correlated with adipose tissue mass.[8-10] Although rare individuals with extreme obesity are leptin deficient, most obese persons have hyperleptinemia proportionate to body fat and appear to be leptin resistant.[8] Leptin might be another mediator between body fat and bone. In vitro studies have shown that leptin is expressed in and secreted from primary cultures of human osteoblasts during the mineralization period[11] and it may enhance osteogenic activity in the marrow of obese individuals.[12] Moreover, leptin may be implicated in fetal and growing bone metabolism[13-15] and may reduce bone loss in ovariectomized rats,[16] suggesting its potential bone anabolic effect in both the first and last stages of life.

In several cross-sectional studies, researchers have found a correlation between serum leptin and BMD in humans. Some report that circulating leptin levels are not associated with BMD,[17-24] while others report that leptin is positively associated,[25-30] and yet others report a negative association between leptin levels and BMD.[31-34]

Most of these studies were performed in a small population samples and in different nations. To our knowledge there is no published study about association of leptin and BMD in Iranian population. Also, considering the controversies in the mentioned published data, we decided to study this phenomenon in a larger sample of postmenopausal Iranian women. This study explores the relationship of fasting plasma leptin with BMD as well as some bone-related markers in a group of healthy postmenopausal women, representative of an urban Iranian postmenopausal population.

Materials and Methods

One thousand and two-hundred (600 women and 600 men) healthy Iranian individuals were randomly selected from all regions of Shiraz. All were in the age range of 20-79 years and all were originally Iranian. According to the municipality of Shiraz, the city is divided into 88 areas. We selected the areas with even numbers. In each area, the population between 20-79 years of age was selected using a cluster random sampling. The response rate was ninety-five percent. The study was approved by the local ethics committee with written informed consent being obtained from patients. Participants were evaluated by taking of medical history including years since menopause (YSM) and performing of limited physical examinations with measurement of weight and height for calculation of body mass index (BMI).

Three hundred and thirty postmenopausal women entered the study. Inclusion criterion was amenorrhea for at least 12 months. Exclusion criteria were history of metabolic bone disease, diabetes mellitus, thyroid and parathyroid disorders, abnormal renal function test, a history of use of hormone replacement therapy, bisphosphonates, calcitonin, corticosteroids and any medication known to affect bone metabolism.

The BMD was determined at the lumbar spine (L1-L4) and the neck of femur in each participant by dual-energy X-ray absorptiometry (DXA) using the fast scan mode (DPX-L, Lunar Co., Madison, WI, USA). Quality control procedures were followed in accordance with the manufacturer's recommendations. Instrument variation was determined regularly by a daily calibration routine using a phantom supplied by the manufactures. The coefficient variation (CV) of the instrument was less than 1.2% for the lumbar spine and 1.1% for the femoral neck.

Blood samples were taken in the morning after a 12-h overnight fast for plasma leptin and serum parathyroid hormone (PTH), creatinin, calcium, albumin, phosphorus, and alkaline phosphatase. Plasma leptin concentrations were determined by radioimmunoassay (RIA) (human leptin RIA kit, DRG Diagnostics, Germany). The intra-assay and inter- assay CVs for the determination of leptin in plasma were 4.7% and 3.0% respectively. Serum intact PTH was measured by enzyme immunoassay (IBL, Germany), and intera-

assay and inter-assay precisions for the determination of intact PTH were less than 2.8% and 8.3% respectively. Serum creatinin, calcium, albumin (for calcium adjustment), phosphorus and alkaline phosphatase were measured using commercially available kits on the Cobas autoanalyzer.

Statistical analysis: Statistical analysis was performed using SPSS for Windows, version 11.5 (SPSS Inc. 1989-2002, Chicago, IL, USA). One-way ANOVA test was used for comparison of mean plasma leptin concentration between normal, osteopenic and osteoporotic groups. Pearson's correlation coefficient was used to assess the correlation between BMD at lumbar spine/neck of femur and plasma leptin concentration and other variables. Partial correlations were used to examine the relationship between BMD and plasma leptin adjusted for BMI and other variables. Stepwise multiple regression analysis was also used to determine the predictors of BMD at the lumbar spine and the neck of femur. P values less than 0.05 were considered as significant.

