Clinical Implications of Vitamin D in Oral Diseases- A Review

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Authors’ contributions

The sole author designed, analyzed, interpreted and prepared the manuscript.

ABSTRACT

Oral health is a reflection of systemic health. The various nutritional deficiencies not only affect the systemic health but also have an impact on oral health. The prevalence of Vitamin D deficiency (VDD) is rampant globally. Vitamin D (VD) is not only essential for skeletal growth during childhood and adulthood but has a great impact on oral tissues and odontogenesis. VDD has several implications on oral health from childhood to adulthood. VD can negatively influence the oral health of the mother and child and VD supplementation brings positive outcomes during and after pregnancy. In children, severe VDD can impair tooth mineralization, resulting in defects of enamel and dentin and predispose patients to caries. A remarkably high prevalence of periodontitis is seen in VDD and has implications on systemic health as well. A high prevalence of VDD is seen in oropharyngeal cancers. This review aims to provide the biological role of VD and its receptor, its implication on oral health and future strategies for targeted therapies in oral pathologies.

Keywords: Vitamin D; vitamin D receptor; periodontitis; tooth demineralisation; oral cancer.

1. INTRODUCTION

Oral health is a reflection of general body health. The proper functioning of the human physiological and biochemical system requires a balanced interplay of several Vitamins and minerals. Vitamin D is one such vitamin with diverse functions and is essential for maintaining
Homeostasis of the body [1]. It's a well-known fact that Vitamin D plays an important role in preserving balance of bone and calcium levels. The other important functions include obtaining a balance of various physiological functions involving the skin, musculoskeletal, neuromuscular and immunological system. Currently, there is a renewed interest on the role of Vitamin D in the inhibition of tumour proliferation, anti-bacterial and anti-inflammatory functions [2].

Vitamin D and its metabolites are steroid hormones and hormone precursors. The nutrition obtained from various fish and fish oils is a minor source and major resource of Vitamin D is from exposure to sunlight [3]. Vitamin D is a non specific term and includes Vitamin D2 and D3. The synthesis of Vitamin D2 is from ultraviolet irradiation of ergosterol from yeast and Vitamin D3 from ultraviolet irradiation of 7-dehydrocholesterol from lanolin. The true estimate of Vitamin D is estimation of serum 25-hydroxyvitamin D (25(OH)D) and the gold standard diagnostic test for assessing vitamin D deficiency (VDD) [4].

The prevalence of VDD world-wide is on a rise and has garnered a lot of public attention [3,5,6]. This is a matter of concern as it is a requirement in special conditions like childhood growth, pregnancy, infections and cancer [7,8]. VDD is caused mainly due to insufficient exposure to sunlight with optimum level of ultraviolet B rays [4]. Other causes of VDD include impaired intake of VD rich diet or impaired absorption from genetic metabolic diseases (de Boer, 2007). Patients on anti-epileptic drugs like phenytoin, carbamazepine and oxcarbazepine increase the excretion of VD and predispose to VD deficiency [9].

Nutritional deficiency has a significant role in oral health and recent investigations have highlighted its role in a variety of oral pathologies [10]. VDD is implicated in Odontogenesis, Periodontitis, Oral ulcers and Oral Cancer. The latest innovations in this arena helped us to compile the effects of VDD on oral health and its complications. This review will discuss the role of Vitamin D in the pathogenesis of various oral disorders and future implications of VDD.

1.1 Physiological Role of Vitamin D and Vitamin D Receptor

Exposure to sunlight with UV B rays is the most critical factor in attaining the required levels of vitamin D [11]. The biologically inactive forms of VD i.e Vitamin D2 and D3 are converted in the liver into 25(OH)D which then is converted to the biologically active form $1,25(OH)_2D$ by the proximal tubular cells of the renal nephrons [4].

As the half-life of $1,25(OH)_2D$ is approximately 4 hours, and that of $25(OH)D$ is 2-3 weeks the biologically active form is used to assess the serum levels of vitamin D. The various vitamin D metabolites circulate in the blood by binding to specific proteins and as they approach the target organs, they disassociate to gain entry to the cells and carry out the requires function [12].

Various factors control the VD levels and include age, sunlight exposure (duration and intensity), diet such as fish and oils, calcium levels in blood, parathyroid hormone, direct feedback by $1,25(OH)_2D$ and fibroblast growth factor 23. Certain disorders like malabsorption syndromes, sarcoidosis, and impaired calcium metabolism and medications like glucocorticoids, anticonvulsants, and barbiturates have a detrimental effect on VD levels [13].

