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Relationship between serum leptin levels and bone mineral density: A systematic review and meta-analysis

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ABSTRACT

Background: The association between leptin and bone mineral density (BMD) is controversial because of conflicting findings from previous studies.
Methods: This meta-analysis aimed to provide an overview of the serum leptin levels and BMD in a healthy population. We reviewed the PubMed, Embase, and Cochrane Library databases until July 2014 for research on the association between leptin levels and BMD in healthy people.
Results: We included and analyzed 45 studies in this systematic review and meta-analysis. The pooled correlations between leptin and BMD were analyzed by using the method of the inverse of the variance. Leptin was positively associated with BMD and the bone mineral content (BMC), especially in postmenopausal women (pooled *r*: 0.13–0.49). Overall, high serum leptin levels were associated with higher BMD levels.
Conclusions: This meta-analysis suggests that serum leptin levels are positively associated with BMD and BMC, especially in postmenopausal women.

1. Introduction

Leptin (LEP, also called OB for obese) is an adipocyte-derived hormone produced predominantly by the white adipose tissue, which regulates appetite and weight, body metabolism, and reproductive functions with the LEP receptor (LEPR) [1]. The LEP gene, located at chromosome 7q31.3, encodes the 16 kDa protein that has been consistently shown to be associated with endocrinologic metabolism [2]. LEP can also regulate osteoblast cell proliferation and differentiation in vitro [3–5] and osteoclast cells [3,6,7]. LEPR is expressed by many cells, including osteoblasts [3,8]. LEP affects bone metabolism mainly through the central nervous system, especially via the hypothalamus [9,10]. Moreover, LEP has been found to be involved in osteoporosis pathophysiology, and it may regulate bone metabolism. A number of investigators have studied the possible relationships between LEP and bone mineral density (BMD). However, the influence of the serum LEP levels on BMD and BMC remains unclear. BMD is an indirect clinical indicator of osteoporosis.

2. Materials and methods

2.1. Publication selection

We searched the PubMed, Cochrane Library, and Embase databases until July 2014 using the following search terms: bone mineral density or absorptiometry, osteoporosis or fractures, and leptin. The reference lists of the selected articles used in this study were manually examined carefully to identify relevant studies that were not indexed during the database searches. No language restriction was applied. Studies had to meet the following inclusion criteria: (1) human studies that had an original transversal or longitudinal design; (2) studies that reported on the association between the serum LEP levels and BMD and/or fractures; (3) studies that included healthy populations who were evaluated for their serum LEP levels and BMD or fracture risk; (4) studies on patients who did not receive metabolism medications (i.e., vitamin D and calcium); (5) studies on patients who did not perform high physical activities; and (6) studies that measured BMD using dual-energy radiography absorptiometry. If several articles using the same data were published, only the most informative one was included. The included studies were judged independently by 2 collaborators (P. C. L and K. L.), and any disagreements were resolved through discussion.

2.2. Methods

The population's characteristics (i.e., mean age, gender menopausal status, BMI, osteoporotic status, number of patients, BMD assessment

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[site, method, and units], and BMC assessment [site, method, units]) were recorded. Correlations between the LEP levels and BMD and BMC were also collected. We examined the population's inclusion criteria and also the quality of the reporting to ensure that we used high quality publications. Studies were excluded if the definitions of interest outcomes (i.e., BMD, BMC, or osteoporotic status) were unclear. We conducted this meta-analysis to gain a better understanding of the association between the serum LEP levels and BMD and/or BMC. Unadjusted correlations were pooled by using the inverse of the variance method, and a Fisher's *z*-transformation was used on the correlation coefficients. Subgroup analysis was performed according to the different populations and the subjects' menopausal status. The pooled results were analyzed by using the correlation coefficient r (COR) with 95% confidence intervals (CI). *P* values <0.05 were considered statically significant. The statistical analyses were performed using R, ver 3.0.3 (The R Project for Statistical Computing; http://www.r-project.org/). Additionally, the meta package (ver 3.1-2) and metacor package (rmeta and gsl packages) were used to calculate the pooled CORs for the different populations and bone sites.

2.3. Statistical analysis

Statistical heterogeneity among the studies was evaluated by *Q*-statistic and was quantified by the I^2 statistic. A fixed-effects model and a random-effects model were used to obtain a summary of the CORs. If the *Q* or I^2 statistic was significant, a random-effects model was used; otherwise, a fixed-effects model was used. Funnel plots and the Egger test (a $P < 0.05$ was considered statistically significant) were used to visually evaluate for the presence of publication bias. A sensitivity analysis was conducted in which the studies were excluded to thereby determine the stability of the combined CORs.

