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# Association between serum 25-hydroxy-vitamin D levels and clinical periodontal markers

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## Abstract

***Aim:*** *Vitamin D (vit-D) has become important for periodontal disease owing to its role in autoimmunity, bone mineral metabolism, and inflammation. Our aim was to determine the relationship between serum vit-D levels, clinical periodontal parameters, and blood serum biomarkers.*

***Materials and methods:*** *The participants were evaluated in 2 groups as chronic periodontitis (n=30) and periodontally healthy patients (n=30). Periodontal parameters and fasting venous blood samples were taken from the patients to assess each patient's periodontal status and for biochemical analyses (vit-D, OPG, RANKL, CTx, TNF-α).*

***Results:*** *TNF-α, OPG, CTx, vit-D levels in chronic periodontitis group were found to be statistically higher than control group. There were positive correlation between TNF-α and CTx, OPG and vit-D, as well as CTx and vit-D levels. Vit-D, OPG mean values of chronic periodontitis group with adequate vit-D levels (>75nmol/l) were found to be statistically significantly higher than inadequate individuals (<75nmol/l) and TNF-α, CTxve RANKL levels were found lower (p<0.001).*

***Conclusion:*** *According to our findings, the poor oral hygiene level in chronic periodontitis patients was the main factor strongly associated with chronic periodontitis. Vitamin D levels significantly increased the serum levels of OPG that caused a reduction in levels of RANKL. So, 25-OH vit D was effective in the pathogenesis of chronic periodontitis. However, further studies are needed for better understanding of the impact of vit-D deficiency on periodontal diseases.*

***Keywords:*** *25-OH vitamin D; chronic Periodontitis; RANKL; osteoprotogerin; C- terminal telopeptide; TNF-α*

## Introduction

Periodontitis is an inflammatory disease of tooth-supporting tissue that affects a majority of the population, especially the adult population [1]. Periodontitis is characterized by progressive periodontal ligament and alveolar bone loss with increased pocket depth, recession, or both, ultimately leading to tooth loss if left untreated [1,2]. Historically, periodontitis had been primarily considered an inflammatory disease of the tooth-supporting tissues caused by a specific group of microorganisms. More recently, inflammatory and immune responses have been identified as being critical in the pathogenesis of periodontitis, and thus focus had been directed toward the identification of the determinants of the local host response to bacteria and bacterial products [1,3]. This relationship extends beyond the oral cavity to include hormonal changes, diabetes, stress, genetic susceptibility, smoking, alcohol consumption, and other lifestyle factors [4]. Eating habits and low intake of specific nutrients have also been associated with periodontitis [5].

Vitamin D (vit-D) has been shown to play an essential role in bone mineral homeostasis. Further, in its active form, 1,25-dihydroxyvitamin D3 [1.25-(OH)2D3], it may act as a bioactive protein promoting the formation of new bones [6]. Vit-D is a secosteroid hormone believed to potentially influence the risk of periodontal disease through the following three mechanisms: maintenance of oral bone health, anti-inflammatory activities, and anti-microbial activities [7]. In a previous research, vit-D has been shown to inhibit the monocyte production of pro-inflammatory cytokines,interleukin (IL)-1B and tumor necrosis factor-α (TNF-α), that play crucial roles in the pathogenesis of periodontitis by impairing wound healing and inducing bone resorption [8]. It is well established that 25-hydroxyvitamin D3 (25(OH)D3), the storage form of vit-D, plays an important role in bone mineralization and in the modulation of periodontal inflammation [9,10]. Although vit-D seems to be important and protective against periodontitis, few studies have investigated the protective effects of vit-D against periodontitis.

Given that one of the most important clinical features of periodontitis is bone destruction, interest has been focused on whether bone metabolism is altered during the development and progression of periodontitis. Moreover, vit-D has become important for periodontal disease owing to its role in autoimmunity, bone

mineral metabolism, and inflammation. Our aim was to investigate the relationship between serum vit-D levels, clinical periodontal parameters, and blood serum biomarkers.

