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Postmenopausal Osteoporosis and Periodontal Disease: The Role of RANKL/OPG in Bone Metabolism

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Abstract

This study investigates the relationship between postmenopausal osteoporosis/osteopenia and periodontal disease, focusing on the RANKL/OPG system as a key regulator of bone remodeling. Given the shared pathophysiological mechanisms underlying systemic and alveolar bone loss, we analyzed RANKL and OPG levels in gingival fluid from postmenopausal women with osteoporosis/osteopenia and periodontal disease.

A total of 81 actively affected periodontal sites from postmenopausal women aged 45-70 years were analyzed. Results showed that RANKL levels were significantly elevated, while OPG levels were reduced in osteoporotic patients, leading to an increased RANKL/OPG ratio ($p < 0.01$). A positive correlation was found between the RANKL/OPG ratio and clinical attachment loss ($p = 0.0146$), suggesting a direct link between systemic bone resorption and periodontal degradation.

These findings reinforce the hypothesis that osteoporosis contributes to alveolar bone loss via dysregulation of the RANKL/OPG axis. The overall relationship between osteoporosis and periodontal disease highlights the importance of interdisciplinary approaches to managing bone and periodontal health. Future research should explore additional therapeutic strategies targeting both systemic and local bone metabolism.

Keywords
Postmenopausal osteoporosis; Osteopenia; Periodontal disease; Osteoimmune system; RANKL/OPG axis; Bone metabolism; Gingival fluid; Bone remodeling.

Introduction

The relationship between postmenopausal osteoporosis/osteopenia and periodontal disease has gained increasing attention due to their shared mechanisms of bone resorption and inflammatory regulation. Osteoporosis is a systemic bone condition marked by a reduction in bone mass and deterioration of its microstructure, which results in increased bone fragility and a higher risk of fractures. This imbalance in bone remodeling is primarily mediated by the RANKL/OPG system, which regulates osteoclast differentiation and activity [1].

Periodontal disease, on the other hand, is a chronic inflammatory condition affecting the supporting structures of the teeth, leading to alveolar bone resorption and eventual tooth loss. The progression of periodontal disease is driven by bacterial infection and an exaggerated host immune response, with RANKL-mediated osteoclastogenesis playing a central role [2]. Pro-inflammatory cytokines, including interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-α), play a key role in the degradation of periodontal tissue by upregulating RANKL expression and promoting osteoclast differentiation. These cytokines play a key role in alveolar bone resorption, exacerbating periodontal destruction in susceptible individuals [3].

One of the authors conducted a research study to evaluate whether oral fluid analysis could serve as a routine diagnostic method. The study assessed saliva and gingival crevicular fluid in systemically healthy, osteopenic, and osteoporotic patients. Although the differences were not statistically significant, notable variations were observed in the concentration of certain elements, particularly calcium. Calcium levels were found to be higher in the gingival crevicular fluid of osteopenic patients. This finding may reflect increased bone turnover or early bone loss occurring at this stage of the disease, potentially transitioning to a more stable phase in established osteoporosis [4].

Recent epidemiological and clinical evidence supports a potential association between osteoporosis and periodontal disease. Osteoporotic individuals, particularly postmenopausal women, exhibit increased alveolar bone loss and clinical attachment loss compared to systemically healthy controls, indicating that a decrease in bone mineral density (BMD) could have an adverse effect on the tissues supporting the periodontium [5,6]. A recent population-based study in Taiwanese adults aged 40 to 44 years demonstrated a significant association between low bone mineral density (BMD) and periodontal disease. Participants diagnosed with osteopenia or osteoporosis presented higher Community Periodontal Index (CPI) scores and increased periodontal pocket depth compared to individuals with normal BMD. Importantly, after controlling for potential confounding factors, low BMD persisted as an independent risk factor for periodontitis, supporting the hypothesis of a systemic link between skeletal and periodontal bone loss [7]. Nonetheless, findings remain partially inconsistent, and some studies argue that the observed associations may reflect shared risk factors—such as aging, estrogen deficiency, smoking, and systemic inflammation—rather than a direct causal relationship [8]. Further longitudinal and mechanistic research is needed to clarify the nature of this interplay.

