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Circulating Periostin Levels in Osteoporosis and Related Fractures

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ABSTRACT

Objective: Periostin, a protein involved in bone remodeling, is linked to osteoporosis. Elevated levels of periostin are associated with an increased risk of fractures due to its role in bone repair and turnover. This meta-analysis aims to investigate the usability of serum periostin levels as a potential biomarker in individuals with osteoporosis and patients at risk of osteoporotic fractures.

Methods: This study was conducted in accordance with the PRISMA guideline. We identified studies reporting periostin levels associated with osteoporosis and osteoporotic fractures through a systematic search in PubMed, Cochrane Library, Web of Science, and Scopus databases. From a total of 175 studies, nine studies meeting the inclusion criteria were included for quantitative synthesis (meta-analysis). Meta-analysis was performed using Revman 5.4.1 software, and forest plots were generated using standardized mean differences (SMD).

Results: When serum periostin levels (ng/mL) were compared between individuals with osteoporosis and healthy controls, periostin levels were found to be significantly higher in patients with osteoporosis (SMD: 1.29, 95% CI: 0.87-1.71). In addition, in the comparison between individuals with and without osteoporosis, periostin levels were found to be significantly higher in patients with fractures (SMD: 11.23, 95% CI: 5.64-16.82). However, significant heterogeneity was observed across studies (I^2: 99% and 72%).

Conclusions: This meta-analysis supports the use of serum periostin levels as a potential biomarker of osteoporosis and osteoporotic fracture risk. However, heterogeneity across studies suggests that caution should be exercised in interpreting these findings. In order for periostin to be more widely used in clinical practice, standardized measurement protocols should be developed and confirmatory studies should be conducted in different populations. periostin to be more widely used in clinical practice, standardized measurement protocols should be developed and confirmatory studies should be conducted in different populations.

Keywords: Bone Mineral Density, Osteoporotic Fractures, Osteoporosis, Periostin

INTRODUCTION

Osteoporosis is a bone disease that is especially common in post-menopausal women and is characterized by a decrease in bone mineral density (BMD) and deterioration of bone microarchitecture.[1] Osteoporosis remains a significant public health concern due to its association with an elevated risk of fractures and a consequent decline in quality of life. Osteoporosis also affects approximately 200 million women worldwide, with a high incidence of fractures in men and women over the age of 50 (one-third of women and one-fifth of men). Osteoporotic fractures not only seriously affect the quality of life, but also cause significant fracture-related morbidity, mortality, and heavy expenses associated with health care management.[2] Periostin is a matricellular protein primarily expressed in connective tissues that are subjected to mechanical loading, such as bones, tendons, and periodontal ligaments.[3] Structurally, periostin is part of the fasciclin family of proteins and plays a pivotal role in maintaining tissue architecture by binding to integrins on cell surfaces, thereby activating several signaling pathways, including Wnt/β-catenin, NF-κB, and FAK.[4] These pathways are involved in cellular proliferation, differentiation, and tissue repair processes.[5] In bones, periostin is highly expressed in the periosteum, where it regulates bone formation and remodeling by promoting osteoblast differentiation and collagen production.[6] This protein's dynamic expression in response to mechanical stress and injury

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underscores its importance in skeletal maintenance and repair. In experimental animal studies, it has been stated that periostin plays an important role in differentiation, mineralization and proliferation in osteoblasts.[7]

In studies examining the relationship between periostin and osteoporosis, it has been suggested that periostin expression is upregulated in response to bone injury and may be involved in compensatory mechanisms aimed at increasing bone formation in osteoporotic conditions.[8] In studies examining serum periostin levels, high serum periostin levels have been reported, especially in postmenopausal women with osteoporosis.[9-14] High periostin levels in patients with osteoporosis may also be associated with age, but one study reported that serum periostin did not change significantly from age 30 to 70 but increased in those aged 16-18 and over 70s.[15] The role of periostin in bone tissue and the changes in serum levels in patients with osteoporosis make it a promising candidate for monitoring bone health in these patients and potentially predicting fracture risk.[16,17]

Studies have been conducted to determine the role of serum periostin levels as a biomarker for osteoporosis. In these studies, the correlation between periostin levels and BMD was examined, and while some studies found a negative correlation,[8,14,18] others did not find any correlation.[19-21] The relationship between periostin and osteoporotic fractures has also been investigated, and it has been shown that periostin plays an important role in the early stages of bone healing.[17] Elevated periostin levels are associated with the recruitment of osteoprogenitor cells and new bone formation; these processes are critical for fracture repair.[8,22,23] Studies have shown that periostin levels are significantly increased after fractures, especially in the hip, and may remain elevated throughout the healing process.[18,20,24]

