Vitamin D: Pharmacology and Clinical Challenges in Oral Health Care

Eriny Girgis[1] and Ayman Antoun Reyad[2]

[1]City of Coventry Health Centre, Coventry and Warwickshire Partnership NHS trust, CV1 4FS; [2]School of Pharmacy, University of Wolverhampton, WV1 1LY

Abstract

Vitamin D is a hormone produced endogenously through cutaneous transformation of 7-dehydrocholesterol by UVB-irradiation and exerts its effects through binding to its intracellular receptor. It has skeletal and non-skeletal functions and could be involved in oral health conditions especially periodontitis. In this review, we report the beneficial roles of vitamin D related to oral health. Vitamin D deficiency prevalence is high especially among the elderly and is associated with oral health complications such as periodontitis with a possible role and effects of vitamin D supplementation in the managerment of oral health conditions. 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, periodontists and pharmacists regarding vitamin D deficiency implications in oral health conditions could guide the management of oral conditions such as periodontitis.

Keywords: Vitamin D, oral health care, vitamin D receptor, periodontitis, oral health

Introduction

Vitamin D is a fat-soluble hormone with endocrine and autocrine functions (Razzaque, 2018) and can be obtained through absorption or ultraviolet irradiation (Powers and Gilchrest, 2012). Vitamin D is activated through a 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 is an essential factor for calcium and phosphorus homeostasis required for bone metabolism (Slebioda *et al.*, 2016). $1,25(OH)_2D$ is also involved in essential processes such as cell proliferation, differentiation, apoptosis, immune and hormonal regulation (Radlovic *et al.*, 2012). Several factors can reduce vitamin D synthesis such as sun avoidance practices, sun protection creams and melanin deposits in the skin (Macdonald, 2013). These factors increase the risk of vitamin D deficiency, a major global health issue, affecting more than one billion people worldwide and leads to adverse 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).

This review considers 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

The main target of Vitamin D 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). $1,25(OH)_2D$ affects receptor activator of nuclear factor κB ligand (RANKL) expression (Nakamichi and Takahashi, 2015; Takahashi, 2013) and also regulates 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 is involved in the differentiation of bone marrow macrophages into osteoclasts (Mizoguchi, 2011).

Correspondence to: Ayman Antoun Reyad, School of Pharmacy, University of Wolverhampton, WV1 1LY.
Email: A.AntounReyad@wlv.ac.uk

This process is also assisted by constitutively macrophage-colony stimulating factor (M-CSF) (Nakamichi *et al.*, 2018). Osteoblasts act as regulatory cells to control calcium homeostasis, through expressed non-genomic actions including 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 transcription of target genes such as those coding for bone matrix proteins (Farach-Carson and Ridall, 1998). Vitamin D also interacts with calcium-binding proteins such as calbindin and osteocalcin playing a significant role in dentinogenesis and amelogenesis (Berdal *et al.*, 1995; Berdal *et al.*, 1989). This interaction alters 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 is expressed by several immunological cells such as T-, B- lymphocytes, macrophages, mast cells and regulatory T cells (Tregs). Vitamin D also 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 play important roles in the pathogenesis of several conditions such as external apical root resorption and permanent loss of dental root structure (Nieto-Nieto *et al.*, 2017). There is also an association between VDR polymorphisms and fluorosis susceptibility pattern (Pramanik and Saha, 2017). VDR polymorphisms are also involved in periodontal disease via changes in bone mineral density or immunomodulatory effects (Martelli *et al.*, 2014; Amano *et al.*, 2009). The association of VDR polymorphisms with aggressive and chronic periodontitis has been demonstrated in a Taiwanese population (Ho *et al.*, 2017). On the other hand a recent meta-analysis has shown that VDR TaqI polymorphism is 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 dental pulp, periodontal ligament and alveolar bone. Metabolic bone diseases - disorders of bone remodelling - can often be first diagnosed from abnormalities in the oral cavity or on dental radiographs (Zachariasen, 1990) and may result from inadequate vitamin D levels (Uwitonze *et al.*, 2018). Low bone-mineral density can also occur in alveolar bone and people with osteoporosis may suffer from increased risk of tooth loss (Stewart and Hanning, 2012).

