Dentistry 3000
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Periodontal and Biochemical Correlations during Alendronate Treatment in Postmenopausal Women: A Longitudinal Study

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Abstract

Objective: Postmenopausal osteoporosis (OP) is a prevalent condition often treated with bisphosphonates like alendronate, which may influence periodontal health. In this study, we aimed to evaluate the relationship between clinical periodontal parameters [probing pocket depth (PPD), clinical attachment level (CAL)], biochemical markers [osteoprotegerin (OPG), and calcium (Ca)] and alendronate therapy.

Methods: This case-control study was carried out on 60 females aged from 55 to 65. All participants were divided into two groups equally, group A that included healthy postmenopausal females with healthy periodontium and group B included patients with osteoporosis. Patients were followed up for one year through for three consecutive periods (0, 6, and 12 months) after receiving alendronate (ALN) treatment. Patients with osteoporosis or ALN were further subdivided equally based on gingivitis and periodontitis. Blood samples were gathered for quantitative proportions of OPG through enzyme–linked immune sorbent assay (ELISA). Additionally, calcium was analyzed using full automated calcium detector device. The clinical periodontal parameters (PPD, and CAL) were reported for all teeth except for third molars and kept in specifically designed case sheet documents following assortment of serum.

Results: There was a significant decrease in PPD and CAL after 12 months of ALN treatment. However, there was significant increase in serum OPG and calcium level at each consecutive recall follow up in comparison to no ALN treatment. Additionally, our study revealed a positive correlation between OPG and calcium at base line in patients with osteoporosis ($p<0.001$).

Conclusion: Probing pocket depth, clinical attachment level and osteoprotegerin and calcium serum levels improved significantly with alendronate therapy.

Keywords: Postmenopausal, Osteoporosis, Alendronate, Periodontal clinical parameters, Calcium, Bone remodeling markers, Osteoprotegrin.

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Introduction

The literature has shown that postmenopausal women with osteoporosis or osteopenia may experience more significant clinical attachment loss compared to those with normal bone mineral density [1]. This finding suggests a possible interaction between osteoporosis and periodontal health, emphasizing the importance of investigating and appropriately managing both conditions in this patient group. An association between chronic periodontitis and osteoporosis was also found, especially among postmenopausal women [2]. This finding highlights the complex link between periodontal health and bone mineral density, suggesting that these conditions may influence each other's development [3].

Research has indicated that combining oral treatments and drug therapy for osteoporosis may help reduce the risk of tooth loss compared to oral care alone. Alendronate (ALN), an amino-bisphosphonate, is an individual of the second generations of bisphosphonates which are chemical analogs of pyrophosphate (a result of human metabolism) established to be capable of inhibition of bone

Dentistry 3000
Vol 13 No 1 (2025) DOI 10.5195/d3000.2025.813

resorption by osteoclast through modulation of bone mineralization. Various studies confirmed that the systemic use of ALN in humans and some animal models reduced bone loss and increased bone density. It was also proved that treatment with ALN in postmenopausal women with osteoporosis carries a considerable improvement in bone mass [4].

Osteoprotegrin (OPG) and receptor activator of nuclear factor kappa-B ligand (RANKL) act as negative and positive regulators in osteoclastogenesis and bone resorption. OPG is a soluble molecule that inhibits osteoclast differentiation. It binds to RANKL and inhibits its interaction with RANK leading to neutralization and inhibition of OC formation (4), as well as provoking apoptosis of matured OC [5]. Evidence obtained from experimental studies advocated that increase bone resorption after menopause may be due to excessive activation of osteoclast (OC) by increase pro-inflammatory cytokines production such as TNF-α due to decrease estrogenic secretion, which considered as critical factor in the pathogenesis and development of PD as well as osteoporosis [6].

