Vitamin D in Periodontal Health and Disease – A Narrative Review

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ABSTRACT
Vitamin D is a fat-soluble vitamin that primarily aids calcium absorption, promoting growth and mineralization of bones. Recent research on Vitamin D has unravelled the many facets of vitamin D including its role in periodontal health and disease. With larger section of people around the world getting easily afflicted with Vitamin D deficiency as well as chronic periodontitis this review will scrutinize the involvement and nutraceutical importance of vitamin D in periodontal health and disease.

1. Introduction

Vitamin D is a fat-soluble vitamin that plays a key role in the health of bone and teeth. Vitamin D, considered as steroid hormone acts on the intestine, kidneys and bone and regulates bone remodelling that involves bone formation and resorption.

Vitamin exists in two forms vitamin D2 and D3, while vitamin D2 is predominantly formed from ergosterol of yeast under UV irradiation. Vitamin D3 is obtained from 7 dehydrocholesterol present in skin on exposure to UV rays.

Vitamin as a prohormone is involved in calcium homeostasis. Vitamin D regulates the absorption and excretion of calcium and phosphorus from the intestine. In addition to bone formation the role of Vitamin D in health of the periodontium is actively researched.

Furthermore, the implications of vitamin D is not only with the health of bone and teeth but also plays a significant role in immunopathological reaction especially with periodontitis.

Role of vitamin D in Vitamin D increases the intestinal absorption of calcium and decreases the secretion of parathyroid hormone, which consequently decreases systemic bone resorption. In addition, vitamin D stimulates osteoblastic bone production and alkaline phosphatase activity, optimizes bone remodeling and covers bone mass by increasing bone matrix proteins [1,2]

Periodontitis (PD) is an infectious inflammatory disease of multifactorial etiology affecting the periodontium (gums) and gradually destroying the tooth supporting alveolar bone leading to alveolar bone loss and edentulism. Periodontitis is a chronic inflammatory disease initiated by the shift of symbiosis to dysbiosis of oral microbiota.[3]

Periodontitis is characterized by the destruction of the periodontium, connective tissue attachment loss and alveolar bone resorption which leads to tooth loss, by periodontal pocket formation. [4]. PD is diagnosed when periodontal attachment to the tooth is lost and alveolar bone resorption is evident on radiographs.

Lower vitamin D levels are also associated with higher periodontal destruction and severe periodontitis stage[5]. Therefore, the present study aimed to understand the role of vitamin D in periodontitis.

Vitamin D Normal Levels in Body Fluids

The recommended daily amount (RDA) is 400 international units (IU) for children up to age 12 months, 600 IU for people ages 1 to 70 years, and 800 IU for people over 70 years. The serum and salivary 25 (OH) D level is defined as a deficiency if below 10 ng/mL, insufficiency if between 11–

20 ng/mL, and optimal if ≥20 ng/mL. The 1.25 (OH) D serum and saliva are deemed deficient if ≤48 pmol/L and normal if >48 pmol/L.[5]

Prevalence of Vitamin D Deficiency

It was estimated that 1 billion people worldwide have vitamin D deficiency or insufficiency [2].

70 - 100% of the general population all over India bear Vitamin D deficiency. [6]. From the study made by Al Zarooni [7] we can observe that Vitamin D deficiency was similar in both male and female (male 83.1%, female 83.8%) as insufficiency (male 12.7%, female 11.2%)[43] and Al Quaiz [8]stated that, younger adults and males are more prone to vitamin D deficiency than the older participants and females .On examining few surveys it's found that Vitamin D deficiency is more among illiterate and non-working women than the literate and working women[9]

Scientific evidences supporting vitamin D deficiency in India even among medical fraternity is reported [10,11].

2. Bone Mineralization and Resorption Under the Influence of Vitamin D

Vitamin D helps to attune skeletal integrity and mineral homeostasis through intestinal, bone, and renal resorption ·From the review of Dr. Michael F. Holick we can perceive that decreased serum levels of 25-hydroxyvitamin D, significantly reduces the intestinal absorption of calcium that is associated with increased parathyroid hormone which activates osteoblasts, and stimulates the transformation of pre osteoclasts into mature osteoclasts that can dissolve the mineralized collagen matrix in bone. Thus, intensifying the bones to lose their density and hardness by constant release of calcium into the bloodstream.

