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The Impact of Vitamin D Deficiency on General and Oral Health during Childhood

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Abstract **Review Article**

Severe vitamin D deficiency may cause rickets in infants or children, though it is now uncommon in developed countries. However, subclinical vitamin D deficiency is more prevalent, and it is associated with osteoporosis and higher incidence of falls or fractures. Since vitamin D receptors are present all over the body, insufficient vitamin D status may correlate with several extra-skeletal effects, such as immune dysfunction. Vitamin D deficiency (VDD) is associated with a wide variety of oral health disorders, and impaired VD synthesis may expedite some of these conditions. In children, severe VDD can induce defective tooth mineralization, resulting in dentin and enamel defects. As a consequence, these defects may increase the risk of the onset and progression of dental caries. Further, VDD has been associated with higher prevalence of periodontitis and gingival inflammation.

Keywords: Vitamin D, vitamin D deficiency, oral health, dental caries, hypomineralization.

INTRODUCTION

Vitamin D is essential for calcium and bone homeostasis, especially in children because childhood and adolescence are the most critical periods for bone development. The role of Vitamin D is not limited to bone health as it also has important roles in many extra-skeletal targets throughout the body, such as the muscles, immune system, and the cardiovascular system [1, 2]. Severe vitamin D deficiency (VDD) is a well-established cause of disease, including hypocalcemia and skeletal abnormalities (e.g., rickets) [3-5]. Although severe deficiency causing classic bone manifestations is now rare, many adults and children endure a subclinical VDD state that may predispose them to neurologic, cardiovascular, respiratory, and immune pathology [6-8] as well as variety of oral health disorders [9, 10].

This review will discuss vitamin D metabolism and its role on body systems and also on oral health.

Vitamin D metabolism

Vitamin D is a fat-soluble vitamin. The major route to obtain vitamin D is dermal synthesis after ultraviolet- B (UVB) radiation, accounting for 90% of vitamin D replenishment and only a few foods naturally contain vitamin D (oily fish, cod liver oil, egg yolks, shiitake mushrooms, liver or organ meats) [11]. There are two sources of vitamin D, Cholecalciferol (vitamin D3) is from animal sources and ergocalciferol (vitamin D2) is from plants[12] (10) Cholesterol-like precursor (7-dehydrocholesterol) in skin epidermal cells can be converted after UVB radiation (wavelength 290-315 nm) into pre-vitamin D, which also isomerizes to vitamin D3. Both vitamin D3 and D2 are biologically inactive. They need further enzymatic conversion to their active forms. Firstly, it undergoes 25-hydroxylation in liver to 25(OH)D (calcidiol), the major circulating form of vitamin D, with a half-life of 2-3 weeks. Then it is converted in kidneys through 1-alpha-hydroxylation to its most active form, 1,25(OH)2D (calcitriol), with a half-life of 4-6 hours. This process is driven by parathyroid hormone (PTH) and other mediators, including hypophosphatemia and growth hormone [13, 14]. The 1-alpha-hydroxylation also takes place in non-renal sites, such as alveolar macrophages, osteoblasts, lymph nodes, placenta, colon, breasts and keratinocytes, suggesting possible autocrine-paracrine role of calcitriol [13, 14]. It functions through a vitamin

D receptor (VDR) that is universally expressed in nucleated cells. Its most important biological role is promoting enterocyte differentiation and intestinal calcium absorption, facilitating calcium homeostasis. At the time of hypocalcemia, the plasma level of ionized calcium falls and this is detected by parathyroid gland calcium receptors. PTH is secreted by parathyroid gland, which stimulates 1-alpha-hydroxylation in kidneys to make more calcitriol from circulating calcidiol. The elevation of calcitriol increases calcium transport within intestines, bones, and kidneys, and further regulates the osteoblast and osteoclast activity. As plasma calcium rises back to normal, further secretion of PTH decreases. This physiologic loop of vitamin D and calcium homeostasis demonstrates that enough circulating calcidiol is essential to maintain adequate calcitriol synthesis and plasma calcium level [12]. However, vitamin D deficiency may result in inadequate circulating calcidiol, which decreases calcitriol synthesis and calcium absorption, elevating PTH levels. It is reasonable to focus on plasma calcidiol and PTH level to assess vitamin D clinically. Additionally, because VDRs are found not only in small intestine, but also in colon, osteoblasts, activated T and B lymphocytes, mononuclear cells, beta islet cells and major organs, such as brain, heart, skin, gonads, prostate and breasts[14], coexisting extra-skeletal effects of vitamin D deficiency are to be expected.