Research Gap and Contribution: Despite the growing body of research on the role of periostin in bone health, particularly in the context of osteoporosis and fractures, the clinical utility of serum periostin as a biomarker remains uncertain. Previous studies have yielded conflicting results regarding its correlation with bone mineral density (BMD) and its potential to predict fracture risk independently of traditional markers. Moreover, the variability in study designs, population characteristics, and periostin measurement methods has led to substantial heterogeneity, complicating the interpretation of findings. This meta-analysis aims to address these gaps by systematically synthesizing the available evidence on serum periostin levels in osteoporosis and related fractures. By consolidating data from multiple studies, this work provides a more comprehensive understanding of periostin's role in bone metabolism and its potential as a biomarker for osteoporosis and fracture risk. This contribution is significant as it seeks to clarify the inconsistencies in the literature and offers insights that could guide future research and clinical practice, ultimately advancing the field of osteoporosis management.

The aim of this meta-analysis is to systematically review and synthesize the available evidence on serum periostin levels in osteoporosis and osteoporotic fractures. The data obtained from this meta-analysis will shed light on whether periostin can be used as a biomarker in both the diagnosis of osteoporosis and the determination of osteoporotic fracture risk.

METHODS

All steps in this meta-analysis were carried out in accordance with the "PRISMA (Systematic Reviews and Meta-Analyses for Preferred Reporting Items)" guideline.

Eligibility criteria

We included studies that measure circulating periostin levels in individuals with osteoporosis, studies that measure serum periostin levels in individuals with fractures, comparative studies between healthy individuals and those with osteoporosis, studies published in peer-reviewed journals, and articles available in English. To minimize heterogeneity, meta-analysis included only studies conducted on plasma and serum samples. All studies used a cross-sectional design in which cases were diagnosed mostly according to BMD T-score, which represents the number of standard deviations below the mean peak bone density of an adult. Specifically, cases were defined by a T-score less than 2.5 standard deviations below peak BMD at the femoral neck or lumbar spine, in accordance with WHO guidelines.

We excluded studies that did not measure circulating periostin levels, animal studies, case reports and reviews, studies without full text, and articles not available in English.

Literature search strategy

An electronic literature search was conducted on May 20, 2024, utilizing the PubMed, Cochrane Library, Web of Science, and Scopus databases. Additionally, a bibliographic scan of the published articles was performed. The search strategy included the following keywords: ("periostin"[MeSH Terms] OR "periostin"[All Fields]) AND ("bone and bones"[MeSH Terms] OR ("bone"[All Fields] AND "bones"[All Fields]) OR "bone and bones"[All Fields] OR "bone"[All Fields]). The articles identified from the search were imported into the Endnote 21 reference manager program (Clarivate Analytics), where duplicate entries were removed.

Two independent researchers reviewed the titles and abstracts for potential eligibility for inclusion in the meta-analysis.

Data extraction

The following information was extracted from the studies included in the meta-analysis; Authors, Year of publication, Study design (e.g., cross-sectional, cohort), sample size, and population characteristics (age, gender, health status). Additionally, the number of participants in each group (osteoporosis, healthy controls, fracture individuals), Mean age and standard deviation, Gender distribution, BMD for relevant anatomical regions (e.g. lumbar spine, hip), Periostin levels (mean ± standard deviation) were also included in the meta-analysis. obtained from the studies.

Study output

The primary outcome of this meta-analysis is to determine the difference in circulating periostin levels between individuals with osteoporosis and healthy controls and between individuals with fractures and those without fractures. The results will be synthesized to provide a comprehensive understanding of the role of periostin in bone health and fracture risk. In particular, we aimed to:

- Compare serum periostin levels between osteoporotic individuals and healthy controls.
- Compare serum periostin levels between people with and without fractures.

Statistical analysis

The meta-analysis was performed using Revman 5.4.1 software. Standardized mean differences were applied to generate forest plots for continuous data. Statistical significance was determined at a threshold of $P < 0.05$, with 95% confidence intervals (CIs) provided. A random-effects model was utilized, and studies were weighted using the generic inverse variance method (Q statistic: $P < 0.10$, $I2 > 50\%$). For meta-analyses that included more than 10 studies, publication bias was assessed according to the recommendations for testing funnel plot asymmetry outlined in the Cochrane Handbook. To assess the robustness of the findings, a sensitivity analysis was conducted by sequentially excluding each study from the analysis for each oxidation marker.

