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SYSTEMATIC REVIEW

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Vitamin D deficiency and oral health: a systematic review of literature

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Abstract

Background Vitamin D (VD) levels are gaining increasing interest in dentistry due to their association with several oral diseases.

Objective This study aimed to evaluate the relationship between vitamin D deficiency and various oral disorders.

Materials and methods A broad search on the MEDLINE database via the PubMed interface and on the Spring Link platform was carried out using keywords related to the subject. An additional electronic search of gray literature was conducted via Google Scholar. Inclusion criteria were listed for the selection of articles and a reading grid was designed for the extraction of data relating to the research question. The quality of included studies was assessed using JBI's critical appraisal tools.

Results A total of 57 studies were identified. After reading the full text, 16 studies were included and selected for qualitative analysis. There is an association between vitamin D deficiency and different oral disorders. Indeed, ten publications assessed the association between vitamin deficiency and periodontal disease, three examined the relationship between vitamin D deficit and dental caries, and one examined the intriguing relationship between vitamin D deficiency and tooth mineralization and two articles interested in vitamin D deficiency and stomatitis.

Conclusion The analysis of these selected articles shows that Vitamin D deficiency can lead to various oral health disorders during growth and adulthood. Indeed, it can be linked to tooth mineralization defects and increasing the risk of dental caries. Severe Vitamin D deficiency also increases the prevalence of periodontitis and gingival inflammation. It may also be linked to certain oral pathology entities, such as oral cancers and jaw osteonecrosis.

Keywords Vitamin D deficiency, Oral health, Tooth defects, Dental caries, Periodontitis, Oral cancer

Introduction

Vitamin D is a steroid hormone obtained from sunlight, diet, and supplements [1]. Vitamin D2 and D3 are produced through ultraviolet irradiation of ergo sterol from yeast and 7-dehydrocholesterol from lanolin, respectively. Serum 25-hydroxyvitamin D (25[OH] D) is a widely accepted biomarker for vitamin D status [2].

Through regulating intestinal absorption, vitamin D functions as a hormone, promoting blood calcium and phosphate balance. Moreover, it controls the innate immune system, cell maturation, and differentiation as an autocrine and paracrine agent [3].

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Vitamin D deficiency (VDD) is a global concern, particularly in children, pregnancy, some forms of cancer, and infection prevention [4]. VDD can arise from lack of exposure to sunlight with adequate ultraviolet B rays, nutritional deficits due to inadequate intakes of vitamin D, or hereditary disorders from absorption and metabolic conversion [5].

Periodontal and dental pathologies being the two most common oral pathologies world wide [6]. The importance of diet in these conditions has grown in recognition. Research has shown that VDD hinders odontogenesis, which leads to a hypomineralized dentition that is more vulnerable to caries infections and breakage [7]. Furthermore, VDD is linked to lower periodontal health and may have a role in the immune system's reaction to periodontal infection [8, 9]. In fact, through immunomodulation, vitamin D influences the pathophysiology of periodontal diseases (PD) and raises bone mineral density (BMD), reducing bone resorption, and fighting against agents causing PD [10].

These most current discoveries prompted us to develop a systematic analysis with the goal of evaluating the relationship between vitamin D deficiency and various oral disorders.

Materials and methods

Protocol registration

The study was conducted from October 20 2023 to October 30, 2024 at the Faculty of Dental Medicine of Monastir (FMDM).

This systematic review followed preferred reporting items for systematic reviews (PRISMA) guidelines [5] (Figure S1). The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database, registration number CRD 42,024,552,782 (Figure S2).

Constitution of the working group

An organized analysis of the literature requires the formation of a working group in order to avoid the subjective judgments of a single person.

A Hospital-University Assistant (Saida Ziada) and a DDS (Aws Wishahe) formed the working group and were authorized to answer the research question.

Organization of work

The study required rigor and diligence on the part of the members of the working group in the critical reading of the articles in addition in the extraction and synthesis of the data. The responsibilities of initial screening and validation of the articles were equally shared between the two reviewers S.Z and A.W.

In the event of disagreements, SS, a senior University Hospital Professor, reviewed the conflicting decisions and made the final determination.

Research strategy

The PECO (Population/Exposure/Comparison/Outcome) method guided the research strategy and the formulation of the research question. (Table S1)

Method in which:

- P: People who need oral and dental health care.
- E: People who suffer from vitamin D deficiency.
- C: People with normal vitamin D levels.
- O: Relationship between vitamin D deficiency and oral health.

The research for the systematic review was taken up by defining the keywords related vitamins, lack of vitamin D, dental health, tooth defects, dental caries, periodontitis, periodontal health and periodontal disease.

Our focused research question was "to determine the implication between the vitamin D deficiency and oral diseases and particularly with a higher risk of tooth defects, dental caries, periodontitis and oral treatments failure".

Research was conducted across three electronic databases: PubMed, Google scholar and Spring Link with time restrictions. Vocabulary and grammar were modified to match databases specifications. During the search, the key words and controlled vocabulary (Medical Subject Heading Terms) were combined with Boolean operators "OR" / "AND" to establish the following Boolean formula: (vitamin d deficiency [MeSH Terms]) AND (oral health [MeSH Terms])) OR (vitamin d deficiency [MeSH Terms])) AND (dental caries [MeSH Terms])) OR (vitamin d deficiency [MeSH Terms])) AND (apical periodontitis [MeSH Terms])) OR (vitamin d deficiency [MeSH Terms])) AND (periodontal diseases [MeSH Terms])

MeSH terms are specific to PubMed. Google Scholar and SpringerLink rely on keyword-based search algorithms The search strategies for these databases used natural language keywords and Boolean operators rather than MeSH terms to ensure a more accurate and comprehensive search (Table S1).

Selection of the articles

These articles were selected according to Inclusion criteria(the original articles; studies conducted on human subjects with vitamin D deficiency; articles published in the English language between 2013 and 2024; studies that examine the epidemiological relationship between vitamin D status and dental health, include cohort, case control and sectional studies) and exclusion criteria(letter to editor; documents with incomplete or unclear analytical

data and inconsistent outcome indicators; repetitive literature and narrative review; systematic reviews and meta-analyses and in vitro studies).

Research and critical reading of articles

All articles obtained following the search on the three databases were downloaded.

Two reviewers review each article according to the inclusion and non-inclusion criteria independently. Then, the results are compared and in the event of a difference of opinion, a third person can make a decision.

A grid was developed by the working group and summarizes the relevant data relating to the research question. Then, this grid was carefully completed for each article selected(FigureS3).

Results

General description of the research results

Searching with the Boolean equation on spring link, after activation of the filters: language is English, date since 2013, discipline is medicine and public health, sub discipline is dentistry and content type is article, fifty two articles were identified then when only full free text were included, nine articles were identified.

Similarly, the search on PubMed was made, after activation of the filters: language is English, date since 2013, species humans and text availability free full text; twenty-four articles were identified.

During the search on Google Scholar and after we activate the filters on, the number of articles was large. For this reason, we are limited to the articles that were published in the last year. Ten pages were reviewed and all of them were consulted. We found twenty-eight articles and nine of them were available for download (free full text).

