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REVIEW

Association of Vitamin D level and periodontitis: a comprehensive review

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Abstract

Periodontitis is a chronic inflammatory disease affecting approximately 40% of the human population, resulting from the immune response to microbial infections in periodontal tissues. While inflammation serves to protect against pathogens, it also leads to tissue damage and is associated with various systemic diseases. Risk factors include diabetes, smoking, and stress, with increasing evidence linking periodontitis to Vitamin D deficiency, which impacts over one billion people worldwide. Vitamin D is essential for maintaining bone health and supporting immune function, and its deficiency has been shown to adversely affect periodontal health. Adequate Vitamin D levels are crucial for effective management of periodontitis, as inflammation can lead to decreased 25(OH)D levels. Recent advancements in point-of-care technology now allows for rapid chairside testing of Vitamin D, significantly enhancing diagnostic efficiency in dental practices. Research indicates that Vitamin D plays a significant role in modulating immune responses, particularly by suppressing pro-inflammatory cytokines. Patients with periodontitis often exhibit lower Vitamin D levels, and supplementation has been shown to improve clinical outcomes, such as clinical attachment level (CAL) and bleeding index (BI). Thus, the use of adjunctive Vitamin D during non-surgical periodontal therapy (NSPT) may enhance treatment effectiveness, although further longitudinal studies are needed to determine optimal dosages and long-term effects. In conclusion, maintaining adequate Vitamin D levels may offer protective benefits against the progression of periodontitis.

Keywords Vitamin D deficiency · Periodontal disease · Bone metabolism · Immune regulation · Non-surgical periodontal therapy · Inflammation

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Introduction

Periodontitis is a chronic, noncommunicable disease (NCD), that affects approximately 40% of the global population, often leading to early tooth loss [1]. It arises from the body's immune response to microbial infections in periodontal tissues. Initially, this inflammation serves as a defense mechanism, but the formation of bacterial plaque triggers the release of pro-inflammatory molecules, leading to tissue damage [2]. Beyond oral health, periodontitis significantly impacts quality of life and is associated with systemic diseases. Factors that may exacerbate periodontitis include diabetes, HIV, smoking, genetics, hormonal changes, and stress [1].

Recent studies have explored the link between periodontitis and Vitamin D deficiency [3]. Vitamin D, a fat-soluble pro-hormone, plays an essential role in calcium-phosphorus balance, bone metabolism, and immune regulation, with notable anti-inflammatory effects. It exists in two main forms: Vitamin D3, synthesized in the skin through UVB exposure and found in certain fish, and Vitamin D2, sourced mainly from plants. D3 accounts for the majority of Vitamin D intake in the human diet [4]. The status of Vitamin D is typically assessed through serum 25-hydroxy Vitamin D (25 OHD3) levels, measured either through lab tests or, more recently, chairside diagnostic kits [5].

Alarmingly, around 40% of Europeans have insufficient Vitamin D, with 13% severely deficient [6, 7]. However, a lack of consensus on the definition of Vitamin D sufficiency complicates efforts to accurately estimate its prevalence [7]. Factors contributing to low Vitamin D levels include lifestyle changes, such as fast-paced living, poor nutrition, and long hours spent indoors, as well as genetic variations in the Vitamin D receptor [3, 8]. This deficiency, attributed to lifestyle changes and genetic factors, may worsen periodontal health. Studies indicate that low Vitamin D is linked to increased periodontitis severity and poorer therapeutic outcomes. A European consensus highlighted the negative impact of Vitamin D deficiency on periodontal health [3, 9, 10].

This review aims to [1] examine the impact of Vitamin D on periodontal health [2], compare Vitamin D levels in periodontitis patients to those in healthy individuals [3], explore diagnostic methods for Vitamin D deficiency in dental settings, and [4] assess the benefits of Vitamin D supplementation as an adjunct to periodontal therapy. Focusing on data from the past five years, this review includes recent meta-analyses, systematic reviews, and cohort studies.

Materials and methods

This narrative review was conducted using a systematic search of relevant studies across multiple databases, including PubMed, Scopus, and Web of Science. The search strategy focused on key terms such as "periodontitis and Vitamin D," "Vitamin D as an adjuvant/adjunct to periodontal therapy", "Vitamin D and inflammation", "Vitamin D and immune response," tailored to identify recent publications from the last five years.

