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REVIEW

# Vitamin D and Its Relevance in the Etiopathogenesis of Oral Cavity Diseases

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**Abstract** Vitamin D belongs to a group of fat-soluble secosteroids which assume many roles in the human organism. In humans the most important forms are vitamin D3 and vitamin D2. Their primary function is the regulation of the calcium and phosphorus balance, which promote the growth of healthy bony tissue. Studies over the past few years have revealed a much wider role of vitamin D involving the aging processes, carcinogenesis, the carbohydrate balance as well as the effects on the course of various infections. In this paper we discuss the basic functions of vitamin D in the human body and the mechanisms of its activity and we summarize recent reports on the impact of vitamin D on the oral cavity with a special emphasis on autoimmunologic diseases, including: recurrent aphthous stomatitis, Behçet syndrome and Sjögren syndrome.

**Keywords** Vitamin D · Oral cavity diseases · Oral mucosa · Autoimmunologic conditions

## Introduction

Vitamin D belongs to a group of steroidal organic fat-soluble compounds (Lips 2006; Miller and Portale 2001; Myszka and Klinger 2014). It has long been established that the primary function of vitamin D is the maintenance of the calcium-phosphate balance and the regulation of bony tissue metabolism in the human body (Hewison 2012b; Prietl et al. 2013). In addition, during the past decade it has been shown that vitamin D and its derivatives play an important role as immunomodulating agents, in controlling autoimmunologic conditions, infections and neoplasms (Hewison 2012a; Ponsonby et al. 2005). The identification of vitamin D receptors (VDR) in macrophages, keratinocytes, endothelial and neoplasmatic cells has revealed new extra-bony mechanisms of vitamin D activity, including immunomodulating and antiproliferative functions (Jurutka et al. 2007; Myszka and Klinger 2014). The results of the most recent studies indicate that vitamin D deficiency greatly increases the risk of developing and modifying the course of several autoimmunologically related diseases, including: lupus erythematosus, rheumatoid arthritis, asthma, inflammatory bowel diseases, multiple sclerosis and type I diabetes (Cantorna et al. 2004; Cantorna 2006; Kamen et al. 2006; Mok et al. 2012; Mostowska et al. 2013; Pelajo et al. 2010; Petri et al. 2013).

To date the effects of vitamin D levels on the health of the oral cavity has received little attention in the medical research literature and therefore the subject warrants further examination. Here we present a narrative review of the current research literature on the role of vitamin D in oral cavity disorders, of both soft and hard oral tissues. The literature was sourced through the PubMed using "vitamin D, oral cavity diseases" as key words. Relevant papers were also sought in the references cited within these publications.

## Vitamin D Structure and Metabolism

A common feature of the structure of vitamin D-group compounds is the presence of four rings and a lateral chain in each molecule (Grygiel-Górniak and Puszczewicz 2014;

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Lips 2006). The two basic forms of vitamin D: ergocalciferol (vitamin D2, which appears in plants, yeasts and fungi) and cholecalciferol (vitamin D3, of an animal origin), differ in the structure of the side chain attached to the sterol group (Lips 2006; Miller and Portale 2001; Myszka and Klinger 2014).

Both forms are biologically inactive. The active form in humans is 1α,25-dihydroxy vitamin D [1,25$(OH)_2$D], which is derived from provitamin D3 (7-dehydrocholesterol). Provitamin D3 is present in epithelial basal and spinous layers and in fibroblasts of the dermis. On exposure to sunlight (UVB radiation, 290–315 nm) provitamin D3 is transformed into cholecalciferol, which undergoes photoisomerization at body temperature and is then released into intracellular space and into the blood. The initial hydroxylation of cholecalciferol occurs in liver at the C25 position and is catalyzed by a group of 25-hydroxylases, consisting of cytochromes CYP27A1, CYP3A4 and CYP2R1. This results in the formation of 25-hydroxycholecalciferol (25(OH)D3; calcidiol).

Subsequent hydroxylation catalyzed by 1α-hydroxylasis (CYP27B1) occurs at the C1 and/or C24 position, mainly in the kidneys and to a lesser degree in bony tissue, lungs, liver, placenta, parotid glands, keratinocytes, neoplasmatic cells and macrophages. Hydroxylation at the C1 position produces the biologically active calcitriol [1,25(OH)2D3]. Hydroxylation of calcidiol at C24 position leads to the formation of 24,25-dihydroxycholecalciferol, and is catalyzed by CYP24 a hydroxylase commonly found in body tissues. The key role of this derivative is the metabolism of the cartilage and bony tissue. The serum levels of both hydroxylated derivatives are regulated by a feedback mechanism and are dependent on the 1,25(OH)2D3 concentration in the organism together with the indirect regulatory role of calcium and phosphoric ions, calcitonin, somatotropin, parathyroid hormone and other hormones (Grygiel-Górniak and Puszczewicz 2014; Hewison 2012b; Miller and Portale 2001).

Since 1998 normal serum vitamin D (25(OH)D) concentration for the Central European population have been established as 30–50 ng/ml. Levels between 21 and 29 ng/ml indicate vitamin D insufficiency, while concentrations below 20 ng/ml are defined as vitamin D deficiency and require medical intervention (Holick et al. 2011, Pludowski et al. 2013a, b, Yin and Agrawal 2014). A 25(OH)D serum level of 50–100 ng/ml reflects a high vitamin D supply, which may require some modifications to the vitamin D intake especially for the upper concentrations (>100 ng/ml) at which potentially negative health outcomes may arise. Serum levels in excess of 200 ng/ml are considered to be toxic (Pludowski et al. 2013a, b).

## Vitamin D Mechanism of Action

The mechanism of vitamin D activity is both genomic and extra-genomic (Fernandes de Abreu et al. 2009; Lips 2006; Pawlak and Doboszyńska 2014). The genomic action is mediated by the VDR which belongs to the nuclear receptor subfamily (Jurutka et al. 2007; Valdivielso and Fernandez 2006). It acts as a ligand activated transcription factor by modifying the transcription on binding the selected sequences in the target genes promoter regions, called vitamin D responsive elements. The bonding of 1,25(OH)2D-VDR complex with a specific DNA sequence is preceded by heterodimerization with the retinoid X receptor (Fernandes de Abreu et al. 2009; Tuohimaa 2009; Valdivielso and Fernandez 2006). Vitamin D as calcitriol is known to modify the expression of more than 200 vitamin D-responsive genes. Vitamin D receptors maintain the structure and function of the skeleton and are located in the tissues and organs responsible for calcium-phosphate homeostasis, such as bones, kidneys and parotid glands (Grygiel-Górniak and Puszczewicz 2014). Stumpf et al. (1979), reported the presence of VDRs in other organs, such as skin, brain and immune cells. That led to further research focused on the extra-bony effects of vitamin D (Grygiel-Górniak and Puszczewicz 2014; Lips 2006). The VDR encoding gene is located on the chromosome 12 in position 12q13.11 and consists of two promoter regions, eight protein encoding exons, and six untranslated exons (Martelli et al. 2014). Some specific VDR gene alleles can influence the action of vitamin D on a cellular level, including calcium metabolism, transcription, cellular divisions and initiation of the immunologic response (Myszka and Klinger 2014; Valdivielso and Fernandez 2006). The role of the selected VDR gene polymorphisms in the pathogenesis of inflammatory, neurologic and metabolic conditions is currently an active area of research (Myszka and Klinger 2014).

