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Association of Vitamin D, IL-6, TNF-α, CRP and Periodontal Health Status in the Eastern Black Sea Region

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Abstract

Objective: It is well established that vitamin D deficiency may increase risk of periodontitis, and that supplementation with vitamin D can contribute to maintain periodontal health. Since the Eastern Black Sea Region receives little sunlight due to its location, individuals living in this region don't produce enough vitamin D and these individuals generally have vitamin D deficiency. The goal of this study was to analyze that association of vitamin D and periodontal health status in a study population of the Eastern Black Sea Region.

Methods: In this study, which was planned as a case control study, it was planned to reach a total of 72 samples, with at least 24 samples in each group in the sample calculation. As a result of data collection, 29 individuals with periodontitis, 28 individuals with gingivitis and 25 periodontally healthy individuals, a total of 82 individuals were included in the study. Cytokines in inflamed periodontal tissues have a marked effect on host modulation and onset and progression of periodontal disease. Venous blood samples were collected from the individuals. Periodontal clinical parameters were measured. Serum levels of 1.25(OH)2D3, 25(OH)D, C-reactive protein (CRP), tumor necrosis factor α (TNF-α) and interleukin 6 (IL-6) were assessed.

Results: Periodontally healthy group had statistically significantly lower periodontal clinical parameter values compared to gingivitis and periodontitis group ($p<0.05$). The serum 1.25(OH)2D3 level was lower in the periodontitis group compared to the periodontally healthy group and gingivitis group ($p<0.05$). But there was no statistically significant difference in the periodontitis 10.20 (3.70-29.50) ng/mL, gingivitis 11.35 (5.60-29.50) ng/mL and periodontally healthy groups 9.10 (2.90-55.40) ng/mL in terms of serum 25(OH)D levels ($p>0.05$).

Conclusion: The outcomes of this study support the idea that lower serum 1.25(OH)2D3 level has a negative effect on periodontal health status. Our data suggest that vitamin D supplementation to people living in the Eastern Black Sea Region would be beneficial in reducing the risk of developing periodontal disease. Further studies are needed on this subject.

Keywords: Cytokine, gingivitis, pathogenesis of periodontal disease, periodontitis, 1.25-hydroxyvitamin D

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INTRODUCTION

Periodontal diseases are chronic infectious inflammatory diseases that lead to alveolar bone loss and destruction of periodontal tissues (1). Although the major etiologic factor is bacteria at the onset of periodontitis, many environmental factors, genetic factors and systemic disorders, such as heart disease, diabetes, obesity and metabolic syndrome, play roles in the progression and development of the disease. Periodontal diseases and interactions between these systemic conditions are associated with the inflammatory process related to the common pathophysiological mechanism (2).

Today, periodontal pathogenic microorganisms and virulence factors are known to cause a systemic inflammatory response by mixing into the blood circulation (2). Increased serum levels of acute-phase proteins such as C-reactive protein (CRP), an important indicator of systemic inflammation (3), and other cytokines associated with inflammation, support this association (2). Tumour necrosis factor α (TNF-α) and interleukin 6 (IL-6) are important cytokines in the initiation of systemic inflammation and play a role in the progression and severity of periodontitis (2). In addition, it has been demonstrated by many studies that cytokines such as TNF-α and IL-6 are higher in individuals with periodontitis than in periodontally healthy individuals (4-8).

Vitamin D is a host-derived molecule and has a secosteroid structure that is not only taken into the body after dietary consumption (D2 and D3), but is also produced by a person's own skin after exposure to ultraviolet (UV) radiation from sunlight (D3) (9). Vitamin D2 (ergocalciferol) is the product of the UVB 290–315 mm irradiation of ergosterol. Also it can be ingested as a supplement or with fortified foods (10). Vitamin D3 (cholecalciferol) is produced after the exposure of 7-dehydrocholesterol to UVB radiation in the human epidermis.

