



# Vitamin D Target Genes in Dental Health

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## Abstract

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**INTRODUCTION:** Vitamin D is an important molecule which plays pivotal role in overall human health and metabolism. This vitamin acts as both vitamin as well as hormone, and thus, dual nature of this vitamin makes it as one of the important chemicals required for the overall health, harmonious growth, and development. Recently, this vitamin is gaining large attention in dentistry, and it is becoming master regulator of dental health. It is well studied that vitamin D plays major role in calcium absorption for bone and teeth mineralisation, it acts as odontogenic inducer of differentiation of human dental pulp cells and in tooth development.

**STUDY SELECTION, DATA, AND SOURCES:** Vitamin D regulates various signalling pathways in dental network and plays a beneficial role. Synthesis of vitamin D takes place in multiple steps in human body. The natural form of vitamin D is fat soluble in nature and is produced in the skin from 7-dehydrocholesterol molecules. Natural Sunlight through its ultraviolet B (UVB) energy converts the precursor 7-dehydrocholesterol molecules to vitamin D<sub>3</sub>. Advanced and unhealthy lifestyle of modern times has led to the deficiency of vitamin D and metabolic syndrome.

**CONCLUSIONS:** Deficiency of vitamin D also leads to various dental problems including dental caries, gingivitis, and periodontal disease. In this short review, we are discussing the role of vitamin D and importance of its target genes in dental health.

**CLINICAL RELEVANCE:** Vitamin D has a major role in managing the oral health this article updates the clinician with the different genes which are responsible for the regulation of vitamin D in different tissues.

## Introduction

Oral hygiene and dental health are regulated by multifactorial and complex aetiology [1], [2]. Genetic and epigenetic factors are known to play a major role in maintaining the structure of enamel and dentin, immune response, salivary content, and secretory volume [3]. Along with these factors, nutritional status and oral microbiota also can contribute to the overall dental health [4]. Vitamin D is one of the major and very essential vitamins required for the growth, development, and metabolism in human body [5]. It is the only vitamin which can be produced naturally with the help of Sun light by our skin cells [6]. The globalization and modernisation of lifestyle has led to sedentary life, which has rapidly increased the metabolic syndrome among the population at both eastern and western hemisphere of the globe [7]. The metabolic syndrome also has link to the vitamin status in the human body and is directly proportional to the duration of sunshine exposure by individual people [8]. It is well established fact that vitamin D plays major role in calcium absorption, bone formation, fat, and glucose metabolism in the body [5]. It also protects various types of cells from oxidative stress and chronic inflammation [9].

Therefore, vitamin D is a multifaceted molecule with huge beneficial effects on various vital organs of the human body. This review article is focussing and shedding a light more on vitamin D target genes and their role in Dental health [2]. Almost all the molecular actions and functions of vitamin D are mediated through its receptor called vitamin D receptor (VDR). Activated vitamin D binds to its receptor and VDR, and this interaction aids in binding of other VDR interacting partners such as RXR- $\alpha$  to form a protein-protein complex. This VDR, RXR, and vitamin D complex bind to vitamin D response elements (VDRE) region on various target genes and transcriptionally regulates their expression and molecular functions [10]. These vitamin D-induced genes will play crucial role in odontoblastic differentiation of human dental pulp cells (HDPCs) and also calcium-binding proteins and various extracellular matrix proteins which help in mineralization of the tooth and help in enamel, dentin, and cementum growth, stromal vascularization and formation of parenchymal dental pulp tissue [2], [11]. Vitamin D also activates immune cells and induces few defense peptides (such as LL-37) which fight against harmful oral bacteria which are involved in dental caries and gingival inflammation [12]. All the biochemical, molecular, endocrinal, and immunological function of vitamin D has a colossal therapeutic role in overall

dental health. This article gives new insights about the role of Vitamin D-induced genes in Dental health.

### Vitamin D target genes in dental health

There are many genes which are expressed with the inducing action of vitamin D on its receptor through VDRE in odontoblasts and preameloblasts. Some of the most common and important genes which are induced by this vitamin D includes its own receptor VDR, Enamelin, Amelogenin, Dentin phosphoproteins, Dentin matrix protein1 (DMP1), and Cathelicidin antimicrobial protein [2], [13].