Extra-genomic vitamin D effects are mediated by the receptors of a different structure to the nuclear VDRs and are classified as membrane-associated protein disulfide isomerases, family A, member 3. The process involves the activation of proteases and cell kinases, followed by the release of prostaglandins. The result is a stimulation of some intracellular signaling paths (like MAP and Raf kinase paths) in various cell types, e.g. in enterocytes, monocytes, vascular smooth muscle cells, osteoblasts and chondrocytes. The interaction with a second messenger such as MAP or cyclic AMP involves calcium channels and leads to increased calcium absorption and osteoclastic bone resorption, as well as the stimulation of cell differentiation and the modulation of muscle function and insulin secretion (Lips 2006). While the effects of genomic

reactions appear within hours or days, the extra-genomic activity is considerably faster (s/min), hence the name "rapid response" (Fernandes de Abreu et al. 2009; Kuryłowicz et al. 2007). Although the rapid response activities are termed "non-genomic or extra-genomic", such actions often modulate the level of transcription of vitamin D responsive genes resulting in changes to gene transcription. The ability to exert rapid effects on a variety of tissues is not restricted to 1α25(OH)2D3. For example, it has been demonstrated that other steroid hormones, including testosterone, estrogen and aldosterone also exert extra-genomic actions by inducing transmembrane signaling paths (Ryan et al. 2015).

## Vitamin D Functions in a Human Body

The basic, so called "classical" effect of vitamin D is the regulation of the calcium-phosphate balance in the organism (Hewison 2012b; Prietl et al. 2013). Vitamin D is involved in metabolic processes of the bony tissue and teeth. By stimulating calcium and phosphorus absorption from the digestive tract, it prevents over-secretion in kidneys where, like the parathyroid hormone, it stimulates the reabsorption of calcium and phosphorus and facilitates their release from the bony tissue by simulating the osteoclasts differentiation during hypocalcemia (Jurutka et al. 2007; Prietl et al. 2013). As a result appropriate calcium concentration in serum is maintained enabling bone and teeth mineralization (St-Arnaud 2008). Insufficient vitamin D supply in childhood or genetically mediated disturbances in vitamin D metabolism, may lead to the development of the rickets—a disease characterized by decreased bone mineralization and low bone mass. The equivalent condition in adults is defined as osteomalacia (Grygiel-Górniak and Puszczewicz 2014).

Vitamin D also exhibits immunomodulating properties (Fletcher et al. 2012; Hewison 2012a; Myszka and Klinger 2014). The presence of VDRs has been detected in T and B lymphocytes, monocytes, macrophages and dendritic cells (Jurutka et al. 2007). Vitamin D stimulates the innate immunologic response by mediating monocytes differentiation into macrophages and enhancing their chemotactic and phagocytic activity (Myszka and Klinger 2014). The activation of innate immunologic response mechanisms occurs via the stimulation of Toll-like (TLR) membrane receptors, located on the surface of polymorphonuclear cells and epithelial cells. The process activates the pathways that produce antibacterial proteins: cathelicidins and defensins (Adams et al. 2007; Bikle 2008; Youssef et al. 2011). Vitamin D also modulates the mechanisms of the adaptive immunologic response: it inhibits the maturation and differentiation of dendritic cells, decreases the secretion of Th1-type cytokines and enhances the secretion of Th2-type cytokines, and promotes the formation of T regulatory lymphocytes (Hewison 2012a; Myszka and Klinger 2014).

Cantorna et al. (1998) demonstrated the immunosuppressive action of vitamin D by showing that the rate of transplant rejections in laboratory mice treated with vitamin D was lower than in the group treated with cyclosporine. At the same time the treatment with vitamin D did not increase the risk of opportunistic infections, including candidiasis (Cantorna et al. 1998).

The anticancerogenic effect of vitamin D is related to the inhibition of neoplastic cell proliferation and the stimulation of cell differentiation, the activation of cell apoptosis and the inhibition of angiogenesis (Kuryłowicz et al. 2007; Tuohimaa 2009). Vitamin D is also involved in the regulation of the cell cycle. After binding of 1,25(OH)2D3 with the VDR in neoplastic cells, cell division is inhibited between stages G1 and G0 (Grygiel-Górniak and Puszczewicz 2014). This may be due to the reduced expression of the cycline-dependent kinases and by the inhibition of the phosphorylation of retinoblastoma and other proteins from this family, e.g. p107 and p130. Another possible mechanism by which vitamin D modifies the cell cycle is the inhibition of prostaglandins activity. However, apoptosis in neoplasmatic cells is probably induced by the regulation of protooncogene *bcl*-2 expression and proapoptic protein Bax and by the release of cytochrome c from mitochondria (Kuryłowicz et al. 2007). The inhibition of angiogenesis is mainly due to the suppression of the activation of interleukin (IL)-8 gene transcription, which is a potent stimulator of neovascularization (Kuryłowicz et al. 2007). Initially the antiproliferative vitamin D effect was observed in leukemic cell lines, but further observations revealed anticancerogenic properties in cell lines derived from prostate, lung, breast and gall bladder cancers (Grygiel-Górniak and Puszczewicz 2014; Kuryłowicz et al. 2007).

The neuromodulating effect of vitamin D is related to the presence of VDRs in the central and peripheral nervous systems (Grygiel-Górniak and Puszczewicz 2014). Here, vitamin D deficiency is a modifier of dementia and cognitive disorders (Fernandes de Abreu et al. 2009; Grygiel-Górniak and Puszczewicz 2014). It has been shown that vitamin D hypovitaminosis increases the risk of sclerosis multiplex, schizophrenia, seasonal affective disorders, Parkinson's and Alzheimer's diseases (Mark and Carson 2006; Ponsonby et al. 2005; Prietl et al. 2013; Tuohimaa et al. 2009). Both deficiency and hypervitaminosis enhance aging of the central nervous system (Tuohimaa 2009; Tuohimaa et al. 2009). Laboratory experiments with rats have indicated local stimulation of choline acetyltransferase in the brain after the administration of

1,25(OH)2D3. However, the withdrawal of vitamin D from the diet of pregnant rats resulted in the attenuation of the nerve growth factor expression both in the tested rats and in their offspring (Grygiel-Górniak and Puszczewicz 2014). Studies of the cell lines showed that vitamin D enhanced the production of proteins responsible for axogenesis, such as synapsin-1 (Fernandes de Abreu et al. 2009). Vitamin D deficiency was also found to decrease the expression of proteins related to organelles cellular transport and synaptic contacts (kinesin, dynactin, connexin 43, drebrin) (Fernandes de Abreu et al. 2009). The neuroprotective effect of vitamin D is related to the stimulation of calcium binding protein synthesis and the inhibition of nitric oxide synthetases (Fernandes de Abreu et al. 2009).