The prevalence of vitamin D insufficiency and deficiency is affected by latitude and seasonal changes (11). The prevalence decreases in summer and increases in spring and winter (12). The production of vitamin D is the highest when the sun is at its apex and decreases when the angle narrows. The production of vitamin D in the regions above and below 33˚ latitude is almost non-existent (13.) The eastern Black Sea Region where our study was conducted is located 41° northern latitude. For this reason, there is almost no vitamin D production in winter in eastern Black

Sea Region and vitamin D deficiency is common.

The roles of vitamin D in regulating bone metabolism and inflammatory response, the preservation of serum phosphate and calcium levels, and bone development and continuity suggest that it also has effects on periodontal health. Dietrich et al. (14) suggest that vitamin D has positive effects on gingival inflammation, periodontal diseases and tooth loss. Therefore, sufficient serum levels of vitamin D can be significant in the therapy and prevention of periodontal diseases. The purpose of this study was to analyse that association of vitamin D and periodontal health status in a study population of the Eastern Black Sea Region.

METHODS

Study groups

Design of the clinical trial

This study was planned as a case-control study. It is planned to reach a total of 72 samples, with at least 24 samples in each group, with 95% confidence, 85% theoretical power and 0.4 effect size in the sample calculation. The sample was increased by 20% in case of missing data. As a result of data collection, it was completed with 29 samples in periodontitis, 28 samples in gingivitis and 25 samples in periodontally healthy controls. Analyzes were completed with a total of 82 samples.

This study was approved by the human subjects ethics committee of our university (meeting date: 07 April 2016; Ethics Committee Decision No. 2016/09) with regard to the Declaration of Helsinki. The aim and content of the research were clarified to the individuals included in the study, and voluntary consent forms were signed. Individuals with certain exclusion criteria were not included in the study and a total of 82 participants were included, including 29 periodontitis, 28 gingivitis, 25 periodontally healthy controls.

The volunteers were selected from among individuals who referred for periodontal examination to our faculty. Inclusion criteria for this study; being systemically healthy, not using antibiotics and immunosuppressive drugs for the past three months, not smoking, not receiving periodontal treatment in the past six months, not taking supplemental vitamin D. Individuals who had been systemic diseases, under antibiotic or immunosuppressive medication for the past three months, smokers, periodontal therapy within the past six months, supplementary or additional vitamin D were excluded.

The subjects were divided into three groups according to the 2017 classification of periodontal diseases. The groups were defined as follows: periodontitis group (group 1, n = 29), interdental clinical attachment level (CAL) ≥2 mm, probing depth (PD) ≥4 mm, history of multiple tooth loss, presence of deep

periodontal lesions extending to the apical portion of the root; gingivitis group (group 2, n=28), no CAL, PD ≤3 mm, bleeding on probing (BOP) ≥10%, no radiographic bone loss; periodontally healthy control group (group 3, n=25), no CAL, PD ≤3 mm, minimal BOP (≤10%), no radiographic bone loss. All periodontal examinations and measurements were performed in the November–March period.

Periodontal examination

In the periodontal examination of the mouth, a Williams periodontal probe was used. CAL and PD were measured on six surfaces of each teeth (buccal, mesiobuccal, distobuccal, lingual/palatal, distolingual and mesiolingual) excluding the third molars. PD was measured as distance from gingival margin to the base of pocket. CAL was recorded by measuring the distance between the cement–enamel junction and the base of the pocket. A total of 10–15 s after probing, the amount of bleeding was recorded as bleeding (+) or no bleeding (-) on the four surfaces of the teeth (buccal, palatal/lingual, mesial, distal). The gingival index (GI) and plaque index (PI) (Silness&Löe) were measured by evaluating mesial, distal, buccal and palatal/lingual gingiva of each tooth.