### Vitamin D receptor (VDR)

Vitamin D receptor is a nuclear receptor and a ligand activated transcription factor which forms a ligand-receptor complex with hormonally active form of vitamin D, 1,25(OH)<sub>2</sub>D<sub>3</sub>. This receptor-ligand complex along with other transcription factors binds to the promoter regions of many numbers of genes and regulates their expression [14]. It is also known as calcitriol receptor and previously the gene name was known as nuclear receptor subfamily 1, group I, member 1 (NR111). This VDR gene is located on chromosome number 12 in humans, 15 in mouse. It interacts with other related nuclear receptors such PPAR- $\gamma$ , RXR- $\alpha$ , and LXR- $\alpha$  and thyroid hormone receptor (TR) [15], [16]. The molecular weight of this protein is approximately 50 kDa [17]. Almost all the endocrinal and non-endocrinal function of vitamin D take place through this receptor. This receptor induces its own expression levels as well as other gene expression as a transcription factor with the action of vitamin D [18]. Therefore, VDR itself is a vitamin D target gene (Figure 1).

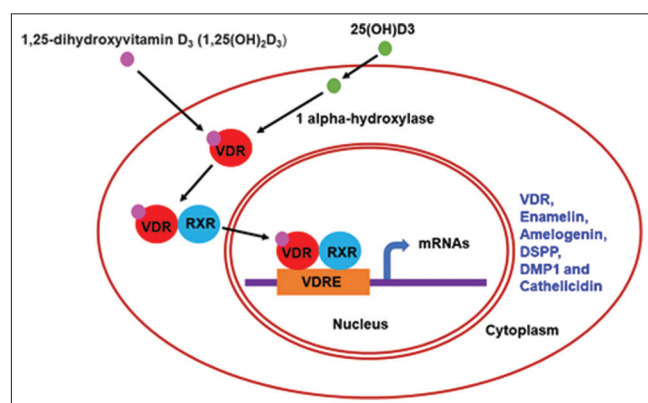


Figure 1: The molecular mechanism of action of vitamin D on its target genes which are associated with dental health

## Amelogenins

Amelogenins are a group of enamel proteins with special features, and in female, these proteins are

expressed from AMELX gene (which is located on X chromosome). On other hand in males, it is expressed as AMELY gene (which is located on Y chromosome) by alternative splicing or proteolysis which encodes these Amelogenins [19]. These amelogenin proteins have molecular weight approximately of 20-kDa with hydrophobic nature. These proteins are involved in amelogenesis, the development of enamel of the teeth. These genes also have VDRE on their promoter region, and therefore, they can be induced by active form of vitamin D through VDR [20], [21]. Therefore, any deficiency in vitamin D has deleterious effects due to less expression of amelogenins. Any mutation in these genes leads to amelogenesis imperfecta a genetic disorder with the characteristic malformations of enamel of the teeth (hypoplasia and hypo mineralization) [22].

### Enamelin

Enamelin is one of the highly conserved and very important protein which plays major role in amelogenesis (enamel development). It is a 65-kDa acidic protein and the genes located on chromosome 4 in humans and 5 in mice and is encoded by the gene called ENAM in humans and is associated with enamel matrix protein (EMPs) in the teeth [23], [24]. It is also known by other names such as ENAM, ADAI, AI1C, and AIH2. The promoter region of this gene has VDRE and vitamin D and VDR can induce its expression very easily to maintain enamel health [21]. This enamelin belongs to the part of the non-amelogenin proteins which comprise approximately 10% of the total matrix proteins of enamel tissues of the teeth. Hence, enamelin is the least abundant (approximately 1–5%) of total matrix proteins of the total enamel tissue. It is very well studied and known that amelogenesis imperfecta (AI) a group of inherited genetic disorders are caused by mutations in the ENAM gene [25]. Thus, this amelogenesis imperfecta (AI) is a heterogeneous, heritable condition with the clinical symptoms of abnormal enamel malformation in the teeth.

### Dentin phosphoprotein

Dentin phosphoprotein is one of the highly essential proteins which are required for regulation of mineralization of dentin in teeth [26]. It is also known as phosphophoryn, and it is highly negative in nature and due to this negative property dentin phosphoprotein can attract large amounts of calcium which is required for dentin mineralization. It belongs to the class of Dentin sialo phosphoprotein (DSPP), a major non-collagenous matrix protein of odontoblasts. In humans it is encoded by a gene called DSPP which is located on chromosome 4 and mouse DSPP gene is located on chromosome number 5 [27]. This DSPP undergoes proteolytically cleaved into two separate proteins called dentin sialoprotein (DSP) and dentin phosphoprotein

(DPP) [28]. The promoter region of DSPP gene has VDRE response element and treatment with vitamin D significantly up regulated the expression of DSPP in human dental pulp cells (HDPCs) *in vitro*. DSPP is also a vitamin D responsive gene and plays significant role in dentin health [11].

