Original Research Paper

Volume - 10 | Issue - 7 | July - 2020 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Periodontology

VITAMIN D AND PERIODONTIUM: A REVIEW ARTICLE

Dr. Nupur Sah	Reader and Guide, Department of Periodontics, Y.M.T Dental College and Hospital, Kharghar, Navi Mumbai, India
Dr. Shalmali Karnik*	1 st year Post graduate student, Department of Periodontics, Y.M.T Dental College and Hospital, Kharghar, Navi Mumbai, India*Corresponding Author
Dr. Eshani Yeragi	3 rd year Post graduate student, Department of Periodontics, Y.M.T Dental College and Hospital, Kharghar, Navi Mumbai, India
Dr. Kajal Mahajan	3 rd year Post graduate student, Department of Periodontics, Y.M.T Dental College and Hospital, Kharghar, Navi Mumbai, India

ABSTRACT Vitamin D plays an important role in various physiological processes.Adequate levels of Vitamin D are essential for maintaining periodontal health and its deficiency is associated with periodontal disease.This actions of vitamin D may be attributed to its role in maintaining calcium homeostasis,immunomodulatory effect,cellular growth and differentiation,anti-inflammatory effect and several vitamin D gene polymorphisms.This review focuses on vitamin D metabolism and underlines the role of Vitamin D on periodontium.

KEYWORDS : : Vitamin D,Periodontitis,Vitamin D nuclear receptor gene polymorphism, vitamin D supplementation

INTRODUCTION

Periodontitis is an infectious disease that leads to the destruction of the supporting tissues of the teeth.[1] Severity and progression of periodontitis may depend on environmental and genetic factors that modifies host immune response against periodontal microorganisms. Various studies have been done in the past to support the fact that vitamin D may constitute one such factor.Functions of Vitamin D include its anti-inflammatory, immune modulatory, and skeletal homeostasis properties. Deficiency or dysfunction related to gene polymorphism may trigger the development of periodontitis.This review focuses on the function of vitamin D in maintaining periodontal health.

PHYSIOLOGY AND METABOLISM

Vitamin D comes in two forms: Vitamin D2(ergocalciferol) and vitamin D3 (cholecalciferol).Vitamin D is produced from 7-dehydrocholestrol by human skin on exposure to ultraviolet-B radiation.7-dehydrocholestrol is first hydroxylated into 25-hydroxycholecalciferol (calcidiol) by enzyme 25-hydroxylase (CYP2R1) in liver.25-hydroxycholecalciferol undergoes hydroxylation by 25-hydroxy-1-α-hydroxylase (CYP27B1) again in the kidney into the 1,25-Dihydroxycholecalciferol (calcitriol). [Fig.1] Fibroblast growth factor 23 reduces serum phosphate and 1,25(OH)2D3 levels by suppressing CYP27B1 expression.[4]

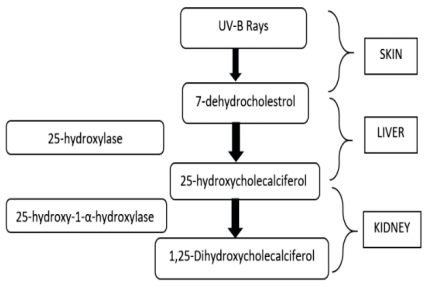

Fig.1. Synthesis of vitamin

The molecular structure of vitamin D is closely allied to that of classic steroid hormones in that they have the same root cyclopentanoper hydrophenanthrene ring structure.[35]Researchers consider 1,25(OH)2D3 to be a steroid hormone and believe that it functions in the same way as other steroid hormones, by interacting with its cognate vitamin D receptor[VDR].Major biological function of 1,25(OH)2D3 is to maintain normal blood calcium-phosphorus levels. In addition to these effects on calcium–phosphorus metabolism, several studies have shown that 1,25(OH)2D3 also has extra skeletal actions,[36]probably because,majority cells express VDR inside them.

