Review Article

Review of literatures: Importance of vitamin D in dentistry

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Abstract

This article is aimed to review of literatures on vitamin D roles in overall health and its effects in dentistry, particularly, periodontal disease, orthodontics tooth movement, dental implant osseointegration and also osteonecrosis of the jaw. On account of new insights of vitamin D implication in immune response. This article will also focus on vitamin D effects on oral response to various dental procedures.

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Introduction

Nutrition is important for overall health and also for dental health of population. The effect of nutritional deficiency can be detrimental to some specific organs. Vitamin D is important of skeletal health. Recent studies focused on non-classical effect of vitamin D in axis of enhancing immune responses. This article will highlight the important of vitamin D in dentistry including periodontal structures and dental implants.

Vitamin D and total health

Vitamin D or sunshine vitamin is one of lipid soluble vitamins. Vitamin D can be categorized into 2 existing forms, ergocalciferol (vitamin D_2) mainly found in plant and cholecalciferol (vitamin D_3) from egg yolk, oily fish and direct conversion in skin from sunlight exposure. Vitamin D metabolism starts in skin where 7-dehydroxycholesterol metabolized upon UV-light exposure (Figure 1). Vitamin D then bound to proteins such as vitamin D binding protein (DBP) and albumin and transported throughout body through blood stream. After hydroxylation in skin, vitamin D then get converted to 25-hydroxyvitamin D form in liver. Afterwards, 25-hydroxylases encoding from CYP27B1 gene were then converted to active form of vitamin D; 1,25-dihydroxyvitamin D in proximal tubule of kidneys. Active form of vitamin D ligands to vitamin D receptor (VDR) inside the cells and act as transcription factor of cells. Various cells were detected with VDR for example, goblet cells in intestines, collecting duct cells in kidneys, hepatocytes, osteocytes, chondrocytes, sebaceous glands, immune cells and dendritic cells (Berger et al., 1988, Iida et al., 1993, Sandgren et al., 1991, Stumpf et al., 1979, Veldman et al., 2000).

Since the first report of Rickets disease by Daniel Whistler in 1645, this childhood disease which manifest in bow leg, stunted growth, and may present with complications such as bone fracture and muscle spasm was responsible for more than 90% of death of children before age of 4 in 18th century (Mayer, 1957). Following series of study about sunlight exposures and cod liver oil (Chick, 1976, Clarke, 1962, Mayer, 1957, Mellanby, 1976, Smerdon, 1950) researchers were able

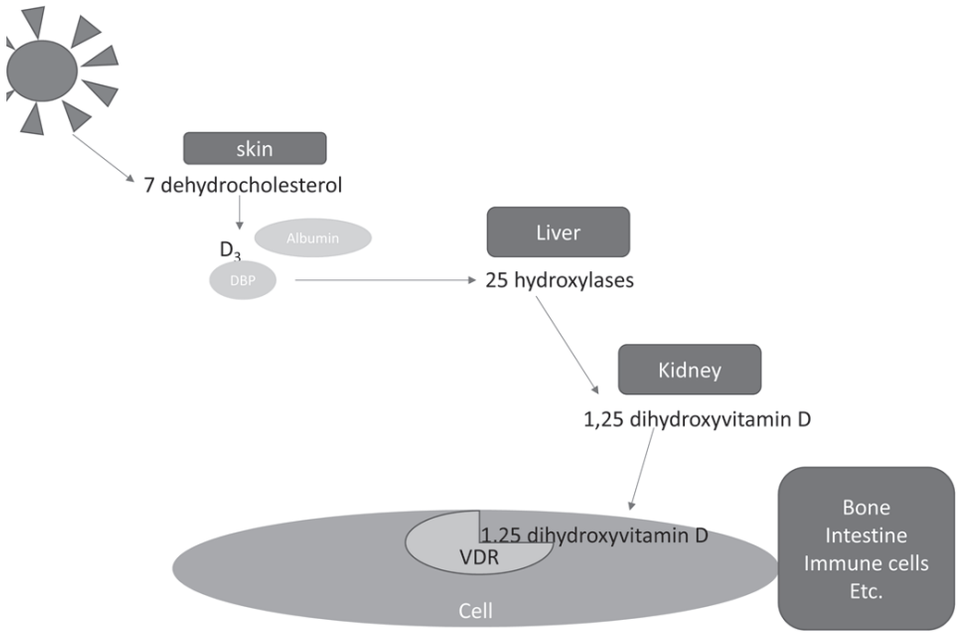

Figure 1: Diagram of vitamin D conversion in body.

