The Biological Pathways of Vitamin D in Preventing Osteoclastogenesis of Alveolar Bone in Periodontitis: An Overview

by Mochammad Taha Maruf

The Biological Pathways of Vitamin D in Preventing Osteoclastogenesis of Alveolar Bone in Periodontitis: An Overview

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Abstract

Periodontitis is a chronic inflammatory disease of the periodontal tissue caused by an imbalance of bacteria and host responses. It is characterized by loss of periodontal adhesions, deepening of the periodontal pocket, and resorption of alveolar bone. Alveolar bone resorption in periodontitis occurs due to the osteoclastogenesis activated by proinflammatory cytokines via the activation of RANKL-OPG and TNF-α signaling pathways. Low serum vitamin D levels are often found in people with periodontitis.

Vitamin D is a secosteroid hormone that plays a role in bone metabolism and suppressing cytokine production in the alveolar bone osteoclastogenesis process. Via VDR, vitamin D will affect RANKL and OPG expression regulation, resulting in a decrease in the RANKL/OPG ratio, which reduces osteoclast differentiation. In addition, vitamin D suppresses the c-Fos protein expression, a transcription factor for osteoclast differentiation. This review will highlight the interaction between vitamin D and osteoclastogenesis, especially in molecular pathways.

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Introduction

Periodontitis is a disease with a high prevalence throughout the world, including in Indonesia. Based on the results of primary health research in 2018, the prevalence of oral and dental disease in Indonesia is 57.6%, with a periodontitis prevalence of 74,1%.[1] Periodontitis is characterized by loss of periodontal attachment, increased periodontal pocket, and alveolar bone resorption. It is one of the biggest causes of tooth loss and other causes such as dental caries, trauma, and impacted teeth extraction orthodontic and prosthodontic purposes. The effect of tooth loss affects the quality of life of a person in terms of aesthetic and functional aspects and systemic health conditions.[2,3,4]

Vitamin D is a secosteroid hormone produced in the skin through exposure to ultraviolet light and can be sourced from food or supplementation. The most abundant form of vitamin D in plasma is 25-hydroxyvitamin D (25(OH)D), which is also a form of storage for vitamin D.[5,6] Vitamin D has immunomodulatory, anti-inflammatory, anti-proliferative, apoptotic cell effects and immune function. [5,7] Vitamin D plays an essential part in bone and calcium metabolism and maintaining serum calcium and phosphate concentrations within normal limits.[6]

Several observational studies comparing vitamin D levels in patients serum with periodontitis and those without periodontitis have been widely studied and show different results. Zhan et al. found that high 25(OH)D serum reduced the risk of tooth loss.[2] Rafique et al. also reported low levels of 1,25(OH)2D in patients with periodontitis.[8] A longitudinal study on the effect of vitamin D supplementation on the clinical picture of periodontal conditions has also been conducted by Alshoubi et al.[9], who claimed that vitamin D intake could inhibit the severity of periodontal conditions in older men. Jayachandran et al. observed that supplementation of vitamin D (250 IU/day) and calcium (500 mg/day) showed positive results for periodontal tissue repair.[10]

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Preventing or inhibiting the osteoclastogenesis process in alveolar bone periodontitis is a challenge to stop alveolar bone resorption. The prognosis for the outcome of periodontal treatment in stopping the bone resorption process is closely related to the molecular identification associated with alveolar bone resorption mediators. As research continues to develop regarding the relationship and effects of vitamin D on periodontitis and the use of vitamin D as additional supplementation in periodontal therapy, it is necessary to conduct a theoretical study of the anti-inflammatory and antibacterial mechanisms of vitamin D in inhibiting osteoclastogenesis of alveolar bone in periodontitis.

