REVIEW ARTICLE

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Serum vitamin D levels and chronic periodontitis in adult, Caucasian population—a systematic review

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The aim of this systematic review was to explore the relationship between serum vitamin D levels and periodontal disease. The review followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The focused PICO question was: Are serum vitamin D levels (I) associated with gingivitis or periodontitis (C) in healthy humans (P)? PubMed (Medline), Embase, Science Direct, the Cochrane library, and grey literature were searched up to 31 July 2017. Two reviewers independently selected studies and extracted data. Quality, risk of bias, and heterogeneity of the studies were assessed using the Newcastle-Ottawa Scale. In total, 365 studies were identified and 24 were analyzed. Seven studies fulfilled the inclusion criteria. Four case-control studies showed an influence of vitamin D and its metabolites on periodontal health status/disease. One interventional study suggested the proposed anti-inflammatory role of vitamin D. Two cross-sectional studies failed to show a relationship between vitamin D and periodontal condition. The literature on the effect of serum vitamin D levels on periodontal status remains scarce and controversial. Some data, however, support a "perio-protective" role for vitamin D. There is a need for well-designed randomized clinical trials to explore the possible anti-inflammatory effect of vitamin D on periodontal health.

KEYWORDS
gingivitis, periodontal disease, periodontitis, serum vitamin D, vitamin D deficiency

1 | INTRODUCTION

Periodontal diseases, comprising gingivitis and periodontitis, are a group of infection-induced inflammatory conditions of the periodontal structures. The fact of being highly prevalent and, what is more, having an impact on up to 90% of the population worldwide, makes them the most common chronic inflammatory conditions of humans.[1,2] The destructive form of periodontal disease, periodontitis, affects approximately 50% of adults and more than 60% of subjects over 65 years of age, with severe periodontitis affecting 10%-15% of populations.[3-5] Periodontitis is initiated by an unbalanced interaction between the oral microbial community and the host inflammatory response to microbial challenge. Such dysregulated immune-inflammatory processes are responsible for the majority of host tissue destruction in susceptible individuals, leading to tooth loss.[1,4]

Currently, there is a growing body of evidence proposing the impact/involvement of nutrition in a number of inflammatory diseases and conditions, such as cardiovascular diseases, type 2 diabetes, rheumatoid arthritis and inflammatory bowel disease, all of which have been associated with periodontitis.[6] The effect of nutrition could be in modulating the inflammatory process in the host. In this respect, growing interest has been shown in the biological actions of vitamin D in relation to periodontal diseases.

The biologic plausibility supporting such a connection is based on several mechanisms. First, vitamin D plays a key role in bone metabolism through the regulation of calcium and phosphate balance.[7] Second, in vitro studies have identified vitamin D receptors in many cells and tissues of the human body involved in the inflammatory/

immune systems, suggesting that inflammation may be modulated by vitamin D.[8,9] As argued in the review by Stein et al,[10] vitamin D could exert its "perio-protective" role by shaping both the innate and the adaptive immune response, thus favoring resolution of the inflammation.

Analysis of cross-sectional data of the third National Health and Nutrition Examination Survey (NHANES III) found that the serum concentrations of 25-hydroxyvitamin D (25(OH)D) were significantly and inversely associated with bleeding on gingival probing in all age groups.[11] Dietrich et al[12] also reported an inverse association with clinical attachment loss in men and women aged 50 years or older.

Recent evidence from a case-control study by Boggess et al[13] reported decreased serum levels of vitamin D associated with maternal periodontal disease during pregnancy, and the same was true for the periodontitis in postmenopausal women with osteoporosis.[14]

In 2011, Bashutski et al[15] assessed the outcomes of periodontal surgery and teriparatide or placebo administration in vitamin-D-sufficient and -insufficient individuals and found that at 1 year, infrabony defect resolution was greater in teriparatide-treated vitamin-D-sufficient individuals compared with vitamin-D-deficient individuals. A 5-year prospective study found that a 3-year supplementation with calcium and vitamin D decreased the risk of tooth loss in elderly men and women.[16] Likewise, periodontal maintenance patients taking calcium and vitamin D supplements had better periodontal health, than those who did not.[17] Moreover, Hujoel et al, in a systematic review of controlled clinical trials, suggested that supplemental vitamin D was associated with a 47% reduced risk of caries. What is more, higher overall study quality score translated into higher vitamin D effectiveness. For instance, restricting the analysis to studies with nonbiased treatment assignment increased the percentage reduction in caries rate from 47% to 54%.[18]

These findings might suggest a protective and beneficial effect of vitamin D on oral health and periodontal condition.

