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The Relationship between Serum Leptin Level and Bone Mineral Denisty in Postmenopausal Osteoporotic Women

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Abstract :

Postmenopausal osteoporosis is a heterogeneous disorder characterized by a progressive loss of bone tissue that begins after menopause and leads to fracture within 15-20 years from the cessation of the ovarian function. Human leptin is a protein of 167 amino acids. It is manufactured primarily in the adipocytes of white adipose tissue, and the level of circulating leptin is proportional to the total amount of fat in the body. Leptin's effects on bone are mediated via a central neuroendocrine signaling pathway, as well as directly on bone marrow stem cells to enhance their differentiation to osteoblasts and inhibit their differentiation to adipocytes.

Aim of the Study: to detect the relation between serum leptin level, total lipid profile and bone mineral denisty in postmenopausal osteoporotic women.

Subjects and Methods: The study was carried on 40 postmenopausal females. According to Dual Emergy X-ray absorptiometry (DEXA), the subjects were divided into group A, Tt-score $\leq$-2.5, group B, t-score <-1, leptin and lipid profile were measured for all subjects.

Conclusion: The current study has provided evidence that bone mineral density is influced by serum leptin level in postmenopausal osteoporotic women and positive correlation between serum leptin level and bone mineral density was found.

Recommendation: Serum leptin level measurement could be used as a simple and non invasive method for screening programs for osteoporosis in postmenopausal women but the accuracy of this test still needs furtherer studies.

Abbreviation: Ob gene : Obese gene; BMD : Bone Mineral Density;
NOF: National Osteoporosis Foundation; M-CSF : Monocyte colony stimulating factor;
BMI: Body mass index; DEXA: Dual-energy X-ray absorptiometry

Key words: serum leplin, Bone Mineral Denisty; Postmenopausal Osteoporotic Women

Introduction

World Health Organization defined osteoporosis as having a Bone Mineral Density (BMD) that is 2.5 standard deviations below peak bone mineral density[(1)].

Osteoporosis affects over 200 million people worldwide including 40% of women aged 50 years and over, and 65% of women aged 70 years and over **Kanis et al.**.[(2)]

Among the hormones involved in bone and mineral metabolism, leptin has become a subject of considerable interest. Leptin has been reported to have bone anabolic, anti-resorptive, and anti-osteoclastogenic effects [(3)]**.** Leptin is a circulating neurohormone produced primarily by adipose tissue as the product of the obese (ob) gene [(4)]**.** In addition to white adipose tissue, it can also be produced by brown adipose tissue, placenta (syncytiotrophoblasts), ovaries, skeletal muscle, stomach (the lower part of the fundic glands), mammary epithelial cells, bone marrow and liver cells [(5)]**(Margetic et al.).** Leptin interacts with several types of receptors (Ob-Ra-Ob-Rf, or LepRa-LepRf) that in turn are encoded by a single gene, Ob-Rb is the only receptor isoform that can signal intracellularly via the JAK state and MAPK signal transduction pathways and is present in hypothalamic nuclei [(6)]**.** Leptin can also act directly on bone marrow stem cells to enhance their differentiation to osteoblasts and inhibit their differentiation to adipocytes [(7)] **Shoshana et al.** Postmenopausal Osteoporosis is something that most women are concerned about. The rate at which bone regeneration takes place slows down with age. The rate of regeneration decreases even more after a women goes through menopause. Therefore, women are more susceptible to osteoporosis after menopause [(8)]**(Admi, et al.).** Estrogen acts on estrogen receptor-α (ERα) and receptor-β (ERβ) which has high affinity towards osteoblasts and osteoclasts [(9)]**(Manolagas et al.).** Two Primary Mechanisms Promote Increased Osteoclastogenesis and Bone Resorption in the Absence of Estrogen**.** Under estrogen-deficient conditions, T cells produce elevated levels of

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proinflammatory cytokines including TNF-alpha, IL-1, and IL-6. These cytokines promote increased RANK L expression on osteoblasts and stromal cells, which leads to osteoclast differentiation in the presence of M-CSF [10].

Subjects s and Methods:

Patients:

This study included 40 postmenopausal females collected from the Outpatient Clinic of Rheumatology and Rehabilitation at Alzahraa hospital and Sayed Galal hospital during the period from October 2011 to August 2012.

Informed consent was obtained from all participants.

Patients were devided according to their Dual- Energy X-Ray Absorptiomety (DEXA) T- score into two groups:

1-Group A (cases): includes 30 post menopausal females with T- score at lumbar spine and neck of the femure below -2.5 .