Vitamin D deficiency

The best indicator of the human body's vitamin D status is the concentration of serum calcidiol [15]. The optimal calcidiol level for either skeletal or extra-skeletal health varies for different populations. In adults, the essential level of vitamin D is determined through studies of calcium homeostasis, bone mineralization and PTH levels. Adult PTH has negative correlation with serum calcidiol level, though this relationship is weak in children. The Institute of Medicine (IOM) concluded a serum level of 20 ng/mL was optimal for skeletal health [15], whereas other experts, including the Endocrine Society (ENDO), the International Osteoporosis Foundation (IOF), the National Osteoporosis Foundation (NOF) and the American Geriatrics Society (AGS) stated that at least 30 ng/mL was needed for disease prevention [16-22]. In children, optimal vitamin D status is based upon clinical evidence for rickets or bone turnover, such as elevation of serum ALP. The consensus for adequate calcidiol concentration in children has not yet been established because of inconsistent evidence. The American Academy of Pediatrics (AAP) classified calcidiol > 20 ng/mL as sufficiency [13], whereas the Pediatric Endocrine Society used a higher threshold in 2011, regarding calcidiol < 30 ng/mL as insufficiency [21]. In 2016, the Global Consensus also defined calcidiol > 20 ng/ mL as sufficiency but adjusted other criteria [22].

Risk factors of Vitamin D deficiency

UVB is more prevalent during the hours of 10am to 3pm. During spring, summer and autumn, 10-15 minutes of sun exposure (over arms and face, or arms and legs/hands) from 10am to 3pm can produce adequate vitamin D in light-skinned populations [13]. However, epidermal melanin of darker skinned individuals means more exposure is needed for cutaneous vitamin D synthesis. It is estimated that Asians from the Indian subcontinent require 3 times as much sun exposure as Caucasians, whereas Africans may need 6-10 times more [23]. Infants and adolescents are populations at risk because of rapid skeletal growth after birth and during puberty [12]. Weisberg showed that 96% of cases of rickets occurred in breastfed children [24]. Because breast milk is known to contain very little vitamin D even in vitamin D-replete mothers [13, 25] exclusively breastfed infants, especially those born to vitamin D-deficient mothers, are more at risk for rickets. Preterm infants are even more prone to vitamin D deficiency due to lack of transplacental transfer of vitamin D during the third trimester [26] and negligible sun exposure in postpartum hospital [26]. Age-related declines in dermal synthesis of vitamin D, diminishing rate of hydroxylation, and poorer response of target tissues further explain the elevated risk for vitamin D deficiency in the elderly [12, 27]. Studies showed that children, particularly infants, may require less sun exposure than adults to produce adequate quantities of vitamin D because of their greater surface area to volume ratio and better capacity to produce vitamin D [28]. However, obese people still have higher risk due to sequestration of vitamin D in adipose tissue [13, 29]. Cutaneous vitamin D synthesis depends on surface of skin exposed and duration of sun exposure. Extent of clothing due to cultural or religious factors and using topical sunscreen may block effective dermal synthesis. A sunblock of SPF 30 can reduce vitamin D production by 95% [30]. Chronic diseases involving intestinal malabsorption, or liver and renal insufficiencies may also reduce vitamin D production [31]. Some anticonvulsants or antiretroviral agents can precipitate vitamin D deficiency by enhancing catabolism of calcidiol and calcitriol, while Ketoconazole may further block 1-hydroxylation [31].

Vitamin D and bone health

Severe vitamin D deficiency may cause rickets in infants or children and osteomalacia in adults, although these are uncommon diseases in most developed countries. However, subclinical vitamin D deficiency is more prevalent, and may be associated with osteoporosis and higher incidence of falls or fractures. A previous public health evaluation concluded that calcium supplementation of healthy children did not significantly decrease the incidence of fractures [32]. A healthy balanced diet that fulfilled the recommended calcium intake was superior to routine calcium supplementations [13, 14]. However, due to limited natural dietary sources of vitamin D and insufficient sun exposure in most children and adolescents, vitamin D supplementation is necessary. Routine screening of calcidiol levels is not

recommended, except for those with higher risk, or in children who present with poor growth, gross motor delay or unusual irritabilities; those who are hospitalized or institutionalized with limited sun exposure; or those with elevated serum alkaline phosphatase (ALP) levels (>500IU/L in neonates or >1000IU/L in children up to 9 years) [13, 16, 17].

Vitamin D and immune system

Functional VDR has been identified in almost all immune cells, including antigen-presenting cells (APCs) and T lymphocytes [33, 34], thus providing an indirect evidence of vitamin D action on immune system. Vitamin D exerts its action on both innate and adaptive immune system through VDR [33, 35, 36]. Overall, the immunomodulatory effects of vitamin D mostly depend upon the capacity of its biologically-active form calcitriol to regulate expression of several genes involved in cell proliferation, differentiation, and function [35, 37, 38]. Examples of the relationships between vitamin D and these illnesses are; Tuberculosis [39, 40], Respiratory tract infections [41, 42], Asthma [43-45], and Atopic dermatitis [46, 47].