RESULTS

Study selection and characteristics

A systematic search across four major databases—PubMed, Cochrane Library, Web of Science, and Scopus—yielded a total of 175 records. After eliminating duplicates, 75 unique studies remained for screening. The screening process, which involved evaluating titles and abstracts, resulted in the exclusion of 41 studies that did not meet the inclusion criteria. Subsequently, 59 full-text articles were assessed for eligibility. Among these, a significant number of studies were excluded due to various reasons, such as lack of healthy controls, being experimental animal studies, or failure to report periostin levels.

Ultimately, 9 studies met all the eligibility criteria and were included in the quantitative synthesis (meta-analysis) (Figure 1). Detailed demographic information such as the number of participants (N), age, gender distribution (M/F), and BMD values of the control group and osteoporosis patients included in the meta-analysis were summarized in Table 1. The included studies were predominantly cross-sectional in design and covered diverse populations across different geographical regions. The primary focus was on assessing periostin levels in patients with osteoporosis compared to healthy controls, with particular attention to distinguishing patients with and without fractures. This comprehensive meta-analysis serves to consolidate.

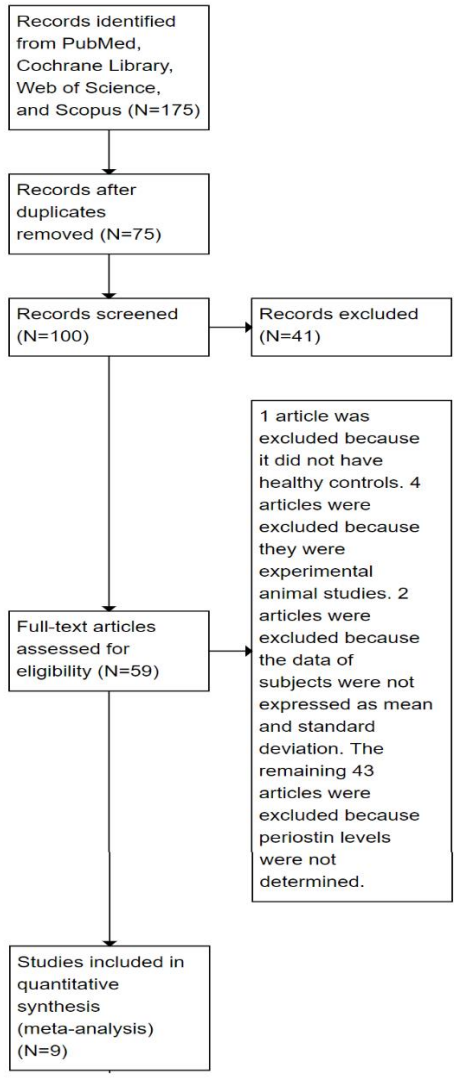

Figure 1. Study Selection Flowchart

Table 1. Overview of Participant Demographics and Bone Mineral Density in Osteoporosis Studies

Studies	Study design	Control group age				Patients with osteoporosis			
		N	Age	Gender M/F	BMD	N	Age	Gender M/F	BMD
Yiğitol et al.[14]	Cross section	30	47.2±10.6	9/21	-	40	50.5 ± 14.0	5/35	-2.15±0.76 (L1-L4 T score)
Li et al. [10]	Cross section	29	55.17±6.59	0/29	0.977±0.085 g/cm^2 (LS)	65	62.17±7.71	0/65	0.726±0.108 g/cm^2 (LS)
Anastasilakis et al.[9]	Prospective cohort	30	65.7 ± 1.4	0/30	-0.75±0.11 (LS)	46	65.7±1.0	0/46	-2.51±0.09
Mahamood et al.[11]	Cross section	25	50.5±6.2	9/16	-0.35±0.4 (LS)	27	52.3±7.1	7/20	-3.48±0.7
Maimoun et al.[12]	Cross section	40	42.6±13.3	17/23	0.925±0.47 g/cm^2 (Total hip)	131	42.8±13.7	8/16	0.690±0.221 g/cm^2 (Total hip)
	Study design	**No-Fracture**				**Fracture**			
		N	**Age**	**Gender M/F**	**BMD**	**N**	**Age**	**Gender M/F**	**BMD**
Bonnet[19]	Cross section	629	65.1±1.5	0/629	0.97±0.18	66	65.0±1.4	0/66	1.07±0.20
Guo[18]	Cross section	315	65.22± 9.71	0/315	0.87 (0.80–0.94)	70	68.10 ± 9.38	0/70	0.78(0.63–0.88)
Pepe[20]	Cross section	25	67.48± 9.51	0/25	0.834 ± 0.167	25	68.64 ± 5.98	0/25	0.818 ± 0.122
Rousseau[24]	Cross section	532	66±8	0/532	0.856±0.12	75	72±9	0/75	0.767±0.11

N: Number of participants, M/F: Number of male/female participants, BMD: Bone mineral density (g/cm^2), L1-L4 T score: T scores for the L1-L4 vertebrae, Total hip: BMD value for the hip region, LS: Lumbar spin

Meta-Analysis of periostin levels in osteoporosis

The meta-analysis included data from five studies that compared periostin levels in patients with osteoporosis against healthy controls. The standardized mean difference (SMD) was used as the summary statistic, given the continuous nature of the periostin levels and the need to standardize the effects across studies that may have used different measurement scales.