The scientific search of articles on this topic was updated on 30/10/2024. As a result, twenty new articles were found, two of them met the inclusion criteria and were retained, while the other eighteen did not meet the inclusion criteria and were removed. (TabeS2-S8)

Finally, sixteen articles were included in the systematic review. (Fig. 1)

These articles included eleven cross-sectional, three case control and two retrospective studies. The histogram (Fig. 2) shows the distribution of articles published from 2013 to 2024 according to their types:

The following Table 1 presents the sixteen articles included in this systematic review.

Extraction of data from selected articles

A reading grid allowed the extraction of the data necessary for carrying out this systematic review. In this following Table 2 we assembled the caracteristics of the included studies regarding 25-hydroxyvitamin D (25 (OH) D) levels.

Characterizations of the selected articles

All articles selected were in English, eleven articles were cross-sectional studies, three article were case control studies and two retrospective studies. (Fig. 2)

Ten publications addressed the association between vitamin deficiency and periodontal disease, three examined the relationship between vitamin D deficit and dental caries, and one examined the intriguing relationship between vitamin D deficiency and tooth mineralization and two articles interested in vitamin D deficiency and stomatitis.

Nine research studies were carried out in the United States, five in Europe, one in Asia and one in Africa. No research has been conducted in Australia or South America.

Assessment of the risk of the selected articles

The evaluation of the literature and the assessment of risk of bias are essential steps in ensuring the credibility and reliability of a systematic review. These processes help determine whether the studies included are free from systematic errors and provide accurate results.

For this review, the JBI critical evaluation tools (Joanna Briggs Institute (JBI) checklist of 2020), questions each adapted to a specific study design to was utilized to assess the quality and risk of bias of the included articles, ensuring a rigorous evaluation of their methodological soundness.

The risk of bias was low to moderate (Table S9-S11).

Discussion

The connection between oral health and vitamin D deficiency

Dental diseases

Tooth mineralization Teeth are mineralized structures made of cementum, dentin, and enamel that are encircled by alveolar bone. The process by which teeth mineralize and skeletons happens simultaneously, but in the event that a disruption in mineral metabolism, tooth failures will resemble those in bone tissue. For teeth and bone to mineralize, vitamin D is necessary. Uncontrolled vitamin D levels can result in the "rachitic tooth," a malformed and hypomineralized structure that is extremely prone to breakage and decay [8, 26, 27].

Severe vitamin D deficiency (VDD) results in hypophosphatemia and hypocalcemia along with secondary hyperparathyroidism. This increases the amount of calcium absorbed through the intestines and the amount of 1,25-dihydroxyvitamin D (1,25[OH]2D) produced by the kidneys. It also increases bone turnover, which raises serum Ca2 + levels and reduces the amount of inorganic phosphate in serum. After then, the initial hypophosphatemia becomes much worse, and mineralization