to identify vitamin D as functional molecules responsible for regulation of bony metabolism (McCollum et al., 1995). Later, vitamin D was reported to act as prohormone rather than vitamin because of its structure; similar to other steroid hormones (Figure 2). Classical function of vitamin D plays an important role in regulation of calcium and phosphate to calcification site. In the knockout mice study, results showed that VDR-knockout mice exhibited defect in bone formation and mineralization after weaning. However, with high calcium rescue diet, mice showed normal development. These results highlighted the role of vitamin D in calcium intestinal absorption.

Osteoblasts and osteoclasts are potent 1,25 $(OH)_2D_3$ responding cells. Effects of vitamin D on these two cells depend upon various factors such as time of treatment, maturation of cells, duration of treatment. Both *In vivo* and *In vitro* studies suggested that 1,25$(OH)_2D_3$ is the potent osteoclastic stimulation. 1,25$(OH)_2D_3$ enhances monocytic differentiation into pre-osteoclast cells and also recruitment of osteoclasts (Piemonti et al., 2000). However, chronic stimulation of 1,25$(OH)_2D_3$ results in suppression of bone resorption. Stimulation of 1,25$(OH)_2D_3$ on osteoblast increases proliferation rate and production of type I collagen, alkaline phosphatase and osteocalcin. Therefore, 1,25$(OH)_2D_3$ also act as potent bone forming stimulator as well as osteoclastic function.

Kidney is the main organ in producing 1,25 $(OH)_2D_3$ for vitamin D endocrine system. Parathyroid hormone and calcitonin positively regulate production of 1,25$(OH)_2D_3$ while 1,25$(OH)_2D_3$ suppress CYP27B1 (encoding 25 hydroxylase enzyme for 1,25 dihydroxy-vitamin D conversion) expression (Murayama et al., 1999). Chronic kidney disease patients often have vitamin D deficiency which associated with negative bone regeneration and negative fracture healing.

In earlier day, vitamin D was used to treat Tuberculosis, since these patients showed low 25(OH)D_3 serum level compared with healthy group (Nnoaham and Clarke, 2008). However, incubation of 1,25$(OH)_2D_3$ alone with *M. tuberculosis* did not show any effect to bacterial proliferation but when monocytes were primed with 1,25$(OH)_2D_3$ and inoculated with *M. tuberculosis,* there was restriction of Uracil uptake in bacteria and cause inhibition of bacterial growth (Rook et al., 1986). These evidences suggested that vitamin D plays notable role to induce host immune response.

In terms of significant of vitamin D to oral health, immunohistochemistry of VDR was found in periodontal ligament, cementoblasts, gingiva, periosteum and cells associate with bone (Dvorak et al., 2012). Therefore, these structures might also be under vitamin D controlled.

