

## The Role of Vitamin D in Periodontal and Peri-Implant Health

Shervin Molayem<sup>1\*</sup>, Steven Lin<sup>2</sup> and Carla Cruvinel Pontes<sup>3</sup>

<sup>1</sup>Director, Mouth-Body Research Institute, Los Angeles, California

<sup>2</sup>Author, Functional Dentist, Australia

<sup>3</sup>Researcher, Mouth-Body Research Institute, Cape Town, South Africa

\***Corresponding author:** Shervin Molayem, Director, Mouth-Body Research Institute, Los Angeles, California.

**Citation:** Molayem S, Lin S, Pontes CC. (2021) Director, Mouth-Body Research Institute, Los Angeles, California. *J Oral Med and Dent Res.* 2(2):1-17.

**Received:** November 24, 2021 | **Published:** December 27, 2021

**Copyright** © 2021 by Molayem S, et al. All rights reserved. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

### Abstract

The study of rickets led to the discovery of vitamin D, which is a fat-soluble steroid hormone, whose precursor is converted into active metabolites in the skin when subjects to ultraviolet light. Few foods are rich in vitamin D, with sensible exposure to sunlight being the main natural source for the production of this vitamin. Vitamin D is carried by vitamin D-Binding Protein (DBP) in the circulation and binds to host cells through the Vitamin D Receptor (VDR). Several diseases and conditions have been linked to vitamin D deficiency and insufficiency, including periodontal disease. Vitamin D insufficiency is highly prevalent worldwide. It negatively impacts bone growth and metabolism, and multiple aspects of the immune response, mainly through the regulation of anti-microbial peptides such as Cathelicidin and  $\beta$ -defensins. Low vitamin D levels have been linked to increased gingival inflammation, periodontal destruction, alveolar bone loss, and tooth loss. It can also possibly affect osseointegration, although it has been explored in clinical studies on dental implants to a lesser degree. It is currently unclear whether vitamin D gene polymorphisms constitute risk factors for periodontitis. Higher levels of vitamin D can favor non-surgical and surgical periodontal treatment outcomes, which can be achieved through a combination of dietary changes, increased sunlight exposure, and supplementation. Serum levels of vitamin D should be

investigated in patients with severe periodontitis. Despite limited evidence on the benefits of vitamin D supplementation, higher levels of this critical micronutrient can be beneficial for restoring homeostasis in periodontitis patients.

### **Keywords**

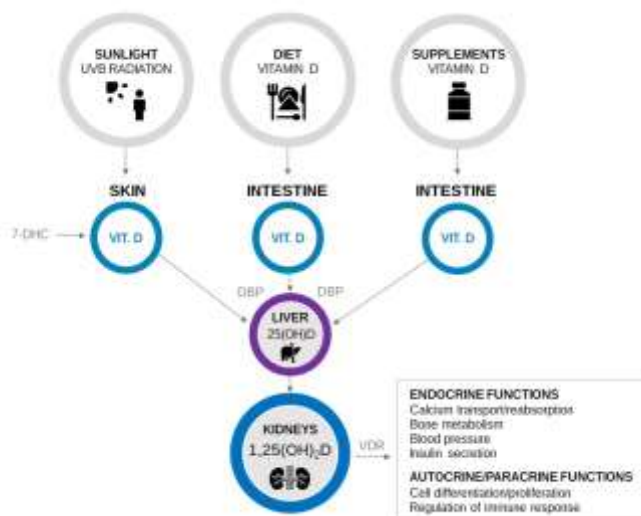
Rickets; Vitamin D; Gingival inflammation; Periodontitis; Peri-implant health

## **Introduction**

The discovery of the fat-soluble steroid hormone known as vitamin D (or calciferol) resulted from the study of rickets in the 1920s [1]. In the skin, a photochemical reaction triggered by exposure to ultraviolet light B (UV-B) converts the vitamin D precursor 7-dehydrocholesterol into vitamin D<sub>3</sub>(cholecalciferol). While vitamin D<sub>3</sub> is the natural form in humans, vitamin D<sub>2</sub> is found in fungi, yeast, and dietary foods. Typically, the term vitamin D refers to both vitamins D<sub>2</sub> and D<sub>3</sub>. In the liver, vitamin D is converted into its active metabolite 25-hydroxyvitamin D(25(OH)D or calcidiol), well-established biomarker for vitamin D serum levels [2,3]. Given the lipophilic nature of vitamin D and its metabolites, they bind to carrier proteins such as vitamin D binding protein (DBP) when transported through the blood circulation [4]. Primarily in the kidneys, 25(OH)D is converted into 1,25(OH)<sub>2</sub>D (also known as calcitriol), which presents several endocrine functions, including calcium transport and absorption, bone metabolism, blood pressure, and insulin secretion. Calcitriol also exerts autocrine and paracrine functions, affecting the immune response, cell proliferation, and differentiation. Thus, vitamin D plays a fundamental part in the maintenance of homeostasis and health [5].

In the skin, the precursor of vitamin 7-dehydrocholesterol (7-DHC) is converted into pre-vitamin D<sub>3</sub> and vitamin D<sub>3</sub> when exposed to UVB radiation. Diet and/or supplements are additional sources of vitamin D. From the skin and small intestine, vitamin D binds to vitamin D-binding protein (DBP) for transport to the liver via blood circulation. In the liver, vitamin D is converted into 25-hydroxyvitamin D (25(OH)D). In the kidneys, 25(OH)D is converted into 1,25(OH)<sub>2</sub>D, which is the active vitamin D metabolite responsible for its endocrine, autocrine, and paracrine functions.

Autoimmune diseases, infectious diseases, type 2 diabetes, preeclampsia, hypertension, cardiovascular disease, oral diseases, neurological disease, osteoporosis, different types of cancer, and higher overall mortality have been associated with vitamin D deficiency [6,7]. Deficiency is generally defined as values of 25(OH)D below 30 ng/ml [2,8,9]. It constitutes a public health challenge, affecting approximately 1 billion people around the globe. Insufficiency or subclinical deficiency can affect upto 50% of the world population [10,11]. General factors that contribute to low vitamin D levels and include decreased dietary intake, limited exposure to sunlight, reduced endogenous synthesis due to certain diseases, and lower hepatic catabolism due to certain medications [12]. Older age, obesity, dark skin, and conditions that change fat metabolism constitute additional factors that affect vitamin D status. Severe deficiency leads to incomplete mineralization of osseous tissues, which manifests as rickets in children, and osteomalacia in adults [6] (Figure 1).



**Figure 1:** Vitamin D conversion into its active metabolite and functions.

Based on the importance of adequate vitamin D levels for growth, development, homeostasis, and health, this review aims to present the current state of the art on the association between vitamin D deficiency, periodontal and peri-implant disease, and the effect of vitamin D supplements on periodontal and peri-implant health.

