



Relationship between Clinical Indicators of Periodontal Disease and Serum Level of Vitamin D

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Abstract

Background

Vitamin D is obtained through food and nutritional supplements, or is synthesized in the skin by sunshine. It is then transferred to the liver and kidney through the bloodstream and hydroxylated by specific enzyme (cytochrome P450 family 27 subfamily A member 1, cytochrome P450 family 27 subfamily B member 1) to form 25-hydroxy vitamin D and 1,25-dihydroxy vitamin D. The vitamin D synthesis facilitates calcium and phosphorus absorption from the intestines. Parathyroid hormone helps to synthesize 1,25-dihydroxy vitamin D to aid calcium absorption.

Objectives

Many researchers have investigated the relationship between the serum vitamin D levels and periodontal disease. And periodontal disease indicators such as bleeding on probing, pocket depth, clinical attachment level, gingival index, and cemento enamel junction-alveolar crest have been used to identify the effects of vitamin D on periodontal disease. The effects of vitamin D on bacteria or cytokines have also been investigated. In this review article, vitamin D levels according to the status of periodontal disease were summarized.

Data sources

PubMed was searched electronically, and randomized clinical trials, cross-sectional studies, and case-control studies were included in the review.

Study Appraisal and Synthesis Methods

Articles that the classification of periodontitis was accurately described, indicators for identifying periodontitis was clearly marked, and the form of



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Keywords

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vitamin D measured in the study was accurately described were selected. Only highly relevant journals were selected and summarized.

Results

Most of the research has found positive associations between the serum 25-hydroxy vitamin D level and periodontal health, and the clinical parameters of periodontal disease were reduced by vitamin D.

Limitations

Detailed categorization of the characteristics associated with the 25-hydroxy vitamin D level should be needed in future studies.

Conclusions

This review article can be used as a guide by clinicians and as a reference book for patient's education.

Introduction

Vitamin D is obtained through food and nutritional supplements, or is synthesized in the skin from the UV-B radiated by sunshine. It is then transferred to the liver through the bloodstream, where it is hydroxylated by 25-hydroxylase to form 25(OH)D (calcidiol, calcifediol). As 25(OH)D is a fairly stable compound in the human body, it is commonly used as an indicator of the blood vitamin D concentration. The 25(OH)D is then transferred to the kidneys, where it undergoes another hydroxylation by 1α -hydroxylase to form $1,25(\text{OH})_2\text{D}$ (calcitriol), a biologically active form of vitamin D. The vitamin D synthesis facilitates calcium and phosphorus absorption from the intestines to maintain the serum concentrations within normal ranges. If the calcium levels decrease, the parathyroid hormone (PTH) helps to synthesize $1,25(\text{OH})_2\text{D}$ to aid calcium absorption [Figure 1].¹

As individual's bone mass increases and decreases over their lifetime, calcium is necessary to maintain bone balance. When the bone balance is disrupted, diseases associated with the skeletal bone-such as periodontitis-occur. Therefore, a calcium intake is important. However, there are thresholds of calcium utilization even when the calcium intake increases. When calcium levels are too low, the skeletal calcium is resorbed to maintain the body's calcium homeostasis. This mechanism is mediated by the PTH and vitamin D. Therefore, the vitamin D hormone is essential to the human body to maintain a healthy and normal condition [Figure 1].¹

Sufficient vitamin D level is necessary for the maintenance of periodontal health,² and intake of vitamin D can decrease the gingivitis and chronic periodontitis.³ Because vitamin D has anti-bacterial and anti-inflammatory effect,⁴ and it also has anti-proliferative effects and initiates cell apoptosis. In addition, vitamin D is also important for bone metabolism, alveolar bone resorption and preventing tooth loss.³

The Food and Nutrition Board (FNB) have issued guidelines on the recommended dietary allowances (RDAs) for healthy vitamin D concentrations.⁵ The RDAs for vitamin D areas follows: 400 IU between 0 and 12 months of age, 600 IU between 1 and 70 years old, and 800 IU after 70 years old. These quantities do not differ between men and women. The serum 25(OH) D concentration can be used as a vitamin D indicator. Less than 12 ng / ml indicates a deficiency, 12-20 ng / ml is an inadequate level, more than 20 ng / ml is an adequate level for bone and overall health, and more than 50 ng / ml signals potential adverse effects from vitamin D in individuals. The Institute of Medicine also concluded that for maximum bone health, a serum 25(OH)D level over 20 ng / ml was adequate.⁶ In the Endocrine Society's Practice Guidelines (ESPG) on vitamin D, deficiency was defined as $25(\text{OH})\text{D} < 20$ ng / ml, insufficiency as 21-29 ng / ml, and sufficiency as at least 30 ng / ml for maximum bone health.⁷ These criteria are also accepted by the National Osteoporosis Foundation, the International Osteoporosis Foundation, the American Association for Clinical Endocrinologists, and the American Geriatric Society.^{8,9}