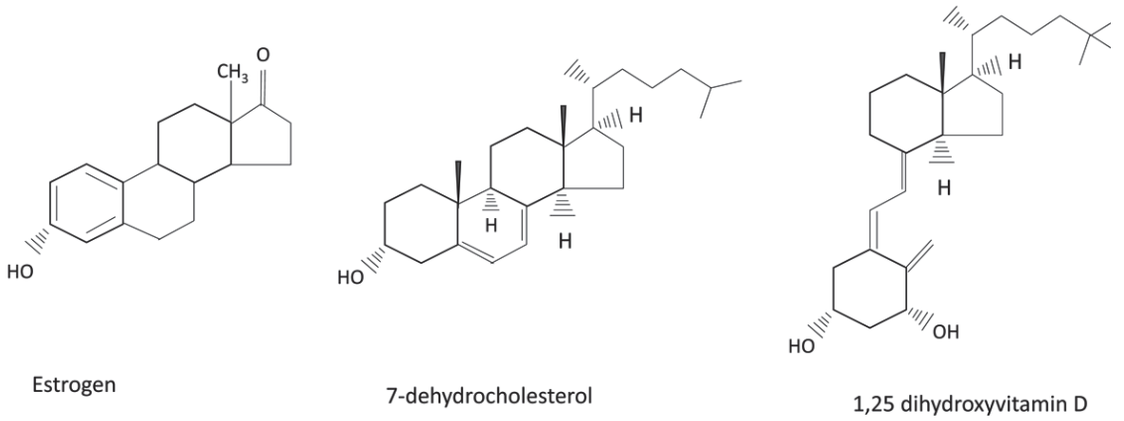

Figure 2: Chemical structures of Estrogen, 7-dehydrocholesterol and 1,25 dihydroxyvitamin D.

Vitamin D insufficiency, Vitamin D deficiency and Vitamin D intoxication

Measuring vitamin D hormone was done with prohormone form as indicator for hormonal supply. The most stable form of vitamin D is prohormone 25(OH)D_3 which has half-life of about 3 weeks. Major effects of vitamin D deficiency are osteoporosis and fractures. Vitamin D deficiency has also been found to associate with colorectal cancer, cardiovascular disease, metabolic syndrome and pregnancy related outcomes from systematic review (Theodoratou et al., 2014). Patients who has 25(OH)D_3 levels between 71-90 nmol/l showed lower risks of fracture rates (Chapuy et al., 1994). Therefore, 75 nmol/l of serum 25(OH)D_3 was proposed as optimal serum vitamin D level. However, meta-analysis reported that vitamin D supplement with calcium can help reduce risk of hip fractures but not vitamin D alone (Bolland et al., 2014).

According to Mayo Medical Laboratories, reference range for total serum 25-hydroxyvitamin D, 25 hydroxyvitamin D serum less than 10 ng/ml is considered severe vitamin D deficiency. 10-24 ng/ml is considered mild to moderate vitamin D deficiency while 25-80 ng/ml is considered optimal level of vitamin D (to convert from ng/ml to nmol/L, multiply by 2.496) (Kennel et al., 2010, Thacher and Clarke, 2011).

Excessive supplementation of vitamin D has become a topic of interest, since vitamin D fortified-food has been introduced and cases of toxicity were reported. Thin epiphyseal plate and large quantity of osteoid were found in long bones of rats feeding with overdose vitamin D (Ham and Lewis, 1934). However, the most frequent symptoms of vitamin D toxicity in human is hypercalcemia. Some other symptoms include gastrointestinal disorders, drowsiness, irregular heartbeat or muscle and joint pain. Vitamin D intoxication in human was reported as a resulted from chronic ingestion of these vitamin D contained food such as overfortified milk and peanut oil solution (Blank et al., 1995). These patients showed average range of serum 25(OH)D_3 of 847-1652 nmol/L. Highest record of natural exposed level of serum 25(OH)D_3 was 225 nmol/L from sunshine and 275 nmol/L from ultraviolet light treatment. However, hypercalcemia was found when 25(OH)D_3 serum level above 375-500 nmol/L (Pettifor et al., 1995). Therefore, with normal daily consumption of food and exposure of sunlight, vitamin D toxicity is rarely found.

