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REVIEW ARTICLE

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The role of vitamin D in periodontal health and disease

Emily Ming-Chieh Lu

Centre for Host-Microbiome Interactions, Faculty of Dentistry, Oral and Craniofacial Sciences, King's College London, Guy's Hospital, London, UK

Correspondence
Emily Ming-Chieh Lu, Centre for Host-Microbiome Interactions, Faculty of Dentistry, Oral and Craniofacial Sciences, King's College London, Guy's Hospital, Floor 18, Tower Wing, London SE1 9RT, UK.
Email: emily.lu@kcl.ac.uk

Abstract

Vitamin D plays an essential role in calcium and bone metabolism, immune regulation and possesses profound anti-inflammatory effects. Evidence suggests that low serum vitamin D is associated with increased severity of periodontitis, a chronic inflammatory condition characterised by destruction of the supporting tissues surrounding the tooth, which has several shared risk factors with other chronic non-communicable diseases. The biological functions of vitamin D are mediated by its strong anti-microbial, anti-inflammatory, and host modulatory properties. Experimental periodontitis models involving targeted deletion of 1α-hydroxylase, the enzyme responsible for the conversion of inactive substrate to active $1,25(OH)_2D_3$ (calcitriol), showed augmented alveolar bone loss and gingival inflammation. Vitamin D receptor (VDR) gene polymorphisms have also been associated with increased severity of periodontitis. Thus, the involvement of vitamin D in the pathogenesis of periodontitis is biological plausible. Clinical studies have consistently demonstrated an inverse relationship between serum $25OHD_3$ and periodontal disease inflammation. However, due to the paucity of well-designed longitudinal studies, there is less support for the impact of vitamin D status on periodontal disease progression and tooth loss. The evidence emphasises the importance of maintaining vitamin D sufficiency in supporting periodontal health. This review aims to first examine the biological mechanisms by which vitamin D might influence the pathogenesis of periodontal disease and second, discuss the clinical evidence which implicate the role of vitamin D in periodontal disease.

KEYWORDS
alveolar bone loss, anti-inflammatory, anti-microbial, calcitriol, host-modulatory, periodontal disease, tooth loss, Vitamin D

1 | INTRODUCTION

Vitamin D is a group of fat-soluble hormones which are essential for calcium metabolism, bone turnover, immune regulation and has profound anti-inflammatory effects.[1] Vitamin D also plays a protective role against a myriad of chronic diseases such as type I diabetes, multiple sclerosis, rheumatoid arthritis, cancers, heart disease, and infectious diseases.[2,3]

A deficiency in vitamin D is associated with accelerated bone turnover, reduction in bone density, and increased risk of bone fractures.[1] Children who are vitamin D deficient are at risk of developing rickets, a condition which is characterised by failure of bone to

become completely mineralised and thus the development of skeletal deformities.[4] It is estimated that approximately 1 billion people worldwide have vitamin D deficiency.[1] However, due to the lack of consensus in the medical community regarding the definition of vitamin D deficiency in terms of exacting serum $25OHD_3$ levels,[5] the exact prevalence is difficult to estimate.

Periodontitis is characterised by a host inflammatory response to invading bacteria, resulting in the destruction of the connective tissues and alveolar bone loss.[6] It is the primary cause of tooth loss in adults[7] and has several shared risk factors with other chronic non-communicable diseases.[8] A recent European consensus stated that poor nutrition and an inadequate vitamin D status impacts on periodontal health and oral functions.[9] In particular, low serum vitamin D is linked to increased severity of periodontitis[10,11] and poorer periodontal treatment response.[12]

The aim of this narrative review is two-fold: (1) to comprehensively examine the biological basis by which vitamin D might influence the pathogenesis of periodontal disease and thus the biological plausibility to implicate vitamin D deficiency as a risk factor for periodontal disease progression and tooth loss and (2) to appraise the clinical studies examining the association between vitamin D and periodontal disease and discuss the influence of supplementation on periodontal treatment outcomes.

2 | THE VITAMIN D PATHWAY AND THE MOLECULAR EFFECTS OF CALCITRIOL

Vitamin D_3 (cholecalciferol) is produced in the skin from 7-derydrocholesterol after exposure to ultraviolet light. Vitamin D_2 (calciferol) is available in some foods and dietary supplements.[13] Both exposure to ultraviolet light and dietary intake form the primary sources of vitamin D, which are metabolised to $25OHD_3$ in the liver and further hydroxylated in the kidneys by CYP27B1 to produce $1,25(OH)_2D_3$ (calcitriol), the active hormone involved in calcium absorption in the gut.[14,15]

Calcitriol has wide-ranging molecular effects which include maintenance of bone density, modulation of the innate and adaptive immune responses, regulation of the rein–angiotensin system, suppression of parathyroid hormone (PTH) synthesis and release, and inhibition of proliferation and differentiation of cancer cells[15] (Figure 1). Molecular effects of calcitriol are mediated via the activation of vitamin D receptors (VDRs), which are expressed in a number of immune cells, as well as epithelial cells.[15]

