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Review

Vitamin D: A vital micronutrient for periodontal health

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Abstract

Vitamin D is a vital micronutrient essential for maintaining overall health. It plays a key role in modulating both cellular and humoral immune responses, supporting cardiovascular function, and regulating cell growth and differentiation. Deficiency in vitamin D—often due to inadequate dietary intake—has been linked to a range of systemic disorders and is particularly detrimental to oral and periodontal health. Lower serum levels of vitamin D are associated with increased severity of periodontitis and a reduced response to periodontal therapies. The active form of vitamin D, calcitriol, exhibits potent immunomodulatory and anti-inflammatory properties. Widespread vitamin D deficiency also compromises bone health by impairing calcium absorption in the gut and disrupting calcium homeostasis, leading to decreased bone density and a higher risk of fractures, especially in the elderly.

Keywords: vitamin D, osteoporosis, periodontal health, Vitamin D receptor, calcitriol

Introduction

Various nutrients significantly influence periodontal health. These nutrients are categorized into micronutrients and macronutrients. Micronutrients are essential components needed in minor or trace amounts. Conversely, macronutrients are necessitated in substantial amounts and encompass minerals, proteins, carbs, lipids, oxygen, and water [1]. Vitamin D, a lipid-soluble compound, stands out as it functions more like a hormonal steroid than a typical vitamin; similar to cholesterol, the body synthesizes it, interacts with target cells through specific receptors, and is regulated by feedback mechanisms [2].

Vitamin D's main role is to control bone formation and the metabolism of calcium and phosphorus. Additionally, by encouraging the formation of bone matrix proteins, vitamin D increases bone mass, enhances bone remodelling, and stimulates osteoblast activity and alkaline phosphatase function [3].

Vitamin D impacts humoral and cellular immune responses, cardiovascular health, and cell maturation and distinctness. Research indicates that it is also linked to various systemic diseases, including neurological disorders, cancers, metabolic syndrome, infections, and COVID-19, generating increased interest in exploring its mechanisms of action [4–7]. Furthermore, large developing data encourage the idea that vitamin D possesses inflammation-reducing and infection-fighting properties [8, 9].

The skin produces vitamin D3 when exposed to ultraviolet sunlight, or it can be sourced through the diet. Adequate dietary intake becomes essential when sun exposure is limited, such as during winter. A severe lack of vitamin D can result in numerous preventable illnesses, like osteoporosis, diseases of autoimmune nature, multiple forms of cancer, and specific cardiovascular issues like hypertension. Naturally occurring foods containing vitamin D are extremely rare and primarily consist of fatty fish, fish liver oils, eggs from

Vitamin D-treated chickens, and specific fortified foods. However, achieving adequate vitamin D intake can be challenging globally due to variations in geographical location and food availability [10].

Vitamin D deficiency remains highly prevalent, with over 1 billion people estimated to have insufficient levels of this Vitamin despite widespread fortification of foods and supplementation [11]. A current European agreement highlighted that a vitamin D deficit and poor nutrition are detrimental to oral and periodontal health. Vitamin D, because of its effects on immunity, bone density, and bone metabolism, may be linked to the development of periodontal disease [12]. Numerous studies have identified a link between osteoporosis, reduced density, loss of alveolar bone, and tooth loss. A lack of this essential Vitamin in the bloodstream has been closely related to advanced periodontitis and reduced effectiveness of periodontal therapy. Due to its influence on immunology, bone density, and metabolism, vitamin D deficits may raise the probability of developing periodontitis [13].