Effect of vitamin D on immune cells

One of the most important contemporary aspects of vitamin D is immunomodulatory effect. Earlier reports about Rickets patients were accompanied with increased susceptibility to infection and impaired phagocytosis (Stroder and Kasal, 1970). Since then, many adaptive and innate immune cells were studied and reported to contain functional VDR. Moreover, these cells such as macrophage and dendritic cells express CYP27B1 encoding 1α-hydroxylase that can convert precursor vitamin D (25(OH)D_3) to active form (1,25$(OH)_2D_3$). The pivotal research by Liu, et al. in 2006 highlighted antimicrobial function of vitamin D in monocytes and macrophages (Liu et al., 2006). Vitamin D receptor and vitamin D-1-hydroxylase genes were upregulated upon activation of Toll-like receptor (membrane receptors that recognize molecules derived from microbial) and resulted in induction of cathelicidin (antimicrobial peptide) and β-defensin2 leaded to killing of *Mycobacterium tuberculosis*. This study reinstated the important of vitamin D in host response to microbial. Since then, vitamin D has been at the center of innate immunity response study.

Vitamin D also plays substantial roles in adaptive immune system. Intracrine production of vitamin D has been shown to support generation of Tolerogenic regulatory T (Treg) cells and suppress inflammatory IL-17-expressing T cells (Th17 cells) (Jeffery et al., 2012). Vitamin D also decreases maturation of

dendritic cells, therefore suppresses antigen presentation and decreases T cells proliferation (Hewison et al., 2003). These evidences encourage the role of vitamin D in autoimmune disease, however further clinical trials of vitamin D supplementation are needed to support this claim.

Limited evidences were shown involving vitamin D to oral immune system. Nevertheless, human gingival epithelial cells display ability to produce β-defensins and cathelicidin peptides. Vitamin D increases the expression and antibacterial activity of cathelicidin against *Aggregatibacter actinomycetemcomitans* (McMahon et al., 2011). In addition, vitamin D also inhibited *Porphyromonas gingivalis* intracellular growth in infected gingival epithelial cells (Menzel et al., 2019). These studies demonstrated the important of vitamin D to oral innate immune response.

Vitamin D and periodontal disease

Periodontal disease is a chronic infection of oral cavity that affected more than 50% of adult population. Periodontal disease associated with others significant health related issues such as Diabetes mellitus, high blood pressure and heart disease. Periodontal disease is associated with both classical (skeletal health) and non-classical (immune response) functions of vitamin D.

Several evidences demonstrate the relationships between vitamin D deficiency and periodontal disease. Wild-type C57Bl/6 mice with dietary restriction of vitamin D demonstrated alveolar bone loss and increased gingival inflammation (Menzel et al., 2019). Study by National health and nutritional examination (NHANES II) in US population showed inversely significant correlation between periodontal attachment loss and serum $25(OH)D_3$ concentrations in men and women above 50 years of age (Dietrich et al., 2004). This correlation was not associated with bone mineral density in femoral region or in men and women under 50 years old. This suggested the role of vitamin D in periodontal health. Low vitamin D level as well as higher concentration of plasma RANKL and OPG were found to be associated with periodontal disease in osteoporotic women (Jabbar et al., 2011).

Another study showed that patients who receiving periodontal maintenance therapy with vitamin D (≥400 IU/day) and calcium (≥1,000 mg/day) supplementation demonstrated better periodontal health compared with patients who did not take supplementation. Shallower probing depth, fewer bleeding sites, lower gingival index values, less attachment loss including less alveolar crest height loss were found in supplementation takers (Garcia et al., 2011; Miley et al., 2009b).

Periodontal disease in pregnant women is also prevalence. A case-controlled study of pregnant women who has clinical moderate to severe periodontal diseases showed that vitamin D insufficiency (serum $25(OH)D_3$ level <75 nmol/L) is associated with maternal periodontal disease during pregnancy (Boggess et al., 2011).

Various studies advocated for the role of genetics in periodontal disease. In Italian population, chronic periodontal disease and aggressive periodontal patients were found to have association with *Taq*I polymorphisms (rs731236) of VDR (Vitamin D receptor) gene (Martelli et al., 2011). Moreover, polymorphism of *Taq*I Restriction Fragment Length Polymorphism (RFLP)(t) in VDR gene also increases the risk of developing localized early-onset periodontal diseases (Hennig et al., 1999).