Bone is resorbed by osteoclasts, and is deposited by osteoblasts by the process called ossification. Receptor activator of nuclear factor kappa-B ligand (RANKL) and Osteoprotegerin [OPG] (RANKL antagonist) are produced by osteoblasts and other cells such as activated CD4 + T lymphocytes to regulate the bone remodelling. Binding of RANKL to RANK results in the differentiation of osteoclast progenitor cells into mature osteoclast. These mature osteoclasts remove calcium and phosphorus from the bone, maintaining calcium and phosphorus levels in the blood.

Whereas, OPG (osteoprotegerin) acts as a soluble receptor for RANKL, inhibiting RANK-RANKL interaction and the maturation of osteoclast progenitor cells. Therefore, the mature osteoclast formation is determined by the relative ratio of RANKL to OPG in the osteoclast precursor microenvironment. The RANKL gene promoter contains vitamin D and glucocorticoid response elements. Studies have shown that vitamin D-VDR stimulates RANKL expression in cells such as osteoblasts and bone marrow-derived stromal cells.

Vitamin D down regulates OPG, increased RANKL expression and decreased expression of OPG caused by vitamin D would favour the differentiation and activation of osteoclasts that eventually causes increased bone resorption. However, Hofbauer et al. stated a sparking effect of vitamin D on OPG, and Kondo et al. stated that vitamin D initially represses OPG, but long-term exposure to vitamin D leads to a recovery of OPG expression. This suggests that the catabolic effects of vitamin D can be ephemeral. Anabolic effects of vitamin D on osteoblasts, includes stimulation of osteopontin and alkaline phosphatase [13-17].

3. Vitamin D and Periodontitis

Vitamin D has a significant role in the modulation of the immune system, inflammation system and ossification process. All these characteristics show significant associations between periodontal health and intake of vitamin D.A study by Madi et al has shown that vitamin D status is found to be positively correlated with periodontal health in a Saudi population [37]. various studies done by several authors shows a positive association between vitamin D status and periodontal health correlating serum and salivary levels of Vitamin D with pocket depth and alveolar bone loss [5,22,35,36]. A study Dietrich et al

has shown the relationship between serum levels of Vitamin D and periodontal inflammation [33].

Nathalia Gracia et al in a systematic review as concluded that there is probably little correlation between vitamin and periodontitis [38]. Also, study by Zhan et al contradicts the role of vitamin D in periodontal health[39].

In spite of the perplexing reports available vitamin D is considered as a nutraceutical component playing a key role in periodontal health. The most important characteristics of vitamin D in periodontal health are reported as follows.

Anti-Inflammatory Property of Vitamin D in Periodontal Health

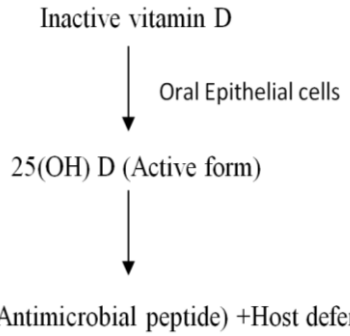
It is far and wide known that periodontitis is a chronic host mediated response causing periodontal destruction by the release of pro-inflammatory cytokines by local tissues and immune cells in response to the bacteria of dental plaque and their products and metabolites which results in destruction of connective tissue and alveolar bone. Vitamin D has anti-inflammatory properties that can inhibit the inflammatory cytokines and makes the monocyte/macrophages to secrete molecules that have a strong antibiotic effect.

Vitamin D as an Immuno Modulating Agent

Human B defensin (hBD) and cathelicidin are two naturally occurring antimicrobial peptides that are expressed by gingival epithelial cells as host response to microbial stimuli.They are seen in gingiva,buccal mucosa and epithelial cells.Wang et al,2004 has reported that vitamin D upregulates the expression of the aforementioned antimicrobial peptides in periodontitis[28] .In line with this a recent study by Bayirli,2020 has also concluded that serum deficiency of vit D is associated with low GCF levels of hBD and cathelicidin in GCF of periodontitis subjects[29].