### Periodontal Disease and Vitamin D

Vitamin D deficiency has numerous detrimental effects on the body that contribute to systemic and oral changes. Dental caries and periodontitis, the two most ubiquitous oral conditions globally, have been associated with low levels of vitamin D [13]. The key destructive feature resulting from periodontal disease is alveolar bone loss, which is irreversible and can ultimately lead to tooth loss. This process is mediated by cytokines, and low bone density has been suggested as a risk factor for alveolar bone resorption. Studies on osteoporosis and low bone density indicate a positive correlation between these conditions and periodontal bone loss [14,15]. In the medical literature, randomized clinical trials (RCTs) have reported the beneficial effects of vitamin D supplementation on bone mineral density, which reduces the risk of fractures in the elderly [16,17].

In the oral cavity, vitamin D deficiency negatively impacts mineral density, growth, and preservation of the alveolar bone, increasing susceptibility to alveolar bone loss [18]. Furthermore, vitamin D's metabolite 1,25(OH)<sub>2</sub>D presents immunomodulatory effects that lead to reduced cytokine production, inflammation, and cellular proliferation, and increased production of antimicrobial peptides. Altogether, vitamin D has the potential to protect against bacterial infections and alveolar bone loss [19-21].

The relation between vitamin D and periodontal disease was explored in a large population-based US study. Serum levels of 25-hydroxyvitamin D(3) [25(OH)D(3)] were analyzed in 11,202 participants from the National Health and Nutrition Examination Survey (NHANES). In participants over 50 years, there was a significant association between low levels of vitamin D(3) and periodontal attachment loss, irrespective of total hip bone mineral density. This association was not influenced by smoking status,

race, socioeconomic factors, gingival bleeding, or use of estrogen among women [19].

In another study from the same group, over 77,000 NHANES participants were examined for gingival bleeding and serum levels of vitamin D<sub>3</sub>. Those with the highest vitamin D<sub>3</sub> levels had a 20% lower risk for gingival bleeding when compared to participants with the lowest levels. These findings suggest that vitamin D<sub>3</sub> may present anti-inflammatory activity in the periodontium [22]. Findings from a cross-sectional study on elderly males revealed that low total vitamin D intake increased the risk for severe periodontitis and alveolar bone loss [23].

Systematic reviews addressing this topic provide conflicting findings. With only one study on vitamin D included in their review, Van der Putten, et al. (2009) [24] found no correlation between nutritional deficiencies in non-institutionalized elderly and vitamin D status. In the systematic review from Pinto, et al. (2018) [25] 65% of the included studies associated vitamin D deficiency with periodontitis. Similarly, Peric, et al. (2018) [26] found a potential effect of vitamin D on the periodontium, despite the scarcity of robust studies. An association between periodontal disease and low vitamin D levels was reported in the systematic review by Varela-Lopez et al. [27].

According to a recent systematic review and meta-analysis from Machado, et al. (2020) [28] chronic periodontitis was associated with lower levels of 25(OH)D. The authors highlighted that periodontitis patients are likely to present reduced serum levels of vitamin D, however more powerful studies are warranted to elucidate the clinical consequences of this deficiency [28]. The majority of clinical studies on vitamin D suggest that vitamin D deficiency is a predisposing factor for gingival inflammation and chronic periodontitis (Table 1).

Year	N	Biomarker	Results
2004	11202	25(OH)D <sub>3</sub>	Association - vitamin D deficiency and periodontal disease
2005	6700	25(OH)D	Association - vitamin D deficiency and gingival inflammation
2019	74	25(OH)D	Vitamin D deficiency - potential risk factor for aggressive periodontitis
2013	44 cases, 32 controls	25(OH)D <sub>3</sub>	Higher vitamin D and DBP in aggressive periodontitis
2014	59 cases, 58 controls	DBP	Higher plasma levels, lower GCF levels DBP associated with aggressive periodontitis
2020	21	25(OH)D <sub>3</sub>	Negative correlation between vitamin D <sub>3</sub> and salivary cytokine levels
2019	42	Vitamin D	Vitamin D levels associated with periodontitis through radiographic bone loss
2019	150	1,25(OH) <sub>2</sub> D	Low vitamin D levels, high DBP levels associated with periodontitis
2018	15000	Vitamin D	Decreased vitamin D in females associated with periodontitis
2017	29 cases, 29 controls	25(OH)D	Vitamin D deficiency associated with periodontal disease
2016	24 cases, 24 controls	25(OH)D	Lower vitamin D levels significantly associated with periodontitis
2012	21	Vitamin D	High vitamin D linked to better periodontal clinical markers, fewer missing

			teeth, less pathogenic bacteria
2014	20 cases, 20 controls	25(OH)D	Vitamin D associated with periodontal disease
2016	71	Vitamin D	Pregnant women more deficient in Vitamin D than non-pregnant women, but no association between low vitamin D levels and periodontal disease
2019	5604	25(OH)D	Low vitamin D had modest association with periodontal disease parameters
2011	123 cases, 123 controls	25[OH]D	Vitamin D insufficiency associated with maternal periodontal disease during pregnancy
2013	920	25(OH)D	Vitamin D inversely associated with gingival bleeding in postmenopausal women
2009	178	25(OH)D3	Plasma calcifediol levels might be associated with periodontal inflammation in aggressive periodontitis
2016	780	25(OH)D	No association between vitamin D status and tooth loss in postmenopausal females
2015	6011	25(OH)D	Association between vitamin D deficiency and periodontal status in current smokers
2020	701	25(OH)D	No association between vitamin D and CPI scores
2015	1262	25(OH)D	No association between vitamin D periodontal parameter
2015	55 cases, 30 controls	1,25(OH) <sub>2</sub> D	Low vitamin D appeared to be associated with periodontitis
2014	1904	25(OH)D	Vitamin D might be protective against tooth loss
2014	42730	25(OH)D	Association between predictors of vitamin D and lower incidence of tooth loss and periodontitis
2010	19	25(OH)D3	Low local and systemic vitamin D in patients with aggressive periodontitis
2020	5405	25(OH)D	Vitamin D levels associated with number of remaining teeth and severity of periodontitis.

**Table 1:** Clinical studies investigating the link between vitamin D and periodontal disease in otherwise healthy patients.

DBP- Vitamin D-Binding Protein; GCF-Gingival Crevicular Fluid; CPI-Community Periodontal Index.

A few studies have reported higher levels of vitamin D and DBP in patients with generalized aggressive periodontitis when compared to controls with a healthy periodontium [29-31]. Hence, while in chronic periodontitis vitamin D deficiency seems to contribute to gingival inflammation and alveolar bone destruction, the opposite could be true for aggressive periodontitis, i.e. inflammation is likely promoted by high gingival levels of vitamin D3. One possible explanation for these findings is the high concentration of the 25-hydroxylase enzyme in acute inflammation, which increases vitamin D3 levels [29]. However, Anbarcioglu, et al. [32] reported contradictory results of lower vitamin D levels in 47 aggressive periodontitis patients, compared to 27 controls with a healthy periodontium.