The cardioprotective effect of vitamin D results from its ability to inhibit the renin synthesis and the regulation of myocardial contractibility. High blood pressure and high plasma renin activity correlate with low calcitriol concentration in serum (Grygiel-Górniak and Puszczewicz 2014). Epidemiologic data indicate a greater risk of myocardial infarction, stroke and arteriosclerosis in people with vitamin D deficiency (Grygiel-Górniak and Puszczewicz 2014; Yin and Agrawal 2014). Cardiovascular disease (CVD) incidence and prevalence was found to increase with low serum 25(OH)D levels according to Weyland et al. (2014). The authors demonstrated an inverse association between 25(OH)D levels and CVD risk factors in various populations, locations and circumstances (Weyland et al. 2014). Autier and Gandini (2007) in the meta-analysis of randomized, controlled trials demonstrated a decrement in mortality from cardiovascular events in approximately 7 % of subjects using vitamin D supplements. However, Schnatz and Manson (2014), who reviewed the results of the studies of vitamin D supplementation and cardiovascular risk factors or CVD, concluded that most vitamin D supplementation trials have not demonstrated an improvement in CVD. However, most of the studies used relatively low doses of vitamin D (Schnatz and Manson 2014).

The impact of vitamin D on carbohydrates metabolism is related to its ability to stimulate β cells in pancreatic Langerhans islets in the synthesis of proteins and the transformation of proinsulin into insulin (Szodoray et al. 2008; Żukowska-Szczechowska and Kiszka 2011). Deficiency of vitamin D may lead to the impairment of insulin secretion. However, not all the findings support a direct correlation between serum vitamin D levels and the risk of type 2 diabetes. The previously discussed immunomodulating properties of vitamin D play an important role in controlling the autoimmunologic mechanism associated with the development of type 1 diabetes and in modifying the course of inflammation in type 2 diabetes (Baeke et al. 2010; Ponsonby et al. 2005; Prietl et al. 2013; Szodoray et al. 2008).

Antiinfectious properties of vitamin D have also been reported. The antibacterial effects are related to the stimulation of the synthesis of antibacterial peptides, including cathelicidin and β-defensins 2 and 3 (Bikle 2008; Hewison 2012b; Roider et al. 2013). However, the mechanisms are still unclear. Wang et al. (2013b) reported that the enhancement of the cathelicidin synthesis in the oral epithelial cells is due to CYP24A1 hydroxylase regulation. Liu et al. (2006) found that the induction of cathelicidin was due to up-regulated expression of the VDR and vitamin D-1-hydroxylase. In their study stimulation of TLRs in human macrophages induced the catalytic conversion of 25(OH)D3 to active 1,25(OH)2D3, as well as the expression of the vitamin D receptor and VDR targets (including cathelicidin). They also demonstrated an association between an increased susceptibility of African-American individuals to tuberculosis and low 25-hydroxy vitamin D serum concentrations which were insufficient to support the induction of cathelicidin messenger RNA (Liu et al. 2006).

It was found that upper and lower respiratory tract viral infections respond to the antiviral activity of vitamin D. Vitamin D deficiency partially due to the limited production in the skin as a result of decreased sun exposure in the fall and winter, resulted in more frequent recurrences and higher severity of the disease symptoms (Yin and Agrawal 2014; Youssef et al. 2011). The results confirmed the protective effect of vitamin D with infections such as influenza, HIV and hepatitis (Youssef et al. 2011).

The basic vitamin D functions are presented on Fig. 1.

## The Role of Vitamin D in the Oral Cavity Diseases

As part of its diverse mechanisms of action, vitamin D also modifies the course of various systemic conditions. As a regulator of mineral balance and bony tissue metabolism and a potent antiinflammatory and immunomodulating agent, vitamin D can significantly affect oral cavity homeostasis. The role of vitamin D as a modifier of autoimmunologic conditions of the oral cavity is of considerable importance. Many studies have reported the role of vitamin D as a modifying factor in recurrent aphthous stomatitis (RAS) and related syndromes such as: Behçet's disease and PFAPA (periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis), in Sjögren's syndrome, periodontitis and oral squamous cell carcinoma (OSCC) (Bazrafshani et al. 2002; Karatay et al. 2011; Khabbazi et al. 2014; Martelli et al. 2011, 2014; Sun et al. 2002; Toniato Borges et al. 2009).

Table 1 presents the results of studies into the impact of vitamin D on oral cavity diseases.


**Fig. 1** Systemic effects of vitamin D

## RAS

RAS is an oral condition characterized by the presence of erosions and ulcers appearing regularly on the oral mucosa. The lesions are painful and their size ranges from 1 mm to a few cm in diameter. The lesion size is one of the diagnostic criteria used in RAS classification, which is divided into three categories: major (Sutton's; MaRAS), minor (Mikulicz's; MiRAS) and herpetiform (HeRAS) aphthae (Natah et al. 2004; Scully et al. 2003). Although the etiopathogenesis of this condition is not fully understood, several studies have suggested that the main cause is related to genetically mediated immunologic disturbances modified by environmental factors, which may include: stress, smoking and iron, zinc or vitamin B12 deficiencies (Bazrafshani et al. 2002; Scully et al. 2003; Natah et al. 2004). The autoimmunologic background of RAS and the immunomodulating effects of vitamin D in modifying the course of the disease is of great significance. An attempt to determine the influence of polymorphisms in VDR encoding genes and tumor necrosis factor (TNF)-α and TNF-β encoding genes on frequency of minor RAS (MiRAS) was made by Bazrafshani et al. (2002), who analyzed biologic material from 95 subjects with RAS and from 90 healthy controls. There appeared to be no correlation between the disease frequency, the tested VDR and proinflammatory cytokine polymorphisms. However, a positive correlation was observed in patients with Behcet's syndrome and PFAPA. In both diseases the presence of recurrent aphthae in the oral cavity was one of the crucial symptoms (Do et al. 2008; Faezi et al. 2014; Karatay et al. 2011; Khabbazi et al. 2014; Stagi et al. 2014). The findings indicate the need for further studies on a larger population with RAS.