Results

Three hundred and thirty persons entered the study. Thirty-four were excluded; 20 had a history of endocrinological disorders (such as diabetes mellitus, hyperthyroidism), 8 were on hormone replacement therapy and 6 were on drug therapy known to interfere with bone metabolism (such as corticosteroids, vitamin D, bisphosphonates). Finally, two hundred and ninety six persons remained for this study. The mean age was 60.75±7.46 years and mean YSM was 12.39±8.54. Thirty-six (12.2%) were normal (T score > -1.0 in both skeletal areas), 118 (39.8%) had osteopenia (-1.0 ≥ T score > -2.5) and 142 (48%) were osteoporotic (T score ≤ -2.5 in any skeletal area). Mean BMI was 27.51±5.3 kg/m^2 and mean plasma leptin concentration was 18.12±9.08 ng/ml. Anthropometric and biochemical characteristics of participants are shown in table 1.

The mean plasma leptin concentration was significantly lower in individuals with osteoporosis in comparison with normal and osteopenic subjects. (Table 1) BMD at the lumbar spine and at the femoral neck were positively and significantly correlated with BMI and plasma leptin concentration, whereas negatively and significantly correlated with age, YSM, alkaline phosphatase level. Plasma leptin concentration was positively and significantly correlated with BMI, BMD at both skeletal areas and creatinin, but had significant negative correlation with age (Table 2 and fig.1). There was no relationship between plasma leptin concentration and bone-related markers like alkaline phosphatase (Table 2).

Table 1. Comparison of anthropometric and biochemical characteristics* between normal, osteopenic and osteoporotic postmenopausal women (n=296) by ANOVA test

Characteristics	Normal (n=36)	Osteopenia (n=118)	Osteoporosis (n=142)	P value
Age (years)	56.9±4.7*	59.2±6.9	63.2±7.7	<0.0001
Years since menopause	8.02±4.2	10.74±8.1	14.49±8.1	<0.0001
BMI (kg/m^2)	28.8±3.6	28.5±3.9	25.4±4.2	<0.0001
Adjusted calcium (mg/dL)	9.7±0.5	9.60±1.0	9.9±1.2	0.35
Phosphorus (mg/dL)	3.46±0.54	3.45±0.58	3.49±0.59	0.87
Alkaline phosphatase (IU/L)	206±64	227±60	243±65	0.005
Creatinin (mg/dL)	0.96±0.1	0.91±0.1	0.88±0.2	0.019
PTH (pg/mL)	11.07±11.5	13.27±12.7	12.38±11.2	0.62
Leptin (ng/mL)	21.3±9.9	20.3±9.0	15.5±8.3	<0.0001