Studies were included if they specifically addressed the relationship between Vitamin D and periodontal health, were published in peer-reviewed journals, and provided measurable data on Vitamin D levels in patients with periodontitis. Exclusion criteria included studies lacking quantitative data and those not available in English.

To assess the quality of included studies, we evaluated each study for risk of bias based on factors such as sample size, study design, and outcome reporting. The findings from these studies were synthesized to provide a comprehensive overview of current knowledge on Vitamin D's role in periodontal health and its potential as a therapeutic adjunct.

Definition of Vitamin D deficiency and prevalence (global problem)

While there is broad agreement that a severe deficiency is indicated by serum 25OHD3 levels below 12 ng/mL (30 nmol/L), the definition of what constitutes an adequate level is more debated. The U.S. Institute of Medicine defines adequate levels as being between 20 and 50 ng/mL (50–125 nmol/L) for the general population [11]. In contrast, the Endocrine Society considers levels below 30 ng/mL (75 nmol/L) to be insufficient, particularly for specific groups such as individuals with or at risk for osteoporosis, those with chronic kidney disease, those with intestinal malabsorption, and the elderly who are at a high risk of falling [4, 12]. It's important to note that serum 25(OH)D levels can vary throughout life, influenced by factors like season, latitude, sunlight exposure, skin type, and BMI. Additionally, variability in testing methods further complicates the definition of "normal" Vitamin D levels, which has significant implications for both epidemiological studies and clinical practices. According to the task force group composed of expert representatives of the Italian Society for Osteoporosis, mineral metabolism and bone disease (SIOMMMS), it was suggested that a serum 25(OH)D level of at least 20 ng/mL (50 nmol/L) is adequate for the general population, while a level of 30 ng/mL (75 nmol/L) or higher may be optimal for those with osteoporosis, bone metabolism disorders, or at risk for Vitamin D deficiency [13].

Vitamin D deficiency and insufficiency impact over one billion people globally, making it a significant public health issue across all age groups. This problem persists even in low-latitude countries, where it was once assumed that UV radiation would be sufficient to prevent deficiencies, and in industrialized nations where Vitamin D fortification has been in place for years. In Europe, an estimated 40% of the population is Vitamin D deficient, while 13% have insufficient levels of Vitamin D [6, 14].

Cause for Vitamin D deficiency

Vitamin D deficiency can occur if daily intake falls below recommended levels for an extended period, sunlight exposure is insufficient, the kidneys are unable to convert 25(OH)D into its active form, or if Vitamin D absorption from the digestive system is poor. Diets lacking in Vitamin D are often seen in individuals with milk allergies or lactose intolerance, as well in those following ovo-vegetarian or vegan diets [15].

Obtaining sufficient Vitamin D from natural food sources alone is challenging, so many people rely on fortified foods, sunlight, or supplements to maintain adequate

levels. Breastfed infants are at risk since human milk typically doesn't provide enough Vitamin D [15, 16]. Older adults face a higher risk due to reduced skin synthesis and spending less time outdoors. Those with limited sun exposure, such as individuals who are homebound, wear covering clothing, or have jobs limiting sunlight, may also need supplements [17]. People with dark skin have a reduced ability to produce Vitamin D because of increased melanin, while those with conditions that limit fat absorption such as liver disease, cystic fibrosis, or Crohn's disease may struggle to absorb enough Vitamin D and require supplementation. Additionally, individuals with obesity or those who have undergone gastric bypass surgery may have lower Vitamin D levels and often need supplements to maintain adequate levels [15].

Moreover, Vitamin D deficiency can occur due to polymorphisms in the Vitamin D receptor (VDR) gene, which affects how the body responds to Vitamin D [18]. These genetic variations, known as single nucleotide polymorphisms (SNPs), can alter the function of VDRs, leading to reduced effectiveness in how Vitamin D supports bone and immune health. For example, the FokI polymorphism in the VDR gene has been linked to a higher risk of periodontitis, because it can impair the body's ability to regulate bone resorption properly [19]. This weakened response to Vitamin D due to VDR gene variations can contribute to Vitamin D deficiency and related health issues [3, 20–24].