Laboratory analysis

Venous blood samples were collected from the individuals on the day of dental examination. Serum samples were centrifuged and then were separated into tubes, stored at -20˚C until assays. Serum samples' analysis were exercised in accordance with manufacturer's order. TNF-α levels in serum were analyzed by the EASIA method (enzyme-amplified sensitivity immunoassay; DIAsource ImmunAssays S.A., Belgium). The sensitivity of the method was 0.7 pg/mL, and the intra- and inter-study coefficients of variation (CVs) by percentage were 6.3 and 3.3, respectively. 1.25(OH)2D3 levels in serum were analyzed using radioimmunoassay (RIA) method in a Stratec PC-RIA MAS (Germany) auto-analyser. The CRP levels were studied in an Abbott Architect c8000 (USA) auto-analyser with the immunoturbidimetric method, and 25(OH)D vitamin levels were studied in an Abbott Architect i2000 (USA) auto-analyser with the chemiluminescent microparticle immunoassay (CMIA) method. IL-6 levels were studied through an enzyme-labelled chemiluminescent immunometric assay in a Siemens Immulite 2000 Xp (Germany) auto-analyser.

Statistical analysis

Statistical analyses were exercised with SPSS 20 programme (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp). Shapiro–Wilk's was used to investigating the appropriateness of variables for a normal distribution. In the analysis of the differences between the groups because the variables did not comply with a normal distribution were analyzed using Mann–

Whitney U and Kruskal–Wallis H tests. When statistically significant differences occurred in the Kruskal–Wallis H test, intergroup differences were determined with using post-hoc test. The correlations were analyzed using Spearman correlation analysis.

RESULTS

Clinical characteristics of all groups were presented in Table 1. Group 3 had significantly lower BOP, PD, GI and PI values (P<0.05) compared to Group 1 and Group 2. Group 2 had significantly lower BOP, PD, GI and PI values (P<0.05) compared to Group 1.

Table 1: All groups' probing depth (PD), clinical attachment level (CAL), bleeding in probing (BOP), plaque index (PI), gingival index (GI) and age values.

	Group			H	p	Post hoc		
	Group 1	Group 2	Group 3			1–2	1–3	2–3
	Median (min–max)	Median (min–max)	Median (min–max)					
PI	2.75 (2.12–3.00)	1.69 (1.25–2.25)	0.25 (0.12–0.62)	71.3	0.001*	0.035*	0.013*	0.042*
BOP	83.33 (70–100)	70.09 (53.57–87.50)	9 (4.46–19.7)	59.4	0.001*	0.003*	0.001*	0.014*
PPD	4.13 (3.14–5.72)	2.18 (1.46–2.84)	1.14 (1.01–2.28)	70	0.001*	0.039*	0.018*	0.031*
CAL	4.42 (3.21–5.78)	0 (0–0)	0 (0–0)	76.1	0.001*	0.0001*	0.0001*	0.99
GI	2.75 (2–3)	1.75 (1.25–2.25)	0.13 (0.06–0.19)	71.2	0.001*	0.033*	0.019*	0.026
Age	44 (32-57)	35 (28-47)	34 (27-41)	22.80	0.001*	<0.001*	<0.001*	*0.271

PPD (probing pocket depth), CAL (clinical attachment level), BOP (bleeding in probing), PI (plaque index), GI (gingival index)
H, p: H and p values for Kruskal-Wallis test.
*Statistically significant at p<0.05.

Table 2: Distribution of laboratory findings according to groups.

	Group			**H**	**p**	**Post hoc**		
	Group 1	**Group 2**	**Group 3**			**1-2**	**1-3**	**2-3**
	Median (Min-Max)	**Median (Min-Max)**	**Median (Min-Max)**					
25(OH)D (ng/mL)	*10.20(3.70-29.50)*	11.35(5.60-29.50)	9.10(2.90-55.40)	4.07	0.131			
$1,25(OH)_3$ (pg/mL)	27(22-33)	32.5(27-38)	34(29-36)	43.5	0.001*	0.034*	0.023*	0.651
TNF-α (pg/mL)	5.24(0.61-26.18)	5.91(0.84-12.87)	6.41(0.31-13.74)	0.2	0.904			
CRP (mg/dL)	0.02(0.019-2.79)	0.02(0.019-0.65)	0.02(0.019-0.86)	0.9	0.631			
IL-6 (pg/mL)	1.9(1.9-7.47)	1.9(1.9-5.55)	1.9(1.9-10.1)	1.3	0.532			

25(OH)D (25-hydroxyvitamin D), $1.25(OH)_2D_3$ (1.25-hydroxyvitamin D), TNF-α (tumour necrosis factor-α), CRP (C-reactive protein), IL-6 (interleukin-6).
H, p: H and p values for Kruskal-Wallis test.
*Statistically significant at p<0.05.