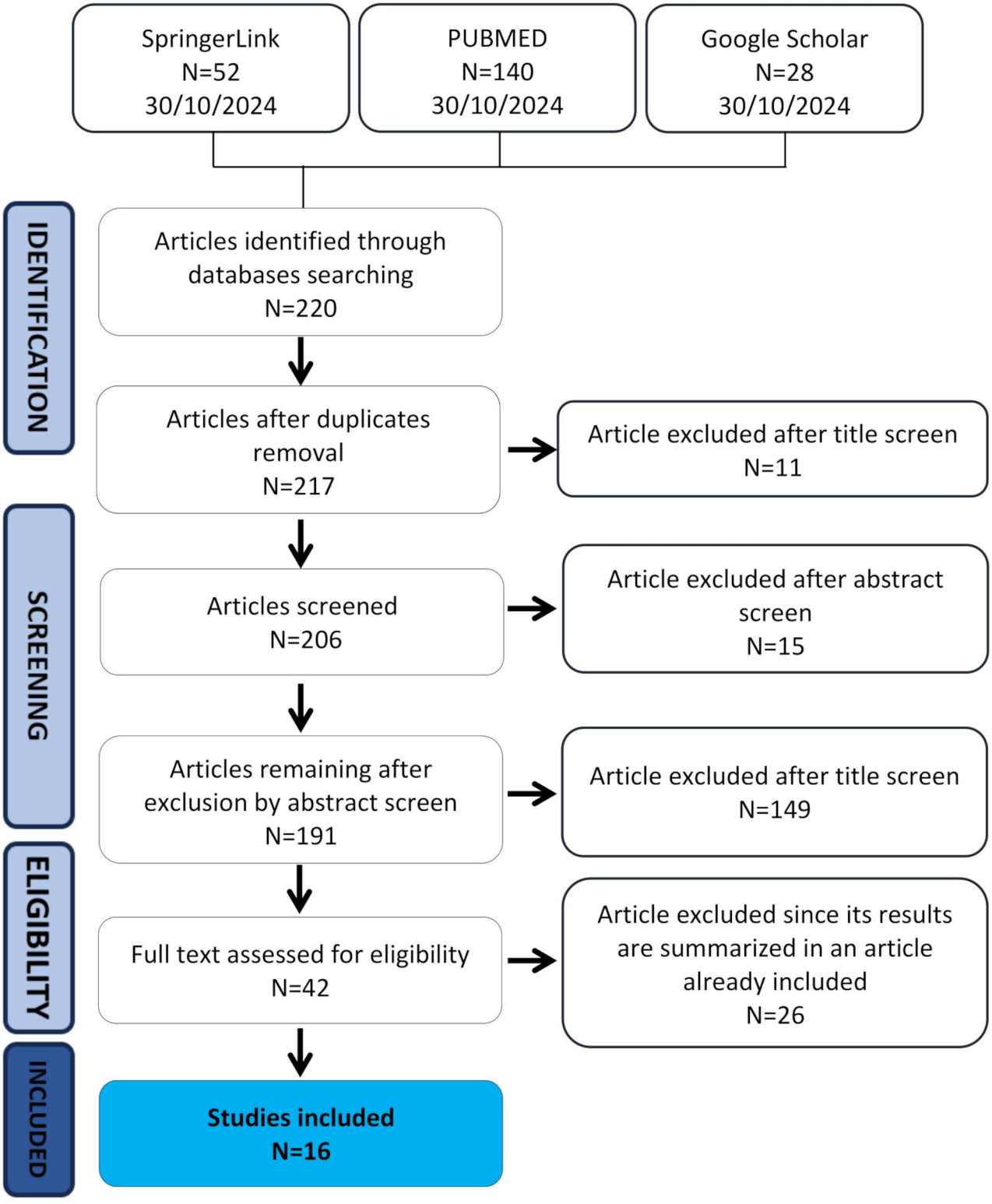

Fig. 1 Flow diagram of the study

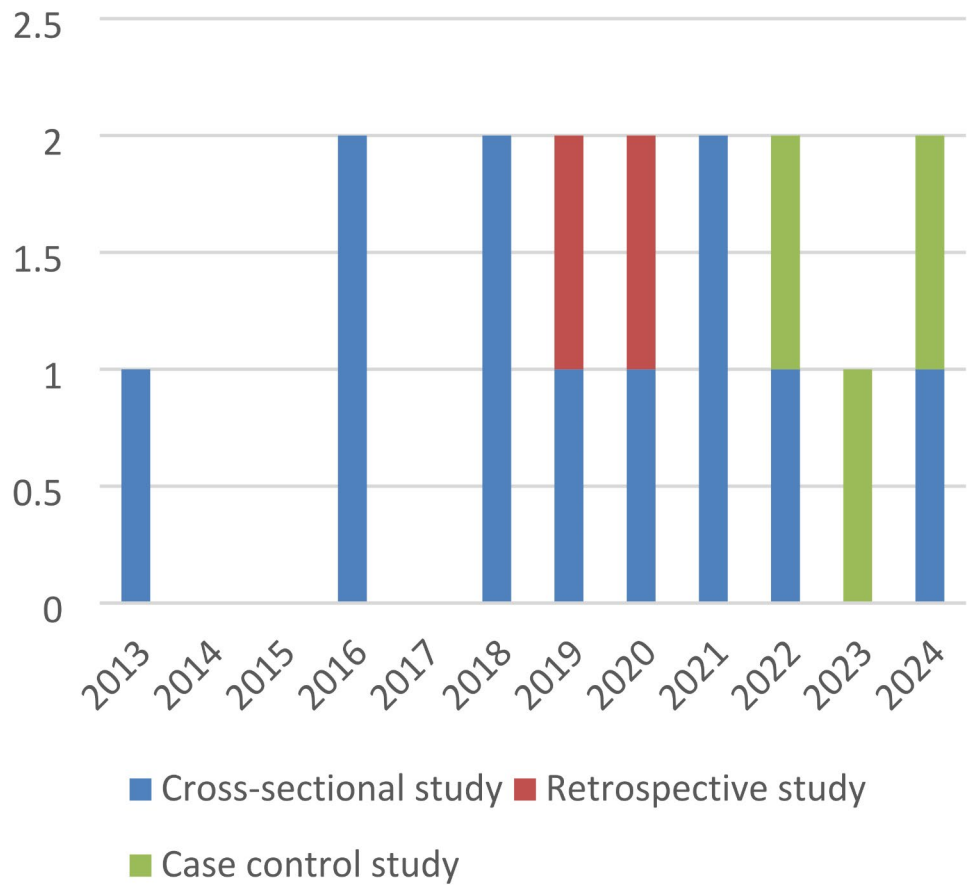

Fig. 2 Histogram of included articles (cross-sectional study / case control study /retrospective study)

problems arise from the disappearance of vitamin D signaling pathways in tooth cells that have low levels of phosphate and Ca2 + ions [27, 28].

A signaling route via vitamin D receptors (VDR) can be started by some circulating vitamin D. This mechanism regulates gene expression through vitamin D elements (VDRE). The immune system, skeletal muscle, detoxification, energy metabolism, cell migration and life cycle, immunological response, and bone are all impacted by these sensitive genes. Dentin and enamel are formed when VDR is upregulated by vitamin D. This brings us to the induction of structural gene products, such as calcium-binding proteins and extracellular matrix proteins [27].

A pilot study was conducted by Reed SG et al. in 2017 to investigate the correlation between prenatal vitamin D and enamel hypoplasia in human primary maxillary central incisors concluded that even in the absence of fetal abnormalities, maternal 25 (OH) D levels can affect deciduous dentition. Maternal 25 (OH) D levels that are out of equilibrium may directly affect the health and dental development of the unborn child. The particular week of gestation that maternal VDD occurred determines the type of mineralization deficiency [29].

Dental caries Recent dental health studies have identified an association between prenatal 25OHD and dental caries prevalence by age 6, even if the correlations strengths varied, possibly due to the timing of 25OHD collection.

An observational study was conducted by Beckett DM et al. in 2022 on mothers with 25OHD deficiency throughout the pregnancy's third trimester found that children with mothers with 25OHD insufficiency in the third trimester had over three times the rate of dental caries at age 6, in contrast to those who mothers lacking 25OHD. This study offers novel evidence that maternal vitamin D deficiency in the third trimester of pregnancy is linked to a significantly higher incidence of caries in the primary dentition by the time the child is six years old. Nevertheless, there was no correlation seen between the incidence or severity of enamel defects and early life 25OHD. This information confirms the benefits of vitamin D supplementation throughout pregnancy and the early years of life, as well as the benefits of healthy teeth for bone and mineral development.

But according to this study cord blood and 5-month serum 25OHD levels were not significant predictors for dental caries, and no associations were observed between

