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Vitamin D deficiency in patients with aggressive periodontitis

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Abstract

Objectives: Vitamin D deficiency is a frequent health problem worldwide, especially as fewer people spend much time in the sun. Vitamin D deficiency is linked to several infectious and inflammatory conditions, including periodontal disease. However, its role in aggressive periodontitis (AgP) has not been well studied. We evaluated the association between vitamin D concentration and periodontal disease, both AgP and chronic (CP) periodontitis.

Method and Materials: Forty-seven AgP 55 CP and 27 control subjects participated. All patients were tested for serum vitamin D concentration (25(OH)D), parathyroid hormone, and serum bone-related biomarkers (alkaline phosphatases, calcium, and phosphorus) regulated by vitamin D.

Results: The patients with AgP had lower serum 25(OH)D concentration (11.22 ± 4.8 ng/ml) than controls (16.9 ± 6.4 ng/ml) and patients with CP (16.13 ± 8.3 ng/ml; overall p value 0.0002). These associations remained significant after adjustment for age and gender (p = 0.002). No significant differences were observed in any bone-related biomarker among the three groups, and no association was observed with periodontal disease indices.

Conclusions: Our results suggest that vitamin D deficiency may be a potential risk factor for AgP. Given the high prevalence of vitamin D deficiency in AgP patients, routine screening for vitamin D status may be advisable in these subjects.

KEYWORDS
aggressive periodontitis, inflammatory diseases, risk factor, vitamin D deficiency

1 | INTRODUCTION

Periodontal diseases are complex inflammatory destructive disorders of the tissues surrounding and supporting the teeth (Pihlstrom, Michalowicz, & Johnson, 2005). Although bacteria are required for the onset of periodontal disease, the severity and rate of progression are influenced by a number of risk factors, which include age, systemic conditions, smoking, and genetic makeup (Van Dyke & Dave, 2005). Systemic factors such as diabetes mellitus modify the host response to bacterial challenge, resulting in greater susceptibility to disease (Genco & Williams, 2010). Recently, there has been more interest in determining the role of serum vitamin D concentration in inflammatory conditions such as tuberculosis, arthritis, and periodontal disease.

Vitamin D, a fat-soluble biomolecule, is best known for its role in regulating calcium and phosphate metabolism. Vitamin D deficiency causes rickets in children and affects osteomalacia and osteoporosis in adults (Christodoulou, Goula, Ververidis, & Drosos, 2013). However, its role is not limited to bone metabolism but also to other biological processes: cell proliferation, differentiation, and,

especially, immune function (Chun, Liu, Modlin, Adams, & Hewison, 2014; McMahon et al., 2011). The serum vitamin D concentration thus has been associated with infectious and chronic inflammatory diseases. Moreover, inadequate vitamin D stores seem to predispose to hypertension, diabetes mellitus (Pittas, Lau, Hu, & Dawson-Hughes, 2007; Svoren, Volkening, Wood, & Laffel, 2009), cardiovascular diseases (Wang et al., 2008), autoimmune diseases, and cancer (Holick, 2010).

The prototypical example of a link between vitamin D deficiency and susceptibility to infection is tuberculosis (TB; Walker & Modlin, 2009). Prior to the discovery of antibiotics, cod liver oil (Grad, 2004; dietary source of vitamin D) and sunlight exposure (environmental source of vitamin D) were used to treat TB (Venturini et al., 2014). Likewise, the higher incidence of respiratory infection among children with nutritional rickets was noticed by early clinicians. However, at that time, the link was interpreted as being caused by decreased lung compliance secondary to the rib deformities common in severe rickets (Walker & Modlin, 2009). The role of vitamin D in the regulation of immunity did not begin to unravel until much later.