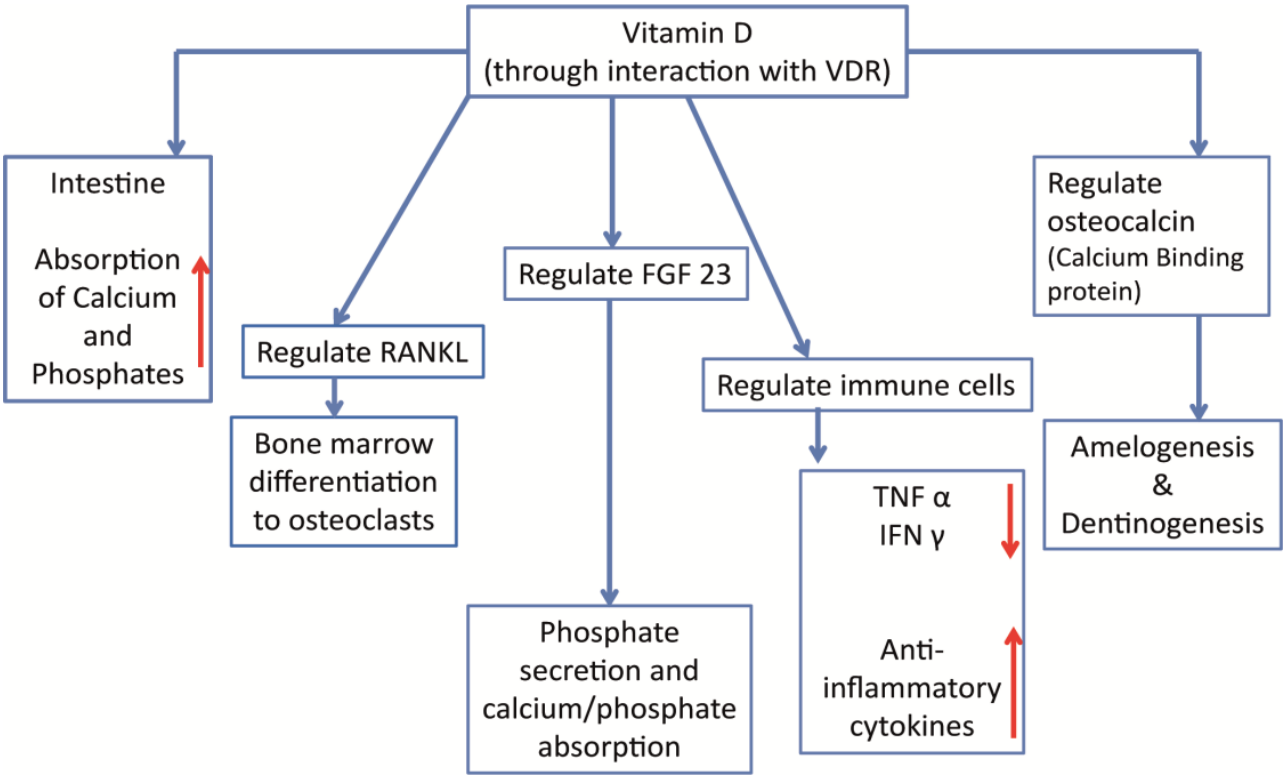

Figure 1: Pharmacology of Vitamin D
Vitamin D major mechanisms of action through its interaction with VDR. This interaction affects calcium/phosphates absorption, bone marrow differentiation to osteoclasts, phosphate secretion, cytokines production and amelogenesis/dentinogenesis through cellular signalling molecules such as RANKL and FGF.

Patients suffering from Rickets have a defective dentition (Foster *et al.*, 2014), poor tooth and bone 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 mandibular and dental abnormalities (Ma, 2013).