Activation of vitamin D is enabled in gingiva under inflammation and microbial plaque accumulation as gingival fibroblasts produce 25hyroxylase and the cell receptors 1 alpha hydroxylase due to which 1,25(OH)D3 is formed. This in turn activates the VDR gene and participate expression of genes that produces proteins facilitating tight junction in epithelial cells. Ginigival cells under the influence of Vitamin D also secrete antimicrobial peptides such as beta defensins [30,31,32].

The vitamin D receptor (VDR) is widely expressed in immune cells such as antigen – presenting cells, natural killer cells, T cells and B cells [18]. Beta-Defensins (anti-microbial peptide) exhibit antimicrobial activity against oral microbes including periodontitis-related bacteria like Actinobacilus actinomycetemcomitans, Porphyromonas gingivalis, Fusobacterium nucleatum, Candia and Papilloma virus. Several studies reveals the relation between the polymorphism of VDR gene and periodontitis[19]. Due to lack of appropriate immune response in vitamin D deficient patients, they fail to respond properly to invading pathogens in periodontal diseases. Figure represent the mechanism of Vitamin D against the periodontitis-related bacteria [20].



VitD also plays a significant role by influencing T and B lymphocytes [21]. A meta analysis by Vannessa et al shows that the level of vitD3 to be less in chronic periodontitis when compared to that of healthy controls[22]

Vitamin D in Bone Metabolism

Vitamin D has a prevalent role in bone metabolism. It increases mineralization of bone in the mandible and inhibit the resorption of alveolar bone [23,24]. One of the conspicuous feature of periodontal disease is resorption of alveolar bone caused by the host immune response to bacterial insult, in due course leads to loss of teeth. From the previous studies, we can observe that alveolar bone loss due to periodontitis is more prevalent in osteoporosis which occurs in vitamin D deficiency condition.

Prevalence of periodontal disease increases with age. According to the Global Burden of Disease Study (2016), severe periodontal disease was the 11th most prevalent condition in the world. Study done by Muhammad Nazir shows that Hundred percent of older persons in China, India, and Croatia have periodontal disease [25].

Vitamin D Therapy in Periodontitis

Periodontitis is mainly caused by bacterial invasion that give rise to inflammation and in severe cases resorption of alveolar bone and eventually loss of teeth. [26,40]. Vitamin D has anti-microbial actions, anti-inflammatory properties and increases the calcium absorption thereby reducing the resorption of alveolar bone thus, teeth are held tight in the alveolar process. Hence, proper intake of Vitamin D can help in treating periodontitis. It was found that vitamin D offered effective outcome in wound healing and periodontal surgeries [27]. Vitamin D receptors (VDR) are helpful in the treatment of periodontitis through its anti-microbial peptides against periodontopathic bacteria, immunomodulatory effects against pro inflammatory cytokines and bone anabolic effects against the alveolar bone loss.

4. Conclusion

Vitamin D, beyond its potential in preventing bone related diseases like rickets, osteoporosis, osteopenia and osteomalacia by increasing calcium absorption and bone mineralization, numerous study reports support the present review and explains its significant role in periodontitis. Major problems of periodontitis are pathogenic bacteria, inflammation and alveolar bone loss, which can be counteracted by the unique properties of vitamin D like immune response, anti-inflammatory and calcification of bone. Vitamin D deficiency also leads to poor oral health and aggravates periodontitis. On the whole, the current review suggests that vitamin D plays a crucial role in periodontal health.

References:

[1] Holick M.F., Chen T.C. Vitamin D deficiency: A worldwide problem with health consequences. Am. J. Clin. Nutr. 2008;87:1080–1086. doi: 10.1093/ajcn/87.4.1080S

[2] Wilson L.R., Tripkovic L., Hart K.H., Lanham-New S.A. Vitamin D deficiency as a public health issue: Using Vitamin D2 or Vitamin D3 in future fortification strategies. Proc. Nutr. Soc. 2017;76:1–8. doi: 10.1017/S0029665117000349.