The discovery of vitamin D receptors in immune cells (Bhalla, Amento, Clemens, Holick, & Krane, 1983; Provvedini, Tsoukas, Deftos, & Manolagas, 1983) suggested that these cells are responsive to vitamin D, which may play an important role in the regulation of the immune response. Indeed, vitamin D enhances innate immunity by inducing expression of antimicrobial peptides (Hertting et al., 2010; Wang et al., 2004). It also functions as an anti-inflammatory agent; Zhang et al. (2012) demonstrated that vitamin D attenuates inflammation by inhibiting lipopolysaccharide-induced pro-inflammatory cytokines (interleukin [IL]-6 and tumor necrosis factor [TNF]-α) production in a dose-dependent manner. Furthermore, these cytokines regulate adaptive immune responses by inhibiting lymphocyte proliferation, stimulating monocyte differentiation, and promoting a tolerogenic T-cell response (Aranow, 2011; Griffin, Xing, & Kumar, 2003).

Involvement of vitamin D in the pathogenesis of inflammatory periodontal disease has been the subject of much research over recent years. Interestingly, in a study conducted in Australia, a correlation between increasing tooth loss and geographic latitude was found. In this study, edentulousness rates among 35–44-year-olds in southern states were twice that in similar age groups in the more northerly states (Powell, 1983). One possible explanation for this association is that the southern states are closer to the southern pole in south hemispheres are more likely to have less sun exposure, the primary environmental source of vitamin D. The association between latitude and disease prevalence is also reported for other infectious (MacLachlan, Lavender, & Cowie, 2012) and autoimmune (Dobson, Giovannoni, & Ramagopalan, 2013; Szilagyi, Leighton, Burstein, & Xue, 2014) diseases. Although numerous studies examined the role of Vitamin D in chronic periodontitis (CP), there remains a scarcity of research examining the relation between aggressive periodontitis (AgP) and vitamin D status.

The purpose of the present study was to evaluate the potential association between serum vitamin D and periodontal diseases, namely generalized AgP and CP and whether serum concentrations of bone-related biomarkers (alkaline phosphatases, calcium, and phosphorus) regulated by vitamin D are related to these diseases and measures of periodontal disease.

2 | PATIENTS AND METHODS

Forty seven patients with generalized AgP, 55 patients with generalized CP, and 27 controls were selected from the patient pool of the Department of Periodontology, School of Dental Medicine, Ondokuz Mayıs University, from 2012 to 2013. Diagnosis and classification of periodontal diseases (AgP and CP) was done according to the 1999 American Academy of Periodontology classification (Armitage, 1999) based on clinical and radiographic data. Patients were found to have generalized AgP when they presented with the following: disease onset up to 35 years of age with at least 8 teeth affected (>5 mm in CAL), at least 3 of which were not first molars or incisors, and amounts of microbial deposits inconsistent with the severity of the disease. Subjects were classified as having generalized CP if they satisfied the following criteria: periodontal pocket depth >4 mm, inter-proximal attachment loss of >3 mm, radiographic evidence of alveolar bone loss, attachment loss on more than 8 teeth, and attachment loss consistent with microbial deposits. Control subjects (27 subjects) with no previous or existing evidence of periodontal diseases were recruited from the staff and academic personnel of the Dental Hospital. Subjects who showed neither attachment loss nor a history of periodontitis and with no pocket depths of >3 mm at more than one site were classified as healthy controls.

The nature and purpose of the study were explained to all the subjects, and informed consent was obtained. The study was conducted in accordance with the Declaration of Helsinki. The study protocol had been reviewed and approved by the local ethics committee of the Ondokuz Mayıs University (approval date: 11.08.2011 and no: 2011/368). A fasting venous blood sample was obtained in the morning in a standardized fashion after an overnight fast only from January to May of 2012 and 2013. All patients were tested for serum alkaline phosphatase, calcium, phosphorus, albumin, vitamin D, and parathyroid hormone (PTH).