The pooled mean difference was 1.29 (95% CI: 0.87, 1.71), indicating that periostin levels were significantly higher in osteoporosis patients compared to healthy controls. The data for the comparison are shown as a forest plot in Figure 2. This finding underscores the potential role of periostin as a biomarker for bone metabolism and osteoporosis. Periostin, a matricellular protein involved in bone remodeling, has been implicated in the pathogenesis of osteoporosis due to its role in enhancing osteoblast differentiation and bone formation. The elevated levels observed in osteoporosis patients suggest a compensatory response to bone loss, potentially reflecting an attempt by the body to promote bone repair and remodeling.

Despite the statistically significant findings, there was substantial heterogeneity among the included studies, with an I^2 value of 99% and a Q statistic p-value of <0.00001. This high degree of heterogeneity indicates that the effect sizes varied considerably between studies. Several factors may contribute to this variability, including differences in study populations, measurement techniques, and the specific subtypes of osteoporosis assessed. Further subgroup analyses and meta-regression could help elucidate the sources of heterogeneity, although such analyses were beyond the scope of this study due to the limited number of studies included.

Periostin levels in osteoporosis with and without fracture

A separate meta-analysis was conducted to compare periostin levels in osteoporosis patients with fractures versus those without fractures. This analysis included four studies (Figure 3) and revealed a pooled mean difference of 11.23 (95% CI: 5.64, 16.82), indicating significantly higher periostin levels in patients with fractures compared to those without. This finding suggests that periostin may serve as a marker of fracture risk in osteoporosis patients, potentially reflecting increased bone turnover and remodeling activity in response to bone injury.

The heterogeneity in this analysis was moderate, with an I^2 value of 72% and a Q statistic p-value of 0.01, indicating that while there was some variability in the effect sizes, the

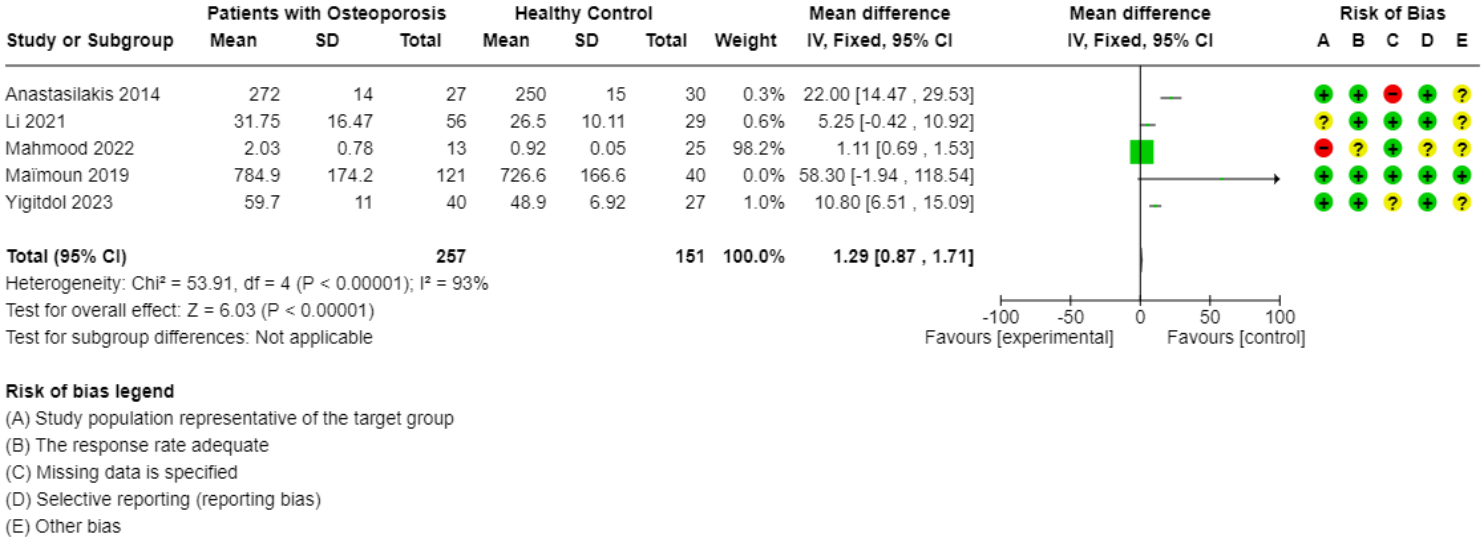

Figure 2. Forest Plot of Periostin Levels in Osteoporosis Patients versus Healthy Controls