Osteoclastogenesis in Periodontitis

Osteoclasts are the only cells that can cause bone resorption so that osteoclasts take part in the homeostasis process in normal bone conditions and pathological conditions. Hormones and cytokines influence the activation and differentiation of osteoclasts. Activation and formation of osteoclasts can be inhibited by several factors such as bisphosphonates, calcitonin, IL-18, IL-4, OPG, IFN-γ, TGF-β, FGF-2, and estrogen. Meanwhile, osteoblasts and bone marrow stromal cells can stimulate RANKL production to form osteoclasts through several factors such as IL-1, IL-6, IL-11, TNF, PGE2, M-CSF, and vitamin D3. Bone degradation results in the release of local growth factors from the matrix, such as BMP, TGF-β, or FGF, which will stimulate the maturation of osteoblast precursors that produce OPG as the primary inhibitor of osteoclastogenesis.[11]

Several studies have also shown that osteoblast cells also influence osteoclast cell differentiation because osteoblasts produce M-CSF.[12] In vitro and in vivo studies report that TNF-α also mediates osteoclast formation. TNF-α can affect the formation of osteoclasts due to the pathogenesis of inflammation. TNF-α induces biological reactions via two receptors, namely the TNF type 1 receptor (TNFR1) and the TNF type 2 receptor (TNFR2). Each of these receptors has a different intracellular signaling pathway. TNFR1 causes osteoclast differentiation, while TNFR 2 inhibits osteoclast differentiation.[13]

Osteoclastogenesis in periodontitis can occur via the RANK-RANKL-OPG signaling pathway[11,14] and TNF-α signaling.[15] Increased expression of the Activator Receptor of Nuclear Factor-Lig B Ligand (RANKL) is known to have an essential role in the osteoclastogenesis process. Osteoprotegerin (OPG) produced by gingival fibroblasts will block RANKL and RANK binding, which will form osteoclasts. An increased RANKL/OPG ratio in periodontitis will cause an increase in osteoclasts and lead to alveolar bone resorption.[11,14,16,17]

TNF-α also affects osteoclastogenesis in periodontitis, even though RANK-RANKL signaling does not occur. The effect of TNF-α on osteoclast resorptive activation in the absence of RANKL is highly dependent on the lymphocyte-monocyte interaction to produce IL-1. Another study found that IL-1 and lipopolysaccharide stimulate osteoclastogenesis by two parallel mechanisms by increasing RANKL expression and suppressing OPG, which is mediated by prostaglandin E2 production.[14]

RANK-RANKL-OPG Signaling Pathway

RANKL is a TNF member expressed by osteoblasts or stromal cells in two forms: membrane-bound RANKL (mRANKL) and soluble RANKL (sRANKL).[16,18] The activation and differentiation of osteoclasts are modulated by three TNF ligand members and the superfamily receptor, namely RANK-RANK-OPG. These three types of peptides play a significant role in osteoclast activity and differentiation from molecular mechanisms. RANKL will bind to its receptors, namely RANK, on the surface of preosteoclasts and osteoclasts, causing osteoclast formation. OPG is a decoy receptor produced by various osteoblasts and stromal cells that inhibit osteoclast formation by blocking RANK-RANKL attachment. OPG will bind RANKL, thus blocking RANK-RANKL attachment. There was an increase in the RANKL/OPG ratio in periodontitis where the RANKL expression was higher than OPG.[16]

Periodontitis increases stimulation of the cellular inflammatory response of T cells, B cells, macrophages, and neutrophils in the gingival connective tissue, thereby increasing the secretion of inflammatory mediators. These inflammatory cells also interact with stromal cells, including osteoblasts, periodontal ligaments, and gingival fibroblasts. Under physiological conditions, lymphocyte production of RANKL does not cause alveolar bone resorption. However, in pathological inflammatory conditions, T lymphocytes will overproduce sRANKL and cause alveolar bone resorption. It was found that in periodontitis, the largest source of RANKL expression was T and B lymphocytes, with the most RANKL form being sRANKL, although mRANKL was also found in smaller amounts.[16] Bacteria that cause periodontitis, such as *Aggregatibacter actinomycetemcomitans* (Aa) and *Porphyromonas gingivalis* (Pg) have a unique mechanism in inducing RANKL expression on osteoblasts, periodontal ligament fibroblasts, and gingival fibroblasts. Lipopolysaccharide (LPS) from these bacteria will induce RANKL expression on osteoblasts, periodontal ligament fibroblasts, and gingival fibroblasts.[19]