## Behçet's Disease

Behçet's disease is a systemic condition with an autoimmunologic background, characterized by the concomitant presence of oral and genital ulcerations, arthritis, uveitis and retinal vasculitis, neurological disturbances and less commonly erythema nodosum, deep vein thrombosis and gastro-intestinal inflammations (Karatay et al. 2011;

**Table 1** A summary results of studies on the role of vitamin D in the oral cavity diseases

| Oral cavity disease | Population studied (contributing country) | Species tested | Results | References |
|---|---|---|---|---|
| RAS | S: 95 (MiRAS)<br>C: 90<br>(Great Britain) | VDR gene polymorphisms | No correlation | Bazrafshani et al. (2002) |
| Behçet's syndrome | S: 32<br>C: 31<br>(Turkey) | 25[OH]D (serum) | ↓ level in study group | Karatay et al. (2011) |
| | S: 48<br>C: 47<br>(Iran) | 25[OH]D (serum) | ↓ level in study group | Khabbazi et al. (2014) |
| | S: 112<br>C: 112<br>(Iran) | 25[OH]D (serum) | ↓ level in study group | Faezi et al. (2014) |
| | S: 41<br>C: 15<br>(South Korea) | 25[OH]D (serum) | ↓ level in study group | Do et al. (2008)) |
| PFAPA | S: 25<br>C: 25<br>(Italy) | 25[OH]D (serum) | ↓ number of fever episodes, ↓ duration of episodes after vitamin D supplementation | Stagi et al. (2014) |
| Sjögren's syndrome | S: 41<br>C: 41<br>(Danmark) | 25[OH]D (serum) | ↓ level in study group | Bang et al. (1999) |
| | S: 25<br>C: 15<br>(Hungary) | 25[OH]2D3 (serum) | No correlation | Szodoray et al. (2010) |
| | S: 35<br>C: 1674<br>(Danmark) | 1α,25[OH]2D3<br>(serum)<br>25[OH]D (serum) | No correlation<br>↓ level in study group | Muller et al. (1990) |
| | S: 30<br>C: 46<br>(Italy) | 25[OH]D3 (serum) | No correlation | Baldini et al. (2014) |

**Table 1** continued

| Oral cavity disease | Population studied (contributing country) | Species tested | Results | References |
|---|---|---|---|---|
| Periodontitis | S: 24 (AP)<br>37 (EOP)<br>C: 37<br>(Japan) | VDR gene polymorphisms | ↑ TaqI (Tt) frequency in EOP<br>No correlation in AP and C groups | Sun et al. (2002) |
| | S: 198<br>(Japan) | VDR gene polymorphisms | ↑ TaqI (TT) frequency in CP | Tachi et al. (2003) |
| | S: 51 (AgP)<br>57 (CP)<br>C: 100<br>(Great Britain) | VDR gene polymorphisms | ↑ TaqI (TT) frequency in CP | Brett et al. (2005) |
| | S: 79 (CP)<br>224 (AgP)<br>C: 231<br>(Great Britain) | VDR gene polymorphisms | ↑ TaqI (TT) frequency in smokers with CP | Nibali et al. (2008) |
| | S: 107<br>C: 121<br>(China) | VDR gene polymorphisms | ↑ TaqI (TT) frequency in CP | Wang et al. (2009) |
| | S: 115 (CP)<br>58 (AgP)<br>C: 65<br>(Italy) | VDR gene polymorphisms | ↑ TaqI (TT) frequency in CP ↑ TaqI (tt) in AgP | Martelli et al. (2011) |
| | S: 99 (CP)<br>63 (AgP)<br>C: 126<br>(Jordan) | VDR gene polymorphisms | ↑ BsmI (bb) and ApaI (aa) frequency in CP, ↓ in AgP | Karasneh et al. (2013) |
| | S: 30<br>C: 30<br>(Brazil) | VDR gene polymorphisms | ↑ TaqI (Tt) frequency in CP | Toniato Borges et al. (2009) |
| | S: 562<br>(USA) | Total vitamin D daily intake | Total vitamin D intake ≥800 IU/day compared to <400 IU/day → ↓ severe periodontal disease and ↓rate of moderate-to-severe ABL for higher doses | Alshouibi et al. (2013) |
| | S: 920<br>(USA) | 25[OH]D (serum) | ↓ level →<br>↑ rate of gingival bleeding | Millen et al. (2013) |
| | S: 23 (on vitamin D supplement)<br>C: 28 (no supplement)<br>(USA) | Vitamin D supplementation (≥ 400 IU/day) | No influence on periodontal tissues after 12 months of supplementation | Garcia et al. (2011) |

**Table 1** continued

| Oral cavity disease | Population studied (contributing country) | Species tested | Results | References |
|---|---|---|---|---|
| | S: 11202 (USA) | 25[OH]D (serum) | ↓ level → ↑ PAL in people ≥50 years old | Dietrich et al. (2004) |
| Candidiasis | S: 84 ($HIV^+$) (USA) | 25[OH]D (serum) | ↓ level → ↑ risk of OC | Sroussi et al. (2012) |
| Tooth caries | S: 144 (S-ECC) C: 122 (Canada) | 25[OH]D (serum) | ↓ level in study group | Schroth et al. (2013) |
| | S: 106 (Argentina) | CaI | ↓CaI → ↑DMFT and PI | Antonenko et al. (2015) |
| | | 25[OH]D (serum) | No correlation | |
| OSCC | S: 110 (OSCC) C: 122 (Serbia) | VDR and CYP24A1 gene polymorphisms | CYP24A1 gene polymorphism (rs2296241) ↑ susceptibility to OSCC; wild type ff genotype of FokI polymorphism → worse survival | Zeljic et al. (2012) |

*RAS* recurrent aphthous stomatitis, *CP* chronic periodontitis, *AgP* aggressive periodontitis, *AP* adult periodontitis, *EOP* early-onset periodontitis, *OC* oral candidiasis, *S-ECC* severe early childhood caries, *OSCC* oral squamous cell carcinoma, *S* study group, *C* control group, *PAL* periodontal attachment loss, *CaI* calcium intake, *DMFT* decayed-missing-filled teeth index, *PI* Löe Silness plaque index, *PFAPA* periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis

Khabbazi et al. 2014). As with RAS, the etiopathogenesis of the syndrome has not been defined. It was found that as a consequence of the disease the autoimmunologic reaction leads to vasculitis (Karatay et al. 2011; Khabbazi et al. 2014). Based on the observation of 32 patients with Behçet's disease, Karatay et al. (2011) demonstrated that their serum 25-hydroxy vitamin D levels were significantly lower compared to healthy controls. Similar observations were reported by Khabbazi et al. (2014) who compared serum levels of vitamin D in 48 subjects with Behçet's disease and 47 healthy volunteers as a control group. Also in a study by Faezi et al. (2014) the serum vitamin D concentrations were found to be significantly lower in patients with Behçet's syndrome than in controls. Do et al. (2008) demonstrated that during the active phase of Behçet's disease the expression of TLR-2 and TLR-4 was found to increase in monocytes, which correlated with a lower 25-hydroxy vitamin D level compared with a control group of healthy adults. The modulating effect of vitamin D on the expression of monocytic TLRs suggests a potential for therapeutic utilization of vitamin D in patients with Behçet's disease (Do et al. 2008).