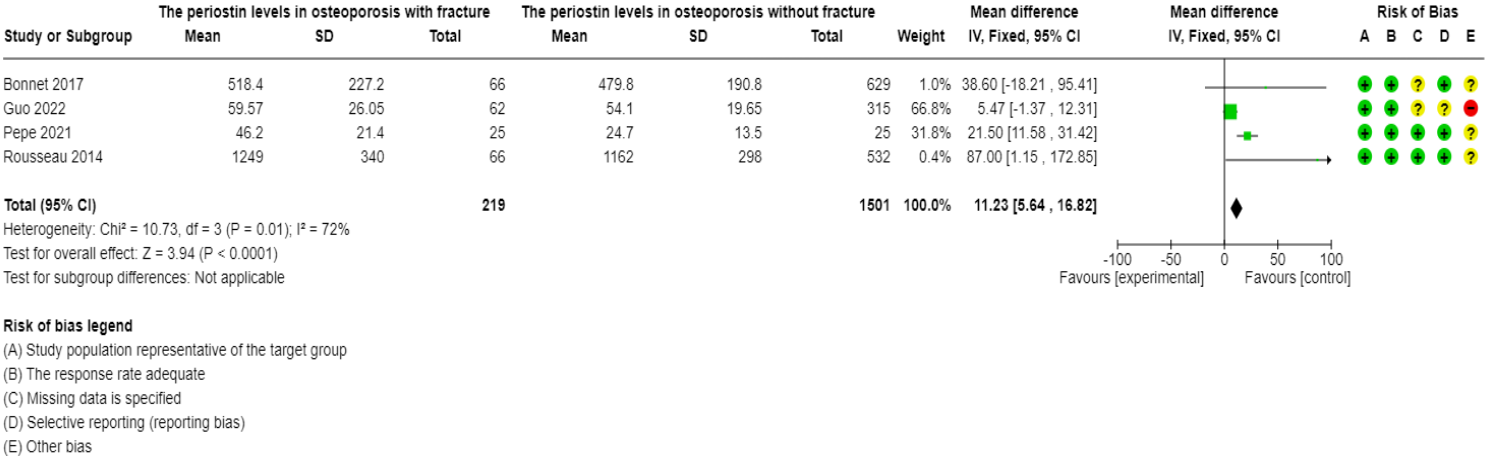

Figure 3. Forest Plot of Periostin Levels in Osteoporosis Patients with Fracture versus Without Fracture

overall trend was consistent across studies. The moderate heterogeneity could be attributed to differences in fracture types, study populations, and periostin measurement techniques.

Publication bias

Publication bias was assessed through funnel plots. The funnel plot for studies comparing periostin levels between osteoporosis patients and healthy controls (Figure 4) appeared relatively symmetrical, suggesting minimal publication bias. However, the interpretation of funnel plots should be approached with caution due to the limited number of studies included.

In contrast, the funnel plot for studies comparing periostin levels between osteoporosis patients with and without fractures (Figure 5) showed slight asymmetry, indicating the possibility of publication bias or small-study effects. This finding, however, must be interpreted cautiously due to the small sample size and potential variability in the included studies. Further research with larger sample sizes is needed to confirm these findings and assess the robustness of the results.