Calcium is the major component of the bone, where it is present at more than 99% as calcium-phosphate complexes, and provides the skeleton strength and structure, making the bone a metabolic reservoir to maintain the intra- and extra-cellular calcium pool. The remaining part is present in blood, in extracellular fluids, in muscles and other tissues, where it is responsible for mediating muscle contraction, vascular contraction and vasodilatation, nerve impulse transmission, and intra and extracellular signaling [7]. Therefore, the aim of the study was to evaluate the effects on clinical attachment level (CAL), probing pocket depth (PPD), osteoprotegerin (OPG), and calcium (Ca) with alendronate therapy.

Material and Methods

This case-control study was carried out on 60 females aged from age from 55 to 65. All participants were divided into two groups equally where control group included 30 systemically healthy postmenopausal females with healthy periodontium and case group included 30 postmenopausal females. Patients were checked at three times readings: (1) first newly diagnosed with osteoporosis and periodontitis (OP group) and baseline data was recorded, (2) after six months of receiving alendronate treatment (ALN6 group), (3) after 12 months of ALN treatment (ALN12 group). Sample collection occurred from 11th November 2022 until 6th May 2024. The samples were collected from patients treated at the department of Rheumatology of Baqubah Teaching Hospital in Baqubah city. Each subject was informed about the aims and protocol of the study, and they were permitted to accept or reject to participate in the study.

Exclusion Criteria

Females with systemic conditions or medication intake affecting BMD or PD severity, postmenopausal women, those with recent disorders, those treated with NSAIDs, HRT, or other bone metabolism-modifying treatments, smoking females, those with edentulous, systemic lupus, rheumatoid arthritis, periodontal therapy, alcohol use, and neoplastic diseases.

Inclusion criteria

Postmenopausal women without osteoporosis, with good general health, are considered a control group. Postmenopausal women with osteoporosis, and chronic periodontitis at least 4 sites with deep periodontal pockets depth of ≥4 mm and 1-2 mm or more of clinical attachment loss (CAL)

Dentistry 3000
Vol 13 No 1 (2025) DOI 10.5195/d3000.2025.813

Identification of OP

All participants included in this study were scanned by densitometry (central DEXA Stratos 3D). Depending on this scan woman were diagnosed as OP, osteopenia or normal healthy (non–osteopenia, non-osteoporotic). DEXA scan type (Stratos 3D) used to obtain T-score at spine (L1-L4), neck, G.T, and Inter of femur (Total hip). BMD rate is compared with the mean of a healthy young people expressed in the number of standard deviations (SD), a name defines as a T-score. T-score of -2.5 or fewer was diagnosed as OP, where as a T-score of -1 to -2.5 was diagnosed as osteopenia. According to the WHO definition, osteoporosis is present when the T-score is at least - 2.5 SD.

Collection of Serum Sample

Venous blood samples of 5 milliliters (mL) were drawn from all subjects in a disposable plane tube; the samples were placed in a cooling package for inhibition of microorganism growth. Each donor number and group was written on each corresponding tube, and then the blood was allowed to clot at 37C for 15-20 minutes, and then centrifuged at 3000 rpm for approximately 10-15 minutes then serum were obtained. The laboratory tests were done in the laboratory of Baqubah teaching hospital.

Assessment of Probing Pocket Depth (PPD)

It is defined as the millimeters distance from gingival margin to the most apical penetration of periodontal probe inserted into the gingival crevice or periodontal pocket without pressure or force. The considered locations were buccal, palatal/lingual, mesio buccal and disto buccal line angles [8].

Assessment of Clinical Attachment Loss (CAL)

It is the distance from the CEJ to the location of the inserted probe tip (bottom of gingival crevice or periodontal pocket), the level of the CEJ could be determined by feeling it with probe. The measurements were made at four surfaces of each tooth except 3rd molars by using Marquis periodontal probe. The distance was measured indirectly by subtracting the distance from the gingival margin to the CEJ from PPD. In some cases, when there was gingival recession, loss of attachment was measured either directly or by adding the distance from the gingival margin to the CEJ to the PPD. Tooth expulsion may occur due to tooth demolition, crown coverage, extended fillings, bad carious teeth, or heavy calculus covering teeth.

Biochemical assays

The supernatant was separated using micropipette into two eppendorf tubes and stored at -20° C in deep freeze for later analysis by Enzyme Linked Immunosorbent Assay (ELISA) kit for quantitative determination of OPG, and calcium detected using full automated device.