Influence of Vitamin D on periodontal health and disease/ Comparison of Vitamin D levels in patients with and without periodontitis

Research has extensively highlighted the diverse immune-regulating functions of Vitamin D and its significant anti-inflammatory properties. Vitamin D deficiency has been increasingly linked to a higher incidence and severity of chronic inflammatory conditions, including periodontitis. These conditions also encompass cardiovascular disease [25], inflammatory bowel disease [26], asthma [27], chronic obstructive pulmonary disease (COPD) [28], and various autoimmune disorders [29, 30]. Studies have shown that supplementing Vitamin D in deficient individuals can decrease the severity of these chronic inflammatory diseases by reducing levels of pro-inflammatory mediators [31–34].

Numerous studies have underscored the association between lower Vitamin D levels and an increased risk of periodontitis, reinforcing Vitamin D's critical role in periodontal health. Gong et al. (2022) found that Vitamin D's active form, calcitriol, reduced alveolar bone loss and gingival inflammation in mice with a targeted deletion of the CYP27B1 gene, which impairs the conversion of Vitamin D to its active form. The absence of 1,25(OH)2D intensified inflammation and bone destruction, likely through heightened T-cell infiltration and pro-inflammatory cytokine production [35]. Similarly, clinical studies by Koppolu et al. (2023) [5] and Bhargava et al. (2019) reported that patients with periodontitis had significantly lower serum Vitamin D levels compared to individuals with gingivitis or healthy gums. Bhargava's study, in particular, highlighted the correlation between Vitamin D deficiency and worsening periodontal markers, such as gingival inflammation and clinical attachment loss [36]. Extending these findings to older populations, Iwasaki et al. (2023) showed that low serum 25(OH)D3 levels correlated with increased periodontal inflammation, as

measured by the periodontal inflamed surface area (PISA) [37]. Meta-analyses further corroborate these results; Du et al. (2022) identified a significant link between certain Vitamin D receptor polymorphisms and severe periodontitis in the Chinese population [20, 21, 38], while Zhou et al. (2021) reported a non-linear relationship between serum 25(OH)D3 levels and severe periodontitis in the U.S., particularly for levels below 102 nmol/L [39]. Li et al. (2023) also emphasized the heightened risk among women under 60 with insufficient Vitamin D, underscoring Vitamin D's potential role in periodontal disease prevention [40]. The latest research continues to support the strong link between low Vitamin D levels and an increased risk of periodontitis. This is also evident in older adults and pregnant women [41, 42]. Higher Vitamin D levels are associated with reduced gum inflammation and a lower likelihood of developing periodontal disease. These findings suggest that maintaining adequate Vitamin D levels may play a crucial role in preserving periodontal health, potentially offering a protective effect against the development and progression of periodontitis [3]. (Table 1).

Vitamin D diagnosis in dental practice

The primary marker for assessing Vitamin D status is the serum concentration of 25-hydroxyvitamin D (25(OH)D), which reflects both the Vitamin D produced by the body and that obtained from dietary sources and supplements. In the bloodstream, 25(OH)D has a relatively long half-life of approximately 15 days. Serum 25(OH)D levels are measured in both nanomoles per liter (nmol/L) and nanograms per milliliter (ng/mL), with the conversion being 1 nmol/L equaling 0.4 ng/mL, and 1 ng/mL equaling 2.5 nmol/L [43]. Unlike 25(OH)D, circulating levels of calcitriol (1,25(OH)2D3) the active form of Vitamin D are not reliable indicators of Vitamin D status. The renal 1α-hydroxylation process that converts 25(OH)D to 1,25(OH)2D is tightly regulated by several factors, including parathyroid hormone (PTH), fibroblast growth factor 23 (FGF23), calcium, phosphate, and calcitriol itself. This regulation, combined with the short half-life of calcitriol (measured in hours), means its serum levels are closely controlled by other factors and do not drop until Vitamin D deficiency becomes severe [43, 44].

Over 85% of 25(OH)D and 1,25(OH)2D is bound to Vitamin D-binding protein (VDBP), with most of the remainder attached to albumin. Only about 0.03% circulates unbound [45]. While it has been proposed that bioavailable or free 25(OH)D may better indicate Vitamin D status, particularly in individuals with different VDBP genotypes, research suggests that these forms largely reflect total 25(OH)D and provide limited additional clinical insights. Since 25(OH)D functions as a prohormone and isn't hormonally active, its free form isn't regulated by feedback systems [46]. As long as sufficient 25(OH)D is available for conversion into 1,25(OH)2D, the specific amounts of free or bioavailable 25(OH)D appear to be of minimal significance [44].