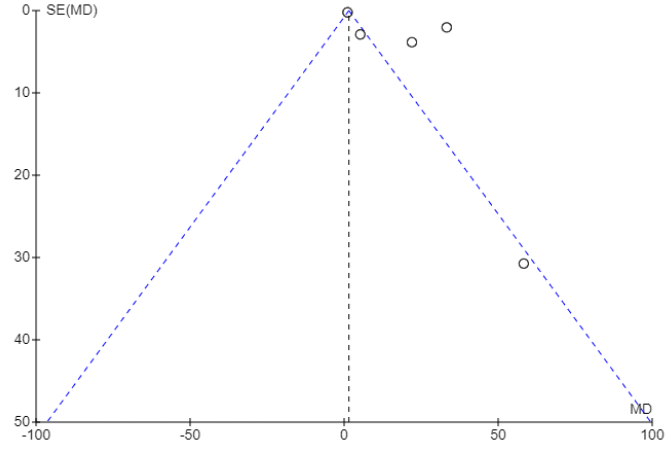

Figure 4. Funnel Plot for Assessing Publication Bias in Osteoporosis

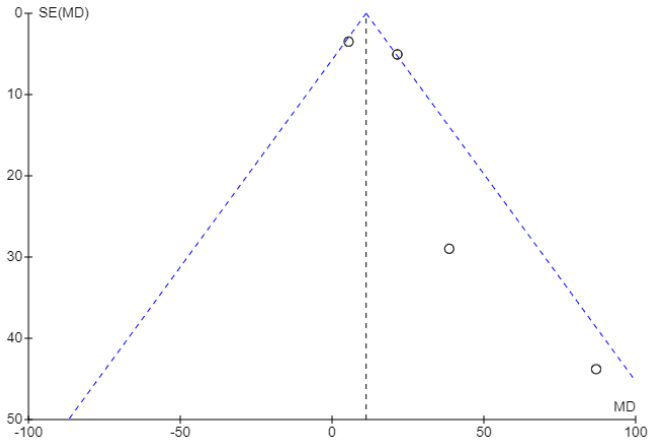

Figure 5. Funnel Plot for Assessing Publication Bias in Fracture studies

Risk of bias

The risk of bias assessment, conducted according to the Cochrane Handbook guidelines, revealed varying levels of bias across the included studies (Figures 6 and 7). Several studies demonstrated a low risk of bias in key domains, such as the representativeness of the study population and the adequacy of the response rate. However, selective reporting bias emerged as a concern in some studies, with potential implications for the validity of the results. In particular, the selective reporting of outcomes and the failure to pre-specify primary outcomes in some studies could introduce bias and affect the interpretation of the findings.

The summary graph (Figure 6) highlights the distribution of bias across different domains. While the majority of studies had a low risk of bias in terms of the study population and response rate, other areas, such as selective reporting and other potential biases, were more variable. This variability underscores the importance of critically appraising the quality of evidence and considering the risk of bias when interpreting the results of meta-analyses.

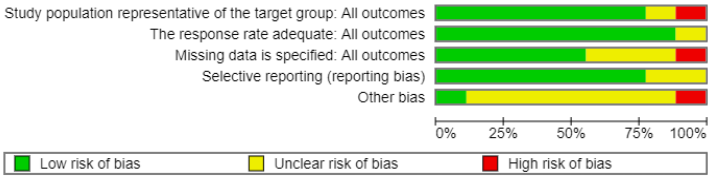

Figure 6. Risk of Bias Assessment Across Studies for All Outcomes

Sensitivity analysis

To evaluate the robustness of the findings, a one-study removed sensitivity analysis was conducted. This analysis involved systematically excluding each study from the meta-analysis to assess the impact on the overall effect estimates. The results confirmed that the pooled effect sizes remained consistent, indicating that the findings were robust and not unduly influenced by any single study. This sensitivity analysis provides additional confidence in the validity of the results and supports the conclusion that periostin levels are significantly associated with osteoporosis and fracture risk.

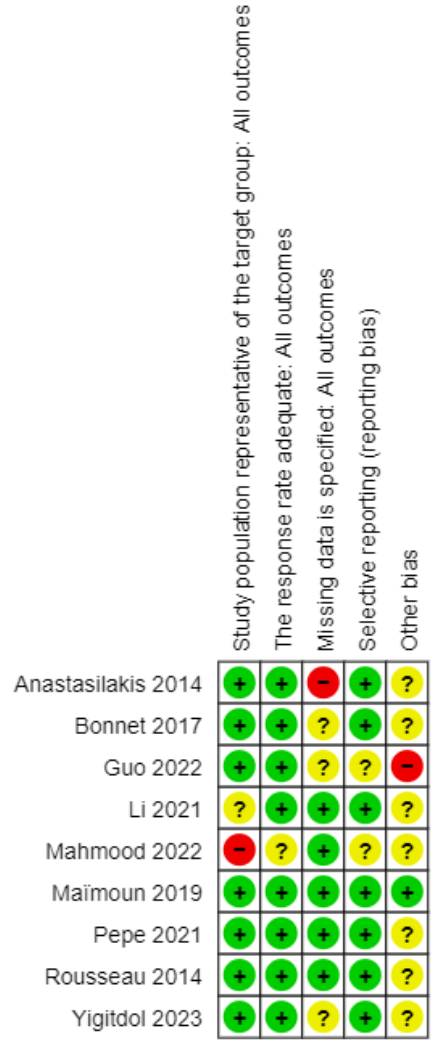

Figure 7. Risk of Bias Summary

DISCUSSION

To our knowledge, this is the first meta-analysis to elucidate and quantify the association of serum periostin levels with fractures in osteoporosis and osteoporosis.