*: Mean±SD

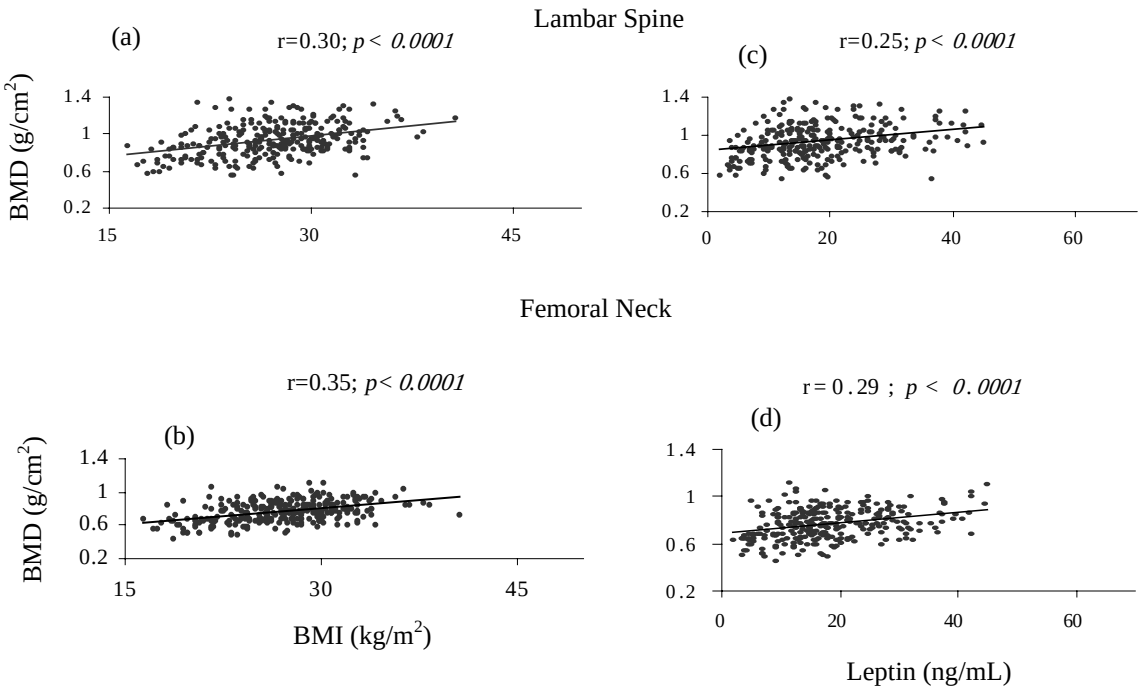

Fig.1. Relationship between bone mineral density (BMD) at lumbar spine (a)/femoral neck (b) and body mass index (BMI) and plasma leptin concentration in 296 postmenopausal Iranian women. Relationship between related BMD and plasma leptin concentration in the same population (c and d).

Table 2. Correlates of plasma leptin concentration and bone mineral density (BMD) at the lumbar spine and the neck of femur

	Plasma leptin		Lumbar spine BMD		Femoral neck BMD	
Variables	**r ***	**P value**	**r ***	**P value**	**r ***	**P value**
Age (years)	-0.17	0.003	-0.31	<0.0001	-0.4	<0.0001
Years since menopause	-0.07	0.23	-0.31	<0.0001	-0.33	<0.0001
BMI (kg/m^2)	0.51	<0.0001	0.3	<0.0001	0.35	<0.0001
Adjusted calcium (mg/dL)	-0.02	0.69	-0.1	0.07	-0.04	0.48
Phosphorus (mg/dL)	-0.02	0.67	0.007	0.9	0.06	0.31
Alkaline phosphatase (IU/L)	-0.01	0.91	-0.22	<0.0001	-0.19	0.001
Creatinin (mg/dL)	0.23	<0.0001	0.19	0.001	0.1	0.07
PTH (pg/mL)	0.03	0.63	0	0.99	-0.04	0.5
Plasma leptin (ng/mL)	-----	-------	0.25	<0.0001	0.29	<0.0001
BMD at lumbar spine (g/cm^2)	0.25	<0.0001	-----	-------	0.67	<0.0001
BMD at femoral neck (g/cm^2)	0.29	<0.0001	0.67	<0.0001	-----	-------

*: r =Pearson's correlation coefficients

Results from partial correlation analyses as shown in table 3 suggest that the significant positive association of BMD with plasma leptin concentration remained significant when adjusted for age, YSM, alkaline phosphatase and creatinin. However, this relationship did not remain statistically significant after adjustment for BMI. In addition, the relationship between BMI and BMD at both skeletal areas remained statistically significant after controlling for plasma leptin concentration. (r=0.28; P<0.0001 for BMD at lumbar spine / r = 0.32; P<0.0001 for BMD at femoral neck).