However, establishing an RDA for vitamin D is difficult, as it is synthesized from sunshine and the intake depends on the individual's lifestyle. The country of residence and the seasons can affect the vitamin D synthesis, as they entail different levels of exposure to sunshine. Holick reported that people who live close to the equator and Puerto Rican farmers have high 25(OH)D concentrations.¹⁰ Zittermann reviewed the vitamin D status of European populations in summer and winter. The results suggested that the vitamin D levels were higher in summer than in winter.¹¹

Many researchers have investigated the relationship between the serum vitamin D levels and periodontal disease, and periodontal disease indicators such as the bleeding on probing (BOP),¹²⁻¹⁴ pocket depth (PD),^{12,3,15-21} clinical attachment level (CAL),^{13,14,16-21} gingival index (GI),¹³⁻¹⁶ and cemento-enamel junction-alveolar crest (CEJ-AC)^{13,14} have been used to identify the effects of vitamin D on periodontal disease [Figure 2]. The effects of vitamin D on bacteria or cytokines have also been investigated.

Most previous studies have focused on one of the different forms of periodontal disease and suggested a correlation with the vitamin D levels.¹²⁻²¹ However, periodontal disease is a progressive disease that can be gradually aggravated by personal habits. Therefore, it is important to understand its overall flow. To this end, this study collected and analyzed data to identify the vitamin D levels for each periodontal disease classification, so as to provide clear information to clinicians and researchers.

Materials and Methods

PubMed (MEDLINE) was searched electronically, and randomized clinical trials, cross-sectional studies, and case-control studies were included in the review. The following terms and combinations were used to search the database:

"gingivitis AND vitamin D"; "gingivitis AND calciferol"; "chronic periodontitis AND vitamin D"; "chronic periodontitis AND calciferol"; "aggressive periodontitis AND vitamin D"; "aggressive periodontitis AND calciferol"; "bleeding on probing AND vitamin D"; "bleeding on probing AND calciferol"; "pocket depth AND vitamin D"; "pocket depth AND calciferol"; "clinical attachment level AND

vitamin D"; "clinical attachment level AND calciferol"; "gingival index AND vitamin D"; "gingival index AND calciferol"; "cemento-enamel junction-alveolar crest AND vitamin D"; "cemento-enamel junction-alveolar crest AND calciferol"; "vitamin D AND review"; "periodontal disease AND review";

Among 194 articles, 29 papers were finally selected. Articles that the classification of periodontitis was accurately described, indicators for identifying periodontitis was clearly marked, and the form of vitamin D measured in the study was accurately described were selected. To remove the author's prejudice and convey accurate information, negative correlation results between periodontitis and vitamin D were also selected.

Non - English language studies and those with unavailable full text or unpublished data were excluded. Only highly relevant journals were selected after reading their abstracts.

Results

Vitamin D Concentration and Periodontal Disease

Periodontitis is a chronic inflammatory disease caused by bacteria; whose severity can be affected by cytokines and osteoclasts.²² The American Academy of Periodontology (AAP) criteria are widely used to classify the disease.²³ Researchers who study the vitamin D levels in relation to periodontal disease commonly focus on three categories from the AAP's classification: gingivitis, chronic periodontitis, and aggressive periodontitis [Table 1].

The standards for gingivitis were set as Pocket Depth (PD) < 3¹⁵ or not suggested.¹² Subjects were recruited in India from June 2010, and they underwent post-recruitment follow-up from February to May 2011. The 25(OH)D concentrations (ng / ml) rose from 22.5 ± 7.0 to 52.2 ± 10.2, 26.8 ± 0.7 to 43.7 ± 8.8, and 24.0 ± 5.1 to 36.8 ± 6.1 after 2000, 1000, and 500 IU / day of vitamin D oral supplementation for 3 months, respectively. All the groups had an adequate vitamin D status according to the FNB's RDAs on their first visit, and the 25(OH) D concentrations increased with the doses of vitamin D. It was particularly highly increased in the group that received a 2000 IU dose of vitamin D oral supplementation, and the 25(OH)D concentration was involved in the vitamin D adverse effect group

of individuals that showed potential adverse effects. However, according to the ESPG, all the groups had an insufficiency vitamin D status on their first visit and sufficiency vitamin D status on their final visit. And, it has a significant anti-inflammatory effect on the gingival according to the concentrations.¹⁵ Although the vitamin DRDAs for adults are 600 IU, tolerable upper intake levels were found to be 4000 IU (data not shown,⁶). Therefore, the subjects may not have had health problems. Another team assayed the serum 25(OH)D concentrations in white volunteers in the mid western United States in October. They divided the subjects into five groups according to

their 25(OH)D concentrations (quintile, nmol/l): (1) 31.3 ± 6.6 , (2) 47.8 ± 3.8 , (3) 60.8 ± 3.9 , (4) 75.8 ± 4.9 , (5) 106.0 ± 21.1 . The quintile (1) and (2) groups had inadequate vitamin D levels, while the (3)-(5) groups had adequate vitamin D levels according to the FNB's RDAs.¹² In gingivitis, the serum 25(OH)D levels were linked to an inadequate or adequate vitamin D status. This is probably due to the mild symptoms of gingivitis.