3 | THE ROLE OF CALCITRIOL IN THE MAINTENANCE OF BONE MINERAL DENSITY AND PERIODONTAL HEALTH

Calcitriol is the biologically active hormone principally responsible for systemic calcium and phosphate homeostasis. It is required for the mineralisation of cartilage and bone matrix and also plays an important role in the regulation of osteoblast gene expression.[16] Calcitriol is produced from circulating inactive vitamin D $25OHD_3$ by 1α-hydroxylase (Cyp27B1), the enzyme which is responsible for the conversion of inactive $25OHD_3$ to the active $1,25(OH)_2D_3$ hormone. The importance of calcitriol in the maintenance of bone mineral density is highlighted in a recent animal study where targeted deletion of the CYP27B1 gene in mice resulted in an increased alveolar bone loss and an increase in production of pro-inflammatory cytokines, including interleukin-1β (IL1-β), tumour necrosis factor-α (TNF-α), matrix metalloproteinases 3 and 6 (MMP-3 and MMP-8).[17]

The critical role of calcitriol in the maintenance of periodontal health is reinforced in a subsequent study where ligature-induced periodontitis in CYP27B1 knock-out mice resulted in severe alveolar bone loss and gingival inflammation compared with ligature-induced periodontitis in wild-type (WT) mice. However, exogenous administration of calcitriol alleviated alveolar bone and gingival inflammation in these ligated WT mice.[18] These animal studies provide an insight into the role of vitamin D in the pathogenesis of periodontitis and suggest a potential therapeutic role of calcitriol in the management of periodontitis.

Low serum vitamin D levels stimulate the secretion of PTH, which increases calcium retention and inhibits phosphate reabsorption. PTH increases osteoclastic activity in bone and increases the production of calcitriol. The result is the release of stored calcium into the circulation and the absorption of calcium from the intestine. PTH regulates the formation of calcitriol by directly controlling the expression of 1α-hydroxylase and thus regulating the secretion of calcitriol.[19] The latter is responsible for the subsequent increase in absorption of calcium and phosphate from the intestine and kidney, promoting bone mineralisation and absorption, and a reduction in PTH synthesis and release via a feedback mechanism.[15]

4 | CALCITRIOL IS INVOLVED IN EPITHELIAL DEFENCE AGAINST PATHOGENS

The molecular mechanisms underlying the production of Calcitriol within the periodontium follows that of the vitamin D pathway was reviewed in section 1. Both human gingival cells and human PDLCs produce 25-hydroyxlase, which is responsible for the production of $25OHD_3$.[20] Following microbial interaction with cell membrane receptors, $25OHD_3$ becomes further hydroxylated via CYP27B1 to produce Calcitriol. The active hormone then binds to VDR in immune and epithelial cells and thus participates in the epithelium defence mechanism against the pathogen.[15]

Calcitriol contributes to the overall improvement in oral health by being involved in the first line of defence for epithelial cells. IL-1β and *Porphyromonas gingivalis* lipopolysaccharide (LPS) both strongly upregulated 25-hydroxylase mRNA expression in human gingival fibroblast (HGF) and periodontal ligament cells (HPDLC),[20] suggesting that HGFs and HPDLCs were responsible for the secretion of