Results of the stepwise multiple regression analysis presented in table 4 show that BMI, YSM, alkaline phosphatase, creatinin and age were the main predictors of BMD at the lumbar spine. The main predictors of BMD at the neck of femur were age, BMI and alkaline phosphatase. Although BMI remained a significant predictor and showed a positive and independent association with BMD at both skeletal areas, plasma leptin concentration was not a predictor of BMD at either skeletal area.

Table 3. Associations between plasma leptin concentration and bone mineral density (BMD) before and after adjustment for different variables

	Person's correlation		**Partial correlations**	
Skeletal site	r (p value)	r* (p value)	r† (p value)	r ‡(p value)
BMD at Lumbar spine	0.25 (<0.0001)	0.22 (<0.0001)	.18(0.003)	0.00 (0.99)
BMD at femoral neck	0.29 (<0.0001)	0.27 (0.0001)	0.24 (<0.0001)	0.04 (0.54)

*Adjusted for age, years since menopause; †Adjusted for age, years since menopause, alkaline phosphatase, creatinin; ‡Adjusted for age, years since menopause, alkaline phosphatase, creatinin and BMI

Table 4. Predictors of bone mineral density (BMD) at the lumbar spine and the neck of femur

Lumbar spine *				**Femoral neck** †			
Independent variables	β coefficient	SE	p value	Independent variables	β coefficient	SE	p value
BMI	0.12	0.002	<0.0001	Age	-0.007	0.001	<0.0001
YSM	-0.004	0.002	0.015	BMI	0.11	0.002	<0.0001
Alkaline phosphatase	0.0001	0.0001	0.003	Alkaline phosphatase	0.0001	0.0001	0.003
Creatinin	0.165	0.6	0.006				
Age	-0.005	0.002	0.009				

* Dependent variable: BMD at the lumbar spine; † Dependent variable: BMD at the neck of femur

Discussion

In this population-based, cross-sectional study of healthy postmenopausal Iranian women, we found that mean plasma leptin concentration was significantly lower in osteoporotic individuals. Also there was a strong positive correlation between plasma leptin concentration and BMI and BMD at spine and hip, but the association between plasma leptin and BMD was no longer significant after adjustment for BMI, i.e. plasma leptin concentration had a dependent association with BMD.

Although obesity is a major risk factor for many diseases and has become a severe burden on healthcare costs in societies, it may have at least one beneficial effect, that of preventing osteoporosis. The effect of obesity on bone has not been fully explained, and because both bone mass and leptin are related to body weight, it has been suggested that this hormone may be a mediator of this effect. In human studies there are conflicting data on the relationship between BMD and serum leptin.[21,35-37] The effects of leptin on bone vary with age, gender and bone site. During the first few years of life, leptin may enhance bone growth via its angiogenic properties and its osteogenic effect on cortical bone; in life, leptin may decrease bone remodeling and improve the balance between bone formation and bone resorption, particularly when trabecular bone turnover is high.[38]

The only data from humans come from cross-sectional epidemiological studies and anecdotal case-reports. The relation between serum leptin levels and bone parameters seems to differ between males and females.[38] In females, serum leptin levels and BMD were directly correlated in some cross-sectional studies,[17,26] but not in others.[39,40] Pasco et al. reported a direct relation between serum leptin levels and bone mineral content (BMC) in a group of healthy non-obese Australian women, aged 20-91 years, even after adjustment for fat mass.[29] Martini et al. showed significant positive associations between leptin and BMI (stronger with fat mass than lean mass) as well as with bone turnover markers and bone mass. These last two associations became nonsignificant after adjustment for BMI.[18] As in our study an independent effect of BMI on BMD remained after adjustment for plasma leptin concentration. Yamauchi et al. also demonstrated an effect of leptin on bone mass in 139 postmenopausal women, independent of percentage of fat. In this group, plasma leptin (but not percentage of fat) was significantly lower in women with vertebral fractures than in those without fractures.[28] This is in accordance with our result of lower mean plasma leptin concentration in osteoporotic women. In males, there was either no relation[26] or a negative relation[32] between leptin and BMD. The reasons for this sex-specific difference are poorly understood but may involve the two- to three-fold higher leptin levels in females than in males, independent from fat mass. Similarly anecdotal case-reports support a direct or indirect effect of leptin on bone.[38] Patients with anorexia nervosa experience more bone loss than those with hypothalamic amenorrhea.[41] Although this difference may be related in part to nutritional factors,[42] another possible mechanism is the marked decrease in serum leptin levels associated with anorexia nervosa.[43] Furthermore, replacement estrogen therapy fails to prevent bone loss induced by anorexia nervosa.[42]

