The role of Leptin (hormone adipocytes) and its effect on Osteoporosis in postmenopausal women

Haider Kamel Mohammed[1,*], and *Haider* salih jaffat[2]

Department of Biology, Faculty of Science, University of Kufa, Najaf, Iraq

Abstract. Leptin has been recognized as a critical factor in regulating energy expenditure and bone cell function. The role of Leptin in regulating osteocyte function within the adipocyte population has been widely recognized. Leptin stimulates bone cell proliferation and plays a role in developing many skeletal disorders, regulatory mechanisms and mode of action of Leptin. This suggests that levels of Leptin are linked to obesity (BMI). The primary aim of this study was to examine the potential relationship between circulating leptin levels and BMI, as well as specific indices such as t-score and biomarkers in postmenopausal women. Blood samples were collected from (90) postmenopausal women, (35) who were diagnosed with Osteoporosis, (25) samples who were diagnosed with Osteopenia, and (30) samples as a control group. Patients were diagnosed as osteoporotic and controls as usual by measuring bone mineral density (BMD) using dual-energy X-ray absorptiometry (DEXA). The results of bone turnover markers, which included Leptin hormone in the sera of Osteoporotic patients, was 211.30± 65.24 (pg/mL) less than it was in the sera of control women mean of 283.20 ±106.15 (pg/mL), indicating a significant increase for the comparison is 0.002. The study showed that low levels of Leptin lead to low bone density, which leads to Osteoporosis.

1 Introduction

Osteoporosis is a skeletal disease that involves the degradation of bone tissue and the loss of bone mas . Osteoporosis, characterized by porous bones, leads to an elevated risk of bone fragility and fracture susceptibility. Osteoporosis can affect both men and women, but it is more prevalent and tends to start sooner in women. Typically, Osteoporosis doe not cause any symptoms until a bone fracture occurs [1]. There are two types of Osteoporosis: primary and secondary. Primary Osteoporosis can strike people of any age in both sexes, although it typically strikes women after menopause and males later in life [2]. On the other hand, the use of medications like steroids leads to secondary Osteoporosis. Other examples of diseases or disorders are hypogonadism and celiac disease [3]. Osteoporosis diagnosis entails evaluating bone mineral density using dual-energy X-ray absorptiometry (DEXA) scanning. Osteoporosis is defined by the World Health Organization (WHO) using the T-score, which

* Corresponding author: haiderkamw3@gmail.com

compares an individual's bone mineral density (BMD) to that of a reference sample of young adults. An individual with a T-score of -2.5 or below is diagnosed with Osteoporosis, but a T-score ranging from -1.0 to -2.5 indicates low bone mass or Osteopenia. Accurate diagnosis requires both clinical evaluation and consideration of other risk factors [4]. Risk Factors Several factors contribute to the development of Osteoporosis :Age: The risk of Osteoporosis grows with advancing Age. As individuals age, particularly women after menopause, their bones tend to undergo a process of thinning and weakening [5]. Sex: Females have males. Menopause can expedite bone loss due to hormonal changes, including a decline in estrogen levels [6]. Hormonal changes: Besides menopause, other hormonal imbalances can contribute to Osteoporosis. Low levels of testosterone in men and overactive thyroid conditions (hyperthyroidism) can also lead to bone loss. Lack of calcium and vitamin D: Calcium and vitamin D are necessary for preserving bone health. Insufficient consumption of certain nutrients can elevate the likelihood of developing osteoporosis. Consuming foods that are high in calcium, such as dairy products and leafy greens, is essential. Additionally, it is important to expose oneself to sunlight in order to synthesize vitamin D [7]. Leptin is a protein hormone that is mostly produced by adipocytes, or fat cells, and it probably plays a major role in controlling the long-term energy balance [8, 9]. Leptin levels, one of the primary indicators of energy status, have an impact on motivated behaviors such as feeding and foraging that are aimed at maintaining energy stores as well as hunger and satiety. The quantity of energy reserves, primarily triglycerides kept in adipose tissue, is correlated with the level of Leptin in the blood. The brain interprets high leptin levels as high energy reserves, while low leptin levels imply that energy [10]. Leptin has been demonstrated to promote the development of osteoblasts from marrow stromal cells and hinder the activity of osteoclasts. Neuroendocrine pathways and neurotransmitters are crucial in regulating bone remodeling [11]. Changes in body weight in adult women are linked to concurrent alterations in circulating levels of A recent in vitro study has shown that Leptin affects the differentiation of human marrow stromal cells into osteoblasts, suggesting its potential role in bone mass regulation.