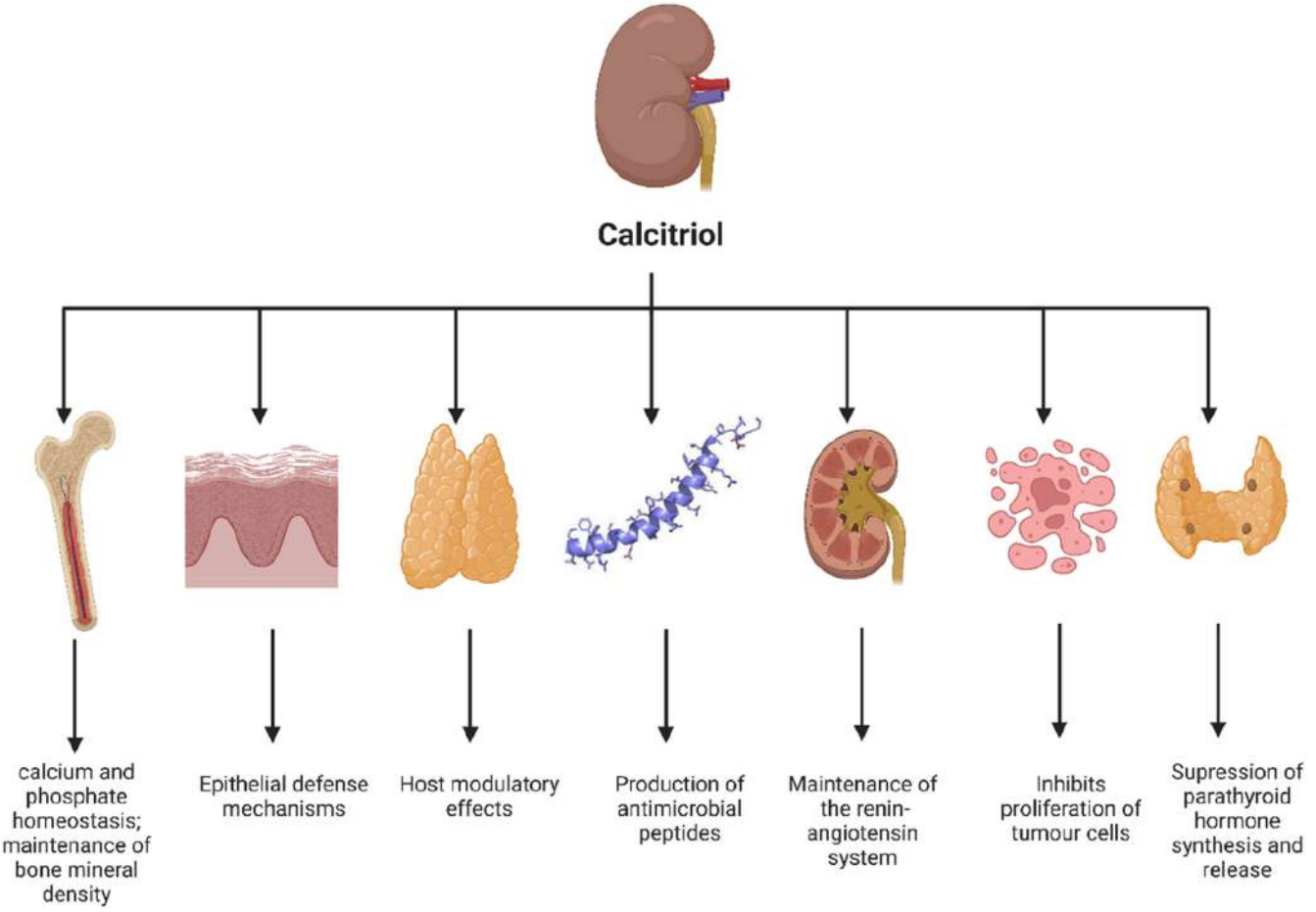

FIGURE 1 The wide ranging physiological and pharmacological roles of Cacitriol ($1,25(OH)_2D_3$) are mediated via the activation of vitamin D receptors (VDRs).

$25OHD_3$ in the inflammatory milieu. This is important as the successful conversion to calcitriol is dependent on the presence of adequate serum $25OHD_3$.[21] Calcitriol binds to VDR in immune cells (monocytes, macrophages, dendritic cells), to enhance the macrophage chemotactic and phagocytic activities by simulating the expression of 1-α-hydroxylase in monocytes and macrophages to produce calcitriol in an autocrine manner. This, in turn increases lysosomal enzyme activity and phagocytosis. Calcitriol also binds to the VDR of junctional and gingival epithelial cells[22] and thus participates in epithelial defence mechanisms against the invading pathogens.[19,23] To this end, activation of Toll-like-receptors, TLR2/1 and TLF4 results in the induction of 1α-hydroxylase,[24] thus increasing the production of calcitriol.

The upregulation of the expression of CP27B1 enzyme also increases the production of the proteins responsible for tight junctions, gap junctions and adheren junctions,[25,26] improving cell to cell communication and strengthening the epithelial barrier.[19] In particular, calcitriol has been shown to attenuate TNF-α-induced downregulation of the development of E-cadherin junctions, in human gingival keratinocytes, by decreasing the production of MMP-9 and downregulating nuclear factor kappa B (NF-KB) signalling. Thus, enabling vitamin D to strengthen the epithelial barrier and therefore protect the periodontium from bacterial invasion.[22]

5 | ANTIBACTERIAL PROPERTIES OF CALCITRIOL

Calcitriol possesses strong antibacterial and LPS neutralising activity.[27] For example, it can directly inhibit growth of *P. gingivalis* and selectively inhibit the expression of important virulence factors such as adhesins (fimA, hagA and hagB) and proteinases (rgpA, rgpB and kgp).[28] Recently, it has been shown that its inhibitory effect on *P. gingivalis* might be mediated through active autophagy.[29]

In particular, calcitriol is responsible for the production of antimicrobial peptides, including β-defensins and cathelicidins.[21,30,31] LL-37 is the only human cathelicidin, with potent antimicrobial activity against both gram-positive and gram-negative bacteria, as well as some viruses.[32,33] It is involved in chemotaxis, production of cytokines and chemokines, cellular reproduction, vascular permeability, wound healing and neutralisation of bacterial endotoxins.[19,34] Cathelicidin hCAP-18 gene[35] is upregulated in

response to live bacteria,[36] bacterial products such as LPS[37,38] and calcitriol,[21,31] in human keratinocytes,[39] oncocytes[40] and neutrophils,[21] via the activation of TLR 2/1, which increases calcitriol in an autocrine manner.