3. Results

After excluded the duplicate and unrelated articles, we assessed 1,342 articles in detail. After carefully screening the titles, 1,240 articles were excluded for not investigating the topic of interest. After reviewing the abstracts, 57 more articles were excluded, leaving 45 studies for further review of the full publication. All of the 45 studies met the selection criteria and were suitable for the meta-analysis [2,11–53]. Most of the studies were cross-sectional, including 9 on men [11–17,33,36], 14 on premenopausal women [2,11,16,18–22,26,40,43,44,47,53], 27 on postmenopausal women [2,11,12,16,19,22–35,37–39,48,51,53], 5 on girls [41,42,45,46,49], and only 1 on boys [49]. Pooling the included studies for the COR analyses involved a combined sample size of 7,674 patients (41 boys, 2,965 men, 422 girls, 1,442 premenopausal women, and 2,804 postmenopausal women) across 45 studies.

3.1. Overall effects of leptin on bone mineral density

We performed a pooled correlation analyses on all the studies according to the populations and the subjects' menopausal status (Table 1). LEP appeared to be positively correlated with BMD at total body and with higher pooled correlations in girls and postmenopausal women (pooled *r*: 0.10–0.31), expect for boys ($r = -0.31$) [49]. Positive correlations between LEP and BMD at total hip were also observed in men and premenopausal and postmenopausal women (pooled *r*: 0.10–0.31). In girls, higher pooled correlations were significantly observed at total body ($r = 0.31$) and the distal forearm BMD ($r = 0.31$). In postmenopausal women, higher pooled correlations were significantly observed at the lumbar spine ($r = 0.13$), total body ($r = 0.23$), femoral neck ($r = 0.23$), total hip ($r = 0.31$), trochanter ($r = 0.16$), pelvis ($r = 0.49$), and radius BMD ($r = 0.25$). In premenopausal women, higher pooled correlations were significantly observed at the lumbar spine ($r = 0.08$), total body ($r = 0.19$), femoral neck ($r = 0.09$), total hip ($r = 0.27$), and radius BMD ($r = 0.26$). In men, correlations between LEP and BMD were found only at the total hip ($r = 0.1$) and total body ($r = 0.1$).

3.2. Overall effects of LEP on bone mineral content

Consistent and inverse correlations were found between the circulating serum LEP levels and BMC at total body in boys ($r = -0.37$) and girls ($r = -0.21$) (Table 1). LEP appeared to be positively correlated with BMC at total body and with higher pooled correlations in premenopausal and postmenopausal women (pooled *r*: 0.24–0.26). At the femoral neck, positive correlations between LEP and BMC were observed in men and postmenopausal women (pooled *r*: 0.24–0.3).

4. Discussion

Osteoporosis is a common chronic disorder that mostly affects the elderly population. It has been proposed that low BMD patients are at a high risk for osteoporosis and fractures. While the relationship between serum LEP levels and bone metabolism is complex, no final conclusion has been made on this topic. Because of the limiting variability caused by comorbidities and treatments, we voluntarily decided to focus our meta-analysis on only healthy patients by excluding studies with populations who were receiving bone medication drugs, except for calcium and vitamin D as daily therapy. Multiple factors can account for lower BMD and BMC levels. Calcium and vitamin D therapy should be an important factor, and vitamin D is an important factor for skeletal integrity. The serum 25(OH)D level is associated with muscle strength, and a high serum 25(OH)D level can reduce the incidence of falls and fractures [54]. Although fat mass and BMI may be confounding factors for BMD and BMC, serum LEP levels seem to have a positive role in bone metabolism; a previous meta-analysis showed that high serum LEP levels were associated with BMD [55]. These effects may be direct and indirect, particularly through the central nervous system of the brain [10].

Our meta-analysis included 45 studies that assessed the influence of the serum LEP levels on BMD and BMC in different healthy populations. The serum LEP levels appeared to be positively correlated with BMD and BMC, especially in girls and postmenopausal women. We found differences in the BMD and BMC between the menopausal statuses of most bone sites (Table 1).

However, the serum LEP levels were negatively associated with BMD and BMC in boys. We also found that the serum LEP levels were positively correlated with the lumbar spine BMD in premenopausal and postmenopausal women. Although in the present study, the serum LEP levels were negatively associated with the lumbar spine BMD [11].

There were some limitations to our meta-analysis. First, the sample size in any given population was not sufficiently large, which could have increased the probability of false positives or false negatives. Therefore, it may be very difficult to deduct conclusions since the number of included studies on a specific population was small. In this meta-analysis, the studies and numbers of boy patients were so few; thus, we could not determine an association between the serum LEP levels and the BMD. Besides, studies involving different populations from different ethnicities were warranted to estimate the associations between the serum LEP levels and BMD and/or BMC values. Second, because of the unavailability of original data from the eligible studies, it was difficult to evaluate the influences of some special environmental and lifestyle factors such as diet, physical activity, alcohol consumption, smoking status, and exposure to sunlight in bone metabolism. Third, the influence of publication bias could not be completely excluded for the common reason that positive results are supposed to be published much more easily and quickly than articles with negative findings.