Vitamin D: Pharmacology and Clinical Challenges in Oral Health Care

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Abstract

Vitamin D is a hormone, produced endogenously through cutaneous transformation of 7-dehydrocholesterol by UVB-irradiation with skeletal and non-skeletal functions and could be involved in oral health conditions especially periodontitis. Vitamin D main mechanism of action occurs through binding to its intracellular receptor. In this article, we aim to review the beneficial role of vitamin D in dentistry. Articles related to vitamin D and oral health were screened and reviewed with the main findings and clinical implications presented. Vitamin D deficiency prevalence is high especially among the elderly and is associated with oral health complications such as periodontitis with a possible role of vitamin D supplementation in oral health conditions' management. The review discusses the main findings as although the majority of the literature demonstrates vitamin D essential role, some research suggest excess vitamin D supplementation could lead to other health issues. Thus, further research is needed to define vitamin D target levels and establish effective strategies for managing patients suffering from oral health conditions especially periodontitis. Improving the knowledge of dental practitioners, periodontologists and pharmacists regarding vitamin D deficiency implications in oral health conditions could guide the management of oral conditions especially periodontitis.

Keywords: Vitamin D, Oral health care, Vitamin D receptor, Periodontitis, Oral health conditions

Introduction

Vitamin D is a fat-soluble hormone with endocrine and autocrine functions (Razzaque, 2018) and could be obtained through absorption or ultraviolet irradiation (Powers and Gilchrest, 2012). Vitamin D is then activated through hydroxylation process in the liver and kidney to produce the active hormone $1,25(OH)_2D$ (Powers and Gilchrest, 2012). The active hormone acts as a signalling molecule and an essential factor of calcium and phosphorus homeostasis for bony tissue growth (Slebioda *et al.*, 2016). $1,25(OH)_2D$ is also involved in essential life processes such as proliferation, differentiation, apoptosis, immune and hormonal regulation (Radlovic *et al.*, 2012). Several factors could reduce vitamin D synthesis such as sun avoidance practices, sun protection creams and melanin in skin (Macdonald, 2013). These factors could increase the risk of vitamin D deficiency, a major global health issue affecting more than one billion person worldwide and leading to health conditions such as pre-eclampsia, childhood dental caries, periodontitis, cardiovascular and neurological disorders (Holick, 2017). As periodontitis is considered an inflammatory condition caused by the imbalance between the virulence factors produced by microorganisms and the inflammatory host response, appreciating the role of vitamins especially vitamin D in modulating the immune system is of primary importance. Other risk factors for periodontal disease progression include smoking, diabetes, obesity and steroids (Goyal *et al.*, 2017).
In this review, we aim to review the current developments in our understanding of vitamin D pharmacology and how vitamin D deficiency could influence the pathogenesis of oral conditions such as periodontitis. Research articles were reviewed after a comprehensive search using the Medline (PubMed) for the following

MESH terms “dental and vitamin D”, “Oral health and vitamin D” and “Oral disorders and vitamin D”.

Vitamin D Pharmacology

Vitamin D main target is the ubiquitously expressed nuclear vitamin D receptor (VDR) (Radlovic *et al.*, 2012), which is a regulator of insulin, aromatase and osteocalcin (Boisen *et al.*, 2017). 1,25$(OH)_2$D affect receptor activator of nuclear factor κB ligand (RANKL) expression (Nakamichi and Takahashi, 2015; Takahashi, 2013) and regulate fibroblast growth factor 23 (FGF23) - a bone-derived hormone (Bhattacharyya *et al.*, 2012; Nakamura *et al.*, 2009). RANKL is one of two cytokines expressed by osteoblasts and involved in bone marrow macrophages differentiation into osteoclasts (Mizoguchi, 2011) alongside constitutively macrophage-colony stimulating factor (M-CSF) (Nakamichi *et al.*, 2018). Osteoblasts acts as regulatory cells to control calcium homeostasis, where rapid non-genomic actions include activation of voltage-sensitive Ca^{2+} channels, elevation of intracellular Ca^{2+} concentrations, induction of phospholipid turnover and activation of second messenger systems. Longer term actions of vitamin D binding to its nuclear receptors include target genes transcription such as the genes coding bone matrix proteins (Farach-Carson and Ridall, 1998). Vitamin D also interacts with calcium-binding proteins such as calbindin and osteocalcin with a role in dentinogenesis and amelogenesis (Berdal *et al.*, 1995; Berdal *et al.*, 1989).