2 Materials and methods

2.1 Ethical issues

This study was approved by the Institutional Research Ethics Committee of the Department of Life Sciences, College of Science, University of Kufa, Iraq.

2.2 Patients

This study was conducted in DEXA (dual-energy X-ray absorptiometry) at Al-Sadr Teaching Hospital in Najaf Governorate / Iraq in the period (of February 2024– March 2024). In postmenopausal Iraqi women, Ninety females. Female 90 have the number of patients (35 osteoporosis and 25 osteopenia) contributed at present. According to the study, their ages ranged between 45 and 75 years. These patients were registered as osteoporosis patients in the Medical Rehabilitation Center of Al-Sadr Teaching Hospital in Najaf Governorate - Iraq. Dual-e nergy X-ray absorptiometry (DEXA) technology has been used to diagnose individuals with osteoporosis or osteopenia. In order to determine whether there were any systemic disorders that would have an impact on the parameters under study, the complete medical history of the patients was evaluated .Control group: Thirty women over 45 years old - that is, reaching menopause - were selected to form the control group. These people had

no physical or emotional health problems, and were in excellent condition. They were found to not have osteoporosis, a diagnosis that was further supported by a DEXA scan.

2.3 Statistical analysis

Statistical analysis was done according to percentages to compare between samples using SPSS V.9 computer software [12, 13].

3 Result

3.1 Demographic and clinical characteristics in Postmenopausal Osteoporotic Women and the Control Group

The findings of the current study in Table 1. show variables of demographic and clinical characteristics in 90 postmenopausal women, including 60 osteoporotic women, compared with 30 without Osteoporosis

Mean Age 56.71±8.47 years and distribution with percentages for osteoporotic patients compared with the control group mean Age about 53.53±6.43 years, there is no statistically significant difference p-value is 0.074.