## PFAPA Syndrome

Stagi et al. (2014) found that vitamin D deficiency is an important modifier of immunologic response in PFAPA syndrome, where aphthous ulcers in the oral cavity are one of the characteristic symptoms which is accompanied by the episodes of fever, pharyngitis and cervical lymphadenopathy. The disease belongs to the wider group of periodic fever syndromes (Stagi et al. 2014). To date the etiopathogenesis of the condition remains undefined, but an autoimmunologic association has been suggested. It was found that the supplementation of vitamin D with a dose of 400 IU (international units) per day during the winter season resulted in an improvement of clinical condition in 25 patients with a fully symptomatic version of the disease. This was inferred by the reduction in the number and the duration of fever episodes (Stagi et al. 2014).

## Sjögren Syndrome

Sjögren syndrome is a disease with an autoimmunologic background, the course of which, may be modified by vitamin D. The primary form of this condition causes progressive damage to the secretory salivary cells, which leads to xerostomia together with a dysfunction in tear secretion, followed by conjunctivitis and keratitis. In its secondary form the symptoms are accompanied by other autoimmunologic conditions, for example rheumatoid

arthritis or systemic lupus erythematosus (Baldini et al. 2014; Bang et al. 1999; Muller et al. 1990). The etiopathogenetic mechanisms of this disease is not has fully understood. There are conflicting reports on effects of vitamin D levels on the development and course of Sjögren syndrome. Bang et al. (1999) observed an inverse correlation between the serum 25(OH)D level and the severity of clinical symptoms and the concentration of inflammatory markers in 41 patients with primary Sjögren's syndrome (pSS). A reduction of 25(OH)D levels in subjects with pSS was also reported by Muller et al. (1990). However, both the study and the control groups had similar concentrations of the most active vitamin D metabolite—1,25(OH)2D3. In contrast, Baldini et al. (2014) did not observe a reduction in serum 25(OH)D3 level in patients with primary Sjögren syndrome when compared with the controls. Their observations however were conducted on a relatively small study group (30 patients, 46 healthy controls) (Baldini et al. 2014). Despite this limitation, similar conclusions were reported by Szodoray et al. (2010).

## Periodontitis

Vitamin D can modify the course of periodontitis due to its immunomodulatory and antimicrobial properties or via the effects on bone metabolism. Local production of 1,25(OH)2D by various immune cells is a key factor in the regulation of the innate and acquired immune response at local sites of inflammation. The results of in vitro and in vivo experiments have shown the ability of 1,25(OH)2D to inhibit the monocyte production of pro-inflammatory cytokines IL-1b and TNF-α both of which play central roles in the pathogenesis of periodontitis by impairing wound healing and inducing bone resorption (Jimenez et al. 2014; Stein et al. 2014).

Individual susceptibility to periodontitis is largely dependent on the genetic profile of the host which modulates the composition of the subgingival microbiota (Martelli et al. 2014). Several studies have revealed the presence of particular VDR gene allelic forms which influence the frequency of periodontitis. *Taq*I polymorphism in VDR gene, particularly the of TT genotype, was associated with an increased risk of chronic periodontitis (CP) as reported by Tachi et al. (2003), Wang et al. (2009), Brett et al. (2005), Nibali et al. (2008) and Martelli et al. (2011) while Toniato Borges et al. (2009) observed a higher incidence of CP in patients with Tt genotype. Sun et al. (2002) suggested the involvement of Tt genotype in the development of early-onset periodontitis. The evidence for the participation of *Apa*l polymorphisms in periodontitis is unequivocal. Inagaki et al. (2003) and Naito et al. (2007) reported that the AA genotype was associated with a higher risk of severe CP and with more advanced alveolar bone loss. However, Karasneh et al. (2013) observed that CP occurred more frequently in subjects with AA genotype. In addition, studies of the impact of *Bsm*l and *Fok*l polymorphisms on the development of periodontal inflammation have provided ambiguous results. The role of *CDX2* polymorphisms in the etiopathogenesis of periodontitis has not been confirmed (Martelli et al. 2011).

An inverse relationship between periodontal disease indicators and vitamin D levels was demonstrated in a study by Alshouibi et al. (2013), where the total vitamin D intake ≥800 IU/day was associated with lower odds of severe periodontal disease and moderate-to-severe alveolar bone loss compared with an intake <400 IU/day. It was also observed that low serum levels of vitamin D adversely affect the healing process in post-operative wounds after periodontal surgical procedures. According to Bashutski et al. (2011) vitamin D serum concentrations ≥20 ng/ml prior to periodontal surgery in patients with severe chronic periodontitis was associated with improved clinical attachment levels and reduced probing depth 12 months after surgery. In observations reported by Dietrich et al. (2004) and Miley et al. (2009) a higher serum vitamin D level in periodontal patients correlated with a less severe loss of the clinical attachment. Millen et al. (2013) demonstrated an inverse correlation between the serum vitamin D level and the frequency of gum bleeding and periodontitis in postmenopausal women. However, vitamin D supplementation (400 IU/day for 1 year) did not significantly improve the condition of periodontal tissues during routine periodontal procedures in 23 dental clinic patients (Garcia et al. 2011).

The results of experimental studies have confirmed the role of vitamin D as a modifier of immune response in the periodontium. Li et al. (2013) found that supplementation with vitamin D reduced alveolar bone loss, reduced serum TNF-α levels and inhibited the NF-κβ expression in the gingival epithelium of diabetic mice. An enhanced expression of VDR and a reduced expression of TLR-4 in the gingival epithelium was demonstrated in the study. It was also suggested that the regulation of periodontitis occurred via JAK (Janus family kinase) 1/STAT (signal transducer and activator of transcription) three signaling path (Wang et al. 2013a). In an in vitro study Tang et al. (2013) demonstrated that vitamin D reduced periodontitis related to *Porphyromonas gingivalis* by the inhibition of IL-8 expression in periodontal ligament cells.

## Oral Candidiasis

Sroussi et al. (2012) showed that vitamin D deficiency in HIV-positive patients increased the risk of oral candidiasis. This opportunistic infection develops as a result of

immunodeficiency in infected subjects. The other predisposing factors for candidiasis in this group included a decrement in the salivary concentration of the antimicrobial peptide calpronectin, the adverse effect of antiviral drugs and some specific sexual practices and habits. In the study by Sroussi et al. (2012) a CD4 lymphocyte count <200 and vitamin D deficiency appeared to be the most crucial environmental factors leading to candidiasis in HIV-positive subjects.

## Oral Cancer

The anticarcinogenic properties of vitamin D have also been reported. Head and neck squamous cell carcinomas, which include OSCC, were found to be related to high mortality and low survival rate. Susceptibility to oral cancer is partially attributable to environmental risk factors including smoking, alcohol abuse, poor oral hygiene and human papilloma virus infections. The identification of genes involved in OSCC is still under investigation.