Table 1 Articles included in our systematic review

Author	Title	Objective	Published	Results
Egle Jagelavi˘ciene, Inga Vaitkevi˘ciene, Dovile Šilingait, Egle Šink ˙ unait and Goda Daugelait [4]	The Relationship between Vitamin D and Periodontal Pathology	To evaluate the role of vitamin D in preventing periodontal diseases and reaching a successful outcome of the conservative and surgical treatment.	12 June 2018	Vitamin D plays a significant role in maintaining healthy periodontal and jaw bone tissues, alleviating inflammation processes, stimulating post-operative healing of periodontal tissues and the recovery of clinical parameters.
João Botelho, Vanessa Machado, Luís Proença, Ana Sintra Delgado and José João Mende [11]	Vitamin D Deficiency and Oral Health: A Comprehensive Review	To summarize how VDD may hamper oral development and play a part in certain oral conditions.	9 May 2020	VDD is highly implicated with oral diseases and has been linked with a higher risk of tooth defects, caries, periodontitis and oral treatments failure. The maintenance of appropriate 25(OH)D levels has shown to be associated with better oral development and health throughout life.
Gaetano Isola, Giuseppe Palazzo, Alessandro Polizzi, Paolo Murabito, Clemente Giuffrida and Alberto Lo Gullo [12]	Association of Systemic Sclerosis and Periodontitis with Vitamin D Levels	To analyze the association among systemic sclerosis (SSc), periodontitis (PT); we also evaluated the impact of PT and SSc on vitamin D levels.	23 February 2021	The multivariate regression analysis showed that PT ($p = 0.011$) and CRP ($p = 0.031$) were both predictors of vitamin D levels. Subjects with PT and SSc plus PT had significant lower vitamin D values with respect to SSc and to healthy subjects. In addition, PT seems negatively associated with levels of vitamin D in all analyzed patients.
Marina Peri´c, Dominique Maiter, Etienne Cavalier, Jérôme F. Lasserre and Selena Toma [13]	The Effects of 6-Month Vitamin D Supplementation during the Non-Surgical Treatment of Periodontitis in Vitamin-D-Deficient Patients: A Randomized Double-Blind Placebo-Controlled Study	To assess the effects of weekly vitamin D (VD) supplementation on clinical and biological parameters after scaling and roots planning (SRP) in the treatment of periodontitis and served to validate the VD dosage regimen.	25 September 2020	A total of 59 patients were screened, 27 were included and 26 completed 3 months (M) and 21 completed 6 M control. Test ($n = 13$) and control groups ($n = 14$) had similar 25(OH) vitamin D3 levels at baseline (17.6 ± 7.4 vs. 14.4 ± 5.2, respectively). After one month, there was a significant difference between groups (32.9 ± 5.2 vs. 16.1 ± 4.7), also seen at M3 and M6 (t-test, $p < 0.001$). Periodontal treatment was successful in both groups, since it resulted in a reduction of all measured clinical parameters at M3 and M6 (probing pocket depth (PPD), full mouth bleeding and plaque). However, the reduction in PPD was greater in the test group.
Mi-Ra Lee, Su-Jin Han, Hee-Eun Kim and Jun-Seon Choi [14]	Relationship between Vitamin D Deficiency and Periodontitis in Korean Adults Aged ≥ 60 Years	To examine the relationship between periodontitis and vitamin D status (plasma 25 (OH) D) levels.	5 April 2021	Univariate analyses showed that periodontitis was not significantly associated with plasma 25(OH)D levels. In the multivariate logistic regression model adjusted for sociodemographic characteristics, the difference in the prevalence of periodontitis between those with a normal range of 25(OH)D and those with low plasma of 25(OH)D levels was not statistically significant. Vitamin D intake has been reported to have benefits in maintaining periodontal health; however, total plasma 25(OH)D levels showed no significant association with periodontitis based on CPI scores in this study.
Mohamed M. Meghil, Lance Hutchens, Anas Raed, Neha A. Multani, Mythilypriya Rajendran, Haidong Zhu, Stephen Looney, Mahmoud and Christopher W. Cutler [15]	The Influence of Vitamin D Supplementation on Local and Systemic Inflammatory Markers in Periodontitis Patients: A pilot study	To investigate the influence of 12 weeks of 25(OH) D vitamin D supplementation on mediators of systemic inflammation in dark-skinned, periodontitis patients.	25 July 2019	Vitamin D supplementation increased serum 25(OH)D levels approximately 2-fold over baseline levels; moreover, VDS group had reduced peripheral blood CD3 and CD3 + CD8 + cytotoxic T lymphocyte (CTLs) counts and reduced pro-inflammatory salivary cytokines. In contrast, VDS group had higher levels of the autophagy-related proteins and other proteins crucial for anti-microbial autophagy in whole blood PBMCs.
Panagiotis Dragonas, Linda M. Kaste, Martha Nunn, Praveen K. Gajendrareddy and Kathleen M. Weber [16]	Vitamin D deficiency and periodontal clinical attachment loss in HIV-seropositive women	To investigate the correlation between low vitamin D (VitD) serum levels and the severity of periodontal disease in women with HIV infection.	6 June 2018	VitD deficiency was positively associated with higher mCAL ($P = 0.012$). After adjustment for race, age, smoking, and HIV viral load, an association was found between VitD deficiency and mCAL (Beta 0.438; $P = 0.036$).
Sonja Pavlesen, Xiaodan Mai, Jean Wactawski-Wende, Michael J. LaMonte, Kathy M. Hovey, Robert J. Genco, and Amy E. Millen [17]	Vitamin D Status and Tooth Loss in Postmenopausal Females: The Buffalo Osteoporosis and Periodontal Disease (OsteoPerio) Study	To examine the association between plasma 25- hydroxyvitamin D (25[OH] D) concentrations and the prevalence 5-year tooth loss rate in a group of postmenopausal women.	2016 August	No statistically significant association was observed between 25(OH)D and the history or incidence of tooth loss caused by periodontal disease. An increased odds of the history of tooth loss attributable to caries was observed with increasing concentrations of 25(OH)D (P-trend = < 0.05) but was not confirmed in prospective analyses.

Table 1 (continued)

Author	Title	Objective	Published	Results
Orlando J. Abreu, Dimitris N. Tatakis, Augusto R. Elias-Boneta,, Maria S. Pousa and Cristina Palacios [18]	Low vitamin D status strongly associated with periodontitis in Puerto Rican adults	To evaluate among a pilot study the association between vitamin D levels and periodontal disease in Puerto Rican adults.	2 September 2016	Mean serum 25 (OH) D levels were significantly lower in cases (18.5 ± 4.6 ng/ml) than in controls (24.2 ± 7.1 ng/ml; $p = 0.006$). Lower odds of periodontal disease were observed per unit of 25 (OH) D level (OR 0.885; 95% CI 0.785, 0.997; $p < 0.05$).
Monik Jimenez, Edward Giovannucci, Elizabeth Krall Kaye, Kaumudi J Joshipura and Thomas Dietrich [19]	Predicted vitamin D status and incidence of tooth loss and periodontitis	To assess the correlation between the occurrence of periodontitis and tooth loss and to predict a score of plasma 25 (OH) D.	7 March 2013	There was a dose-dependent significant inverse association across quintiles of the predicted 25(OH) D score and incidence of tooth loss.
João Botelho, Yago Leira, João Viana, Vanessa Machado, Patrícia Lyra, José Manuel Aldrey and Juan Blanco [20]	The Role of Inflammatory Diet and Vitamin D on the Link between Periodontitis and Cognitive Function	To explore the association of periodontitis with cognitive functioning and the mediation effect of an inflammatory diet and serum vitamin D levels in this link.	12 March 2021	Vitamin D showed a weak association between CERAD-DRT, AFT and DSST and was estimated to between 8.1% and 73.2% of the association between periodontitis and cognitive dysfunction ($p < 0.05$).
Deanna M. Beckett, Jonathan M. Broadbent, Carolina Loch, Erin K. Mahoney, Bernadette K. Drummond and Benjamin J. Wheeler [21]	Dental Consequences of Vitamin D Deficiency during Pregnancy and Early Infancy—An Observational Study	To investigate the effects of vitamin D deficiency/insufficiency on teeth in a cohort of 81 children from New Zealand during pregnancy and early childhood.	9 February 2022	Of the 81 children, 55% had experienced dental caries and 64% had at least one enamel defect present. Vitamin D insufficiency (25OHD < 50 nmol/L) at all timepoints was not associated with enamel defect prevalence, but during third trimester pregnancy it was associated with an increased caries risk IRR of 3.55 (CI 1.15–10.92) by age 6.
Chen Li, Jinmei Zhang, Lufei Wang, Jingmei Yang [22]	A case of early-onset periodontitis with vitamin D deficiency	To present a case of 12-year-old girl affected by early-onset periodontitis accompanied with vitamin D deficiency.	2023	Based on the clinical and serological findings, this patient was ultimately diagnosed with early-onset periodontitis accompanied with vitamin D deficiency.
Iwona Olszewska-Czyz, and Elena Firkova [23]	Vitamin D3 Serum Levels in Periodontitis Patients: A Case–Control Study	To assess the blood levels of vitamin D3 in both healthy individuals and patients suffering from periodontitis.	24 April 2022	Vitamin D3 levels were found to be statistically significantly lower among periodontitis patients (31.34; SD = 5.62) compared with healthy controls (39.64; SD = 8.77). Vitamin D3 deficiency was corresponding to the stage and grade of the disease as well as the clinical attachment and bone loss.
Rania Shalaby, Marwa El Nawawy, Khaled Selim, Samah Bahaa, Sahar El Refai, AbeerAbd El Maksoud [24]	The role of vitamin D in amelioration of oral lichen planus and its effect on salivary and tissue IFN-γ level: a randomized clinical trial	To investigate the role of VD as an adjunct to steroids in the management of VD-deficient OLP patients as well as its inhibitory effect on IFN-γ through measurement of salivary and tissue IFN-γ levels in OLP patients.	17 July 2024	Results revealed a statistically significant correlation between changes in serum vitamin D levels before and after treatment and salivary as well as tissue IFN- levels ($P \leq 0.001$).
Shabnam Tehrani, Ladan Abbasian, Seyed Ali Dehghan Manshadi, Malihe Hasannezhad, Sara Ghaderkhani4, Amirreza Keyvanfar, Azar Darvishi and AmirHossein Aghdaee [25]	Vitamin D deficiency and oral candidiasis in patients with HIV infection: A case–control study	To investigate the association between vitamin D levels and oral candidiasis in patients with HIV infection.	19 February 2024	Based on the findings, most patients with HIV infection suffer from vitamin D deficiency, especially those with oral candidiasis. Hypovitaminosis D was significantly associated with an increased risk of oral candidiasis. Thus, vitamin D supplementation may assist HIV-positive patients in improving their oral health and preventing oral candidiasis.