25(OH)D levels in serum were below the limits of vitamin D deficiency (< 20 ng/mL) and insufficiency (< 30 ng/mL) in all three groups. As showed in Table 2, there was no statistically significant difference in the periodontitis *10.20(3.70-29.50)* ng/mL, gingivitis 11.35(5.60-29.50) ng/mL and periodontally healthy groups 9.10(2.90-55.40) ng/mL in

terms of serum 25(OH)D levels (P>0.05). Group 1 (periodontitis group) had significantly lower mean $1.25(OH)_2D_3$ value 27(22-33) pg/mL compared to Group 2 (gingivitis group) 32.5(27-38) pg/mL and Group 3 (periodontally healthy group) 34(29-36) pg/mL (P<0.05) (Table 2).

As showed in Table 2, there was no statistically significant difference between TNF-α, IL-6, CRP levels and all three groups (P>0.05).

There was no statistically significant correlation between laboratory parameters and clinical parameters and mean 25(OH)D values (p>0.05). There was inverse association between 1.25(OH)2D3 values and PI, BOP, PD, CAL, GI and CRP (p< 0.05). While 1.25(OH)2D3 values increased, it was found that the aforementioned variables decreased (Table 3).

Table 3: Correlation of serum vitamin D levels with clinical parameters and laboratory findings.

		Age	PI	BOP	PD	CAL	GI	TNF-α (pg/mL)	CRP (mg/mL)	IL-6 (pg/mL)
25(OH)D (ng/mL)	***r***	-0.077	0.002	0.078	-0.108	-0.174	0.008	0.216	-0.008	-0.031
	p	0.492	0.983	0.489	0.333	0.117	0.945	0.051	0.942	0.780
	n	82	82	82	82	29	82	82	82	82
$1.25(OH)_2D_3$ (pg/mL)	***r***	-0.570	-0.626	-0.497	-0.703	-0.729	-0.603	0.042	-0.228	-0.072
	p	<0.001**	<0.001**	<0.001**	<0.001**	<0.001**	<0.001**	0.707	0.039*	0.523
	n	82	82	82	82	29	82	82	82	82

PD (probing depth), CAL (clinical attachment level), BOP (bleeding in probing), PI (plaque index), GI (gingival index)
25(OH)D (25-hydroxyvitamin D), $1.25(OH)_2D_3$ (1.25-hydroxyvitamin D), TNF-α (tumour necrosis factor-α), CRP (C-reactive protein), IL-6 (interleukin-6).
*Statistically significant at $p \leq 0.05$. ** Statistically significant at $p \leq 0.001$.
r, correlation coefficient

DISCUSSION

The primary finding in present study is that there is association between periodontal health status and serum 1.25(OH)2D3 level. While 1.25(OH)2D3 level in serum was found to be lower in the group with periodontitis than group with gingivitis and periodontally healthy group. Other finding was that there is no association between periodontal health status and serum 25(OH)D level. The association observed between serum 1.25(OH)2D3 level and tissue destruction and periodontal inflammation can be explained by the effects of vitamin D on calcium–bone metabolism and the immunomodulatory effects of vitamin D. Antonoglou et al. (15) observed a significant increase in the level of serum 1.25(OH)2D3 after the elimination of periodontal inflammation and suggested that possible favorable effects of vitamin D could be dedicated to immunomodulatory functions. Rafique et al. (16) reported that the serum 1.25(OH)2D3 level was significantly lower in the periodontitis group compared to the healthy