The guidelines proposed by the Endocrine Society Clinical Practice [11], has proposed following parameters; “VDD is defined as levels of $25(OH)D$ below 50 nmol/L and insufficiency as $25(OH)D$ levels of 52.5–72.5 nmol/L.” According to the guidelines, the patients with VDD, can be prescribed with a daily dose of 6000 IU of either vitamin D2 or vitamin D3, followed by a maintenance dose of 1500–2000 IU/day [14,15].

The VDR is a part of the greater superfamily of nuclear receptors [16]. The other important biologic roles apart from maintaining skeletal and calcium balance are its important action as an anti-inflammatory and anti-fibrotic. Apart from this it helps in diabetic nephropathy deterrence, decrease of proteinuria, hypertension and atherosclerosis [17,18]. This highlights the role of estimation of VDR in tissues to understand the physio-pathological importance of vitamin D and its role in development of pioneering modalities for targeted therapy [19].

$1,25(OH)_2D$ performs most of its roles with help of VDR by nature of its functions as a transcription factor. VDR makes a heterodimer with the retinoid X receptor (RXR), and this VDR/RXR binds to vitamin D response elements in target genes, regulating gene expression either by activation or by repression of gene transcription [20,21]. The $1,25(OH)_2D$/VDR
signalling pathway networks with other signalling pathways in the functioning of numerous vital biological functions, like calcium and bone homeostasis, inflammation, cell mediated immunity, cell-cycle progression, and apoptosis. These actions assist the 1,25(OH)₂D/VDR signalling to mediate antibacterial, antiviral, and anti-inflammatory activities [15,2]. These functions are implicated in the dental and oral pathologies and will be discussed hereafter.

1.2 Implications of VDD on Oral Health

1.2.1 Oral mucosal susceptibility

The oral mucosal epithelium acts as a physical barrier to protect the underlying deeper tissues from incursion by microorganisms with their associated antigens and toxins, and from minor mechanical damage [22]. The keratinocytes of the basal and spinous strata of the oral epithelium produce 1,25(OH)₂D, and express VDR. The combination of 1,25(OH)₂D/VDR has a significant role in the propagation, differentiation, and apoptosis of keratinocytes. They influence the immune reactivity in the epithelium. All these results have been corroborated in animal studies. (Barrea et al. 2017)

Vitamin D together with the VDR augments the antibacterial property of immune cells. VDR is expressed by the cells of the innate and the adaptive immune systems. Few of the cells also express CYP27B1 and produce the biologically active 1,25(OH)₂D. Activation of Toll-like receptor (TLR) of native immunocytes (e.g., monocytes, macrophages, and keratinocytes), also enhance expression of CYP27B1 and VDR, with the production of 1,25(OH)₂D. The 1,25(OH)₂D/VDR signalling in the immunocytes encode genes for antibacterial agents like cathelicidin and β-defensin. The above mechanisms explains the role of vitamin 1,25(OH)₂D/VDR signalling, in enhancing the antibacterial reactivity of native immune cells [23] (Christakos et al. 2013).

The 1,25(OH)₂D/VDR signalling pathway has a role in the autoimmune and immune related disorders of the oral cavity. It can reduce the maturation of antigen-presenting dendritic cells and subsequent activation of antigen specific T cells and thereby modify the production of proinflammatory cytokines [24]. There are no substantial studies to prove this association, and augmenting the standard treatment regimen with vitamin D supplementation has not resulted in a positive outcome in the management of these disorders [23]. Some studies have proposed that VDR polymorphism, and presence of risk factors like tobacco smoke and alcohol are associated with increased risk of chronic periodontitis and other inflammatory conditions of the oral cavity [25].

1.2.2 Effect of VDD in tooth mineralization and caries

The mineralization procedure of skeleton and teeth befall concomitantly and dysregulation of this process impact both the bone tissue and odontogenesis. A dysregulation of VD levels results in “rachitic tooth”, characterised by a defective and hypo-mineralized tooth vulnerable, to fracture and decay. As the VD level (<10 ng/mL) it causes hypocalcaemia and hypophosphatemia resulting in secondary hyperparathyroidism [26]. This in turn increases intestinal absorption of calcium (Ca⁺²), and renal production of 1,25(OH)₂D, increasing bone turnover leading to elevated serum levels of Ca⁺² and low serum levels of inorganic phosphate. The reduction in vitamin D signalling pathways in tooth cells augmented by decreased levels of Ca⁺² and phosphate ions resulting in defective mineralization of teeth. The activation of VDR alter the structural gene products, (e.g., enamels, amelogenins, dentin sialoglycoproteins, and dentin phosphoproteins), resulting in the formation of defective dentin and enamel [27,28].