The global picture of the skeletal effects of leptin remains highly speculative and requires additional studies. Nevertheless, most studies, as does our study support the hypothesis that leptin may be involved in bone metabolism and may act as a mediator between fat mass and bone tissue. Although we found that leptin was not an independent factor for BMD, it might be due to some limitations of our study including the small sample size of postmenopausal women. The second limitation was that the study was on conducted population of an urban area of Shiraz which is not representative of the entire Iranian population.

In summary, our results suggest that mean plasma leptin concentration is related to presence of osteoporosis. Also, the plasma leptin concentrations strongly and positively correlated with both BMI and BMD at the lumbar spine and the neck of femur. The relationship between plasma leptin and BMD at both skeletal areas was no longer significant after adjustment for BMI. Our observations are consistent with previous reports and suggest that the relationship between plasma leptin concentration and bone mass may be mediated through the obesity rather than a direct relationship of plasma leptin concentration with bone density.

Acknowledgments

We wish to thank the women who participated in this study. We are grateful to Mr. M. Monjazeb and Mr. M. Moaiedifar (personnel of the Endocrine and Metabolism Research Center, Namazi Hospital) for their kind technical assistance. Bone mineral density measurements were done by Mr. P. Talee-Zadeh (Namazi Hospital). We thank Dr. N. Zare the statistician at the Center of Clinical Research Development of the Namazi Hospital and Miss Z. Tolabzadeh for typing the manuscript. This study was supported by a grant from Shiraz University of Medical Sciences.