Osteoporosis is a common disease in middle aged postmenopausal women with bone weakness affecting the alveolar ridges that support dentures and leads to the need for new dentures and continued tooth loss (Bandela *et al.*, 2015; Faine, 1995). Several studies have confirmed the correlation between osteoporosis and alveolar bone loss in individuals suffering from periodontal disease (Loza *et al.*, 1996). Vitamin D supplementation can be used in the managvement of osteoporosis management (Nakamichi *et al.*, 2018) and to assist in 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 supplementation may reduce orthodontic treatment time, 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, and may be caused by the use of antiresorptive medications such as bisphosphonates (Rosella *et al.*, 2016). Osteoclast inhibitors such as denosumab; used in patients with bone metastases; can also lead to jaw osteonecrosis (1.8%) and hypocalcaemia (9.6%). Vitamin D supplementation in conjunction with good oral hygiene and regular dental reviews are required for these patients (Domschke and Schuetz, 2014; Vescovi and Nammour, 2010; Pittman *et al.*, 2017) (Table 1).

Vitamin D and periodontitis/ peri-implant diseases

Increasing evidence indicates that low vitamin D serum levels may correlate with gingival inflammation (Stein *et al.*, 2014). Furthermore, severe periodontal disease may be associated with low dietary calcium and vitamin D (Genco and Borgnakke, 2013). Studies have shown that vitamin D supplementation can reduce the rate of alveolar bone loss in these patients (Intini *et al.*, 2014). On the other hand, other studies have demonstrated the association between elevated plasma vitamin D levels with aggressive periodontitis (Liu *et al.*, 2009), and that initial periodontal therapy can reduce systemic vitamin D levels significantly (Liu *et al.*, 2010) (Table 1). Expression of 1alpha-hydroxylase has been demonstrated in cultures of human gingival fibroblasts and periodontal ligament cells tissue (Liu *et al.*, 2012). Vitamin D induced cationic antimicrobial protein expression can be reduced by blocking VDR in these cells (Gao *et al.*, 2018). Vitamin D may also play a role in stimulating the antibacterial defence of gingival cells (McMahon *et al.*, 2011), further supporting a role for vitamin D actions on the immune system in periodontal tissues.

The success of osseointegrated dental implants depends on the stable integration and maintenance of implant fixtures in alveolar bone. This process involves complex molecular pathways involving vitamin D (Nishimura, 2013) and a prominent role of osteocytes and immune cells (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 could be considered (Apostu *et al.*, 2017) (Table 1).

Vitamin D and paediatric oral health

Clinical trials have identified vitamin D as a promising caries-preventive agent (Hujoel, 2013). An association has been noted between maternal vitamin D concentrations at term and paediatric dental caries (Theodoratou *et al.*, 2014). Low prenatal or maternal vitamin D levels can lead to enamel defects (Berdal et al., 2000) and detrimental effects on bone and tooth development. Vitamin D supplementation during pregnancy is 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 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), implying a beneficial oral health effect through direct effects on bone metabolism (Stein *et al.*, 2014). Calbindins and alkaline phosphatase handling proteins - affecting calcium and phosphate balance- are present in dental mineral tissues (Berdal *et al.*, 2000).

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.

The prevalence of vitamin D deficiency is increasing worldwide (Wimalawansa *et al*., 2018) and is associated with oral health disorders such as dental caries and periodontal disease (Uwitonze *et al*., 2018). The best 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 considered (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 supports the use of vitamin D supplementation as an adjunct to conventional periodontal treatment (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 to play in monitoring optimal vitamin D levels (Leizaola-Cardesa *et al*., 2016) especially in periodontitis patients (Palacios *et al*., 2009) and inherited disorders of vitamin D metabolism that have oral manifestations (Witkop, 1976). Clinicians should be cautious as prolonged/ disproportionate consumption of vitamin D may be toxic, 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).

Acknowlegements

No funding sources were provided and No conflicts of interests exist.

References

Amano Y, Komiyama K and Makishima M. Vitamin D and periodontal disease. *Journal of Oral Science* 2009; **51:** 11-20.

Apostu D, Lucaciu O, Lucaciu G D et al.. Systemic drugs that influence titanium implant osseointegration. *Drug Metabolism Reviews* 2017; **49:** 92-104.