### Periodontal Treatment and Vitamin D Levels

Gao, et al. [33] evaluated the effect of vitamin D short-term supplementation as an adjunct to non-

surgical periodontal treatment. Findings from this RCT showed statistically significant improvement in attachment loss and pocket probing depth as a result of supplementation, although of small magnitude [33]. In a non-randomized clinical trial, lower gingival bleeding, and higher bone density were observed after non-surgical periodontal therapy in participants who took vitamin D and calcium supplements for 3 months [34].

Bashutski, et al. [35] observed that vitamin D deficient patients presented less gain in clinical attachment and lower pocket depth reduction one year after periodontal surgery when compared to vitamin D sufficient patients. The authors suggested that adequate vitamin D levels possibly promote the formation of bone during healing [35].

A study evaluating periodontal patients enrolled in a maintenance program compared those who had taken vitamin D and calcium supplements for a minimum of 18 months to those who did not take these supplements. Although there was a tendency for worse attachment loss, gingival bleeding, and pocket probing depth for the non-supplement group, these differences did not reach statistical significance. The authors highlighted that their findings could be partially explained by the generally low intake of vitamin D [36,37].

In a small group of patients with generalized aggressive periodontitis, despite the initially high vitamin D levels, non-surgical periodontal therapy was able to lower serum levels of vitamin D3 levels at 6 months follow-up [30]. As mentioned in the previous section, not all studies support higher vitamin D levels in aggressive periodontitis patients, hence further studies are warranted [32]. Given the importance of vitamin D in bone homeostasis and immune function, inadequate levels likely contribute to negative periodontal treatment outcomes in chronic periodontitis patients.

### **Vitamin D Supplementation and Periodontal Health**

In a RCT, vitamin D and calcium supplementation was linked to decreased risk for tooth loss in healthy elderly participants over 3 years [38]. In another study, supplementation with calcium and vitamin D was associated with a 36% decrease in post-extraction ridge resorption in immediate denture participants when compared to placebo after 1 year [39]. When the periodontal status of older men was analyzed in relation to vitamin D levels, those with the highest daily vitamin D intake had the lowest risk for severe periodontitis, described in terms of pocket depth, clinical attachment, and alveolar bone loss [23]. Hiremath, et al. [40] analyzed the effect of three different doses of vitamin D supplementation (2000 UI, 1000 UI, and 500 UI) on gingivitis as compared to placebo. After 3 months of supplementation, there was significantly less gingival inflammation in the vitamin D groups, with the highest doses presenting quicker results [40].

In a small sample of patients subjected to maxillary sinus augmentation, supplementation with vitamin D3 and calcium for 6-8 months did not influence bone formation nor graft resorption when compared to the placebo group [41]. Despite the apparent benefit of vitamin D supplementation on periodontal health from the dental literature, there are still unanswered questions about the ideal dose, the impact of sunlight exposure and diet on patient outcomes, and the effect of the supplements, given that the majority of research explored the combination of calcium and vitamin D (Table 2). Because vitamin D

deficiency affects calcium absorption, the impact of this combination should be compared to vitamin D in the prevention and management of periodontal disease [42].

Year	N	Supplement	Follow-up	Outcomes
2001	145	Vit.D+ Ca or placebo	2 year	Calcium and vitamin D for osteoporosis prevention are beneficial for tooth retention.
1979	46	Vit.D or placebo	1 year	Alveolar bone loss was reduced by 36% in immediate denture patients receiving supplement
2011	51	Vit.D+ Ca	1 year	Modest positive effect of supplementation on periodontal health
2009	51	Vit.D+ Ca	Cross-sectional	In periodontal maintenance, there was a trend for better periodontal health with supplementation
2020	360	Vit.D or placebo	3 months	Vitamin D supplementation improved periodontal conditions, but with small effect size
2015	77	Vit.D+ Ca	3 months	Supplementation had positive effect on periodontal health as adjunct to non-surgical treatment
2013	96	Vit.D or placebo	3 months	Vitamin D had dose-dependent anti-inflammatory effect on gingivitis
2011	40	Vit.D+ Ca	1 year	Vitamin D deficiency at the time of periodontal surgery negatively affects treatment outcomes
2013	562	Vit.D	Cross-sectional	High vitamin D intake lowered odds of severe periodontal disease and alveolar bone loss
2015	20	Vit. D3 + Ca	6-8 months	In maxillary sinus augmentation, supplementation did not affect bone formation or graft resorption

**Table 2:** Clinical studies on the effects of vitamin D supplementation on periodontal disease.

### Vitamin D-Binding Protein

In the circulation, the major carrier for vitamin D is DBP, a molecule mainly secreted by hepatic cells. DBP is highly expressed in plasma and presents multiple other functions, such as actin-binding, macrophage activation, osteoclast activation, bone metabolism, and leukocyte chemotaxis [43]. In generalized aggressive periodontitis, plasma DBP levels were higher when compared to healthy controls and correlated to periodontal disease severity [31,44].

In a small study that included 13 patients with chronic periodontitis and 19 controls, higher salivary levels of DBP were reported in relation to control subjects without periodontitis and presented a positive correlation with gingival index scores [45]. Similarly, in a case-control study from Rafique, et al. [46] high DBP levels combined with low vitamin D levels were observed in chronic periodontitis cases when compared to controls. In a healthy adult, 85% of circulating 25(OH)D is bound to DBP, and about 15% is bound to albumin. Therefore, although DBP has the potential to participate in periodontal destruction, 25(OH)D seems to be the best biomarker for vitamin D levels, as it includes molecules bound to both proteins [43].

### **Antimicrobial Properties of Vitamin D**

Cellular expression of anti-microbial peptides constitutes a key defense mechanism when the body is faced with bacterial challenges. The antimicrobial effects of these peptides are typically linked to the creation of pores in bacterial membranes. These molecules also present other important immune functions, being produced by a variety of cells, including epithelial cells, macrophages, lymphocytes, and neutrophils. One of the mechanisms explaining the antimicrobial and immunomodulatory roles of vitamin D is through the regulation of two major peptide groups: beta-defensins and cathelicidin [47,48].

When vitamin D metabolites bind to vitamin D receptors (VDR), which are expressed by the majority of cells, peptide expression is triggered to boost the host response to microorganisms [49]. Cathelicidin LL-37 presents potent antimicrobial activity against Gram-positive and negative bacteria and certain viruses. It possesses chemotactic function and influences the maturation of dendritic cells. Cytokines, bacterial products, and vitamin D3 can induce the expression of cathelicidin LL-37 [50]. Beta-defensins are particularly abundant in human epithelial cells. Similarly to LL-37,  $\beta$ -defensins have broad-spectrum antimicrobial activity, being an important feature of the body's immune defense [51].