Additionally, age distribution recorded 48.3% (29 out of total) of women patients were aged 45 - 54 years. 18(30%) were age range 55 - 64 years, and 13(21.7%) of osteoporotic patients older than 66 years. Age distribution analysis out of the total osteoporotic patients, 25(42%) were aged between 45-54 years, compared to 19(63%) in the control group, also 19(32%) of osteoporotic patients age range of 55-64 years, while only 8(27%) of the control group fell within this age range, moreover older osteoporotic patients 66 years 16(26%) were compared to only 3(10%) in the Control group. The mean BMI of osteoporotic women is 21.10±3.65 kg/m^2, which increased in Underweight patients 32(53%) more than patients with normal weight 21(35%), overweight 5(8%), and obese 2(4%), revealed to significant (p-value 0.001) decrease when compared to the mean BMI of the control group is 25.58±3.88 kg/m^2, which involved, 15(50%) with normal weight, more than 3(10%) Underweight, 10(33%) Overweight, and 6(20%) obese women, respectively. Statistical significance ($p<0.05$) decrease in the T-score of osteoporotic patients is -2.48 ± 0.77, as compared with the control group is 1.12 ± 0.71, p=0.001. The results show that the osteoporotic women significantly elevated in mean ESR of 41.90 ± 10.18 mm/hr. To compare with the groups of control mean of 11.57 ± 4.63 mm/hr., the p-value is 0.001. The results of Leptin hormone indicating a significant decrease (p=0.002) in the sera of Osteoporotic patients were 211.30± 65.24 (pg/mL) lower than the control women mean of 283.20 ±106.15 (pg/mL). Meanwhile, Figure 1. designed levels of leptin hormone in Osteoporosis and Osteopenia have a significant decrease ($p<0.05$) in means leptin (pg/mL) of 209.75±63.23 and 213.47±69.21 compared to the control group. Vitamin D (V.D.) levels show a significant lowest in osteoporotic postmenopausal at 15.21 ± 8.03 ng/mL, less than 22.89 ± 8.48 ng/mL in the control group, p-value of 0.001. Levels of serum minerals such as calcium, magnesium, and sodium documented that women of osteoporotic postmenopausal have a significant ($p<0.05$) decrease in Ca (mg/mL) mean of (7.91 ± 0.80 vs. 9.19 ± 0.96, p-value 0.001), Mg (mg/mL) level of 1.71 ± 0.27 vs. 1.93 ± 0.30, a p-value of 0.002), and Na (pmol/mL) level of 127.39 ± 22.38 vs. 138.37 ± 3.61, the p-value is 0.009) is compared with the control women. Serum U.A. (mg/dL) level explained a statistically significant increase in women Osteoporotic patients of 7.78 ± 1.66, compared with 4.65 ± 1.38 in the control group, p-value 0.001. Therefore, levels of Alb (mg/dL) recorded a significant decline in these patients as compared

to the control group mean of (2.50 ± 0.58 vs. 3.84 ± 1.00), with the p-value for the comparison being 0.001.

Table 1. Demographic and clinical characteristics in Postmenopausal Osteoporotic Women and the Control Group

Variables	Osteoporotic patients n=60	Control n=30	p-value
Age (year)	55.87±8.18	52.89±5.79	0.078 ns
45-54	29(48.3%)	20(66.7%)	
55-64	18(30%)	8(26.7%)	
>66	13(21.7%)	2(6.6%)	
T-score	-2.48±0.77	1.12±0.71	0.001*
BMI (kg/m^2)	21.76±2.50	25.53±3.09	0.001*
Underweight Normal weight Overweight	29(48%) 29(48%) 2(4%)	14(47%) 13(43%) 3(10%)	
ESR (mm/hr.)	41.90±10.18	11.57±4.63	0.001*
VD (ng/mL)	15.21±8.03	22.89±8.48	0.001*
Deficiency Insufficient Sufficient	46(77%) 9(15%) 5(8%)	10(33%) 12(40%) 8(27%)	
Leptin (pg/mL)	211.30±65.24	283.20±106.15	0.002*
Ca (mg/mL)	7.91±0.80	9.19±0.96	0.001*
U.A. (mg/dL)	7.78±1.66	4.65±1.38	0.001*
Mg (mg/mL)	1.71±0.27	1.93±0.30	0.002*
Na (pmol/mL)	127.39±22.38	138.37±3.61	0.009*
Alb (mg/dL)	2.50±0.58	3.84±1.00	0.001*

Significant differences at *p<0.05. Independent T-test.