Studies by Zeljic et al. (2012) of a cohort of 110 patients with OSCC and 122 healthy controls demonstrated that the presence of VDR and CYP24A1 gene polymorphisms affected oral cancer risk and survival. CYP24A1 gene polymorphism (rs2296241) was found to increase susceptibility to oral cancer, while the wild type ff genotype of FokI polymorphism was associated with lower survival rates. In a study of predictors of vitamin D status, and incidence of cancer and mortality Giovannucci et al. (2006) found that low vitamin D serum levels was associated with an increase in the incidence of cancer and mortality in men, particularly for digestive-system cancers. Based on multivariable Cox proportional hazards models it was concluded that an increment of 25 nmol/L in predicted 25(OH)D levels was associated with a 17 % reduction in total cancer incidence and 45 % reduction in digestive-system cancer mortality (Giovannucci et al. 2006). In a study on the OSCC cell lines, Sundaram et al. (2014) demonstrated that 1,25(OH)2D3 increased the expression of microsomal hyroxylase CYP2R1 genes, belonging to the supra family cytochrome P450 monooxygenases, and VDR genes. This led to the inhibition of the proliferation of OSCC cell lines. The authors concluded that in future, vitamin D analogues could be used as therapeutic agents for limiting the growth of OSCC-type tumors (Sundaram et al. 2014).

## Bone and Teeth Metabolism

The level of vitamin D also affects the condition of hard tissues of the oral cavity and therefore it may play a role in the mineralization of teeth and bony tissue regeneration. A study on mice showed that vitamin D improved osseointegration after the insertion of dental implants. Histomorphometric analysis revealed that animals which received vitamin D supplements, had higher values of bone-implant contact and bone volume around the implants compared with the controls (Liu et al. 2014). In another study Zhang et al. (2007) demonstrated that the reduction in VDR resulted in the development of teeth structure disturbances in experimental mice. The teeth structure abnormalities included disturbed dentine production, enlargement of the teeth chambers, decrement of the dentine thickness and mineralization and a reduction in dentine tubules number (Zhang et al. 2007).

## Tooth Carries

Dentin and enamel defects formed during tooth development due to disturbed vitamin D metabolism may increase the incidence of tooth caries. Several reports have demonstrated an association between serum vitamin D concentration and caries susceptibility Schroth et al. (2013) observed that pre-school children with decreased serum vitamin D and calcium levels are significantly more prone to the development of teeth caries. In their study caries-free children were twice as likely to have optimal 25(OH)D concentrations ($\geq$75 nmol/L) while those with severe early childhood caries (S-ECC) were almost three times more likely to have deficient levels (<35 nmol/L). The poor nutritional status of children with S-ECC may in part, lead to a severely reduced quality of life due to oral pain and disturbed sleep, which in turn, may alter their eating habits (Schroth et al. 2013). In addition, Grant (2011) observed that solar UVB exposure from the different regions of US, inversely correlated with dental caries and tooth loss. The mechanism of action was most probably related to the stimulation of vitamin D production and the induction of antimicrobial peptides such as cathelicidin and defensins. Serum 25(OH)D concentrations at or above 30–40 ng/ml were considered to reduce the development of caries (Grant 2011). Furthermore, meta-analysis of 24 controlled clinical trials that evaluated supplemental dietary vitamin D or ultraviolet radiation in over 2800 patients suggested that vitamin D may prevent dental caries (Hujoel 2013). Supplementary ultraviolet radiation, vitamin $D_3$ and vitamin $D_2$ were associated with a significant reduction in caries compared with no supplement (Hujoel 2013). However, in Antonenko et al. (2015) study, who evaluated the association between oral health, calcium intake (CaI) and vitamin D nutritional status in 106 young females, there was a negative correlation between CaI and caries, as measured by the decayed-missing-filled teeth index and Löe Silness

plaque index. Moreover, the CaI/protein intake index correlated negatively with tooth loss. No correlations were found between 25(OH)D levels and the studied parameters, which contrasts with the previously cited reports on the impact of vitamin D deficiency on the susceptibility to carries (Antonenko et al. 2015).

## Conclusion

The role of vitamin D in maintaining the oral cavity homeostasis is indubitable. Its impact on the bony tissue and teeth metabolism has been recognized for many years in addition to periodontologic and implantologic treatment. Other, more recently discovered non-classical mechanisms of action include a role in the etiopathogenesis of numerous autoimmunologic, infectious and neoplasmatic diseases of the oral cavity. The limited data of the effects of vitamin D on the course of oral cavity disturbances indicate the necessity for broader and more profound research in this area. A better understanding of vitamin D mechanisms of action and the confirmation of its role as one of the environmental factors capable of modifying the course of several oral cavity conditions creates an opportunity for the implementation of treatment and prophylaxis methods based on properly adjusted vitamin D supplementation in general medicine and in dentistry.

## References


Adams JS, Liu PT, Chun R et al (2007) Vitamin D in the human immune response. Ann NY Acad Sci 1117:94–105

Alshouibi EN, Kaye EK, Cabral HJ et al (2013) Vitamin D and periodontal health in older men. J Dent Res 92:689–693

Antonenko O, Bryk G, Brito G et al (2015) Oral health in young women having low calcium and vitamin D nutritional status. Clin Oral Investig 19:1199–1206

Autier P, Gandini S (2007) Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials. Arch Intern Med 167:1730–1737

Baeke F, Takiishi T, Korf H et al (2010) Vitamin D: modulator of the immune system. Curr Opin Pharmacol 10:482–496

Baldini C, Sedie AD, Luciano N et al (2014) Vitamin D in "early" primary Sjögren syndrome: Does it play a role in influencing disease phenotypes? Rheumatol Int 34:1159–1164

Bang B, Asmussen K, Sorensen OH et al (1999) Reduced 25-hydroxy vitamin D levels in primary Sjogren's syndrome. Correlation to disease manifestations. Scand J Rheumatol 28:180–183

Bashutski JD, Eber RM, Kinney JS et al (2011) The impact of vitamin D status on periodontal surgery outcomes. J Dent Res 90:1007–1012

Bazrafshani MR, Hajeer AH, Ollier WE et al (2002) Recurrent aphthous stomatitis and gene polymorphisms for the inflammatory markers TNF-α, TNF-β and the vitamin D receptor: no association detected. Oral Dis 8:303–307

Bikle DD (2008) Vitamin D and the immune system: role in protection against bacterial infection. Curr Opin Nephrol Hypertens 17:348–352

Brett PM, Zygogianni P, Griffiths GS et al (2005) Functional gene polymorphisms in aggressive and chronic periodontitis. J Dent Res 84:1149–1153

Cantorna MT (2006) Vitamin D and its role in immunology: multiple sclerosis and inflammatory bowel disease. Prog Biophys Mol Biol 92:60–64