The first study to demonstrate the effect of vitamin D on the innate immune defence in the oral cavity was in performed in 2011, when it was shown that human gingival epithelial cells treated with calcitriol for 24 h led to a 13-fold increase in production of LL37, compared with the control untreated gingival epithelial cells.[41] The findings suggest that the administration of calcitriol and the production of cathelicidins enhance the innate immune defence of the oral epithelia.

6 | ANTI-INFLAMMATORY AND HOST MODULATORY EFFECTS OF CALCITRIOL

Calcitriol modulates the adaptive immune response by suppressing the proliferation of T-lymphocytes and secretion of immunoglobulins, inhibiting the transformation of B-lymphocytes into plasma cells. Thus, the host-modulatory effects facilitate an environment which favours the resolution of inflammation. In vitro studies have shown that calcitriol suppressed *P. gingivalis* stimulated IL-8 production from HPDLCs[42,43] and the attenuation of *P. gingivalis*-induced NF-kB activation in human monocytic cell line[28] and oral epithelial cells.[44] In addition, calcitriol inhibited the LPS-induced overexpression of IL-6 in oral keratinocytes[44] and suppressed IL-1β-signalling in HPDLCs.[45]

Calcitriol inhibits cytokine production by T-helper (Th1) cells whilst selectively promoting Th2 cytokines.[46,47] Th1 cells are thought to release cytokines that trigger the local inflammatory reaction and induce tissue injury, while Th2 cells secrete cytokines that promote reparative responses and facilitate periodontal repair.[48] Other Th subsets such as Treg and T17 also play antagonistic roles in bone disease and repair.[49,50] In particular, the administration of calcitriol suppressed IL-17 production,[51] and has been associated with increased incidence of periodontal disease.[52] Thus, calcitriol selectively stimulated specific Th cell subsets and their respective cytokines. Such specific suppression of systemic Th cells has been shown to inhibit alveolar bone loss in experimental periodontitis animal models.[53]

The administration of calcitriol or its precursor $25OHD_3$ in experimental periodontitis models significantly reduced inflammation by suppressing the expression of receptor activator of nuclear factor kappa beta ligand (RANKL), TNF-α, IL-1, IL-6, as well as a reduction in alveolar bone loss.[44,54] The latter is mediated by an upregulation of Th2 and Treg subsets while reducing the Th1 and Th17 cells.[53] These findings are supported by clinical studies which showed an inverse association between higher vitamin serum $25OHD_3$ and lower IL-6 levels.[55]

The anti-inflammatory effects of vitamin D were reinforced in a recent pilot study where the effects of vitamin D supplementation were examined in moderate to severe periodontitis who have received a single visit of non-surgical periodontal therapy.[56] Vitamin D supplementation reduced systemic inflammation and induced the secretion of autophagy-related proteins and other proteins involved in anti-microbial autophagy in whole blood peripheral blood mononuclear cells (PBMCs).[57]

7 | VITAMIN D RECEPTOR POLYMORPHISM

Since the physiological and pharmacological effects of vitamin D are mediated by VDRs, the presence of VDR gene variants and its possible association with periodontitis is of great interest to scientists. Unlike hereditary $1,25(OH)_2D_3$ resistant rickets, which is a rare monogenetic condition caused by a point mutation in the VDR gene,[58] single nucleotide polymorphisms (SNPs) are more subtle variations in genetic sequences, can occur more frequently. Specific VDR genotypes have been shown to be associated with periodontitis, with increased alveolar bone loss, clinical attachment loss, and tooth loss.[56,59–62] One recent meta-analyses concluded that *FokI* polymorphism was significantly associated with increased susceptibility to periodontitis,[63] while another recent meta-analysis reported that both *BsmI* and *FokI* polymorphisms were correlated with higher risk of developing periodontitis in the overall population.[64] The presence of polymorphisms in the VDR gene supports the role of vitamin D in periodontal health.

Importantly, the *VDR-FokI* polymorphism (rs 2228570) is the only known SNP which could lead to alterations in the protein sequence of VDR and thus affect biological functions.[65] The molecular mechanisms underpinning the relationship between *VDR-FokI* genotype and periodontitis was recently investigated. This line of work is of particular importance because similar studies on the correlation between VDR gene variants and periodontitis are rare, as most VDR SNPs do not change the VDR protein sequence. The genotype FF-VDR has demonstrated the strongest transcriptional activity compared with Ff-VDR and ff-VDR.[66] Additionally, it was also shown that FF-VDR upregulated the expression of RANKL in HGF and HPDLCs, following stimulation by $1,25(OH)_2D_3$. Since the increase in RANKL/OPG ratio potentiates osteoclastogenesis and bone resorption, this could provide the molecular basis for the higher susceptibility of FF genotype to periodontitis.[67]

8 | DEFINING SERUM $25OHD_3$ THRESHOLDS

$25OHD_3$ is largely stable and with a half-life of about 60 days.[68] Therefore, the serum levels of $25OHD_3$ provides a reliable molecular biomarker for an individual's vitamin D status,[23] over extended periods of time, of up to 5 years.[69,70] It also reflects the contribution from endogenous production of vitamin D, as well as dietary sources.

