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Review Article

The Role of Osteocalcin in Patients with Osteoporosis: A Systematic Review

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Abstract

Background: Osteoporosis is the most common systemic skeletal disease worldwide. We aimed to review the latest studies related to osteocalcin and osteoporosis to clarify this relationship more precisely.

Methods: A systematic literature search was performed to review studies on the effects of osteocalcin on osteoporosis, on studied published between January 2013 and January 2023. We systematically reviewed Web of Science, PubMed, ProQuest, Scopus, and Google Scholar.

Results: The search yielded 4903 records, including 1063 from PubMed, 2307 from Scopus, 1084 from Web of Science, 408 from ProQuest, and 41 from Google Scholar, and twelve articles were included for data extraction and quality assessment. A significant increase in the serum level of osteocalcin was observed in postmenopausal women with osteoporosis ($P<0.05$), and there was a negative correlation between bone mineral density and the serum level of osteocalcin.

Conclusion: Osteocalcin could be a promising marker for the diagnosis and screening of patients with osteoporosis.

Keywords: Bone mineral density; Postmenopausal women; Osteocalcin; Osteoporosis

Introduction

Osteoporosis (OP) is the most common systemic skeletal disease in the world, the consequences of which have a significant impact on the quality of life of patients and increases the mortality of patients (1). Considering the extensive consequences that osteoporosis has for affected people, our increasing understanding of the factors affecting the risk of fracture helps assess the individual risk of fracture (2).

From the age of 50 yr onwards, fractures caused by osteoporosis increase more in women than in men, and fractures, especially spine and hip fractures, lead to increased morbidity and mortality (3). Timely treatment and the search for new bi-

omarkers to identify people at high risk of osteoporosis are effective ways to delay the progression of the disease and improve the treatment outcome and thus improve the quality of life of patients (4).

Osteocalcin is an osteoblast-derived protein that regulates bone mineralization and acts as an osteoblast-derived endocrine hormone (5). Osteocalcin, the most abundant non-collagenous protein in bone, acts as a hormone and is clinically essential for bone strength, as well as a marker for bone formation (6). Osteocalcin can activate both osteoblasts and osteoclasts in the early stages of bone formation (7). Osteocalcin is a protein-dependent on vitamin K and secreted in the final stages of osteoblast differentiation, which plays a role in regulating osteoclast and osteoblast activity and bone mineralization (8). Elevated serum osteocalcin levels are related to rapid bone loss. Osteoporosis leads to a decrease in the formation of hydroxyapatite crystals and, as a result, an increase in serum osteocalcin levels (9). The increase in the serum level of osteocalcin in postmenopausal women with osteoporosis provides evidence that it plays an important role in the development of early osteoporosis, so the determination of serum osteocalcin may be used as a marker in the diagnostic criteria of early osteoporosis (10). However, the role of osteocalcin in age-related bone loss in women remains elusive (11).

There are still uncertainties about the exact relationship between osteocalcin and osteoporosis, so we aimed to review the latest studies related to osteocalcin and osteoporosis to clarify this relationship more precisely.

Methods

Literature Search

A systematic literature search was performed to review studies on the effects of osteocalcin on osteoporosis according to the Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines (12). The articles were published between January 2013 and January 2023. We systematically reviewed Web of Science, PubMed, ProQuest, Scopus, and Google Scholar.

Inclusion and exclusion criteria

The inclusion criteria for this study included the following: All experimental studies involving human participants that evaluate the relationship between osteocalcin, osteoporosis, and bone mineral density were examined in this study. Also, one of the conditions for the inclusion of articles was that the full text of the article was available in English. The exclusion criteria were: qualitative studies, insufficient information to extract the method and results of the study, 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

Screening was performed by searching the terms "osteocalcin", "osteoporosis", and "bone loss ". Eligibility criteria and quality assessment studies were eligible for inclusion if they examined osteoporosis, osteocalcin, or bone loss. Duplicate articles were identified and removed. All associations of osteocalcin and osteoporosis and low BMD examined in each included article were considered. The inclusion and exclusion criteria for screening the titles and abstracts of the remaining articles in this study were reviewed by two reviewers independently. Then the full-text screening of the eligible articles was done carefully. In the next step, a consensus meeting was held with the third reviewer to resolve the differences. Finally, for more relevant studies, the list of references and citations of eligible articles were checked manually.