Mutations in VD metabolism results in various genetic disorders. The key reasons of VDD, due to genetic mutations, are abnormal enzyme secretion i.e., vitamin D-dependent rickets type 1, (VDDR-I) and anomalous VDR function or signalling, vitamin D-dependent rickets type 2, (VDDR-IIa), hereditary defects in the vitamin D receptor system, (HDVDR) [27]. These genetic disorders result in defective mineralized tissues, in spite of otherwise normal vitamin D consumption or sunlight exposure and, eventually, predispose to odontogenic hypoplasia in conditions like (i.e., amelogenesis imperfecta, dentinogenesis imperfecta, enamel hypoplasia) or higher risk of caries [27,1].

VDD deficiency in pregnancy reflected by decreased maternal levels of VD causes defective deciduous dentition. VDD during pregnancy at 12–16, 20–32 and 36–40 weeks causes defects at the incisal third, middle third and cervical third respectively [29]. In a randomized clinical trial (RCT) conducted in pregnant mothers on VD supplementation,
decreased VD levels of <15 ng/ml resulted in a 14% higher risk of developing defective deciduous dentition [30]. On the contrary, high-dose of maternal vitamin D supplementation reduced the enamel defects by 50% [31].

Therefore, it is imperative that normal levels of VD should be maintained throughout pregnancy and after delivery to reduce the enamel defects.

1.2.3 Effect of VDD on periodontal health

Periodontitis is a polymicrobial disease caused by plaque and is associated with persistent chronic inflammation of the periodontium [2]. The classical signs are increased gingival exudate, presence of deep periodontal pockets, bleeding on probing, and loss of alveolar crestal bone. The pathogenesis is complex and multifactorial with an interplay between bacterial agents and bacteria-induced immunoinflammatory responses, on a background of inherent genetic predisposition [32]. Presence of risk factors such as smoking, uncontrolled diabetes, vitamin D deficiency, and deep periodontal pockets favour the production of periodontopathic bacteria, and aggravate the course of the disease [33].

Periodontitis accounts for one of the two most predominant oral diseases globally and is the sixth most prevalent disease with strong socioeconomic and systemic implications, impacting the quality of life [34]. There is an increasing trend of association between periodontitis and systemic conditions such as diabetes, ischemic stroke, cardiovascular disease (CVD), rheumatoid arthritis, inflammatory bowel disease, stress, solid-organ transplanted individuals or preterm birth [35]. Furthermore, the outcome of nutrition on periodontal health, specifically VDD, has been critically evaluated. According to the European consensus, VDD impacts the periodontal health and oral functions [36]. VDD can contribute to periodontitis by upregulating the inflammatory activity and downregulating the antimicrobial activity [37].

Data from the previous cross-sectional studies have equated the levels of Vitamin D between individuals with periodontitis and without periodontitis; with varied results. Some studies showed positive association and some did not [38,39,40]. The results of few studies showed an association between decreased VD and periodontal destruction, severe periodontitis stages and higher tooth loss [41]. In otherwise healthy patients, decreased levels of VD were also associated with periodontitis [2].

The host immunity triggers the inflammatory and immune actions against periodontal pathogens. There is an upregulation of interleukins and growth factors in patients with decreased salivary levels of VD in comparison to periodontally healthy patients (namely IL-35, IL-17A and transforming growth factor). Vitamin D supplementation decreases the level of salivary cytokines prior to nonsurgical periodontal treatment [40].

Research in rodents have demonstrated reduced number of live *Porphyromonas gingivalis* in VD supplemented. This could be due to active autophagy which reduces the inflammatory burden of periodontitis in rodent models. There is a decrease in the levels of (RANKL, TNF-α, IL-1, MMP-9); thus suppressing IL-6 and protecting the alveolar bone by preventing bone loss [42] (Hu, et al. 2019).

Genetics has also been proposed to play a role in initiation of periodontitis. An increased risk of developing periodontitis was demonstrated in two evidence-based studies. They proposed that, a number of VDR polymorphisms were correlated with higher risk of developing periodontitis [43,44]. Therefore, there is sufficient evidence to postulate that VDD contributes to the pathogenesis of periodontitis, by disturbing the tooth and bone mineral density and severity of periodontitis [1]. The association between periodontitis and maternal VDD is a rising concern. Decreased levels of VD were associated with moderate to severe periodontitis in comparison to mothers with healthy periodontium [45,46]. Non-surgical periodontal treatment during pregnancy reduced the risk of any adverse pregnancy outcomes; nevertheless, concurrent VD supplementation displayed only a minor clinical improvement in birthweight [1]. Future studies in this direction would help us evaluate the effect of Vitamin D on periodontal health and maternal health.