Therefore, the focus of this systematic review was to find the evidence that could support or reject the possible impact of vitamin D serum levels in the etiology and therapy of periodontal diseases. Hence, two focused PICO questions were created:

1. Are serum vitamin D levels (I) associated with gingivitis or periodontitis (O) in healthy humans (P)?
2. Does nonsurgical periodontal therapy (I) have a different outcome in chronic periodontitis patients (P), with or without baseline vitamin D deficiency (C) regarding periodontal pocket depth reduction as the main clinical periodontal parameter (O)?

However, because of the paucity and methodological heterogeneity of the published studies, which strongly differed in at least one of the PICO parameters (thus making any comparison and regrouping ineffective), the second question could not have been assessed in an evidence-based manner according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)[19] statement and was therefore excluded from the current systematic review.

2 | MATERIAL AND METHODS

2.1 | Protocol

This systematic review was prepared according to the 27-item PRISMA Checklist.[19] Furthermore, the Assessment of Multiple Systematic Reviews guidelines (AMSTAR)[20] was followed.

The protocol is registered at the International Prospective Register of Systematic Reviews (PROSPERO) under the number CRD42017064420 (available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017064420).

2.2 | Study design

The protocol was developed in advance with the following focused PICO question:

Are serum vitamin D levels (I) associated with gingivitis or periodontitis (O) in healthy humans (P)?
Population: healthy humans
Intervention: participants with normal serum vitamin D levels
Comparison: participants with serum vitamin D deficiency
Outcome: gingivitis or periodontitis

2.3 | Eligibility criteria

2.3.1 | Inclusion criteria

- Randomized clinical trials, controlled clinical trials, observational studies (case series, cohort studies, and cross-sectional studies)
- Adult Caucasian population (≥18 years)
- Patients without systemic diseases or medications
- Patients diagnosed with gingivitis
- Patients diagnosed with chronic periodontitis (localized and generalized)
- Patients diagnosed with vitamin D sufficiency/deficiency/insufficiency confirmed with a blood test
- Patients included in initial nonsurgical periodontal treatment
- Patients not taking vitamin D supplementation prior to inclusion in the study
- Patients with chronic periodontitis receiving vitamin D during initial nonsurgical periodontal treatment
- Patients with gingivitis receiving vitamin D
- Overall enrolment of ≥10 patients

2.3.2 | Exclusion criteria

- Not original studies (eg reviews), case reports, retrospective studies and case series

- Nonhuman studies (in vitro studies and studies on animal models)
- Patients diagnosed with aggressive periodontitis
- Studies in which no blood test was performed in order to detect the level of the vitamin D
- Self-reported/via questionnaire evaluated gingivitis, periodontitis, and vitamin D status
- Patients receiving surgical periodontal treatment
- Patients receiving vitamin D + calcium administration during initial nonsurgical periodontal treatment
- Patients attending regular periodontal maintenance programs
- Pregnant or lactating women

2.4 | Information sources and search strategy

A detailed individual search strategy was developed for each of the bibliographic databases – MEDLINE via Pubmed, EMBASE, the Cochrane library, and Science Direct – without restrictions concerning language and date of publication. Additionally, the potential studies eligible for inclusion were searched for in the grey literature sources.

The following databases were explored: http://www.opengrey.eu/, https://www.openaire.eu/, and *Research gate*. The authors conducted a manual search of two periodontics-related journal issues published in the most recent 2 years (from January 2015 to July 2017), namely *Journal of Clinical Periodontology* and *Journal of Periodontology*. Electronic and manual searches were conducted independently by two authors (MP, JFL), from January 2017 to July 2017.

The search was performed using a combination of controlled vocabulary and key words. Details regarding the search strategy are presented in Table S1.

References were managed via reference manager software (EndNote X7; Thomson Reuters, Philadelphia, PA, USA).

2.5 | Study selection and data collection process

Studies fulfilling all the eligibility criteria were processed for data extraction. Predefined data extraction forms were used for assessment of each publication. Data were collected independently by one author (MP) and confirmed by a second author (JFL). When the study results were published more than once, the most complete data set was identified and included.