Vitamin D and dental caries

Dental caries is the primary cause of tooth loss in children and adults under 40 years old (Murray et al., 1996). In 1920s and 1930s, reduction of caries formation was reported to associate with vitamin D and ultraviolet-B (UVB) irradiance. Mellanby, et al. in 1928 suggested that children with vitamin D supplement diets demonstrated fewer number of new caries and more arrested carious lesions. Furthermore, Gram

positive bacteria were found in ground section of dentinal tubules of arrested lesion, however, these micro-organisms were inactive (Mellanby and Pattison, 1928). Geographic variation has also been displayed with correlation with dental caries. Area with high altitude tends to receive less UV from sunlight, hence less vitamin D conversion in skin. Meta-analysis showed vitamin D supplementation was linked with decreased in dental caries in children (Theodoratou et al., 2014). Nonetheless, no correlation between $25(OH)D_3$ level and dental caries in children was found in participants of National Health and Nutritional examination survey (NHANES) 2005-2006 (Herzog et al., 2016).

Daily requirement of vitamin D is dramatically escalated in pregnancy mothers from 70 I.U. per day to 400-500 I.U. per day (Pitkin et al., 1972). Low prematernal $25(OH)D_3$ level (41±20 vs 52±27 nmol/L) is associated with early childhood caries in 1 year old children (P=.05) (Schroth et al., 2014). Early childhood caries were found to be linked with enamel hypoplasia in the study. In 1973 study of infants' teeth with neonatal tetany showed shelf or hump of demarcated thicker enamel near the gingiva from incisors to molars separated normal ivory-colored enamel at the base from yellow-colored enamel at the tip. Hyperparathyroidism in mother secondary to vitamin D deficiency could be responsible for the damage of unerupted deciduous teeth.

Vitamin D and orthodontic treatment

Tooth movement is crucial in orthodontics to create normal functional occlusion. It occurs by bone remodeling around tooth according to force application. Many theories are dedicated to elucidating the tooth movement mechanism such as pressure-tension hypothesis, piezoelectric concept and theory of vascular occlusion. Mainly, osteoclasts are recruited to the compression side of the periodontal ligaments and resorb the alveolar bone which result in movement of teeth according to the applied force.

Vitamin D injection has been implicated in speeding tooth movement rate. Cats received local injection of $1,25(OH)_2D_3$ solution with dimethylsulfoxide (DMSO) in canine retraction showed teeth have moved 60% faster than control group. Histological section showed increased number of activated mononuclear osteoclasts in that area (Collins and Sinclair, 1988). In addition, local injection of $1,25(OH)_2D_3$ in young and mature Wistar rats demonstrated markedly increased tooth movement (126%, 245% respectively) without changed calcium, phosphate levels and alkaline phosphatase activity in serum (Takano-Yamamoto et al., 1992). Moreover, vitamin D also involves in induction of osteoclastogenesis. Receptor activator of nuclear factor kappa B (RANK) is cell surface receptor that expressed on osteoclast precursors for Receptor activator of nuclear factor kappa B ligand (RANKL). RANK-RANKL activation leads to osteoclast maturation and survival of osteoclasts. $1,25(OH)_2D_3$-VDR stimulates the upregulation of RANKL (osteoclast differentiation factor) expression in osteoblasts and induce osteoclastogenesis cascade (Tsukii et al., 1998). RANKL gene transfer to periodontal tissue experiment also showed acceleration of tooth movement in rats (Kanzaki et al., 2006). Nevertheless, effect of vitamin D on osteoclastogenesis was transient. Local injection of $1,25(OH)_2D_3$ in proximal tibia of rats showed increased in number of osteoclasts and active resorption surfaces at earlier day but decreasing dramatically after day 6 (Boyce and Weisbrode, 1985). On the contrary, since osteoprotegerin (OPG) is decoy receptor for RANKL. Increasing amount of OPG will decrease osteoclastogenesis. Attempt was made to verify OPG role in orthodontic tooth movement. Local OPG gene transfer to periodontal tissue showed inhibition of tooth movement in Wistar rats (Kanzaki et al., 2004). These collective results suggested the role of local application of vitamin D in bone remodeling which may involve RANKL, OPG activations.