Beyond epidemiological correlations, molecular and cellular interactions between the skeletal and immune systems—termed the osteoimmune system—provide a mechanistic basis for this relationship. The interplay between osteoclasts, osteoblasts, and immune cells in both conditions suggests that systemic factors influencing bone metabolism may also impact periodontal health. The RANKL/OPG system is a key regulatory pathway involved in bone remodeling, and its dysregulation has been implicated in both osteoporosis and periodontitis [9].

Despite the proposed association, the precise mechanisms linking osteoporosis and periodontal disease remain incompletely understood. It is unclear whether osteoporosis directly contributes to alveolar bone resorption or whether both conditions share common risk factors that predispose individuals to periodontal tissue breakdown. Factors such as estrogen deficiency, inflammatory cytokine production, genetic predisposition, and lifestyle factors (e.g., smoking, diet, and physical activity) may contribute to the observed correlations between systemic and oral bone loss [10,8].

Estrogen plays a protective role in bone homeostasis by modulating the expression of key cytokines involved in osteoclastogenesis [11,12]. Its deficiency post-menopause leads to an increase in pro-inflammatory mediators, such as IL-1 and TNF-α, exacerbating bone resorption and increasing susceptibility to osteoporosis and periodontal disease [13].

The objective of this study was to examine the link between osteoporosis/osteopenia and periodontal disease by analyzing RANKL and OPG levels in gingival fluid. By investigating the molecular signatures of bone metabolism in periodontal tissues, we sought to determine whether systemic bone loss influences alveolar bone homeostasis and to elucidate whether systemic bone loss contributes to periodontal destruction through shared molecular mechanisms, particularly the RANKL/OPG axis.

Materials and Methods

Study design and population

This cross-sectional study included postmenopausal women diagnosed with osteoporosis/osteopenia and periodontal disease. Patients were recruited from the outpatient clinics of the Gynecology and Periodontology Departments at the University Hospital of Maternity and Neonatology and the Faculty of Dentistry, National University of Córdoba. Inclusion criteria encompassed postmenopausal women aged 45-70 years with osteoporosis or osteopenia confirmed by Dual-Energy X-ray Absorptiometry (DEXA) and diagnosed with periodontal disease involving at least five affected sites. Exclusion criteria included current smoking, systemic inflammatory diseases, necrotizing periodontal disease, recent antibiotic or anti-inflammatory therapy, and the presence of acute or chronic medical conditions affecting bone metabolism. Ethical Considerations Ethical approval was obtained from the Institutional Review Board of the University Hospital of Maternity and Neonatology (Approval No: 001). Written informed consent was obtained from all participants before enrollent, in accordance with the Declaration of Helsinki.

- **Clinical examination and periodontal assessment:** Periodontal status was assessed by calibrated periodontists using standard clinical parameters, including probing depth (PD), clinical attachment loss (CAL), bleeding on probing (BOP), and plaque index (PI). A patient was considered

a case of periodontitis if they met the following criteria: interdental clinical attachment loss detectable at ≥2 non-adjacent teeth, or buccal/oral CAL ≥3 mm with probing depth >3 mm detectable at ≥2 teeth. This case definition aligns with the current classification system for periodontitis proposed by the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions [14].