2.6 | Risk of bias in individual studies

Risk of bias in individual studies/quality assessment was carried out by two of the authors (MP and JFL) independently. Disagreements were resolved by discussion until a consensus was reached. The Newcastle-Ottawa Scale (NOS)[21] was followed to assess case-control studies. In order to evaluate the methodological quality of the included cross-sectional studies, a modified NOS[22] was used.
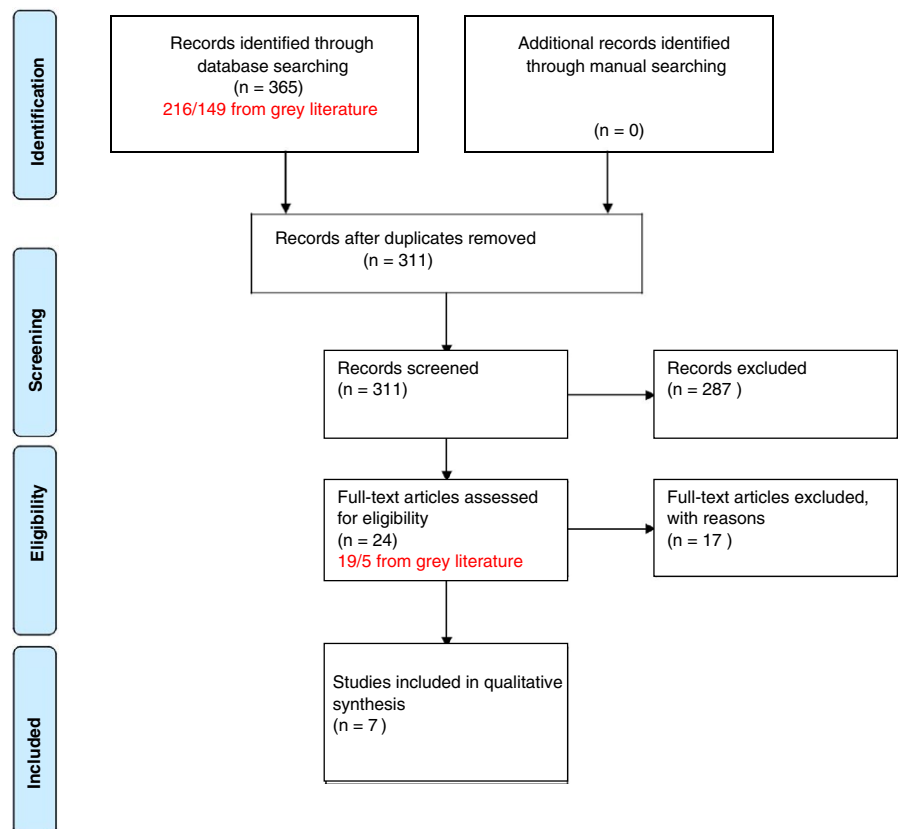

FIGURE 1 Prisma flow chart of literature search and inclusion From: Moher et al.[19] For more information, visit www.prisma-statement.org

Table 1 Characteristics of included studies

Author (year) Country Study design	A) Subjects: a) perio cases b) control group B) Mean age a) perio cases b) control group C) Female (%) a) perio cases b) control group D) Study duration	Diagnostic criteria for gingivitis	Diagnostic criteria for chronic periodontitis	Diagnostic criteria for vitamin D deficiency	Exposure (observational studies)	Intervention (experimental study-uncontrolled trial)
Abreu et al (2016)[27] Puerto Rico Case-control	A) a) 19 b) 19 B) a) 47.6 ± 8.7 b) 46.7 ± 8.2 C) a) 14 (73.7) b) 14 (73.7) D) n/a	n/a	Cases were classified as moderate or severe periodontitis based on the 2003 definitions by the CDC and the American Academy of Periodontology Working Group for moderate periodontitis (≥2 interproximal sites with AL ≥4 mm (not on same tooth) or ≥2 interproximal sites with PD ≥5 mm (not on same tooth); and severe periodontitis (≥2 interproximal sites with AL ≥6 mm (not on same tooth) and ≥1 interproximal sites with PD ≥5 mm)	For this study, vitamin D levels were categorized as deficient if levels were ≤12 ng/mL, inadequate if levels were 12-19 ng/mL, and adequate if levels were ≥20 ng/mL, as suggested by the Institute of Medicine criteria. However, the authors further divided the adequate group into 20-30 ng/mL (adequate) and >30 ng/mL (optimal) as suggested by the Endocrine Society for optimal health	Although there is little variation in UVB irradiation levels associated with the month in Puerto Rico, the study was conducted during the months of May, June, and July 2014 to decrease seasonal variability	n/a
Antonoglou et al (2014)[24] Finland Case-control	A) a) 55 b) 30 B) a) 46.3 ± 13.5 b) 41.9 ± 12.7 C) a) 34 (61.8) b) 19 (63.3) D) n/a	n/a	Not reported	The 50 and 25 nmol/L were used as cut-off points for 25(OH)D deficiency and insufficiency, respectively.	No data on vitamin D supplementation were available. As serum 25(OH)D level is dependent on an individual's exposure to sunlight, only subjects examined during the same period (autumn) were included in the 25(OH)D analyses.	n/a
Eshghi et al (2016)[23] Iran Case-control	A) a) 30 b) 30 B) a) 34 b) 34 C) 100% D) n/a	n/a	Patients were divided into two subgroups "A: severe chronic periodontitis, B: moderate chronic periodontitis" (workshop 1999)	10-29 ng/mL was considered as insufficiency and <10 ng/mL was assumed as vitamin D deficiency	Not reported	n/a