In the periodontium, gingival epithelial cells and neutrophils are the primary sources of  $\beta$ -defensins and LL-37. These peptides have also been identified in saliva, and gingival crevicular fluid (GCF) [50-52]. According to Hosokawa, et al. [52] LL-37, and  $\beta$ -defensin 2 levels were elevated in inflamed gingiva when compared to healthy gingiva. In vitamin D deficient patients with chronic periodontitis or gingivitis, lower levels of LL-37 and  $\beta$ -defensin 2 were observed in the GCF and gingival tissues when compared to patients with adequate vitamin D levels [53]. Vitamin D deficiency lowers the expression of these anti-microbial peptides in the oral mucosa and periodontal tissues, making the immune response to periodontal pathogens less effective. These findings suggest a potential therapeutic role for vitamin D in periodontitis patients [50].

### **Peri-Implant Disease and Vitamin D**

The success of implant-based restorations depends primarily on osseointegration, which can be affected by multiple factors. While external factors linked to the surgical protocol and implant design have received a lot of focus, host factors such as vitamin D deficiency can possibly contribute to implant failure [54]. The impact of vitamin D status on peri-implant tissues has been less explored in relation to its effect on periodontal tissues.

The majorities of studies in this field is experimental and have focused on the potential of vitamin D surface treatment or as a supplement to improve osseointegration, bone to implant contact (BIC), dental implant's survival, and success (Table 3). In vitamin D3 deficient rats subjected to miniature dental implants placed in the femur, lower BIC and lower push-in test values were reported in comparison to vitamin D sufficient rats [55]. As a supplement, results from other animal studies on vitamin D3 provide overall positive results, with increased BIC, bone volume, and improved osseointegration reported by the majority [56-59]. Two studies show a lack of effect of supplementation



on BIC and bone formation [60,61].

Year	N	Biomarker	Focus	Results
2021	122	25(OH)D3	Clinical bone formation	In vitamin D deficient patients, supplementation increased bone formation around implants
2020	32	Vit.D3	Clinical bone loss	Vitamin D deficient patients who received supplements tended to present less marginal bone loss
2019	53	25(OH)D3	Clinical early implant failure	Vitamin D lower in peri-implantitis group compared with peri-implant mucositis and peri-implant healthy groups
2018	885	Vit. D	Clinical early implant failure	Trend toward increased incidence of early implant failure in the presence of low vitamin D levels
2016	822	Vit. D	Clinical early implant failure	No association between low vitamin D levels and early implant failure
Year	Method	Results		
2015	Fibroblast behavior	Vitamin D3 surface treatment led to positive effects on soft tissue integration due to better fibroblast behavior		
2012	Vit.D3 supplement	Supplementation improved implant osseointegration in osteoporotic rats		
2014	Vit.D3 coating	Vitamin D3 coating did not improve bone formation around dental implants		
2013	Vit.D3 supplement	Vitamin D3 and insulin enhanced implant osseointegration in diabetic rats		
2012	Vit.D3 supplement	Vitamin D deficiency had a negative impact on cortical peri-implant bone formation in ovariectomized rats		
2014	Vit.D3 supplement	Supplementation improved the fixation of titanium implants in rats with chronic kidney disease.		
2011	Vit.D3 coating	Vitamin D3 coating may stimulate bone formation adjacent to dental implants.		
2016	Vit.D3 supplement	No differences between groups with and without supplement regarding bone volume		
2009	Vitamin D3 deficiency	BIC and push-in implant test had lower values in vitamin D3 deficient rats		

**Table 3:** Studies on the link between vitamin and peri-implant tissues. BIC – bone-to-implant contact.

The impact of coating dental implant abutments with a vitamin D precursor (7-dehydrocholesterol), vitamin E, and ultraviolet-irradiation was investigated by Satue, et al. [62]. The authors reported a positive effect on soft tissue integration. Naito, et al. [60] reported a lack of difference in the osseointegration of titanium implants with and without a Vitamin D3 coating. On the contrary, Cho, et al. [63] reported a beneficial effect of vitamin D3 coating on bone formation around dental implants placed in rabbits' tibia. When comparing the cellular behavior around different abutment surface modifications in a systematic review, Corvino, et al. [64] concluded that the use of vitamin D precursor coating led to worse results than machined titanium in terms of fibroblast behavior.

Very few clinical studies have been conducted to evaluate the possible effects of vitamin D deficiency in peri-implant diseases. Two case reports provide information on early implant failure in three patients who were vitamin D deficient [65,66]. In one of the reports, supplementation with vitamin D after implant failure resulted in the successful osseointegration of new implants [66]. In two retrospective studies, Mangano, et al. [67] evaluated early implant loss and vitamin D levels in over 800 patients. Despite a trend for reduced vitamin D levels in patients who lost dental implants in one study, there was no statistically significant association between vitamin D levels and implant failure [67,68]. In a cross-sectional study including 53 participants, mean vitamin D3 GCF levels were lower in peri-implantitis sites as compared to peri-implant mucositis and healthy peri-implant sites. Low vitamin D3 levels were associated with worse peri-implant status, measured as clinical attachment level, pocket depth, gingival bleeding, and plaque index [69]. Higher vitamin D levels on the dental implant surgery day were associated with lower marginal bone loss after 6 and 12 months in the RCT from Kwiatak and co-workers [70]. Accordingly, on a prospective clinical trial, there was a tendency for less peri-implant bone loss in patients taking vitamin D3 supplements [71]. Despite the limited number of studies, clinical findings support a potential role for supplementation in vitamin D deficient patients subjected to implant-based tooth replacement.

### **Vitamin-D Gene Polymorphisms in Periodontal and Peri-Implant Diseases**

The active vitamin D metabolites bind to VDRs in the cellular surface to control the expression of several proteins. Polymorphisms in the VDR gene have been associated with the regulation of osseous metabolism and suggested to increase genetic susceptibility to a number of conditions, including but not limited to osteoporosis, cancer, chronic liver disease, tuberculosis, and autoimmune diseases. The most explored VDR gene single nucleotide polymorphisms in the VDR gene are BsmI, Apal, FokI and TaqI [72].

Numerous studies have explored the potential link between chronic periodontitis and BsmI, Apal, FokI, and TaqI VDR polymorphisms. In 2011, findings from a systematic review and meta-analysis including 15 studies from Deng, et al. [73] suggest that the BsmI, Apal, and TaqI were related to increased susceptibility to chronic periodontitis in Asians, with association observed for aggressive periodontitis. Later, the systematic review and meta-analysis from Mashhadiabbas, et al. (2018) [74] comprehensively summarized the results of 10 studies on the BsmI polymorphism, 16 studies on the TaqI polymorphism, 5 studies on the FokI polymorphism, and 7 studies on the Apal polymorphism. Overall, there was no association between the VDR polymorphisms and risk for chronic periodontitis. However, when subgroup analysis was performed according to ethnicity, Caucasians presenting the BsmI polymorphism may be at higher risk for chronic periodontitis [74]. The mechanism through which the BsmI polymorphism has not been established, as it does not lead to functional changes in VDRs, but might influence the stability of VDR mRNA [75].