Data Extraction and Quality Assessment

Two authors independently extracted data from selected studies and prepared a type of standard data extraction form, including the following items mentioned in the form: characteristics of the study (the first author's last name, year of publication, country), Participant characteristics (gender, and age of sample), study design (type of

study, how to measure leptin, studied groups) and the main result of the study. The extraction forms were compared by another author and differences were reviewed, discussed, and edited.

The performance and reporting quality of the articles presented for the evaluation of osteocalcin and osteoporosis studies were evaluated by two independent reviewers, and the overall evaluation included recommendations for designing and conducting an evaluation of the role of osteocalcin as a biomarker for osteoporosis. The risk of bias (quality) of human studies was evaluated by 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, as defined in the standard quality assessment criteria (13).

Results

A PRISMA flow chart is shown to identify studies screened in this study (Fig. 1).

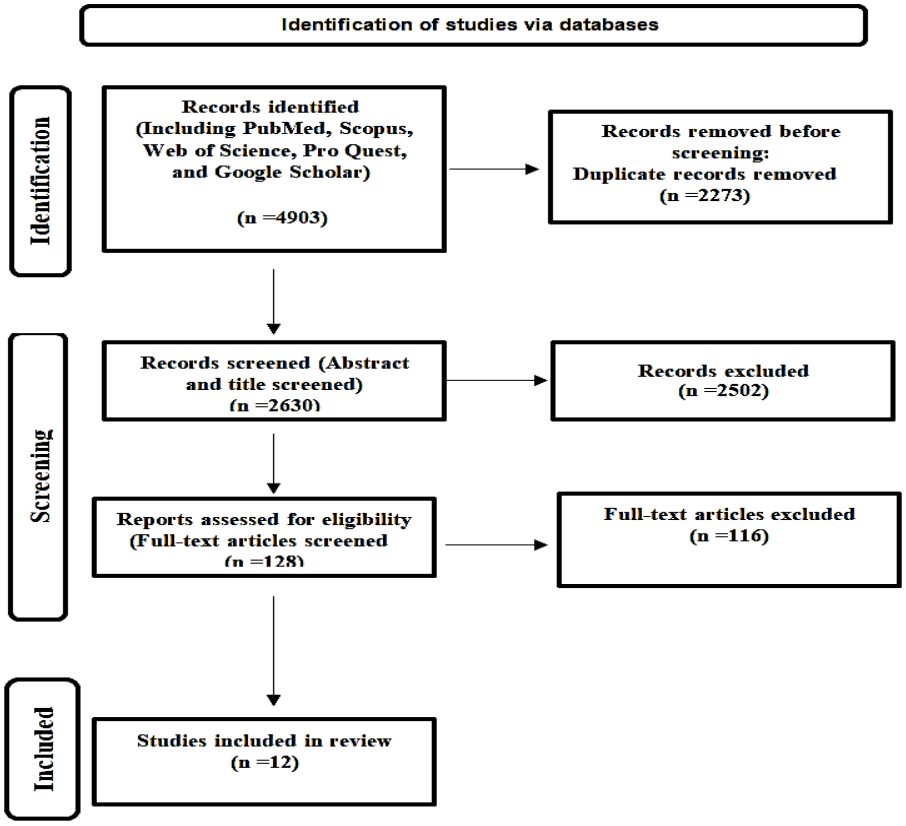

Fig. 1: The Diagram of the literature search and selection process was limited to studies that investigated the relationship between osteoporosis and osteocalcin

The articles included in this study were from seven countries (India, Iraq, Kenya, Jakarta, China, Egypt, and Pakistan) (9, 10, 11, 14-22) most of which were conducted in India (n=5) (9, 11, 20-22). The date of these studies was from 2013 to 2023. Eleven studies were conducted exclusively on women and only one study was conducted on both women and men (17) (Table 1).