Despite its reliability as an indicator of vitamin D status, there is a lack of consensus amongst the scientific community defining serum concentrations associated for deficiency and adequacy. While some

studies suggest serum $25OHD_3$ between 36–40 ng/ml are desirable,[1,71] the Endocrine Society recommended a concentration of greater than 30 ng/ml to maximise the therapeutic effects of vitamin D.[72,73] Most studies, however, agree that the normal range for serum $25OHD_3$ lies between 20–100 ng/ml and a concentration <20 ng/ml is considered vitamin D-deficient.[5]

9 | THE ASSOCIATION BETWEEN SERUM 25OHD3 AND PERIODONTAL DISEASE

The latest meta-analysis concluded that periodontitis was associated with lower serum vitamin D levels.[74] This supports previous studies which suggest that low calcitriol levels were associated with chronic periodontitis.[75,76] However, studies which have investigated the associations between vitamin D and periodontal disease were mainly cross-sectional or case–control studies and therefore included only data collected from one time-point.

The association between serum $25OHD_3$, gingival inflammation and periodontitis was examined using cross-sectional National Health and Nutrition Examination Survey (NHANES III) dataset. Analyses of this large cross-sectional dataset revealed an inverse relationship between serum $25OHD_3$, mean attachment loss in men and women aged 50 years and older.[10] A separate analysis demonstrated that the odds of bleeding on probing was 20% less among participants in the highest compared with the lowest quintile of $25OHD_3$.[77] Such inverse relationship between serum $25OHD_3$ and gingival inflammation has been subsequently observed in other studies,[78–80] and is consistent with the anti-inflammatory role of vitamin D. These findings are supported by numerous case-control studies which demonstrated a significant association between lower serum vitamin D and periodontitis.[11,81–83]

It also appears that the impact of vitamin D status on periodontal disease might be more pronounced in certain vulnerable groups of patients. For example, in the OsteoPerio study, which was a large cross-sectional study of well-characterised postmenopausal women, it was revealed that participants with adequate $25OHD_3$ (>50 nmol/L) had 33% lower odds of periodontal disease compared with those with deficient vitamin D status (<50 nmol/L).[78] In this case, the outcome measure for periodontal diagnosis was based on the Centres for Disease Control and Prevention/ American Academy of Periodontology (CDC/AAP) definition, which was based on clinical attachment loss (CAL) and periodontal probing depth (PPD). There was no association between $25OHD_3$, and periodontal disease defined by alveolar crestal height and tooth loss. The reduction in Vitamin D concentration was associated with an increase in gingival bleeding (but not tooth loss). The findings suggest that vitamin D status might influence periodontal health, but the association was perhaps more important in reducing the acute measures of periodontal inflammation (PPD and gingival bleeding scores) rather than measures that reflect past destructive periodontal disease, such as CAL, alveolar crestal height (ACH) and tooth loss.[84]

Furthermore, postmenopausal women with osteoporosis had lower serum $25OHD_3$ levels compared with age-matched controls without osteoporosis. Lowered serum $25OHD_3$ was also associated with periodontal disease and elevated levels of RANKL and osteoprotegerin (OPG),[85] consistent with previous reports that lower serum vitamin D is linked with increasing levels of cytokines such as IL-6, RANKL, TNFα, all of which are involved in stimulating osteoclastogensis.[86,87]

A recent cross-sectional study of a cohort of pregnant women, revealed that vitamin D deficiency was associated with poorer oral health and advanced periodontal disease.[88] The findings were consistent with a previous case control study, where it was shown that women who were vitamin D deficient (<75 nmoL/L) were more susceptible to periodontal disease during pregnancy.[89] Additionally, there was also a significant correlation between vitamin D deficient women and preterm birth (PTB) plus lower birth weight (LBW). These results were consistent with the findings from a recent meta-analysis which demonstrated that vitamin D deficiency in the second trimester was associated with an increased risk of PTB.[90]

Lastly, the association between serum $25OHD_3$ and periodontal disease appears to be influenced by age. Analyses of the NHANES III dataset showed a relationship between serum $25OHD_3$and mean attachment loss, only in participants aged ≥50 years.[10] This finding was reinforced in a more recent population based cross-sectional study of Koreans aged 50 years and older, where it was reported that lower serum $25OHD_3$ was significantly associated with tooth loss and severe periodontitis.[91] In contrast, the Finnish Health Survey of 1262 non-diabetic, non-smoking participants aged between 30–49 years found no association between serum $25OHD_3$25OHD and periodontitis, as measured by PPD.[92] These findings were echoed by the analyses of 106 female participants aged between 20 and 30 years, which found no association between serum $25OHD_3$ and the number of missing teeth.[93] Collectively, the studies suggest an association between serum $25OHD_3$ and periodontitis in an older group of participants, not in relatively young subjects with low risk of periodontitis.