Statistical analysis

Statistical analysis was performed with IBM® SPSS® (ver. 26. SPSS Inc., IBM Corporation, Armonk, NY, USA). Descriptive data were presented by mean, standard deviation, simple linear regression graph. Pearson correlation analysis was used to describe the association between numerical variables within each group. Shapiro-Wilks test was used to evaluate the normality of the distribution of data. ANOVA test used to evaluate the difference between k related mean with Tukey HSD, Independent t test used to compare means between two groups, Dun test for multiple comparisons with control. Receiving Operating Characteristic Curve (ROC) for diagnostic

Dentistry 3000
Vol 13 No 1 (2025) DOI 10.5195/d3000.2025.813

capability as for discrimination or differentiation is varied.

Results

In the present study, it was found that there was a statistically significant difference between both groups regarding age while there was insignificant difference between both groups regarding menopause duration, and BMI (Table 1).

Table 1. Demographic data of the study groups.

	Control		OP		P-value
	Mean	±SD	Mean	±SD	
Age	48.512	3.656	50.512	4.583	0.07
Years since menopause	7.067	3.258	8.533	2.532	0.06
BMI	33.656	3.549	31.657	4.543	0.065

PPD and CAL Findings

In the present study, it was found that PPD was decreased in ALN12 group compared to ALN6 and OP groups (p=0.000). Additionally, CAL demonstrated declining in OP in comparison to ALN6 and ALN12 groups (p=0.000) (Table 2).

Table 2. PPD and CAL in PD.

Variable	Mean	±SD	P-value
PPD (OPp)	7.393	0.515	0.000
PPD (ALNp6)	6.327	0.489	
PPD (ALNp12)	5.307	0.438	
CAL (OPp)	7.947	0.673	0.000
CAL (ALNp6)	7.133	0.719	
CAL (ALNp12)	6.087	0.595	

Serum biomarkers

In the present study, it was found that there was a statistically significant difference between case and control groups regarding OPG levels where mean OPG in control group was higher than in OP. Furthermore, mean OPG in remaining subgroups (ALN6, ALN12) was increased after six and one year of ALN treatment as

Dentistry 3000
Vol 13 No 1 (2025) DOI 10.5195/d3000.2025.813

compared to control group (6.967, 11.253 and 3.417, respectively).

For serum calcium, it was found that there was a statistically significant difference between cases and controls regarding Ca level where mean level in control group was higher than in OP (9.613 and 7.027, respectively). After six months of treatment, there was a statistically significant difference among groups where mean of ALN6 levels were still lower than control group (8.260 and 9.613, respectively). After 12 months, there was a statistically significant difference among groups where mean calcium levels in ALN12 groups were higher than control group (10.253 and 9.613, respectively) (Table 3).

Table 3. Biomarker comparisons.

	OPG		Calcium	
	Mean	±SD	Mean	±SD
Control	3.417	0.432	9.613	0.637
OP	1.533	0.522	7.027	0.219
ALN6	6.967	0.694	8.260	0.422
ALN12	11.253	1.120	10.253	0.300
P-value	0.000		0.000	

Serum Osteoprotegrin (OPG)

In the present study, it was found that serum OPG concentration increased from baseline OPG (OP) until 6 months (ALN6) then after 12 months (ALN12) of treatment with significant difference. Additionally, mean of OPG concentration in periodontitis state (PD) among study groups (OP, ALN6, and ALN12) with highly significant difference between them (p=0.000) (Table 4).

Dentistry 3000
Vol 13 No 1 (2025) DOI 10.5195/d3000.2025.813

Table 4. OPG among people with periodontitis.

Time	PD	
	Mean	±SD
OPG (OP)	1.533	0.522
OPG (ALN6)	6.967	0.694
OPG (ALN12)	11.253	1.120
P-value	0.000	

Serum Calcium Levels

There was a significant difference among groups with calcium levels increased from baseline to 12 months (Table 5).

Table 5. Calcium in periodontitis.

