Indian Journal of Forensic Medicine and Toxicology
Volume 16 No. 4, October-December 2022

Pivotal Role of Vitamin D on Periodontium

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How to cite this article: Suhina Mitra, Deepa G Kamath. Pivotal Role of Vitamin D on Periodontium. Indian Journal of Forensic Medicine and Toxicology 2022;16(4).

Abstract

Vitamin D is a fat-soluble vitamin with pleiotropic effects on the body. Major portion of the vitamin is synthesized in the epidermis under the influence of sunlight. Vitamin D is essential for the maintenance of periodontal health. It plays an important role in maintaining oral health through bone and mineral metabolism and innate immunity. While vitamin D deficiency has been associated with periodontitis, little information exists regarding its effect on wound healing and periodontal surgery outcomes. Vitamin D and its receptor, the vitamin D receptor (VDR), maintains the integrity of the periodontium. Owing to the immunomodulatory, anti-inflammatory, and antibacterial properties of 1,25(OH)2 D / VDR signalling, a sufficient serum level of vitamin D is necessary to maintain proper periodontal health. In cases of established chronic periodontitis, vitamin D supplementation is associated with reduction in the severity of periodontitis. Vitamin D has a 'perio-protective' effect and can decrease susceptibility to periodontal diseases. This review addresses the basics of Vitamin D metabolism and underlines the role of Vitamin D on periodontal health, disease, and therapy. The rationale for using vitamin D supplementation to help maintain periodontal health and as an adjunct to standard periodontal treatment has also been discussed.

Key words: Alveolar bone metabolism, Immunomodulatory effect, Vitamin D, Vitamin D receptor polymorphism, Wound Healing

Introduction

Vitamin D is a fat-soluble vitamin. In the last two decades there is major improvement in the understanding of the bioactivities relating to vitamin D. It has a major role in various functions such as promoting growth, remodelling of bone and teeth, controlling the regulation of calcium as well as phosphate metabolism etc. It exerts favourable effects on the oral health, this is mainly done by regulating the anti-microbial peptide production. Vitamin D deficiency can cause anomalies in tooth development, defects in enamel and dentin and also cause increase in dental caries incidence.(1)

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Individuals with inadequate levels of vitamin D areat greater risk for osteoporosis as well as infectious and inflammatory diseases. Insufficient vitamin D leads to reduced density of bone mineral. Intake of fatty foods which have inadequate vitamin D levels not only leads to obesity, but also increases the incidence of periodontal diseases in both children as well as adolescents. On the other hand, consumption of foods that are rich in riboflavin, fibre, calcium and vitamin D tends to lower the chances of gingivitis. It has been established that consumption of appropriate amounts of vitamin D which may be of either exogenous or endogenous in origin, leads to the preservation of periodontal health.[1]

Synthesis of Vitamin D

Vitamin D synthesis takes place in the skin. It is initiated through ultraviolet radiation from sunlight. Vitamin D can be obtained exogenously as well, this through foods such as oily salt fish (mackerel, salmon, and tuna), cod liver oil and egg yolk. There are several countries which are in short supply of these natural food sources, hence in order to compensate this, fortification of dairy products with vitamin D is done. There are various over-the-counter dietary supplements available too. Proper vitamin D synthesis is crucial for the proper physiological functioning of various systems of the body.[2]

The Ultraviolet B radiation comes in contact with the skin and causes the conversion of 7-dehydrocholesterol in to Vitamin D3 (cholecalciferol). The rest is absorbed from the gut either as Vitamin D3 or as Vitamin D2 (ergocalciferol).[1] Vitamin D2 and D3 are biologically inactive forms. Firstly, hydroxylation takes place in the liver leading to the formation of 25(OH)D. Then this formed 25(OH)D, gets hydroxylated again in the kidney, giving rise to 1, $25(OH)_2D$, which is biologically active. The process of synthesis of Vitamin D has been shown in (Figure 1)