2-Group B (controls):10 postmenopausal females with T- score at lumbar spine and neck of the femure above -1.

Inclusion criteria:

-Postmenopausal femals above 50 years old.

Exclusion criteria:

1- Patients with established medical conditions known to alter BMD and which may cause secondary osteoporosis e.g. hyperthyroidism; hyperparathyroidism, chronic renal insufficiency; chronic liver disease and malignancy.
2- Patients receiving drugs for treatment of osteoporosis in the previous 6 months, like bisphosphonates, hormone-replacement therapy (HRT), calcium, vitamin D, calcitonin.
3- Patients taking drugs that are known to affect bone metabolism e.g. glucocorticoids, heparin, anticonvulsants, diuretics and cytotoxics..

Methods:

Each participant have been subjected to;

1- Full history taking.
2- Full physical examination including: body weight, body height .
3- Bone densitometry (using DEXA scan).
4- Laboratory investigation including serum leptin level and total lipid profile including serum total cholesterol, serum triglycerides,serum low denisty lipoprotein and serum high denisty lipoprotein.

1-Full history taking

2-**Full physical examination** including: body weight, body height and body mass index was calculated according to the equation:

BMI=WEIGHT(kg) /Height(m2)

3-**Bone densitometry (using DEXA scan)**

Two areas of the skeleton were tested; the lumbar spine and the hip.

Plasma leptin concentration

Plasma leptin concentration was determined by using the DAI Leptin enzyme-linked immunosorbent assay (ELISA) solid phase enzyme emmunsorbent asseay based on sandwich supplied by [DRG international in company Int. U.S.A] EIA/2395.

Total serum lipid profile.

Total cholesterol (TC), low density lipoprotein (LDL), high density lipoprotein (HDL) cholesterol in the serum samples of the subjects were measured by immunoassay (ELISA).

Results

The age of the cases in our study was ranging between (50- 70) years with mean (57.3± 13.2) years, and the age of the controls ranging between (50-69) years with mean (61±15.2) years as shown in (table 1).

Table (1): Descriptive data of our studied groups are demonstrated in table (1).

Parameter	cases		Control	
	Mean	Std. Deviation	Mean	Std. Deviation
Age	57.3	13.2	61.2	15.2
Age of Menopause	48.2	227.1	52	12.4
Duration menopause	10	5.21846	6.56	5.20502
BMI	31.065	4.9 6065	29.554	4.650

Table (2): Comparstion between cases control as regad

parameter	Cases	controls	p-value
Lumbar T-score	(-3.17±0.71)	0.31 ±0.81	p < 0.01(HS)
Neck of the femure T-score	-2.65+0.76	0.28 +0.79	p < 0.01

Table (3): Comparison of biochemical marks between cases and control

parameter	Cases	controls	p-value
Serum leptin	44.73±11.29	75.35±15.68	p < 0.05(S)
Serum cholesterol	208.6+30.6	166.8+41.6	p < 0.05
Serum LDL	141.5+35.9	88+22.2	p < 0.05
Serum HDL	40.20+8.1	28.90+5.9	p < 0.05
Serum TG	130+80.8	166+82.6	P 0.05

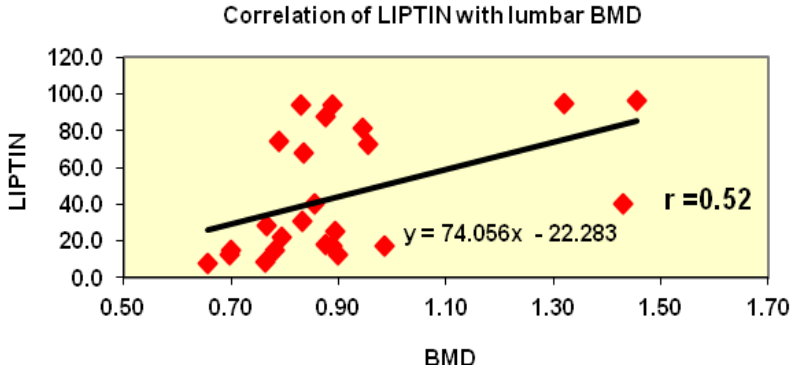

Fig. (1): Showing the correlation between serum leptin level and lumbar BMD between cases and controls.

As regard T-score at lumbar spine (L2-L4); for the cases show was highly significant as shown in table (2). Estimation of serum leptin level for the cases with significant statistical difference between patients and controls as shown in table (3). Estimation of serum total cholesterol level for the csaes significant statistical difference between patients and controls as shown in table (3).