References

1. Riggs BL, Melton LJ 3rd. Involutional osteoporosis. N Engl J Med 1986; 314: 1676-86.
2. Melton LJ 3rd, Kan SH, Frye MA, Wahner HW, O'Fallon WM, Riggs BL. Epidemiology of vertebral fractures in women. Am J Epidemiol 1989; 129: 1000-11.
3. Lindsay R, Cosman F, Herrington BS, Himmelstein S. Bone mass and body composition in normal women. J Bone Miner Res 1992; 7: 55-63.
4. Rubin CT, Lanyon LE. Regulation of bone mass by mechanical strain magnitude. Calcif Tissue Int 1985; 37: 411-7.
5. Frumar AM, Meldrum DR, Geola F, Shamonki IM, Tataryn IV, Deftos LJ, et al. Relationship of fasting urinary calcium to circulating estrogen and body weight in postmenopausal women. J Clin Endocrinol Metab 1980; 50: 70.
6. Albala C, Yanez M, Devoto E, Sostin C, Zeballos L, Santos JL. Obesity as a protective factor for postmenopausal osteoporosis. Int J Obes Relat Metab Disord 1996; 20: 1027-32.
7. Reid IR, Evans MC, Cooper GJ, Ames RW, Stapleton J. Circulating insulin levels are related to bone density in normal postmenopausal women. Am J Physiol 1993; 265: E655-9.
8. Considine RV, Sinha MK, Heiman ML, Kriauciunas A, Stephens TW, Nyce MR, et al. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. N Engl J Med 1996; 334: 292-5.
9. Ruhl CE, Everhart JE. Leptin concentrations in the United States: relations with demographic and anthropometric measures. Am J Clin Nutr 2001; 74: 295-301.
10. Ostlund RE Jr, Yang JW, Klein S, Gingerich R. Relation between plasma leptin concentration and body fat, gender, diet, age, and metabolic covariates. J Clin Endocrinol Metab 1996; 81: 3909-13.
11. Reseland JE, Syversen U, Bakke I, Qvigstad G, Eide LG, Hjertner O, et al. Leptin is expressed in and secreted from primary cultures of human osteoblasts and promotes bone mineralization. J Bone Miner Res 2001; 16: 1426-33.
12. Thomas T, Gori F, Khosla S, Jensen MD, Burguera B, Riggs BL. Leptin acts on human marrow stromal cells to enhance differentiation to osteoblasts and to inhibit differentiation to adipocytes. Endocrinology 1999; 140: 1630-8.
13. Matkovic V, Ilich JZ, Skugor M, Badenhop NE, Goel P, Clairmont A, et al. Leptin is inversely related to age at menarche in human females. J Clin Endocrinol Metab 1997; 82: 3239-45.
14. Ogueh O, Sooranna S, Nicolaides KH, Johnson MR. The relationship between leptin concentration and bone metabolism in the human fetus. J Clin Endocrinol Metab 2000; 85: 1997-9.
15. Steppon CM, Crawford DT, Chidsey-frink KL, Ke H, Swick AG. Leptin is a potent stimulator of bone growth in ob/ob mice. Regul Pept 2000; 92: 73-8.
16. Burguera B, Hofbauer LC, Thomas T, Gori F, Evans GL, Khosla S, et al. Leptin reduces ovariectomy-induced bone loss in rats. Endocrinology 2001; 142: 3546-53.
17. Goulding A, Taylor RW. Plasma leptin values in relation to bone mass and density and to dynamic biochemical markers of bone resorption and formation in postmenopausal women. Calcif Tissue Int 1998; 63: 456-8.