This interaction alters the renal calcium and phosphate reabsorption (Razzaque, 2012) with dental matrix protein-1, an osteocyte product, participating in FGF23-mediated regulation of phosphorus homeostasis (Civitelli and Ziambaras, 2011). Vitamin D possesses other non-calcaemic actions such as anti-proliferative, pro-differentiative and immunomodulatory activities (Nagpal *et al.*, 2001). VDR was

discovered in several immunological cells such as T-, B- lymphocytes, macrophages, mast cells and regulatory T cells (Tregs); while vitamin D acts as a regulator of immune function by suppressing inflammatory cytokines such as tumour necrosis factors (TNF) and interferon gamma and stimulating anti-inflammatory cytokines generation (Figure 1) (Toniato *et al.*, 2015). VDR genetic polymorphisms plays an important role in the pathogenesis of several conditions such as external apical root resorption and permanent loss of dental root structure (Nieto-Nieto *et al.*, 2017) and there is association between VDR polymorphisms and fluorosis susceptibility pattern (Pramanik and Saha, 2017). VDR polymorphisms were also involved in periodontal disease through changes in bone mineral density or immunomodulatory effects (Martelli *et al.*, 2014; Amano *et al.*, 2009). Another study highlighted the association of VDR polymorphisms with aggressive and chronic periodontitis in a Taiwanese population (Ho *et al.*, 2017), while a recent meta-analysis in Chinese population showed that VDR TaqI polymorphism was not associated with periodontitis risk, raising the need for further research in this field (Ji *et al.*, 2016).

Deficiency of vitamin D and Oral disorders:

Teeth are mineralized organs composed of three hard tissues: enamel, dentin and cementum, while supported by the surrounding alveolar bone. Various oral diseases such as metabolic bone diseases - disorders of bone remodelling - often first diagnosed from abnormalities in the oral cavity or on dental radiographs (Zachariasen, 1990) could result from inadequate vitamin D level (Uwitonze *et al.*, 2018). Low bone-mineral density could occur in alveolar bone and people with osteoporosis could suffer from increased risk of tooth loss (Stewart and Hanning, 2012), while rickets' sufferers possessed defective dentition (Foster *et al.*, 2014), poor development and calcification of the alveolus leading to loss of lamina dura and

periodontal ligament with defects in the dentinoenamel junction and cementum (Cohen and Becker, 1976). X-linked hypophosphataemic (XLH) rickets sufferers have decreased renal phosphate reabsorption, hypophosphatemia and inappropriate vitamin D levels with abnormally high pulp volume/tooth volume ratio, thin enamel and spontaneous dental abscesses without any signs of dental caries or trauma (Sabandal *et al.*, 2015; Kienitz *et al.*, 2011; Seow, 2003). Patients with rickets-like genetic diseases such as pycnodysostosis also show obtuse mandibular angle and dental abnormalities (Ma, 2013).

Osteoporosis is a common disease in middle aged post-menopausal women with bone weakness affecting the ridges holding dentures leading to need of new dentures and continued teeth loss (Bandela *et al.*, 2015; Faine, 1995). Several studies confirmed the correlation between osteoporosis and alveolar bone loss in periodontal disease (Loza *et al.*, 1996). At the pharmacological concentration, vitamin D could be used in osteoporosis management (Nakamichi *et al.*, 2018) and supporting tooth retention (Krall, 2006).

Other clinical conditions associated with vitamin D deficiency such as hypophosphatasia are characterized by defective mineralization of bone and/or teeth with premature exfoliation of primary teeth, dry mouth, multiple dental caries and abnormal morphology (Geng *et al.*, 2018). Calcium and vitamin D supplements should be also considered in Rothmund-Thomson syndrome, characterized by skeletal and dental abnormalities (Wang and Plon, 2019). Vitamin D could reduce orthodontic treatment time with advantages including reduction in predisposition to caries, gingival recession and root resorption (Nimeri *et al.*, 2013).

Medication-related osteonecrosis of the jaw (MRONJ) is a severe adverse drug reaction leading to the progressive bone destruction in the maxillofacial region,

caused by antiresorptive medications such as bisphosphonates (Rosella *et al.*, 2016). Osteoclast inhibitors such as denosumab; used in patients with bone metastases; could lead to jaw osteonecrosis (1.8%) and hypocalcaemia (9.6%); where calcium and vitamin D supplementation with good oral hygiene and regular dental reviews are required (Domschke and Schuetz, 2014; Vescovi and Nammour, 2010; Pittman *et al.*, 2017) (Table 1).