control group. Bhargava et al. (17) found, low serum 25(OH)D levels in individuals with chronic periodontitis. In study performed by Alzahrani et al. (18), the serum 25(OH)D level has been found to be lower in the periodontitis group than in the control group. In another study conducted by Antonoglou et al. (9), the association between periodontal health and 1.25(OH)2D3 and 25(OH)D levels in serum has been examined; while 1.25(OH)2D3 level in serum was found to be related to periodontal health status, 25(OH)D level in serum was not found to be related. Pradhan et al. (19) found, no significant association between vitamin D and periodontitis. Similarly, in the present study, the level of serum 1.25(OH)2D3 has been found to be associated to periodontal health status, while no relation has been found between periodontal health status and 25(OH)D level in serum. In the periodontitis group, the serum 1.25(OH)2D3 level was remarkably lower than in the gingivitis and periodontally healthy group. 25(OH)D level in serum was below the limits of vitamin D insufficiency (< 30 ng/mL) and vitamin D deficiency (< 20 ng/mL) in all three groups, except for only 3 subjects. The reason for this is that the eastern Black Sea region, where the study was conducted, receives too little sunlight since it is situated on the the 41st parallel North (13).

The anti-inflammatory feature of vitamin D has been supported by many studies. Bhargava et al. (17) reported that there was a statistically significant relationship between serum 25(OH)D level and GI, PD and CAL, while there was no statistically significant relationship between 25(OH)D level and PI. Isola et al. (20) found an inverse relationship between 25(OH)D level and PD, CAL, PI and BOP. Dietrich et al. (21) found in their study conducted in 2005 that there was less bleeding on probing in the group with high level of serum 25(OH)D. They suggested that this negative relation could be due to an anti-inflammatory effect when the serum 25(OH)D level is ≥ 90–100 nmol/L. Hiremath et al. (22) reported on the anti-inflammatory effects of various doses of vitamin D on gingivitis: gingivitis scores changed in proportion to the dose of vitamin D supplementation, and significant anti-inflammatory effects were observed after vitamin D supplementation. Garcia et al. (23) declared that calcium and vitamin D supplementation had a favourable effect on periodontal health status and that high doses of vitamin D could have a reducing effect on the severity of periodontal disease. Alshouibi et al. (24) researched the relationship between periodontal health and vitamin D intake and concluded that vitamin D intake can have protective effect versus the progression of periodontal disease. Contrary to some previous studies, one of the reasons why we could not find a relationship between serum 25(OH)D levels and periodontal health in our study may be the lower serum 25(OH)D levels in our

subjects. Only 3% (3 subjects) of our subjects had values above the recommended level of 30 ng/mL (25). This situation is accordance with the results of the study of Millen et al. (26), who recommended an adequate serum 25(OH)D level of 30 ng/mL, and Dietrich et al. (21), who reported that serum 25(OH)D level should be 36-40 ng/mL for anti-inflammatory effect to be observed.

Vitamin D has a significant role in calcium homeostasis, bone growth and protection. The anti-inflammatory roles of 1.25(OH)2D3 have been extensively studied, and it has been shown that they inhibit cytokine production and antigen-induced T cell proliferation, and they act as an immunomodulatory agent (27, 28). According to these findings, it may be reasonable to consider a low serum vitamin D level as an indicator of inflammatory status in periodontium.

There is no consensus on what the needed level of serum 25(OH)D should be for homeostasis, bone metabolism and adequate immunity. Dietrich et al. (21) have suggested that serum 25(OH)D level should be ≥ 90–100 nM/L for an anti-inflammatory impact of vitamin D on gingival inflammation. Millen et al. (26) reported that there was less bleeding on probing and shallower periodontal pockets in patients with a level of serum 25(OH)D ≥ 50 nM/L than in those with an inadequate level (< 50 nM/L).