Vitamin D pathway and synthesis

In the early 1900s, a class of fat-soluble prohormones known as vitamin D was discovered when cod liver oil was shown to have anti-rachitic properties. The form of Vitamin discovered in the oil extracted from cod liver was designated as the letter "D", following the previously recognized vitamins A, B, and C. Two of the main inactive precursors of vitamin D in the body are Vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol. On skin exposure to UVB radiation (290–320 nm wavelengths), Previtamin D3, which serves as the precursor to vitamin D3, is produced by transforming 7-dehydrocholesterol. Through a heat-dependent reaction, pre-vitamin D3 is quickly transformed into Vitamin D. Prolonged exposure to UV radiation can further alter pre-vitamin D3 into inactive byproducts, such as lumisterol and tachysterol. Vitamin D2 originates from plants and is produced externally by irradiating ergosterol and absorbed into the bloodstream through dietary intake. Both vitamin D obtained from sunlight and food are processed in the liver into 25-hydroxyvitamin D (calcidiol) [25(OH)D], the primary form of vitamin D in the bloodstream, used to assess vitamin D status. The activation of vitamin D involves two steps: first, the liver enzyme 25-hydroxylase converts cholecalciferol into 25-hydroxycholecalciferol (25[OH]D); next, the kidney enzyme 1α-hydroxylase transforms 25-hydroxycholecalciferol into calcitriol, the biologically active form of the Vitamin [14, 15].

Low blood vitamin D levels trigger the release of parathyroid hormone (PTH). Parathyroid hormone enhances calcium preservation and suppresses phosphate reabsorption. PTH also promotes the production of calcitriol and stimulates bone-resorbing activity, thereby increasing calcium absorption in the intestines and releasing stored calcium into the blood. PTH regulates calcitriol formation by controlling the enzyme 1α-hydroxylase, thereby managing calcitriol secretion. Then, through feedback, calcitriol decreases PTH synthesis and release while increasing the intestinal and kidney absorption of phosphate and calcium, thus boosting bone mineralization. VDR's (Vitamin D receptors) present on various immune and epithelial cells enable the molecular actions of calcitriol [15].

Vitamin D insufficiency

The vitamin D committee asserts that the deficit of this essential nutrient, a significantly neglected global health issue, impacts approximately fifty percent of the world's population, irrespective of age [16]. Vitamin D in humans is primarily obtained through sun exposure and limited dietary sources, as natural supplies are relatively scarce. Fatty fish abundant in Omega-3, such as sardines, mackerel, and salmon, provide an excellent supply of vitamin D3. Although the concentrations of this Vitamin in egg yolks might vary, they are not the best source of vitamin D due to their high cholesterol content.

Vitamin D-rich fortified foods, such as orange juice, dairy and breads, are available. Humans obtain vitamin D from dietary sources and sun exposure. Because 25-hydroxyvitamin D is easily detectable and has a prolonged half-life in the bloodstream, it is a reliable biomarker for assessing vitamin D levels (about two to three weeks). There are several reasons for a vitamin D deficit, categorized into two groups: those related to insufficient UVB exposure and those linked to medical or physical conditions [14].

Experts define vitamin D insufficiency as a blood level of 20 ng/mL (50 nmol/L) or lower. Similarly, vitamin D concentrations between 21 and 29 ng/mL (52 to 72 nmol/L) are considered insufficient. At least 30 ng per milliliter are deemed appropriate Vitamin D concentrations [17, 18]. The Endocrine Society recommends maintaining vitamin D levels above 30 ng/ml for optimal therapeutic effect [19]. Adults with vitamin D

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deficiency have documented prevalence rates ranging from 14% to 59%, with greater rates seen in Asian nations [20]. When identifying a patient with vitamin D deficiency, achieving adequate serum cholecalciferol levels within a minimum of eight weeks is advisable by administering daily dosages of 6,000 IU or 50,000 IU weekly dosages [21].

Physiologic role of Vitamin D

Vitamin D receptor

Calcitriol (1,25[OH]2D), primarily influences the body by binding to the VDR, to which it is hugely attracted, which regulates several genes [22]. A large proportion of body tissues and cells contain vitamin D receptors. Calcitriol controls the growth of cells, specialization, blood vessel formation, insulin and renin production, and macrophage cathelicidin synthesis. Furthermore, it enhances the expression of CYP24R, which facilitates the breakdown of calcitriol and 25(OH)D by converting them into inactive metabolites. 1α-hydroxylase activity exists in several tissues and cells, facilitating the resident synthesis of calcitriol, which may affect around 200 genes and promote the health benefits of vitamin D [23].

There are also quick non-genomic consequences, including the endothelium being directly stabilized. Vitamin D influences the kidneys, bones, and intestines by regulating calcium and phosphate mineral metabolism, making its adequate levels essential for balance and preventing secondary hyperparathyroidism [22].