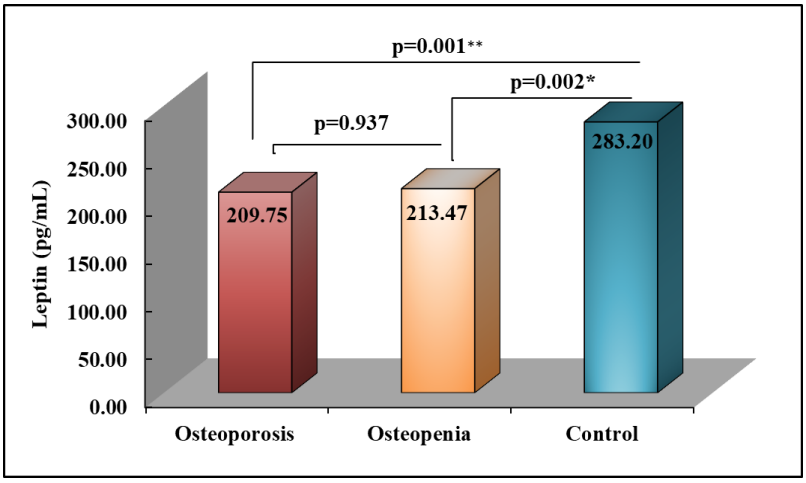

Fig. 1. Serum Leptin levels in postmenopausal osteoporotic women compared with the control group. Significant differences at p-value *<0.05, **<0.01.

3.2 Correlations of Leptin hormone with clinical parameters in postmenopausal osteoporotic women

The results are in Table 2. Revealed that Age was a statistically significant negative moderate strength correlation with leptin levels (r = -0.293, p = 0.023). There is a highly statistically

significant positive correlation with BMI (r = 0.488, p = 0.0001) and moderate strength of correlation with T-score (r = 0.368, p = 0.004), respectively. The relationship of Leptin with ESR and U.A. showed a significant negative correlation (r = -0.274, p = 0.034) and (r = -0.389, p=0.002), while strong strength positive correlated with V.D. (r = 0.351, p = 0.006), and moderate strength of correlation Ca (r = 0.289, p=0.025). Moreover, serum levels of Mg (p = 0.323), Na (p = 0.767), and Alb (p = 0.568) do not appear to have a significant association with leptin levels

Table 2. Correlations of Leptin hormone with clinical parameters in postmenopausal osteoporotic women

	Leptin (pg/mL)	
	r	**p-value**
Age (year)	-0.293*	0.023
BMI (kg/m^2)	0.488**	0.0001
T-score	0.368**	0.004
ESR (mm/hr.)	-0.274*	0.034
VD (ng/mL)	0.351**	0.006
Ca (mg/mL)	0.289*	0.025
U.A. (mg/dL)	-0.389**	0.002
Mg (mg/mL)	0.130	0.323
Na (pmol/mL)	0.039	0.767
Alb (mg/dL)	-0.075	0.568

Linear regression results are in Table 3. Indicated to that predictor variables as risk factors in osteoporotic in postmenopausal women. Leptin hormones showed that Age was not statistically significant as a predictor (**B**: -0.643, p-value: 0.524; 95.0% C.I.: -2.653 to 1.367). A positive relationship with BMI (**B**: 8.017; p-value: 0.001; 95.0% C.I: 3.359 to 12.675). And T-scores (**B**: 31.066; p-value: 0.004; 95.0% C.I: 3.359 to 12.675). A statistically significant predictor of osteoporotic severity. Also, V.D. was a predictor relationship with osteoporotic postmenopausal women (**B**:2.258; p-value: 0.038; 95.0% C.I: 0.132 to 4.383). Moreover, the U.A. was a predictor of osteoporotic severity, negatively related to Leptin hormone was statistically significant (**B**: -12.886; p-value: 0.014; 95.0% C.I: -23.014 to 2.759). The results indicate that ESR (p=0.192), Ca (p=0.147), Mg (p=0.621), Na (p=0.773) and Alb (p=0.742) were no significant predictors of Leptin hormone in osteoporotic postmenopausal women respectively.