To assess whether there is an association between vitamin D and different forms of periodontal diseases, we measured plasma 25-hydroxyvitamin D [25(OH)D]. When the skin is exposed to sunlight, the ultraviolet irradiation is converted to previtamin D3 (cholecalciferol) through a photochemical reaction of 7-dehydrocholesterol. Once vitamin D is made in the skin or ingested from the diet, it travels to the liver where it is converted to 25-hydroxyvitamin D [25(OH)D]. The 25(OH)D then is transported to the kidney and is metabolized to its active form 1,25-dihydroxyvitamin D. The circulating 25(OH)2D is a reliable marker of vitamin D status as opposed to 1,25(OH)D (Holick, 2009; Hollis, 2007).

Patients with systemic diseases, smokers, pregnant or lactating women, use of antibiotic or anti-inflammatory drugs within 6 months, periodontal treatment within 12 months, subjects younger than

18 years, patients receiving vitamin D, bisphosphonates, and calcium supplements were excluded.

Patients were given a thorough periodontal examination, including probing depth, clinical attachment level (AL), bleeding on probing (BOP; Ainamo & Bay, 1975), and plaque index (PI; Silness & Löe, 1964).

2.1 | Laboratory measurements

All blood samples were drawn in the morning after overnight fasting. Serum 25(OH) D level (ng/ml) was measured by liquid chromatography-mass spectrometry (LC-MS/MS; München, Germany). LC-MS/MS is an accurate and considered as the gold standard assay by many commentators (Bruce et al., 2013; Farrell et al., 2012; Hollis, 2007). The measurement of serum calcium, phosphate, and parathyroid hormone was analyzed to exclude secondary causes that might affect vitamin D level. PTH was determined by electrochemiluminescence immunoassay with a Cobas moduler E 601 analyzer (Roche Diagnostics, Mannheim, Germany). Serum phosphorus, calcium, and alkaline phosphatase (ALP) levels were measured using standard colorimetric assay (Cobas c701, Roche Diagnostics, Mannheim, Germany). The manufacturer's instructions were followed during the analysis.

2.2 | Statistical analyses

Dichotomous variables are presented as percentages. Continuous variables are expressed as the mean ± standard deviation. Categorical data of two or more groups were compared by the Pearson chi-square test. The continuous variables normally distributed among the three groups were tested using one-way analysis of variance (ANOVA) and adjusted for the effects of significant covariates. Tukey's HSD post hoc test was used for post hoc comparisons. Logistic regression analysis was employed to estimate the associations between the serum 25(OH)D concentration and periodontal disease status, with the mean 25(OH)D value treated as a continuous variable and adjusted for the effects of established risk factors such as age and sex. Statistical analysis was performed using R program (https://www.cran.r-project.org/bin/windows/base), and $p < 0.05$ was considered statistically significant.

Sample size calculation: On the basis of a previous study on vitamin D (Liu et al., 2009), the sample size calculation revealed that 14 patient per group would be necessary to demonstrate an effect size of 0.5 with α of 0.05% and 80% power (GPower 3.1; Faul, Erdfelder, Buchner, & Lang, 2009).

3 | RESULTS

Descriptive data on the demographics of the subjects are presented in Table 1. All subjects were non-smokers. Of the AgP patients, 17 (36%) were male, and of those with CP, 25 (45%) were male. The control group consisted of 16 male patients (59%) patients. The mean age for AgP was 29.87 years (range 21–40 years), for CP 39.43 years (range 30–47 years), and for the control group 30.93 years (range 26–39 years). The patients with CP were significantly older than those in the other two groups ($p < 0.001$), whereas the differences in ages of the generalized AgP and control groups were not.

The means of the clinical measurements are summarized in Table 1. Generally, higher periodontal indices were detected in the AgP group; lower indices were detected in the CP group; and as expected, the lowest indices were found in healthy controls. The AgP patients demonstrated more severe disease, in general, as evidenced by deeper pockets and more attachment loss.