Vitamin D and skeletal health

Calcium and phosphate mineral metabolism equilibrium is modulated by calcitriol, which influences the kidneys, bones, and intestines. Vitamin D primarily affects bone through its capacity to sustain mineral homeostasis and its direct pleiotropic effects on osteoblasts [22]. It promotes the mineralization of bone by improving gut intake of minerals like calcium and phosphate and facilitates their assimilation in the renal system, thereby ensuring an adequate amount for crystallization in the collagen matrix. It also directly influences bone by inducing osteocalcin expression and stimulating RANK-dependent bone resorption.

Moreover, 1,25(OH)2D regulates the calcium and phosphate balance in concert with PTH and fibroblast growth factor 23. It elevates urinary calcium excretion, diminishes PTH synthesis, enhances FGF23 production, and augments urinary phosphate excretion [24, 25].

Effects of calcitriol on the immune system and inflammation

Calcitriol regulates the adaptive immune response by inhibiting T-lymphocyte proliferation and immunoglobulin release and inhibiting B-lymphocytes from developing into plasma cells. These effects help create an environment that facilitates inflammation resolution.

Vitamin D strongly stimulates antimicrobial peptides. Cathelicidin and various defensins, including hBD-2, cannot be synthesized by the organism without enough blood 25(OH)D concentrations. In human keratinocytes, vitamin D3 enhances the release of these antimicrobial peptides. These peptides, which include cathelicidins, defensins, statins, granulations, lactoferrin, and hepcidins, have various mechanisms to kill bacteria, effectively targeting the pathogenic cytoplasmic membrane [26, 27].

Numerous cells, including dendritic cells, cells of the epithelium, and macrophages, possess TLRs (Toll-like receptors). These receptors are essential for the body's natural immune defense and the synthesis of antimicrobial peptides induced by vitamin D. These receptors induce immune responses by identifying patterns of molecules linked to microbial infections. Upon infection, activated macrophages and monocytes, triggered by TLR signaling and inflammatory cytokines like interferon-gamma (IFN-Ɣ), express CYP27B1gene. The synthesis of enzymes required to transform 25(OH) D into calcitriol, the active form of vitamin D, is stimulated by this gene. By stimulating the formation of cathelicidin LL-37, which is an antimicrobial peptide, the active vitamin D thereby promotes an upsurge in the monocytes and macrophages' antimicrobial activity via VDR-retinoid X receptor signaling. Defensins and other naturally occurring antimicrobial peptides are stimulated by Vitamin D, thereby strengthening the innate immune defense [28]. Cathelicidin inhibits their growth by altering the membranes of invading bacteria and fungi. It also demonstrates direct antiviral actions by rupturing the envelopes of numerous respiratory viruses and reducing the viability of the cells they infect [29]. This ability has been demonstrated in diseases including sarcoidosis, TB, fungal infections, and several lymphomas that include granulomatous inflammation [29].

Calcitriol alters antigen-presenting cell growth and function by encouraging the shift to a leless-developed,ore tolerogenic state. This change is marked by reduced production of accessory signaling proteins and the cell surface major histocompatibility complex (MHC) class II [30].

VDR stimulation by calcitriol on endothelial cell membranes enhances eNOS activity via intracellular signaling pathways, increasing intracellular calcium levels. Vitamin D and its metabolites protect the vascular endothelium from vascular malfunction and tissue damage brought on by systemic and localized inflammation [31]. Vitamin D signaling in the gut epithelium promotes the survival of intestinal epithelium cells and reduces damage induced by bacterial lipopolysaccharides [32]. Vitamin D boosts mucosal barrier function by increasing proteins that detect pathogens and strengthen epithelial junctions [33].

Periodontal health and Vitamin D interrelationship

Periodontitis is brought on by an imbalance between the body's inflammatory response and oral microbes. Alveolar bone loss and connective tissue degeneration are caused by proinflammatory mediators and cytokines released by the host. Environmental and genetic factors affecting the immune response to periodontal pathogens can influence disease progression and severity [34]. Research has established a correlation between inadequate concentrations of vitamin D and advanced periodontitis. A recent European agreement emphasized the detrimental effects of low vitamin D and malnutrition on periodontal and dental health. Numerous studies have associated insufficient vitamin D levels with advanced periodontal disease that does not respond well to treatment [35–37].