The relationship between bone tissue and periostin has gained the interest of researchers in this field, and studies have been conducted to investigate the function of periostin in bone tissue. Periostin, a matricellular protein encoded by the POSTN gene, plays a critical role in bone metabolism by influencing osteoblast differentiation, migration, and survival. It is primarily expressed in osteocytes and periosteal osteoblasts, contributing to the biomechanical properties of bone through the regulation of collagen cross-linking and fibrillogenic, which is essential for bone strength and

mineralization.[25,26] Additionally, periostin plays a role in the signaling pathways that regulate bone turnover and remodeling. It is also associated with osteogenic differentiation in bone marrow stromal cells, particularly under the influence of estrogen, which is significant in the context of osteoporosis management.[27]

Important results have been obtained in studies examining the relationship between osteoporosis and periostin. Anastasilakis et al. divided postmenopausal osteoporotic women into two groups, low and normal, according to their BMD and examined serum periostin levels and reported that there was no statistically significant difference. Zoledronic acid is a bisphosphonate drug used to prevent bone loss and treat osteoporosis by inhibiting bone resorption. They also reported that zoledronic acid treatment did not affect serum periostin levels. In the same study, although there was no statistically significant difference between the control and treatment groups in baseline serum periostin levels, the periostin levels of the patient treatment group were higher than the control group.[9] Li et al compared periostin levels in patients with type 2 diabetes with normal BMD and those with osteoporosis. As a result, they reported that periostin levels in patients with type 2 diabetes and those with osteoporosis were statistically significantly higher than the periostin levels in patients with type 2 diabetes and normal BMD.[10] In the study conducted by Mahmood and Abbas, they determined the periostin levels in serum samples obtained from the healthy control group (n=25), the osteopenic patient group (n=26) and the osteoporotic patient group (n=27) and reported that the highest periostin levels were observed in the osteoporotic patients and the lowest levels were observed in the healthy control group.[11] Similar to other studies, Maïmoun et al reported that periostin levels were higher in patients with osteoporosis and spinal cord injury than in the control group without spinal cord injury.[12] Mohamed et al compared the periostin levels of Egyptian postmenopausal osteoporotic women with a healthy control group and reported that the periostin levels in the patient group were statistically significantly higher.[13] In their study on patients with primary hyperparathyroidism, Yiğitdol et al reported that the pericytin levels of patients with osteoporosis (n=14) were statistically significantly higher than those without osteoporosis.[14] Li et al compared periostin levels in postmenopausal women with osteoporosis with those in women with normal BMD in the Shanghai, China population and found no statistically significant difference.[21] Yan et al. compared the periostin levels of women with postmenopausal osteoporosis and hip fractures with the control group and reported that the serum periostin levels of patients with hip fractures were statistically significantly higher.[8] In the same study, serum periostin levels were measured in the period after the fracture and it was reported that periostin levels on the 7th day increased. Since serum periostin levels were given as median in this study, they could not be included in the meta-analysis, and in addition, the deficiencies of the statistical method used in this study were stated by Farrokhi et al.[28]

In summary, the majority of studies investigating periostin levels in individuals with osteoporosis and healthy controls reported that periostin levels were increased in the patient group. The results of this meta-analysis confirm that periostin levels are significantly elevated in individuals with osteoporosis compared to healthy controls. This result supports that periostin may serve as a potential biomarker for osteoporosis and may be useful in the clinical assessment and management of this condition. However, the heterogeneity observed in the studies cannot be ignored and must be taken into consideration when interpreting the results.

The role of serum periostin levels as a biomarker for fracture risk in individuals with osteoporotic fractures has been explored in several studies. The majority of these studies have indicated that periostin has the potential to predict fracture risk independently of bone mineral density (BMD). Rousseau et al. conducted a 7-year prospective study within the OFELY cohort and found that higher serum periostin levels were significantly associated with an increased risk of incident fractures in postmenopausal women, independent of BMD. The study demonstrated that women with periostin levels in the highest quartile had a nearly twofold increased risk of fractures compared to those in lower quartiles. Importantly, the combination of high periostin levels and low hip BMD (T-score ≤ -2.5) markedly increased fracture risk, underscoring the additive value of periostin in fracture risk assessment.[24]