Outcome	Effect size: OR, 95% CI, _P_-value	Adjustment for covariates	25(OH)D assay	Conclusion	Comment
The analysis of the conditional multiple logistic regression showed that for every unit (ng/mL) increase in serum 25 (OH)D levels, the odds of periodontal disease was significantly reduced by 12%	The analysis of the conditional multiple logistic regression showed that for every unit (ng/mL) increase in serum 25 (OH) D levels, the odds of periodontal disease was significantly reduced by 12% (OR 0.885; 95% CI 0.785, 0.997; _P_ < .05)	Age Sex BMI	Direct competitive chemiluminescence immunoassay (Liaison; DiaSorin S.p.A., Saluggia, VC, Italy)	In conclusion, lower serum vitamin D levels are significantly associated with periodontitis in Puerto Rican adults. These results suggest that there is value in screening periodontitis patients for low vitamin D status	Calibrated examiner, but calibration modalities not specified, smoking habits not reported. No available data on vitamin D supplementation
75% of the periodontitis and 30% of the control subjects were deficient, while 15% of patients with periodontitis but none of the control subjects had an insufficient level	The results of the logistic regression models showed that the serum 1,25 (OH)2D level (OR = 0.97, 95% CI 0.95-1.00) but not 25(OH)D level (OR = 1.00, 95% CI 0.96-1.07) was associated with periodontal health status. The association between 1,25(OH)2D and periodontal health status remained significant also among nonsmokers (OR = 0.94, 95% CI 0.90-0.99)	Age Sex Smoking BMI Serum HDL Plaque	ELISA (Immunodiagnostics System [IDS], Boldon, Tyne and Wear, UK) for 25(OH)D; 1,25(OH)2D was measured using an enzyme-immunoassay procedure after purification of 1,25(OH)2D by immunoextraction according to the recommendations of the assay manufacturer (IDS)	To summarize, in this study we could not confirm previously reported associations between serum 25(OH) D level and periodontal health. However, we conclude that a low serum 1,25(OH)2D level was associated with periodontitis as it is with other inflammatory diseases	Not reported if the examiner was calibrated. No available data on vitamin D supplementation
Chi-square test showed that vitamin D deficiency was more frequent in the CP group compared with the control group and vitamin D sufficiency was more prevalent in control group than CP group (_P_ = .046)	The OR measures showed that persons with vitamin D level of less than 10 ng/mL were 5.6 times more likely (OR 5.6; 95% CI: 1.13-28.4, _P_ = .035) to have periodontitis compared with those with normal levels of vitamin D (30-100 ng/mL). In a same pattern, subjects with vitamin D levels of 10-29 ng/mL were about 1.46 times at a higher risk (OR 1.46; 95% CI: 0.3-6.9, _P_ = .63) to develop periodontitis than those with sufficient levels of vitamin D	Not reported	ERRATUM ELISA (DIAsource, Belgium) for 25(OH)D and not, as erroneously reported, for 1, 25(OH)2D	The main findings of this study were a negative association between serum 1, 25(OH)2D level and chronic periodontitis and also a significant negative relationship between the periodontal indices and vitamin D levels among premenopausal women	Only the results for 1, 25(OH)2D outlined, no data available for 25(OH)D. Only nonsmokers in perio group included, for control group not specified. Not reported if the examiner was calibrated. No available data on vitamin D supplementation. Not specified if the women were veiled

TABLE 1 (continued)