The standards for moderate to severe chronic periodontitis were set as $CAL \geq 3$,^{13,14} with the PD not suggested.^{13,14,16} In a study, the subjects followed

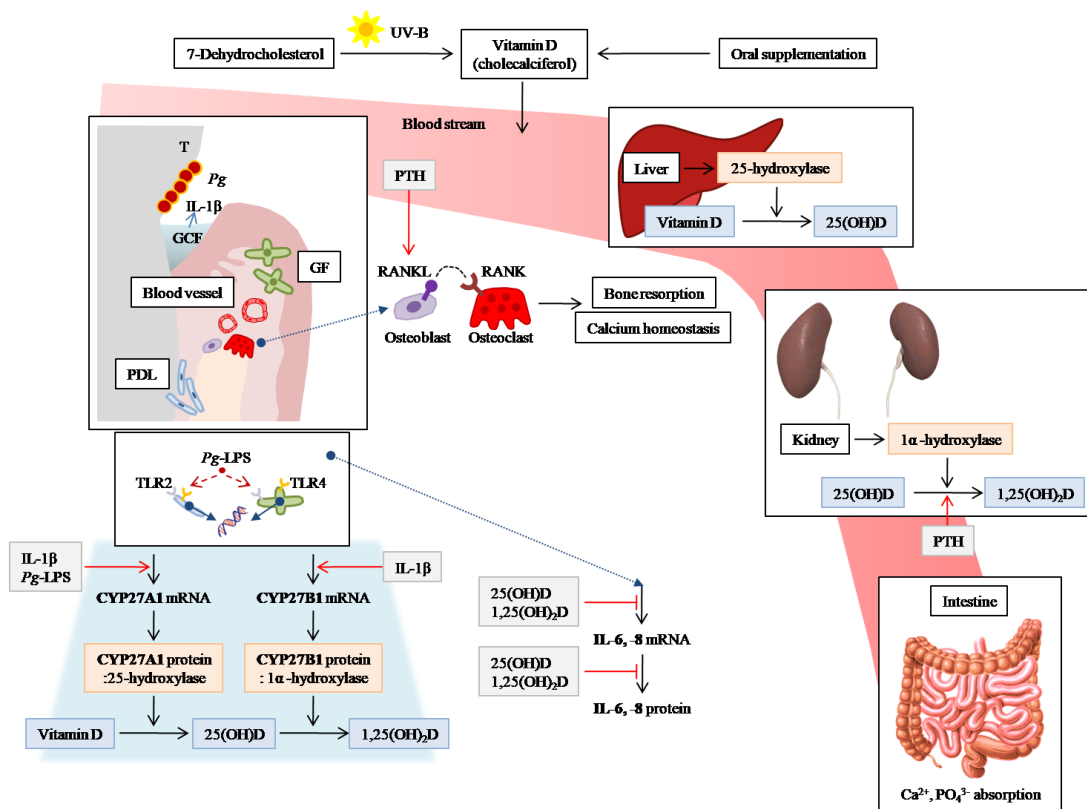


Fig. 1: Vitamin D is obtained through food and supplements or is synthesized in the skin by sunshine. It is then transferred to the liver and kidney through the bloodstream and hydroxylated by specific enzyme (CYP27A1, CYP27B1) to form 25(OH)D and 1,25(OH)₂D. The vitamin D synthesis facilitates calcium and phosphorus absorption from the intestines and the PTH helps to synthesize 1,25(OH)₂D to aid calcium absorption. Also, 25(OH)D and 1,25(OH)₂D can be synthesized by GF and PDL cells to inhibits pro-inflammatory cytokines such as IL-6 and IL-8 produced by Pg-LPS.

T, tooth; GF, gingival fibroblast; PDL, periodontal ligament; GCF, gingival crevicular fluid; IL, interleukin; PTH, parathyroid hormone; LPS, lipopolysaccharide; TLR, toll like receptor; Pg, Porphyromonas gingivalis

