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Vitamin D and Periodontal Health

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Abstract:- The biologically active form of vitamin D, 1,25 dihydroxy vitamin D (1,25(OH)2D), and its receptor, vitamin D receptor (VDR), play critical roles in oral immunity and periodontal health. Vitamin D is essential for a range of organ systems; yet, shortage is common, with 30 to 50 percent of the population suffering from it. Vitamin D insufficiency has been linked to not just low mineral bone density/osteoporosis and osteopenia, but also infectious and chronic inflammatory illnesses, according to research. Vitamin D has been linked to periodontal disease due to its effects on bone and mineral metabolism, innate immunity, and various vitamin D receptor gene polymorphisms.

Keywords:- *Periodontal disease, Vitamin D receptor gene polymorphism, Vitamin D.*

I. INTRODUCTION

Periodontitis is a complex chronic disease caused predominantly by tooth plaque microorganisms, with other local and systemic variables affecting the disease [1]. Vitamin D is a prohormone that regulates calcium and phosphate levels as well as bone structure [2]. Vitamin D is a secosteroid in which one of the rings has been broken by ultraviolet B (UVB) radiation, and de novo production in the skin is the principal source of vitamin D. Vitamin D insufficiency has long been related with bone health, and it is well known that it causes rickets in children and osteomalacia/osteoporosis in adults[3].

Vitamin D's active form regulates calcium and skeletal homeostasis, as well as acting as an anti-inflammatory and anti-microbial agent that may benefit periodontal health by acting as an antibiotic against periodontal pathogens and inhibiting inflammatory mediators that contribute to periodontal destruction. [4] With the discovery of the vitamin D receptor (VDR) in inflammatory cells, it has also been discovered that the active form of vitamin D, 1,25 dihydroxyvitamin D, inhibits cytokine production and inflammatory cell proliferation, thus playing an important role in a variety of chronic inflammatory disease conditions. It has an influence on periodontal disease through influencing bone density and by modulating the immune system. [1]

II. MECHANISM OF ACTION

The ligand for a transcription factor called the vitamin D receptor (VDR) is the hormonal form of vitamin D, 1,25(OH)2D. VDR is a transcription factor that belongs to the nuclear receptor family of steroid hormones. The cells of the intestine, bone, kidneys, and parathyroid gland, which are target tissues in the regulation of calcium and phosphate homeostasis and bone metabolism, are rich in these receptors. It is divided into three domains:

- the N-terminal DNA binding domain, which has two zinc fingers that bind to the grooves of DNA at discrete locations (VDREs),
- •the C-terminal ligand binding domain, and
- •the hinge region that connects these two domains, as illustrated in figure 1 [4].

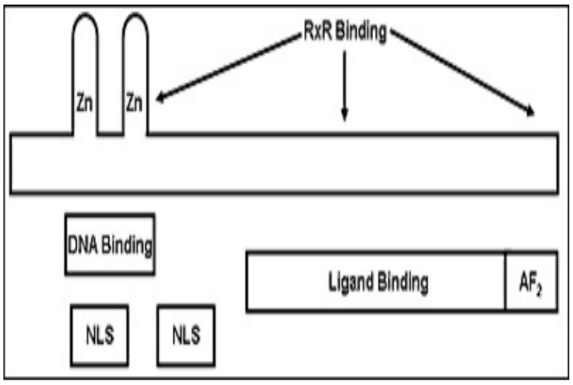

Fig. 1: Vitamin D receptor Model

A. Vitamin D-initiated gene transcription.

1,25(OH)2D molecule penetrates the target cell and attaches to the VDR receptor. After then, the VDR forms a heterodimer with the retinoid X receptor (RXR). This improves the VDR/RXR complex's affinity for the vitamin D response element (VDRE), a nucleotide sequence in the promoter region of the vitamin D responsive gene. When the VDR/RXR complex binds to the VDRE, a complex of proteins known as coactivators binds to the VDR/RXR complex. The DRIP (Mediator) coactivator complex bridges the gap between the VDRE and RNA polymerase II, as well as other proteins in the TATA box initiation complex (or other transcription regulatory elements).SRC coactivators recruit histone acetyl transferases (HAT) to the gene, allowing the transcription machinery to work by opening up the structure of the gene. The gene is transcribed to produce the matching mRNA, which then leaves the nucleus to be translated into the protein [4].