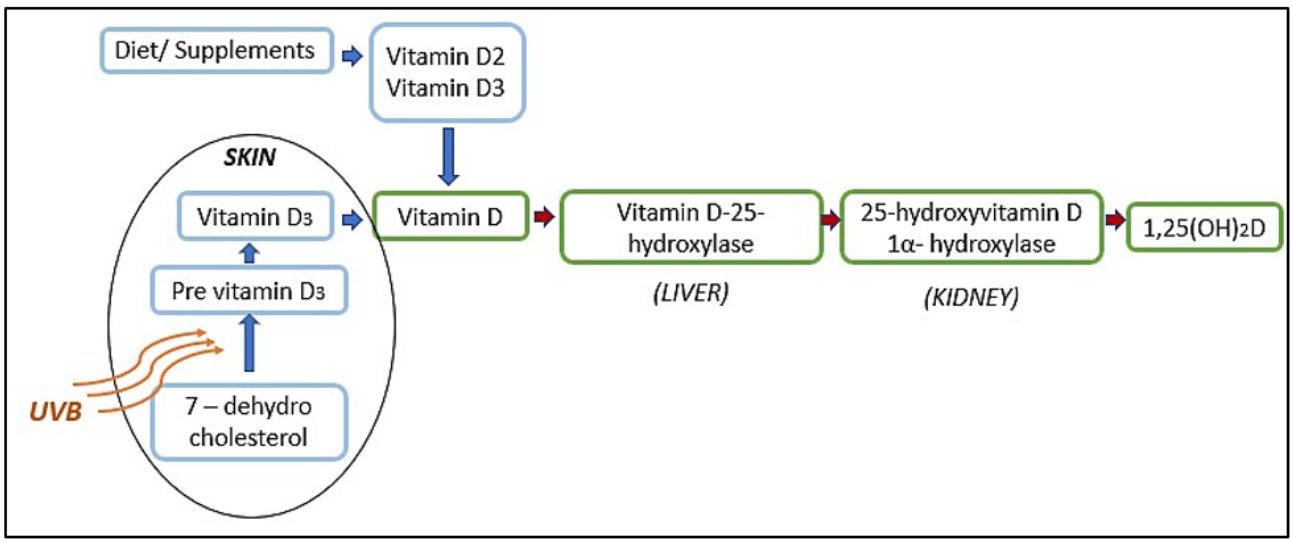

Figure 1: The process of synthesis of Vitamin D

400-600 IU is known to be the recommended daily consumption of vitamin D for adults. 800 - 1,000 IU is advised for the prevention of osteoporosis. Almost a billion people across the world are estimated to have Vitamin D deficiency. Vitamin D and periodontal health has a strong relation. This can be explained by its various functions, which includes its role in metabolism of alveolar bone, the modulation of host response and vitamin D receptor polymorphism.[2]

Vitamin - D Effect on the Periodontium

Previous studies indicate that insufficient Vitamin D can causes a greater risk of periodontal diseases. It has also been noted that supplementation of Vitamin D can cause improvement in periodontal health, increase in the density of bone in maxilla and mandible and may also cause reduction in alveolar bone resorption. A study was conducted by Dietrich et. al. (2004) based on the "US National Health and

Nutrition Examination Survey", in which an inverse association between the concentrations of vitamin D and the amounts of clinical attachment loss was reported. This study included individuals who were greater than fifty years of age. The participants with reduced amounts of vitamin D had more loss in periodontal attachment when in relation to those with high amounts of vitamin D.[3]

It was also noted that Vitamin D showed an increased protective characteristic in men. The anti-inflammatory property of Vitamin D was investigated by Jönsson et. al. (2013).[4] The Third US National Health and Nutrition Examination Survey data was used in order to study the synergistic effect of hormone replacement therapy (HRT) and serum Vitamin D on the loss of clinical attachment and tooth in the case of postmenopausal women. It was observed that women who were in HRT and who also had high plasma 25-hydroxy Vitamin D levels, seemed to have reduced loss of clinical attachment. On the other hand, women who had reduced Vitamin D levels showed greater loss of clinical attachment. The additive beneficial effects of HRT and adequate levels of Vitamin D also showed a reverse relation to the number of tooth lost in postmenopausal women.

Millen AE et. al. (2014) conducted a prospective study which was five year long. This study included postmenopausal women. There was no association found between the levels of Vitamin D and periodontal disease was observed. It was reported that adequate levels of Vitamin D did not provide any protective effect against the progression of periodontal disease.