Cantorna MT, Hullett DA, Redaelli C et al (1998) 1,25-Dihydroxy vitamin D3 prolongs graft survival without compromising host resistance to infection or bone mineral density. Transplantation 66:828–831

Cantorna MT, Zhu Y, Froicu M et al (2004) Vitamin D status, 1,25-dihydoxyvitamin D3, and the immune system. Am J Clin Nutr 80(6 suppl):717S–1720S

Dietrich T, Joshipura KJ, Dawson-Hughes B et al (2004) Association between serum concentrations of 25-hydroxy vitamin D3 and periodontal disease in the US population. Am J Clin Nutr 80:108–113

Do JE, Kwon SY, Park S et al (2008) Effects of vitamin D on expression of Toll-like receptors of monocytes from patients with Behcet's disease. Rheumatology 47:840–848

Faezi ST, Ansari N, Paragomi P et al (2014) Vitamin D deficiency in patients with Behcet's disease. J Diabetes Metab Disord 13:18

Fernandes de Abreu DA, Eyles D, Féron F (2009) Vitamin D, neuro-immunomodulator: implications for neurodegenerative and autoimmune diseases. Psychoneuroendocrinology 34(Suppl 1):S265–S277

Fletcher JM, Basdeo SA, Allen AC et al (2012) Therapeutic use of vitamin D and its analogues in autoimmunity. Recent Pat Inflamm Allergy Drug Discov 6:22–34

Garcia MN, Hildebolt CF, Miley DD et al (2011) One-year effects of vitamin D and calcium supplementation on chronic periodontitis. J Periodontol 82:25–32

Giovannucci E, Liu Y, Rimm EB et al (2006) Prospective study of predictors of vitamin D status and cancer incidence and mortality in men. J Natl Cancer Inst 98:451–459

Grant WB (2011) A review of the role of solar ultraviolet-B irradiance and vitamin D in reducing risk of dental caries. Dermatoendocrinol 3:193–198

Grygiel-Górniak B, Puszczewicz M (2014) Vitamin D—a new look in medicine and rheumatology. Postepy Hig Med Dosw 68:359–368

Hewison M (2012a) An update of vitamin D and human immunity. Clin Endocrinol 76:315–325

Hewison M (2012b) Vitamin D and immune function: an overview. Proc Nutr Soc 71:50–61

Holick MF, Binkley NC, Bischoff-Ferrari HA et al (2011) Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 96:1911–1930

Hujoel PP (2013) Vitamin D and dental caries in controlled clinical trials: systemic review and meta-analysis. Nutr Rev 71:88–97

Inagaki K, Krall EA, Fleet JC et al (2003) Vitamin D receptor alleles, periodontal disease progression, and tooth loss in the VA dental longitudinal study. J Periodontol 74:161–167

Jimenez M, Giovannucci E, Krall Kaye E et al (2014) Predicted vitamin D status incidence of tooth loss and periodontitis. Public Health Nutr 17:844–852

Jurutka PW, Bartik L, Whitfield GK et al (2007) Vitamin D receptor: key roles in bone mineral pathophysiology, molecular mechanism of action and novel nutritional ligands. J Bone Miner Res 22(Suppl 2):V2–V10

Kamen DL, Cooper GS, Bouali H et al (2006) Vitamin D deficiency in systemic lupus erythematosus. Autoimmun Rev 5:114–117

Karasneh JA, Ababneh KT, Taha AH et al (2013) Association of vitamin D receptor gene polymorphisms with chronic and aggressive periodontitis in Jordanian patients. Eur J Oral Sci 121:551–558

Karatay S, Yildirim K, Karakuzu A et al (2011) Vitamin D status in patients with Behcet's disease. Clinics (Sao Paulo) 66:721–723

Khabbazi A, Rashtchizadeh N, Ghorbanihaghjo A et al (2014) The status of serum vitamin D in patients with active Behcet's diseases compared with controls. Int J Rheum Dis 17:430–434

Kuryłowicz A, Bednarczuk T, Nauman J (2007) The influence of vitamin D deficiency on cancers and autoimmune diseases development (Article in Polish). Endokrynol Pol 58:140–152

Li H, Xie M, Li W et al (2013) 25-Hydroxy vitamin D3 ameliorates periodontitis by modulating the expression of inflammation-associated factors in diabetic mice. Steroids 78:115–120

Lips P (2006) Vitamin D physiology. Prog Biophys Mol Biol 92:4–8

Liu PT, Stenger S, Li H et al (2006) Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. Science 311:1770–1773

Liu W, Zhang S, Zhao D et al (2014) Vitamin D supplementation enhances the fixation of titanium implants in chronic kidney disease mice. PLoS One 9:e95689

Mark BL, Carson JAS (2006) Vitamin D and autoimmune disease-implications for practice from the multiple sclerosis literature. J Am Diet Assoc 106:418–423

Martelli FS, Mengoni A, Martelli M et al (2011) VDR TagI polymorphism is associated with chronic periodontitis in Italian population. Arch Oral Biol 56:1494–1498

Martelli FS, Martelli M, Rosati C et al (2014) Vitamin D: relevance in dental practice. Clin Cases Miner Bone Metabol 11:15–19

Miley DD, Garcia MN, Hildebolt CF et al (2009) Cross-sectional study of vitamin D and calcium supplementation effects in chronic periodontitis. J Periodontol 80:1433–1439

Millen AE, Hovey KM, LaMonte MJ et al (2013) Plasma 25-hydroxy vitamin D concentrations and periodontal disease in post-menopausal women. J Periodontol 84:1243–1256

Miller WL, Portale AA (2001) Genetics of vitamin D biosynthesis and its disorders. Best Pract Res Clin Endocrinol Metab 15:95–109

Mok CC, Birmingham DJ, Leung HW et al (2012) Vitamin D levels in Chinese patients with systemic lupus erythematosus: relationship with diseases activity, vascular risk factors and atherosclerosis. Rheumatology 51:644–652

Mostowska A, Lianeri M, Wudarski M et al (2013) Vitamin D receptor gene BsmI, FokI, ApaI and TaqI polymorphisms and the risk of systemic lupus erythematosus. Mol Biol Rep 40:803–810

Muller K, Oxholm P, Sorensen OH et al (1990) Abnormal vitamin D3 metabolism in patients with primary Sjogren's syndrome. Ann Rheum Dis 49:682–684

Myszka M, Klinger M (2014) The immunomodulatory role of vitamin D (Article in Polish). Postepy Hig Med Dosw 68:865–878

Naito M, Miyaki K, Naito T et al (2007) Association between vitamin D receptor gene haplotypes and chronic periodontitis among Japanese men. Int J Med Sci 4:216–222

Natah SS, Konttinen YT, Enattah NS et al (2004) Recurrent aphthous ulcers today: a review of growing knowledge. Int J Oral Maxillofac Surg 33:221–234