The RANKL-RANK binding attracts the TNF receptor association factor (TRAF) protein adapter, including TRAF 1,2,3,4,5, and 6 initiating the adapter/kinase cascade signal activation. Of the six TRAFs, TRAF 6 is a member that plays a significant role in osteoclast formation. TRAF 6 sends RANK/RANK signals to downstream targets and activates osteoclastogenic transcription factors such as Nuclear Factor-κ B (NF-κ B), c-Jun N-terminal kinase (JNK), extracellular signal-regulated kinase (ERK), p38, Akt, activator protein 1 (AP1), cyclic adenosine monophosphate response element-binding protein (CREB), and nuclear factor of activated T cell 1 (NFATc1). These transcription factors will then induce the expression of osteoclastogenic markers such as tartrate-resistant acid phosphatase (TRAP), dendritic cell-specific transmembrane protein (DC-STAMP), v-ATPase subunit d2 (Atp6v0d2), OC-associated receptor (OSCAR), β3 integrin, osteopetrosis-associated transmembrane protein 1 (OSTM1), B-lymphocyte induced maturation protein 1 (BLIMP1), and cathepsin K (Figure 1). The inflammation in periodontitis triggers the expression of RANK-RANKL T and B lymphocytes. TRAF6 activation through the RANK-RANKL pathway will induce osteoclast production by activation of osteoclastogenesis transcription factors.[12,20]

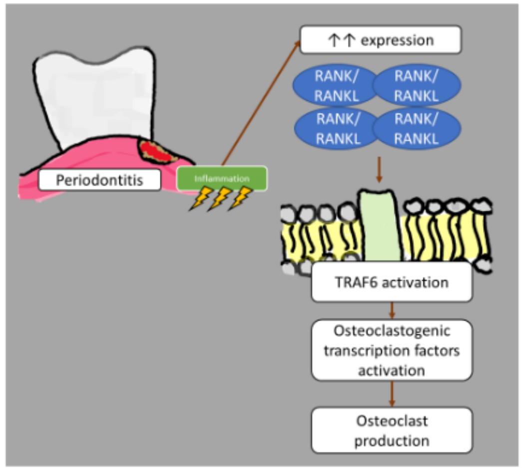

Figure 1. Osteoclastogenesis pathway in periodontitis via RANK/RANKL.

TNF- α Signaling Pathway

TNF-α plays an essential role in the inflammatory process, one of which is periodontitis. TNF-α is an inflammatory cytokine that promotes bone resorption by suppressing osteoblasts' anabolic function and inducing RANKL expression on osteoblasts and stromal cells, triggering osteoclastogenesis.[21] A study by Yuce found an increase in TNF-α levels in the gingival fluid of periodontitis patients, and these levels decreased after periodontal therapy.[22] TNF-α inhibits osteoblast differentiation and thus inhibits bone formation.[18] TNF-α stimulates osteoclastogenesis by increasing the production of M-CSF and RANKL in stromal cells and osteoblasts.[23]

TNF-α is an active protein biologically bound to its parent cells, namely monocytes and T cells, or bound to its soluble form after being cleaved by enzymes. To initiate a cellular response, TNF-α binds to one of its two receptor cells (TNFR).[24] TNF-α receptors (TNFR1/p55TNFR and TNFR2/p75TNFR) are expressed on almost all cell types such as macrophages, lymphocytes, neutrophils, and fibroblasts. In periodontitis, it was reported that TNFR1 and TNFR2 were expressed by sulcus epithelial cells, monocytes/macrophages, fibroblasts, and endothelial cells. Also, in periodontitis, there is an imbalance between TNFR1 and TNFR2. With the increase of the periodontitis severity and alveolar bone resorption, there is a decrease in TNFR2/TNFR1 ratio.[25]

TNFR1 activation can induce cell proliferation, stimulation, and survival or initiate apoptosis and cell death signals.[15] TNFR1 is a TNF receptor that causes osteoclastogenesis. TNF-α and TNFR1 mediate endotoxin that induces osteoclastogenesis and bone resorption via the NF-κB signaling pathway (Figure 2). The inflammation in periodontitis triggers the expression of TNF-α. TNRF1 activation through the TNF-α pathway will induce osteoclast production by activation of osteoclastogenesis and increase bone absorption.