Both 25(OH)D3 and 25(OH)D2 can be converted into the active form of Vitamin D, so measuring total 25(OH)D, including both isomers, is essential. 25(OH)D2 has a different mass due to an extra double bond. Most of the body's 25(OH)D is 25(OH)D3, produced via UVB exposure, but supplementation can include either form. In the

Table 1 Summary of the Studies on Vitamin D and Periodontitis

Study	Type	Country	Key Findings
Gong et al. (2022)	preclinical experimental study	China	1,25(OH)2D deficiency worsens periodontitis, while supplementation alleviates bone loss and inflammation, supporting its use as an adjunct therapy.No adverse events.
Koppolu et al. (2023)	A cross-sectional study	Saudi Arabia	Vitamin D level is sufficient for gingivitis and healthy group than periodontitis in both males and females. The severity of periodontitis was likewise linked to the amount of vitamin D in the individual's blood
Bhargava et al. (2019)	A cross-sectional study	India	Serum 25(OH)D levels are linked to GI, PPD, and CAL but not PI. Patients with chronic periodontitis had low Vitamin D levels, which did not decrease with disease severity.
Iwasaki et al. (2023)	A cross-sectional study	Japan	Low 25(OH)D levels are linked to higher PISA, decreasing sharply until 27.1 ng/mL, then plateauing.
Du et al. (2022)	A systematic review and meta-analysis	China	6 studies (6106 participants) showed: - VDR BsmI linked to severe periodontitis in South China (OR 1.46–1.5). - VDR FokI linked to aggressive periodontitis in China (OR 2.01–2.9). - ApaI protective against severe periodontitis in North China (OR 0.41). - TaqI showed no association.
Zhou et al. (2021)	cross-section study	China	In 2928 participants (avg. age 50, 48.7% male), severe periodontitis (10.8%) was negatively linked to serum 25(OH)D (OR 0.75). Risk decreased below 102 nmol/L but plateaued above. Subgroup effects varied by race, alcohol use, diabetes, and insurance.
Li et al. (2023)	Scientific Research Report	China	Vitamin D was negatively associated with periodontal disease; odds ratios compared to Q1 were 0.8 (Q2), 0.84 (Q3), and 0.74 (Q4) ($P<0.05$). Subgroup analysis showed a stronger effect in women under 60. Boost tree analysis was a good model for predicting periodontal disease. Vitamin D may protect against periodontal disease.
Ferrillo et al. (2021)	cross-sectional study,	Italy	high prevalence of PTB and LBW in pregnant women with periodontal disease and Vitamin D deficiency. It suggests screening for oral health and 25(OH)D levels and calls for further research on oral care and Vitamin D supplementation to reduce PTB and LBW.
Kim H et al. (2020)	cross-sectional study	South Korea	Low Vitamin D was linked to tooth loss and severe periodontitis, especially in males, in Koreans aged 50+. Sufficient 25(OH)D levels were associated with a low frequency of severe (7)periodontitis.

United States, 25(OH)D2 is commonly prescribed, while 25(OH)D3 is more typical in Europe. Testing methods should either distinguish and sum both forms or measure them together in an equimolar fashion [44].

For measuring 25(OH)D, laboratories use either automated immunoassays or liquid chromatography tandem mass spectrometry (LC-MS/MS). Automated immunoassays are widely used for their speed and convenience, especially in high-volume testing environments. However, they often compromise on accuracy, particularly when distinguishing between Vitamin D2 and D3-an important distinction in regions

where Vitamin D2 is prescribed. These assays typically rely on polyclonal antibodies with variable affinities for 25(OH)D3 and 25(OH)D2, which may lead to inconsistent results. Additionally, their accuracy can be unreliable in certain populations, such as pregnant women, dialysis patients, or those with liver disease. While the tests require costly reagents, the equipment is common and affordable to maintain [44].