Table 3. Linear regression analysis of Leptin to available marker in Osteoporotic Severity

Predictors	**Unstandardized Coefficients**		**t**	**Sig.**	**95.0% Confidence Interval for B**	
	B	**Std. Error**			**Lower Bound**	**Upper Bound**
Age (year)	-0.643	1.004	-0.640	0.524	-2.653	1.367
BMI (kg/m^2)	8.017	2.326	3.446	0.001*	3.359	12.675
T-score	31.066	10.300	3.016	0.004*	10.448	51.684
ESR (mm/hr)	-1.111	0.842	-1.320	0.192	-2.798	0.575

VD (ng/mL)	2.258	1.061	2.127	0.038*	0.132	4.383
Ca (mg/mL)	15.713	10.687	1.470	0.147	-5.714	37.140
U.A. (mg/dL)	-12.886	5.051	-2.551	0.014*	-23.014	-2.759
Mg (mg/mL)	15.399	30.944	0.498	0.621	-46.640	77.437
Na (pmol/mL)	0.110	0.380	0.290	0.773	-0.652	0.873
Alb (mg/dL)	-4.884	14.747	-0.331	0.742	-34.449	24.681

a. Independent Variable: Leptin hormone
Significant differences at p-value *<0.05. B: (Effect size). 95%C. I: 95%Confidence Interval

3.3 ROC and AUC Analysis of Leptin hormone for discrimination postmenopausal osteoporotic women

Analysis for discrimination performance for Leptin hormone in postmenopausal Osteoporosis by the receiver operating characteristic (ROC) and area under the curve (AUC). Finding in Table 4 and Figure 2. The results showed that Leptin has a good predictive ability (AUC = 0.71, 95%CI: 0.59-0.83, p=0.0001) with moderate sensitivity and specificity of 69 % 75% at a cut-off value <231.68).

Table 4. ROC and AUC Analysis of Leptin Hormone to Predict Osteoporotic Women

Predictor	Leptin (pg/mL)
AUC	0.710
SE	0.061
P-Value	<0.001**
95% C.I	0.590-0.830
Cut-Off	< 231.68
Sensitivity	0.690
Specificity	0.750

Significant differences at **p<0.01. AUC: Area Under the Curve. 95%C. I: 95%Confidence Interval. S.E.: standard error.

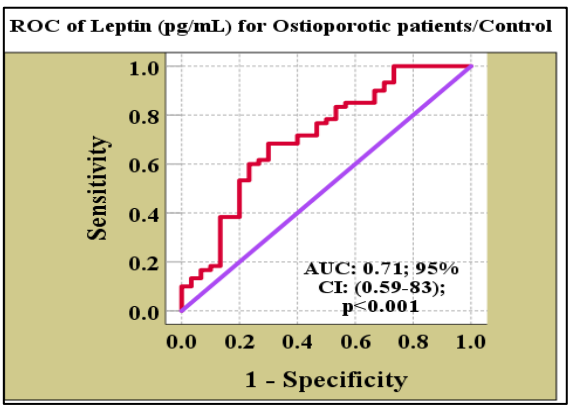

Fig. 2. ROC of Leptin in Osteoporotic patients

4 Discussion

The findings demonstrated a decline in the leptin hormone levels following menstruation, which aligns with the research conducted by [14]. Osteoporosis is characterized by decreased bone density and the deterioration of bone tissue, leading to an increased risk of fractures and bone fragility. This condition is prevalent, particularly among older individuals and women who have gone through menopause. While the precise factors contributing to Osteoporosis are varied, numerous research studies have explored the potential role of Leptin in developing this condition. Leptin, mostly secreted by adipose tissue, governs the metabolism of glucose and lipids and possesses anti-inflammatory and anti-atherogenic characteristics [15]. Multiple research has investigated the correlation between Leptin and Osteoporosis, repeatedly finding that persons with Osteoporosis have lower leptin levels than healthy controls [16]. leptin are two important adipokines that control bone metabolism [17]. Leptin, which is recognized for its ability to increase the sensitivity of insulin, has been demonstrated to stimulate the development of osteoblasts (cells that create bone) and hinder the formation of osteoclasts (cells that break down bone), thereby encouraging bone formation and preventing bone loss [17]. On the other hand, Leptin is a hormone that controls both appetite and energy usage. Additionally, it plays a significant role in bone metabolism. Studies have demonstrated that Leptin stimulates the proliferation and differentiation of osteoblasts, which are the cells responsible for bone synthesis [16]. Studies have shown that Leptin stimulates the formation of osteoblasts from marrow stromal cells and suppresses the action of osteoclasts. Leptin acts as a blocker of bone breakdown and enhances the production of osteoprotegerin (OPG). As a result, bone density is preserved, and osteoclast activity is reduced. Furthermore, a direct association exists between the levels of Leptin and the rise in osteocalcin.