Transactivation Of Vitamin D Receptor

1,25(OH)2D binds to VDR to exert its actions. VDRs are distributed widely,and its content is highest in the tissues involved in calcium homeostasis, such as the bone, intestine, kidney and parathyroid gland.[2]

The organization of the human VDR protein,as in other nuclear receptors,has been divided into five regions(A-E)[Fig. 2A][33].The C region contains a DNA-binding domain with two zinc fingers and is the domain with strongest sequence homology among the member of the superfamily.The C-terminal ligand-binding domain(E region)forms a heterodimerization interface and contains a ligand dependent transactivation domain called the activation function 2(AF2).The N-terminal A/B region contains a ligand-independent transactivation domain called the AF1.AF1 domains play a role in tissue specific function of steroid hormone receptors,and AF1 function of VDR may be limited because of its short A/B region.[5]VDR forms a heterodimer with retinoid X receptor[RXR].VDR is localized in both the cytosol and nucleus and accumulates in the nucleus in response to 1,25(OH)2D3 binding.[6]

The VDR-RXR heterodimer binds preferentially to a DNA response element that consists of two hexanucleotide(AGGTCA or a related sequence) direct repeat motif separated by three nucleotides (Dr3) [Fig. 2B][5,33].The DR3 VDR-binding element has been identified in the regulatory regions of many target genes,including CYP24A1,calbindin D9k,cathelicidin and transient receptor potential vanilloid type 6(TRPV6).An everted repeat of the hexanucleotide motif separated by six nucleotides(ER6) is another VDR-binding element that regulates expression of the human CYP3A4 gene.[7]

Nuclear receptors,including VDR, undergo a conformational change in the cofactor binding site and AF2 domain upon ligand binding,a structural rearrangement that results in the dynamic exchange of cofactor complexes.[8]In the absence of ligand, corepressors bind to the AF2 surface,composed of portions of helix 3, loop 3-4, helices 4/5, and helix 11.Ligand binding alters the AF2 surface by repositioning helix 12 [Fig. 2B][33],reduces the affinity for corepressors, and increases the affinity for coactivator recruitment, allowing nuclear receptors to induce the transcription of specific genes.Cofactor complexes have been classified into three functional categories. [9] Members of the first cofactor complex class regulate transcription directly via interactions with general transcription factors and RNA polymerase II. Members of the second cofactor complex class modify histone tails by acetylation or deacetylation. The third class of complexes is involved in ATP-dependent dynamic chromatin remodeling. Ligand-bound VDR is not only involved in transactivation but in some contexts can also mediate transrepression. [10] Dynamic and coordinated interaction of cofactor complexes and VDR is required for efficient regulation of transcription.[33]

VDR POLYMORPHISM

VDR is expressed widely in immune cells.Studies have shown that VDR polymorphisms at restriction fragment length polymorphisms (RFLP) positions Taq-I,Bsm-I,Apa-I and Fok-I are associated with aggressive and/or chronic periodontitis in different ethnic populations.[18-25]

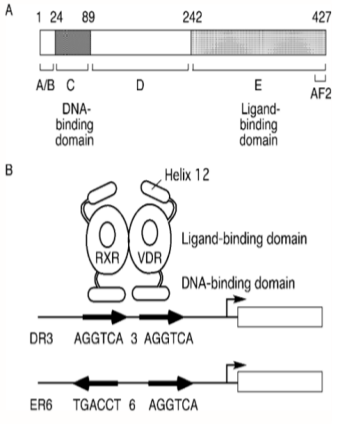

Fig.2(A)Human VDR consists of 427 amino acids (B)VDR-RXR heterodimer binds to DR3 and ER6 in the promoter region of target genes.[33]

BONE METABOLISM

Vitamin D maintains serum calcium and phosphate levels by stimulating intestinal absorption, bone resorption and renal reabsorption.

Binding of receptor activator of NF-kB ligand(RANKL) to receptor activator of NF-kB(RANK), expressed on the surface of osteoclast progenitor cells, causes them to differentiate into mature osteoclasts.Osteoprotegerin(OPG) acts as a soluble receptor for RANKL,inhibiting RANK-RANKL interaction and the maturation of osteoclast progenitor cells.1,25(OH)2D has been shown to down regulate OPG, and this combination of increased RANKL expression and decreased expression of OPG caused by 1,25(OH)2D would favor differentiation and activation of osteoclasts and increased bone resorption.[11]

Kitazawa et al[11] reported that while vitamin D initially reduced expression of OPG,long-term exposure to vitamin D led to a recovery of OPG expression.This suggested that the catabolic effects of vitamin D were transient and the anabolic effects resulted in stimulation of osteopontin and alkaline phosphatase activity in osteoblasts.Therefore,vitamin D appears to stimulate bone resorption necessary for bone remodeling.Furthermore,it may facilitate osteoblastic proliferation and differentiation after long periods of exposure.