In humans, 25-hydroxylase is produced by gingival and periodontal ligament cells, and it converts vitamin D3 into 25-hydroxyvitamin D3 (25OHD3). Calcitriol binds to VDRs in the immune cells, boosting macrophage chemotaxis and phagocytosis by inducing 1-α-hydroxylase expression for autocrine calcitriol production. As a result, lysosomal enzyme activity and phagocytosis increase [38]. Because it prevents immune cells from producing cytokines and causes monocytes and macrophages to release potent peptides with antibacterial properties, calcitriol is helpful in the treatment of periodontal diseases [39]. Monocytes produce inflammatory signaling molecules, like Tumor Necrosis Factor-α, Interleukin-1, and Interleukin-6, in response to bacterial invasion. These are strong osteoclastogenic substances that induce alveolar bone resorption and modulate the body's inflammatory response through signal transmission between cells. IL-1 induces the production of matrix metalloproteinases (MMPs). MMPs degrade the extracellular framework, induce vasodilation followed by edema, and synthesize prostaglandin E2 (PGE2), which promotes further bone resorption [39]. Moreover, it has been shown that calcitriol diminishes the liberation of TNF-α, IL-1α, IL-2, and IL-6 signaling molecules [40, 41].

VDR ligands stimulate innate immune response by generating antimicrobial peptides and have bone anabolic effects, suggesting their potential use in preventing aggressive and chronic forms of periodontitis [42, 43].

Hiremath *et al*. demonstrated the inflammation-reducing property of vitamin D at concentrations of 500 to 2000 IU. They found that higher doses resulted in a faster onset of these effects. Patients with vitamin D deficiency may experience improvements by using oral supplements for 2–3 months [44]. Studies indicate that maintaining a serum 25(OH)D3 level of no less than 80 nmol/L is beneficial for bone density, while levels between 90–100 nmol/L support periodontal health.

Consistently low levels below 90–100 nmol/L can worsen the progression of periodontal disease, leading to tooth loss [45, 46]. Severe periodontal damage and Reduced vitamin D levels are associated with advanced periodontitis, whereas higher levels correlate with decreased bleeding on probing (BoP) [35, 47].

There is widespread knowledge that skeletal health maintenance largely depends on vitamin D levels. Vitamin D insufficiency is associated with various diseases, such as lower respiratory tract infections, and chronic inflammatory and systemic conditions, like metabolic disorders and insulin resistance, among others. These disorders are also associated with periodontal problems [48]. Laboratory research on vitamin D has established the advantageous properties of osteoblast and stem cell development. The study demonstrated that osteoblasts, in conjunction with Vitamin D, possess considerable potential for bone repair. Additionally, the development of stem cells into osteoblasts was facilitated by vitamin D [49].

A study examined the correlation between gingival inflammation, periodontitis, and serum 25OHD3 levels using evidence from the National Health and Nutrition Examination Survey (NHANES III). Analysis of this extensive collection of records revealed an inverse correlation linking average loss of attachment

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and serum 25OHD3 levels in individuals over 50 years of age, regardless of sex [35]. Furthermore, a three-year randomized controlled trial showed that older adults consuming daily doses of calcium (500 mg) along with vitamin D (700 IU) could help prevent femoral bone deterioration and had a 60% lower risk of dental loss when matched to those in the control group [50].

Diabetes mellitus, cardiovascular disorders, and premature low birthweight infants are linked to periodontal disease and proinflammatory cytokines. Consequently, obesity is associated with these diseases. Since 25(OH)D and vitamin D are retained in body fat, blood levels of the Vitamin are frequently diminished in individuals with obesity. Aggressive forms of localized periodontal disease, characterized by clinical attachment loss and tooth and bone loss, are correlated with specific genotypes of VDRs [51]. Decreased blood concentration of 25(OH)D is correlated with periodontitis. However, the effectiveness of supplementation of vitamin D in conjunction with nonsurgical periodontal treatment h is unknown due to a paucity of research [52]. Future studies should investigate the biological mechanisms that underlie the influence of vitamin D and periodontal tissues.