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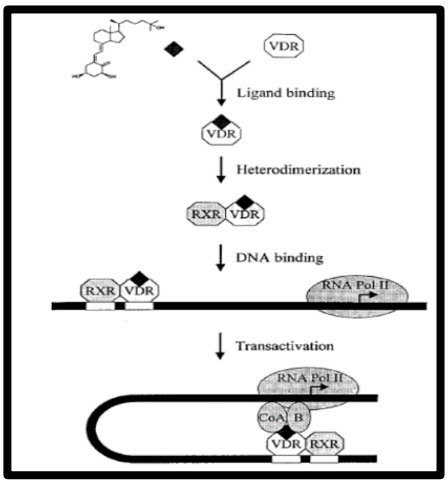

Fig. 2

FIGURE 2 depicts the main steps in 1,25(OH)2D3-mediated transcriptional regulation: I Ligand binding to the vitamin D receptor (VDR), (ii) VDR heterodimerization with the retinoid X receptor (RXR), (iii) VDR/RXR complex binding to the vitamin D response element, and (iv) recruitment of RNA polymerase II (Pol II) complex components, including direct interactions with coactivators (CoA) and transcription factor IIB (B)[5].

B. Vitamin D receptor regulation

The content of the vitamin D receptor is another major predictor of transcriptional activity in a target cell (VDR). Both the rate of synthesis and the rate of degradation will dictate the composition of the VDR. Both of them are governed by laws. In vivo and in cell culture, the modulation of VDR levels has been explored in depth for a variety of target cells. Many of the regulators are cell or tissue specific, and species variances may exist. 1,25(OH)2D3 is the most widely used VDR regulator.

At least two methods can cause ligand-dependent upregulation. 1,25(OH)2D3 upregulates VDR mRNA in a few organs (e.g., parathyroid glands and kidneys, but not the intestine), probably through calcium alterations. However, 1,25(OH)2D3 enhances VDR protein through ligand-dependent stability in almost all cell types [5].

III. TARGET TISSUE RESPONSES: CALCIUM REGULATING ORGANS

A. Intestinal Calcium Absorption

One of the oldest and best-known activities of vitamin D is intestinal calcium absorption, specifically the active component of transcellular calcium absorption, which was initially characterised in vitro by Schachter and Rosen [6] in 1959 and in vivo by Wasserman et al. [7] in 1961. Both transcellular and paracellular routes are involved in calcium absorption from the luminal contents of the intestine. In the duodenum, the transcellular route predominates, and it is this pathway that is predominantly regulated by 1,25 dihydroxy vitamin D (1,25(OH)2D). [8]

B. Actions on Bone

Rickets is the major manifestation of nutritional vitamin D deficiency, altered vitamin D responsiveness (hereditary vitamin D resistant rickets), and insufficient synthesis of 1,25(OH)2D (pseudo vitamin D deficiency) caused by mutations in the CYP27B1 gene. This would suggest that vitamin D, specifically 1,25(OH)2D, is essential for bone health. VDR are also found in bone cells, and vitamin D metabolites have been demonstrated to regulate a variety of bone functions.

The diversity of impacts that vitamin D metabolites have on systemic calcium homeostatic mechanisms, which have an impact on bone, further complicates establishing the role of vitamin D metabolites in bone. Vitamin D deficiency causes hypocalcemia and hypophosphatemia, which, as previously stated, is sufficient to produce rickets. Furthermore, because PTH has its own activities on bone and cartilage, part of the skeletal phenotype in vitamin D deficiency is related to the hyperparathyroidism that occurs in the vitamin D deficient condition [4].

Within bone, vitamin D metabolites can change the expression and/or secretion of a variety of skeletally derived factors, including insulin-like growth factor-1 (IGF-I), its receptors, and binding proteins, transforming growth factor (TGF), vascular endothelial growth factor (VEGF), interleukin-6 (IL-6), IL-4, and endothelin receptors, all of which can have their own effects on bone as well as modulate theactions of the vitamin D metabolites on bone.

Reduced alkaline phosphatase activity of hypertrophic chondrocytes, changes in the lipid composition of the matrix possibly due to reduced phospholipase activity, and altered proteoglycan degradation due to changes in metalloproteinase activity are all linked to the impairment of endochondral bone formation seen in vitamin D deficiency. For optimum endochondral bone formation, both 1,25(OH)2D and 24,25(OH)2D appear to be necessary. The response of osteoblasts to 1,25(OH)2D varies depending on their maturity level16.