IMMUNOMODULATORY PROPERTIES

Vitamin D causes the inhibition of B-cell-mediated antibody production, cytokine production,and T-cell proliferation.It also causes the inhibition of the maturation and differentiation of dendritic cells and thus lowering its immune stimulating ability.It also suppress IL-12 and enhances IL-10 production in these dendritic cells.[12]

Vitamin D has also been shown to have a stimulatory effect on monocytes, invitro,suggesting its role in immune hemostasis rather than a purely suppressive effect on the immune system [Figure 3a][14]

Epithelial cells and macrophages increase the expression of antimicrobial peptides on exposure to microbes,which is dependent on the presence of vitamin D.[3] β-defensins exhibit antimicrobial activity against Porphyromonas gingivalis, Fusobacterium nucleatum, Aggregatibacter actinomycetamcomitans.[16]Vitamin D induces β-defensin-3 secretion by human gingival epithelium cells and human periodontal ligament cells, reducing the host-cell infectivity by Porphyromonas gingivalis.[17] Cathelicidin has a broad antimicrobial activity against bacteria,as well as certain viruses and fungi.Vitamin D treatment up-regulated cathelicidin mRNA in several cell lines and primary cultures including keratinocytes, neutrophils, and macrophages [Figure 3b].[15]

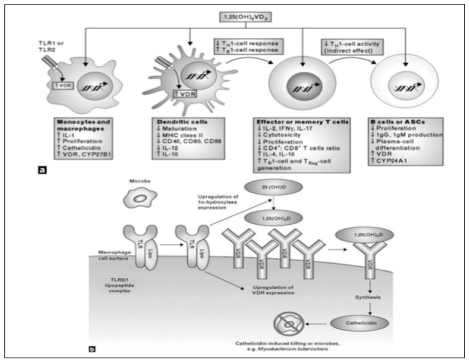

Fig.3(a)1,25(OH)2D effect on immune cells [14] (b)Effect on cathelicidin [15]

T helper 1[Th1] cells secrete pro-inflammatory cytokines like interferon gamma [IFNγ],IL-2, IL-12, and tumor necrosis factor alpha.Th2 cells express IL-4, IL-5, and IL-13,which further propagate the Th2 response.1,25(OH)2D exerts a strong suppressive effect on the expression of IL-2 and IFNγ in a VDR-regulated mechanism. The suppression of IL-2 production, in turn, inhibits T-cell proliferation. Also, suppression of pro-inflammatory cytokines results in exertion of anti-inflammatory effect.Vitamin D exerts its anti-inflammatory actions on prostaglandin synthesis and cyclooxygenase pathways.Production of matrix metalloproteinases is also inhibited which will reduce lipopolysaccharide induced tissue destruction seen in periodontitis.[13]

WOUND HEALING

1,25(OH)2D/VDR signaling promotes proliferation and differentiation of keratinocytes and mobilization of monocytes/macrophages in the early phase of tissue healing.In vivo experiments conducted in VDR-deficient laboratory animals show impaired granulation tissue formation, characterized by decreased vascularization,and poor extracellular matrix composition.[32]

VITAMIN D DEFICIENCY

It is estimated that worldwide, approximately 1 billion people suffer Vitamin D deficiency.[26] The plasma 25(OH)D levels >30 ng/mL are considered sufficient, with 40–60 ng/mL being the preferred range.[27] Vitamin D deficiency is defined as plasma 25(OH)D levels below 25 nmol/l and levels below 12 nmol/l are considered as a state of severe deficiency, which may cause osteomalacia.[28]

VITAMIN D SUPPLEMENTATION

The traditional and most cost-effective way of obtaining vitamin D is through sunlight.[29]Vitamin D obtained from dietary sources is relatively low (except fatty fish=100–1000 IU) so there arises a need for vitamin D supplementation.[30]D2 and D3 forms of Vitamin D are available as dietary supplements containing 300– 400 IU/capsule.The treatment of Vitamin D-deficient individuals should start by 50,000 IU of Vitamin D for 8–12 weeks.A single dose of 50,000 IU of D2 or D3 produces a similar increase in the total 25(OH)D concentration. However, D3 is considered more effective than D2 primarily to differences in serum half-life as D3 has a longer half-life;thus,it reduces the frequency of the doses required.[34]