The quantity of vitamin D production in the skin depends on the season, latitude and amount of sunlight coming from different angles at varied times of the day (13). Antonoglou et al. (9), in a study conducted in 2015, investigated serum 25(OH)D and 1.25(OH)2D3 values in blood samples taken in different seasons and found that serum vitamin D values vary depending on the season. Therefore, serum samples were collected in the same period (winter; November-March) from our study groups. In our study, a remarkable and inverse relationship has been found between 1.25(OH)2D3 levels and clinical parameters as well as between CRP and 1.25(OH)2D3 levels ($p<0.05$). This negative relationship of 1.25(OH)2D3 with tissue destruction and periodontal inflammation may be clarified by the immune modulatory effects of vitamin D and bone-associated functions.

CRP is a plasma protein that reflects the grade of the acute-phase response of inflammation and is used by many investigators for the prediction and early diagnosis of periodontal disease (3). There are several studies showing a favourable association between CRP and the severity of periodontal disease, as well as a reduction in the level of serum CRP after non-surgical periodontal therapy (29-33). Podzimek et al. (3) reported that the CRP level increases with the severity of periodontal disease in a study designed to evaluate the systemic level of CRP and

compare its relationship with periodontal clinical parameters. Also, in the research of Jayaprakash et al. (32), in which they examined the effect of periodontal therapy on the serum CRP levels in individuals with chronic periodontitis and chronic gingivitis, a higher CRP value in the patients with chronic periodontitis was detected; it has been suggested that there was a reduced in CRP values in the patients with chronic gingivitis and chronic periodontitis after three months of treatment. There was no statistically significant relationship among CRP and the groups in our study ($p>0.05$). Unlike other studies, we think that the reason why there was no statistically significant difference in serum CRP levels between our study groups may be due to the fact that they were in stable or active periods of periodontitis. In our study, samples may have been collected during the stable period of periodontitis. In addition, there may not be a difference due to reasons such as the sample sizes selected in the studies and the differences in the evaluation methods, the sensitivity of the kits used.

In a research conducted by Andrukhov et al. (34) it was suggested that vitamin D3 may play a significant role in the regulation of periodontal inflammation through the production of cytokines by periodontal ligament cells. According to this finding, both 1.25(OH)2D3 and 25(OH)D are thought to affect the inflammatory process in periodontal disease. In the study conducted by Yousefimanesh et al. (35) in order to explain the importance of TNF-α in the destruction of periodontal tissues, saliva samples of those in the periodontally healthy control group and those with chronic periodontitis were examined; no statistically significant relationship was found between TNF-α levels and two groups ($p>0.05$). Likewise, there was no association between groups and TNF-α values ($p>0.05$) in our study. The reasons why we could not find a statistically significant difference in TNF-α levels between the groups may be the selection of individuals in different age groups in the studies, the number of samples, the differences in the sampling and evaluation methods.

In this study, 25(OH)D and 1.25(OH)2D3 values have been measured in a certain time interval to prevent the effect of different sun angles in different months from affecting the capacity for vitamin D production in the skin. Overall, this research promotes the idea that vitamin D deficiency has a negative effect on periodontal health status.

CONCLUSION

The Eastern Black Sea Region receives little sunlight because of its northern location. Therefore, vitamin D deficiency is often observed there. In light of this information, we hypothesise that vitamin D supplementation will be beneficial in reducing the risk of periodontal disease for people living in

geographic locations with relatively less sunlight than other locations. However, more studies need to be conducted on this issue. In addition, further studies are needed to better understand the preventive effect of vitamin D on periodontal tissue destruction, with larger sample numbers and locally evaluation of the parameters by collecting gingival crevicular fluid, saliva or tissue biopsies samples.

Ethics Committee Approval: This study was approved by the human subjects ethics committee of Recep Tayyip Erdoğan University (meeting date: 07 April 2016; Ethics Committee Decision No. 2016/09).

***Informed Consent*:** The aim and content of the research were clarified to the individuals included in the study, and voluntary consent forms were signed.

Author Contributions: Concept- HY, MZK, Design: HY, MZK, Supervision- HY, MZK, MA, Materials-HY, MZK, Data Collection and/or Processing- HY, MZK, MA, Analysis and/or Interpretation- HY, MZK, MA, Literature Search- HY, MZK, Writing Manuscript- HY.

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