3.1 | Laboratory measurements

The mean serum 25(OH)D concentration was significantly lower (11.22 ± 4.8 ng/ml) in the AgP than in control subjects (16.9 ± 6.4 ng/ml; $p = 0.002$) and CP patients (16.13 ±0.8.3 ng/ml; $p = 0.001$; overall p value 0.0002; Figure 1). When the 25(OH)D concentration was treated as a continuous variable, the value was inversely associated with the presence of AgP ($p < 0.0002$) and adjustment for age and sex did not alter this association ($p = 0.002$). Moreover, we stratify data by gender, in order to compensate for the difference in the gender composition ratios of AgP patients and control group ($p = 0.05$). Means of serum 25(OH)D levels for each cohort were calculated for men and women separately. After stratifying the data by gender, similar to overall analysis, there was statistically significant difference in the mean serum 25(OH)D concentration in AgP patient and control groups among male (AgP 12.54 ± 4.84, control 16.04 ± 6.15; $p = 0.01$) and female patients (AgP 10.47 ± 4.75 control 18.38 ± 6.84; $p = 0.002$).

TABLE 1 Study population characteristics

Clinical parameters	Control (n = 27)	Aggressive periodontitis (n = 47)	Chronic periodontitis (n = 55)
Probing depth	1.61 ± 0.3^{bc}	3.58 ± 1.1^{ac}	3.03 ± 1.0^{ab}
Clinical attachment level	0.00 ± 0^{bc}	4.16 ± 0.6^{ac}	3.31 ± 0.8^{ab}
Bleeding on probing	13%	72%	68%
Plaque index	0.5 ± 0.4^{bc}	1.73 ± 0.7^{a}	1.82 ± 0.8^{a}
Gingival index	0.34 ± 0.3^{bc}	1.67 ± 0.5^{a}	1.55 ± 0.6^{a}
Age mean ± SD	30.93 ± 3.8^{c}	29.87 ± 5.2^{c}	39.43 ± 4.7^{ab}
Gender (n) % men	(16) 59%^{b}	(17) 36%^{a}	(25) 45%

Note. Different letters indicate significant differences ($p < 0.05$).

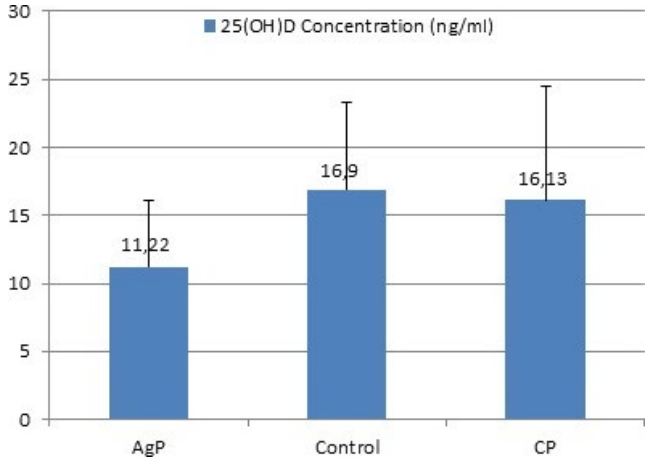

FIGURE 1 Comparison of Serum 25(OH)D level in periodontitis patients and controls. Serum 25(OH)D in patients with AgP was significantly lower than those in healthy controls. When the 25(OH)D concentration was treated as a continuous variable, the value was inversely associated with the presence of AgP ($p = 0.002$). Adjustment for age and sex did not alter this association ($p = 0.002$). On the other hand, no significant differences were observed in patients with CP and healthy controls ($p = 0.88$) [Colour figure can be viewed at wileyonlinelibrary.com]

In addition to disease risk, we also assessed the effect of the serum vitamin D levels on clinical variables such as CAL, PD, BOP, and GI. None of the periodontal indices was associated with the 25(OH)D concentration in either the AgP or the CP patients.

Serum 25(OH)D concentrations in patients with CP were not significantly different from those in control subjects but elevated compared with the AgP group (adjusted $p = 0.001$; Figure 1). As presented in Table 2, no significant differences were observed for any bone-related biomarkers regulated by vitamin D among the three groups such as calcium, phosphate, or alkaline phosphatase. Similarly, no significant difference was observed for the serum PTH concentration among the three groups. Adjustment for age and gender did not alter this association.