25OHD levels at any given moment and the development of any type of dental enamel defect [21].

Previous studies have investigated vitamin D in association with enamel defects and/or dental caries experience, and in the absence of 25OHD information, methods often include vitamin D supplementation or self-reported vitamin D intake from dietary sources [30, 31].

Naverro et al. investigated 25OHD at birth and found no association with dental caries experience at age six. However, Borsting et al. in 2019 investigated enamel hypomineralisation in 855 children aged 7–9 years, using available maternal serum 25OHD obtained during the second and third trimester of pregnancy as a marker for vitamin D levels [32, 33]. The study highlights the

Table 2 Characteristics of the included studies regarding 25-hydroxyvitamin D (25 (OH) D) levels

Authors	Year, Country	*N.* of Subjects	Vitamin D level normal /non	Male /Female	Smokers *n* (%)	Mean Age ± SD	The relationship of vitamin D with oral diseases	Method / Site sample
Gaetano Isola et al. [12]	Italy 2021	160	Healthy subjects (30.5 (28.8–32.3) ng/mL) PT 19.1 (17.6–26.8) ng/mL SSc (21.1 (15.4–22.9) ng/mL)	NR	NR	NR	Systemic Sclerosis and Periodontitis	CAL / Serum
Marina Peric et al. [13]	Belgium 2020	59	VD ≥ 30 ng/mL	NR	NR	Don't care	Periodontitis	CAL / Serum
Mi-Ra Lee et al- [14]	Korea 2021	701	VDD 20 ng/mL	NR	Tested	≥ 60 Years	Periodontitis	CLIA / Serum
Mohamed M. Meghil et al [15]	Georgia 2022	23	NR	NR	NR	NR	Periodontitis	ELISA / Serum
Panagiotis Dragonas et al. [16]	USA 2018	74	Insufficiency [≤ 30 ng/mL] deficiency [≤ 20 ng/ mL]) w	Women	NR	39.6 years	Periodontal	CAL / Tooth
Sonja Pavlesen et al. [17]	USA 2017	1,362	VD ≥ 75 nmol/L, VD insuffiency < 50nmol/L VDD < 30nmol/L	Women	NR	> 45 years	Osteoporosis and Periodontal Disease	CAL / serum
Orlando J. Abreu et al. [18]	USA 2016	48	Sufficiency ≥ 20 nm/ml Insufficiency 12–19 nm/ml Deficiency ≤ 12 nm/ml	NR	NR	35 to 64 years	Periodontitis	CAL / Serum
Monik Jimenez et al [19]	USA 2013	42 730	VD ≥ 75nmol/l	NR	NR	40–75 years	Periodontitis	CAL / Serum
João Botelho et al. [20]	USA 2021	2062	NR	NR	NR	60 years	Periodontitis and Cognitive Function	CAL / Sample
Deanna M. Beckett et al. [21]	New Zealand 2022	81	Sufficiency ≥ 50 nmol/L Insufficiency < 50 nmol/L Deficiency ≥ 30 nmol/L	NR	Non	66 years	Mineralization and caries dental	Observational study
Rania Shalaby et al. [24]	Egypt 2024	40	≤ 30ng/ml deficiency or insufficiency	NR	NR	NR	Oral lichen planus	ELISA

CLIA; Chemiluminescence Immunoassay, CAL;Clinical Attachment Loss; ELISA; Enzyme-Linked Immunosorbent Assay, SSc; Systemic Sclerosis, PT; Periodontitis, NR; Non Revealed

importance of vitamin D supplementation while expecting and infants, particularly highlighting the value of dental health as a potential marker of overall mineral and skeletal health in early life [34].

Pulp stones Recent papers reported the escalation of dental problems such as periodontitis and caries with Vitamin D deficiency. Although no study has investigated the incidence of pulpal calcification while in case of vitamin D leves modification. Only one case report was reported by Giunta JL et al. mentioned focal pulp calcifications in maxillary permanent central incisors in hypercalcemia, which was due to secondary to excess and note deficiency vitamin D because of excessive milk consumption [35]. A retrospective study conducted by Gürhan C et al. in 2024 aimed to evaluate the effect of serum calcium, parathyroid hormone (PTH), vitamin D, and uric acid levels on pulp stone formation. The current study has not verified those of the case report, and large-scale clinical studies are required to clarify the effect of vitamin D on pulp stone etiology [36].

Periodontal diseases

Gum and periodontal diseases A study conducted by Lee MR et al. in 2021 in Korea discovered that a lack of vitamin D in Korean adults aged ≥ 60 years is connected to increased prevalence of gingivitis. A vital function for vitamin D in maintaining gum health, as it plays a direct role in bone metabolism, antibiotic effects against gum disease pathogens, and interrupts inflammatory mediators that stimulate gum tissue destruction. However, few studies have provided direct proof that the level of vitamin D is an important factor in the creation of periodontal disease. The study's hypothesis was that, depending on variables including age and plasma 25 (OH) D levels, vitamin D insufficiency is not linked to periodontitis. It also found that adults older than 60 years, the age group with the highest prevalence of chronic periodontitis in

South Korea, are more prone to accumulate more pathogenic oral biofilm on tooth surfaces compared to younger age groups. The study also found that vitamin D's impact on periodontal health may be limited in cases where oral hygiene care is not thoroughly performed. The optimal plasma 25 (OH)D concentration was not precisely defined, and the study found that as the level increased, the number of people meeting the standard decreased significantly [14].