Table 1: Vitamin D and periodontal disease

Reference	Type and population	Vitamin D analysis	concentration of 25(OH)D in serum				Oral status	Standard of oral condition		Sites	Clinical parameters	Results
			ng/ml		nmol/L			CAL (mm)	PD (mm)			
			First visit	Final visit	First visit	Final visit						
Hiremath VP <i>et al.</i> (11)	RCT n=96 Clinics	Oral supp. (2000 IU/day 1000 IU/day 500 IU/day placebo)	22.5±7.0	52.2±10.2*	56.1±17.5	130.3±25.5*	G	Ns.	<3		GI*	Dose dependent anti-inflammatory effect of vitamin D on gingivitis.
			26.8±0.7	43.7±8.8*	66.9±1.8	109.0±22.0*						
			24.0±5.1	36.8±6.1*	59.9±12.7	91.9±15.2*						
			28.2±3.1	28.5±4.0	70.3±7.7	71.2±10.0						
Dietrich T <i>et al.</i> (12)	CS n=6,700 NHANESIII	25(OH)D in serum	12.5±2.6		31.3±6.6		G	Ns.		MB	BOP*	Positive association between 25(OH)D and periodontal health
			19.2±1.5		47.8±3.8							
			24.4±1.6		60.8±3.9							
			30.4±2.0		75.8±4.9							
	CS n=51 Clinics	Oral supp. ≥400 IU/day (+Ca≥1,000 mg/day)	Ns.		Ns.		CP	≥3 (↑ 2 ip) - Received periodontal maintenance programs	Ns.	All	BOP, PD, CAL, GI, CEJ-AC	Borderline statistically significant
Garcia MN <i>et al.</i> (14)	Cohort n=51 Clinics	Oral supp. ≥400 IU/day (+Ca≥1,000 mg/day)	Ns.		Ns.		CP	≥3 (↑ 2 ip) - Received periodontal maintenance programs	Ns.	All	BOP* CAL* GI* CEJ-AC	Positive association between oral supp. (vitamin D with Ca) and periodontal health
Perayil J <i>et al.</i> (15)	RCT n=77 Clinics	Oral supp. ≥250 IU/day (+Ca≥500 mg/day)	First visit	3 months	First visit	3 months	CP	3-4 (↑ 1 t) - Received SRP and curettage	Ns.	All	PD* CAL* GI*	Positive association between oral supp. (vitamin D with Ca) and periodontal health
			(T)	(T)	(T)	(T)						
			26.0±1.3	36.0±1.2*	64.9±3.2	89.9±3.0*						
			(N)	(N)	(N)	(N) 63.9±0.5						
Abreu OJ <i>et al.</i> (16)	CC, CS n=38 Clinics	25(OH)D in serum	(P) 18.5±4.6*		(P) 46.2±11.5*		MP SP	(MP) ≥4 (↑ 2 ip)	(MP) ≥5 (↑ 2 ip)	All	PD* CAL*	Positive association between 25(OH)D and periodontal health
			(C) 24.2±7.1		(C) 60.4±17.7							

RCT, randomised clinical trial; CS, cross-sectional study; CC, case-control; NHANESIII, third National Health and Nutrition Examination Survey; Oral supp., oral supplementation;

Ca, calcium; Ns., not suggested; T, taker group; N, non-taker group; P, periodontitis; C, control; CAL, clinical attachment loss; PD, pocket depth; ↑, at least; ip, interproximal; t, teeth;

B, buccal; L, lingual; MB, mesio-buccal; ML, mesio-lingual; DB, disto-buccal; DL, disto-lingual; All, include 6 sites on the teeth (B, L, MB, ML, DB, DL);

GI, gingival index; BOP, bleeding on probing; CEJ-AC, cemento-enamel junction-alveolar crest; G, gingivitis; CP, chronic periodontitis; MP, moderate periodontitis; SP, severe periodontitis;

SRP, scaling and root planning;

* Significant differences compared to placebo or control group.

periodontal maintenance programs during the course of the research.^{13,14,16} They were recruited between June 2007 and February 2008,¹³ and took vitamin D (≥ 400 IU / day) and calcium (≥ 1000 mg / day) for >18 months (Taker group) or not (Non - Taker group).¹³⁻¹⁴ In another study, subjects were recruited in India between November 2012 and December 2013, and took vitamin D (≥ 250 IU / day) and calcium (≥ 500 mg / day) for 3 months (Taker group) or not (Non - Taker group).¹⁶ The vitamin D dose was capped based on the FNB's RDAs on the final visit.^{13, 14,16} However, the concentration of 25(OH)D (ng / ml) in the serum increased from 26.0 ± 1.3 to 36.0 ± 1.2 ($p = 0.001$).¹⁶ In the chronic periodontitis group, the level of 25(OH)D in the serum was adequate before and after the therapy and the oral supplementation, but the 25(OH)D level was increased after the therapy and supplementation.¹⁶

