



Osteoporosis and Leptin: A Systematic Review

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Abstract

Background: Leptin has a great effect on bone through direct or indirect involvement in bone remodeling. Considering the ambiguities that exist regarding the effect of leptin on bone and bone-related diseases including osteoporosis, in this study, we aimed to conduct a systematic review of various studies on the effect of leptin on osteoporosis, which may find an answer to the existing ambiguities.

Methods: The search was performed to review studies on the effects of leptin on osteoporosis by using several databases including Scopus, PubMed, Web of Science, and Google Scholar. Electronic searches were conducted on 5 Jan 2023. There was no limit on the publication date of the articles. The risk of bias for the animal study was assessed with the CAMARADES checklist, and the study quality assessment was also assessed based on the guidelines for in vivo experiments (ARRIVE). In this study, the risk of bias (quality) of human studies was assessed using the quality assessment checklists by NHLBI.

Results: Overall, 34 articles were included for data extraction and quality assessment. Overall, 27 human studies and seven animal studies were included in the article. The results of most of the studies conducted in this study showed that leptin has a physiological role in maintaining bone mass and better bone quality and reduces bone marrow adipogenesis and increases bone mineral density (BMD). As plasma leptin levels increased, BMD values or bone formation biomarkers increased.

Conclusion: Leptin has an inhibitory role against bone resorption and increasing osteoprotegerin (OPG) levels, which, as a result, maintains bone density and reduces osteoclast activity, and has a positive relationship with increasing osteocalcin.

Keywords: Leptin; Bone losses; Bone resorption

Introduction

Osteoporosis is one of the most common non-communicable diseases in today's world. Hundreds of millions of people have osteoporosis, and many more are at risk (1). Osteoporosis is the most common metabolic bone disease in the

world, the resulting fractures impose a huge medical and personal burden on the people who suffer from them and bring significant economic consequences (2). The most common fractures caused by osteoporosis are vertebral, proximal



femur, and distal radius fractures, which severely affect a person's quality of life (3). One of the most obvious symptoms of osteoporosis is fracture and pain caused by osteoporosis, which is one of the main reasons for reducing the quality of life of these patients (4). In osteoporosis, transient factors play a role in skeletal fragility, including defects in the properties of bone tissue materials, and defects in the microarchitecture of trabeculae (5).

Obesity may be harmful to bones. The process that induces osteoblastogenesis can inhibit adipogenesis and vice versa, for example, in menopause, there is a decrease in bone mass and an increase in fat at the same time (6). Factors that increase adipogenesis cause insufficient bone mass and osteoporosis because they both cause fatty marrow and inhibit osteoblastogenesis, which results in a decrease in the number of osteoblasts and bone formation (7). An increase in markers of bone resorption and a decrease in markers of bone formation in postmenopausal women with obesity were observed in studies (8). Leptin (obesity gene product), which is one of the most important cytokines known in fat tissue, is a 16 kDa protein that has a great effect on bone regeneration (9). The role of leptin in bone physiology is determined by the balance of direct and indirect effects on bone, such as anabolic effects on cartilage and osteoblasts and indirect effects on bone through the hypothalamus and sympathetic nervous system (10). However, it is not yet clear which effect of leptin (direct or indirect effect) regulates bone metabolism (9). Leptin can be an important biomarker for postmenopausal osteoporosis, so leptin can become a useful screening test for clinical follow-up of these patients (11).

Previous systematic review and meta-analysis results showed that leptin appears to be positively correlated with bone mineral density (BMD) in the whole body and with a higher pooled correlation in postmenopausal girls and women. However, serum leptin level was negatively correlated with BMD and bone mineral content (BMC) in boys. Conclusions may be difficult because the number of included studies on a specific popula-

tion was small, and studies on different populations of different ethnicities were necessary to estimate the association between serum leptin levels and BMD and BMC values (12).

Given that the relationship between serum leptin levels and bone metabolism is complex, no definitive conclusions have been drawn on this issue (12, 13). As far as we know studies that have examined both human and animal studies to determine the relationship between leptin serum level and BMD is necessary to reach a more specific result.