Ballmer P E. Vitamins and metals: possible hazards for humans. *Schweizerische Medizinische Wochenschrift* 1996; **126:** 607-611.

Bandela V, Munagapati B, Karnati R K, Venkata G R and Nidudhur S R. Osteoporosis: Its Prosthodontic Considerations - A Review. *Journal of Clinical and Diagnostic Research* 2015; **9:** ZE01-4.

Berdal A, Cuisinier-Gleizes P, Balmain N et al. The systemic environment and dental development. From the clinical to the molecular approach. *Revue de Stomatologie et de Chirurgie Maxillo-faciale* 1989; **90:** 111-114.

Berdal A, Lezot F, Nefussi J R and Sautier J M. Mineralized dental tissues: a unique example of skeletal biodiversity derived from cephaic neural crest. *Morphologie : Bulletin de l'Association des Anatomistes* 2000; **84:** 5-10.

Berdal A, Papagerakis P, Hotton D, Bailleul-Forestier I and Davideau J L. Ameloblasts and odontoblasts, target-cells for 1,25-dihydroxyvitamin D3: a review. *The International Journal of Developmental Biology* 1995; **39:** 257-262.

Bhattacharyya N, Chong W H, Gafni R I and Collins M T. Fibroblast growth factor 23: state of the field and future directions. *Trends in Endocrinology and Metabolism* 2012; **23:** 610-618.

Bischoff-Ferrari H A. Optimal serum 25-hydroxyvitamin D levels for multiple health outcomes. *Advances in Experimental Medicine and Biology* 2014; **810:** 500-525.

Bischoff-Ferrari H A, Shao A, Dawson-Hughes B, Hathcock J, Giovannucci E and Willett W C. Benefit-risk assessment of vitamin D supplementation. *Osteoporosis international* 2010; **21:** 1121-1132.

Boisen I M, Bollehuus Hansen L, Mortensen L J, Lanske B, Juul A and Blomberg Jensen M. Possible influence of vitamin D on male reproduction. *The Journal of Steroid Biochemistry and Molecular Biology* 2017; **173:** 215-222.

Choi H S, Min Y K, Byun D W, Hahn M H, Kim K M, Kim B J and Oh K W. Korean Society for Bone and Mineral Research Task Force Report: Perspectives on Intermittent High-dose Vitamin D Supplementation. *Journal of Bone Metabolism* 2017; **24:** 141-145.

Choukroun J, Khoury G, Khoury et al. Two neglected biologic risk factors in bone grafting and implantology: high low-density lipoprotein cholesterol and low serum vitamin D. *Journal of Oral Implantology* 2014; **40:** 110-114.

Civitelli R and Ziambaras K. Calcium and phosphate homeostasis: concerted interplay of new regulators. *Journal of Endocrinological Investigation* 2011; **34:** 3-7.

Cohen S and Becker G L. Origin, diagnosis, and treatment of the dental manifestations of vitamin D-resistant rickets: review of the literature and report of case. *Journal of the American Dental Association* 1976; **92:** 120-129.

Davies M. High-dose vitamin D therapy: indications, benefits and hazards. *International Journal for Vitamin and Nutrition Research* 1989; **30:** 81-86.

Domschke C and Schuetz F. Side effects of bone-targeted therapies in advanced breast cancer. *Breast Care* 2014; **9:** 332-336.

Drabkin A, Rothman M S, Wassenaar E, Mascolo M and Mehler P S. Assessment and clinical management of bone disease in adults with eating disorders: a review. *Journal of Eating Disorders* 2017; **5:** 42-017-0172-0. eCollection 2017.

Faine M P. Dietary factors related to preservation of oral and skeletal bone mass in women. *The Journal of Prosthetic Dentistry* 1995; **73:** 65-72.

Farach-Carson M C and Ridall A L. Dual 1,25-dihydroxyvitamin D3 signal response pathways in osteoblasts: cross-talk between genomic and membrane-initiated pathways. *American Journal of Kidney Diseases :* 1998; **31:** 729-742.