5 Conclusion

These findings suggest different factors that may influence the severity or progression of Osteoporosis in patients. For example, Age and levels of bone-related Leptin appear to have significant associations with Osteoporosis. In addition, BMI and ESR also show significant associations, indicating potential complexities in the relationship between these variables. And Osteoporosis. In summary, this analysis indicates that age, BMI, ESR and leptin levels are significantly associated with Osteoporosis in the studied group.

References

1. N.C. Harvey, E.M. Curtis, N.R. Fuggle, E.M. Dennison, British medical bulletin, **133(1),** 105–117 (2020)
2. M. Cchadha, R. Chaddha, H. Divakar, H. Kalyan, S. Seth, P. Shah, et al., Open Journal of Orthopedics, **12**, 153–182 (2022)
3. A. Lubkowskaaa, A. Radecka, J. Mieszkowskiii, Adiponectin as Biomarker of Osteoporosis, 1–34 (2015)
4. Dlll Glaser, F.S. Kaplan, J. Spine, Osteoporosis: definition and clinical presentation, 22, 12S-16S (1997)
5. J. Yang, O.J. Park, J. Kim, S. Han, Y. Yang, C.H. Yun, et al., Frontiers in Endocrinology, 10, 815 (2019)
6. S. Shahid & M. U. Hashmi, The Professional Medical Journal, **27(01)**, 205–209 (2020)

7. L. Zhang, H. Hu, J. Wu, X. Wang, H. Qu, S. Guo, et al., *Plasma Asprosin Levels Are Associated with Glucose Metabolism, Lipid, and Sex Hormone Profiles in Females with Metabolic-Related Diseases,* Mediators of Inflammation (2018)
8. S. Shahid & M. U. Hashmi, The Professional Medical Journal, **27(01),** 205–209 (2020)
9. H.A. Al-Hussaniy, A.H. Alburghaif, M.A. Naji, Journal of Medicine and Life, 14(5), 600–605 (2021)
10. J. Hebebrand, T. Hildebrandt, H. Schlögl, J. Seitz, S. Denecke, D. Vieira, Neuroscience and Biobehavioral Reviews, **141**, 104807 (2022)
11. G. Hipmair, N. Böhler, W. Maschek, F. Soriguer, G. Rojo-Martínez, W. Schimetta & R. Pichler, Neuroendocrinology letters, **31(1),** 155-160 (2010)
12. M Shaarawy, AF Abassi, H Hassan, ME Salem, Fertility and sterility, **79(4),** 919–24 (2003)
13. HMR Alhasnawi, Ahmed Abduljabbar Jaloob Aljanaby, Gene Reports, **26**, 101520 (2022) https://doi.org/10.1016/j.genrep.2022.101520.
14. MR Azeez, AAJ Aljanaby, IÇ Öcal, Journal of Experimental Biology and Agricultural Sciences, **9(3),** 378-387 (2021)
15. K. Gkastaris, D.G. Goulis, M. Potoupnis, A.D. Anastasilakis, G. Kapetanos, Journal of Musculoskeletal & Neuronal Interactions, **20(3),** 372 (2020)
16. Tai, Tong-Yuan, et al., Scientific Reports, **12.1**, 8090 (2022)
17. C. Savvidis, S. Tournis & A. D. Dede, Hormones, **17(2),** 205–217 (2018).
18. Z. Huang, Hepatology, **74,** 214–232 (2021)