Considering the ambiguities that exist regarding the effect of leptin on bone and bone-related diseases including osteoporosis, in this study, we decided to conduct a systematic review of various studies on the effect of leptin on osteoporosis, which may find an answer to the existing ambiguities.

Methods

Literature Search

A systematic literature search was performed to review studies on the effects of leptin on osteoporosis according to the Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines (14). Moreover, in this research, there was no limit on the publication date of the articles. The search was performed using several databases including Scopus, PubMed, web of science, and Google Scholar. Electronic searches were conducted on 5 Jan 2023.

This study was approved by the Ethics Committee of Abadan University of Medical Sciences (Ethical Code: IR.ABADANUMS.REC.1401.138).

Inclusion criteria

The inclusion criteria for this study included the following: All experimental studies involving human participants or animal subjects that investigated the association of leptin with osteoporosis, BMD, bone fractures, bone resorption or bone formation and whose data were available were considered eligible. Besides, one of the con-

ditions for the inclusion of articles was that the full text of the article was available in English. These studies included little published empirical research.

The primary outcome was the investigation of leptin concentration in people with osteoporosis and the secondary outcome was the relationship between leptin with osteoporosis and BMD.

Exclusion criteria

In this study, the exclusion criteria were qualitative studies, insufficient information to extract the method and results of the study, studies without data of interest and inadequate design, poor methodological quality, not having the full text of the article in English, book chapters, review articles, case studies, or discussion articles, meta-analysis, theses, conference abstract, etc.

Study Selection

In this study, screening was performed by searching the terms "leptin", "osteoporosis", and "bone losses". Studies were eligible for inclusion if they examined osteoporosis, leptin, or bone losses. Duplicate articles were identified and removed. Studies that investigated leptin and bone losses or osteoporosis were considered. The inclusion and exclusion criteria for screening the titles and abstracts of the remaining articles in this study were reviewed. Then the full-text screening of the eligible articles was done carefully. Finally, for more relevant studies, the list of references and citations of eligible articles were checked manually.

Data Extraction

Data was extracted from selected studies and prepared two types of standard data extraction forms, including for human and animal studies, the following items were mentioned in the form: characteristics of the study, participant characteristics (for human studies) and characteristics of the animals used (for animal studies), study design, and the main result of the study.

The performance and reporting quality of the articles presented for the evaluation of leptin and osteoporosis studies were evaluated by two inde-

pendent reviewers (NS; TB), and the overall evaluation included recommendations for designing and conducting an evaluation of the role of leptin as a biomarker for osteoporosis. The extraction forms were compared by another reviewer (SMM) and differences were reviewed, discussed, and edited.

Quality Assessment

The risk of bias (quality) of human studies using quality assessment checklists for observational and cross-sectional cohort studies by the National Heart, Lung, and Blood Institute (NHLBI), which defines quality based on a set of 14 criteria, was evaluated (15). Quality was rated according to the NHLBI instrument as *0* for poor (0-4 out of 14 questions), *I* for fair (5-10 out of 14 questions), or *II* for good (11-14 out of 14 questions) (15). Moreover, the risk of bias for the animal study was assessed by the Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies (CAMARADES) checklist (16). In addition, since part of the studies in this research was animals, the study quality assessment was also reviewed according to the Animal Research: Reporting of in Vivo Experiments (ARRIVE) guidelines (17).

Results

Results of Study Selection

The database search retrieved 7384 records (PubMed=1980, Scopus=2208, Web of Science=3140, and Google scholar=56), of which 3516 were duplicated and removed in the first step. Titles and abstracts of the remaining 3868 studies were reviewed. We excluded 3336 articles that did not meet the inclusion criteria in this study. Upon review of the full text of the remaining 532 articles, 498 articles were excluded in the screening stage after the full-text review of the articles, and 34 articles were included in this study for data extraction and quality assessment. A PRISMA flow chart is shown in Fig. 1 to identify studies.