Jimenez M et. al. (2014) conducted a cross-sectional study on 11,202 patients of the "NHANES III (National Health and Nutrition Examination Survey)".[6] The study included older patients (over fifty years of age). A reverse association was observed between vitamin D level in serum and clinical attachment loss (CAL). This was seen in men as well as in women. Thus, observations from earlier studies suggest that to prevent periodontal disease progression in case of middle age group adults, it is important to provide Vitamin D supplementation. This was suggested in accordance to the key function of vitamin D in bone metabolism. This also took into account that elderly patients are at a greater risk for diseases relating to the bone. [6] The various effects of Vitamin D on Periodontal health has been shown in (FIGURE 2)

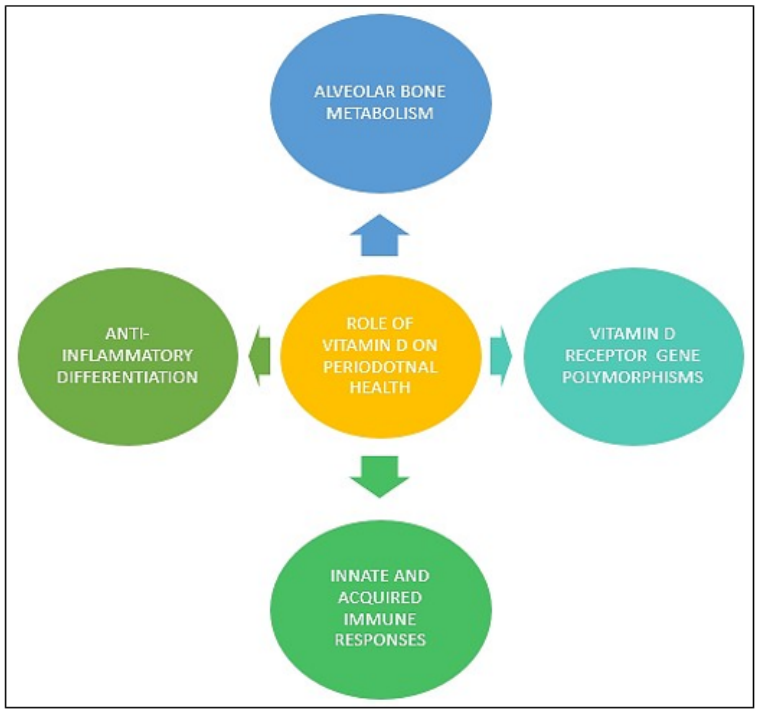

Figure 2: The various effects of Vitamin D on Periodontal health

Schulze-Späte et. al. (2015) conducted a longitudinal study and reported that although men suffering from severe periodontitis revealed deficiency in Vitamin D, the measurement of Vitamin D could not be considered as a good predictor for the progression of the disease, when taking chronic periodontitis in to consideration.[7]

Adegboye A.R et. al. (2016) conducted longitudinal study in the U.S. under the name of "Health Professionals Follow-Up Study".[8] Patients of the age group 40 – 75 years were included in this study. A reverse relation was present between the 25(OH)D score and the number teeth lost and periodontal disease cases. This association was dose-dependent in nature.[8]

Laky M et. al. (2017) conducted a longitudinal study on 1904 participants in order to study the association of poor Vitamin D status in relation to periodontitis effected individuals and healthy controls. [9] Follow up was done for a period of 5 to 6 years. There was a 13% reduction in the mortality of tooth with every simultaneous 10µg/L increase in 25-hydroxy Vitamin D in the serum. Anti-inflammatory effects of Vitamin D is exerted on the synthesis process of prostaglandin as well as cyclooxygenase pathways. It causes Inhibition of matrix metalloproteinases (MMPs), which in turn reduces the tissue destruction which is seen in periodontitis. [9]

Vitamin D and Wound Healing

Bacterial insult causes a host immune response which leads to alveolar bone loss which is characteristic on Periodontitis. Vitamin D plays a crucial role in maintaining bone as well as regulation of immunity. It has been suspected that deficiency in vitamin D could have a negative impact on the periodontium. It has been indicated that to achieve perfect wound healing, there is a need to have appropriate Vitamin D levels, especially in the postsurgical time period.

Bashutski et. al. (2011) conducted a study to assess the outcomes of periodontal surgery and teriparatide administration in vitamin-D-sufficient and -insufficient individuals.[10] They reported that there was a greater gain in clinical attachment level in addition to a reduction in pocket-depth in case of placebo patients with sufficient vitamin D in comparison to vitamin D deficient patients. This study concluded that vitamin D status influenced postsurgical healing. It was seen that at the time of periodontal surgery, having inadequate levels of vitamin D could lead to a negative effect on the treatment outcomes for up to one year. These findings are in line with other studies in which vitamin D deficiency was related with delayed periodontal healing. Thus it is stated that vitamin D may have a role in bone healing in the oral cavity.[10]