## Material and methods

### Study design and ethical approval

The study was a non-blinded, cross-sectional, clinical study (Clinical Trial number: NCT03088488). Signed, informed consent was obtained from each study participant. The study was performed according to the principles of the Declaration of Helsinki and was approved by the Clinical Research Ethics Committee of Ordu University (No: 2015/3). Considering the study conducted by Balcı Yüceet al. [11], a sample size of 30 was determined for each group, according to the power analysis and sample size test for alpha = 0.05 and test power of 90%.

### Subjects

Sixty patients (35 women) aged 25-45 years (mean ± standard deviation: 30.8 ± 4.9 years) who had presented to our faculty for periodontal and other dental problems and consented to participate were enrolled in the study. Participants who had undergone antibiotic and periodontal treatments within the previous 3 months, showed evidence of a systemic disease, were allergic to any drugs such as a local anesthetic agent, had malocclusion or any parafunctional habit, smoked, or had <20 natural teeth were excluded from the study.

Patients were divided in to 2 groups of 30 patients each, as follows:

- Group 1 – subjects with healthy periodontal status
- Group 2 – subjects with untreated chronic periodontitis (indicted by radiographic evidence of bone loss and clinical attachment loss >5 mm in more than six teeth)

### Specific objectives

The null hypothesis was that vit-D level is lower in the chronic periodontitis patients and that vit-D deficiency is a risk factor for chronic periodontitis.

### Clinical evaluation of periodontal health

The plaque index (PI), gingival index (GI), probing depth (PD), and clinical attachment level (CAL) of teeth were measured by passing an explorer tip gently within the sulcus on the tooth's mesial, distal, buccal, and lingual surfaces using a manual probe (Hu-Friedy Manufacturing Inc., Chicago, IL, USA).

### Laboratory evaluations

In this study, fasting venous blood samples were drawn for all patients at the time of taking clinical measurements. The sample tubes were centrifuged with a centrifuge (NF 1200R, Nuve, Ankara, Turkey) at 4000 rpm for 10 min. The serum samples were then stored at -80°C until all samples were collected.

Human TNF-α (eBioscience), human total C-telopeptide (CTx-1) (Elabscience), human soluble receptor activator of nuclear factor kappa-B ligand (sRANKL) total (Biovendor), human osteoprotegerin (OPG) (eBioscience), and 25(OH)-vit-D direct (Immundiagnostic) kits were used for assaying the serum concentrations of TNF-α, CTx, RANKL, OPG, and 25-OH vit-D, according to the manufacturers' instructions, using the solid phase sandwich enzyme-linked immunosorbent assay (ELISA) method (Biotek ELx800 ELISA reader, Biotek ELx50 ELISA washer/ BioTek Instruments, Inc., Vermont, USA).

### Statistical analyses

All statistical analyses were performed using a computerized statistical software program (SPSS 11.5 for Windows, SPSS Inc., Chicago, IL, USA). Student-t test was used to compare the normally distributed quantitative parameters of the two groups. Pearson's correlation analysis was used to determine the relationship between periodontal health and the levels of serum biomarkers. Data are presented as the mean ± standard deviation (SD) values, and the level of statistical significance was set at 5% for all analyses.

## Results

### Baseline demographic and lifestyle characteristics of patients

The investigation was carried out on 60 patients, and all participants completed the study. Demographic details and clinical dental variables of the patients of both groups, according to their age, teeth brushing practice, and sex are shown in table 1.The average number of teeth was not significantly different in the patients of the two groups ($p>0.05$); however, the average age and frequency of brushing teeth were significantly different ($p<0.05$).

Tables 2 and 3 show the distribution of mean PPD and mean CAL according to selected potential risk factors. A total of 253 individuals (44,0%) showed a mean PPD of ≥4 to <6.00 mm and 180 (31.3%) had a mean PPD of >6.00 mm. Similarly, 103 individuals (17.9%) showed a mean CAL of 3-4.0 mm and 386 (67.1%) showed a mean CAL of ≥5.0 mm.

### Clinical and laboratory findings

Periodontal parameters of the subjects are shown in Table 1. There were statistically significant differences in the clinical periodontal scores (PI, GI, CAL, and PD) of the groups ($p<0.05$). The values of these measurements were higher for Group 2 patients than for the Group 1 (control group) patients.