Only a few studies have investigated dental implant failures and the prevalence of VDR gene polymorphisms. Alvim-Pereira, et al. [76] compared 80 patients who suffered at least one dental implant loss to controls and patients who never lost an implant. Local factors such as primary stability and implant position were linked to implant loss, however, no association was observed between the TaqI

polymorphism and implant loss [76]. A recent study compared patients with a single implant loss to those with multiple losses in terms of clinical parameters and VDR gene polymorphisms. The authors performed a complete mapping of the VDR gene and reported that the rs3782905 VDR polymorphism was associated with loss of two or more dental implants [77].

Despite the high number of studies addressing VDR gene polymorphisms in periodontal disease, currently, there is no single vitamin D gene polymorphism that can explain susceptibility to periodontitis, which points out the complexity of the interplay between environmental, host, and genetic factors in different ethnic groups.

## Sources of Vitamin D

### Diet

Dietary sources of vitamin D are limited and include oily fish, such as rainbow trout, herring, mackerel, sardines, tuna, and salmon, red meat, beef liver, egg yolks, liver, fortified foods, such as breakfast cereals, and certain mushrooms [78]. A small study where participants in the experimental group followed a healthy diet for four weeks demonstrated that a diet rich in Omega-3 fatty acids, fibers, vitamin C, and D can contribute to periodontal health [42]. Despite a similar plaque index, the experimental group presented lower gingival index, bleeding on probing, and periodontal inflamed surface area than the control group.<sup>79</sup>The Recommended Dietary Allowance (RDA) for adults older than 19 years is 600 IU daily. The RDA for the elderly (>70 years) is 800 IU daily. The highest daily intake should not exceed 4,000 IU [6].

### Sunlight

Exposure to sunlight (UV-B) is the best source of vitamin D due to the high potential for the skin to produce and store it. Furthermore, whereas most foods can provide limited amounts of vitamin D, the skin can produce between 80 and 100% of the body's requirements. When exposed to sunlight in the skin, the vitamin D precursor 7-dehydrocholesterol absorbs radiation, being converted into pre-vitamin D<sub>3</sub> and vitamin D<sub>3</sub> [80].

Several factors can limit vitamin D skin production, such as the use of dark clothing, skin pigmentation, air pollution, aging, use of sunscreen, geographic location, time of the day, and getting the sunlight through glass or plastic [81]. The medical literature recommends sensible sun exposure to boost vitamin D production, which translates into being exposed to sunlight for 50% of the time required to cause mild sunburn. It has been estimated that 30 minutes of midday sun exposure during summer in Oslo, Norway, produces the equivalent of 10,000–20,000 IU of vitamin D [82]. Depending on the factors mentioned above, 10-20 minutes of unprotected sun exposure a few times a week can help increase vitamin D levels in the general population; however, potentially negative side effects of UV irradiation should also be considered [6].

### Supplementation

The ideal vitamin D concentrations (25(OH)D) to promote general health range from 30 to 50 ng/mL. It

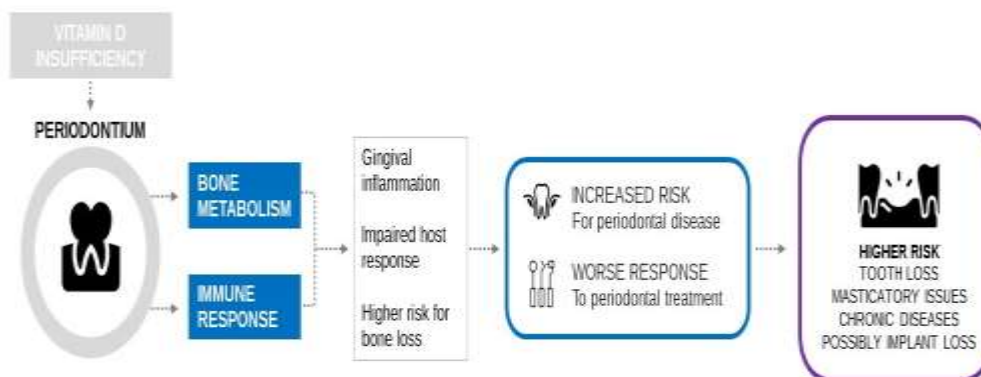
has been suggested that dietary vitamin D sources might not be enough to maintain adequate vitamin D levels during the year, particularly in countries that are distant from the Equator. When regular sensible sun exposure is not possible, supplementation can elevate vitamin D levels more efficiently. The potential benefits of adequate vitamin levels include, but are not limited to reduced risk for neurodegenerative disorders, infections, heart failure, stroke, cardiovascular disease, diabetes, cancer, autoimmune diseases, and infections [2,6,83]. In the oral cavity, vitamin D insufficiency has been linked to higher risk for chronic periodontitis, recurrent aphthous stomatitis, oral cancer, caries, and defective tooth mineralization, with potential effects on orthodontic tooth movement, and dental implant osseointegration and BIC [13,54,61,84].

For the general population, the RDA of 600 IU daily for healthy adults below 70 years of age and 800 IU for those 70 years and older should be used as a reference for supplementation. Adequate vitamin D levels for patients suffering from a specific disease might require 3,000-5,000 IU per day to achieve serum concentrations between 30-60 ng/mL [2,8,9]. For patients with laboratory-confirmed vitamin D deficiency, individual doses should be adjusted according to age and bodyweight, and supplementation should carry on for 1-3 months. Vitamin D supplements can adversely affect certain medications, such as orlistat, statins, steroids and thiazide diuretics [83].

### **Take-Home Message**

Reduced vitamin D levels increase the risk for multiple diseases, including chronic periodontitis. Vitamin D is essential for the regulation of bone tissues and the immune system, playing an important role in the maintenance of periodontal health. It also presents anti-inflammatory properties, mainly through the promotion of potent anti-microbial peptides in the oral and gingival epithelium, such as cathelicidin LL-37 and defensins.

While severe vitamin D deficiency has a strong impact on the body, insufficiency is even more prevalent and likely to affect gingival inflammation, alveolar bone metabolism, mineral density, and periodontal disease progression, ultimately increasing the risk for tooth loss and reduced masticatory function. It can also affect the results of periodontal surgical and non-surgical treatment and dental implant placement. Severe chronic periodontitis patients should ideally be investigated for serum vitamin D levels. If levels are lower than 30 ng/mL, increased dietary consumption of vitamin D-rich foods, increased exposure to sunlight, and/or supplementation should be considered in collaboration with the patient's general practitioner. Although findings from studies on the effect of vitamin D supplements in the gingiva are conflicting, the majority of clinical studies report positive effects on the periodontium after 1-3 months. Furthermore, vitamin D supplements are generally safe, presenting a low risk for side effects. The combination of calcium and vitamin D seems beneficial, although further studies are required to define specific advantages of this combination versus vitamin D alone (Figure 2).