Bonnet et al. expanded on these findings by identifying that a cathepsin K-generated periostin fragment, termed K-periostin, was predictive of incident low-trauma fractures in postmenopausal women, independent of traditional risk factors including BMD and FRAX scores. This study emphasized the role of periostin in bone quality rather than quantity, suggesting that it may reflect microarchitectural deterioration that is not captured by conventional BMD measurements.[19]

Pepe et al. further explored the association between k-periostin levels and fracture risk in postmenopausal women with primary hyperparathyroidism (PHPT). Their findings revealed that women with fractures had significantly higher k-periostin levels compared to those without fractures,

indicating that periostin fragments could serve as an independent marker of bone fragility in this population. This study supports the notion that periostin levels are elevated in conditions of increased bone turnover and remodeling, which are characteristic of PHPT and may contribute to skeletal fragility.[20]

Guo et al. investigated genetic polymorphisms related to periostin and their association with serum periostin levels and fracture risk. They identified specific genetic variants that modulate periostin expression, linking them to an increased predisposition to fractures in individuals with osteoporosis. This genetic perspective adds a layer of complexity to the understanding of periostin's role in bone metabolism and fracture susceptibility.[18] In addition to these studies, a previous study by Xiao et al also stated that the periostin gene may be a candidate in fracture risk assessment.[23]

There are also studies that claim the opposite of the above studies. One of these studies is conducted by Luo and Deng, they stated that there was no significant correlation between serum periostin levels and initial BMD, PTH, P1NP, β-CTx and N-MID-OT levels. Based on their results, they stated that serum periostin levels cannot be used as a biomarker in the initial stage of bone loss in postmenopausal women.[29] In contrast to the findings of elevated periostin levels associated with higher fracture risk, a study by Kerschan-Schindl et al. observed a different pattern in patients with hip fractures undergoing hemi-arthroplasty. This study noted that while periostin levels did increase postoperatively, this increase was primarily interpreted as a marker of bone healing rather than an indicator of fracture risk. The rise in periostin was linked to the natural bone remodeling processes following surgical intervention, rather than being a pre-existing risk factor for fractures. The authors also emphasized that during the bone healing phase, traditional markers like periostin might not accurately reflect overall bone metabolism or fracture susceptibility.[30] Our meta-analysis results demonstrated that individuals with osteoporotic fractures had significantly higher serum periostin levels compared to those without fractures. This result supports the hypothesis that elevated periostin levels may be associated with an increased risk of fractures in osteoporotic patients. However, the presence of substantial heterogeneity among the studies suggests that the relationship between periostin levels and fracture risk may vary depending on the study population and other contextual factors.

In conclusion, considering the comprehensive analysis and synthesis of available data, this meta-analysis concluded that elevated serum periostin levels are consistently associated with osteoporosis and may serve as a promising biomarker for determining fracture risk, although significant variability in study results suggests that further research is needed. This research should aim to standardize measurement techniques and solidify the clinical utility of periostin in osteoporosis management and fracture risk assessment by investigating its role in different populations and contexts. Despite these challenges, the findings highlight the potential of periostin as a valuable tool for understanding bone health dynamics, but its application in routine clinical practice will require careful consideration of the observed heterogeneity.

Limitations

Despite the robust findings presented in this meta-analysis, several limitations should be acknowledged. First, the high degree of heterogeneity observed across studies, particularly in terms of study populations, periostin measurement techniques, and definitions of osteoporosis and fractures, may limit the generalizability of the results. This variability underscores the need for standardized protocols in future research. Second, the meta-analysis was restricted to studies published in English, which may introduce language bias and limit the inclusion of potentially relevant data. Third, the cross-sectional design of most included studies precludes the establishment of a causal relationship between elevated periostin levels and fracture risk. Longitudinal studies are necessary to confirm whether periostin is a reliable predictor of future fractures. One of the other limitations of our study is the presence of different age groups in the meta-analyzed articles. Adding studies in closer age groups may yield clearer and comparable results.

Ethics Committee Approval: Ethical approval and informed consent are not required in our study as no research was conducted on human or animal specimens.
Peer-review: Externally peer-reviewed.
Author Contributions: Concept - HH.A; Design - Hİ.A; Supervision - HH.A; Resources - Hİ.A; Materials - Hİ.A; Data Collection and/or Processing - Hİ.A; Analysis and/or Interpretation - HH.A; Literature Search - Hİ.A; Writing Manuscript – Hİ.A; Critical Review - HH.A; Other – HH.A, Hİ.A
Conflict of Interest: The authors have no conflicts of interest to declare.
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