Calcitriol also functions as an inhibitor of dendritic cell maturation, which reduces the activation of acquired immunity and may increase the risk of autoimmune disease [48], such as type I diabetes, multiple sclerosis, and inflammatory bowel disease [11]. However, because reports conflict on the association between vitamin D status and these diseases, supplementation is not recommended at present [49].

Vitamin D and other systemic effects

Observational studies demonstrated the association between vitamin D deficiency and the risk of hypertension or cardiovascular events, higher incidence of cancers, more musculoskeletal pain or migraine, and neuropsychiatric disorders such as schizophrenia, dementia or depression [17]. However, current evidence for vitamin D intervention in treating or preventing these diseases is lacking.

Vitamin D Deficiency Impact on Oral Health

A recent comprehensive review on the effect of VDD on oral health discussed in details how VDD can have adverse effects on both hard and soft tissues in the oral cavity [50]. The effect of hard tissue is mainly during childhood [50].

A. Vitamin D Deficiency in Tooth Mineralization and Caries

Teeth are mineralized organs, surrounded by alveolar bone, and formed by three distinctive hard tissues: enamel, dentin, and cementum. The tooth mineralization process occurs parallel to skeletal mineralization, yet if mineral metabolism is disturbed then failures will occur similarly to those that occur in bone tissue. Vitamin D plays a key role in bone and tooth mineralization, and when levels are unregulated it can lead to defective and hypomineralized organ highly susceptible to fracture and decay [51, 52].

The main biological basis relies on the fact that severe VDD (<10 ng/mL) causes hypocalcemia and hypophosphatemia with secondary hyperparathyroidism (driven by hypocalcemia) [53, 54]. This hyperparathyroidism promotes intestinal absorption of calcium (Ca2+), and renal production of 1 α,25-dihydroxyvitamin D (1,25[OH]2D), increasing bone turnover leading to elevated serum levels of Ca2+ and low serum levels of inorganic phosphate (Pi) [53, 54]. The initial hypophosphatemia is then severely worsened. Ultimately, the loss of vitamin D signaling pathways in tooth cells with low concentrations of Ca2+ and phosphate ions inhibit proper mineralization of teeth and mineralization defects occur [51].

Dental caries is an infectious disease that has a complex and multifactorial etiology. Environmental factors, such as cariogenic diet with a high carbohydrate content, cariogenic bacteria, and poor oral hygiene were the most widely studied risk factors [55-57]. However, when exposed to the same environmental risk factors, some patients are more susceptible or resistant to caries than others, so that environmental factors alone are insufficient to explain the prevalence and incidence of caries [58-60]. Currently the evidence highlights the association of low levels of vitamin D and the high prevalence of caries in both children and adults, although the mechanism remains unclear [61-68]. Additionally, vitamin D exerts several roles in the control of the human immune system, and an optimal vitamin D concentration (≥75 nmol/L) is associated with lower odds for dental caries in children [9, 69, 70].

A recent systematic review of controlled clinical trials, with data from 2827 children, investigated the impact of vitamin D supplementation on dental caries prevention [71, 72]. The results of this study show that vitamin D supplementation reduced the risk of caries in about 47%, but with low certainty [71]. Another research supports that caries-free children were twice as likely to have optimal vitamin D concentrations and those with severe early childhood caries were at nearly three times the odds of having deficient levels (<35 nmol/L) [9]. On the one hand, it is important to clarify that serum vitamin D does not change the major structure of teeth since this structure remains constant until some extrinsic factor causes its wear. It can be explained as vitamin D prevents caries lesions through immune regulation, promoting microbial eradication with peptide activity as discussed above.

B. Vitamin D Deficiency and Periodontitis

Periodontitis is a complex polymicrobial disease induced by plaque and with persistent chronic inflammation [73]. The systemic link between

periodontitis and other diseases and conditions has raised, such as diabetes [74], ischemic stroke [75], cardiovascular disease (CVD) [76], rheumatoid arthritis [77, 91], inflammatory bowel disease [78], stress [79], solid-organ transplanted individuals [80], or preterm birth [81]. Furthermore, the impact of nutrition on periodontal health, and in particular VDD, has been intensively investigated [82-86] and a recent European consensus stated that an inadequate vitamin D status impacts periodontal health and oral functions [87].

Many cross-sectional studies have compared the levels of Vitamin D between individuals with periodontitis and without periodontitis; however, the results remain diverse. While most reports show that periodontitis was associated with lower levels of Vitamin D compared to non-periodontitis [88-92], another has reported no differences [93]. Further, vitamin D concentrations were associated with higher periodontal destruction, severe periodontitis stages and higher tooth loss [94-97].

CONCLUSION

Vitamin D is an essential nutrient not only important in bone health but also beneficial to many other systems. VDD is highly implicated with oral diseases and has been linked with a higher risk of tooth defects, caries, periodontitis and oral treatments failure. The maintenance of appropriate 25(OH)D levels has shown to be associated with better health throughout life. 25(OH)D levels should be considered to ensure a balanced general and oral health.

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