Foster B L, Nociti F H,Jr and Somerman M J. The rachitic tooth. *Endocrine Reviews* 2014; **35:** 1-34.

Gao Z, Liu K and Meng H. Preliminary investigation of the vitamin D pathway in periodontal connective tissue cells. *Journal of Periodontology* 2018; **89:** 294-302.

Genco R J and Borgnakke W S. Risk factors for periodontal disease. *Periodontology 2000* 2013; **62:** 59-94.

Geng Y, Zhao Y and Zhang Z. Tubulointerstitial nephritis-induced hypophosphatemic osteomalacia in Sjogren's syndrome: a case report and review of the literature. *Clinical Rheumatology* 2018; **37:** 257-263.

Goyal L, Goyal T and Gupta N D. Osteoporosis and Periodontitis in Postmenopausal Women: A Systematic Review. *Journal of Mid-life Health* 2017; **8:** 151-158.

Grant W B, Wimalawansa S J, Holick M F et al. Emphasizing the health benefits of vitamin D for those with neurodevelopmental disorders and intellectual disabilities. *Nutrients* 2015; **7:** 1538-1564.

Ho Y P, Lin Y C, Yang Y et al. Association of vitamin D receptor gene polymorphisms and periodontitis in a Taiwanese Han population. *Journal of Dental Sciences* 2017; **12:** 360-367.

Holick M F. The vitamin D deficiency pandemic: Approaches for diagnosis, treatment and prevention. *Reviews in Endocrine and Metabolic Disorders* 2017; **18:** 153-165.

Hujoel P P. Vitamin D and dental caries in controlled clinical trials: systematic review and meta-analysis. *Nutrition Reviews* 2013; **71:** 88-97.

Insua A, Monje A, Wang H L and Miron R J. Basis of bone metabolism around dental implants during osseointegration and peri-implant bone loss. *Journal of Biomedical Materials Research.Part A* 2017; **105:** 2075-2089.

Intini G, Katsuragi Y, Kirkwood K L and Yang S. Alveolar bone loss: mechanisms, potential therapeutic targets, and interventions. *Advances in Dental Research* 2014; **26:** 38-46.

Jeffery L E, Raza K and Hewison M. Vitamin D in rheumatoid arthritis-towards clinical application. *Nature reviews.Rheumatology* 2016; **12:** 201-210.

Ji X W, Wang Y, Cao C and Zhong L J. Assessment of the link between Vitamin D receptor TaqI gene polymorphism and periodontitis: a meta-analysis in a Chinese population. *Genetics and Molecular Research* 2016; **15:** 10.4238/gmr.15048883.

Karras S N, Fakhoury H, Muscogiuri G et al. Maternal vitamin D levels during pregnancy and neonatal health: evidence to date and clinical implications. *Therapeutic Advances in Musculoskeletal Disease* 2016; **8:** 124-135.

Kienitz T, Ventz M, Kaminsky E and Quinkler M. Novel PHEX nonsense mutation in a patient with X-linked hypophosphatemic rickets and review of current therapeutic regimens. *Experimental and Clinical Endocrinology & Diabetes* 2011; **119:** 431-435.

Krall E A. Osteoporosis and the risk of tooth loss. *Clinical Calcium* 2006; **16:** 287-290.

Leizaola-Cardesa I O, Aguilar-Salvatierra A, Gonzalez-Jaranay M, Moreu G, Sala-Romero M J and Gomez-Moreno G. Bisphosphonates, vitamin D, parathyroid hormone, and osteonecrosis of the jaw. Could there be a missing link? *Medicina Oral, Patologia Oral y Cirugia Bucal* 2016; **21:** e236-40.

Liu K, Meng H and Hou J. Characterization of the autocrine/paracrine function of vitamin D in human gingival fibroblasts and periodontal ligament cells. *PloS One* 2012; **7:** e39878.

Liu K, Meng H, Lu R et al. Initial periodontal therapy reduced systemic and local 25-hydroxy vitamin D(3) and interleukin-1beta in patients with aggressive periodontitis. *Journal of Periodontology* 2010; **81:** 260-266.