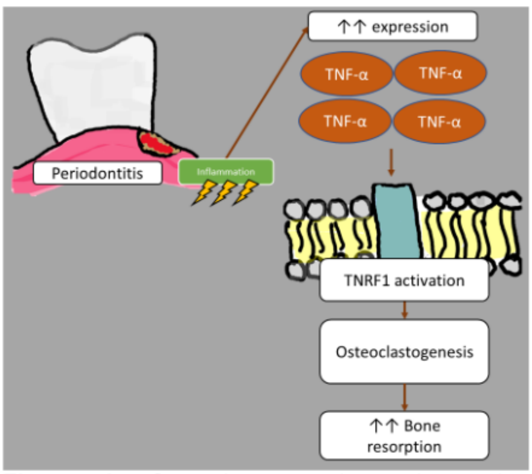

Figure 2. Osteoclastogenesis pathway in periodontitis via TNF-α.

The study showed that reduced TNFR1 expression significantly suppressed the RANKL signaling pathway, including NF-κB and AP1 activation. TNFR1 is needed in optimizing RANKL expression, which induces osteoclastogenesis.[26] Ochi et al. showed that OPG administration caused TNFR1 deficiency and inhibited osteoclastogenesis in periodontitis due to LPS.[27]

Production, Metabolism, and Function of Vitamin D

Vitamin D is produced in the skin through exposure to ultraviolet (UV) light. Vitamin D, either from the skin or food, is metabolized in the liver by CYP27A1 enzyme to 25 (OH) D. The metabolic process then continues in the proximal tubule of the kidney to become 1,25 (OH) 2D by the enzyme 1,25-hydroxylase (CYP27B1). The primary 1,25 (OH) 2D production in the kidneys is stimulated by parathyroid hormone (PTH) and is inhibited by calcium, phosphate, and fibroblast growth factor 23 (FGF23). 1,25 (OH) 2D also functions as an immune system against infection as an innate and adaptive immune system. 1,25 (OH) 2D has a significant role in bone metabolism related to its ability to increase serum calcium and phosphate levels through increased intestinal absorption of calcium and phosphate and directly affects osteoclasts and osteoblasts. The direct effect of 25 (OH) D and 1,25 (OH) 2D on osteoclasts, osteoblasts, and chondrocytes are through the expression of Vitamin D receptors (VDR) and production of 1,25 (OH) 2D. Vitamin D signaling is essential in both bone formation and bone resorption. 1,25 (OH) 2D is also associated with the regulation of osteopontin, osteocalcin, RANKL, and OPG molecules, where these molecules play a role in bone metabolism.[28,29]

Antimicrobial and Anti-inflammation Effect of Vitamin D in Periodontitis

Various research results show a positive effect between vitamin D levels in serum on the healing of periodontitis with parameters of gingival bleeding/bleeding on probing (BOP), pocket depth, clinical attachment level (CAL), gingival index (GI), and cementoenamel junction distance-alveolar crest (CEJ-AC) (Table 1). The clinical parameters of periodontal disease were used further to identify the effect of vitamin D on periodontitis. The effect of vitamin D on bacteria and cytokines in periodontitis has also been widely studied, showing a decrease in the population of periodontitis-causing bacteria such as *Tannerella forsythia*, *Porphyromonas gingivalis*, and *Treponema denticola* after six months of therapy with vitamin D.[30]

Vitamin D has an antimicrobial and anti-inflammatory effect that plays a role in suppressing cytokine production in periodontal inflammation, thereby inhibiting osteoclastogenesis. Infection with *Porphyromonas gingivalis* on the gingiva and periodontal treated with vitamin D supplementation showed low expression of inflammatory cytokines and high expression of β-defensins.[31] The antimicrobial, anti-inflammatory, and immunomodulating effects of 1,25 (OH) 2D play a role in maintaining oral tissue homeostasis and protecting against bacterial plaque that causes periodontitis. It has been reported that vitamin D deficiency or vitamin D receptor (VDR) polymorphism is associated with an increased risk of chronic periodontitis.[32]