Vitamin D and periodontitis/ peri-implant diseases

Increasing evidence connect low vitamin D serum levels and gingival inflammation (Stein *et al.*, 2014), while severe periodontal disease could occur with low dietary calcium and vitamin D (Genco and Borgnakke, 2013). Scientific results have shown that vitamin D supplementation could reduce rate of alveolar bone loss (Intini *et al.*, 2014). On the other hand, other studies highlighted the association between elevated plasma vitamin D levels with aggressive periodontitis (Liu *et al.*, 2009), while initial periodontal therapy reduced systemic vitamin D significantly (Liu *et al.*, 2010) (Table 1). The same research group demonstrated expression of 1alpha-hydroxylase in human gingival fibroblasts and periodontal ligament cells tissue cultures (Liu *et al.*, 2012) and that vitamin D induced cationic antimicrobial protein expression, an effect reduced by blocking VDR (Gao *et al.*, 2018). Other researchers showed vitamin D role in stimulating the antibacterial defence of gingival cells (McMahon *et al.*, 2011), further supporting vitamin D actions on the immune system in periodontal tissues.

Osseointegration-based dental implants success depends on the stable integration and maintenance of implant fixtures in alveolar bone with complex molecular pathways involving vitamin D (Nishimura, 2013) and a prominent role of osteocytes and immune cells in dental implant osseointegration and maintenance (Insua *et al.*,

2017). Vitamin D deficiency slows implant osseointegration and increases the risk of graft infection (Choukroun *et al.*, 2014). Thus it is recommended that following implant fixation, medications to enhance osseointegration such as vitamin D should be given (Apostu *et al.*, 2017) (Table 1).

Vitamin D and paediatric oral health

Clinical trials identified vitamin D as a promising caries-preventive agent (Hujoel, 2013) with clear association between maternal vitamin D concentrations at term and paediatric dental caries (Theodoratou *et al.*, 2014) as low prenatal or maternal vitamin D levels could lead to enamel defects (Berdal *et al.*, 2000) and detrimental effect on bone and teeth development, while vitamin D supplementation during pregnancy was associated with reduction in the risk of infancy dental caries (Karras *et al.*, 2016) (Table 1).

Discussion

Vitamin D is produced photochemically from its provitamin, 7-dehydrocholesterol (Davies, 1989) with an important role in regulating calcium and maintaining healthy teeth (Rowe, 2004). Vitamin D influences phosphate co-transporters in the intestine and kidney, thus affecting phosphate balance (Ohnishi and Razzaque, 2013). Vitamin D is metabolised by a hepatic 25-hydroxylase into 25-hydroxyvitamin D and by a renal 1alpha-hydroxylase into $1,25(OH)_2D$ (Zittermann, 2003). Vitamin D has immunomodulatory and anti-inflammatory properties (Jeffery *et al.*, 2016), supporting its beneficial oral health effects through direct effect on bone metabolism (Stein *et al.*, 2014) as calbindins and alkaline phosphatase handling proteins - affecting calcium and phosphate balance- are present in dental mineral tissues (Berdal *et al.*, 2000).

The prevalence of vitamin D deficiency is increasing worldwide (Wimalawansa *et al.*, 2018) and associated with oral health disorders such as dental caries and periodontal disease (Uwitonze *et al.*, 2018). The most advantageous vitamin D serum levels for dental health are 75 nmol/l (30 ng/ml) with 800 IU (20 microg) of cholecalciferol administration per day needed (Bischoff-Ferrari, 2014) and even higher oral doses (1,800 to 4,000 IU) could be used (Bischoff-Ferrari *et al.*, 2010). Periodontitis is characterized by bone resorption, local inflammatory bone loss and tooth loss with osteoporosis as a risk factor; some evidence describes vitamin D supplementation as a concomitant management (Wang and McCauley, 2016), while other evidence highlighted an association between elevated plasma vitamin D and aggressive periodontitis with a role of vitamin D in stimulating the antibacterial defence of gingival cells (McMahon *et al.*, 2011; Liu *et al.*, 2012).