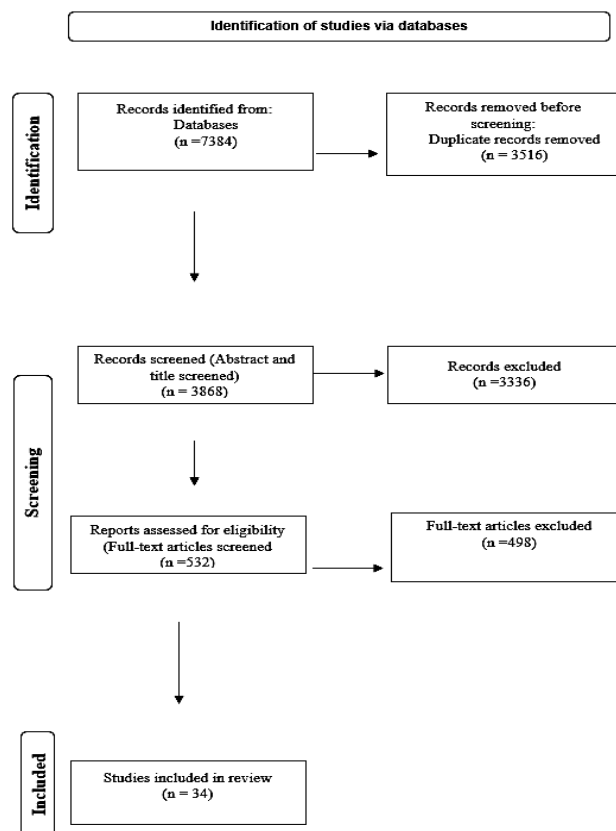


Fig. 1: The Diagram of the literature search and selection process was limited to studies that investigated the relationship between osteoporosis and leptin

Overview of Included Studies

The articles included in this study were from seventeen countries, most of conducted in China (n=8) (18-24). The date of these studies was from 2000 to 2022. Human studies were 27 studies (18-21, 25-46), of which fifteen studies (11, 19-20, 25-36) were exclusively related to women, nine studies were conducted on both women and men (18, 21, 37-42), and three studies were exclusively conducted on men (43-46) (Table 1).

Seven animal studies (22-24, 47-50) were included in the article, three studies were conducted only on females (23, 47, 48) and 4 studies were conducted on both females and males (22, 24, 49, 50). Four studies were conducted on rats (22-23, 47, 48), two studies on mice (49, 50), and one study on both (24) (Table 2).

Relationship between leptin and osteoporosis in the Human study

In most human studies, there was an association between plasma leptin levels and BMD values or with biomarkers of bone formation or bone resorption, including the studies mentioned.

Among the important risk factors for the occurrence of long bone fractures are higher adiponectin levels and low leptin levels, and in the higher quartiles of serum leptin levels, the rate of long bone fractures was significantly lower (26). There is an association between susceptibility to osteoporosis and single nucleotide polymorphism (SNP) of the leptin receptor gene, and three of the six SNPs were different between the osteoporosis and control groups (18). In elderly men, the possible role of leptin in bone homeostasis independently of free estradiol and body composition was reported in studies (43). Increased leptin and

parathyroid hormone (PTH) were observed in obese children, associated with 25(OH) D deficiency and bone turnover markers, and could play an important role in the pathogenesis of obesity and bone-related diseases such as fractures and osteoporosis (37). In men, there is a negative correlation between leptin levels and bone mass independent of body mass index (BMI) and body weight (44). In healthy adults, in the regulation of bone metabolism, leptin can play an effective role and can potentially play a role in preventing osteoporosis (38). In postmenopausal Korean women, the leptin receptor (LEPR) polymorphism can be one of the factors affecting femoral neck BMD, and polymorphism analysis can be effective in identifying women at risk of osteoporosis (29). Leptin binding capacity was lower in osteoporotic mesenchymal stem cells compared to control cells during adipogenic and osteogenic differentiation, so they showed less sensitivity to leptin action during early differentiation (30). Leptin can be an independent negative predictor of areal BMD in several measured locations and bone parameters that can reflect cortical bone size (45).

In postmenopausal women, leptin is associated with BMD and vertebral fractures, and leptin may play an important role in better bone quality and maintaining bone mass (31). Significantly, lower serum levels and expression of leptin in adipose tissue were observed in patients with osteoporosis compared to patients without osteoporosis (46). In women with osteoporosis, compared to women who did not have osteoporosis, the concentration of adiponectin is higher, but the concentration of leptin, BMI, and body weight are lower (32).