Liu K, Meng H, Tang X, Xu L et al. Elevated plasma calcifediol is associated with aggressive periodontitis. *Journal of Periodontology* 2009; **80:** 1114-1120.

Loza J C, Carpio L C and Dziak R. Osteoporosis and its relationship to oral bone loss. *Current opinion in periodontology* 1996; **3:** 27-33.

Ma H W. Rickets-like genetic diseases. *Zhongguo dang dai er ke za zhi = Chinese Journal of Contemporary Pediatrics* 2013; **15:** 923-927.

Macdonald H M. Contributions of sunlight and diet to vitamin D status. *Calcified Tissue International* 2013; **92:** 163-176.

Martelli F S, Martelli M, Rosati C and Fanti E. Vitamin D: relevance in dental practice. *Clinical Cases in Mineral and Bone Metabolism* 2014; **11:** 15-19.

McMahon L, Schwartz K, Yilmaz O, Brown E, Ryan L K and Diamond G. Vitamin D-mediated induction of innate immunity in gingival epithelial cells. *Infection and Immunity* 2011; **79:** 2250-2256.

Mizoguchi T. RANKL signaling and bone diseases. Quiescent osteoclast precursors and RANKL signaling. *Clinical Calcium* 2011; **21:** 1187-1192.

Nagpal S, Lu J and Boehm M F. Vitamin D analogs: mechanism of action and therapeutic applications. *Current Medicinal Chemistry* 2001; **8:** 1661-1679.

Nakamichi Y and Takahashi N. Current Topics on Vitamin D. The role of active forms of vitamin D in regulation of bone remodeling. *Clinical Calcium* 2015; **25:** 395-402.

Nakamichi Y, Udagawa N, Suda T and Takahashi N. Mechanisms involved in bone resorption regulated by vitamin D. *The Journal of Steroid Biochemistry and Molecular Biology* 2018; **177:** 70-76.

Nakamura K. Vitamin D insufficiency in Japanese adults. *Clinical Calcium* 2006; **16:** 1096-1101.

Nakamura M, Nakamichi Y, Nakamura H and Udagawa N. Osteoclastogenesis and bone resorption. *Japanese Journal of Clinical Medicine* 2009; **67:** 889-896.

Nieto-Nieto N, Solano J E and Yanez-Vico R. External apical root resorption concurrent with orthodontic forces: the genetic influence. *Acta Odontologica Scandinavica* 2017; **75:** 280-287.

Nimeri G, Kau C H, Abou-Kheir N S and Corona R. Acceleration of tooth movement during orthodontic treatment--a frontier in orthodontics. *Progress in Orthodontics* 2013; **14:** 42-1042-14-42.

Nishimura I. Genetic networks in osseointegration. *Journal of Dental Research* 2013; **92:** 109S-118S.

Ohnishi M and Razzaque M S. Osteo-renal cross-talk and phosphate metabolism by the FGF23-Klotho system. *Contributions to Nephrology* 2013; **180:** 1-13.

Palacios C, Joshipura K and Willett W. Nutrition and health: guidelines for dental practitioners. *Oral Diseases* 2009; **15:** 369-381.

Pittman K, Antill Y C, Goldrick A, Goh J and de Boer R H. Denosumab: Prevention and management of hypocalcemia, osteonecrosis of the jaw and atypical fractures. *Asia-Pacific[journal of Clinical Oncology* 2017; **13:** 266-276.

Powers J G and Gilchrest B A. What you and your patients need to know about vitamin D. *Seminars in Cutaneous Medicine and Surgery* 2012; **31:** 2-10.

Pramanik S and Saha D. The genetic influence in fluorosis. *Environmental Toxicology and Pharmacology* 2017; **56:** 157-162.

Radlovic N, Mladenovic M, Simic D and Radlovic P. Vitamin D in the light of current knowledge. *Srpski Arhiv za Celokupno Lekarstvo* 2012; **140:** 110-114.

Razzaque M S. Can adverse effects of excessive vitamin D supplementation occur without developing hypervitaminosis D? *The Journal of Steroid Biochemistry and Molecular Biology* 2018; **180:** 81-86.