10 | LONGITUDINAL STUDIES EXAMINING VITAMIN D STATUS AND PERIODONTAL DISEASE PROGRESSION

There were only a limited number of longitudinal studies assessing the impact of vitamin D status and periodontal disease progression and tooth loss (Table 1). Some of these long-term studies suggest that vitamin D does not offer a "perio-protective" effect on periodontitis. The studies were limited by the inclusion of self-reported questionnaires for tooth loss and dietary vitamin D intake. Many of the studies also focus on specific populations in the society, making it difficult to extrapolate findings.

One of the first studies which implicated vitamin D sufficiency as a protective factor against progression of periodontal disease, was the Dental Longitudinal study, which examined total vitamin

TABLE 1 Longitudinal studies examining vitamin D status and periodontal disease progression

Author/year	Participants	Method by which vitamin D was assessed	Outcome	Findings
Alshouibi, 2013	Male participants of the Dental Longitudinal Study (1986–1998), mean age 62.9	Total vitamin D intake estimated from FFQ and supplements	PPD, CAL, and ACH	Total vitamin D intake ≥800 IU was associated with lower odds of severe periodontal disease (based on AAP classification) and moderate-to-severe ABL, relative to intake <400 IU/day
Zhan, 2014	Study of Health in Pomerania (SHIP). Data from SHIP-I (2002–2006) and SHIP-2 (2008–2012), with mean follow-up of 5.9 years	Serum $25OHD_3$ was measured on the IDS-iSYS Multi-Discipline Automated Analyser	CAL, Tooth loss	Serum 25OHD was inversely associated with incidence of tooth loss: each 10ug/L increase in serum 25OHD was associated with a 13% decreased risk of tooth loss.
Jiminez, 2014	Health professional follow-up study, aged 40–75 years followed from 1986–2006	Predicted $25OHD_3$ score from linear regression model	Self-reported incident periodontitis and tooth loss	The highest quintile predicted 25OHD score were associated with 14% lower risk of tooth loss compared with those in the lowest quintile
Millen, 2015	Postmenopausal women in the OsteoPerio Study, baseline (1997–2000), to follow-up (2002–2005)	Plasma $25OHD_3$ was assessed using the DiaSorin LIAISON® chemiluminescence immunoassay	GI, PPD, CAL, ACH	Serum 25OHD was not associated with periodontal disease progression in terms of alveolar crest height, clinical attachment level, probing depth and percentage bleeding on probing
Schulze-Spate, 2015	Participants of the Osteoporotic Fractures in Men Study (MrOS), from 2002 to 2005 and 2005 to 2005	Serum $25OHD_3$ determined by LC–MS/MS assay	Periodontitis as defined by the Biofilm-Gingival Interface (BGI) Level classification system	
Pavlesen, 2016	Postmenopausal women in the OsteoPerio study; from baseline (1997–2000) to follow-up (2002–2005)	Plasma $25OHD_3$ was assessed using the DiaSorin LIAISON® chemiluminescence immunoassay; average daily vitamin D intake from Food frequency questionnaire (FFQ) and supplements	Self-reported tooth loss	Serum 25OHD was not associated with 5-year incidence of tooth loss

D intake and periodontal health in a cohort of well-characterised older men.[94] This was a repeated-measures cross-sectional study, which showed that participants who received less than 400 IU of vitamin D per day, presented with more advanced levels of alveolar bone loss and more severe periodontal disease, compared with participants who received more than 800 IU of vitamin D daily.[94] Therefore, the data suggest that the total vitamin D intake was inversely associated with the odds of severe periodontal disease. However, while both clinical and radiographic indicators were used to confirm periodontal disease progression, no serum $25OHD_3$ was measured. Instead, vitamin D was determined via self-reported diet questionnaires. The latter is a major limitation, as dietary intake does not adequately predict vitamin D status in individuals.[95]

Findings from other prospective, observational studies also support the "perio-protective" role of vitamin D.[96,97] Many studies have demonstrated the association between vitamin D status and tooth loss. In a study of Health in Pomerania in Germany, it was shown that serum $25OHD_3$ was inversely associated with incidence of tooth loss in a dose–response relationship.[96] However, the fact that there was no association between incidence changes in clinical attachment loss and serum $25OHD_3$, suggests that tooth loss could be due reasons other than periodontitis, such as caries. The latter is supported by a meta-analysis study which demonstrated the benefits of vitamin D supplementation in reducing caries risk.[98]

In the Health Professionals Follow-up study,[97] participants with the highest quintile predicted $25OHD_3$ scores were associated with a 14% lowered risk of tooth loss compared with participants in the lowest quintile. While this study was the largest prospective study involving over 42 000 participants with the longest follow-up period of 20 years, the major limitation with this study was that serum vitamin D was not determined and incident tooth loss was measured via self-reported questionnaires.[99]