Time	PD	
	Mean	±SD
OP	7.027	0.219
ALN6	8.260	0.422
ALN12	10.253	0.300
P-value	0.000	

Correlation between biomarkers and PPD and CAL

There were not significant correlations except for after 12 months in periodontitis patients (Table 6).

Dentistry 3000
Vol 13 No 1 (2025) DOI 10.5195/d3000.2025.813

Table 6. Correlation between biomarkers with PPD and CAL.

Variable	OPG0		OPG6		OPG12		Ca0		Ca6		Ca12	
	r	p	r	p	r	p	r	p	r	p	r	p
OP	0.328	0.233					0.306	0.267				
ALN6			0.050	0.860					0.130	0.644		
ALN12					0.381	0.162					-0.030	0.915
OP	0.125	0.658					-0.160	0.570				
ALN6			0.286	0.302					0.386	0.155		
ALN12					-0.315	0.253					0.465	0.081

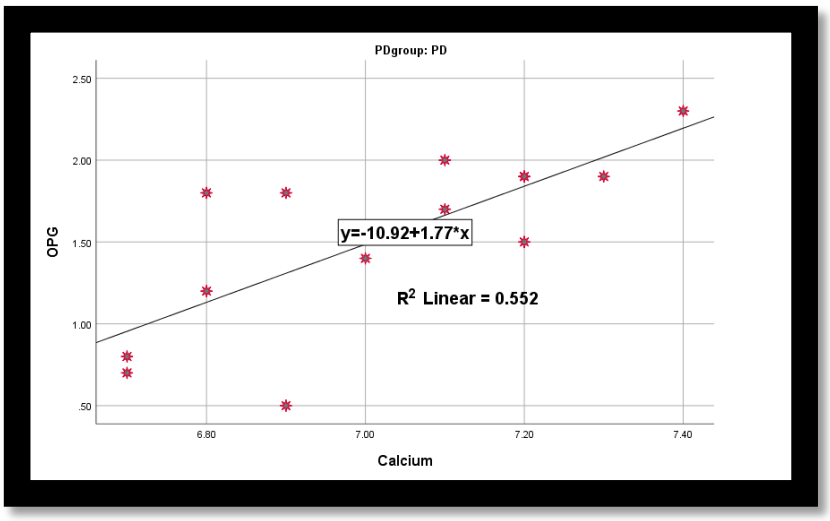
Correlation between biomarkers and time

There was a positive correlation between OPG and calcium at baseline (Table 7 and Figure 1).

Table 7. Correlation between biomarkers among study groups and time.

PD-group		Ca0		Ca6		Ca12	
		r	p	r	p	r	p
PD	OP	0.743	0.002				
	ALN6			0.110	0.697		
	ALN12					0.091	0.747

Dentistry 3000
Vol 13 No 1 (2025) DOI 10.5195/d3000.2025.813



`Figure 1. Correlation between OPG and calcium in patients with periodontitis.

Discussion

Osteoporosis is one of the risk factors that have been implicated in the progression of periodontal disease [9]. Several studies showed that there is a relationship between oral and systemic bone loss as well as an association of osteoporosis with periodontal diseases [10,11]. Estrogen hormone plays vital protective effect as anti-resorptive agent on alveolar bone, since it improves OPG production and decrease RANKL expression, therefore estrogen deficiency after menopause considered as a key feature for development of osteoporosis, progression of periodontitis, alveolar bone resorption, and osteoporotic changes in the jaw [12]. In the present study, it was found that there was there was a significant difference between both groups regarding age while there was insignificant difference between both groups regarding menopause duration, and BMI. The development of OP is predisposed by the apparent degradation of the components, organization, and functions of bone because of age progression. Age, in conjunction with intrinsic and extrinsic factors, accelerates the loss of bone mass because of uneven bone remodeling. Consequently, bone resorption exceeds bone creation, a phenomenon that is particularly evident in women after menopause, when estrogen is no longer produced [13]. There are several studies that proved the correlation between age progression and OP [14-16]. In line with our results, Rocha et al. revealed that there was insignificant difference between case and control group regarding age where the mean age in case group was 57.8 ± 2.9 while the mean age in control group was 58.0 ± 2.8 [17]. Additionally, Laza et al. included 64 patients in the study who were divided equally into two groups patients who did not follow systemic therapy with bisphosphonates and patients who followed systemic therapy with bisphosphonates (alendronate 70mg/week, for 12 months) [18]. Numerous studies have demonstrated a positive relationship between BMI and BMD. Walsh and colleagues reported a significant correlation between BMI and bone mineral density (BMD) and proposed that potential mechanisms may include