The standards for moderate and severe periodontitis were set as $CAL \geq 4$ and $PD \geq 5$, and $CAL \geq 6$ and $PD \geq 5$, respectively.¹⁷⁻¹⁹ In a study of Hispanic adults, the 25(OH)D concentration (ng / ml) was 18.5 ± 4.6 in the periodontitis group and 24.2 ± 7.1 in the healthy control group ($p = 0.006$).¹⁷ The periodontitis group had an inadequate vitamin D status, while the healthy control group had adequate vitamin D levels according to the FNB's RDAs. In this study, the vitamin D status categories (≤ 12 : deficient, 12-19: inadequate, 20 -30: adequate, >30: optimal) differed from those defined by the FNB. The adequate group was further divided into adequate and optimal groups.¹⁷ In the periodontitis group, 63.2% of the subjects had inadequate levels, and 36.8% had adequate levels. In the healthy control group, 31.6% had inadequate levels, 47.4% had adequate levels, and 21.1% has optimal levels of vitamin D.¹⁷ Another research team recruited subjects from 2008 to 2010, and measured their 25(OH)D concentrations. The 25(OH)D concentrations (nmol/l) were 65.0 ± 39.3 in the severe periodontitis group and 87.1 ± 39.0 in the healthy control group ($p < 0.05$). Both groups had adequate vitamin D levels according to the FNB's RDAs. However, the levels were higher in the control group than in the severe periodontitis group.¹⁸ Another study recruited subjects in Denmark in 2007-2008 to study the calcium, vitamin D, case in, and whey protein levels of periodontitis patients. However, the serum 25(OH)D concentrations were not reported.¹⁹

In another study, the clinical parameters were divided into three groups ($PD < 2.8$, < 3.4 , ≥ 3.4) and the bacterial species associated with periodontitis were investigated.^{24,25} The median of 25(OH)D concentrations (ng/ml) in the serum were 29.8, 25.2, and 25.0, respectively, showing no significant differences. All the groups had adequate vitamin D levels according to the FNB's RDAs.

One research team set standards of $PD > 6$ for aggressive periodontitis, and $CAL \geq 1$ and $PD \geq 5$ for chronic periodontitis.^{20,21} The researchers recruited subjects from July 2001 to October 2007. The subject's 25(OH)D concentrations (nmol/l) were 29.3 ± 17.2 in the aggressive periodontitis group, 25.5 ± 14.3 in the chronic periodontitis group, and 21.6 ± 14.4 in the control group, respectively. All the groups showed vitamin D deficiency according to the FNB's RDAs. However, the 25(OH)D level was significantly higher in the aggressive periodontitis group than in the control group ($p < 0.05$), and no significant differences were found between the aggressive periodontitis and chronic periodontitis groups or between the chronic periodontitis and control groups.²⁰ The same team recruited subjects from November 2006 to February 2007 and measured their 25(OH)D concentrations (nmol/l) in the serum (systemic) and in the gingival crevicular fluid (GCF, local). The subjects received periodontal therapy from baseline, and their 25(OH)D concentrations were measured at base line, at 2 months, and at 6 months post - therapy. The serum 25(OH)D concentration was 29.3 ± 4.9 at baseline, and it decreased to 22.5 ± 3.9 after 2 months of therapy ($p < 0.05$). The GCF 25(OH)D concentration was 8946.8 at baseline, 5655.3 at 2 months ($p < 0.05$), and 3444.8 at 6 months ($p < 0.05$) after the treatment.²¹ And these results contradicted other data.^{20,21} A possible explanation for this is that the researchers failed to consider the demographic characteristics and the latitude and seasons, habits, and lifestyle, or the exposure time to sunshine and the extra vitamin D supply from the subjects' customary diet. Therefore, researchers should consider control factors such as seasonal changes in future studies. Interestingly, the vitamin D levels were much higher in the GCF than in the serum,²¹ possibly because 25(OH)D and $1,25(OH)_2D$ can be synthesized by the gingival fibroblast (GF) and periodontal ligament (PDL) cells [Figure 1].

Vitamin D Concentration and Clinical Parameters -Bleeding on Probing

Bleeding on probing (BOP) is one of the symptoms of gingivitis and periodontitis. It is widely used by dental clinics as a clinical parameter for oral

examination and study. To evaluate the effect of the vitamin D concentration on gingivitis, Dietrich *et al.* performed a cross-sectional study of 6,700 subjects. The authors took venous blood samples and defined quintiles according to the vitamin D concentrations.