After completion of the initial repletion phase, patient can be kept on maintenance dose which includes either 50,000 IU Vitamin D2/D3 every 2 weeks or 1000–2000 IU Vitamin D3 daily or the exposure of sunlight UVB rays for 5–10 minutes.[31]

A study demonstrated,Vitamin D supplementation per day for 3 years reduced the risk of tooth loss by 60%.However,the major limitation of this investigation was that the study included the supplementation of calcium along with Vitamin D; therefore, the effects of Vitamin D alone could not be studied.[29]

CONCLUSION

Vitamin D plays important role in maintaining and proper functioning of periodontium. Deficiency of vitamin D and VDR polymorphism may increase the severity of periodontitis. Thus, further research in vitamin D is needed to make important contributions in the treatment of periodontitis.

REFERENCES

[1] Page RC,Kornman KS.The pathogenesis of human periodontitis: an introduction. Periodontol 2000 1997;14:9–11.
[2] DeLuca HF.Overview of general physiologic features and functions of Vitamin D.Am J Clin Nutr 2004;80:1689S-96S
[3] Cannell JJ,Hollis BW,Zasloff M,Heaney RP.Diagnosis and treatment of vitamin D deficiency.Expert Opin Pharmacother 2008;9(l):107-118.
[4] Fukumoto S.Physiological regulation and disorders of phosphate metabolism–Pivotal role of fibroblast growth factor 23.Intern Med 2008;47:337-43.
[5] Haussler MR,Whitfield GK,Haussler CA,Hsieh JC,Thompson PD,Selznick SH,Dominguez CE,Jurutka PW.The nuclear vitamin D receptor:biological and molecular regulatory properties revealed.J Bone Miner Res 1998;13:325-49.
[6] Michigami T,Suga A,Yamazaki M,Shimizu C,Cai G,Okada S,Ozono K.Identification of amino acid sequence in the hinge region of human vitamin D receptor that transfers a cytosolic protein to the nucleus.J Biol Chem 1999;274:33531-38.
[7] Thummel KE,Brimer C,Yasuda K,Thottassery J,Senn T,Lin Y,Ishizuka H,Kharasch E,Schuetz J,Schuetz E.Transcriptional control of intestinal cytochrome P-4503A by 1α,25-dihydroxy vitamin D3.Mol Pharmacol 2001;60:1399-1406.
[8] Rosenfeld MG,Lunyak VV,Glass CK.Sensors and signals:a coactivator/ corepressor/ epigenetic code for integrating signal-dependent programs of transcriptional response.Genes Dev 200 6;20:1405-28.
[9] Kim MS,Fujiki R,Kitagawa H,Kato S.1α,25(OH)2D3-induced DNA methylation suppresses the human CYP27B1 gene.Mol Cell Endocrinol 2007;265:168-173.
[10] Kato S,Fujiki R,Kim MS,Kitagawa H.Ligand-induced transrepressive function of VDR requires a chromatin remodeling complex,WINAC.J Steroid Biochem Mol Biol 2007;103:372-80.
[11] 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;89:771-7.
[12] Kamen DL,Tangpricha V.Vitamin D and molecular actions on the immune system:Modulation of innate and autoimmunity.J Mol Med (Berl) 2010;88:441-50.
[13] Tang X,Pan Y,Zhao Y.Vitamin D inhibits the expression of interleukin-8 in human periodontal ligament cells stimulated with porphyromonas gingivalis.Arch Oral Biol 2013;58:397-407.
[14] Mora JR,Iwata M,von Andrian UH.Vitamin effects on the immune system:Vitamins A and D take centre stage.Nat Rev Immunol 2008;8:685-98.
[15] Wang TT,Nestel FP,Bourdeau V,Nagai Y,Wang Q,Liao J,et al.Cutting edge:1,25-dihydroxyvitamin D3 is a direct inducer of antimicrobial peptide gene expression.J Immunol 2004;173:2909-12.