LC-MS/MS, on the other hand, provides highly accurate measurements and effectively differentiates between various Vitamin D metabolites, avoiding the cross-reactivity issues seen in immunoassays. Although the initial setup and training for LC-MS/MS are expensive, the ongoing cost of chemicals for each test is relatively low. LC-MS/MS can also assess multiple metabolites in one test, offering a comprehensive view of Vitamin D metabolism. However, the method is still less developed for measuring other metabolites, such as 1,25(OH)2D and 24,25(OH)2D, despite the availability of fully automated systems [44].

For dental practices, assessing Vitamin D levels can be time-consuming and costly, but there is a simpler alternative: chairside rapid test kits pre-coated with Vitamin D antigen [5]. These kits provide a fast and easy way to assess Vitamin D levels in a short time. A study by Paz et al. in 2021 found no significant difference between the results from chairside tests and standard blood sample tests, confirming their accuracy [47].

These test kits offer a quantitative test for total 25-hydroxyvitamin D (25-OH-Vitamin D) using capillary blood collected from a fingertip. They provide a reliable, point-of-care solution, enabling fast clinical decisions without the need for expensive laboratory testing. The Vitamin D test kit delivers results within several minutes, allowing immediate adjustments to treatment plans when necessary. Its simple handling and compact design make it easy to integrate into routine dental procedures [47, 48]. With just a few drops of blood, the test allows quick Vitamin D assessments, helping improve patient care and expanding your role as a trusted healthcare provider.

Influence of adjunctive Vitamin D supplementation during subgingival instrumentation on periodontal parameters

In periodontitis, while periopathogens play a crucial role in the disease's development, the tissue destruction largely stems from the host's deregulated inflammatory response. As the disease is primarily bacterial, treatment aims to reduce bacterial load, inflammation, and restore or stabilize damaged tissue. Mechanical subgingival instrumentation remains the gold standard for non-surgical periodontal therapy. Moreover, adjunctive therapies can be applied nowadays to further improve treatment outcomes [49].

Vitamin D is known for its calcium metabolism, bone turnover, immune regulation and anti-inflammatory effect. It has shown to play a role in epithelial defense against pathogens, exhibiting antibacterial properties, anti-inflammatory effects, and host-modulatory functions. These combined attributes make it a potential adjunctive therapy to complement mechanical subgingival instrumentation [3]. Calcitriol enhances oral health by boosting immune responses. IL-1β and lipopolysaccharide (LPS) from *Porphyromonas gingivalis* (Pg) upregulate 25-hydroxylase mRNA in human gingival fibroblast (HGF) and periodontal ligament cells (HPDLC), leading to

more 25OHD3 production in inflammatory environments [50]. The successful conversion of 25OHD3 to calcitriol depends on sufficient serum levels of 25OHD3 [3, 51]. Once calcitriol binds to VDR in immune cells (like monocytes, macrophages, and dendritic cells), it increases the chemotactic and phagocytic activities of macrophages. This boosts the production of lysosomal enzymes and aids in pathogen clearance. Calcitriol exhibits powerful antibacterial activity and neutralizes lipopolysaccharides (LPS), directly inhibiting the growth of Pg and selectively suppressing key virulence factors such as adhesins and proteinases. It is also thought to promote autophagy, which contributes to its inhibitory effects on Pg [3, 52, 53]. Additionally, calcitriol stimulates the production of antimicrobial peptides like β-defensins and LL-37, a cathelicidin with broad antimicrobial action against both gram-positive and gram-negative bacteria, as well as some viruses.

LL-37 not only combats pathogens but also aids in chemotaxis, cytokine production, wound healing, and neutralizing bacterial toxins. The production of LL-37 and other antimicrobial peptides is upregulated in response to calcitriol, bacterial products, and the activation of Toll-like receptors [54].