Table 2: Vitamin D and bacterial species or biochemical parameters

Reference	Type and population	Vitamin D analysis	concentration of 25(OH)D in serum		Oral status	Standard of oral condition		Results	
			ng/ml	nmol/L		CAL (mm)	PD (mm)		
Teles FR <i>et al.</i> (20)	Cohort n=56 Clinic	25(OH)D in serum	29.8 ^{\$}	74.38 ^{\$}	CP	Ns.	<2.8	- Red complex: <i>Tannerella forsythia</i> * <i>Porphyromonas gingivalis</i> * <i>Treponemadenticola</i> * - Orange complex: <i>Prevotellanigrescens</i> <i>Eubacteriumnodatum</i>	
			25.2 ^{\$}	62.90 ^{\$}		Ns.	<3.4		
			25 ^{\$}	62.40 ^{\$}		Ns.	≥3.4		
Liu K <i>et al.</i> (21)	Cohort n=178 Clinic	25(OH)D in serum	(AgP) 11.7±6.9*	(AgP) 29.3±17.2*	AgP	Ns.	>6 (↑ 8 t)	OC	0.90*
								ALP	60.2±18.2
			(CP) 10.2±5.7	(CP) 25.5±14.3	CP	≥1 (↑ 2 ip)	≥5 (↑ 2 ip)	OC	0.70
							ALP	63.1±24.4	
		(C) 8.7±5.8	(C) 21.6±14.4	C	≤3	≤3	OC	0.70	
							ALP	64.1±16.6	
Liu K <i>et al.</i> (22)	Cohort n=19 Clinic	25(OH)D in serum	(First visit) 11.7±2.0	(First visit) 29.3±4.9	AgP	Ns.	>6 (↑ 8 t)	OC	1.03±0.46
								IL-1β	6.71
								IL-6	1.00
		(2 months) 9.0±1.6*	(2 months) 22.5±3.9*	OC				1.01±0.37	
				IL-1β				3.23*	
				IL-6				1.06	
	25(OH)D in GCF	(First visit) 3,584.5	(First visit) 8,946.8	- Received periodontal therapy (TBI and SRP)	OC	109			
					IL-1β	10,592			
					IL-6	3,798			
		(2 months) 2,265.8*	(2 months) 5,655.3*		OC	81			
					IL-1β	5,499*			
					IL-6	3,730			
(6 months) 1,380.1*	(6 months) 3,444.8*	OC	98						
		IL-1β	3,963*						
		IL-6	4,531						

AgP, aggressive periodontitis; CP, chronic periodontitis; C, control; CAL, clinical attachment loss; PD, pocket depth; Ns., not suggested; ↑, at least; ip, interproximal; t, teeth;

TBI, tooth brushing instruction; SRP, scaling and root planning; OC, osteocalcin; ALP, alkaline phosphatase; IL, interleukin; GCF, gingival crevicular fluid;

\$ Mesian value

* Significant differences compared to control or first visit group.

** Significantly correlated

They measured the proportion of bleeding in mesio-buccal teeth, and calculated the P value. The bleeding proportion was 0.11 ± 0.18 in the lowest vitamin D quintile and 0.08 ± 0.15 in the highest quintile. The data revealed a negative association between the serum concentration of vitamin D and the bleeding proportion ($p < 0.001$).¹² Another team (Miley *et al.*) studied 51 subjects from clinics to identify the effect of vitamin D and calcium supplementation on chronic periodontitis. They divided the subjects into a Taker group (intake vitamin D ≥ 400 IU / day with calcium $\geq 1,000$ mg/day) and a Non-Taker group, and measured the bleeding (%) at six tooth sites (Buccal, Lingual, Mesio-Buccal, Mesio-Lingual, Disto-Buccal, Disto-Lingual). The mean of the bleeding sites was 60 in the Taker group and 66 in the Non-Taker group.

The results showed no significant difference ($p = 0.08$), but a border line statistical significance. This study had a small population, as the researchers had difficulty finding subjects who took adequate amounts of supplementation to meet their criteria.¹³ The same team (Garcia *et al.*) reported a similar study designed to determine whether the differences persisted over a 1-year period. To this end, they measured the BOP at baseline, at 6 months, and at 12 months. The differences between the Taker and Non-Taker groups were 7.90% at baseline, 19.83% at 6 months, and 5.13% at 12 months, and the significance overtime was < 0.0001 in the Taker group and 0.002 in the Non-Taker group. These results showed that intakes of calcium and vitamin D can improve periodontal health.¹⁴

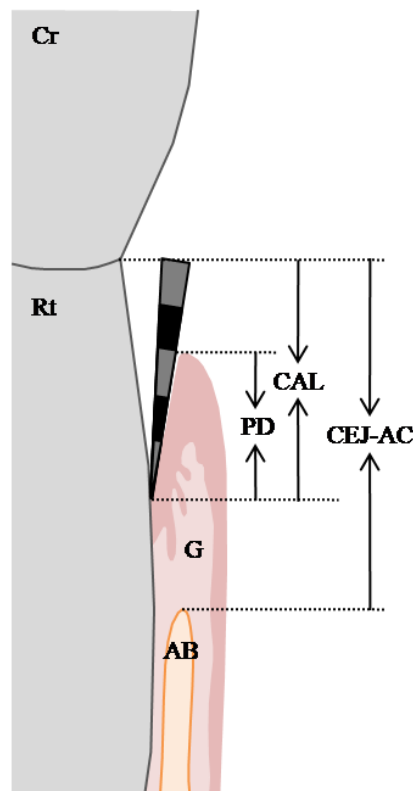


Fig. 2: Many researchers have investigated the relationship between the serum vitamin D levels and periodontal disease, and periodontal disease indexes such as the bleeding on probing (BOP), pocket depth (PD), clinical attachment level (CAL), gingival index (GI), and cemento-enamel junction-alveolar crest (CEJ-AC) have been used to identify the effects of vitamin D on periodontal disease.