- **Systemic bone assessment:** Bone mineral density (BMD) was evaluated using Dual-Energy X-ray Absorptiometry (DEXA) at both the lumbar spine and femoral neck. Osteoporosis was defined as a T-score ≤ -2.5, and osteopenia as a T-score between -1.0 and -2.5, according to the World Health Organization (WHO) [15].
- **Gingival fluid collection and biomarker analysis:** Gingival crevicular fluid (GCF) samples were collected from periodontally affected sites using standardized paper strips inserted into the gingival sulcus for 30 seconds. Samples were immediately transferred to sterile tubes and stored at -80°C until analysis. RANKL and OPG levels were quantified using enzyme-linked immunosorbent assay (ELISA) kits (manufacturer details), following the manufacturer's instructions. The RANKL/OPG ratio was calculated to assess the balance between osteoclastogenic and anti-resorptive activity.
- **Statistical analysis:** Data were analyzed using SPSS software (version 25.0, IBM Corp.). Descriptive statistics were presented as mean ± standard deviation (SD). Group comparisons were performed using independent t-tests for normally distributed variables and Mann-Whitney U tests for non-parametric data. Correlation analyses between RANKL, OPG levels, and clinical periodontal parameters were conducted using Pearson's and Spearman's correlation coefficients. A p-value < 0.05 was considered statistically significant.

Figures and Tables

Clinical Characteristics	Control (n=15)	Osteoporosis/Osteopenia (n=66)	p-value
Age (years)	53.07 ± 3.770	56.21 ± 8.864	0.1835
PD (mm/site)	3.267 ± 1.163	3.288 ± 1.134	0.9482
CAL (mm/site)	3.333 ± 1.447	3.030 ± 1.301	0.4273
BOP (%)	54.54 ± 24.72	62.31 ± 35.17	0.4206
PI (%)	58.71 ± 26.14	67.11 ± 29.18	0.3086

Table 1: Clinical characteristics of studied individuals, comparing the osteoporosis/osteopenia group and the control group. This table presents demographic and periodontal parameters, including age, probing depth (PD), clinical attachment level (CAL), plaque index (PI), and bleeding on probing (BOP). Statistical analysis (t-test and

Mann-Whitney U test) revealed no significant differences between groups ($p > 0.05$), ensuring comparability of baseline characteristics.

Clinical Characteristics	RANKL	OPG	RANKL/OPG
PD (mm/site)	0.217522	-0.002292	0.202614
CAL (mm/site)	0.2332602 *	-0.028976	0.2273469 *
BOP (%)	0.010963	-0.076247	0.049084
PI (%)	-0.039656	-0.139213	-0.014202
Age (years)	0.191594	0.120808	0.046592

Table 2: Correlation between RANKL, OPG levels, and periodontal parameters in patients with osteopenia or osteoporosis and healthy controls. This table details the statistical relationships between cytokine levels and clinical measures of periodontal disease severity. Pearson and Spearman correlation coefficients indicate a significant positive association between RANKL/OPG ratio and CAL ($p = 0.0146$), while no significant correlations were observed with PD, PI, or BOP ($p > 0.05$).

Correlation between RANKL, OPG, and clinical parameters in patients with osteopenia or osteoporosis and healthy controls

Statistically significant correlation ($p < 0.05$)

The graph presents the **RANKL (pg/ml) concentration** in individuals with **normal bone condition (Control)** and those with **pathological bone condition (Pathology)**. The horizontal bars indicate the mean and standard deviation. A statistically significant difference (**$p < 0.001$**) reveals an increased RANKL level in the pathological group, which may suggest enhanced osteoclastogenesis and bone resorption.

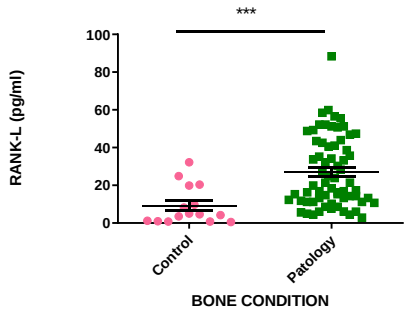

Figure 1: Distribution of RANKL levels in gingival crevicular fluid (GCF) of patients with osteoporosis/osteopenia and periodontal disease, compared to the control group. Box plots illustrate median values and interquartile ranges, with statistical analysis (Mann-Whitney U test) indicating significantly higher RANKL levels in the osteoporosis/osteopenia group ($p < 0.01$).