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

Authors	*Year/ Country*	*Sex*	*Age(yr)*	*osteocalcin measure-ment*	*Participants*	*Relationship of osteocalcin with osteopo-rosis, BMD and bone bi-omarkers*	*Quality assessment*
Bhadricha et al. (11)	2019/ India	F	between 25 and 65 year	ELISA	Normal healthy women partic-ipants (n = 138)	Related	Fair
Mulbah et al. (15)	2018/ Kenya	F	aged 50 years and above	ELISA	61 postmenopausal women	Related	Good
Roomi et al. (14)	2022/ Iraq	F	Group I: 58.20± 6.01 Group II: 58.70± 5.01 Group III: 57.91± 5.40	ELISA	160 postmenopausal women	Related	Good
Hutomo et al. (16)	2017/ Jakarta	F	age from 48 to 87 years	ELISA	71 postmenopausal women	Non Related	Good
Xu et al. (17)	2022/ China	F/M	aged 17–89 years;	ELISA	900 subjects	Related	Good
Hamdi et al.(10)	2013/ *Iraq*	F	51-68 years	ELISA	44 postmenopausal	Related	Fair
Alam et al. (20)	2019/ India	F	45 to 80 years	LIAISON osteocalcin assay	147 post-menopausal women	Related	Fair
Kamel et al. (18)	2013/ Egypt	F	Group I: 49.13 ± 5.96 Group II: 50.73 ± 4.86 Group III: 62.66 ± 5.39	ELISA	90 female postmenopausal women	Related	Good
Singh et al. (9)	2015/ India	F	40-70 years	ELISA	82 post-menopausal females,	Related	Good
Chidre et al. (21)	2017/ India	F	above the age of 40	NR	314 women	Related	Fair
Naeem et al. (19)	2016/ Pakistan	F	up to 60 years of age	ECLIA	203 postmenopausal females	None Related	Good
Rai et al. (22)	2018/ India	F	Group I: 28.37±5.28 Group II: 57.09±7.16 Group III: 68.34±8.13	chemilumi-nescent method	105 women	Related	Good

There was a negative correlation between femoral neck bone density and osteocalcin levels, osteocalcin levels ≥ 25.1 ng/ml were observed in women with osteoporosis (T score ≤ -2.5 SD) (15). A significant decrease in BMD, osteopontin, and serum osteocalcin levels was observed in postmenopausal Iraqi women with type2 diabetes, and these results might be helpful in osteoporosis screening (14). In one of the studies, the average level of osteocalcin (ucOC) was observed in men more than in women, and the relationship between the decrease in BMD values and the higher level of osteocalcin was observed (17). In postmenopausal women with osteoporosis, the mean serum level of osteocalcin was significantly higher than the control group (P<0.0001). There was a positive correlation between the serum level of osteocalcin and age (10). A strong negative correlation was observed between BMD and osteocalcin (r=-0.77, P<0.05) and the serum level of osteocalcin in postmenopausal women with osteoporosis (22.62±2.25) was significantly higher (P<0.05) than postmenopausal women without osteoporosis (9.87±1.04) (20). Osteocalcin and insulin-like growth factor 1 levels in postmenopausal women with diabetes provided useful information about bone status, but soluble receptor activator of nuclear factor- kappaB Ligand (sRANKL) and osteoprotegerin levels did not (18). In another study, a negative correlation was observed between BMD grading and serum osteocalcin levels, and serum osteocalcin levels in postmenopausal women with osteoporosis and non-osteoporotic postmenopausal women showed a statistically significant difference (9).

Osteocalcin is a promising marker for the detection of osteoporosis (21). A significant decrease in the mean level of serum osteocalcin has been observed in postmenopausal women with fractures compared to postmenopausal or premenopausal women (22). Among the twelve studies reviewed, two showed results that require further consideration as they differed from the findings of other studies. Specifically, these two studies did not observe a significant difference in the serum levels of osteocalcin and beta-C-terminal telopeptide in groups with osteoporosis, osteopenia, and normal bone density (19). Additionally, there was no significant relationship found between the state of osteoporosis and the serum level of osteocalcin (16) (Table 1).