Importance of Vitamin D in osteoporosis management

Osteoporosis is a bone-related condition, distinguished by the deterioration of both their organic and inorganic components, resulting in greater vulnerability and an elevated likelihood of fractures. Common warning signs exist for both periodontitis and osteoporosis, suggesting a potential bilateral association between the two conditions [48]. Osteoporosis predisposes individuals to alveolar bone loss associated with periodontal disease; periodontal disease may thus serve as a sign of osteoporosis. Reduced bone mass in regions impacted by periodontitis may intensify the body's immune reaction to periodontal pathogens, leading to elevated levels of systemic cytokines. As a result, this raises the risk of tooth loss and further decreases bone density [53].

The cytokine network critical for osteoclastogenesis comprises the decoy protein osteoprotegerin (OPG), its receptor partner RANK (Receptor Activator of Nuclear Factor Kappa-B), and the ligand RANKL (Receptor Activator of Nuclear Factor Kappa-B Ligand). RANKL, synthesized by osteoblasts and activated T lymphocytes, is crucial for the development, activation, and survival of osteoclasts. OPG counteracts the bone-resorptive actions of RANKL. Multiple hormones, including glucocorticoids, vitamin D, and estrogen, modulate RANKL and OPG levels. Women with osteoporosis frequently suffer from periodontal disease, linked with diminished vitamin D and elevated RANKL and OPG levels. The basis for the association between these disorders is increased cytokines [54].

Osteoporosis decreases bone density, including in the alveolar bone. When periodontal pathogens invade this weakened jawbone, they increase alveolar porosity, alter the trabecular pattern, and accelerate bone resorption. Periodontal infections raise systemic proinflammatory cytokines, further speeding up bone loss. Vitamin D insufficiency increases the likelihood of osteoporotic fractures, while calcitriol therapy enhances the density of bone and diminishes spinal fractures. Furthermore, calcitriol diminishes inflammation, favoring responses and bolsters immunity, indicating that VDR ligands may effectively address osteoporosis-related periodontal disease [48].

Adults who do not get adequate vitamin D may develop osteopenia and osteoporosis, which raises their risk of fractures. Research indicates that vitamin D is effective in reducing fracture risk. Also, daily oral doses of 700–800 international units of vitamin D significantly lower the occurrence of femoral and non-spinal fractures compared to calcium or a placebo [3].

Table 1: Effects of Vitamin D on target cells.

Intestine	Increased phosphate and calcium absorption
Kidney	Increased reabsorption of both calcium and phosphate
Bone	Promotion of bone calcification
Parathyroid	Decreased PTH synthesis and release
Immune system	Modulation of the immune response
Cardiovascular system	Regulation of renin-angiotensin system
Cancer cells	Suppression of proliferation, differentiation and metastasis in various cancers

Implications in systemic health

To promote the production of calcitriol in tissues and cells like the breast, intestine, alveolus, prostate, and parathyroid, increasing vitamin D intake or exposure to sunlight is essential to elevate serum 25(OH)D concentrations above 30 ng/mL (Table 1) [48].

Vitamin D deficiency can significantly impact health, including the skeletal, immune, cardiovascular, endocrine, neurological, muscular, reproductive, and skin systems. Addressing vitamin D deficiency through exposure to sunlight, a balanced diet, or supplements is crucial to maintaining overall well-being.

Conclusion

Beyond maintaining calcium homeostasis and skeletal health, vitamin D has numerous additional functions. There is evidence that a higher chance of periodontitis is interrelated to low mineral density of bones and systemic osteoporosis. Vitamin D insufficiency can cause an added probability of infections and inflammatory conditions and diseases like cancer, diabetes, arthritis, and cardiovascular disease. Any deficit in the 1,25(OH)2D3-VDR interaction can lead to periodontitis, which is essential for preserving oral balance. By stimulating the innate immune response and producing antimicrobial peptides like beta-defensins and cathelicidin, vitamin D enhances physical barriers against pathogens. Addressing vitamin D deficiency could significantly reduce chronic disease prevalence. Further research is needed to better understand the health risks, especially the link between periodontal disease and low vitamin D concentrations. Additionally, raising awareness of insufficient vitamin D is crucial for researchers, doctors, and patients.

Conflict of interest

The authors declare no conflict of interest.

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