**Figure 2:** Simplified overview on the potential effects of vitamin D insufficiency on the periodontium.

The impact of low vitamin D levels on peri-implant tissues and osseointegration has been explored to a lesser degree. Most studies have investigated vitamin D supplementation or coating to dental implants. There is a potential for vitamin D supplementation to improve peri-implant tissue status, however, there is low evidence to support vitamin D supplementation for healthy patients subjected to dental implant placement.

## Conclusion

Vitamin D is a critical micronutrient that influences the entire body. Low levels of vitamin D are highly prevalent worldwide and constitute a health hazard linked to a higher risk for multiple serious diseases and conditions. In the periodontium, vitamin D promotes bone regulation and immune protection against bacteria. Vitamin D insufficiency can predispose to gingival inflammation, periodontal destruction, and tooth loss, potentially affecting periodontal treatment outcomes. Hence, higher vitamin D levels can be suggested for chronic periodontitis patients, which can be achieved through a combination of diet, sunlight exposure, and/or supplements. More robust studies are required, and factors that affect vitamin D production and metabolism should be addressed such as sun exposure, diet intake, and seasonal fluctuations.

## References

1. Steenbock H, Black A, Nelson MT, Hoppert CA, Riising BM. (1925) Fat-soluble vitamins: XXIII. The induction of growth-promoting and calcifying properties in fats and their unsaponifiable constituents by exposure to light. *Int J Biol Chem.* 64(2):263-98.
2. Holick MF. (2007) Medical progress: Vitamin D deficiency. *N Engl J Med.* 357:266-81.
3. DeLuca H. (2004) Overview of general physiologic features and functions of vitamin D. *Am J Clin Nutr.* 80(6):1689S-96S.
4. Cooke N, Haddad JG. (1989) Vitamin D binding protein (Gc-globulin). *Endocr Rev.* 10(3):294-307.
5. Dusso A, Brown A, Slatopolsky E. (2005) Vitamin D. *Am J Physiol Renal Physiol.* 289:F8-28.
6. Holick M. (2017) The vitamin D deficiency pandemic: Approaches for diagnosis, treatment and prevention. *Rev Endocr Metab Disord.* 18(2):153-65.
7. Pludowski P, Holick MF, Pilz S, Wagner CL, Hollis BW, et al. (2013) Vitamin D effects on musculoskeletal health, immunity, autoimmunity, cardiovascular disease, cancer, fertility, pregnancy, dementia and

- mortality-a review of recent evidence. *Autoimmun Rev.* 12(10):976-89.
8. Glerup H, Mikkelsen K, Poulsen L, Hass E, Overbeck S, et al. (2000) Commonly recommended daily intake of vitamin D is not sufficient if sunlight exposure is limited. *J Intern Med.* 247(2):260-8.
  9. Amrein K, Scherkl M, Hoffmann M, Neuwersch-Sommeregger S, Köstenberger M, et al. (2020) Vitamin D deficiency 2.0: an update on the current status worldwide. *Eur J Clin Nutr.* 74(11):1498-513.
  10. Palacios C, Gonzalez L. (2014) Is vitamin D deficiency a major global public healthproblem? *J Steroid Biochem Mol Biol.* 144:138-45.
  11. Nair R, Maseeh A. (2012) Vitamin D: The “sunshine” vitamin. *J Pharmacol Pharmacother.* 3(2):118.
  12. Sizar O, Khare S, Goyal A, Bansal P, Givler A. (2021) Vitamin D Deficiency. vol. PMID: 30335299. Treasure Island: StatPearls Publishing.
  13. Botelho J, Machado V, Proença L, Delgado AS, Mendes JJ. (2020) Vitamin D deficiency and oral health: A comprehensive review. *Nutrients.* 12(5):1471.
  14. Krall E. (2001) The periodontal-systemic connection: implications for treatment of patients with osteoporosis and periodontal disease. *Ann Periodontol.* 6(1):209-13.
  15. Krall EA, Garcia RI, Dawson-Hughes B. (1996) Increased risk of tooth loss is related to bone loss at the whole body, hip, and spine. *Calcif Tissue Int.* 59(6):433-7.
  16. Trivedi DP, Doll R, Khaw KT. (2003) Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind. *Br Med J.* 326(7387):469.
  17. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. (1997) Effect of Calcium and Vitamin D Supplementation on Bone Density in Men and Women 65 Years of Age or Older. *N Engl J Med.* 337(10):670-6.
  18. Jimenez M, Giovannucci E, Kaye EK, Joshipura KJ, Dietrich T. (2014) Predicted vitamin D status and incidence of tooth loss and periodontitis. *Public Health Nutr.* 17(4):844-52.
  19. Dietrich T, Joshipura KJ, Dawson-Hughes B, Bischoff-Ferrari HA. (2004) Association between serum concentrations of 25-hydroxyvitamin D3 and periodontal disease in the US population. *Am J Clin Nutr.* 80(1):108-13.
  20. Dale BA, Kimball JR, Krisanaprakornkit S, Roberts F, Robinovitch M, et al. (2001) Localized antimicrobial peptide expression in human gingiva. *J Periodontal Res.* 36(5):285-94.
  21. White JH. (2008) Vitamin D signaling, infectious diseases, and regulation of innate immunity. *Infect Immun.* 76(9):3837-43.
  22. Dietrich T, Nunn M, Dawson-Hughes B, Bischoff-Ferrari HA. (2005) Association between serum concentrations of 25-hydroxyvitamin D and gingival inflammation. *Am J Clin Nutr.* 82(3):575-80.
  23. Alshouibi EN, Kaye EK, Cabral HJ, Leone CW, Garcia RI. (2013) Vitamin D and periodontal health in older men. *J Dent Res.* 92(8):689-93.
  24. van der Putten GJ, Vanobbergen J, De Visschere L, Schols J, de Baat C. (2009) Association of some specific nutrient deficiencies with periodontal disease in elderly people: A systematic literature review. *Nutrition.* 25(7-8):717-22.
  25. Pinto JP, Goergen J, Muniz FW, Haas AN. (2018) Vitamin D levels and risk for periodontal disease: A systematic review. *J Periodontal Res.* 53(3):298-305.
  26. Perić M, Cavalier E, Toma S, Lasserre JF. (2018) Serum vitamin D levels and chronic periodontitis in adult, Caucasian population-a systematic review. *J Periodontal Res.* 53(5):645-56.
  27. Varela-López A, Navarro-Hortal MD, Giampieri F, Bullón P, Battino M, et al. (2018) Nutraceuticals in Periodontal Health: A Systematic Review on the Role of Vitamins in Periodontal Health Maintenance. *Mol.* 23(5):1226.
  28. Machado V, Lobo S, Proença L, Mendes JJ, Botelho J. (2020) Vitamin D and Periodontitis: A Systematic Review and Meta-Analysis. *Nutr.* 12(8):2177.