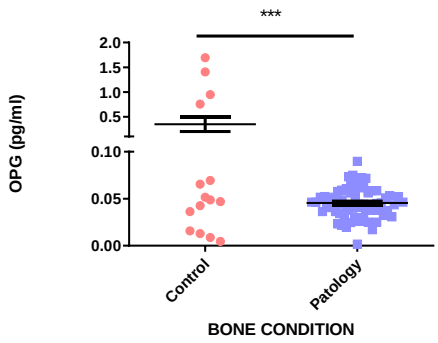

Figure 2: RANKL/OPG ratio in GCF from active periodontal sites, highlighting differences between groups. The increased ratio observed in osteoporosis/osteopenia patients suggests an enhanced osteoclastogenic environment ($p < 0.01$). Statistical comparisons were performed using the Mann-Whitney U test.

This figure illustrates the relationship between the **RANKL/OPG ratio** and **Clinical Attachment Loss (CAL)** in individuals with periodontal pathology (red diamonds) and control subjects (blue triangles). A statistically significant positive correlation was observed in the pathology group (**p = 0.0146**), suggesting a potential association between increased RANKL/OPG ratio and greater CAL. In contrast, no significant correlation was found in the control group (**p = 0.2444**). The dotted lines represent the trend lines for each group.

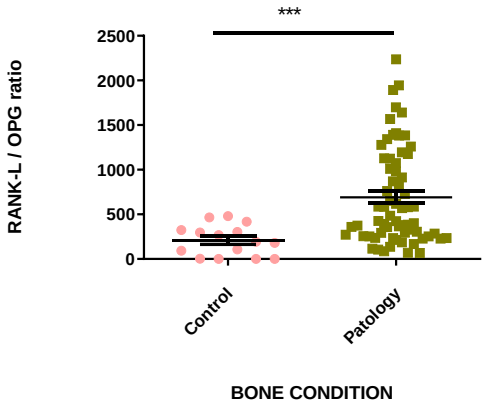

Figure 3: Correlation analysis between clinical attachment level (CAL) and RANKL/OPG ratio in osteoporosis/osteopenia patients with periodontal disease. The scatter plot and regression line illustrate a significant positive correlation ($p = 0.0146$), suggesting that increased RANKL/OPG levels are associated with greater periodontal destruction.

This figure illustrates the relationship between the RANKL/OPG ratio and Clinical Attachment Loss (CAL) in individuals with periodontal pathology (red diamonds) and control subjects (blue triangles). A statistically significant positive correlation was observed in the pathology group ($p = 0.0146$), suggesting a potential association between increased RANKL/OPG ratio and greater CAL. In contrast, no significant correlation was found in the control group ($p = 0.2444$). The dotted lines represent the trend lines for each group.

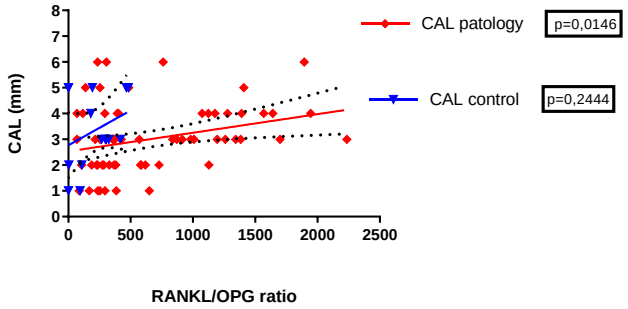

Figure 4: Linear regression model assessing the influence of age on RANKL/OPG ratio levels. No significant correlation was observed ($p > 0.05$), indicating that age alone does not significantly affect cytokine expression in GCF.

This figure presents the linear regression analysis evaluating the relationship between RANKL/OPG ratio and age in the studied population. The trend line indicates a weak positive correlation ($p = 0.3563$), suggesting no statistically significant association between these variables. The dispersion of data points reflects individual variability in RANKL/OPG levels across different ages.