Leptin and IFG-1 have the potential to become important biomarkers related to postmenopausal osteoporosis (PMOP) and suitable and useful screening tests for clinical follow-up of these patients (11). Femur BMD, serum leptin was identified as a positive independent predictor (33). Leptin up regulated the expression of OPG (19).

In postmenopausal women with osteoporosis, circulating leptin may cause bone loss and correlates with high-turnover serum bone markers (39). Leptin and IL-6 are predictive biomarkers of low bone mass in postmenopausal women (20).

Plasma leptin has a strong and positive correlation with volumetric BMD, and BMC, among elderly men and women (40). Polymorphism in LEPR and the leptin genes is associated with an increased risk of osteoporosis through increased expression of pro-inflammatory cytokines (21). A significant correlation between serum leptin level and BMD was observed in women, but not in men (42). Leptin correlated positively with the total hip and spine (35). Leptin can be considered a bone tissue protective factor in postmenopausal women (36). In a small number of studies, no correlation was observed between BMD, bone resorption and formation biomarkers, and leptin (25, 27, 28, 34, 41).

Relationship between leptin and osteoporosis in the animal study

Leptin provided a promising effect on bone through its direct action on bone and matrix mineralization (47). In estrogen-deficient adult mice, serum leptin levels showed a strong positive correlation with bone formation and markers of bone resorption, indicating that leptin is effective in maintaining bone mass (50). It has been observed that with increasing age, and with a decrease in the level of serum sex hormones, an increase in the expression of serum LEP and a decrease in the expression of leptin receptor occurs, which causes a decrease in bone quality, a disturbance in bone metabolism, a decrease in the ratio of OPG/RANKL, and also causes bone resorption may be more than bone formation (22). An increase in peripheral leptin was observed in the ovariectomized group, and treatment with propranolol could regulate the level of peripheral leptin (23).

Table 1: Characteristics of published human articles on the relationship of leptin to osteoporosis

<i>Authors</i>	<i>Year</i>	<i>Age (year) /sex</i>	<i>Leptin Dosage/ measurement</i>	<i>Participants</i>	<i>Relationship of leptin with OP</i>	<i>Quality assessment</i>
Shaarawy et al. (25)	2003	58.8± 0.51/F	RIA	90 POMP osteoporotic women and 30 healthy premenopausal women	Not associated	Good
Nakamura et al. (26)	2020	65.9/ F	RIA	1167 POMP	Related	Good
Ye et al. (18)	2022	over 45 yr old/F/M	PCR	738 Mulao minority people	Related	Fair
Crabbe et al. (43)	2006	71–86/M	RIA	A sample of 352 ambulatory men	Related	Good
Saber et al. (37)	2015	7.55± 3.34 F/M	RIA	60 obese children and 36 lean children	Related	Good
Anagnostis et al. (44)	2012	45.4±15/M	ELISA	Eighty-one male patients	Related	Good
Kocyigit et al. (27)	2013	58.2±6.4/F	ELISA	42 POMP women with osteoporosis and 37 healthy POMP women	Not associated	Good
Odabas et al. (28)	2000	61.2±6 6.5/F	RIA	50 POMP women with osteoporosis and 30 healthy POMP women	Not associated	Good
Prouteau et al. (38)	2006	20±3.0/F/M	ELISA	54 elite judoists	Related	Good
Lee et al. (29)	2014	48 to 65/F	ELISA	592 postmenopausal women aged	Related	Fair
Hess et al. (30)	2005	65–86/F	50 pM I ¹²⁵ leptin	control (six) or osteoporotic (six)	Related	Fair
Lorentzon et al. (45)	2006	18.9± 0.6/M	ELISA	1068 men	Related	Fair
Yamauch et al. (31)	2001	48–78/F	RIA	139 postmenopausal women	Related	Fair
Pobeha (46)	2011	62.2±7.3/ F/M	ELISA	21 patients without, and 18 with osteoporosis	Related	Fair
Mpalaris et al. (32)	2016	46-80/F	RIA	110 post-menopausal women	Related	Good
Zhang et al. (11)	2022	45 to 80 /F	Multiplex kits	1055 postmenopausal women	Related	Good
Rhie et al. (33)	2010	8.3±1.2/F	RIA	48 pre pubertal girls	Related	Fair
Zhang et al. (19)	2009	70–86/F	0.6 mg/ml	17 postmenopausal women	Related	Fair
Hipmair et al. (39)	2010	53–85 / F/M	RIA	44 patients with osteoporosis	Related	Fair
Wang et al. (20)	2022	61.00 /F	ECL	75 Premenopausal females	Related	Good
Dennison et al. (40)	2004	60–75/ F/M	RIA	170 men and 132 women	Related	Good
Sahin et al. (34)	2003	55.1±6.3 /F	EIA	100 POMP women	Not associated	Fair
Ardekani et al. (41)	2014	54.5±15.5/ F/M	ELISA	81 with osteoporosis, 120 controls	Not associated	Fair
Ye et al. (21)	2013	55.3±4.7/ F/M	ELISA	192 with osteoporosis, 221 control	Related	Good
Thomas et al. (42)	2001	F (21-93), M(23-90)	RIA	137 premenopausal women, 165 POMP women, and 343 men	Related (women)	Fair
Roux et al. (35)	2003	53 (45–68)/F	RIA	121 postmenopausal women	Related	Good
Glogowska-Szelag et al. (36)	2019	N/R/F	ELISA	80 women with osteoporosis	Related	Fair