Serum TNF-α, OPG, CTx, RANKL, and vit-D levels of chronic periodontitis patients and healthy subjects are given in table 1. TNF-α, OPG, and CTx levels of the chronic periodontitis group were statistically higher than those of the control group ($p<0.05$). Vit-D levels of the chronic periodontitis group were statistically higher than those of the control group ($p<0.01$), and there was no statistically significant difference between the RANKL levels of the groups ($p>0.05$).

The inter-relationships of the serum TNF-α, OPG, CTx, RANKL, and vit-D levels are given in Table 2. There were positive correlations between TNF-α and CTx ($r=0.178$; $p=0.017$), OPG and vit-D ($r=0.215$; $p=0.003$), as well as CTx and vit-D levels ($r=0.229$; $p=0.003$). Although the serum OPG, CTx, and RANKL levels were negatively correlated to each other, the association was not statistically significant ($p>0.05$).

| | Group 1 (n: 30) | Group 2 (n: 30) | p |
|---|---|---|---|
| **Sex (n)**<br>Female<br>Male | <br>19<br>11 | <br>16<br>14 | |
| **Age** | 27.7±2.6 | 36.0±5.7 | <0.001 |
| **Tooth Brushing (n/day)** | 1.63±0.55 | 0.25±0.25 | <0.001 |
| **Number of teeth** | 26.16±2.01 | 24.05±2.11 | 0.09 |
| **Periodontal Parameters**<br>PI<br>GI<br>PD<br>CAL | <br>0.65±0.30<br>0.50±0.25<br>1.98±0.23<br>1.99±0.22 | <br>1.93±0.37<br>1.83±0.35<br>3.85±0.73<br>4.23±0.78 | <br><0.001<br><0.001<br><0.001<br><0.001 |
| **TNF-α (pg/ml)** | 3.48±1.80 | 4.52±2.68 | 0.013 |
| **OPG (pg/ml)** | 95.46±39.35 | 130.68±74.41 | 0.025 |
| **CTx (ng/ml)** | 0.16±0.04 | 0.18±0.07 | 0.014 |
| **RANKL (pmol/L)** | 446.88±502.18 | 432.64±426.90 | 0.872 |
| **Vit-D (nmol/L)** | 57.34±12.61 | 71.13±13.73 | <0.001 |
| **OPG/RANKL** | 0.39±0.24 | 0.35±0.22 | 0.459 |

***Table 1.*** *Demographic details, clinical, periodontal and serum variables in patients*

| | OPG | CTx | RANKL | Vit-D |
|---|---|---|---|---|
| **TNF-α** | 0.14 | **0.178*** | 0.147 | 0.107 |
| **OPG** | | -0.05 | -0.72 | **0.215*** |
| **CTx** | | | **-0.053** | **0.229*** |
| **RANKL** | | | | 0.087 |

**: Correlation is significant at the p<0.05 level*

***Table 2.*** *The relationship between the serum variables for all patients (n: 60)*

| | OPG | CTx | RANKL | Vit-D |
|---|---|---|---|---|
| **TNF-α** | 0.103 | 0.031 | 0.035 | 0.025 |
| **OPG** | | -0.12 | -0.128 | **0.262*** |
| **CTx** | | | 0.082 | 0.132 |
| **RANKL** | | | | 0.018 |