Dentistry 3000
Vol 13 No 1 (2025) DOI 10.5195/d3000.2025.813

increased loading and heightened aromatase activity [19]. Another study revealed that each unit increase in BMI was linked to a 0.0082 g/cm2 increase in BMD ($p < 0.001$) [20]. Elderly women were more vulnerable to OP due to menopausal transition, in which there is dropping in estrogen hormone that led to acceleration of bone resorption [21]. In contrast, Kerksick et al. found that women with adequate calcium and vitamin D intake experienced minimal differences in bone health, regardless of menopause duration [22]. In the present study, it was found that there was a highly significant difference among study groups (OP, ALN6, and ALN12) regarding mean of OPG concentration in periodontitis state (PD). Lopez et al. suggested that early differences in periodontal disease severity, such as the presence of bone loss in periodontitis, may not be fully reflected in OPG levels at baseline [23]. Kumar et al. reported that periodontitis patients may have slightly lower OPG levels at baseline, because of more pronounced bone resorption associated with chronic inflammation in deeper periodontal pockets [24]. Peacock et al. observed that baseline OPG levels might differ based on systemic factors, such as osteoporosis or age, which could skew initial readings. OPG levels significantly increased in periodontitis patients after treatment with bisphosphonates, with the greatest improvements seen within the first six months and continued stabilization after twelve months [25]. Sedghizadeh et al. confirmed that alendronate treatment significantly elevates OPG levels, particularly in patients with bone loss, as it helps to balance the RANKL/OPG ratio, favoring bone preservation [26]. Özden et al. showed that there was a significant increase in serum level of OPG after 3-6 months of BP treatment in patients with postmenopausal OP and periodontal disease [27]. Conversely, Verde et al. revealed that there was no significant difference in OPG level in GCF after BPs treatment [28]. According to clinical observation in postmenopausal women and experimental animal studies, estrogen deficiency is a critical factor in the development of OP and low alveolar bone density. This is because estrogen regulates the construction of OPG and RANKL by PDL cells, which are characterized by estrogen receptors. Consequently, estrogen can serve as a critical anti-resorptive agent in the alveolar bone [29]. ALN has been revealed as modulators of OC function and bone metabolism as a result it may well inhibit the development of OP. Additionally it is able to induce the production of mediators that inhibit osteoclastogenesis and influences the RANKL/OPG system by increasing OPG and declining RANKL production. It was also able to maintain early osteoblastogenesis and reduce in vitro prostaglandin synthesis. Moreover, it diminishes RANKL secretion by gingival fibroblast, thus reduce the risk of periodontitis [30]. Lopez et al. suggested that periodontal disease, particularly in its more advanced stages (such as periodontitis), could lead to mineralization imbalances, which may explain lower calcium concentrations [23]. Peacock et al. found that bisphosphonate therapy, such as alendronate, increases calcium levels by stabilizing bone mineralization, which can be observed as an elevation in systemic calcium concentrations after six months of treatment [16]. Lopez et al. found that systemic therapy with bisphosphonates significantly reduces pocket depth by stabilizing the inflammatory process, allowing for periodontal tissues to heal and regenerate [23]. The significant reduction in CAL over the course of treatment in the periodontitis