Stimulation of periodontal regeneration in osteoporosis can occur by overexpression of human LEP in bone marrow stromal cells (BMSCs) (24). Gene effects associated with increased leptin levels are associated with stronger and larger femurs

(49). The leptin receptor (LepRb) mutations cause obesity, osteoporosis, and stunting, similar to the phenotype of db/db and ob/ob mice, which completely lack leptin receptor signaling (50).

Table 2: Characteristics of published animal articles on the relationship of Leptin to osteoporosis

<i>Authors</i>	<i>Year</i>	<i>Model/sex</i>	<i>Leptin Dosage/ measurement</i>	<i>Groups</i>	<i>Relationship of leptin with OP</i>	<i>Score</i>
Ahmed et al. (47)	2012	SD rats/F	400 µg kg b.wt.-1) three times weekly for six months	40 (5 groups each comprised 8 rats)	Related	6
Stavropoulou et al. (48)	2005	Wistar rats/F	EIO	40 Ovariectomy (OVX)	Related	7
Sun et al. (22)	2020	SD rats/ F/M	ELISA	162 healthy, SPF-grade 6-month-old	Related	7
Zhang et al. (23)	2013	SD rats/F	ELISA	30, 6-month-old: Sham, OVX, and PRN	Related	7
Zheng et al. (24)	2017	SD rats/ BALB/c nude mice/ F/M	ELISA	50 SD/F, and 6 male BALB/c nude mice	Related	6
Reich et al. (49)	2008	Mice/ F/M	N/R	16 LGXSM recombinant inbred (RI) mouse strains	Related	5
McCabe et al. (50)	2019	Mice/ F/M	ELISA	LepRb Δ65, LL and SS mice on the C57/Bl6 background	Related	6

Quality assessment

In this study, the recommendations of the quality evaluation results in 27 human studies, 14 human studies were good and 13 were fair. Each animal study was given a quality score out of 10 possible points, and the median of the group was calculated as 6.

Discussion

This systematic review summarizes 27 human studies and seven animal studies that were conducted around the world on the relationship be-

tween leptin, and osteoporosis. High quality in human evidence (14 human studies were good and 13 were fair) suggests that leptin levels were low in people with osteoporosis. Besides, the moderate quality of the animal studies in this study also supports these results.