Garcia et. al. (2011) conducted a study to determine whether the patients in periodontal maintenance programs taking vitamin D and calcium supplementation had a trend for better periodontal health compared to patients not taking supplementation. [11] It was observed that periodontitis related parameters were higher in case of non-takers compared to takers. So, it was concluded that there is potential that vitamin D may exert a positive impact on periodontal health. [11]

In a case report by Bashutski et. al. (2012), a patient suffering from periodontitis and an intrabony defect was treated by open flap debridement surgery.[12] The patient was prescribed with 20 mg of teriparatide systemically and oral vitamin D supplements for a duration of six weeks. This case was followed up after four years, where in the patient showed improved clinical as well as radiographic outcomes. It was deduced that the administration of Teriparatide along with oral vitamin D and open-flap debridement surgery could be used as an appropriate treatment for severe intrabony defects. [12]

Schulze-Späte et. al. (2016) conducted a study where in the treatment group referred to the patients who underwent maxillary sinus floor augmentation and received 5000 IU of Vitamin D3, which was compared to a placebo group. [13] There was an increased number osteoclasts, which surrounded the graft material in case of the vitamin D group. This observation reflected the presence elevated metabolic activity in sites which were augmented, in case of the treatment group which received Vitamin D3. Vitamin D deficiency has proved to show a detrimental effect on wound healing. In the early phase of tissue healing, it has been noted that the keratinocyte proliferation

as well as differentiation may be influenced by vitamin D. It also exerts effect on the mobilization of macrophages. [13]

Dental implants coated with Vitamin D_3 have shown improved osseointegration with alveolar bone (Javed F. et. al. 2016). It is also observed that vitamin D_3 when injected intraperitoneally could further enhanced orthodontic tooth movement, thus helping in the acceleration orthodontic treatment in patients who are undergoing bisphosphonate therapy. [14] Further studies are needed in order to substantiate the link between surgical / non-surgical periodontal therapy and the intake of vitamin D.

Vitamin D and Alveolar Bone Metabolism

Periodontal infections act as reservoirs for different bacterial antigens, cytokines, Gram-negative bacteria, and other pro-inflammatory mediators, these are responsible for the spread of diseases throughout the body. The action of pro-inflammatory cytokines and prostaglandins have led to investigate the association between periodontitis and osteoporosis.[15] Inadequate Vitamin D is known to be a major risk factor leading to the development of osteoporosis. Vitamin D helps in regulating the metabolism of calcium. It is an important part of the immune system as well. The utilization of calcium from the body doesn't continue increasing, once it crosses the threshold value, hence its regulation by vitamin D is crucial.

The chief role of 1, 25$(OH)_2$D is to maintain the homeostasis of calcium and bone. Reduction in the resorption of alveolar bone is noticed, in the presence of optimal levels of 1,25$(OH)_2$D, this is considered to be the osteoprotective nature of vitamin D. Osteoblasts produce Receptor activator of nuclear factor kappa-B ligand (RANKL) and Osteoprotegerin (OPG). Expression of Receptor activator of nuclear factor kappa-B (RANK) occurs on the osteoclast progenitor cells. The conversion of an osteoclast precursor cell into a functional mature osteoclast, is caused due to the RANKL to RANK binding.[1] OPG has the ability to aggravate the RANK-RANKL interaction. Vitamin D receptor expression is contained in the RANKL gene promoter structure. The interaction of Vitamin D and its receptor, causes an elevated expression of RANKL in the bone marrow-derived stromal cells as well as in the osteoblasts. Vitamin D also tends to reduce the OPG. Thus, causing activation of osteoclastic activity and resorption of bone. [1]

Kitazawa et. al. (2003) reported that though vitamin D initially decreases the OPG expression, on continuous exposure the OPG levels get elevated.[15] It was concluded that Vitamin D had a transient nature of osteoclastic activity. In addition to this, Vitamin D also has effect on the osteoblasts, by stimulating the osteopontin and alkaline phosphatase activity in. On prolonged exposure it tends to promote osteoblastic proliferation and differentiation.[15]