Discussion

This review analyzed twelve studies from around the world to investigate the connection between osteocalcin and osteoporosis in humans. Of these studies, eight were considered good-quality and four were considered fair-quality. The majority of the evidence gathered from the studies (six good-quality and four fair-quality) indicates that postmenopausal women who have osteoporosis typically have elevated levels of osteocalcin. Additionally, the studies suggest a negative correlation between osteocalcin and BMD.

The findings suggest that osteocalcin has potential as a precise indicator for improved prognosis of osteoporosis. Currently, bone mineral density is the most accurate predictor of osteoporosis fracture (23). In postmenopausal women with osteoporosis, the increase in the serum level of osteocalcin can play an important role in the development of primary osteoporosis (10), and high levels of osteocalcin can be considered as a surrogate marker of primary osteoporosis in postmenopausal women (15). Serum osteocalcin levels are related to the amount of bone formation and therefore can be considered as a specific marker for osteoblast function, and as a result, it may be a better predictor than bone mineral density (20). Postmenopausal women often have high levels of alkaline phosphatase and serum osteocalcin, which are key factors in premature bone density reduction among middle-aged women. These indicators can be used to predict bone density and identify women between the ages of 35 and 65 who may be at risk of osteoporosis (24).

Several factors effect on the severity of osteoporosis such as the level of osteocalcin, sex, age, and PTH (25). Osteocalcin and β-collagen degradation products are good predictors for patients

with osteoporosis and chronic obstructive pulmonary disease. In addition, osteocalcin was positively correlated with bone mineral density, and its amount decreases in these patients (patients with chronic obstructive pulmonary disease and osteoporosis) (26).

A method of fighting osteoporosis by osteocalcin is the selective activation of ATP production, which is involved in the maturation of osteoblasts (27). At the interface around osteocalcin implants, the increased expression of bone-specific matrix proteins and proteins of osteopentin, bone sialoprotein, and CD44 indicate that osteocalcin can accelerate the bone formation and regeneration. As a result, osteocalcin activates both osteoclasts and osteoblasts during early bone formation (7). The osteocalcin fragment directly increased osteoclast formation in the bone matrix in the presence of RANKL and macrophage colony-stimulating factor (MCSF) by bone resorption from Mac-1^{+}c-Fms^{+} cells. As a result, the osteocalcin fragment plays a role in the maturation of osteoclasts, especially in the final stages of osteoclast differentiation (28).

The results showed that the risk of osteoporosis is significantly related to BMI, age, and age of menopause in postmenopausal women and increased levels of osteocalcin and β-CTX are associated with decreased BMD (29). In another study, the measurement of osteocalcin does not replace the measurement of bone mass to evaluate the condition of patients with early osteoporosis and provides only limited values (30).

The results have shown that osteocalcin *HindIII* gene polymorphism is associated with a decrease in bone mineral density and makes women susceptible to osteoporosis in the femoral neck (31). Another study found no correlation between osteocalcin and bone mineral density, indicating heterogeneity of osteocalcin fractions in serum, which makes osteocalcin less important in the assessment of osteoporosis (32). Higher levels of osteocalcin and bone alkaline phosphatase (bALP) were observed in the age group over 59 years than in the age group of 49-59 years, and a significant relationship was found between age and osteocalcin, and bALP in the patient group over 59 years, but there was no relationship with bone mineral density (33).

There were limitations to our study, including that few studies were conducted in men and that there were very few studies in young people with osteoporosis, and it is recommended that more cellular and molecular studies should be performed in these patients.

Conclusion

A significant increase in the serum level of osteocalcin was observed in postmenopausal women with osteoporosis. There was a negative correlation between BMD and the serum level of osteocalcin. As a result, osteocalcin can be a promising marker for the diagnosis and screening of patients with 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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Ethics approval

This article does not contain any studies with human or animal subjects performed by any of the authors. No ethical approval or informed consent statement was required for this review article.

Conflict of interest

The authors declare that there is no conflict of interests.

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