29. Liu K, Meng H, Tang X, Xu L, Zhang L, et al. (2009) Elevated Plasma Calcifediol Is Associated With Aggressive Periodontitis. *J Periodontol.* 80(7):1114-20.
30. Liu K, Meng H, Lu R, Xu L, Zhang L, et al. (2010) Initial Periodontal Therapy Reduced Systemic and Local 25-Hydroxy Vitamin D<sub>3</sub> and Interleukin-1 $\beta$  in Patients With Aggressive Periodontitis. *J Periodontol.* 81(2):260-6.
31. Zhang X, Meng H, Sun X, Xu L, Zhang L, et al. (2013) Elevation of vitamin D-binding protein levels in the plasma of patients with generalized aggressive periodontitis. *J Periodontal Res.* 48(1):74-9.
32. Anbarcioglu E, Kirtiloglu T, Öztürk A, Kolbakir F, Acıkgöz G. (2019) Vitamin D deficiency in patients with aggressive periodontitis. *Oral Dis.* 25:242-49.
33. Gao W, Tang H, Wang D, Zhou X, Song Y, et al. (2020) Effect of short-term vitamin D supplementation after nonsurgical periodontal treatment: A randomized, double-masked, placebo-controlled clinical trial. *J Periodontal Res.* 55:354-62.
34. Perayil J, Menon K, Kurup S, Thomas AE, Fenol A. (2015) Influence of vitamin D & calcium supplementation in the management of periodontitis. *J Clin Diagnostic Res.* b9:ZC35.
35. Bashutski JD, Eber RM, Kinney JS, Benavides E, Maitra S, et al. (2011) The impact of vitamin D status on periodontal surgery outcomes. *J Dent Res.* 90(8):1007-12.
36. Garcia MN, Hildebolt CF, Miley DD, Dixon DA, Couture RA, et al. (2011) One-year effects of vitamin D and calcium supplementation on chronic periodontitis. *J Periodontol.* 82(1):25-32.
37. Miley DD, Garcia MN, Hildebolt CF, Shannon WD, Couture RA, et al. (2009) Cross-sectional study of vitamin D and calcium supplementation effects on chronic periodontitis. *J Periodontol.* 80(9):1433-9.
38. Krall EA, Wehler C, Garcia RI, Harris SS, Dawson-Hughes B. (2001) Calcium and vitamin D supplements reduce tooth loss in the elderly. *Am J Med.* 111(6):452-6.
39. Wical. KE, Brussee P. (1979) Effects of a calcium and vitamin D supplement on alveolar ridge resorption in immediate denture patients. *J Prosthet Dent.* 41(1):4-11.
40. Hiremath VP, Rao CB, Naik V, Prasad KV. (2013) Anti-inflammatory effect of vitamin D on gingivitis: a dose-response randomised control trial. *Oral Heal Prev Dent.* 11(1):61-9.
41. Schulze-Späte U, Dietrich T, Wu C, Wang K, Hasturk H, et al. (2016) Systemic vitamin D supplementation and local bone formation after maxillary sinus augmentation- a randomized, double-blind, placebo-controlled clinical investigation. *Clin Oral Implants Res.* 27(6):701-6.
42. Velden U Van der, Kuzmanova U, Chapple I. (2011) Micronutritional approaches to periodontal therapy. *J Clin Periodontol.* 38:142-58.
43. Bikle DD, Schwartz J. (2019) Vitamin D binding protein, total and free Vitamin D levels in different physiological and pathophysiological conditions. *Front Endocrinol (Lausanne).* 10:317.
44. Zhang X, Meng H, Xu L, Zhang L, Shi D, et al. (2014) Vitamin D-binding protein levels in plasma and gingival crevicular fluid of patients with generalized aggressive periodontitis. *Int J Endocrinol.* 2014.
45. Krayer JW, Emerson DL, Goldschmidt-Clermont PJ, Nel AE, Werner PA, et al. (1987) Qualitative and quantitative studies of Gc (vitamin D-binding protein) in normal subjects and patients with periodontal disease. *J Periodontal Res.* 22(4):259-63.
46. Rafique S, Hingorjo MR, Mumtaz M, Qureshi MA. (2019) The relationship of 1,25-dihydroxyvitamin D and Vitamin D binding protein in periodontitis. *Pakistan J Med Sci.* 35(3):847.
47. Youssef DA, Miller CW, El-Abbassi AM, Cutchins DC, Cutchins C, et al. (2011) Antimicrobial implications of vitamin D. *Dermatoendocrinol.* 3(4):220-9.
48. Greer A, Zenobia C, Darveau RP. (2013) Defensins and LL-37: A review of function in the gingival epithelium. *Periodontol 2000.* 63(1):67-79.
49. Ji S, Hyun J, Park E, Lee BL, Kim KK, et al. (2007) Susceptibility of various oral bacteria to antimicrobial peptides and to phagocytosis by neutrophils. *J Periodontal Res.* 42(5):410-9.