Immunomodulatory Effect of Vitamin D in Periodontium

The discovery of VDR (Vitamin D receptor) on the immune system related cells, lead to ascribe the definite immunomodulatory effect of Vitamin D. The transformation of biologically inactive vitamin D to the bioactive form is regulated by 1α-hydroxylase enzyme, which in turn is stimulated by the macrophages as well as dendritic cells, also known as "antigen-presenting cells". Thus through its antibacterial properties and antigen presenting abilities, Vitamin D has the potential to modulate the innate immune response of the body.[16] In the innate immune response, the toll-like receptors senses the pathogen-associated molecular patterns, then there is an increase in the synthesis of 1,25-(OH) 2D3 in macrophages. This eventually causes the production of antibacterial substances. The antibacterial substances that may be produced are cathelicidin and beta-defensins. [16]

An in vitro study conducted by Gauzzi MC. et. al. (2005) reported that 1,25-(OH) 2D3 lead to the impediment of the proliferation as well as the maturation of dendritic cells. [17] A reduction in major histocompatibility complex molecules was also observed. Vitamin D dampens the ability of antigen presentation and T-cell activation of macrophages and dendritic cells.

In vitro studies conducted by Korf et. al. (2012) showed that silencing of the Vitamin D receptors lead to increased hyperresponsiveness of macrophages on stimulation of LPS. [18] Vitamin D supplementation may cause a modulated response of antibacterial

properties, against the putative periodontal pathogens. Macrophages is categorized into M1 and M2, where in M1 is referred to the pro-inflammatory phenotype and M2, as the anti-inflammatory phenotype. The pro-inflammatory M1 phenotype causes the production of nitric oxide, tumour necrosis factor-alpha (TNF-α), as well as interleukin (IL-1 beta). On the other hand, phenotype M2 causes the production of anti- inflammatory cytokine-IL-10.[18]

Vitamin D has the ability to cause a switch from M1 to M2 (Zhang et. al. 2015).[19] Vitamin D influences the T – helper cells by effecting its proliferation, differentiation, along with their function. Vitamin D tends to regulate the immune response by causing selectively stimulating and inhibiting specific T-helper cells. It causes the production of IL-4, IL-5, and IL-10, which leads to the stimulation of the development of Th2 cell.[19] It also causes the production of interferon-gamma cells, and resulting in the inhibition of Th1cells. Vitamin D provides enhanced antimicrobial as well as anti-inflammatory effects along with its role in T-cell differentiation, makes an aggregate of its pleiotropic immunomodulatory influence.[19]

Vitamin - D Receptor Polymorphism and Periodontium Association

Vitamin D receptor gene polymorphisms is believed to influence the remodelling of alveolar bone. It also regulates the host response in the presence of periodontopathic bacteria. Polymerase chain reaction as well as restriction enzyme digestion is used to study the Vitamin D receptor polymorphisms taking place in the genes.[20] There are various VDR restriction fragment length polymorphisms also known as RFLPs, that are known to be in association with periodontal disease. *Taq* I-*Bsm* I-, *Apa* I-, and *Fok* I are few of the VDR polymorphisms that have been studied in detail. These are investigated on their ability to increase the susceptibility to periodontal diseases. There are mixed conclusions obtained in this regard and further studies are needed in order to have a stronger comprehension of the functional relevance of VDR RFLPs and its relation with the pathogenesis of periodontal disease.[21]

Conclusion

Vitamin D brings into play a multitude of functions beyond its capability to maintain calcium homeostasis, and thereby by becoming an important factor in skeletal health. There is strong evidence suggesting a relation between osteoporosis and the oral bone mineral density. Osteoporosis or reduced levels of bone mass is also considered to be a risk factor for the development of periodontitis. It has been well established the deficiency in vitamin D could increase the chances of infectious diseases with inflammatory pathologic components, this includes diseases such as arthritis, cardiovascular diseases and periodontitis.[21] The characteristic of vitamin D to causes the release of antimicrobial peptides, including beta-defensins and cathelicidin, results in initiation of the innate immune response, which further causes increased strength of the physical barriers and hence the breach of epithelium by various pathogens extremely difficult. Vitamin D also has the ability to modify the adaptive immune response. This is done by the stimulation of specific Th subsets which results in resolution of inflammation. These properties may be stated as examples of the "perio- protective nature" of Vitamin D. Additional studies are essential to interpret the various functions of vitamin D, and the appropriate dosage needed to induce its beneficial effects. One of the he most intriguing function of vitamin D, is its role in wound healing and in what way the specific appropriate levels may modify the results of the periodontal surgery. Further clinical studies are needed to confirm these findings and eventually explain the workings involved in the processes.

Ethical Clearance: Taken from the Institutional Ethics Committee of Manipal College of Dental Sciences – Mangalore

Source of Funding: Nil

Conflict of Interest: Nil

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