### **Dentin matrix protein1 (DMP1)**

This is an extracellular matrix protein and promoter region of this DMP1 gene also has VDRE response element. Treatment with vitamin D positively and significantly up regulated the expression of DMP1 gene in HDPCs *in vitro* [2]. In some cases, vitamin D also acts as a negative repressor for DMP1 gene expression [29]. It is a member of the small integrin-binding ligand N-linked glycoproteins family. In short form, they are called as SIBLING family of proteins and in humans, this matrix protein is encoded by the DMP1 gene which is located on chromosome number 4 and chromosome number 5 in mouse [26], [30]. This protein is a critical mediator and plays very important role in proper mineralization of bone and dentin and is present in various cells of bone and tooth [31]. It is a multifaceted protein with number of acidic domains, phosphorylation sites. It has DNA binding domain as well as cell-cell attachment region. Therefore, in undifferentiated osteoblasts, it is mainly localized in nucleus and acts as a transcription factor and regulates various osteoblast-specific genes expression. Later, it undergoes phosphorylation and relocates to cytoplasm and finally to extracellular matrix, where it is involved in the mineralized matrix formation [32]. This shows the primary importance of vitamin D responsive gene in maintaining proper and harmonious dental health.

### **Cathelicidin anti-microbial protein (CAMP)**

CAMP as name itself reveals that it is an antimicrobial protein, and which is encoded by CAMP gene which is located on chromosome number 3 in humans and chromosome number 9 in mice [33]. Action of vitamin D on immune cells is very important for optimal immune response and maintenance of dental health. Vitamin D is very well known to modulate and induce T-cell responses and for its anti-inflammatory properties through suppression of NF- $\kappa$  transcription factor [34]. Vitamin D is known to boosts innate immune responses by inducing CAMP. In human beings, the CAMP gene encodes a peptide precursor called CAP-18, which is further cleaved into active forms of antimicrobial peptides such as LL-37 and FALL-39 (Figure 2). Before processing, these peptides are stored as inactive peptides primarily in the lysosomes of macrophages and polymorphonuclear leukocytes (PMNs) cells [35]. Therefore, these Cathelicidins peptides LL-37 and FALL-39 serve critical antimicrobial molecules and their role in mammalian innate immune defense against

invasive bacterial infection [36]. These CAMPs family also includes defensins, which are small cysteine-rich cationic proteins known to acts as antimicrobial peptides various types of bacteria. The best example for defensins is beta-defensin 1, which is encoded by the DEFB1 gene. Beta-defensin 1 is an important molecule that confers protection from dental caries and plays major role in dental health [37]. This Beta-defensin 1 is also a vitamin D target gene and it is easily induced by vitamin D and these genes have putative VDR responsive sites (VDRE, VDR responsive elements) on their promoter region [38].

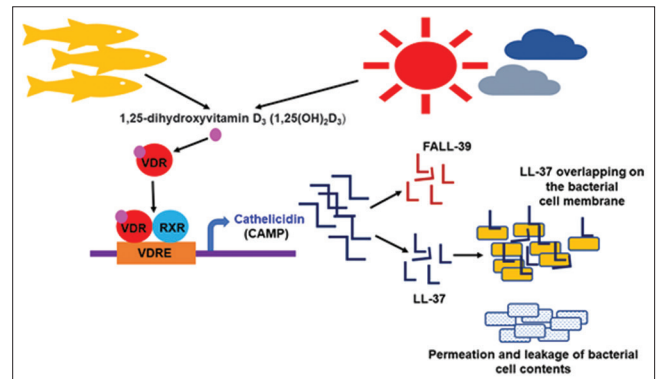


Figure 2: The effect of vitamin D on Cathelicidin antimicrobial protein expression and its antimicrobial activity through LL-37 peptide

### **Mineralization of tooth**

The tooth mineralization process occurs collateral to bone mineralization, any disturbance in mineral metabolism will cause the failure to those that occur in hard tissue. Vitamin D plays a major role in mineralization of bone and tooth, when levels are unregulated it causes defective and hypomineralized tissues which are susceptible to fracture and decay. Circulating vitamin D can initiate a signaling pathway through vitamin D receptors (VDR). VDR is a nuclear receptor and a transcription factor which is gets activated by its ligands mainly through vitamin D and it controls many gene expression through its specific vitamin D elements (VDRE) binding activity [39]. Vitamin D induces and upregulates its own receptor, VDR which, in turn, can induce the expression of many structural gene products, such as calcium-binding proteins and various extracellular matrix proteins (e.g., enamels, amelogenins, dentin sialoglycoproteins, and dentin phosphoproteins), resulting in the formation of dentin and enamel [40], [41]. In addition to this, vitamin D exerts and shows many other activities in the control of the human immune system.