Nibali L, Parkar M, D'Aiuto F et al (2008) Vitamin D receptor polymorphism (–1056 Taq-I) interacts with smoking for the presence and the progression of periodontitis. J Clin Periodontol 35:561–567

Pawlak J, Doboszyńska A (2014) Vitamin D in allergic disorders (Article in Polish). Postepy Hig Med Dosw 68:1152–1170

Pelajo C, Lopez-Benitez JM, Miller LC (2010) Vitamin D and autoimmune rheumatologic disorders. Autoimmun Rev 9:507–510

Petri M, Bello KJ, Fang H et al (2013) Vitamin D in system, ic lupus erythematosus. Arthritis Rheum 65:1865–1871

Pludowski P, Holick MF, Pilz S et al (2013a) Vitamin D effects on musculoskeletal health, immunity, autoimmunity, cardiovascular disease, cancer, fertility, pregnancy, dementia and mortality—a review of recent evidence. Autoimmun Rev 12:976–989

Pludowski P, Karczmarewicz E, Bayer M et al (2013b) Practical guidelines for the supplementation of vitamin D and the treatment of deficits in Central Europe-recommended vitamin D intakes in the general population and groups at risk of vitamin D deficiency. Endokrynol Pol 64:319–327

Ponsonby AL, Lucas RM, van der Mel AF (2005) UVR, vitamin D and three autoimmune diseases—multiple sclerosis, type 1 diabetes, rheumatoid arthritis. Photochem Photobiol 81:1267–1275

Prietl B, Treiber G, Pieber TR et al (2013) Vitamin D and immune function. Nutrients 5:2502–2521

Roider E, Ruzicka T, Schauber J (2013) Vitamin D, the cutaneous barrier, antimicrobial peptides and allergies: Is there a link? Allergy Asthma Immunol Res 5:119–128

Ryan JW, Anderson PH, Morris HA (2015) Pleiotropic activities of vitamin D receptors—adequate activation for multiple health outcomes. Clin Biochem Rev 36:53–61

Schnatz PF, Manson JE (2014) Vitamin D and cardiovascular disease: an appraisal of the evidence. Clin Chem 60:600–609

Schroth RJ, Levi JA, Sellers EA et al (2013) Vitamin D status of children with severe early childhood caries: a case–control study. BMC Pediatr 13:174

Scully C, Gorsky M, Lozada-Nur F (2003) The diagnosis and management of recurrent aphthous stomatitis: a consensus approach. J Am Dent Assoc 134:200–207

Sroussi HY, Burke-Miller J, French AL et al (2012) Association among vitamin D, oral candidiasis, and calprotectinemia in HIV. J Dent Res 91:666–670

Stagi S, Bertini F, Rigante D et al (2014) Vitamin D levels and effects of vitamin D replacement in children with periodic fever, aphthous stomatits, pharyngitis, and cervical adenitis (PFAPA) syndrome. Int J Pediatr Otorhinolaryngol 78:964–968

St-Arnaud R (2008) The direct role of vitamin D on bone homeostasis. Arch Biochem Biophys 473:225–230

Stein SH, Livada R, Tipton DA (2014) Re-evaluating the role of vitamin D in the periodontium. J Periodont Res 49:545–553

Stumpf WE, Sar M, Reid FA et al (1979) Target cells for 1,25-dihydroxy vitamin D3 in intestinal tract, stomach, kidney, skin, pituary, and parathyroid. Science 206:1188–1190

Sun LJ, Meng HX, Cao CF et al (2002) Relationship between vitamin D receptor gene polymorphisms and periodontitis. J Periodont Res 37:263–267

Sundaram K, Sambandam Y, Tsuruga E et al (2014) 1α,25-dihydroxy vitamin D3 modulates CYP2R1 gene expression in human oral squamous cell carcinoma tumor cells. Horm Cancer 5:90–97

Szodoray P, Nakken B, Gaal J et al (2008) The complex role of vitamin D in autoimmune diseases. Scand J Immunol 68:261–269

Szodoray P, Horvath IF, Papp G et al (2010) The immunoregulatory role of vitamins A, D and E in patients with primary Sjögren's syndrome. Rheumatology 49:211–217

Tachi Y, Simpuku H, Nosaka Y et al (2003) Vitamin D receptor gene polymporphism is associated with chronic periodontitis. Life Sci 73:3313–3321

Tang X, Pan Y, Zhao Y (2013) Vitamin D inhibits the expression of interleukin-8 in human periodontal ligament cells stimulated with *Porphyromonas gingivalis*. Arch Oral Biol 58:397–407

Toniato Borges MA, de Figueireiredo LC et al (2009) Microbiological composition associated with vitamin D receptor gene polymorphism in chronic periodontitis. Braz Oral Res 23:203–208

Tuohimaa P (2009) Vitamin D and aging. J Steroid Biochem Mol Biol 114:78–84

Tuohimaa P, Keisala T, Minasyan A et al (2009) Vitamin D nervous system and aging. Psychoneuroendocrinology 34(Suppl 1):S278–S286

Valdivielso JM, Fernandez E (2006) Vitamin D receptor polymorphisms and diseases. Clin Chim Acta 371:1–12

Wang C, Zhao H, Xiao L (2009) Association between vitamin D receptor gene polymorphisms and severe chronic periodontitis in a Chinese population. J Periodontol 80:603–608

Wang Q, Li H, Xie H et al (2013a) 25-hydroxy vitamin D3 attenuates experimental periodontitis through downregulation of TLR4 and JAK1/STAT3 signaling in diabetic mice. J Steroid Biochem Mol Biol 135:43–50

Wang Q, Zhang W, Li H et al (2013b) Effects of 25-hydroxy vitamin D3 on cathelicidin production and antibacterial function of human oral keratinocytes. Cell Immunol 283:45–50

Weyland PG, Grant BD, Howie-Esquivel (2014) Does sufficient evidence exist to support a casual association between vitamin D status and cardiovascular disease risk? An assessment using Hill's criteria for casuality. Nutrients 6:3403–3430

Yin K, Agrawal DK (2014) Vitamin D and inflammatory diseases. J Inflamm Res 7:69–87

Youssef DA, Miller CW, El-Abbassi AM et al (2011) Antimicrobial implications of vitamin D. Dermatoendocrinol 3:220–229

Zeljic K, Supic G, Stamenkovic Radak M et al (2012) Vitamin D receptor, CYP27B1and CYP24A1gene polymorphism association with oral cancer risk and survival. J Oral Pathol Med 41:779–787

Zhang X, Rahemtulla FG, MacDougall MJ et al (2007) Vitamin D receptor deficiency affects dentin maturation in mice. Arch Oral Biol 52:1172–1179

Żukowska-Szczechowska E, Kiszka B (2011) Vitamin D deficiency—diagnosis and management in order to reduce cardiovascular risk in patients with diabetes. Forum Zab Metabol 2:151–157