Author	Year	Title	Finding
Dragonas P, El-Sioufi I, Bobetsis YA, Madianos PN	2020	Association of Vitamin D with periodontal disease: A narrative review	Various vitamin D polymorphisms were associated with chronic and aggressive periodontitis, with different outcomes reported for the various ethnic populations assessed.[12]
Rafique S, Hingorjo MR, Mumtaz M, Qureshi MA.	2019	The relationship of 1,25-dihydroxyvitamin D and vitamin D binding protein in periodontitis	Low 1,25$(OH)_2$D levels and high DBP levels are associated with periodontitis.[13]
Lee DE, Won SY	2019	Relationship between Clinical Indicators of Periodontal Disease and Serum Level of Vitamin D	There is a positive association between the serum 2p-hydroxy vitamin D level and periodontal health.[35]
Kaur M	2018	Low levels of vitamin D and periodontal disease: A review	There is no association to positive association between low levels of vitamin D and clinical parameters of gingival inflammation and periodontal breakdown.[36]
Khammissa RAG, Fourie J, et al.	2018	The Biological Activities of Vitamin D and Its Receptor in Relation to Calcium and Bone Homeostasis, Cancer, Immune and Cardiovascular Systems, Skin Biology, and Oral Health	1,25(OH)2D/VDR signaling has a role in bone homeostasis and can regulate the immune's cellular responses and regulate keratinocyte activity.[37]
Stein SH, Livada R, Tipton DA	2014	Re-evaluating the role of vitamin D in the periodontium	Vitamin D's ability to stimulate the innate and adaptive immune rationale has explained that vitamin D has a "perio-protective" role.[38]

Table 1. The list of studies which showed an association between vitamin D and periodontal disease.

The protective mechanism of vitamin D against periodontitis occurs through two biological pathways: the antimicrobial and anti-inflammatory pathways (Figure 3). The Vitamin D biological pathways show two pathways: antimicrobial and the other as an anti-inflammatory. As antimicrobial, Vitamin D will reduce the oral bacteria population in the oral cavity. Vitamin D will reduce the degradation of connective tissue by inhibiting the expression of MMPs and reducing bone absorption by inhibiting the differentiation of osteoclast progenitor, both pathways affected by the anti-inflammatory effect.

The antimicrobial effect of vitamin D occurs from the bonding between 1,25 (OH) 2D3 and VDR, which then induces cAMP, β-def-2, and β-def-3 peptides by macrophages and monocytes gingival epithelium and periodontal ligament epithelium. These peptides will reduce microbes in the oral cavity and prevent periodontal tissue exposure by these microbial products. The anti-inflammatory effect decreases the production of proinflammatory cytokines such as IL-6 and TNF-α, inhibiting NF-κB and increasing MKP-1 regulation. This reduction in proinflammatory cytokine production will inhibit periodontal connective tissue damage by attenuating matrix metalloproteinases (MMPs) stimulation. Decreased IL-6 and TNF-α production will reduce the RANKL/OPG ratio in osteoblast stromal cells, thereby inhibiting osteoclast progenitor differentiation as a cause of alveolar bone resorption.[6,33]

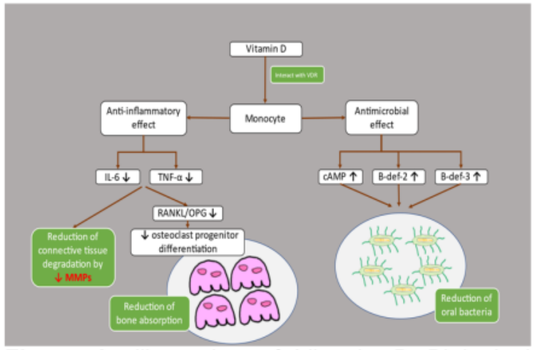

Figure 3. Illustration of Vitamin D Biological Pathways.

Conclusions

Vitamin D can provide a protective mechanism against periodontitis which is antimicrobial and anti-inflammatory. The antimicrobial effect is caused by the induction of cAMP, β-def-2, and β-def-3 peptides due to VDR bonding with 1,25 (OH) 2D3. Inhibiting IL-6 and TNF-a expression can reduce connective tissue inflammation and degradation, also decrease tooth absorption. So vitamin D may be a consideration in treating periodontitis.

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Declaration of Interest

The authors report no conflict of interest.

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