**: Correlation is significant at the p<0.05 level*

***Table 3.*** *The relationship between the serum variables in chronic periodontitis patients (n:30)*

| | | VITAMIN D LEVELS | | |
|---|---|---|---|---|
| | | **Insufficient (<75nmol/l)** | **Sufficient (>75nmol/l)** | **p** |
| N | Group I<br>Group II | 26<br>19 | 4<br>11 | |
| PI | Group I<br>Group II | 0.75±0.42<br>1.93±0.42 | 0.53±0.39<br>1.92±0.28 | 0.326<br>0.925 |
| GI | Group I<br>Group II | 0.67±0.31<br>1.90±0.36 | 0.62±0.12<br>1.70±0.32 | 0.744<br>0.145 |
| PD | Group I<br>Group II | 2.00±0.22<br>3.84±0.81 | 1.89±0.32<br>3.87±0.61 | 0.394<br>0.908 |
| CAL | Group I<br>Group II | 2.00±0.21<br>4.33±0.87 | 1.89±0.31<br>4.24±0.66 | 0.38<br>0.766 |
| Vit-D | Group I<br>Group II | 54.32±10.74<br>57.36±4.91 | 77.01±2.75<br>85.53±7.80 | <.001<br><.001 |
| TNF-α | Group I<br>Group II | 3.34±1.56<br>4.93±2.84 | 4.44±3.19<br>2.58±0.92 | 0.266<br><.001 |
| OPG | Group I<br>Group II | 96.81±41.53<br>100.79±21.68 | 86.71±27.12<br>186.12±81.41 | 0.644<br><.001 |
| CTx | Group I<br>Group II | 0.15±0.04<br>0.20±0.09 | 0.18±0.0.04<br>0.14±0.01 | 0.219<br><.001 |
| RANKL | Group I | 375.23±131.66 | 912.61±770.0.3 | 0.046 |

***Table 4.*** *Distribution of the periodontal and serum variables' values according to the vitamin D levels in patients*

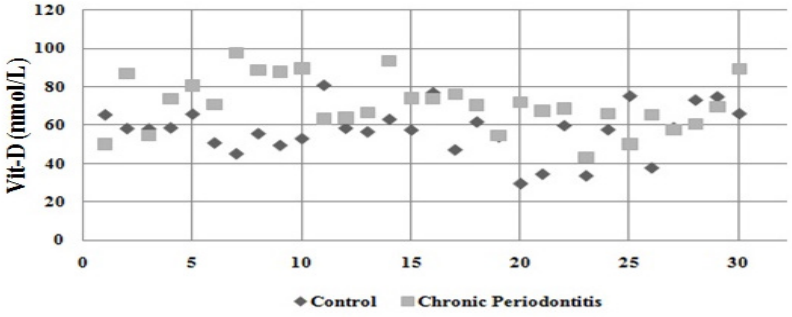


***Figure 1.****Vit-D levels of chronic periodontitis patients and healthy subjects*

| | PI | GI | PD | CAL |
|---|---|---|---|---|
| **TNF-α** | 0,185* | 0,191* | 0,104 | 0,090 |
| **OPG** | 0,162 | 0,058 | 0,094 | 0,070 |
| **CTx** | 0,198* | 0,226* | 0,066 | 0,095 |
| **RANKL** | -0,086 | -0,015 | -0,072 | -0,074 |
| **Vit-D** | 0,354** | 0,361** | 0,412** | 0,405** |

PI: Plaque Index; GI: Gingival Index; PD: Probing Depth; CAL: Clinical Attachment Level
*: Correlation is significant at the p<0.05 level

**: Correlation is significant at the p<0.01 level

***Table 5.*** *The relationship between the serum and clinical periodontal variables for all patients*

The inter-relationships among the serum TNF-α, OPG, CTx, RANKL, and Vit-D levels of the chronic periodontitis group are given in table 3. There was a positive correlation between OPG and Vit-D (r=0,262; p<0.05). Although the serum OPG, CTx, and RANKL levels were negatively correlated to each other, the association was not statistically significant (p>0.05).

Comparisons of the distribution of blood serum levels and periodontal parameters of individuals according to their vit-D levels [10] are given in table 4. Vit-D, OPG mean values of chronic periodontitis group with adequate vit-D levels (>75nmol/l) were found to be statistically significantly higher than inadequate individuals (<75nmol/l) and TNF-α, CTxve RANKL levels were found lower (p<0.001). There was no statistically significant difference between the periodontal parameter levels of individuals according to their vit-D levels (p>0.05). The relationships between the serum TNF-α, OPG, CTx, RANKL, and vit-D levels as well as the clinical periodontal variables are given in table 5. There was a positive correlation of TNF-α with PI and GI (p<0.05), CTx with PI and GI (p<0.05), as well as Vit-D with PI, GI, PD, and CAL (p<0.01). There was a statistically non-significant, negative correlation between the RANKL level and clinical periodontal findings (p>0.05).