Author (year) Country Study design	A) Subjects: a) perio cases b) control group B) Mean age a) perio cases b) control group C) Female (%) a) perio cases b) control group D) Study duration	Diagnostic criteria for gingivitis	Diagnostic criteria for chronic periodontitis	Diagnostic criteria for vitamin D deficiency	Exposure (observational studies)	Intervention (experimental study-uncontrolled trial)
Laky et al (2016)[33] Austria Case-control	A) a) 29 b) 29 B) a) 35.41 ± 7.7 b) 35.45 ± 7.4 C) a) 17 b) 21 D) n/a	n/a	Inclusion criteria for the periodontitis group were a minimum of 5 teeth with a pocket probing depth ≥5 mm	Vitamin D deficiency (ie, <50 nmol/L)	Not reported	n/a
Antonoglou et al (2015)[25] Finland Cross-sectional	A) 1262 B) 39.6 C) 768 (60,86%) D) n/a	n/a (Gingival bleeding was measured after periodontal probing and registered by sextants immediately after probing.)	n/a (Periodontal pocketing, measured by means of the number of teeth with deep (≥4 mm) periodontal pockets per individual.)	n/a	Vitamin D intake (micrograms per day) was assessed using a self-administered, validated FFQ designed to estimate average food intake during the past 12 mo; it included 128 commonly used food items and dishes. The FFQ also included questions about regular use of vitamin supplement	n/a
Hiremath et al (2013)[31] Belgaum, India Cross-sectional	A) 96 B) 32.33 ± 10.51 C) 41 (42.71%) D) n/a	The selected subjects had to have periodontal pockets less than 2 mm. and gingivitis score of <1 measured by the Gingival Index (Löe and Silness, 1963)	n/a	n/a	The subject needed to have serum 25(OH)D concentration of 20- 65 ng/mL	n/a

Outcome	Effect size: OR, 95% CI, *P*-value	Adjustment for covariates	25(OH)D assay	Conclusion	Comment
48.3% of all patients with severe periodontal disease had deficient 25(OH)D levels compared with only 13.8% in the control group	The adjusted odds ratio in the regression model for periodontal disease with insufficient 25(OH)D status was 1.50 (95% CI: 1.13-1.98)	Age Sex Smoking BMI	Enzyme-immunoassay IASON 25-OH-Vitamin D® test kit (IASON GmbH, Graz, Austria)	Our data show that low serum-concentrations of 25(OH)D are significantly associated with periodontal disease, suggesting that insufficient vitamin D levels might be involved in periodontal disease progression	Not reported if the examiner was calibrated. No available data on vitamin D supplementation
Periodontal pocketing and gingival bleeding, measured by means of the number of teeth with deep (≥4 mm) periodontal pockets and the number of bleeding sextants per individual, respectively, were used as the outcome variables	No statistically significant association was found between serum 25(OH)D level and the number of bleeding sextants or teeth with deep (≥4 mm) periodontal pockets. Adding the month of examination to the final model had practically no effect on the associations studied. In addition, there was no statistically significant association between vitamin D intake and the number of bleeding sextants (PRR = 0.98, 95% CI: 0.96-1.01) or the number of teeth with deep (≥4 mm) periodontal pockets (PRR = 0.99, 95% CI: 0.98-1.01). When total energy intake was added to the previous model, the estimates remained practically the same	Age Sex Education Toothbrushing frequency Dental attendance pattern The presence of plaque The number of carious teeth Alcohol consumption Physical activity BMI Serum lipid profile Lipid-lowering medication Concentration of serum CRP	Radioimmunoassay (DiaSorin, Stillwater, MN, USA)	No essential association between serum 25(OH)D level and periodontal condition, measured as either gingival bleeding or deep (≥4 mm) periodontal pockets, was found. Furthermore, there was no statistically significant association found between periodontal infection and vitamin D intake	
The multivariate analysis shows that the total contribution of age, sex, vitamin D, weight, and calculus on gingival status was 38.92% in which the calculus status contributed a maximum of 20.11% compared with the minimum of 0.83% by gender, followed by serum vitamin D 11.77%, age by 3.96% and weight by 2.25% respectively	The relationship of vitamin D with gingival status is found to be negative and statistically significant at *P* < .05; age, weight and calculus were showing significant and positive relationship with gingival status, and abovementioned significant variables were dependent on each other	Age Sex Weight Calculus status	Diasorin vitamin D Direct ELISA kit	The inverse association of serum 25(OH)D concentration and gingivitis is an important finding as it indicates the individuals with low levels of vitamin D would be susceptible to gingivitis	Not reported if the examiner was calibrated. No available data on vitamin D supplementation. Smokers excluded

TABLE 1 (continued)