4 | DISCUSSION

In the present study, we observed an inverse association of serum 25(OH)D concentration and the risk of AgP. On the other hand, no association was observed between serum 25(OH)D and CP. Adjustment for potential confounders, including sex and age, did not alter this association (Figure 1). Additionally, we examined serum concentrations of bone-related biomarkers: alkaline phosphatases, calcium, and phosphorus. There were no significant differences between the serum concentration of bone-related biomarkers and AgP or CP. Furthermore, none of the tested variables was related to measures of periodontal diseases such as attachment loss, BOP, and PI.

Our results contradict to the findings of a previous study (Liu et al., 2009) that demonstrated that elevated concentrations of serum vitamin D were associated with AgP in Chinese subjects, a finding that would seem to conflict empirically with the anti-inflammatory (Dietrich, Nunn, Dawson-Hughes, & Bischoff-Ferrari, 2005) and antimicrobial (Wang et al., 2004) effects of vitamin D or the low vitamin D status and increased risk of clinical attachment loss (Dietrich, Joshipura, Dawson-Hughes, & Bischoff-Ferrari, 2004) and tooth loss. Indeed, the results of our study are supported by a subsequent case–control study that also showed that the 25(OH)D concentration was significantly lower in AgP patients than in a control group (19.5 ± 2.5 ng/ml and 48.6 ± 4.3 ng/ml, respectively; $p < 0.001$; Zyablitskaya, Atrushkevich, & Mkrtumyan, 2013b). The reason for conflicting findings of these studies is not completely clear; we can only speculate. One possible explanation of the discrepancy between our data and those of Liu et al. (2009) is the seasonal fluctuation of vitamin D status. Since Liu et al. (2009) measured patients from July 2001 to October 2007, the seasonal fluctuation in vitamin D concentrations is likely to confound their results, as vitamin D concentrations fluctuate with the season (Kasahara, Singh, & Noymer, 2013). In order to compensate for seasonal fluctuation, we obtained all blood samples from January to May in 2012 and 2013 when vitamin D is reported to have lowest concentration.

Interestingly, a more careful inspection of Liu et al. (2009) study revealed that the mean serum Vitamin D concentrations were critically low, particularly for the control group. One would expect the vitamin D in healthy individuals without any systemic diseases to be at least close to the normal range. The mean serum vitamin D concentration for the control group in that study (8.65 ng/ml = 21.60 nmol/L) was much lower than the value of 20 ng/ml (50 nmol/L) recommended by the Institute of Medicine (Holick, 2011), with vitamin D insufficiency listed at <20 ng/ml and deficiency at <10 ng/ml. There also may be racial differences in vitamin D metabolism and utilization (Loomis, 1967; Meier et al., 1991; Reasner et al., 1990). A review paper (Zhang, Stoecklin, & Eggersdorfer, 2013) examining vitamin D deficiency in the Chinese population reported that

TABLE 2 Comparison of serum 25(OH)D concentration and related biomarkers among study group

Parameter	Control	AgP	CP	*p*-Value
PTH (pg/ml)	51.26 ± 18.5	57.24 ± 19.2	62.99 ± 23.0	0.46
Calcium (mg/dl)	9.59 ± 0.4	9.60 ± 0.4	9.64 ± 0.4	0.92
Phosphorus (mg/dl)	3.39 ± 0.5	3.54 ± 0.5	3.55 ± 1.0	0.07
A. phosphatase (U/L)	64.33 ± 18.7	64.64 ± 16.7	66.63 ± 23.6	0.90

Note. Age and gender adjusted *p*-values.

deficiency is common in this population. However, the reported vitamin D concentration for the control group in the Liu et al. (2009) study was lower than reported for healthy individuals for the same latitude and race (Zhang et al., 2013).