## Discussion

The etiology of periodontal disease has not been fully understood because there is little information about the mechanisms affecting the host response in periodontal diseases, as in other chronic inflammatory diseases. Therefore, studies on the etiopathology of periodontal diseases are limited to the assessment of the role of the host response in disease pathogenesis [12]. Recently, the role of vit-D in bone mineral metabolism [13] has gained attention in terms of its association with periodontal disease because of its role in inflammation [14] and autoimmunity [15]. Thus, our study is an important research that investigated the relationship of vit-D levels with other cytokines, mediators, and levels of periodontal health parameters and compared the association of vit-D levels with periodontal health in healthy individuals and those with chronic periodontitis. In addition, we also studied the effects of RANKL and OPG levels on bone destruction along with an investigation of the clinical parameters. To the best of our knowledge, this is the first study that investigated the relationship between periodontitis and vit-D levels in a Turkish population.

Vit-D synthesis depends on many factors owing to the influence of ultraviolet (UV)-B rays according to a subject's age, pigmentation, use of sunscreen creams, dressing style, and exposure to sunlight from behind a glass [13]. Geographical location, seasons, and daytime sunshine are important factors affecting vit-D synthesis [13]. Therefore, we conducted our study in December, January, and February to standardize the vit-D synthesized through exposure to sunlight and minimize the differences in vit-D synthesis among individuals. The mean serum vit-D level of the entire study population was 63.16 ± 12.89 nmol/L, and a majority of them had vit-D deficiency.

Currently, to understand the pathogenesis of periodontitis, it is important to investigate the mediators and cytokines involved in bone destruction. Increased levels ofIL-1, IL-6, prostaglandin E2 (PGE2), and TNF-α were detected in the gingiva in patients with periodontitis [16]. Recently, cytokines (RANKL, RANK, and OPG receptors) related to the TNF family have been identified in the mechanism of bone destruction [17]. OPG inhibited bone destruction of osteoclasts, and its biological effects on the bone tissue were reversible by the action of RANK/RANKL [18]. Thus, the presence of OPG is necessary for the preservation of physiological bone mass [19].

In our study, when we compared the serum levels of TNF-α, OPG, CTx, and RANKL, we found that TNF-α, OPG, and CTx levels of chronic periodontitis patients were significantly higher than those of the healthy patients (p<0.05). The mean RANKL level of the chronic periodontitis group was lower than that of the healthy group; however, this difference was not statistically significant (p>0.05). We concluded that increased levels of TNF-α and CTx in patients with chronic periodontitis may be due to bone destruction for immune system activation in this disease, and the increase in the OPG levels may have been caused by the low RANKL levels that compensated for the rise in the RANKL levels.

Vit-D influences bone and mineral metabolism, inflammation, and immunological system; thus, our main aim was to examine the vit-D levels of individuals with chronic periodontitis and those with healthy periodontal tissues to determine the relationship of vit-D levels with clinical parameters and blood serum biomarkers. A previous study reported that the relationship of serum 25 (OH) D level with deep periodontal pockets (≥4 mm) and gingival bleeding areas was not statistically significant. Thus, serum 25 (OH) D was not associated with the periodontal status [20]. However, periodontal destruction and low serum vit-D levels were associated in individuals with type 1 diabetes mellitus [21], pregnant women [10], osteoporotic women, postmenopausal women [22], and chronic obstructive pulmonary disease patients [23]. In an experimental study, individuals with adequate vit-D levels showed better healing capability after periodontal surgery than those with vit-D deficiency [24]. In another study, 1-year calcium (Ca) (≥1,000 mg/d) and vit-D (≥10 μg/d) supplementation were found to have a positive effect on periodontal health, and vit-D intake was inversely associated with severe periodontal disease and alveolar bone loss [25]. Dietrich et al. [26] reported an inverse association between gingivitis, periodontal attachment

loss, and serum 25 (OH) D levels. Alshouibi et al. [25] found no association between vit-D uptake and periodontal status in an adult population with high vit-D levels. Vit-D level is important for good periodontal health in pregnant women because it plays an important role in bone metabolism and immune activities [27]. Vit-D deficiency also has a vital role in the development of periodontal diseases and tooth loss not only in pregnant women, but also in non-pregnant women [26]. Thus, the question is whether the association between periodontitis and serum 25 (OH) D depends on the causal relationship or whether serum 25 (OH) D deficiencies is one of the main causes of periodontal destruction or a factor in its progression.