Ameloblasts differentiate from the already existing enamel organ; then, they become organized and polarized in the presecretory phase and then enter the secretory phase, they are partially mineralized organic enamel matrix, synthesized by secretion amelogenin and ameloblastin and smaller amounts of enamelin, tuftelin, and amelotin. Enamel extracellular



matrix (ECM) proteins guides' hydroxyapatite (HAP) crystallite deposition which forms long thin enamel rods and inter rod enamel matrix with crystals of different orientation. These ameloblasts next move to the maturation phase, where the organic matrix is degraded by secretion of proteolytic enzymes including matrix metalloproteinase 20 (MMP20) and kallikrein 4 (KLK4). Many familial associated inherited mutations in enamel-related genes can cause enamel defects under the umbrella of amelogenesis imperfecta, which can be further categorized as hypoplastic (thin enamel layer), hypocalcified (defect in HAP crystals), or hypomaturational (organic matrix insufficiently removed) amelogenesis imperfecta [40], [42], [43]. Finally, this enamel may get reduced and is ultimately lost when the tooth erupts into the oral cavity.

The small integrin binding ligand N-linked glycoprotein (SIBLING) family plays a role in directing mineralization of dentin as well as bone and cementum [44], [45], [46]. The SIBLING family represents a related group of multifunctional, non-collagenous ECM proteins associated with mineralized tissues. In dentin, SIBLING proteins thought to be important in the mineralization process which include dentin sialoprotein (DSP) and dentin phosphoprotein (DPP) [47], [48], [49]. Mutations in the gene DSPP, which encodes both DSP and DPP, have been linked to dentinogenesis imperfecta, a hereditary dentin defect [43], [50], [51], [52]. Dentinogenesis imperfecta features many of the dentin associated defects including disorganized dentinal tubules and disrupted mineralization patterns such as interglobular dentin. The histological results, features, and pattern of interglobular dentin show inability and lack of mineralization foci to merge, leaving regions of hypo mineralized dentin matrix.

Circulating  $1,25(\text{OH})_2\text{D}$  initiates signaling primarily through the vitamin D receptor (VDR), a widely expressed intracellular steroid receptor that, once activated, participates in the modulation of  $1,25(\text{OH})_2\text{D}$ -responsive genes [53], [54]. The VDR and its heterodimeric binding partner, retinoid X receptor, recognize vitamin D-responsive elements in the promoter regions of  $1,25(\text{OH})_2\text{D}$ -responsive genes, thus affecting biological networks including bone, mineral metabolism, immune response, cell life cycle and migration, skeletal muscle, detoxification, and energy metabolism [55]. Expression of several bone- and tooth-related genes is directly regulated by  $1,25(\text{OH})_2\text{D}$ , including SPP1 (gene for osteopontin [OPN]), *BGLAP* (gene for osteocalcin), *LRP5* (gene for low-density lipoprotein-related protein 5), *TNFSF11*, and *TNFSF11B*. Notably, dental cells have been investigated for their ability to respond to  $1,25(\text{OH})_2\text{D}$ -mediated signaling, and ameloblasts, odontoblasts, and cells of the developing periodontium express VDR and  $1,25(\text{OH})_2\text{D}$ -responsive calbindin-D9k and D28k genes [56], [57]. In addition to transcription effects,  $1,25(\text{OH})_2\text{D}$  is reported to produce rapid, non-genomic

(i.e., vitamin D-responsive element-independent) responses, often linked to  $\text{Ca}^{2+}$  fluxes and activation of protein kinase C signaling [53]. Ameloblasts, odontoblasts, osteoblasts, and osteoclasts in the developing craniofacial skeleton were implicated to also participate in the non-genomic pathway based on localization and expression of the membrane-associated rapid-response steroid (MARRS) binding protein for  $1,25(\text{OH})_2\text{D}$  [58], [59].

## Conclusions

The studies clearly shows that vitamin D acts as the master regulator of dental health. Vitamin D has large number of beneficial effects and as a multifaceted molecule, it plays a pivotal role in overall dental health not only by maintaining bone development and mineralization but also through its anti-inflammatory and anti-infectious effects with possible anticancer activity. Deficiency of vitamin D may have various pathological events and diseases and proper nutrition level of vitamin D may protects from all these deficiencies associated maladies.

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