1,25(OH)2D stimulates bone resorption by increasing the number and activity of osteoclasts, in addition to boosting bone growth. Although it is unclear whether mature osteoclasts include the VDR and are directly regulated by 1,25(OH)2D, the VDR in osteoclast precursors is not necessary for osteoclastogenesis. Rather, osteoblasts are involved in the promotion of osteoclastogenesis by 1,25(OH)2D. RANKL (receptor activator of nuclear factor (NF)-kB ligand) is a membrane-associated protein produced by osteoblasts that activates RANK on osteoclasts and their hematopoietic progenitors.This cell-to-cell contact, in combination with the hormone m-CSF, which is also produced by osteoblasts, promotes the development of precursors into osteoclasts and their activity. PTH, PGE2, and IL-11 all increase osteoclastogenesis, and 1,25(OH)2D regulates this process by increasing RANKL. The VDR is required for 1,25(OH)2D to function in osteoblasts, while other hormones and cytokines are not17.

C. Actions of Vitamin D on Kidney

The kidney's regulation of calcium and phosphate transport by vitamin D metabolites has gotten less attention than the intestine's, yet the two tissues share comparable, if not identical, mechanisms. The glomerulus filters eight grammes of calcium per day, with 98 percent of it being reabsorbed. In the proximal tubule, the majority of it is reabsorbed. This is a sodium-dependent paracellular mechanism with little or no control by PTH or 1,25(OH)2D. In the thick ascending limb of the loop of Henle, 20 percent of calcium is reabsorbed, 10-15 percent in the distal tubule, and 5% in the collecting duct [9].Vitamin D regulates calcium movement in the distal tubule, where calcium travels in a sodium-independent manner against an electrochemical gradient (probably transcellular). Phosphate, on the other hand, is reabsorbed in the proximal tubule at a rate of around 80%, and PTH regulates this process.

IV. TARGET TISSUE RESPONSES: NON-CALCIUM TRANSPORTING TISSUES

A. Regulation of Hormone Secretion

a) Parathyroid gland (PTH secretion)

PTH promotes the synthesis of 1,25(OH)2D. 1,25(OH)2D, in turn, inhibits the synthesis of PTH. The transcriptional level is where the regulation takes place. A region of the PTH gene promoter contacts the VDR and facilitates 1,25(OH)2D-mediated repression of the PTH promoter.

Calcium affects 1,25(OH)2D's ability to regulate PTH gene expression. Calcium inhibits PTH generation and secretion by binding to the calcium sensing receptor (CaSR) on the parathyroid cell's plasma membrane. The CaSR in the parathyroid gland is induced by 1,25(OH)2D, making it more sensitive to calcium.

b) Pancreatic beta cells (insulin secretion)

Although the mechanism is unknown, 1,25(OH)2D promotes insulin secretion [81]. Although the findings of randomised controlled trials with vitamin D have not been definitive [10], a number of largely case control and observational studies have revealed that vitamin D insufficiency contributes to an increased risk of type 2 diabetes mellitus.

c) Fibroblast growth factor (FGF23)

FGF23 is predominantly produced by bone, specifically osteoblasts and osteocytes. This process is stimulated by 1,25(OH)2D3, although the mechanism is unknown. FGF23 inhibits 1,25(OH)2D production by the kidney, but this feedback loop, like the one for PTH secretion, keeps the amounts of these critical hormones in check10.

B. Regulation of proliferation and differentiation.

a) Cancer

For nearly 40 years, 1,25(OH)2D has been studied in animal and cell investigations for its possible anticancer effects. The number of cancer cells that express VDR is now extremely large. The ant proliferative and pro differentiating properties of 1,25(OH)2D on most cell types are the acknowledged basis for its promise in the prevention and treatment of cancer. The list of hypothesised mechanisms for these effects is long and, to some extent, cell-specific. 1,25(OH)2D has been demonstrated to boost the expression of cell cycle inhibitors p21 and p27, as well as the expression of the cell adhesion protein E-cadherin, while inhibiting the transcriptional activity of b-catenin by one of these methods.