Residents of long-term care facilities are considered at high risk for oral health conditions as they often lack basic dental care with unnecessary tooth loss, periodontal disease (Wick, 2010) and prevalence of vitamin D insufficiency (Nakamura, 2006) and individuals with neurodevelopmental disorders, intellectual disabilities and eating disorders generally have low vitamin D and adequate calcium/vitamin D supplementation is recommended (Drabkin *et al.*, 2017) in those risk groups with careful medication monitoring to prevent tooth loss, combat caries and decrease periodontal disease (Grant *et al.*, 2015). Clinicians have an important role as many inherited disorders have oral manifestations detected by dental radiographs (Witkop, 1976) to optimise vitamin D levels (Leizaola-Cardesa *et al.*, 2016) especially in periodontitis (Palacios *et al.*, 2009). Clinicians should be cautious as prolonged/ disproportionate consumption of vitamin D may lead to intoxication, even without clear signs of hypervitaminosis D (Razzaque, 2018; Ballmer, 1996).

Although, oral vitamin D intakes up to 250 µg/day have not been associated with harm (Zittermann *et al.*, 2013), clinicians should avoid recommending high serum concentrations (Sanders *et al.*, 2013) especially that the routine use of intermittent vitamin D high-dose was associated with increased risk of falls or fractures (Choi *et al.*, 2017) and tissue/ organ damages (Razzaque, 2018).

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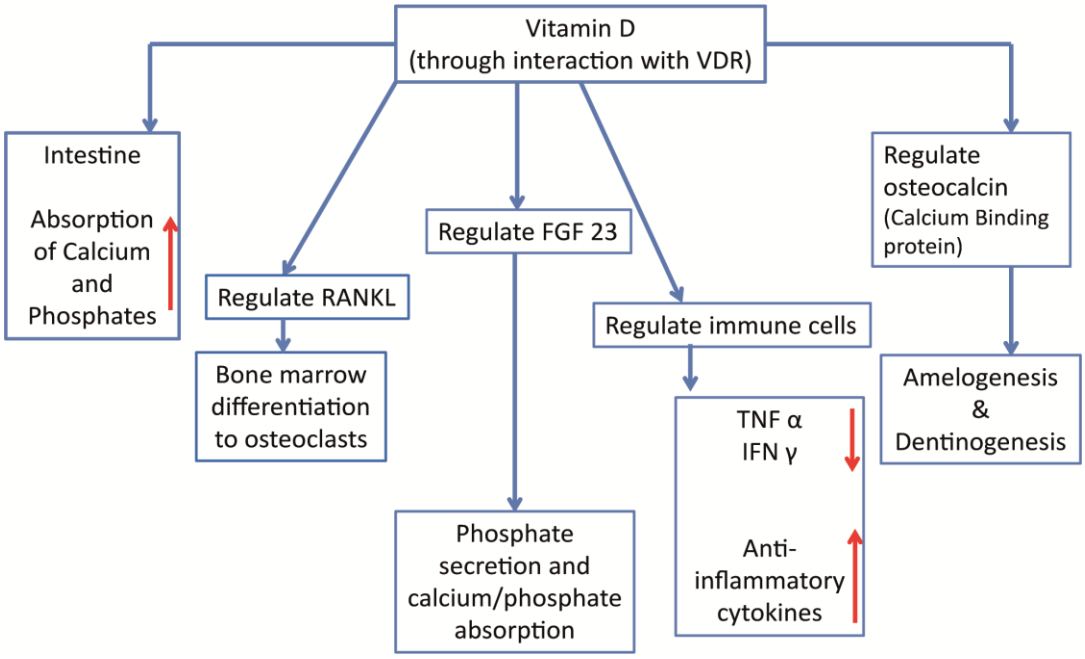
Figure 1: Pharmacology of Vitamin D



Vitamin D major mechanisms of action through its interaction with VDR. This interaction affects calcium/phosphates absorption, bone marrow differentiation to osteoclasts, phosphate secretion, cytokines production and amelogenesis/dentinogenesis through cellular signalling molecules such as RANKL and FGF 23.

Table 1: Vitamin D and Oral Health Care

Condition	Summary of findings regarding vitamin D (as per current clinical research)
Defective dentition/metabolic bone diseases	Possible role for vitamin D supplementation in management of these conditions.
Osteoporosis	Vitamin D supplementation is considered as a recommended management.
Medication-related osteonecrosis of the jaw	Vitamin D supplementation is recommended, further clinical studies are needed.
Periodontitis	Low calcium and vitamin D lead to periodontal disease, however, some studies highlighted association of elevated vitamin D levels with aggressive periodontitis - further studies needed.
Dental implant success	Vitamin D deficiency slows implant osteointegration and increase risk of graft rejection - medications to enhance osseointegration such as vitamin D should be given following implant fixation.
Paediatric caries	Vitamin D is considered a promising caries preventive agent.