Author (year) Country Study design	A) Subjects: a) perio cases b) control group B) Mean age a) perio cases b) control group C) Female (%) a) perio cases b) control group D) Study duration	Diagnostic criteria for gingivitis	Diagnostic criteria for chronic periodontitis	Diagnostic criteria for vitamin D deficiency	Exposure (observational studies)	Intervention (experimental study-uncontrolled trial)
Teles et al (2012)[26] Massachusetts, USA Experimental study (uncontrolled trial)	A) 56 B) 49.5 C) 26 (46,42%) D) 6 mo	n/a	1) patients >20 y of age; 2) >15 natural teeth; 3) >5% sites (approximately 8 sites) with PD >4 mm and/or attachment level >4 mm	n/a	n/a	Individuals of any racial/ethnic group were accepted for the study. After the initial monitoring and sampling, all participants received scaling and root planing at 4 visits using manual instruments and ultrasonic devices and also received oral hygiene instructions. All participants received maintenance subgingival scaling at 3 mo. Clinical parameters and subgingival biofilm samples were collected again 6 mo after treatment

1,25(OH)2D, calcitriol; 25(OH)D, 25-hydroxyvitamin D; 95% CI, 95% confidence interval; AL, attachment loss; BMI, body mass index; CDC, Centers for Disease Control; CP, chronic periodontitis; CRP, C-reactive protein; FFQ, food frequency questionnaire; HDL, high-density lipoprotein; n/a. not available; OR, odds ratio; PD, probing depth, PRR, Predictive-ratio risk; TNF-a, tumor necrosis factor-alpha; UVB, ultraviolet B.

3 | RESULTS

3.1 | Study selection

A total of 365 studies was identified through the electronic search. Manual search did not determine any further study for inclusion. Figure 1 depicts the study flow chart. After removal of duplicates and screening of titles and abstracts, 24 potentially eligible studies were obtained. Full-text analysis led to exclusion of a further 17 studies. As a result, a total number of 7 articles was reached. The 17 studies excluded after full-text assessment and main exclusion reasons are listed in Appendix S2, and the 7 studies included are listed in Appendix S3.

3.2 | Description of characteristics of included studies

All information related to study characteristics and data synthesis are presented in Table 1. Four of the studies were of a case-control design, one was an experimental study (uncontrolled trial), whereas the remaining two had a cross-sectional design. Therefore, none corresponded to the highest level of quality—randomized controlled trial.

3.3 | Quality assessment using the NOS

All 7 studies were assessed using the NOS for case series and the modified NOS for cross-sectional design. The consensus NOS quality score for each study is depicted in the Appendixes S4, S5.

Major bias in these studies was risk of bias in selection of samples because the study population derived mostly from hospital settings and dental schools. Moreover, the blinding of the examiners was not reported in the studies.

Cofounders, such as age, sex, body mass index, and smoking status were reported, except for the study of Eshghi et al.[23] Nonetheless, they were not systematically adjusted for in the

Outcome	Effect size: OR, 95% CI, P-value	Adjustment for covariates	25(OH)D assay	Conclusion	Comment
Seventeen patients were examined at 6 mo after therapy. There were essentially no differences between pretreatment and post-treatment levels of any of the serum analytes, although a trend toward the reduction of TNF-a and increase in vitamin D and adiponectin was detected. All clinical parameters of periodontitis showed improvement after periodontal therapy. In addition, levels of the periodontal pathogens *Tannerella forsythia*, *Treponema denticola*, and *Porphyromonas gingivalis* were considerably reduced after treatment	None of the clinical or microbial parameters were associated with any of the serum analytes ($P > .05$). Using multiple linear regression, it was observed that the best predictors for adiponectin levels were sex (female), BMI (lower), and increasing age ($P = .000\ 078$, $r^2 = 0.278$). For leptin levels, the best predictors were sex (female) and BMI (higher) ($P = .000001$, $r^2 = 0.789$). BMI was the only significant predictor for IL-6 ($P = .00074$, $r^2 = 0.195$) and vitamin D ($P = .03735$, $r^2 = 0.209$)	n/a	Radioimmunoassay (DiaSorin, Stillwater, MN, USA)	Our findings suggest that chronic periodontitis might play a minor role, if any, in serum levels of inflammatory mediators in systemically healthy individuals. The influence of sex and BMI outweighed any potential role that local periodontal infection and inflammation may have on systemic markers of inflammation in the absence of generalized periodontitis or systemic modifying factors	Individuals of any racial/ethnic group were accepted for the study. Calibrated examiner, but calibration modalities not specified; smokers included in the study, nevertheless smoking habits not reported. No available data on vitamin D supplementation

logistic regression model estimating the association between serum vitamin D levels and periodontal health, except for the studies by Antonoglou et al.[24,25]

Periodontal condition was defined by clinical examination, but the examiner's calibration was only reported in the studies from Teles et al[26] and Abreu et al.[27] However, calibration modalities were not specified.