1,25(OH)2D has been demonstrated to accelerate the repair of DNA damage caused by ultraviolet radiation (UVR) in keratinocytes, reduce apoptosis while boosting survival after UVR, and raise p53. The evidence for the role of proper vitamin D intake (including sunshine exposure) in the prevention of a variety of malignancies is extensive4.

b) Skin

The full vitamin D metabolic pathway is only found in epidermal keratinocytes. Vitamin D3 is synthesised in the epidermis from 7-dehydrocholesterol. CYP27A1, a mitochondrial enzyme that 25-hydroxylates vitamin D, and CYP27B1, a mitochondrial enzyme that converts 25OHD to 1,25(OH)2D, are both found in the epidermis.

1,25(OH)2D modulates calcium's ability to influence keratinocyte development. Keratinocytes cultured at calcium concentrations below 0.07mM continue to proliferate but fail or sluggish to create intercellular connections, stratify little if at all, and form cornified envelopes4.

c) Immune system

Since the discovery of vitamin D receptors (VDR) in macrophages, dendritic cells (DC), and activated T and B lymphocytes, as well as macrophages and DC's ability to express CYP27B1, and the ability of 1,25(OH)2D3 to regulate the proliferation and function of these cells, the potential role of vitamin D and its active metabolite 1,25(OH)2D3 in modulating the immune response has been recognised.

In general, 1,25(OH)2D3 enhances the innate immune response by stimulating cathelicidin, an antimicrobial peptide important in defence against invading organisms, while inhibiting the adaptive immune response by inhibiting the maturation of antigen-presenting dendritic cells (DC), reducing T cell proliferation, and shifting the balance of T cell differentiation from Th1 and Th17 pathways to Th2 and Treg pathways.

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a. Adaptive Immune Response
The adaptive immune response is begun by cells that specialise in antigen presentation, such as DC and macrophages, which then activate T and B lymphocytes, which are responsible for subsequent antigen recognition. The type of activated T cell, CD4 or CD8, is crucial.

The context of the antigen given by which cell and in what environment determines CD8, or within the helper T cell class Th1, Th2, Th17, Treg, and minor variants of those. Vitamin D and other systemic variables have an impact on this process. Vitamin D has an inhibiting effect on the adaptive immune system in general.

1,25(OH)2D3 inhibits DC maturation, as seen by decreased expression of costimulatory molecules such as HLA-DR, CD40, CD80, and CD86, reducing their ability to deliver antigen and hence activate T cells. Furthermore, 1,25(OH)2D3 inhibits the development of Th1 cells capable of producing IFN-g and IL-2, as well as Th17 cells capable of producing IL-17, by suppressing IL-12 production, which is important for Th1 development, and IL-23 and IL-6 production, which is important for Th17 development and function. These effects stop antigen from being presented to and recruited by T lymphocytes (IFN-function), g's as well as T lymphocyte proliferation (role of IL-2).

1,25(OH)2D3 regulates a number of cytokines involved in the immune response in both direct and indirect ways. The VDR/RXR complex interacts to a VDRE in the promoter of TNF. 1,25(OH)2D3 inhibits NFkB binding to its response elements in the genes it regulates, such as IL-8 and IL-12, by blocking its activation via an increase in IkBa expression. As a result, 1,25(OH)2D3 inhibits TNF/NFkB activity at many levels.

The potential of 1,25(OH)2D3 to suppress the adaptive immune system appears to be advantageous in a variety of situations where the immune system is directed against oneself, such as autoimmunity. Inflammatory arthritis, psoriasis, autoimmune diabetes (e.g. NOD mice), systemic lupus erythematosus (SLE), experimental allergic encephalitis (EAE) (a model for multiple sclerosis), inflammatory bowel disease (IBD), prostatitis, and thyroiditis have all been shown to be prevented or treated by VDR agonist administration.

b. Innate Immune Response
Toll-like receptors (TLRs) are activated in polymorphonuclear cells (PMNs), monocytes, and macrophages, as well as a variety of epithelial cells such as those in the epidermis, gingiva, gut, vagina, bladder, and lungs, as part of the innate immune response. In human cells, there are ten TLRs that are active (of 11 known mammalian TLRs). TLRs are a noncatalytic transmembrane pathogen-recognition receptor family that interacts with unique membrane patterns (PAMP) emitted by infectious pathogens to activate the host's innate immune system.