The other axis of accelerated tooth-movement is bone formation. Study compared effects of $1,25(OH)_2D_3$ and prostaglandin injection which equally increased the rate of tooth movement, showed significantly greater number of osteoblasts in compression side than in prostaglandin group (Kale et al., 2004). In addition, periodontal ligament was reported as pluripotent structure. Stimulation of periodontal ligament fibroblast cells with $1,25(OH)_2D_3$ resulted in upregulation of alkaline phosphatase and osteocalcin (Basdra and Komposch, 1997). This reaction indicates the ability of periodontal ligament fibroblast to express osteoblast-like phenotype which might help with bone formation. More importantly, local injection of $1,25(OH)_2D_3$ which resulted in sudden increased in osteoclastogenesis, nonetheless, progressive increased in number of osteoblasts and active osteoid surface were found after (Boyce and Weisbrode, 1985). Therefore, even though local injection of vitamin D increased rate of tooth movement, but multiple doses are needed to maintain the increased rate of tooth movement.

Vitamin D and tooth loss and dentures

Association between tooth loss and malnutrition was apparent since the masticatory ability and efficiency are declined in edentulous patients. Difficulty in chewing can cause dietary limitations such as consuming fewer dietary fiber intakes and higher starch (Sheiham et al., 2001). Furthermore, elders are also predisposed to more complicate medical and social conditions that hindrance the dietary intakes. Adequate amount of calcium and phosphorus ratio dietary intakes have been showed to prevent osteoporosis-like changes in oral bone of animals.

3 years double blinded, randomized, placebo-controlled trial of vitamin D and calcium supplementation in elderly aimed to study the risk of hip-fractures also indicated that subjects with supplementation retained one or more teeth compared with placebo-taking group with the same oral hygiene practices condition (Krall et al., 2001). Benefits of calcium and vitamin D supplementation extend beyond not only prevention of osteoporosis, but also might increase tooth retention.

Vitamin D is vital to calcium absorption in intestine. VDR mRNA is strongly correlated with numbers of intestinal calcium channels throughout duodenum, jejunum and ileum (Bouillon et al., 2003, Van Cromphaut et al., 2001). Vitamin D also regulates calcium absorption via paracellular pathway (Fujita et al., 2008) through tight junctions and intercellular spaces. Therefore, elders with vitamin D deficiency often showed mineral deficiency from inability to absorb calcium from intestine. Calcium deficiency contributes to osteoporosis of alveolar bone. Vitamin D might not have direct effect on tooth retention but vitamin D help decrease periodontal disease and maintain dynamic of bone remodeling. Hence, vitamin D indirectly responsible for ability of periodontal structure and alveolar bone in maintaining teeth in elderly.

Vitamin D and dental implants

Dental implant treatment has become preferred treatment of choices for patients with edentulous area. The survival of dental implants depends on quality of osseointegration. Osseointegration is dynamic process of hard tissue integration to titanium surface. A concept of foreign body reaction has been introduced for titanium implant integration. Recent studies indicated that titanium implant stimulates immune system and demonstrates type 2 inflammation (Trindade et al., 2018). Type 2 immune responses include mostly adaptive immune response with specific $CD4^+$ T cells or Th2 cells that secrete interleukin-4 (IL-4), IL-5 and IL-13. Other conditions such as diabetes can influence bone-to-implant contact and osseointegration of titanium implants. Since vitamin D and calcium are involved in bone

homeostasis. Researchers were concerned about the relationship of vitamin D and osseointegration.

The relationship between vitamin D and osseointegration was shown by several studies. Vitamin D depletion in ovariectomized rat associated with significantly decreased in bone-to-implant contact (Dvorak et al., 2012). Repletion of vitamin D in depletion group help restored bone-to-implant contact in cortical area. This effect occurred only in cortical area whereas medulla and periosteal compartment did not show differences. From this depletion-repletion study, it was suggested that vitamin D supplementation can be beneficial for patients with reduced peri-implant bone formation.