In a study conducted by Isola G et al. in 2021 including 38 patients with Systemic Sclerosis (SSc) and 41 healthy controls, individuals with PT(Periodontitis)and SSc had significantly lower blood vitamin D levels than controls. Vitamin D had a negative correlation with probing depth (PD), clinical attachment level (CAL), bleeding on probing (BOP), C - Reactive Protein (CRP), and plaque score (PI), but a positive correlation with the number of teeth. Reduced sun exposure, intestinal malabsorption, inadequate food, and thicker skin are some of the factors that may cause SSc patients to have decreased vitamin D levels [12].

Tissue hypoxia is a major issue in the appearance of vascular-related diseases during SSc, leading to oxidative stress and relative vasospasm. A lack of vitamin D may accelerate vascular disorders in SSc through the stimulation of oxidative stress pathways [37]. Reduced vitamin D levels could also play a part in the etiology of SSc through the regulation of transforming growth factor (TGF)-β, a crucial mediator in the production of fibroblast and collagen during both SSc and PT [36]. Low vitamin D serum could increase the possibility of autoimmune and inflammatory diseases, especially during SSc [38]. It has been demonstrated that high vitamin D levels have a 20% reduced likelihood of acquiring periodontal disease (PT) and tooth loss in adults. Vitamin D has combined anti-inflammatory and antimicrobial activities, promoting the creation of molecules from various mediators and inflammatory cells, with direct pro-inflammatory effects on all tissues, including periodontal tissues [39].

Strong anti-inflammatory properties of vitamin D have been demonstrated in the oral cavity, especially against periodontal pathogenic microorganisms. It lowers the bacterial load on gingival biofilm and lessens tissue damage during periodontitis (PT) by inhibiting Porphyromonas gingivalis (P. gingivalis) and suppressing the related virulence factor. A study discovered a substantial correlation between the quantity of teeth and serum vitamin D levels and periodontal indices. This implies that there might be a connection between vitamin D and PT, with low blood vitamin D levels being associated with increased PT severity [40].

The impacts of PT and gingival health the amount of vitamin D in healthy participants and people with periodontitis (PT) and SSc were also examined in this study. The association between vitamin D levels in the blood and PT was also examined. The findings indicated that a proportionate rise in blood vitamin D levels was linked to a proportionate increase in the number of teeth and a proportionate decrease in periodontal indices. Moreover, PT and CRP levels strongly predicted blood vitamin D levels [12].

The study discovered that the ideal serum vitamin D levels were linked to good gingival health, low levels of BOP and CAL, and decreased levels of interleukin-6 (IL-6), a mediator of tissue destruction during periodontitis. Conversely, low serum levels were linked to high levels of bone morphology (BOP) and gingival health. Increased levels of vitamin D in the blood may provide immunological protection for healthy persons suffering from periodontitis. It's been proven that individuals with periodontitis (PD) and reduced bone loss pressure (BOP) benefit from supplemental diet therapy using calcium and vitamin D supplements. The number of teeth and major periodontal indicators, however, were shown to be strongly linked with blood CRP levels and vitamin D levels. By lowering the inflammatory response and preventing the generation of CRP, vitamin D can be of assistance. The correlation between vitamin D, CRP, and periodontitis (PT) might potentially be elucidated by the link between inflammation and PT. Inflammation may cause an additional systemic release of CRP. The longitudinal association between vitamin D, periodontitis, and periodontal disease (PT) cannot be analyzed because to some limitations in the study [41].

A study conducted by Dragonas et al. aims to investigate the correlation between low blood levels of vitamin D (VitD) and the severity of periodontal disease in women living with HIV infection. The severity of periodontal disease (mCAL) in HIV-positive women was shown to be correlated with vitamin D blood levels in this Chicago research, which involved 74 older women living with the virus. Age at visit, race, level of education, smoking status at the time, CD4 cell count, and HAART status were all included in the research. Patients with a 50% higher mCAL than those without a vitamin D deficiency, which is comparable to the harmful effects of current tobacco use or a higher HIV viral load [16].

The cutoff point for blood vitamin D levels that would indicate noticeably loss health outcomes is up for debate. The multivariate analysis confirms the importance of inadequate vitamin D for its correlation with loss periodontal health, which is in line with findings from two studies carried out at the Wisconsin Institute of Health (WIHS) on oral candidiasis and bacterial vaginosis.

Comparable results have been noted in non-HIV cohorts: women with adequate Vitamin D levels in the blood (VitD) had a 33% decreased risk of periodontal

disease than those with inadequate levels. Women with ongoing or prior periodontal disease had considerably lower blood amounts of vitamin D than women without the condition, according to research by Jabbar et al. [14]

A recent study found there is no correlation between periodontal disease and vitamin D levels in adult HIV-positive Brazilians. The study had strengths and limitations, including statistically significant differences when contrasting mCAL in different VitD status groups but small mCAL numbers and uncertain clinical significance. Given the known and broadly applicable impact of tobacco smoking on periodontal health, it is imperative to acknowledge the therapeutic significance of the data linked to VitD [16].

The study examined data from the Wisconsin HIV Health Survey (WIHS) cohort, which consisted of primarily African American adult women residing in Chicago who were HIV positive. Given that geographical location is a recognized predictor of VitD status, the sample was not typical of all HIV-positive individuals residing in the US. Since periodontal therapy and the extraction of teeth that were inoperable were included in dental care, the split mouth design might not correctly depict periodontal health. The study also discovered that, from 1995 till 2004, a tiny proportion of people were getting HAART, a very advantageous pharmaceutical regimen. Though women did not immediately join the WIHS, over 60% of American HIV-positive individuals are still untreated, according to the most recent data from the Centers for Disease Control and Prevention. Extrapolating leads to HIV seropositive status patients is difficult since HAART was not as successful or as simple to administer as it is now. Notwithstanding these drawbacks, the results are new and have substantial therapeutic value, particularly in light of how they will compare and contrast with future research conducted in the contemporary HAART period [17].

A pilot case-control study in Puerto Ricans showed that serum 25 (OH) D levels were significantly lower in periodontitis patients than in controls. A 12% reduction in the probability of both severe and moderate periodontitis was seen for every unit increase in serum 25 (OH) D levels. This is the first study to evaluate the relationship between serum 25 (OH) D levels and periodontal disease in a population of Hispanic individuals. According to epidemiological research, the patients' periodontal condition appears to be typical of the Puerto Rican population as a whole [18].

Further study indicates a connection between periodontal disease and vitamin D levels. In a case-control research, the median 25 (OH) D levels of pregnant women were found to be lower in the cases (23.6 ng/ml) compared to the controls (40 ng/ml; $p < 0.001$). Pregnant women with serum 25 (OH) D levels < 0.001 were linked to a greater risk of periodontal disease, whereas pregnant women with serum 25 (OH) D levels < 0.001 were linked to a lower risk of periodontal disease. However, in a case-control study of adult Finns, there was no relationship seen between 25 (OH) D levels and periodontal health status.