When TLRs are activated, antimicrobial peptides (AMPs) and reactive oxygen species (ROS) are produced, which destroy the organism. Cathelicidin is one of these AMPs. Cathelicidin has a variety of functions in the innate immune system. 1,25(OH)2D3 stimulates the production of this antimicrobial peptide in both myeloid and epithelial cells. In addition, 1,25(OH)2D3 causes keratinocytes to express the CD14 coreceptor. TLR2 stimulation in macrophages by an antimicrobial peptide or TLR2 stimulation in keratinocytes by injuring the epidermis results in increased expression of CYP27B1, which promotes the synthesis of cathelicidin in the presence of enough substrate (25OHD). The ability of these cells to respond to a challenge in terms of cathelicidin and/or CD14 synthesis is hampered by a lack of substrate (25OHD) or CYP27B1.

V. VITAMIN D AND IMMUNE RESPONSE OF PERIODONTIUM

Dental pulp fibroblasts and periodontal cells produce 25-hydroxylase during an inflammatory phase, which enhances the formation of 25(OH)D3, according to Liu et al. [11]. When pathogenic bacteria bind to cell membrane receptors, 1-hydroxylase is triggered, resulting in the formation of 1,25(OH)D3 from 25(OH)D3. The molecule that results binds to the VDR in immune and epithelial cells and contributes in the epithelial defence mechanism against pathogens. 1,25(OH)D3 stimulates the synthesis of proteins needed in epithelial cells' tight, gap, and desmosome junctions.

Vitamin D slows the undesired process of T-lymphocyte proliferation, immunoglobulin production, and B-lymphocyte transformation into plasma cells, and protects the organism against an overly particular immune response by lowering the secretion of IL-1, IL-6, IL-8, IL-12, and TNF cytokines. During PD pathogenesis, these cytokines are generated in response to bacterial invasion. They result in lymphocyte infiltration, bone resorption, and extracellular matrix degradation.

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VI. CONCENTRATION OF 25-HYDROXYVITAMIN D IN PLASMA AND PERIODONTAL DISEASE

The concentration of vitamin D's metabolite 25(OH)D3 in plasma determines the amount of vitamin D in a human body; it typically ranges from 25 to 138 nmol/L. Vitamin D insufficiency is indicated by a value of less than 37.5 nmol/L. Hypervitaminosis is defined as a concentration more than 200 nmol/L. The plasma concentration must reach 90–100 nmol/L to have an effect on the periodontium [10].

Because periodontal cells' 25-hydroxylase activity increases during acute periodontal inflammation, the concentration of 25(OH)D3 rises. It diminishes with chronic inflammation. The concentration of 25(OH)D3 in periodontal pockets is 300 times higher than in blood plasma due to the synthesis of this enzyme in aggressive periodontitis. Low levels of 25(OH)D3 in the plasma indicate vitamin D deficiency, imbalanced immunological reactions in the body, and periodontal disease progression [12].

VII. VDR POLYMORPHISM AND PERIODONTAL DISEASE

Several VDR restriction fragment length polymorphisms (RFLPs) have been linked to a variety of disorders, including secondary hyperparathyroidism in renal failure, osteoporosis, cancer, nephrolithiasis, diabetes, and periodontal disease. [13]

Bsml, Tru9I, TaqI, EcoRV, and ApaI are RFLPs that are found between exons 8 and 9 and may affect mRNA stability. The RFLP Fokl inserts a start codon in exon 2, resulting in a different start site, and there has been a link between the Taql RFLP and periodontitis.

In Caucasian participants, a link was shown between the less common T allele and localised early onset periodontitis (aggressive periodontitis) [14]. In Japanese and Caucasian patients, the thymine phenotypic allele (TT) genotype and the T allele are linked to chronic periodontitis, whereas in Chinese participants, the TT genotype and T allele are linked to early onset periodontitis (aggressive periodontitis). The results of TaqI RFLP analysis may be influenced by ethnic differences and differing pathways in pathogenesis between aggressive and chronic periodontitis.

The findings suggest that 1,25(OH) 2D3 has a function in periodontal disease prevention and that hypomorphic VDR alleles and low levels of 1,25(OH)2D3 - I,25-dihydroxy vitamin D3 may be linked to periodontal disease [3].

VIII. VITAMIN D DEFICIENCY

Although no consensus exists on the appropriate serum 25(OH) D level, it is inversely related to parathormone (PTH) levels until 25(OH) D reaches 30-40 ng/mL, at which point PTH levels begin to level out. Vitamin D deficiency is defined as a level of 20 ng/mL or less, while insufficiency is defined as a level of 2129 ng/mL or more. Vitamin D deficiency is currently considered an epidemic, with an estimated 1 billion persons worldwide deficient or insufficient in the vitamin [3].