AB, alveolar bone; CAL, clinical attachment level; CEJ-AC, cemento-enamel junction-alveolar crest; Cr, crown G, gingival; PD, pocket depth; Rt, root of teeth;

The mean pocket depth value (PD, mm) was measured by an examiner. It was 7 % greater in the Non - Taker group (2.3) than in the Taker group (2.2, oral supplementation).¹³ In another team, the mean PD values was 6.3 ± 0.5 at baseline, and reduce to 4.3 ± 0.3 after 3 months in Taker group (intake vitamin D ≥ 250 IU / day with calcium ≥ 500 mg/day) ($p=0.001$). The data showed that vitamin D and calcium supplementation had a positive effect on the periodontal health.¹⁶ In other team, the PDs were 2.3 ± 0.4 in the periodontitis group and 1.3 ± 0.3 in the control group, respectively, showing statistical significance ($p < 0.0001$). Orlando *et al.* also investigated that the PD value has negative correlation with vitamin D level. This result indicates that a lower serum level of vitamin D is significantly associated with periodontitis.¹⁷ The PDs were 3.6 ± 0.8 in the periodontitis group and 1.2 ± 0.3 in the control group, respectively, and there was a significant difference between the periodontitis group and the control group ($p < 0.001$).¹⁸ However, there are no correlation between vitamin D level and PD value.¹⁸ The vitamin D supplementation significantly reduced the PD,^{13,16} and the serum 25(OH)D levels reduced periodontal disease by 12%.¹⁷ However, the correlation coefficient of the serum 25(OH)D level with the PD was 0.119 ($p = 0.55$), and this result contradicted other data.¹⁸

Clinical Attachment Level

The clinical attachment loss (CAL, mm) was 12 % greater in the Non-Taker (2.0) than in the Taker group (1.8, oral supplementation).¹³ In another team, the differences in the CAL percentage between the Taker and Non-Taker groups were 11.5 at baseline, 22.8 at 6 months, and 13.0 at 12 months. There was also a significant change over time.¹⁴ In other team, the mean CAL values was 6.3 ± 0.7 at baseline, and reduce to 4.5 ± 0.6 after 3 months in Taker group (intake vitamin D ≥ 250 IU / day with calcium ≥ 500 mg / day) ($p = 0.001$).¹⁶ Orlando *et al.* also investigated that the CAL value has negative correlation with vitamin D level. This result indicates that a lower serum level of vitamin D is significantly associated with periodontitis.¹⁷ The CAL was 3.8 ± 0.8 in the periodontitis group and 0.9 ± 0.6 in the control group, respectively, showing significant differences between the periodontitis and control group ($p < 0.001$). However, there are no correlation between vitamin

D level and CAL value.¹⁸ Another team also reported that the CAL was calculated as the sum of the PD and gingival level measurements, and the mean CAL-including interproximal sites-was 3.6 ± 1.2 in the periodontitis group and 2.1 ± 0.6 in the control group ($p < 0.0001$).¹⁹ The vitamin D supplementation significantly reduced the CAL,^{13, 14,16} and the serum 25(OH)D levels reduced the periodontal disease by 12%.¹⁷ However, the correlation coefficient of the serum 25(OH)D level with the CAL was 0.139 ($p = 0.48$),¹⁸ and the intake of vitamin D alone was not associated with severe periodontitis.¹⁹

Gingival Index

The gingival index (GI) is a system for assessment of the gingival condition that distinguishes the quality of the gingival. The GI has 4 grades: 0 indicates a normal condition, 1 indicates mild inflammation (slight change in color, slight edema, no BOP), 2 indicates moderate inflammation (redness, edema and glazing, no BOP), and 3 indicates severe inflammation (marked redness and edema, ulceration, spontaneous bleeding). In a randomized controlled trial, daily oral supplementations of vitamin D were given in doses of 2000 IU / day to group A, 1000 IU / day to group B, and 500 IU / day to group C, and a placebo was given to group D. The serum levels and GI were measured at baseline, on the 2nd visit on the 30th day, on the 3rd visit on the 60th day, and on the final visit on the 90th day. The mean GI was 2.4 ± 0.5 at baseline and 1.8 ± 0.6 on the 2nd visit in group A ($p < 0.05$), 2.4 ± 0.6 at baseline and 1.2 ± 0.7 on the 3rd visit in group B ($p < 0.05$), 2.2 ± 0.5 at baseline and 0.9 ± 1.0 on the final visit ($p < 0.05$). No significant change was observed in group D (placebo). The results revealed a dose-dependent anti-inflammatory effect of vitamin D on gingivitis.¹⁵ In another team, the GI was 1.00 in the Non-Taker group and 0.73 in the Taker group, showing border line significance.¹³ In other team, the differences in the GI percentages between the Taker and Non-Taker groups were 38.0 at baseline, 40.5 at 6 months, and 24.0 at 12 months. There was also significance over time.¹⁴ In other team, the mean GI values was 2.1 ± 0.4 at baseline, and reduce to 0.3 ± 0.4 after 3 months in Taker group (intake vitamin D ≥ 250 IU / day with calcium ≥ 500 mg/day) ($p = 0.001$).¹⁶ The vitamin D supplementation significantly reduced the GI.¹⁴⁻¹⁶