A statistically significant correlation was found between the OPG and vit-D levels of the subjects ($p<0.05$) and although OPG, CTx, and RANKL levels were negatively correlated, the association was not statistically significant ($p>0.05$). This finding was in keeping with a previous report that also reported an increase in the OPG levels concurrently with a rise in vit-D levels [11]. Thus, a mechanism to prevent bone destruction and restore the balance between the synthesis and destruction of bones was identified. As the OPG level increased, RANKL synthesis was inhibited, and CTx levels were reduced.

In the studies investigating the relationship between vit-D levels and periodontal diseases, lower serum vit-D levels were associated with periodontitis in Puerto Rican adults [28], and vit-D was found to be a potential protector against tooth loss, with the protective effect being partially attributed to its effect on periodontitis in a German population [29]. Another study investigated the relationships between vit-D levels and clinical periodontal parameters in patients with chronic periodontitis and found that patients with the highest serum vit-D levels exhibited less bleeding on probing, better probing depth, less clinical attachment loss, fewer missing teeth, and lower levels of pathogenic bacteria [30].

At the beginning of our study, we expected that vit-D levels of chronic periodontitis patients would be lower; however, we found that the vit-D levels of the chronic periodontitis group were significantly higher than those of the healthy group ($p<0.01$).This suggests that vit-D deficiency or insufficiency is not a major factor in periodontal disease. We also found that the oral hygiene level of an individual was the most influential factor for the onset and progression of the disease owing to the high clinical index values in chronic periodontitis patients.

In patients with chronic periodontitis, the clinical periodontal index values were high, and the blood serum TNF-α and CTx values increased with clinical periodontal destruction, according to the inflammatory response. However, we found that the level of RANKL, a marker of bone destruction, was lower in the chronic periodontitis than in the healthy group. This was attributable to the increased vit-D levels in chronic periodontitis patients and consequently to the increase in the RANKL inhibitor OPG.

Study limitations should be taken into consideration when interpreting the reported results. The expression of RANKL and OPG is modulated by Parathyroid hormone (PTH) regulating osteoclastogenesis. Thus, the differences between the groups in serum might be originated from the PTH levels, which were not unfortunately evaluated in this study. In addition, the major function of serum 25 (OH) D is to maintain serum calcium (Ca) and phosphorus concentrations within normal ranges. When serum calcium levels drop below, PTH increases the synthesis of vitamin D and absorption of calcium from intestine is increased. Inadequate intake of Ca and vitamin D stimulate the PTH production so osteoclastogenesis is occurred. Lack of data in terms of serum P, serum Ca, serum PTH, Vitamin D supplementation intake are the main factors of this study limitations. Thus, it would be good if serum Ca, PTH and the effects of Vit-D support on chronic periodontitis should be evaluated in this study.

## Conclusion

In conclusion, we interpreted that the poor oral hygiene level in chronic periodontitis patients was the main factor strongly associated with chronic periodontitis. There was no difference between the periodontal parameter levels of individuals according to their vit-D levels in chronic periodontitis patients. However, the severity of this destruction was constrained by the increased level of OPG due to the elevated serum vitamin D level and also vitamin D significantly increased the serum levels of OPG that caused a reduction in levels of RANKL. So, 25-OH vit D was effective in the pathogenesis of chronic periodontitis. Additional studies should be performed to expand on our findings and to help correlate bone metabolism biomarkers to periodontal disease occurrence and determine when periodontal disease might progress further. Also, further studies are needed for better understanding of the impact of Vit-D defiency on periodontal diseases or otherwise.

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