The Endocrine Society of Clinical Practice (ESCP) recommends screening for Vitamin D deficiency in those who are at risk, not in people who aren't. In individuals who are at risk for Vitamin D deficiency, the serum circulating 25-hydroxyvitamin D [25(OH) D] level should be examined to determine vitamin D status. According to the ESCP, obese children and adults using anticonvulsant drugs, glucocorticoids, antifungals like ketoconazole, and AIDS treatments should be given at least two to three times the recommended amount of vitamin D for their age group to meet their body's vitamin D requirements.According to the ESCP, the maintenance tolerable upper limits (UL) of vitamin D should be 1000 IU/d for infants up to 6 months, 1500 IU/d for infants from 6 months to 1 year, at least 2500 IU/d for children aged 1–3 years, 3000 IU/d for children aged 4–8 years, and 4000 IU/d for everyone over 8 years. VDD may require higher levels of 2000 IU/d for children aged 0–1, 4000 IU/d for children aged 1–18 years, and 10000 IU/d for children and adults aged 19 years and older [5].

IX. TREATMENT STRATEGY

Sunlight is the most traditional and cost-effective technique to obtain Vitamin D. A 5–10 minute midday, midyear exposure of a light colored Caucasian individual's arms and legs can produce up to 3000 IU of Vitamin D3 in the epidermis of human skin, which can grow to 10,000 IU if a total body exposure is given. However, many factors such as sunscreen, clothes, ageing, pollution, the sun's zenith angle, and reduced outdoor activities have resulted in a reduction in UV radiation exposure today. As a result, many patients and clinicians believe that Vitamin D deficiency can only be treated with Vitamin D received through diet.

The Vitamin D level of most foods, including fortified dairy products (100 IU/8oz), is rather low, with the exception of fatty fish (100–1000 IU/3.5oz). As a result, vitamin D supplementation becomes necessary. Vitamin D2 and D3 are available as dietary supplements with 300–400 IU per capsule [1].

Individuals who are Vitamin D deficient should begin treatment with 50,000 IU of Vitamin D for 8–12 weeks. A single dose of 50,000 IU of D2 or D3 increases total 25(OH)D concentration in a comparable way. After completing the first repletion phase, the patient can be continued on a maintenance dose of 50,000 IU Vitamin D2/D3 every two weeks, 1000–2000 IU Vitamin D3 daily, or 5–10 minutes of exposure to UVB rays from the sun. According to numerous research, every 100 IU of Vitamin D

supplementation delivered induces a 0.5 to 1ng/ml increase in the 25 (OH)D level. Furthermore, various people require different vitamin D dosages. [15]

X. VITAMIN D SUPPLEMENTATION AND PERIODONTITIS

From time to time, several research demonstrating the effect of Vitamin D on periodontal disease are carried out. In a study on the effects of Vitamin D supplementation on tooth loss, it was discovered that taking a daily dose of Vitamin D for three years reduced the risk of tooth loss by 60%. However, a key weakness of this trial was that it contained calcium supplementation in addition to Vitamin D; hence, the effects of Vitamin D alone could not be investigated. Furthermore, tooth loss was a secondary outcome in the study, with tooth counts based on self-reports from study participants. In a separate double-blind placebo-controlled research, those who got Vitamin D supplementation had better periodontal health than those who received placebos.This study, however, included calcium supplementation in addition to Vitamin D. Furthermore, no radiographic analysis was performed, and limited information about periodontal health assessment was provided in this study. Another research of periodontally healthy postmenopausal women [1] found comparable outcomes to the previous investigations.

XI. CONCLUSION

Vitamin D is important in periodontology because its active form, 1,25 (OH)2D, has been shown to influence human periodontal health. Vitamin D's anti-inflammatory, immunological modulatory, and skeletal homeostasis-maintaining properties are responsible for this activity. Several investigations have shown that its shortage or dysfunction as a result of a gene polymorphism can lead to periodontal disease. As a result, vitamin D administration may reduce bone degradation and inflammation, lowering the risk of tooth loss due to periodontal diseases in vitamin D deficient patients. Clinical trials, on the other hand, are necessary to confirm its efficacy.

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