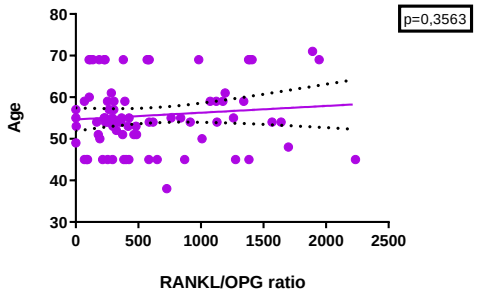

Figure 5: Comparative analysis of CAL and RANKL/OPG ratio in the study population, demonstrating significant trends in osteoporotic patients ($p < 0.01$). The figure highlights the potential use of RANKL/OPG as a biomarker for periodontal disease severity in individuals with compromised systemic bone health.

Discussion

Our findings confirm a strong association between osteoporosis/osteopenia and periodontal disease, in agreement with previous studies reporting elevated RANKL/OPG ratios in osteoporotic patients with periodontitis. Patients with osteoporosis/osteopenia demonstrated increased RANKL levels and decreased OPG levels in gingival fluid, leading to an elevated RANKL/OPG ratio. This suggests that systemic bone loss may contribute to alveolar bone resorption, further exacerbating periodontal disease progression. The significant correlation between RANKL/OPG and clinical attachment loss (CAL) reinforces the hypothesis that systemic bone metabolism influences periodontal degradation beyond local inflammatory factors. The role of the RANKL/OPG system as a key mediator of bone homeostasis has been widely documented in both systemic and oral conditions. RANKL promotes osteoclastogenesis and bone

resorption, whereas OPG acts as a decoy receptor, inhibiting RANKL activity. An increased RANKL/OPG ratio has been implicated in osteoporosis, rheumatoid arthritis, and periodontal disease, highlighting its relevance in bone-destructive disorders. In both osteoporosis and periodontitis, pathological bone loss results from an imbalance between bone resorption and formation. The inflammatory microenvironment in periodontitis further exacerbates osteoclastic activity, reinforcing alveolar bone loss mechanisms similar to those seen in systemic osteoporosis. Additionally, the dysregulation of osteoimmune interactions in periodontal tissues contributes to a pro-resorptive state, amplifying the effects of systemic bone loss at the alveolar level. Our results align with previous studies demonstrating that osteoporosis predisposes individuals to alveolar bone loss through dysregulation of this signaling pathway.

Previous research has investigated the role of bisphosphonates in modulating bone turnover markers, including RANKL and OPG, in gingival fluid. A prior study by Verde et al. (2015) reported no significant effects of bisphosphonate therapy on these biomarkers. This suggests that while bisphosphonates effectively reduce systemic bone turnover, they may have limited effects on inflammatory-driven alveolar bone resorption. While bisphosphonates are commonly prescribed to lower fracture risk in patients with osteoporosis, their role in preserving periodontal bone remains debated. Some studies indicate that long-term bisphosphonate therapy may help maintain alveolar bone density, potentially mitigating periodontal destruction. However, concerns have been raised regarding possible side effects, including delayed bone healing and the development of osteonecrosis of the jaw, particularly in patients undergoing invasive dental procedures.

Studies assessing the impact of systemic osteoporosis on periodontal health have reported mixed results. Some authors suggest that osteoporosis is an independent risk factor for periodontitis due to the shared mechanisms of bone resorption. Others argue that the relationship is influenced by confounding factors such as age, hormonal changes, and lifestyle habits. Our findings contribute to this ongoing debate by providing direct biochemical evidence linking osteoporosis to periodontal bone loss through RANKL/OPG imbalance.