Estimation of serum LDL level for the cases with significant statistical difference between patients and controls as shown in table (3).

Estimation of serum HDL level in our study for the cases with significant statistical difference between patients and controls as shown in table(3).

Serum TG level was with mean for the osteoporotic patients, and) with mean(166+82.6) for controls with no significant statistical difference between patients and controls as shown in table(3)

Discussion

Osteoporosis is a silent slowly progressive skeletal disease. It is characterized by low bone mass, deterioration of bone tissue and disruption of bone architecture, compromised bone strength and an increase in the risk of fracture. The risk for osteoporosis increases after menopause [(11)]

Osteoporosis is a major public health problem in Egypt. Constructed Bone mineral density charts for Egyptian women showed that, in general, they have a lower bone mineral density compared to their western counterparts **Sallam et al.**[(12)]. In our study we aimed to detrmine the association between BMD and circulating serum leptin levels among postmenopausal osteoporotic women. We found that leptin level was significantly lower among osteoporotic females. So higher serum leptin level is associated with higher BMD This result is in agreement with **Yamauchi et al.** [(13)] who had conducted his study to One hundred and thirty-nine postmenopausal women (age 48-78 years, mean 62.5), who visited our outpatient clinic for the evaluation of osteoporosis, had reported that plasma leptin levels were positively correlated with BMD values, and multiple regression analysis revealed that this positive relationship was still observed with BMD values of the femoral neck and of the whole body, even after %fat and age were taken into account. Also **Thomas et al.** [(14)]who assessed the role of the candidate hormones, leptin, insulin, and estrogen in mediating fat mass effects on the skeleton in a sample of 137 premenopausal women (age range 21-54 years), 165 postmenopausal women (34-93 years), and 343 men (23-90 years) recruited from the general population, found that serum leptin correlated with BMD in women but not in men Another study done by **Pasco et al.**[(15)] found a significant positive association between the

BMD and serum leptin in women. **Cornish et al.**[16] found that leptin given peripherally increased bone strength in mice and also increased proliferation of osteoblasts in vitro. On the contrary, **Goulding et al.** [17] have not found any relationship between BMD, bone turnover markers and leptin concentration in postmenopausal women.

Also **Iwamoto** [18] found correlations between some skeletal sites and serum leptin, but not at the whole body, and the correlations with biochemical markers were weak. Aging is associated with changes in plasma levels of several hormones. There are several conflicting reports on leptin level changing during aging**.** In our study we found insignificant negative relation between age and leptin. This result is supported by **Ostlund** [19] who had found that circulating leptin is inversely related to age.

Zhong et al. [20] found that Serum leptin concentration was significantly higher in postmenopausal than premenopausal women ($p<0.001$).

In our study, positive correlation was found between leptin and BMI. **Douchi et al.[21]** had suggested that leptin may be a mediator between body fat and bone ,because serum leptin levels correlates positively with fat mass in healthy subjects. However, **Pasco et al.**[22] found that the positive correlation between leptin and bone mass was independent of body weight. Literature concerning relationships between HDL cholesterol levels and BMD is contradictory**.** Our study found that lipid profile is moderately related to BMD. The level of serum total cholesterol and low density lipoprotein cholesterol were inversely associated BMD of lumbar spines (L2-L4).

Another study done by **Aleksandar et al.** [23] involved 300 women referred to densitometric examination as they belonged to the risk group of postmenopausal women, found that atherogenic lipoproteins negatively correlate with lumbar bone density. so Increase in values of cholesterol, LDL and triglyceride are connected with significant risk increase for the appearance of osteopenia or osteoporosis. Lumbar spine BMD was not associated with total cholesterol (TC), low density lipoprotein, cholesterol (LDL-C), and high density lipoprotein cholesterol (HLD-C) regardless of when the measurement was performed. In the current study, no significant correlation was found between TG and HDL and BMD lumbar spines (L2-L4)**.** This result is consistent with the results of **Zabaglia et al. 1998**[24] who had found no association between serum triglycerides and BMD in menopausal women. But, **Adami et al.** [25] had found that total body and hip BMD were positively related to serum triglycerides in women.

Conclusion

The current study has provided evidence that bone mineral density is influced by serum leptin level in postmenopausal women with statistically significant difference and positive correlation between serum leptin level and bone mineral density.

As regard total lipid profile, in our study inverse correlation between serum leptin level and total serum cholesterol and low density lipoprotein cholesterol levels.

Recommendations

Serum leptin level measurement could be used as a simple and non invasive method for screening programs for osteoporosis in postmenopausal women.

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