[3] Meyle J, Chapple I. Molecular aspects of the pathogenesis of periodontitis. Periodontol 2000. 2015;69(1):7-17.

[4] R Mathangi, B Jayaraman, N Geethapriya, A Venkatesh, S Samuel. The impact of chronic periodontitis on glycemic control and serum lipids in comparison with periodontal health.Journal of Dental Research and Review 7 (4), 159

[5] Thacher TD, Clarke BL. Vitamin D insufficiency. Mayo Clin Proc. 2011 Jan;86(1):50-60. doi: 10.4065/mcp.2010.0567. PMID: 21193656; PMCID: PMC3012634.

[6] Garg R, Agarwal V, Agarwal P, Singh S, Malhotra N. Prevalence of vitamin D deficiency in Indian women. Int J Reprod Contracept Obstet Gynecol 2018; 7:2222-5.

[7] Al Zarooni, A.A.R., Al Marzouqi, F.I., Al Darmaki, S.H. et al. Prevalence of vitamin D deficiency and associated comorbidities among Abu Dhabi Emirates population. BMC Res Notes.2019; 12:503.

[8] AlQuaiz AM, Kazi A, Fouda M, Alyousefi N. Age and gender differences in the prevalence and correlates of vitamin D deficiency. Arch Osteoporos. 2018=;13(1):49.

[9] Ravi Kumar, Kajal Kunwar, Anup Kumar, Nimisha Agrawal - An Observational study to assess the prevalence of Vitamin D deficiency in Indian women. International Journal of Health and Clinical Research, 2020; 3(12):290-294.

[10] Harinarayan CV, Ramalakshmi t, Prasad UV. High prevalence of low dietary calcium, and vitamin D deficiency in healthy south Indians. Am J Clin Nutr 200;85(4):1062-77.

[11] Kochupillai N. The physiology of vitamin D: Current concepts. Indian J Med Res 2008;127:256 -262

[12] Holick MF. Vitamin D deficiency. N Eng l J Med. 2007; 357(3):266581

[13] Lacey DL, Timms E, Tan HL et al. Osteoprotegerin ligand is a cytokine that regulates osteoclast differentiation and activation. Cell 1998; 93:165–176.

[14] Kitazawa S, Kajimoto K, Kondo T, Kitazawa R. Vitamin D3 supports osteoclastogenesis via functional vitamin D response element of human RANKL gene promoter. J Cell Biochem 2003; 89:771–777.

[15] Kondo T, Kitazawa R, Maeda S, Kitazawa S. 1,25 Dihydroxyvitamin D3 rapidly regulates the mouse osteoprotegrin gene through dual pathways. J Bone Miner Res 2004; 19:1411–1419.

[16] Hofbauer LC, Dunstan CR, Spelsberg TC, Riggs BL, Khosla S. Osteoprotegerin production by human osteoblast lineage cells is stimulated by vitamin D, bone morphogenetic protein-2, and cytokines. Biochem Biophys Res Commun 1998; 139:4319–4328.

[17] Erben RG, Bromm S, Stangassinger M. Therapeutic efficacy of 1alpha,25-dihydroxyvitamin D3 and calcium in osteopenic ovariectomized rats: evidence for a direct anabolic effect of 1alpha,25-dihydroxyvitamin D3 on bone. Endocrinol 1998; 139: 4319–4328.

[18] Yusuke Amano, Kazuo Komiyama and Makoto Makishima - Vitamin D and periodontal disease. Journal of Oral Science 2009;51(1): 11-20.

[19] De Brito Júnior RB, Scarel-Caminaga RM, Trevilatto PC, de Souza AP, Barros SP. Polymorphisms in the vitamin D receptor gene are associated with periodontal disease. J Periodontol 2004; 75:1090-5.