Moreover, microarray data from tissue around dental implant in vitamin D deficiency rats demonstrated inhibition of upregulation of circadian rhythm genes; Neuronal PAS domain 2 *(NPAS2)* and Aryl hydrocarbon receptor nuclear translocator-like *(ARNTL/Bmal 1)*. Extracellular matrix genes cluster such as collagen II and X were also down-regulated in vitamin D deficiency group with dental implants. *In vitro* study also showed vitamin D supplementation modulate upregulation of type II and X collagen in cultured mouse mesenchymal stem cells on implant disk (Mengatto et al., 2011). The role of vitamin D in dental implant treatment has not been fully elucidated. Some postulated the role of vitamin D in proteoglycans which might encourage the adhesion of bone to implant surface. In addition, peri-implant bone might be the collective of bone and cartilage extracellular matrix. Hypoxic or xenobiotic microenvironment stimulate circadian rhythm genes such as ARNTL and PAS domain-containing molecules. These genes directly upregulated Collagen II and collagen X in mouse MSC. Some suggested that Titanium implant might be recognized as foreign object (Trindade et al., 2016) and can activate xenobiotic response. Therefore, it was proposed that circadian rhythm genes might be affected by dental implant-mediate microenvironment (Nishimura, 2013) and effect the peri-implant bone development.

Impaired healing of dental implants was found in patients with chronic kidney disease (CKD). Supplementation of $1,25(OH)_2D_3$ before implant placement increased bone-to-implant contact and resistance to push-in method in nephrectomized rats (Liu et al., 2014). On that account, restoring serum $1,25(OH)_2D_3$ levels can improve osseointegration of dental implant in chronic kidney disease.

Vitamin D clearly has significant role in host-immune responses and repletion of vitamin D resulted in restoring compromised osseointegration. Therefore, vitamin D serum levels should be considered when placing dental implants to avoid the devastated complications.

Vitamin D and osteonecrosis of the jaw

Osteonecrosis of the jaw (ONJ) is prevalence in patients who received nitrogen-containing bisphosphonates for their bone cancer therapy. Tooth extraction after bisphosphonate treatment increased the risk of developing ONJ. Experiment with bisphosphonates (Zolendronate) treated rats with vitamin D deficiency demonstrated significant higher risk of ONJ than rats with vitamin D sufficiency (Hokugo et al., 2010).

Vitamin D supplementation in dental clinic

Institute of Medicine (IOM) and Endocrine Society Clinical Practice Guideline (ESCPG) recommended vitamin D intake of 600 IU/day for population aged 1-70 years. Since aging process influence on ability of making vitamin D from skin, function of kidney in producing active form of vitamin D, and ability to respond to vitamin D metabolites to absorb calcium in intestine, recommendation vitamin D daily dose for individual over 70 years is 800 IU/day.

It is beneficial for patients with active oral

disease to get serum vitamin D level measurement. Epidemiological study of young women in Argentina showed 100% of studied women had gingivitis and majority of them (71%) had below normal serum 25(OH)D_3 level (< 30 ng/ml) (Antonenko et al., 2015). Furthermore, according to cross-sectional study with calcium and vitamin D intake in patients with moderate to severe periodontal disease, patients who had been taken calcium (>1,000 mg/day) and vitamin D (>400 IU/day) demonstrated better periodontal health status (Miley et al., 2009a).

Conclusion

Dentists constantly combat against infection of oral cavity and find the way to maintain oral structures. With the range of functions of vitamin D that extends beyond skeletal health but also immune responses, it can be useful for dentistry. Vitamin D supplementation is favorable to those with periodontal disease and dental implants treatment. Optimal doses should be adjusted especially for pregnant women and elderly. More importantly, further research about function of vitamin D in dentistry in various aspects are needed to better understand the role of vitamin D in oral health.

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