Dentistry 3000
Vol 13 No 1 (2025) DOI 10.5195/d3000.2025.813

group demonstrates the beneficial effects of alendronate therapy, which helps to stabilize the periodontal attachment apparatus by addressing both bone resorption and soft tissue inflammation. In line with our results, Laza et al., Özden et al., and Dutra et al. noted that the PPD decrease was more significant for group underwent systemic alendronate therapy. CAL values followed the same trends as PPD [18,27,31]. The prevalence of PD may be overestimated by the examination of the CAL parameter, as the loss of attachment fibers suggests the cumulative effect of pathological periodontal tissue destruction, as well as protective and destructive immunological processes, as well as non-inflammatory causes such as traumatic brushing and nail biting [32]. It was confirmed that the periodontal damage might be drastically affected by the systemic bone loss in OP [33]. Numerous studies verified significant relationship between the two conditions [33-35]. Shen et al. established greater clinical attachment loss and gingival recession in osteoporotic women as compared to non-osteoporotic one [36]. However, Verde et al. revealed that there were no statistical differences in PPD after BPs treatment of postmenopausal women with OP and periodontal disease [28]. The contrary among studies can be justified by although OP does not initiate PD, it may influence disease pattern through reducing bone mass and density, moreover emerging evidence reported that OP increases susceptibility for PD through the effect of periodontal inflammation that mediated destruction of periodontal tissue due to unbalanced expression of inflammatory cytokines [13]. Randomized clinical trials have shown a significant increase in bone mineral density in postmenopausal women diagnosed with osteoporosis after taking alendronate [37]. In addition, the literature shows that both systemic and local administration of alendronate reduced alveolar bone loss in periodontal flap surgical procedures [38]. Bisphosphonates' main effect on the body is their ability to inhibit osteoclast activity. They act both directly by promoting apoptosis and reducing the recruitment of these cells and indirectly by blocking the secretion of prostaglandins and interleukins by osteoclasts, thus limiting their stimulation [39]. This improvement can be partially attributed to the scaling and debridement procedures of the root surfaces and the oral hygiene instructions provided to the patients in both groups, both at the beginning and throughout the study [40,41]. Rocha et al. support the efficacy of alendronate therapy in improving periodontal status in postmenopausal patients diagnosed with osteoporosis and periodontitis. Research to date has demonstrated the ability of alendronate to reduce bone loss in experimentally induced and naturally occurring animal models of periodontitis [17]. Human clinical trials investigating the effect of bisphosphonate therapy on periodontal parameters have reported significant improvements in periodontal clinical status following bisphosphonate treatment. For example, in a matched case control study of 40 patients with type 2 diabetes and stabilized periodontitis, six months of treatment with alendronate 10 mg/day resulted in notable improvements in alveolar bone height and a significant reduction in gingival bleeding [17]. In contrast to the results obtained in our research, some previous studies have shown that using bisphosphonates to treat periodontal disease may not provide significant benefits. For example, in a retrospective cohort study of a small number of patients with periodontitis that investigated the effect of anti- resorptive

Dentistry 3000
Vol 13 No 1 (2025) DOI 10.5195/d3000.2025.813

therapy on alveolar bone loss, the oral medication groups did not show significant improvements in maintaining alveolar bone levels. The results indicate that OPG was the most effective as it demonstrated the highest ability to differentiate between the two groups. Despite its relatively low sensitivity, OPG still showed significant discriminatory power suggesting that, although OPG is not highly sensitive or specific, it may still provide valuable information in the context of the study, potentially acting as an early indicator or a supplementary diagnostic tool. Calcium low AUC and sensitivity suggest that calcium levels do not significantly contribute to differentiating between the study and control groups and it may not be a useful diagnostic marker in this context. Therefore, OPG is promising biomarkers for differentiation between study and control groups. The findings of this study underscore the complex interplay between osteoporosis and periodontal disease, highlighting the role of biochemical markers as potential indicators of disease progression and treatment outcomes. Alendronate treatment appears to beneficially influence serum levels of OPG, and calcium, contributing to improved clinical periodontal parameters. While OPG shows promise as a biomarker for monitoring bone turnover, the overall improvement in T-scores suggests that achieving optimal bone density may require extended treatment duration or combination therapies.

Conflicts of interest

The authors declare no competing interest.

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Dentistry 3000
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