Serum vitamin D levels were evaluated by laboratory tests listed in Table 1 for both forms of vitamin D, namely 25(OH)D and its active form calcitriol (1,25(OH)2D).

In the study by Eshghi et al[23] the authors erroneously reported the values for 1,25(OH)2D instead of 25(OH)D because the test used (DiaSource, Louvain-la-Neuve, Belgium) determines the serum levels of 25(OH)D. What is more, they reported the values of 1,25(OH)2D in the units that are used to report the values of 25(OH)D (ie, in ng/mL instead of pg/mL, which is used for 1,25(OH)2D).

In the study by Teles et al[26] the sample derived from a cohort with chronic periodontitis without the healthy/unexposed cohort. Moreover, adequacy of follow-up was poor, preventing us from deriving any conclusion regarding the changes in the vitamin D serum levels that may be a result of the periodontal therapy (as the vitamin D status was measured at the beginning of the study in 56 individuals and ended with the data of only 17 individuals who completed the treatment). Hence, as a result of the characteristics listed above, it was rather regarded as a cross-sectional design and the NOS scale for cross-sectional studies was used.

4 | DISCUSSION

Vitamin D status of the general population is largely below the recommended level, with estimates of one billion people worldwide having vitamin D deficiency or insufficiency.[28] Vitamin D is acquired

through diet and skin exposure to ultraviolet B light. Skin production of vitamin D is determined by length of exposure, latitude, season, and degree of skin pigmentation. Racial differences in the relationship between 25(OH)D and bone mineral density (BMD) have been reported in the literature. Serum levels of serum 25(OH)D are usually much lower in African American subjects, probably because of decreased formation of vitamin D in skin.[29,30] Therefore, to exclude any racial bias, only studies of the Caucasian population were included in the present review.

In 3 of 4 case-control studies, cases presented a statistically significant proportion of deficient 25(OH)D levels compared with controls. Antonoglou et al[24] failed to show the effect for 25(OH)D; however, a statistically significant association between serum 1,25(OH)D and periodontal condition was found. Namely, subjects with a low level of serum 1,25(OH)2D were more likely to belong to the periodontitis group. Still, in the cross-sectional study by Antonoglou et al[25] no associations between serum 25(OH)D level and teeth with deep (≥4 mm) periodontal pockets or bleeding sextants was detected. On the contrary, Hiremath et al[31] found an inverse association between serum 25(OH)D and the Löe & Silness Gingival Index. Teles et al[26] found positive correlations between serum levels of adiponectin/vitamin D and between interleukin-6/leptin, and negative correlations between interleukin-6/vitamin D and between leptin/vitamin D. However, there was no association between serum analytes and clinical or microbial parameters. The cross-sectional/observational nature of the studies makes it difficult to draw any conclusion about the potential causal relationship between 25(OH)D and periodontal status.

Different classifications were used to assess the periodontal status, which makes the studies heterogeneous. What adds to their heterogeneity even more is the variability in 25(OH)D assays, as well as the different cut-off points for vitamin D adequacy, deficiency, and insufficiency. Accordingly, any comparison should be made recognizing those elements. To address the assay problem, many laboratories around the world should participate in a quarterly quality assurance and surveillance program, the Vitamin D External Quality Assessment Scheme.[32] Additionally, the study populations derive mostly from hospitals, except for that in Antonoglou et al,[25] with a small sample size and without defining the study power, except for Laky et al.[33] Furthermore, comparability of the cases and controls on the basis of the design in case-control studies was rated as low.

Regarding the association between serum vitamin D levels and periodontal status, one must be careful in interpreting the results from the different studies as the definition for the odds ratio may differ among them, which was the case with the (four case-control) studies selected here. An odds ratio depends on the definition of the binary classes (threshold to distinguish between deficient and adequate levels of 25(OH)D). Therefore, there are a variety of cut-off values for vitamin D deficiency across the studies because of the absence of uniformly accepted definitions.[34] In the article of Abreu et al,[27] odds ratio is reported as odds ratio per units of vitamin D level. In this regard, the use of continuous values in statistical analysis rather than defining the threshold for 25(OH)D deficiency/

insufficiency in the studies would make them directly comparable. Consequently, if an odds ratio is calculated in a logistic regression, it is going to be influenced by the other variables in the model (if adjusted). Unfortunately, limited information on the impact of effect modifiers for vitamin D and periodontal condition, such as smoking habits, geographical latitude, season in which blood samples were taken, ethnicity, vitamin D supplementation, calcium intake, diet, sun/ultraviolet light exposure, and body mass index, were provided. Studies were conducted in a limited number of countries and the overall definition of periodontitis across the studies is not consistent. Importantly, as periodontal attachment loss is an accepted measure of cumulative life experience, it should be used in the studies of risk factors for periodontal disease as the primary outcome variable.[35]