A follow-up study by the same group (Liu et al., 2010) in the same population of patients found that initial periodontal therapy decreased the plasma and gingival crevicular level of 25(OH)D and IL-1 level, though no change was detected in osteocalcin and IL-6 levels of AgP patients. While these results support a possible role for 25(OH)D in periodontal inflammation, further independent studies are required for verification.

There is biological plausibility for a role of vitamin D deficiency in AgP. Vitamin D may favorably influence periodontal health through anti-inflammatory effects (Dietrich et al., 2005), antimicrobial effects (Wang et al., 2004), or an effect on bone mineral density (Christodoulou et al., 2013). Because periodontal diseases, including the more severe AgP, are infectious, initiated in response to bacterial insult, it is reasonable to suspect that vitamin D deficiency could negatively affect the immune response and thus the periodontium. Vitamin D promotes the innate immune response by activating natural antimicrobial peptides such as defensins (Youssef et al., 2011). Particularly, beta defensin 2 kills *A. actinomycetemcomitans*, an AgP-associated periodontal pathogen (Greer, Zenobia, & Darveau, 2013). Thus, vitamin D deficiency may compromise the ability of the host to combat periodontal pathogens. Moreover, vitamin D not only stimulates the innate immune response to microbial challenge but also attenuates an overzealous adaptive immune response against pathogens (Walker & Modlin, 2009). In AgP, the disease process is postulated to derive from an inappropriate or exaggerated immune response to pathogenic microorganisms (Page, Offenbacher, Schroeder, Seymour, & Kornman, 1997). Therefore, it is possible that vitamin D deficiency contributes to AgP risk by reducing the capacity of the host to prevent an exaggerated immune response.

The role of vitamin D in the pathogenesis of chronic periodontal disease has received much attention over recent years. Epidemiologic studies demonstrated a link between serum vitamin D concentration and chronic periodontitis (Dietrich et al., 2004, 2005 ; Jimenez, Giovannucci, Kaye, Joshipura, & Dietrich, 2014; Miley et al., 2009). An inverse association between serum vitamin D levels and measures of periodontal disease was reported in the elderly (age >50 years; Dietrich et al., 2004), in postmenopausal women (Millen et al., 2013) and pregnant women (Boggess et al., 2011). Additionally, an inverse association between the serum vitamin D concentration and gingival inflammation was also reported in a dose-dependent manner, as measured by bleeding on provocation (Dietrich et al., 2005).

In a large prospective study with 20 years of follow-up (Jimenez et al., 2014), low vitamin D concentrations were associated with a greater risk of tooth loss along with periodontitis. Further support for the role of vitamin D in periodontal diseases comes from clinical trials showing that vitamin D supplementation can reduce tooth loss and attenuate the severity of the periodontal disease or gingival inflammation (Garcia et al., 2011). This association seems consistent across racial or ethnic groups (Abreu et al., 2016; Joseph et al., 2015; Zyablitskaya et al., 2013b).

In the present study, we observed no association between 25(OH)D and CP. This result concurs with previous findings showing no association between CP and vitamin D concentration (Antonoglou et al., 2015; Liu et al., 2009; Zyablitskaya, Atrushkevich, & Mkrtumian, 2013a) or between AL and vitamin D status in younger individuals (Dietrich et al., 2004) or non-smokers (Lee, Je, Won, Paik, & Bae, 2015). Dietrich et al. (2004) showed that the serum vitamin D (25(OH)D concentration is inversely associated with the extent of clinical attachment only in older persons (age >50 years). They proposed that older subjects are more likely to obtain a benefit from vitamin D because of the higher prevalence and extent of AL in the elderly compared with younger subjects. In our study, the CP group consisted of subjects younger than 50 years (age range 30–47 years), corresponding to ages at which no association was observed by Dietrich et al. (2004) Only one small case–control study (Abreu et al., 2016) showed an association between 25(OH)D concentration and CP; however, in this study, no stratification was done by age group, and this study included some subjects older than 50 years with a mean age of 48 years. Therefore, the possibility of the observed association between 25(OH)D and CP might be secondary to a confounding effect of the patients being older cannot be excluded. Interestingly, in another report, lower vitamin D concentrations were associated with measures of periodontal diseases only in current smokers with CP (Lee et al., 2015). Because smoking is an established risk factor for periodontal disease, we conducted our study only in non-smokers. The reason for the association between serum 25(OH)D3 and CP being limited to the elderly or smokers is not clear. However, it is possible that elderly persons and smokers are more susceptible to the effects of vitamin D deficiency, because their immune systems are weaker.