Razzaque M S. FGF23, klotho and vitamin D interactions: What have we learned from in vivo mouse genetics studies? *Advances in Experimental Medicine and Biology* 2012; **728:** 84-91.

Rosella D, Papi P, Giardino R, Cicalini E, Piccoli L and Pompa G. Medication-related osteonecrosis of the jaw: Clinical and practical guidelines. *Journal of International Society of Preventive and Community Dentistry* 2016; **6:** 97-104.

Rowe P S. The wrickkened pathways of FGF23, MEPE and PHEX. *Critical Reviews in Oral Biology and Medicine* 2004; **15:** 264-281.

Sabandal M M, Robotta P, Burklein S and Schafer E. Review of the dental implications of X-linked hypophosphataemic rickets (XLHR). *Clinical Oral Investigations* 2015; **19:** 759-768.

Sanders K M, Nicholson G C and Ebeling P R. Is high dose vitamin D harmful? *Calcified Tissue International* 2013; **92:** 191-206.

Seow W K. Diagnosis and management of unusual dental abscesses in children. *Australian Dental Journal* 2003; **48:** 156-168.

Slebioda Z, Szponar E and Dorocka-Bobkowska B. Vitamin D and Its Relevance in the Etiopathogenesis of Oral Cavity Diseases. *Archivum Immunologiae et Therapiae Experimentalis* 2016; **64:** 385-397.

Stein S H, Livada R and Tipton D A. Re-evaluating the role of vitamin D in the periodontium. *Journal of Periodontal Research* 2014; **49:** 545-553.

Stewart S and Hanning R. Building osteoporosis prevention into dental practice. *Journal of the Canadian Dental Association* 2012; **78:** c29.

Takahashi N. Mechanism of inhibitory action of eldecalcitol, an active vitamin D analog, on bone resorption in vivo. *Journal of Steroid Biochemistry and Molecular Biology* 2013; **136:** 171-174.

Theodoratou E, Tzoulaki I, Zgaga L and Ioannidis J P. Vitamin D and multiple health outcomes: umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials. *BMJ Clinical Research* 2014; **348:** g2035.

Toniato E, Spinas E, Saggini A et al. Immunomodulatory Effects of Vitamin D on Skin Inflammation. *Journal of Biological Regulators and Homeostatic Agents* 2015; **29:** 563-567.

Uwitonze A M, Murererehe J, Ineza M C et al. Effects of vitamin D status on oral health. *Journal of Steroid Biochemistry and Molecular Biology* 2018; **175:** 190-194.

Vescovi P and Nammour S. Bisphosphonate-Related Osteonecrosis of the Jaw (BRONJ) therapy. A critical review. *Minerva Stomatologica* 2010; **59:** 181-203, 204-13.

Wang L and Plon S. Rothmund-Thomson Syndrome. *GeneReviews* 2019-last update. Available: https://www.ncbi.nlm.nih.gov/books/NBK1237/.

Wang C J and McCauley L K. Osteoporosis and Periodontitis. *Current Osteoporosis Reports* 2016; **14:** 284-291.

Wick J Y. Oral health in the long-term care facility. *The Consultant Pharmacist* 2010; **25:** 214-21, 223-4.

Wimalawansa S J, Razzaque D M S and Al-Daghri N M. Calcium and Vitamin D in Human Health: Hype or Real? *Journal of Steroid Biochemistry and Molecular Biology* 2018; **180:** 4-14.

Witkop C J. Clinical aspects of dental anomalies. *International Dental Journal* 1976; **26:** 378-390.

Zachariasen R. Oral manifestations of metabolic bone disease: vitamin D and osteoporosis. *Compendium* 1990; **11:** 612, 614-8.

Zittermann A. Vitamin D in preventive medicine: are we ignoring the evidence? *The British Journal of Nutrition* 2003; **89:** 552-572.

Zittermann A, Prokop S, Gummert J F and Borgermann J. Safety issues of vitamin D supplementation. *Anti-cancer Agents in Medicinal Chemistry* 2013; **13:** 4-10.