Vitamin D insufficiency affects dental and oral bone disorders, which are dependent on the peculiar way that oral and dental cells respond to this nutrient. Oral epithelial cells have been shown to convert inactive vitamin D to the active form of 25 (OH) D, which in turn induces the synthesis of a variety of host defense mediators, including the antimicrobial peptide LL-37. A related research suggests that proper blood vitamin D levels may reduce susceptibility to gingival inflammation and that gingivitis may be a useful clinical model to evaluate the anti-inflammatory effects of vitamin D [18].

Immunology of periodontal disease According to a study by Liu et al., dental pulp fibroblasts and periodontal cells release 25-hydroxylase during an inflammatory phase, which enhances the formation of 25 (OH) D3. In immunological and epithelial cells, this protein interacts to Vitamin D Receptors (VDR), taking part in the defensive mechanism of the epithelium against pathogens. 1, 25 (OH) D3 promotes the synthesis of proteins required for the tight, gap, and desmosome junctions in epithelial cells, which in turn fosters an environment that is favorable to bacterial invasion from dental plaque [4].

1,25 (OH)D3 increases the production of antimicrobial peptides such as LL-37's β-defensin and cathelicidin, as well as controls the immunological response that is non-specific and causes the release of hydrogen peroxide in monocytes. By influencing B-lymphocytes and T-lymphocytes, which release cytokines and immunoglobulins to kill bacterial infections, vitamin D also has an impact on a particular immune system. These immune responses exacerbate Parkinson's disease (PD) and damage periodontal tissue (PT). The production of immunoglobulins, the conversion of plasma cells from B-lymphocytes, and Vitamin D inhibits all T-lymphocyte growth. By reducing the release of cytokines including IL-1, IL-6, IL-8, IL-12, and TNFα, it suppresses undesirable processes and shields the organism against an overly particular immune response [4].

In their investigation into the anti-inflammatory effects of vitamin D in cell cultures of human periodontal tissue, Tang et al. discovered that 1,25 (OH)D3- and Porphyromonas gingivalis-affected cell cultures produced less IL-8 than did cell cultures affected just by Porphyromonas gingivalis. By finding that greater blood serum concentrations of vitamin D include more adiponectin, which modulates the immune response, and less leptin

and IL-6, Teles et al. validated the anti-inflammatory characteristics of vitamin D [4].

Periodontal healing and treating gum disease with vitamin D supplements A randomized controlled clinical trial for patients of Caucasian origin was conducted by Perić M in 2020 to find out what happens when people with vitamin D insufficiency (blood 25 (OH)D levels < 30 ng/mL)receive a 6-month supply of vitamin D dietary supplements during their non-surgical treatment of gingivitis. According to the findings, taking Vitamin D levels of 25,000 IU once a week as a supplement to periodontal therapy is secure and probably effective therapeutic option that may be linked to a greater level of recovery from periodontal disease [13].

All participants found the suggested dose regimen to be both safe and effective, allowing for a quick rise in serum Vitamin D levels before to the start of periodontal therapy and stable levels throughout the six-month healing period. Throughout the course of the investigation, no negative effects were noted, and all evaluated biomarkers associated with VD metabolism and calcium levels stayed inside the range of references. This dosing schedule could be suggested as a supplement to periodontal therapy [42, 43].

As of right moment, there is no accepted definition or consensus about the appropriate blood levels of 25 (OH) D or what blood levels are deemed "deficient." Most clinical research indicate that serum 25 (OH)D levels between 30 and 60 ng/mL (75 and 150 nmol/L) reflect normal values, whereas levels below 30 ng/mL signify insufficiency. When serum 25 (OH)D is less than 20 ng/mL (50 nmol/L), vitamin D insufficiency is indicated [44].

A controlled trial was carried out by **De Niet S** et al. in order to explore how vitamin D3 supplementation affected patients' ability to repair their periodontal disease. Patients were given instructions to take ampoules at a weekly dosage of 25,000 IU, depending on their own preferences. After six months, the test group demonstrated a greater degree of periodontal healing and a statistically significant intra-group decrease in residual periodontitis, confirming the perio-protective role of vitamin D in periodontitis [45]. Nevertheless, the study had some drawbacks, such as a small sample size and a brief follow-up duration of six months. Furthermore, the supplementation commenced one month before the initiation of treatment, guaranteeing that all test group patients had serum VD levels > 20 ng/mL at the onset of therapy. Data on other PD-related biomarkers found in blood, gingival crevicular fluid (GCF), and saliva are also absent [46].

Stomatitis and the immune system

A study was conducted to explore the effect of vitamin D on oral candidiasis in HIV-infected patients. It found that hypovitaminosis D is linked to an increased risk of oral candidiasis. Vitamin D supplementation, when combined with antiretroviral therapy, helps control viral infections. However, some cases have vitamin D deficiency, suggesting oral candidiasis may develop even with a high CD4 count. Factors contributing to oral candidiasis include low CD4 count, high viral load, drug use, oral candidiasis history, and non-HAART use. Antiretroviral therapy can reduce the risk of oral candidiasis by enhancing the immune system. However, most HIV-infected patients on HAART suffer from hypovitaminosis D, possibly caused by certain antiretroviral drugs, especially Efavirenz. Vitamin D plays a crucial role in regulating innate and adaptive immunity, contributing to antimicrobial peptide expression and autophagy. Lower educational status also increases the risk of oral candidiasis due to poor oral hygiene and antibiotic-resistant Candida colonization [25].

Oral lichen planus (OLP) is a chronic autoimmune, inflammatory disease affecting the skin and oral mucosa. It is an immune-mediated disease involving cytotoxic T-lymphocytes that trigger keratinocyte apoptosis [24]. Treatment modalities include corticosteroids, but they have drawbacks and are contraindicated for various conditions. Vitamin D, with its immune-modulatory, anti-inflammatory, and antimicrobial properties, is believed to play a key role in autoimmune diseases. Vitamin D and its active component, calcitriol, inhibit B-lymphocyte differentiation and proliferation, reducing the production of antibodi. A universal, comprehensive scoring system for clinical evaluation of OLP is needed to standardize treatment outcomes [24].

Two observational studies from India introduced psychological counseling to vitamin D and steroid therapy, reporting significant improvement in symptoms in OLP patients who received vitamin D. Salivary IFN-γ levels, a major TH1 and TH2 cytokine, play a significant role in keratinocyte apoptosis caused by CD8 + T cells in OLP. Saliva is considered a successful, simple, and non-invasive diagnostic tool for detecting pro-inflammatory cytokines in various immunologic diseases. Vitamin D supplementation may be a potential strategy for managing OLP, as it can inhibit the production of IFN-γ through the NF-κβ pathway.

A study by Maboshe et al. found that vitamin D attenuates the seasonal elevation of IFN-γ by 28%, suggesting it reduces inflammation-related effector responses. Vitamin D and VDR play a protective role in regulating microRNA and inhibiting apoptosis. Interprofessional care teams, including pharmacists, can improve clinical

outcomes, minimize side effects, and lower treatment costs by promoting patient therapeutic adherence [24].