[20] Diamond G, Yim S, Rigo I, McMahon L. Measuring antimicrobial peptide activity on epithelial surfaces in cell culture. Methods Mol Biol. 2010; 618:371–82.

[21] Schwalfenberg G.K. A review of the critical role of vitamin D in the functioning of the immune system and the clinical implications of vitamin D deficiency. Mol. Nutr. Food Res. 2011;55:96–108.

[22] Vanessa Machado, Sofia Lobo, Luís Proença, José João Mendes, João Botelho Nutrients. 2020; 12(8): 2177.

[23] Stein SH, Livada R, Tipton DA. Re-evaluating the role of vitamin D in the periodontium. J Periodont Res 2014; 49: 45–553.

[24] Shaili Pradhan, Shweta Agrawal - Serum Vitamin D in Patients with Chronic Periodontitis and Healthy Periodontium. J Nepal Health Res Counc 2020 ; 18(49): 610-4.

[25] Muhammad Nazir , Asim Al-Ansari, Khalifa Al-Khalifa, Muhanad Alhareky, Balgis Gaffar , Khalid Almas - Research Article Global Prevalence of Periodontal Disease and Lack of Its Surveillance. Hindawi Scientific World Journal Volume 2020, Article ID 2146160,

[26] R. Mathangi, Vidyarani Shyamsundar , S. Shila Immunohistochemical evaluation of bone morphogenetic protein 3 in chronic periodontitis influenced by Type2 diabetes mellitus .Drug Invention Today 2020; 14 (1) :91-94.

[27] Bashutski JD, Eber RM, Kinney JS et al. Teriparatide and osseous regeneration in the oral cavity. N Engl J Med 2010;363:2396–2405.

[28] Batuhan A. Bayirli, Ayla Öztürka,, Bahattin Avci - Serum vitamin D concentration is associated with antimicrobial peptide level in periodontal diseases. Archives of Oral Biology 2020;117; 104827.

[29] Liu K., Meng H., Hou J. Activity of 25-hydroxylase in human gingival fibroblasts and periodontal ligament cells. PLoS ONE. 2012;7:e52053.

[30] Bikle D.D. Vitamin D and the immune system: Role in protection against bacterial infection. Curr. Opin. Nephrol. Hypertens. 2008;17:348–352.

[31] McMahon L, Schwartz K, Yilmaz O, Brown E, Ryan LK, Diamond G. Vitamin D-mediated induction of innate immunity in gingival epithelial cells. Infect. Immun. 2011;79:2250–2256.

[32] Dietrich T, Joshipura KJ, Dawson-Hughes B, Bischoff-Ferrari HA. Association between serum concentrations of 25-hydroxyvitamin D3 and periodontal disease in the US population1-3. Am J Clin Nutr 2004; 80:108-13.

[33] Sari DK, Sari LM, Laksmi LI, Farhat. The Moderate Correlation Between 25(OH)D Serum and Saliva in Healthy People with Low Vitamin D Intake. Int J Gen Med. 2021;14:841-850.

[34] Anand N, Chandrasekaran SC, Rajput NS. Vitamin D and periodontal health: Current concepts. J Indian Soc Periodontol 2013; 17:302-8.

[35] Sharma H, Arora R, Bhatnagar MA. Reconnoitering the relationship between “The sunshine Vitamin” and periodontal disease. J Oral Res Rev 2017; 9:89-95.

[36] M. Madi, Pavlic V, Mongith Alammar S, Mohammed Alsulaimi L, Shaker Alotaibi, Mohammed Al Otaibi G et al. The association between vitamin D level and periodontal disease in Saudi population, a preliminary study, The Saudi Dental Journal 2021;33(7):595-600.

[37] Garcia MN, Hildebolt C. Limited Evidence Suggests That Vitamin D May Help Prevent and Treat Periodontal Disease in Adults. J Evid Based Dent Pract. 2020 ;20(1):101342.

[38] Zhan Y, Samietz S, Holtfreter B,Hannemann A , Meisel P, Nauck M et al. Prospective study of serum 25-hydroxy vitamin D and tooth loss. J Dent Res. 2014;93:639-44.