1.2.4 Implications of VDD during orthodontic treatment

It has been proposed that VD might play a key role in tooth movement during orthodontic treatment and has shown promising results [47]. An animal study demonstrated quicker tooth movements after local application of VD [48]. In this direction, prospective studies should be
planned in humans to determine if VDD has a clinically substantial impact on tooth movement. Furthermore, in VDD, vitamin D supplementation during orthodontic treatment, can augment the remodelling process of deposition and resorption during orthodontic tooth movement [1].

1.2.5 VDD in the pathogenesis of oral cancer

VD has a protective effect against cancer. An interplay of various mechanisms by the cancer cells reduces the cellular calcitriol and decrease its antitumor effect. Various cell culture and animal studies have revealed a substantial evidence for the antitumorigenic effects of VD [49]. There is a strong biological foundation for the role of VDD in predisposing to the development of cancer risk and usage of vitamin D or its bioactive analogues in cancer chemoprevention and treatment. The cancer tissues express VDR and in vivo animal studies and in vitro cell culture studies show that 1,25(OH)2D prevents cell proliferation, angiogenesis, invasion and promotes differentiation and apoptosis of cancer cells. The activation of cyclin-dependent kinase inhibitors (e.g., p21, p27) by the 1,25(OH)2D/VDR in the cancer cells, impedes the mitogenic growth factors such IGF-1 and EGF, and enhances the action of TGF-β. These mechanisms help in suppressing the proliferation and growth of cancer cells. [50,20]. The 1,25(OH)2D/VDR signalling pathway also has a major role in suppression of inflammatory pathway of cancer by decreasing the cyclooxygenase-2, prostaglandin, and NF-κB pathways. Thereby, it deactivates the antiapoptotic proteins (e.g., Bcl2) and activate proapoptotic proteins (e.g., Bax, RAK) resulting in apoptosis of cancer cells.

Oral cancer patients invariably have VDD [49]. In a case-control study, VDD was related to an elevated risk of developing squamous cell carcinoma of the oesophagus, oral cavity and pharynx among patients with a habit of severe smoking and alcohol consumption [51]. Few studies demonstrated increased VDR expression in premalignant lesions and oral cancer. Vitamin D supplementation also reduced the adverse effects of chemotherapy on advanced stage cancers thereby decreasing the morbidity and improving the quality of life in these patients [52,53].

Consequently, future studies should be directed towards how VDD relates to oral cancer development and its adjuvant role towards chemotherapy and radiotherapy.

2. DISCUSSION

The importance of VD in maintaining oral health has been well documented in the literature. Exposure to sunlight for at least half an hour twice a week can help us to maintain the required amount of VD for our daily needs [54]. An interesting study performed in Norway has highlighted about the role of sunlight in reducing the risk of periodontal disease. They observed that tooth loss was seen at a greater rate 66% in the northern region as compared to 43% in central region and 11% in southern region [55]. The role of VD in supressing cancer genesis is a topic of interest among researchers. Animal and clinical studies have proposed the usefulness of VD as therapeutic agents to prevent the growth and proliferation of oral squamous cell carcinoma cell lines [56]. VDD has an impact on oral health and is required for maintaining the integrity of the oral mucosa and the supporting structures. VDD has been implicated in periodontitis, oral infections, dental caries, oropharyngeal cancers and dental treatment. Moreover, normal levels of VD have positive effects on maternal and foetal health during pregnancy. The oral diseases associated with VDD can have implications on systemic health. Therefore, it is imperative to maintain normal levels of VD through supplementation and exposure to UV rays.

5. CONCLUSION

There is sufficient evidence about the beneficial effects of VD on oral health. Exposure to sunlight is a single most critical factor to prevent VDD. Future studies should be planned based on exposure to sunlight and development of periodontal diseases and its influence on tooth mineralisation and oral mucosal immunity. Large cohort studies in the population with VD targeted therapies can be beneficial to emphasise the role of VD in halting the progression to oral cancer.

CONSENT
It is not applicable.

ETHICAL APPROVAL
It is not applicable.

COMPETING INTERESTS
Author has declared that no competing interests exist.
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