While the aforementioned studies have supported the role of vitamin D in preventing periodontal disease progression, other studies showed contrasting findings. One of the largest prospective studies evaluating the long-term impact of serum vitamin D status on the progression of periodontitis was the OsteoPerio study.[78,99] The 5-year follow-up study of a cohort of well characterised postmenopausal women revealed that serum $25OHD_3$ was not associated with periodontal disease progression in terms of alveolar crest height, clinical attachment level, probing depth and percentage bleeding on probing.[99] This finding contrasts the results of a previous cross-sectional study on the same cohort of women where adequate vitamin D status was associated with decreased odds of periodontal disease compared with insufficient levels of vitamin D.[78] The 5-year follow-up study suggests that the vitamin D status may not influence periodontal disease progression. Further analyses of the same dataset suggests that serum $25OHD_3$ was not associated with the 5-year incidence of tooth loss in this cohort of postmenopausal women.[78] Similarly, the prospective observational Osteoporotic Fractures in Men study failed to show an association between baseline serum $25OHD_3$ and periodontal disease progression,[77] based on the Biofilm-Gingival Interface (BGI) Level classification system by.[100]

11 | INTERVENTIONAL CLINICAL TRIALS EXAMINING THE IMPACT OF VITAMIN D STATUS AND PERIODONTAL CLINICAL OUTCOMES

There were only a small number of interventional clinical trials examining the impact of vitamin D status and periodontal clinical outcomes (Table 2). A randomised double-blinded, placebo-controlled trial examining the effects of vitamin D supplementation on gingivitis in men and women showed that participants who received 2000,1000 or 500 IU per day of vitamin D over a period of 3 months experienced statistically significant greater reductions in gingival scores compared with the placebo group, suggesting that supplementation reduced gingival inflammation.[101]

A 3-year randomised controlled trial in elderly men and women receiving calcium (500 mg/day) and vitamin D (700 IU/day) supplementation to minimise hip bone loss showed 60% lower odds of tooth loss in the supplemented compared with placebo group.[102] It was not possible, however, to ascertain from these findings whether the influence of supplementation from calcium or vitamin D had the most impact on clinical outcomes. Most probably, the clinical benefits were due to the synergistic effects between calcium and vitamin D.[103] However, a subsequent 2-year follow-up analysis during which time the subjects consumed at least 1000 mg/day of calcium, suggests it was calcium, not vitamin D intake, which might be more important in preventing tooth loss.[102] The major limitation of this study was that tooth loss was a secondary outcome and therefore the dataset was only available in a subgroup of participants who completed both studies. Additionally, the tooth loss was based on self-reported questionnaires, although recent studies suggest demonstrated a high correlation between self-reported and clinical tooth counts at the population level.[104,105]

Two recent randomised controlled trials (RCTs) were conducted on the effects of vitamin D supplementation on changes in clinical outcomes following non-surgical periodontal therapy.[106,107] There was a statistically significant, but modest improvement in clinical outcomes in favour of vitamin D supplementation,[106] while another RCT showed that 6 months vitamin D supplementation did not lead to a significant improvement in clinical outcomes compared with the non-supplemented group.[107] However, due to the paucity of studies, the latest meta-analysis concluded that no conclusion could be drawn regarding the effect of vitamin D supplementation and treatment outcomes following non-surgical periodontal therapy.[74]

Only one RCT examined the effect of presurgical vitamin D status on periodontal surgery outcomes, with or without the administration of teriparatide, a commercially available form of PTH.[12] Administration of teriparatide is known to stimulate osteogenesis and the treatment of osteoporosis.[108] Participants in the PTH group who underwent surgery demonstrated significantly more resolution

TABLE 2 Randomised controlled trials examining impact of vitamin D status and periodontal clinical outcomes

Author/year	Participants	Intervention	Outcome	Findings
Hiremath, 2013	96 participants (aged 18–64 years)	Participants received daily 500 IU, or 1000 IU, or 2000 IU of vitamin D, or placebo over a 3 months period	GI	Participants who received vitamin D supplementation showed reduced gingival inflammation in a dose-dependent relationship. Participants receiving 2000 IU, 1000 IU and 500 IU showed an anti-inflammatory effect after 1 month, 2 months and 3 months respectively. The control group showed no anti-inflammatory effect
Krall, 2001	145 healthy participants, aged ≥65 years	Administration of calcium (500 mg/day) and vitamin D (700 IU/day) or placebo for 3 years	Tooth loss	In the first 3 years, participants who received both calcium and vitamin D supplementation showed 60% reduced odds of tooth loss compared with control group
Gao, 2020	360 patients with moderate or severe periodontitis	3 months after NSPT, participants randomly assigned to daily 2000 IU, 1000 IU or placebo.	Clinical indicators including: PPD, BI, PI, AL, ACH, measured at baseline and after 3 months of intervention	Vitamin D supplementation resulted in significant but modest improvement in clinical outcomes following NSPT
Peric, 2020	27 Healthy Caucasian periodontitis patients presenting serum 25(OH) vitamin D3 below 30 ng/ml	Participants randomly allocated to test group (NSPT + vitamin D) 25 000 IU/week or the control group (NSPT + placebo). The administration of vitamin D or placebo started 1 month prior to and continued until the 6 months after the treatment	Clinical indicators: PPD, FMBS, FMPS	Vitamin D supplementation did not result in significant improvement in clinical outcomes following NSPT at the 6 months follow-up
Bashutski, 2011	40 individuals with severe periodontal disease received open flap debridement surgery in one sextant of the mouth and were followed for 1 year post-surgery	Participants randomly allocated to treatment group, who received teriparatide (commercially available form of PTH, which is known to stimulate osteogenesis) or placebo	Infrabony defect resolution, as assessed by PPD, CAL and radiographic findings	Serum 25OHD at the time of periodontal surgery maybe critical to postsurgical healing. However, administration of vitamin D at the time of surgery did not prevent suboptimal clinical outcomes