CEJ-AC

Cemento enamel junction - alveolar crest (CEJ - AC, mm) measurements were made in the mesial and distal aspects of posterior teeth. The mean CEJ - AC was 19 % greater in the Non - Taker group (2.1) than in the Taker group (1.7, oral supplementation).¹³ In another team, it was evaluated through radiographic assessment, and the differences in the CEJ - AC percentages between the Taker and Non - Taker groups were 17.1 at baseline, 17.3 at 6 months, and 11.6 at 12 months. The CEJ - AC showed no change over time (between base line, 6 months, and 12 months).¹⁴

Vitamin D, Bacteria and Cytokines**Bacteria Species**

There was an increase in pathogenic bacteria in the sub gingival plaque with a greater PD, particularly in the red complex²⁴-including *Tannerella forsythia*, *Porphyromonas gingivalis*, and *Treponema denticola*-and in the orange complex²⁴-including *Prevotellanicrescens*, and *Eubacterium nodatum*. The subjects were assessed at baseline and 6 months after therapy, and the levels of pathogenic bacteria-including *Tannerella forsythia*, *Porphyromonas gingivalis*, and *Treponema denticola*-were significantly reduced after treatment.²⁵

Cytokine

Liu et al. focused on the association between 25(OH)D, bone - related markers, and periodontitis.²⁰ Aggressive periodontitis subjects showed significantly higher PD, CAL, and BOP levels than control subjects, reflecting severe bone destruction. The aggressive periodontitis group showed a high level of osteocalcin, which reflected unbalanced bone remodeling and the need for faster bone formation. A correlation trend was found between the 25(OH)D and ALP levels, which also reflected the bone formation. The same researchers measured the 25(OH)D, osteocalcin, IL-1 β , and IL-6 in the plasma and in the GCF in the periodontitis group after the initial periodontal therapy.²¹ The PD and BI as well as the 25(OH)D and IL-1 β levels were significantly lower after treatment, at 2 and 6 months. The systemic and local osteocalcin levels did not change before and after therapy. The authors concluded that the initial periodontal therapy focused on the elimination of periodontal inflammation, and therefore had no effect on the bone activity. The IL-1 β level was reduced

after therapy, which reflected the alleviating effect of the therapy on inflammation.

In the periodontitis group, the 25(OH)D level was extremely higher in the GCF than in the plasma.²¹ Therefore, GF and PDL cell enzyme activity for vitamin D synthesis was suspected. For vitamin D utilization, a transformation by 25-hydroxylation and 1, α - hydroxylation is necessary. Cytochrome P450 enzymes such as CYP27A1 and CYP27B1 have been identified as vitamin D 25-hydroxylases.²⁶ Some researchers have performed experiments with GF and PDL cells to identify enzyme activity. Results have shown that GF and PDL cells generate enzymes (CYP27A1, CYP27B1) in response to vitamin D.²⁷ Tang et al. investigated the effects of 1,25(OH)₂D on the expression of IL-6 and IL-8 stimulated by *P. gingivalis*. 25(OH)₂D significantly inhibited the IL-8 (mRNA, protein) in PDL cells both in dose- and time-dependent manners.²⁹ Andrukho et al. reported that both 25(OH)D and 1,25(OH)₂D reduced the levels of IL-6, IL-8, and MCP-1 stimulated by *P. gingivalis*-LPS and heat - killed *P. gingivalis* in a dose - dependent manner.³⁰ In De Filippis et al.'s study, 1,25(OH)₂D inhibited the *P. gingivalis* adhesion and infectivity in GF and PDL cells. It also reduced the TNF - α , IL-8, and IL-12 productions, and increased the human β -defensin 3 expression.³¹

Discussion

In this review, the relationship between vitamin D and periodontal diseases indicators were analyzed. And the effects of vitamin D on bacteria or cytokines have also been investigated. The data showed a negative association between vitamin D serum concentration with bleeding proportion, CAL, and GI. And intakes of vitamin D supplementation reduced PD, CAL and GI. Therefore, vitamin D can improve periodontal health. Pathogenic bacteria were also significantly decreased after therapy with vitamin D.

Conclusion

Most of the existing research has found positive associations between the serum 25(OH)D level and periodontal health, and the clinical parameters of periodontal disease were reduced by vitamin D oral supplementation. However, some studies have shown contrary results, as the researchers did not consider the demographic characteristics, latitude, seasons, and lifestyle of the subjects. Therefore,

a more detailed categorization of the geographic, demographic, and lifestyle characteristics associated with the 25(OH)D level will be needed in future studies. In addition, clinicians need to gain a better understanding of the association between periodontal disease and vitamin D deficiency, and patients need to be better educated about the required vitamin D intake amount and food supplementation. In this regard, this review paper

can be used as a guide by clinicians and as a reference book for patients' education.

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Conflict of Interest

The authors declare that there are no conflicts of interest.

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