Bone graft

Because calcium and vitamin D supplements control the levels of phosphorus and calcium in the blood, they are essential in treating systemic bone mineralization (BMD) reduction. Inadequate consumption of these nutrients may result in reduction in bone mass, disturbed mineralization of the bones, and an imbalance of calcium in the negative. A lack of vitamin D can increase the possibility of a bone break in adults by causing osteoprotegerin (OP) and rickets in children. For skeletal bone tissue, the ideal blood plasma 25 (OH)D3 concentration is 80 nmol/L, but for periodontal tissue, it should be between 90 and 100 nmol/L. Lower amounts have been associated with tooth loss and the onset of periodontal disease [4].

Among the four tissues, one that make up the periodontium is the mandibular bone, and there is a direct connection between periodontal disease and OP. All bones in OP patients have decreased bone mineral density (BMD), with the jawbone seeing the biggest rise in tooth loss and alveolar ridge erosion. Compared to women with normal BMD, those with lower skeletal BMD have greater alveolar process resorption and a more advanced type of chronic periodontitis. Because it can lower resorption and raise BMD, vitamin D supplementation may be utilized to prevent and cure periodontal disease in postmenopausal women [4].

Traumatology and fracture susceptibility

Supplementing with vitamin D may lessen dental consequences from falls, such as dental fractures, dislocations, or even expulsions, because of its effect on falls and muscular weakness. Generally speaking, vitamin D affects every aspect of the oral cavity, from the periodontium to the tooth itself [47].

A randomized controlled trial was conducted by Krall EA et al. in 2001.Tooth loss was examined in 145 healthy subjects aged 65 years and older who completed a 3-year, randomized, placebo-controlled trial of the effect of calcium and vitamin D supplementation on bone loss from the hip, as well as a 2-year follow-up study after discontinuation of study supplements. Teeth were counted at 18 months and 5 years. A comprehensive oral examination at 5 years included assessment of caries, oral hygiene, and periodontal disease.

This study discovered a link between the relationship between vitamin D and calcium intake to prevent osteoporosis and tooth loss risk. It suggested these amounts of calcium and vitamin D have a benefical effect on tooth retention. The study did have some limitations, though, such as the fact that tooth counts, caries assessments, and periodontal exams were only available to a nonrandom subset of participants who finished both studies, and that self-reports were used to determine how many teeth were lost between 6- and 18-month examinations. Furthermore, it was uncertain how caries-ridden and periodontal healthy the teeth that had vanished from the preceding five years were. Additionally, because single nutrients were not examined in the trial and most of the participants who voluntarily utilized nutritional supplements during follow-up used both nutrients, the study was unable to distinguish between the effects of calcium and vitamin D [19]. Future research has to address these deficiencies. Prior research employed clinical indications of periodontal disease and oral bone loss as surrogate results, rather than tooth loss as the primary end measure. The likelihood of developing periodontal disease in younger persons was demonstrated to be negatively connected with the amount of calcium consumed, based on a recent analysis of periodontal and nutritional consumption data. But the cross-sectional nature of the study and the absence of information on the usage of calcium supplements hampered it [47].

Additionally, short-term human research as well as animal tests has demonstrated that diets low in calcium lead to osteoporosis-like alterations in alveolar bone. It's unclear if preventing these alterations will stop the advancement of periodontal disease or stop tooth loss [48]. To find a positive relationship between nutritional intakes and oral bone and tooth retention, future research may require follow-up durations of many years at the very least.

Orofacial cancer

The influence of vitamin D and especially its deficiency on the cancer process has been widely studied. Cancers affecting the oral sphere are particularly frequent among alcoholics and tobacco users and often have very dramatic consequences disabling.

They have not yet been the subject of studies on the role played by vitamin D on this type of cancer but taking into account the numerous studies carried out on other types of cancer, we can expect a similar effect. Vitamin D could prevent and slow the development of oropharyngeal cancers [49, 50].

The weak points of this systematic review

Currently, only three databases (PubMed, Google Scholar, and SpringLink) were included in the search. Including more diverse databases could also help mitigate publication bias and enhance the robustness of the findings.

Most of the selected studies were conducted on European and American populations. Therefore, other studies must be directed to other regions of the world.

Most of these studies were limited to specific groups in society and did not take into account many factors that would affect oral health, such as oral hygiene and smoking.

Most articles talk about vitamin D deficiency and gum diseases, and a few articles deal with other topics, such as tooth decay and mineralization.

In addition, the reporting of this systematic review was based on the time frames mentioned. Further updating information in the future is highly recommended. The published studies were relatively heterogenic, in particular the sample size, the intervention and outcomes of the study. Thus, the specific effects of vitamin D on oral health are not clear.

Conclusion

Vitamin D deficiency has been related to a number of systemic conditions, such as infections, autoimmune diseases, metabolic syndrome, malignant tumors, cardiovascular disease, and chronic nephropathy and bone abnormalities.

This systematic review aimed to describe the ways in which VDD may impair oral development and its function in certain oral conditions, as well as to offer thorough evidence of how VD levels should be taken into account to ensure excellent oral health.

Thus, it may be concluded that oral diseases, tooth defects, caries, periodontitis, and unsuccessful oral treatment outcomes are associated with vitamin D (VDD). Better oral growth and health are linked to maintaining adequate 25 (OH)D levels throughout life. To ascertain the effect of VDD correction with supplementation, further data is necessary. In periodontology, vitamin D is essential because it helps synthesize proteins required for the production of mucous membranes, forms a physical barrier, and reduces the damaging effects of chronic periodontitis. Moreover, it preserves the equilibrium of jawbone density and the system. The form of vitamin D and its constituents, such as UV-B, may be linked to a decreased risk of periodontitis and tooth loss.

The consequences of these relationships for primary prevention of caries, periodontitis, and tooth loss require more research. Future research should examine the connection between periodontitis and cognitive decline, as well as the ways in which low vitamin D levels and an inflammatory diet contribute to this relationship.

Abbreviations

BOP	Bleeding On Probing
CAL	Clinical Attachment Loss
CD4	Cluster of Differentiation 4
CLIA	Chemiluminescence Immunoassay
CRP	C - reactive protein
ELISA	Enzyme-Linked Immunosorbent Assay
HAART	Highly Active Anti-Retroviral Therapy
OLP	Oral lichen planus
OP	Osteoprotegerin
PD	Probing Depth
PI	Plaque Score
PT	Periodontitis
SSc	Systemic Sclerosis
TGF	Transforming Growth Factor
VDR	Vitamin D Receptors
WISH	Women Interagency HIV Study

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Author contributions

Concept and design of the study: S.-Z., A.-W. Overall direction and planning: S-Z. Acquisition, integrity, interpretation of data and the accuracy of the data analysis: S-Z. Methodology: S-Z., A.-W.-G. Data analysis: S-Z., A-W. Writing original draft: S-Z, A.-W Review and editing: S-Z. Validation, supervision and critical revision of the manuscript for important intellectual content: N-M,S.-S. All authors have read and agreed to the published version of the manuscript.

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Data availability

The data and the full data analyses are available upon request.

Declarations

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Competing interests

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