Abbreviations: ACH, Alveolar crestal height; CAL, clinical attachment loss; FFQ, validated Food frequency questionnaire; GI, gingival index; IU, international units; NSPT, non-surgical periodontal therapy; PPD, probing pocket depths.

of linear bony defects in the vitamin D sufficient group compared with the vitamin D deficient group. In the placebo group, those who were vitamin D sufficient showed significant improvement in periodontal parameters such as attachment loss and pocket depths. These findings suggest that serum $25OHD_3$ at the time of periodontal surgery may be critical to postsurgical healing. Patients with sufficient serum $25OHD_3$ at the time of periodontal surgery benefitted more than participants with deficient serum $25OHD_3$. However, administration of vitamin D at the time of surgery did not prevent suboptimal clinical outcomes.[12] These findings suggest the importance of achieving sufficient levels of $25OHD_3$ prior to periodontal surgery.

12 | DISCUSSION

The biological functions of vitamin D are mediated by its strong anti-microbial, anti-inflammatory and host modulatory properties.[19] Experimental periodontitis models involving targeted deletion of 1α-hydroxylase, the enzyme responsible for the conversion of inactive substrate to active $1,25(OH)_2D_3$ (calcitriol), showed augmented alveolar bone loss and gingival inflammation.[17,18] VDR gene polymorphisms have also been associated with increased severity of periodontitis.[63,64] Thus, the involvement of vitamin D in the pathogenesis of periodontitis is biological plausible.

Most of the earlier clinical studies which examined the effects of vitamin D status on periodontal health were cross-sectional[10,77,78] and case–control studies.[11,81–83] The findings consistently demonstrated an inverse association between serum $25OHD_3$ and periodontal disease inflammation. However, as these assessments were performed at one point in time, it was not possible to determine a temporal relationship between vitamin D status and periodontal disease. Most of these studies were also focused on specific groups of the population[78,85,88,89] and therefore it was difficult to generalise the findings to a wider population, other than the characterised cohort of participants. A further limitation was that most of the studies employed only soft tissue indicators of periodontal disease (PD, CAL and gingival bleeding) as their primary outcome measure[10,11,77,81,88,89] and therefore, were limited by the lack of skeletal indicators of disease such as alveolar bone height.

There were very few longitudinal, prospective studies available and therefore, it was difficult to ascertain causality. There is some evidence to suggest that vitamin D might be associated with periodontal disease progression and tooth loss.[94,96,97] Other prospective studies however, suggest vitamin D might have more of an impact on the non-skeletal clinical parameters such as gingival bleeding,[101] rather than alveolar bone loss.[80,99] Part of the complexity in making sense of the data relates to the heterogeneity of studies, which have adopted different case definitions to diagnose periodontitis, as well as the lack of consensus to define serum $25OHD_3$ thresholds for vitamin D deficiency and adequacy. There is also some suggestion based on one RCT, that sufficient levels of vitamin D are important in influencing the periodontal surgical outcomes.[12] Thus, the evidence suggests that physiological vitamin D sufficiency, maintained by adequate exposure to sunlight or adequate oral supplementation supports periodontal health.

However, further prospective studies are needed to confirm the benefits of vitamin D supplementation in preventing the progression of periodontal disease. In particular, future studies should focus on populations at greater risk for vitamin D deficiency who are also at increased risk for periodontal disease, to determine optimal dosing and clarify whether vitamin D supplementation of deficient patients would result in superior periodontal clinical outcomes.

13 | CONCLUSION

Preclinical and clinical studies suggest the involvement of vitamin D in the pathogenesis of periodontitis. While clinical studies have consistently demonstrated an inverse relationship between serum $25OHD_3$ and periodontal disease inflammation, further studies are needed to clarify the role of vitamin D in the prevention of periodontal disease progression. The evidence suggests that adequate levels of vitamin D support periodontal health.

CONFLICT OF INTEREST

There are no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Emily Ming-Chieh Lu https://orcid.org/0000-0001-6039-6519

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