There is a small number of studies that directly investigate the effects of adjunctive Vitamin D supplementation in combination with non-surgical periodontal treatment (NSPT), which limits the ability to draw definitive conclusions about its benefits. Nonetheless, the available data suggest potential positive effects of Vitamin D as an adjunct to NSPT. Gao et al. (2020) conducted a study on 360 patients with moderate to severe periodontitis who underwent NSPT and short term Vitamin D supplementation. Participants were randomly assigned to receive either 2000 IU/day, 1000 IU/day of Vitamin D3, or a placebo. The results indicated that the effect of Vitamin D supplementation was modest, showing limited clinical relevance and long-term effectiveness in improving probing pocket depth (PPD) and clinical attachment level (CAL) [55]. The short term follow up may not capture the full benefits of Vitamin D, and should be considered as a long term process, unlike antibiotics which show quicker effect, as highlighted in the study by Perić et al. (2020). They studied the effects of Vitamin D as an adjunct to NSPT in a Caucasian population of total 56 patients. A regimen of 25,000 IU weekly for six months effectively restored normal 25(OH) Vitamin D3 levels and showed a tendency for greater reduction in periodontal pockets ≥ 4 mm. The limitation of the study is however the small sample size. Vitamin D supplementation may be considered for patients with serum levels below 30 ng/mL as an adjunct to periodontal therapy [56]. Lei et al. (2023) reported similar findings but observed different doses of Vitamin D supplementation in conjunction with NSPT for Vitamin D-insufficient patients with diabetic periodontitis. They discovered the difference between two groups after six months of NSPT combined with Vitamin D supplementation. Both the low-dose (25,000 IU/week) and high-dose (50,000 IU/week) groups demonstrated significant improvements. The average PPD decreased in the low-dose group and in the high-dose group, with greater improvement in the high-dose group. CAL also improved, showing better results in the high dose group. Bleeding index (BI) decreased more significantly in the high-dose group compared to the low-dose group. However, the plaque index (PI) showed improvement in both groups, but no significant difference between them. Overall, higher-dose Vitamin D (50,000 IU/week) was more effective in improving periodon-

tal health in patients with Vitamin D insufficiency and periodontitis than the lower dose [57]. The positive effect of Vitamin D supplementation as an adjunct to NSPT on the prevention and treatment of periodontal disease in clinical practice was also noted in the meta-analysis from Liang et al. (2023) [58]. This meta-analysis revealed that combining subgingival instrumentation with Vitamin D supplementation significantly improved CAL compared to mechanical instrumentation alone. Similar to the findings by Machado et al. (2020) this review also supported the association between periodontitis and lower serum Vitamin D levels compared to the general population [59]. While Machado et al. (2020) focused on descriptive analysis of Vitamin D use in NSPT, quantitative evidence was lacking. This meta-analysis addressed that gap, showing that subgingival instrumentation with Vitamin D supplementation significantly improved CAL, although it did not have a notable effect on PPD, gingival index (GI), or bleeding index (BI) [58].

A recent study from Kirkwood et al. (2024) explored the potential of topical application of Vitamin D for periodontal treatment. A study using a mouse model of ligature-induced periodontitis demonstrated that both inactive Vitamin D and its active form, $1,25(OH)_2D_3$, significantly reduced bone loss and inflammation. The study also shows that oral epithelial cells are capable of converting inactive Vitamin D to the active form. Topical treatment with Vitamin D enhanced the production of specialized pro-resolving mediators (SPM) of inflammation in gingival tissues, promoting resolution of inflammation. In addition, it altered the oral microbiome, shifting it toward a healthier composition. Experiments with primary gingival epithelial cells in 3D culture confirmed that Vitamin D prevented lipopolysaccharide-induced secretion of pro-inflammatory cytokines and stimulated SPM production. These findings suggest that topical Vitamin D not only exerts anti-inflammatory effects but also supports a balanced microbiome, making it a promising preventive or adjunctive therapeutic option for periodontal disease [60]. (Table 2).

However, most findings are preliminary and require future validation in larger, longitudinal, well-designed studies.

It is noteworthy to mention, that genetic polymorphisms in the Vitamin D activation pathway may partly explain why sometimes the patients´ response to Vitamin D supplementation or topical application is not beneficial. Variants in the CYP27B1 gene, responsible for converting 25(OH)D into its active form, or polymorphisms in the VDR gene, which affect receptor activity, could modulate the anti-inflammatory and antimicrobial effects of calcitriol in periodontal tissues [61–64]. Future studies should explore how these polymorphisms influence clinical outcomes to better tailor Vitamin D therapies in periodontal treatment.