[16] Abiko Y,Saitoh M,Nishimura M,Yamazaki M,Sawamura D,Kaku T.Role of beta-defensins in oral epithelial health and disease.Med Mol Morphol 2007;40:179–84.
[17] De Filippis A,Fiorentino M,Guida L,Annunziata M,Nastri L,Rizzo A.Vitamin D reduces the inflammatory response by Porphyromonas gingivalis infection by modulating human beta-defensin-3 in human gingival epithelium and periodontal ligament cells.Int Ommunopharmacol 2017;47:106-17.
[18] Hennig BJ,Parkhill JM,Chapple IL,Heasman PA,Taylor JJ.Association of a vitamin D receptor gene polymorphism with localized early-onset periodontal diseases.J Periodontol1999;70:1032-38.
[19] Yoshihara A,Sugita N,Yamamoto K,Kobayashi T,Miyazaki H,Yoshi H.Analysis of vitamin D and Fcγreceptor polymorphisms in Japanese patients with generalized early-onset periodontitis.J Dent Res 2001;80:2051-54.
[20] Sun JL,Meng HX ,Cao CF,Tachi Y,Shinohara M,Ueda M,Imai H,Ohura K.Relationship between vitamin D receptor gene polymorphism and periodontitis.J Periodontal Res 2002;37:263-7.
[21] Tachi Y,Shimpuku H,Nosaka Y,Kawamura T,Shinohara M,Ueda M,Imai H,Ohura K.Vitamin D receptor gene polymorphism is associated with chronic periodontitis.Life Sci 2003;73: 3313-21.
[22] de Brito Junior 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;75:1090-95.
[23] Brett PM,Zygogianni P,Griffiths GS,Tomaz M,Parkar M,D'Aiuto F,Tonetti M.Functional gene polymorphisms in aggressive and chronic periodontitis.J Dent Res 2005;84:1149-53.
[24] Park KS,Nam JH,Choi J.The short vitamin D receptor is associated with increased risk for generalized aggressive periodontitis.J Clin Periodontol 2006;33:524-8.
[25] Meng H,Xu L,Li Q,Han J,Zhao Y.Determinants of host susceptibility in aggressive periodontitis.Periodontol 2000 2007;43:133-159.
[26] Glerup H,Mikkelsen K,Poulsen L,Hass E,Overbeck S,Andersen H,et al.Hypovitaminosis D myopathy without biochemical signs of osteomalacic bone involvement.Calcif Tissue Int 2000;66:419-24.
[27] Singh G,Bonham AJ.A predictive equation to guide Vitamin D replacement dose in patients.J Am Board Fam Med 2014;27:495-509.
[28] Singh G,Drees BM.Normal,healthyand optimum level of 25-hydroxyvitamin D and required daily intake of Vitamin D.Austin J Nutr Food Sci 2015;3:1060
[29] Krall EA,Wehler C,Garcia RI,Harris SS,Dawson-Hughes B.Calcium and Vitamin D supplements reduce tooth loss in the elderly.Am J Med 2001;111:452-6.
[30] Chen TC,Chimeh F,Lu Z,Mathieu J,Person KS,Zhang A ,et al.Factors that influence the cutaneous synthesis and dietary sources of Vitamin D.Arch Biochem Biophys 2007;460(2):213-7.
[31] Bikle DD.Vitamin D and bone.Curr Osteoporos Rep 2012;10:151-9.
[32] Rieger S,Zhao H,Martin P,Abe K,Lisse TS.The role of nuclear hormone receptors in cutaneous wound repair.Cell Biochem Funct 2015;33:1-3.
[33] Amano Y,Komiyama K,Makishima M.Vitamin D and periodontal disease.J Oral Sci 2009;51(1):11-20.
[34] Anand N,Chandrasekaran SC,Rajput NS.Vitamin D and periodontal health:Current concepts.J Indian Soc Periodontol 2013;17:302-8.
[35] Norman AW.From vitamin D to hormone D:fundamentals of the vitamin D endocrine system essential for good health.The American Journal of Clinical Nutrition 2008;88(2):491S–9S.
[36] Shaw NJ,Mughal MZ.Vitamin D and child health:part 2(extraskeletal and other aspects).Arch Dis Child 2013;98(5):368–72..