There is increasing evidence of systemic inflammation resulting from the hematogenous dissemination of both oral microbial agents and their virulence factors deriving from oral biofilms and inflammatory mediators deriving from the inflamed periodontium. In support of this evidence are the elevated serum levels of C-reactive protein and other acute-phase reactants and raised biomarkers of oxidative stress, thus leading to the possible interaction with various systemic diseases, notably diabetes, atherosclerosis, rheumatoid arthritis, and pulmonary infections.[4,36] Beyond the well-known effects of vitamin D on bone structure, data from ecological and observational studies have shown associations between low concentration of serum 25(OH)D and increased risk of cancer, cardiovascular diseases, disorders of glucose metabolism, neurodegenerative diseases, and death. Reports from the International Agency for Research on Cancer and the US Institute of Medicine concluded that insufficient evidence linked 25(OH)D and most nonskeletal health disorders. However, the 2 reports did not provide hypotheses for why so many disorders were associated with low 25(OH)D concentrations.[7] Furthermore, in the systematic review by Autier et al,[7] prospective studies generally documented moderate to strong decreases in cardiovascular disease, serum lipid concentrations, serum markers of inflammation, glucose metabolism disorders, weight gain, infectious diseases, mood disorders, declining cognitive function, and impaired physical functioning in association with increasing concentrations of 25(OH)D. The importance of vitamin D lies in its capacity to modulate immune/inflammatory systems via regulating the production of inflammatory cytokines and inhibiting the proliferation of proinflammatory cells, both of which are crucial for the pathogenesis of inflammatory diseases.[37] Hoe et al[38] examined the effects of 1,25(OH)2D3, the active metabolite of vitamin D, on peripheral blood mononuclear cells and purified immune cell subsets isolated from healthy adults, suggesting that 1,25(OH)2D3 may be an important regulator of the inflammatory response and proposing that further in vivo and clinical studies in known vitamin D (25(OH)D)-deficient populations may reveal more potent effects in this context. Furthermore, de Oliveira et al[9] suggested a potential role of 25(OH)D in chronic inflammation, thus contributing to the growing body of evidence supporting a role for vitamin D

in inflammatory conditions. Controversy, however, exists as to whether or not vitamin D deficiency contributes to the etiology of inflammatory disease or if vitamin D deficiency is simply a manifestation of these diseases.[9,37]

Using Hill's criteria for causation, there is consistent evidence that hypovitaminosis D can be a risk factor for periodontal disease.[39] However, based on this systematic review and because of the lack of evidence-based data from prospective clinical trials, vitamin D is to be considered a risk indicator for periodontal diseases. Whether this relationship is causal in nature, and whether vitamin D can be considered a risk factor for periodontal diseases, needs to be elucidated in future, well designed randomized clinical trials. The inflammatory burden should be assessed at the patient level. The periodontal inflamed surface area (PISA) index[40] could be the appropriate index to use when quantifying the amount of inflamed periodontal tissue in order to evaluate the potential anti-inflammatory effect that may be exerted by vitamin D/vitamin D supplementation.

In summary, all the included studies have some methodological shortcomings, even though strict inclusion and exclusion criteria were applied. This clearly shows the need for further research in the field, especially to clarify the potential benefits of vitamin D supplementation on periodontal health and the adequate dosage regimen to obtain it.

4.1 | Clinical relevance

There are still many open questions concerning our understanding of the effects of vitamin D on periodontal health. Therefore, based on the available scientific data regarding the biological properties of vitamin D, we made the following recommendations for future clinical trials.

Further, well designed studies need to elucidate the role of vitamin D metabolism in periodontal health and if vitamin D supplementation and improved vitamin D status can be of benefit to periodontally compromised patients. These studies should be conducted in patients with low 25(OH)D concentrations at randomization, with careful control of effect modifiers for both vitamin D status and periodontal condition, using high doses to achieve high 25(OH)D concentrations with a proper duration of the treatment to elucidate if long-term effects can be expected.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

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SUPPORTING INFORMATION

Additional supplemental material may be found online in the Supporting Information section at the end of the article.