18. Martini G, Velenti R, Giovani S, Franci B, Campagna S, Nuti R. Influence of insulin-like growth factor-1 and leptin on bone mass in healthy postmenopausal women. Bone 2001; 28: 113-7.
19. Hadji P, Bock K, Gottschalk M, Kalder M, Emons G, Schutz KD. The influence of serum leptin concentrations on bone mass assessed by quantitative ultrasonometry (QUS) in pre- and postmenopausal women. Maturitas 2003; 44: 141-8.
20. Iwamoto I, Douchi T, Kosha S, Murakami M, Fujino T, Nagata Y. Relationship between serum leptin and regional bone mineral density, bone metabolic markers in healthy women. Acta Obstet Gynecol Scand 2000; 79: 1060-4.
21. Ruhl CE, Everhart JE. Relationship of serum leptin concentration with bone mineral density in the United States population. J Bone Miner Res 2002; 17: 1896-1903.
22. Dennison EM, Syddall HE, Fall CH, Javaid MK, Arden NK, Phillips DIW, et al. Plasma leptin concentration and change in bone density among elderly men and women: The Hertfordshire cohort study. Calcif Tissue Int 2004; 74: 401-6.
23. Sahin G, Polat G, Baois S, Milcan A, Baodatoolu O, Erdooan C, et al. Body composition, bone mineral density, and circulating leptin levels in postmenopausal Turkish women. Rheumatol Int 2003; 23: 87-91.
24. Shaarawy M, Abassi AF, Hassan H, Salem ME. Relationship between serum leptin concentrations and bone mineral density as well as biochemical markers of bone turnover in women with postmenopausal osteoporosis. Fertil Steril 2003; 79: 919-24.
25. Blain H, Vuillemin A, Guillemin F, Durant R, Hanesse B, de Talance N, et al. Serum leptin level is a predictor of bone mineral density in postmenopausal women. J Clin Endocrinol Metab 2002; 87: 1030-5.
26. Thomas T, Burguera B, Melton LJ, Atkinson EJ, O'Fallon WM, Riggs BL, et al. Role of serum leptin, insulin and estrogen levels as potential mediators of the relationship between fat mass and bone mineral density in men versus women. Bone 2001; 29: 114-20.
27. Papadopoulou FG, Konstandinidis T, Koliakos G, Krassas GE. The association between leptin and gonadal and adrenal steroids, insulin-like growth factor 1, insulin-like growth factor binding protein 3 and bone mass density in Greek healthy males. Bone 2001; 28: S393 (Abstract).
28. Yamauchi M, Sugimoto T, Yamaguchi T, Nakaoka D, Kanzawa M, Yano S, et al. Plasma leptin concentrations are associated with bone mineral density and the presence of vertebral fractures in postmenopausal women. Clin Endocrinol 2001; 55: 341-7.
29. Pasco JA, Henry MJ, Kotowicz MA, Collier GR, Ball MJ, Ugoni AM, et al. Serum leptin levels are associated with bone mass in nonobese women. J Clin Endocrinol Metab 2001; 86: 1884-7.
30. Zoico E, Zamboni M, Adami S, Vettor R, Mazzali G, Tosoni P, et al. Relationship between leptin levels and bone mineral density in the elderly. Clin Endocrinol (Oxf) 2003; 59: 97-103.
31. Nagy Z, Speer G, Takacs I, Bajnok E, Lakatos P. Serum leptin levels and bone mineral density in postmenopausal women. Bone 2001; 28: S284 (Abstract).
32. Sato M, Takeda N, Sarui H, Takami R, Takami K, Hayashi M, et al. Association between serum leptin concentrations and bone mineral density and biochemical markers of bone turnover in adult men. J Clin Endocrinol Metab 2001; 86: 5273-6.
33. Blum M, Harris SS, Must A, Phillips SM, Dawson-Hughes B. Leptin, body composition and bone mineral density in premenopausal women. Bone 2001; 28: S437 (Abstract).
34. Morberg CM, Tetens I, Black E, Tourbo S, Soerensen TIA, Pedersen O, et al. Leptin and bone mineral density: A cross-sectional study in obese and nonobese men. Clin Endocrinol Metab 2003; 88: 5795-800.
35. Roux C, Arabi A, Porcher R, Garnero P. Serum leptin as a determinant of bone resorption in healthy postmenopausal women. Bone 2003; 33: 847-52.
36. Takeda S, Karsenty G. Central control of bone formation. J Bone Miner Metab 2001; 19: 195-8.
37. Thomas T, Burguera B. Is leptin the link between fat and bone mass? J Bone Miner Res 2002; 17: 1563-9.
38. Thomas T. Leptin: a potential mediator for protective effects of fat mass on bone tissue. Joint Bone Spine 2003; 70: 18-21.
39. Rauch F, Blum WF, Klein K, Allolio B, Schonan E. Does leptin have an effect on bone in adult women?. Calcif Tissue Int 1998; 63: 453-5.
40. Odabasi E, Ozata M, Turan M, Bingol N, Yonem A, Cakir B, et al. Plasma leptin concentrations in postmenopausal women with osteoporosis. Eur J Endocrinol 2000; 142: 170-3.
41. Warren MP, Voussoughian F, Geer EB, Hyle EP, Adberg CL, Ramos RH. Functional hypothalamic amenorrhea: hypoleptinemia and disordered eating. J Clin Endocrinol Metab 1999; 84: 873-7.
42. Karlsson MK, Weigall SJ, Duan Y, Seeman E. Bone size and volumetric density in women with anorexia nervosa receiving estrogen replacement therapy and in women recovered from anorexia nervosa. J Clin Endocrinol Metab 2000; 85: 3177-82.
43. Grinspoon S, Miller K, Coyle C, Krempin J, Armstrong C, Pitts S, et al. Severity of osteopenia in estrogen-deficient women with anorexia nervosa and hypothalamic amenorrhea. J Clin Endocrinol Metab 1999; 84: 2049-55.