The clinical implications of these findings are significant. Given the strong correlation between osteoporosis and alveolar bone resorption, it is essential to integrate periodontal evaluation into osteoporosis management protocols. Postmenopausal women with low bone mineral density should undergo regular periodontal assessments to monitor disease progression and prevent tooth loss. Additionally, periodontal therapies targeting the modulation of RANKL/OPG may offer new treatment avenues for osteoporotic patients. Conventional periodontal treatments, such as scaling and root planing, may not be effective in osteoporotic patients due to their reduced bone regeneration ability. Adjunctive therapies, including biologic inhibitors of RANKL (e.g., denosumab), could be explored to counteract bone resorption at both systemic and local levels. Additionally, anti-inflammatory strategies aimed at cytokines like IL-1β and TNF-α, which are known to increase RANKL expression, could improve periodontal stability in this group.

Despite its strengths, this study has certain limitations. The cross-sectional design precludes the establishment of a causal relationship between osteoporosis and periodontal disease. Longitudinal studies are essential to determine whether individuals with osteoporosis are at an increased risk of developing periodontal disease over time and whether dysregulation of the RANKL/OPG axis precedes

periodontal destruction. Although the sample size was limited, the present findings provide valuable insights into the relationship between bone metabolism markers and periodontal parameters. Larger cohorts in future studies are warranted to validate and expand upon these observations, as well as to include diverse demographic backgrounds to further support the generalizability of our results. Furthermore, investigating the impact of various osteoporosis treatments, such as selective estrogen receptor modulators and parathyroid hormone analogs, on periodontal health would offer important insights for optimizing therapeutic strategies. Finally, while RANKL and OPG are key mediators of bone metabolism, other molecular pathways, such as the Wnt/β-catenin signaling pathway, also play crucial roles in bone remodeling. Future research should incorporate a broader range of biomarkers to obtain a more comprehensive understanding of the mechanisms linking osteoporosis and periodontal disease.

Conclusion

This study reinforces the concept of a bidirectional relationship between postmenopausal osteoporosis/osteopenia and periodontal disease, mediated by dysregulation of the RANKL/OPG axis. The significant increase in RANKL levels and the concomitant decrease in OPG levels in gingival fluid of osteoporotic patients suggest that systemic bone loss may contribute to alveolar bone resorption, thereby exacerbating periodontal destruction. These findings align with previous research demonstrating that osteoporosis influences periodontal disease progression through molecular and cellular mechanisms common to both conditions.

The implications of these results are critical for clinical practice. Given the growing prevalence of osteoporosis and periodontitis in aging populations, a multidisciplinary approach is essential for improving patient outcomes. Dentists and medical professionals should collaborate in screening, prevention, and management strategies for patients at risk of both conditions. Regular periodontal assessments should be integrated into osteoporosis management plans, particularly for postmenopausal women with decreased bone mineral density. Furthermore, the identification of RANKL/OPG imbalance as a potential biomarker for alveolar bone loss highlights the need for further studies on its diagnostic and prognostic value.

Although bisphosphonate therapy is widely used to prevent osteoporotic fractures, our previous findings indicate that it does not significantly alter RANKL or OPG levels in gingival fluid. This suggests that additional therapeutic approaches, potentially including local treatments, may be required to specifically target periodontal bone resorption in osteoporotic individuals. Future investigations should assess the potential efficacy of RANKL inhibitors, selective estrogen receptor modulators, and anti-inflammatory agents in preventing periodontal damage in this patient cohort.

Despite its contributions, this study has certain limitations, including its cross-sectional design and sample size. Longitudinal studies with larger cohorts are needed to establish causal relationships between osteoporosis and periodontal disease. Additionally, exploring the interactions of other bone metabolism regulators, such as the Wnt/β-catenin pathway, could provide deeper insights into the mechanisms linking these two conditions.

In conclusion, our findings highlight the intricate interaction between systemic and local bone metabolism, emphasizing the importance of comprehensive management in patient care. Integrated

management of osteoporosis and periodontal disease may optimize therapeutic outcomes and enhance long-term oral and systemic health in postmenopausal women.

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