In the current study, we also considered other factors that could directly affect vitamin D status such as parathyroid hormone, calcium, or phosphate concentrations. A complex feedback mechanism between parathyroid hormone and vitamin D plays a role in maintaining mineral homeostasis by modulating calcium and phosphate concentrations in the blood and interstitial fluids. There is an inverse relation between serum parathyroid hormone and vitamin D. Vitamin D deficiency triggers secondary hyperparathyroidism in order to keep serum calcium concentrations in the normal range. In the present study, no association was found between periodontitis and serum PTH concentration. It is possible that 25(OH)D and PTH have statistically independent effects despite the biological link between them. Our result eliminates the possibility that the association between vitamin D status and AgP risk was mediated in part by secondary hyperparathyroidism. This finding confirms a previous report showing no association between the changes in serum PTH and CP in systemically healthy individuals (Antonoglou et al., 2015).

The main role of vitamin D, together with PTH, is the regulation of calcium and phosphate balance in the blood and interstitial fluids (Holick et al., 2011). In addition to PTH, serum calcium and phosphorus concentrations can influence the examined association. But among our samples, the values were within normal limits and showed

no association with CP or AgP (Table 1). These findings also exclude the possibility that serum calcium or phosphate concentrations were driving confounders in the association between periodontal diseases and serum vitamin D.

Vitamin D also regulates the expression of bone-related biomarkers such as ALP and osteocalcin. Serum ALP has been considered a biochemical marker of bone turnover (Garnero et al., 2000). Few studies have been published on the relation between serum ALP and periodontitis. In the present study, serum ALP concentrations were within normal limits for all patients, and no differences in serum ALP were detected between groups. This result is consistent with the previous finding (Gibert, Tramini, Sieso, & Piva, 2003) that there is no significant difference in total serum ALP activity of patients with and without attachment loss. However, there was a significant difference in bone-type serum ALP activity in that study. Similarly, no significant difference in ALP concentration was observed in pre-menopausal women (Hattatoğlu-Sönmez et al., 2008). On the other hand, there is a positive association between periodontal disease and the serum ALP concentration (Caúla, Lira-Junior, Tinoco, & Fischer, 2015; Saito et al., 2003).

The current study was limited by its cross-sectional design. It is not possible to identify the causal relation between periodontitis and vitamin D deficiency. Another limitation in our data was the age difference between control group and CP. While the AgP and control group was compatible in terms of age, there was a statistically significant difference between CP and control group. In order to address this issue, we adjusted our analysis for potential confounders such as age and gender. Consequently, the results should be interpreted cautiously, and larger prospective cohort studies are required to confirm the observed association between serum 25(OH)D and AgP.

In summary, our study showed that lower 25(OH)D concentrations were associated with a higher risk of AgP. This result suggests vitamin D deficiency as a possible risk factor for AgP. Therefore, it is recommended to screen for deficiency with a 25(OH)D concentration in AgP patients.

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AUTHOR CONTRIBUTIONS

E. Ambarcioglu made substantial contributions to acquisition, analysis and interpretation of data Tugrul Kirtiloglu, made substantial contributions to conception and design of study and interpretation of data. A. Öztürk made contributions to analysis and interpretation of data and participate in drafting the article. F. Kolbakır made substantial contributions to acquisition, analysis and interpretation of data Gökhan Acıkgöz made substantial contributions to conception and design of study. R. Colak, MD made substantial contributions to conception and design of study and acquisition of data.

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