In postmenopausal women, a significant correlation was observed between plasma leptin level and BMD. Leptin level was significantly lower in women with vertebral fractures than in women without fractures. As a result, leptin can play an important role in better bone quality and maintaining bone mass (31). Findings from a longitu-

dinal study suggest a possible role of leptin as a determinant of bone homeostasis in elderly men. The strengths of this study are the detailed clinical assessment of a community-dwelling study population and the prospective longitudinal BMD data and the possibility of adjustment for major confounders. However, these observations are limited to elderly men and should not be easily generalized to other age groups. Moreover, they seem to differ from the findings for women (43). Another longitudinal study has investigated POMP women, IL-6 and serum leptin can be predictors of the risk of osteoporosis-related fractures for postmenopausal women with low bone mass. This study also has certain limitations. First, only people from the Beijing community were included in this study and only two-year follow-up interviews were conducted, but the strength of this follow-up study was the relatively large sample size and the establishment of a fracture risk prediction model suitable for the clinical characteristics of Chinese postmenopausal women with low bone mass (20).

Another human study showed that serum leptin levels were significantly associated with BMD in women and that leptin regulation moderated the relationship between fat mass and bone density, but these results were not observed in men (42). Leptin can be considered a protective factor for bone tissue in postmenopausal women (36).

In the few human studies included in this study, no association between leptin and BMD was observed (25, 27, 28, 34, 41).

There is an association between decreased levels of leptin and BMD and thus the risk of developing osteoporosis in animal studies but the quality of the articles is moderate, and moderate-level evidence supports this response (22-24, 47-50).

A meta-analysis has been performed regarding the relationship between leptin and BMD. Blood leptin levels were significantly lower and adiponectin levels were significantly higher in subjects with PMOP compared to healthy subjects with normal BMD. Because this study lacked effective longitudinal cohort studies, the causality of the association between adipokines levels and the occurrence of PMOP was not inferred. There

was considerable heterogeneity of results in this meta-analysis, which may significantly weaken the validity of the results. However, this meta-analysis had strong points, such as the relationships between three common adipokines with the occurrence of PMOP were investigated, and at the same time, the differences in the levels of adipokines and the relationships of different adipokines with BMD and BMI were estimated, and the quality of the included studies was average (13). Evidence from another systematic review and meta-analysis showed that leptin had a significant positive association with BMD and BMC in all populations, except in boys, especially in girls and postmenopausal women. There were limitations to this study, such as the sample size was not large enough and the number of studies included on a specific population was small. In this systematic review and meta-analysis, studies and the number of boy patients were very few. Moreover, studies related to different populations of different ethnicities were necessary to estimate the relationship between leptin serum levels and BMD values (12).

Among the limitations of this systematic review, the following can be mentioned: First, animal studies were few. Second, more human studies with a high sample size are needed. Third, most of the studies were reported on women, so there is a need to conduct studies on men as well as compare women and men with osteoporosis. Fourth, the limitation of this study is the small number (4 studies) of prospective longitudinal studies, which suggests that more longitudinal studies should be conducted in both women and men in the future. Fifth, in this study, most of the studies were cross-sectional, prone to bias. Sixth, we did not register the formal protocol of this study in any public platform, but we followed the methodological framework recommended by the Cochrane Manual to reduce the risk of bias. Lastly, because the conditions or prerequisites for a statistical or quantitative combination were not available in this study, including the fact that the data of the articles were heterogeneous and did not have the ability to be combined and statistically analyzed, therefore meta-analysis was not

performed. Studies with long-term follow-up and large sample sizes should be conducted to find higher quality evidence. The threshold of leptin level below which can cause osteoporosis was not known and more studies in this regard are necessary. Animal and human studies are needed for the therapeutic role of leptin and its effective dose. Among the strengths of this systematic review is the high quality of human studies reviewed from different parts of the world.

Conclusion

In most high-quality human studies, there was an association between plasma leptin levels and BMD values or with biomarkers of bone formation. There is moderate evidence in animal studies that leptin has a promising effect on bone through its direct effect on bone formation and matrix mineralization. The peripheral pathway of leptin of regulation bone metabolism is dominant and that leptin has a physiological role in maintaining bone mass and better bone quality. Leptin reduces bone marrow adipogenesis and increases BMD. As a result, leptin is effective in maintaining bone mass. Moreover, no correlation between leptin and BMD was observed. As a result, more studies are needed to determine whether leptin has the potential to become a useful screening test for osteoporosis. More studies with a larger sample size are needed to investigate the cellular and molecular mechanisms of the effect of leptin on osteoporosis.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declared no competing interest.

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