Findings and recommendations

Vitamin D plays a critical role in bone metabolism and immune regulation, and its deficiency can negatively affect periodontal health. Low levels of Vitamin D are linked to inflammation, a key component in periodontal disease (PD). The body may reduce 25(OH)D levels during inflammation as it converts it to its active form to help

Table 2 Adjunctive Vitamin D supplementation during subgingival instrumentation on periodontal parameters

Study	Type of Study	Country of Origin	Cohort Size	Dose of Vitamin D	Results
Gao et al. (2020)	RCT	China	360	1000 IU/day and 2000 IU/day	Modest improvement in PPD and CAL; short-term effect observed.
Perić et al. (2020)	RCT	Belgium	56	25,000 IU/week	Reduced periodontal pockets ≥ 4 mm; effectively restored Vitamin D levels.
Lei et al. (2023)	RCT	China	60	25,000 IU/week (low-dose) and 50,000 IU/week (high-dose)	High-dose showed better PPD, CAL, and BI improvement compared to low-dose.
Liang et al. (2023)	Meta-analysis	China	Total of 16 articles	Variable	Improved CAL; no significant change in PPD, GI, or BI.
Machado et al. (2020)	Systemic review	Portugal	16 articles were included for the qualitative analysis, of which two concerned Vitamin D supplementation. A total of 13 studies were included in the quantitative synthesis regarding 25(OH)D levels in patients with and without periodontitis	Not specified	Periodontitis links to low Vitamin D; due to the shortage of studies, supplementation's role in treatment is unclear.
Kirkwood et al. (2024)	In Vivo (Mouse Model)	USA	N/A	Topical Vitamin D	Reduced bone loss, inflammation, and shifted microbiome toward health-associated species.

manage the immune response. Adequate Vitamin D levels are, therefore, essential for controlling inflammation and improving periodontal health.

Recent advances in technology now allow dental practitioners to perform quick and reliable chairside Vitamin D tests, aiding in more personalized treatment plans. Studies have shown that Vitamin D's anti-inflammatory effects, including the suppression of harmful cytokines and promotion of protective ones, contribute to better periodontal outcomes. Individuals with PD often show lower Vitamin D levels, and supplementation has been found to improve clinical results. While most studies primarily evaluate the impact of vitamin D3 [25(OH)D3] in periodontal therapy, the potential differences in clinical outcomes between 25(OH)D3 and 25(OH)D2 remain unclear. Existing evidence suggests that Vitamin D3 may be more effective in raising

serum 25(OH)D levels and sustaining its biological activity due to its higher affinity for Vitamin D binding protein and slower degradation. Future studies should aim to compare these forms directly in the context of periodontal health to determine their relative efficacy in modulating inflammatory responses and tissue repair.

While there is strong evidence linking low Vitamin D levels to more severe PD, further long-term studies are needed to evaluate the full impact of Vitamin D supplementation during periodontal treatment. Although current data indicate promising benefits, Vitamin D's long-term effectiveness as an adjunct therapy requires more research.

Topical application of inactive Vitamin D in mouse models demonstrated significant reductions in gingival inflammation and bone loss, as well as a shift toward a healthier oral microbiome. This supports the potential for localized treatments in periodontal therapy.

Genetic polymorphisms in the Vitamin D activation pathway (such as variations in CYP2R1, CYP27B1, or VDR genes) may influence the efficacy of Vitamin D supplementation or activation, leading to variability in clinical outcomes.

Future research should focus on further exploring the association between periodontitis and Vitamin D deficiency. This would require robust observational studies that account for key factors such as lifestyle, dietary habits, intraoral health, and medical history. These studies should also consider seasonal variations in Vitamin D levels by being conducted during fall or winter, when lower sunlight exposure reduces the risk of false-negative results.

To establish the efficacy of Vitamin D supplementation as an adjunct to non-surgical periodontal therapy (NSPT), well-structured longitudinal randomized controlled trials (RCTs) are necessary. These should include participants from similar latitudes to control for environmental variability, all adhering to standardized dietary recommendations without additional UVB exposure (e.g., no sunbathing). The study design should align with the clinical practice guidelines provided by the Endocrine Society for Vitamin D supplementation and the European Federation of Periodontology (EFP) for periodontal therapy. Such an approach would provide a rigorous framework to evaluate Vitamin D's role in periodontal health and its potential as an adjunctive treatment.

In conclusion, while the role of Vitamin D in periodontal disease management is supported by growing evidence, more research is necessary to solidify its therapeutic potential and create clear guidelines for its use in clinical practice.

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Declarations

Competing interests The authors declare no competing interests.

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