50. McMahon L, Schwartz K, Yilmaz O, Brown E, Ryan LK, et al. (2011) Vitamin D-Mediated Induction of Innate Immunity in Gingival Epithelial Cells. *Infect Immun.* 79(6):2250-6.
51. Dale B, Fredericks L. (2005) Antimicrobial peptides in the oral environment: expression and function in health and disease. *Curr Issues Mol Biol.* 7(2):119-34.
52. Hosokawa I, Hosokawa Y, Komatsuzawa H, Goncalves RB, Karimbux N, et al. (2006) Innate immune peptide LL-37 displays distinct expression pattern from beta-defensins in inflamed gingival tissue. *Clin Exp Immunol.* 146(2):218-25.
53. Bayirli B, Öztürk A, Avci B. (2020) Serum vitamin D concentration is associated with antimicrobial peptide level in periodontal diseases. *Arch Oral Biol.* 117:104827.
54. Javed F, Malmstrom H, Kellesarian SV, Al-Kheraif AA, Vohra F, et al. (2016) Efficacy of vitamin D3 supplementation on osseointegration of implants. *Implant Dent.* 25(2):281-7.
55. Kelly J, Lin A, Wang CJ, Park S, Nishimura I. (2009) Vitamin D and Bone Physiology: Demonstration of Vitamin D Deficiency in an Implant Osseointegration Rat Model. *J Prosthodont.* 18(6):473-8.
56. Zhang HY, Feng L, Wu H, Xie XD. (2014) The association of IL-6 and IL-6R gene polymorphisms with chronic periodontitis in a Chinese population. *Oral Dis.* 20(1):69-75.
57. Dvorak G, Fügl A, Watzek G, Tangl S, Pokorny P, et al. (2012) Impact of dietary vitamin D on osseointegration in the ovariectomized rat. *Clin Oral Implants Res.* 23(11):1308-13.
58. Zhou C, Li Y, Wang X, Shui X, Hu J. (2012) 1, 25Dihydroxy vitamin D3 improves titanium implant osseointegration in osteoporotic rats. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 114(5):S174-8.
59. Liu W, Zhang S, Zhao D, Zou H, Sun N, et al. (2014) Vitamin D supplementation enhances the fixation of titanium implants in chronic kidney disease mice. *PLoS One.* 9(4):e95689.
60. Naito Y, Jimbo R, Bryington MS, Vandeweghe S, Chrcanovic BR, et al. (2014) The influence of 1 $\alpha$ .25-dihydroxyvitamin d3 coating on implant osseointegration in the rabbit tibia. *J Oral Maxillofac Res.* 5(3).
61. Pimentel SP, Casarin RC, Ribeiro FV, Cirano FR, Rovaris K, et al. (2016) Impact of micronutrients supplementation on bone repair around implants: MicroCT and counter-torque analysis in rats. *J Appl Oral Sci.* 24:45-1.
62. Satue M, Gómez-Florit M, Monjo M, Ramis JM. (2016) Improved human gingival fibroblast response to titanium implants coated with ultraviolet-irradiated vitamin D precursor and vitamin E. *J Periodontal Res.* 51(3):342-9.
63. Cho YJ, Heo SJ, Koak JY, Kim SK, Lee SJ, et al. (2011) Promotion of osseointegration of anodized titanium implants with a 1 $\alpha$ , 25-dihydroxyvitamin D3 submicron particle coating. *Int J Oral Maxillofac Implants.* 26(6)..
64. Pesce P, Menini M, Tommasato G, Patini R, Canullo L. (2020) Influence of Modified Titanium Abutment Surface on Peri-implant Soft Tissue Behavior: A Systematic Review of In Vitro Studies. *Int J Oral Maxillofac Implants.* 12(4):419-29.
65. Bryce G, MacBeth N. (2014) Vitamin D deficiency as a suspected causative factor in the failure of an immediately placed dental implant: a case report. *J R Nav Med Serv .* 100:326-32.
66. Fretwurst T, Grunert S, Woelber JP, Nelson K, Semper-Hogg W. (2016) Vitamin D deficiency in early implant failure: two case reports. *Int J Implant Dent.* 2(1):1-6.
67. Mangano FG, Oskouei SG, Paz A, Mangano N, Mangano C. (2018) Low serum vitamin D and early dental implant failure: Is there a connection? A retrospective clinical study on 1740 implants placed in 885 patients. *J Dent Res Dent Clin Dent Prospects.* 12(3):174.
68. Mangano F, Mortellaro C, Mangano N, Mangano C. (2016) Is Low Serum Vitamin D Associated with Early Dental Implant Failure? A Retrospective Evaluation on 1625 Implants Placed in 822 Patients. *Mediators Inflamm.* 2016.
69. Acipinar S, Karsiyaka Hendek M, Olgun E, Kisa U. (2019) Evaluation of FGF-23 and 25(OH)D 3 levels in peri-



- implant sulcus fluid in peri-implant health and diseases. *Clin Implant Dent Relat Res.* 21(5):1106-12.
70. Kwiatek J, Jaroń A, Trybek G. (2021) Impact of the 25-Hydroxycholecalciferol Concentration and Vitamin D Deficiency Treatment on Changes in the Bone Level at the Implant Site during the Process of Osseointegration: A Prospective, Randomized, Controlled Clinical Trial. *J Clin Med.* 10(3):526.
  71. Garg P, Ghalaut P, Dahiya K, Ravi R, Sharma A, et al. (2020) Comparative evaluation of crestal bone level in patients having low level of Vitamin D treated with dental implant with or without Vitamin D3 supplements. *Natl J Maxillofac Surg.* 11(2):199.
  72. Abouzid M, Karazniewicz-Lada M, Glowka F. (2018) Genetic Determinants of Vitamin D-Related Disorders; Focus on Vitamin D Receptor. *Curr Drug Metab.* 19(12):1042-52.
  73. Deng H, Liu F, Pan Y, Jin X, Wang H, et al. (2011) Bsm1, Taq1, Apal, and Fok1 polymorphisms in the vitamin D receptor gene and periodontitis: a meta-analysis of 15 studies including 1338 cases and 1302 controls. *J Clin Periodontol.* 38(3):199-207.
  74. Mashhadiabbas F, Neamatzadeh H, Nasiri R, Foroughi E, Farahnak S, et al. (2018) Association of vitamin D receptor Bsm1, Taq1, Fok1, and Apal polymorphisms with susceptibility of chronic periodontitis: A systematic review and meta-analysis based on 38 case –control studies. *Dent Res J (Isfahan).* 15(3):155.
  75. Feng M, Li H, Chen SF, Li WF, Zhang FB. (2013) Polymorphisms in the vitamin D receptor gene and risk of autoimmune thyroid diseases: a meta-analysis. *Endocrine.* 43(2):318-26.
  76. Alvim-Pereira F, Montes CC, Thomé G, Olandoski M, Trevilatto PC. (2008) Analysis of association of clinical aspects and vitamin D receptor gene polymorphism with dental implant loss. *Clin Oral Implants Res.* 19(8):786-95.
  77. Munhoz Pereira T, Alvim-Pereira F, Kaiser Alvim-Pereira CC, Ignácio SA, Machado de Souza C, et al. (2019) A complete physical mapping of the vitamin D receptor gene for dental implant loss: A pilot study. *Clin Oral Implants Res.* 30(12):1165-78.
  78. <https://www.hsph.harvard.edu/nutritionsource/vitamin-d/>
  79. Woelber JP, Bremer K, Vach K, König D, Hellwig E, et al. (2016) An oral health optimized diet can reduce gingival and periodontal inflammation in humans- a randomized controlled pilot study. *BMC Oral Health.* 17(1):1-8.
  80. Wacker M, Holick MF. (2013) Sunlight and Vitamin D: A global perspective for health. *Dermatoendocrinol.* 5(1):51-108.
  81. Glerup H, Mikkelsen K, Poulsen L, Hass E, Overbeck S, et al. (2000) Commonly recommended daily intake of vitamin D is not sufficient if sunlight exposure is limited. *J Intern Med.* 247(2):260-8.
  82. Cicarma E, Porojnicu AC, Lagunova Z, Dahlback A, Juzeniene A, et al. (2009) Sun and sun beds: inducers of vitamin D and skin cancer. *Anticancer Research.* 29(9):3495-500.
  83. Pludowski P, Holick MF, Grant WB, Konstantynowicz J, Mascarenhas MR, et al. (2018) Vitamin D supplementation guidelines. *J Steroid Biochem Mol Biol.* 175:125-35.
  84. Diachkova E, Trifonova D, Morozova E, Runova G, Ashurko I, et al. (2021) Vitamin D and Its Role in Oral Diseases Development. Scoping Review. *Dent J.* 9(11):129.