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Review Article

Relationship between vitamin D deficiency and atopy in children

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ABSTRACT

Along with its role in regulation of calcium metabolism and bone health, vitamin D is essential for immune system integrity. Vitamin D is an essential immunomodulatory vitamin that interact with the immune system in response to foreign antigens. This interaction is mediated by the vitamin D receptors (VDR) expressed on the surface of various immune cells. Vitamin D has an inhibitory effect on synthesis and release of immunoglobulin E and thus is closely related to atopic disorders. Vitamin D deficiency is a risk factor for bronchial asthma, and it increased asthma-related exacerbation. Low vitamin D levels are encountered in patients with allergic rhinitis and increase the severity of the disease. Other allergic conditions such as atopic dermatitis, contact dermatitis, and food allergy were reported to be significantly correlated with vitamin D serum levels. Despite the established correlation between vitamin D and atopic disorders, double-blinded randomized controlled studies are still lacking to approve this relationship and to provide clear guidelines for the recommended supplementary doses of vitamin D to prevent or treat these conditions. This article aims to review the relationship between vitamin D deficiency and atopy in children.

Keywords: Atopy, Children, Pediatric, Vitamin D, Vitamin D deficiency

INTRODUCTION

Vitamin D is one of the fat-soluble vitamins that increases intestinal absorption of various electrolytes particularly calcium, phosphate, and magnesium. It is also responsible for other biological effects.[1] The main source of vitamin D for human is exposure to UV sunlight. Vitamin D is endogenously synthetized in the skin when sunlight ultraviolet rays strike it. Very few foods provide a dietary source for vitamin D such as flesh of fatty fish, fish liver oils, cheese, beef liver, and egg yolks. Inside the body, vitamin D must be hydroxylated twice to be activated.[2] While the main role of vitamin D is to regulate calcium metabolism and bone health, it has multiple other functions. Vitamin D is essential for immune system integrity, enhancing muscular contractility, protecting the respiratory system, regulation of blood pressure and coronary vessel patency, regulation of mood, appetite, and maintaining intact cognition. Because of the known role of vitamin D in regulation and modulation of the immune system, it has a close relationship to atopy and atopic disorders.[3] This review articles aims to demonstrate the relationship between vitamin D and atopy.

VITAMIN D METABOLISM, ROLES, AND DEFICIENCY

Physiology of vitamin d metabolism

Vitamin D is considered a hormone rather than a vitamin. There are two main forms of vitamin D in the body. The first (and main source of vitamin D in the body) is vitamin D3 or cholecalciferol. It is synthetized in the skin

from a compound called 7-dehydrocholesterol (7-DHC) when the skin is exposed to ultraviolet rays from sunlight. The process of synthesis of vitamin D3 is a non-enzymatic two-step process.[1] The B ring of cholecalciferol is first broken by the ultraviolet rays forming a pre-D3 compound. Pre-D3 then isomerizes to the active form of vitamin D3 through the influence of heat. Whilst exposure to sunlight is the major source of vitamin D3 for human, few types of food are rich in this form of vitamin D particularly fatty fish. The second form of vitamin D is the ergocalciferol (or vitamin D2) which is taken from diet. It is derived from plant steroids (a compound called sterol ergosterol) and is hydrozylized twice in the body. The first hydroxylation occurs in liver through the 25-hydroxylase enzyme to a semi-active form called 25 hydroxy vitamin D (25(OH)D).[2] The most important 25 hydroxylase is CYP27B1. In the kidney, a second hydroxylation occurs through CYP27B1 1-hydroxylase enzyme to produce the active hormonal form of vitamin D which is the 1,25 dihydroxy vitamin D (1,25 (OH)2 D). Catalysis of vitamin D occurs later by CYP24A1. Vitamin D2 is synthesized in plants and fungi, particularly mushroom, when exposed to ultraviolet rays. It is added to food for fortification. The active form of vitamin D (1,25 (OH)2 D) binds to vitamin D receptor (VDR) stimulating vitamin D response elements (VDREs). Vitamin D receptors (VDRs) are present in almost all body tissues. Therefore, it has various functions in the body.

Vitamin D Roles

Out of 144 study participants, 111(77%) were aware that dog bite causes disease while 33(23%) were not aware that dog bite causes disease.

With the recent growing discovery of the presence of vitamin D receptors (VDR) and CYP27B1 at various sites, many roles of vitamin D have been identified. Along with its main role in regulating calcium metabolism and bone health, vitamin D plays an important pathophysiological role in many diseases such as cancer, infection, skin hyperproliferative disorders, hyperparathyroidism, and autoimmune diseases.[4] Vitamin D is essential to prevent bone diseases such as rickets, osteomalacia, osteoporosis, and bone fracture. This protective effect is mediated through both enhancing intestinal absorption of calcium and phosphate and a direct effect on cartilage to stimulate bone remodeling and development.[5]

Vitamin D is also essential for parathyroid function integrity. Adequate vitamin D level in the circulation is an established protective factor against hyperparathyroidism. The parathyroid gland is rich in Vitamin D receptors (VDR) and CYP27B1 and thus highly sensitive to alteration of 1,25(OH)2 D alterations in the blood. This explains the effectiveness of vitamin D3 analogues (such as falecalcitriol and maxacalcitol) in the treatment of chronic kidney disease-associated secondary hyperparathyroidism.[6]

Vitamin D is also necessary for skin health. Calcipotriol and maxacalcitol analogues of vitamin D3 are approved for treatment of hyperproliferative skin disorders, particularly psoriasis and non-melanoma skin cancer.[7] Vitamin D stimulates dermal cells differentiation, prevents their hyperproliferation, and modulates the immune dysfunction associated with these skin diseases. This ability to suppress hyperproliferative cells made vitamin D analogues promising therapeutic agents for treatment of cancer.[8] Because the adipocytes and pancreatic β cells were also found to express VDRs, vitamin D was discovered to be necessary for prevention of obesity, diabetes, and metabolic syndrome.[9] Furthermore, cardiac cells and muscles express VDR and CYP27B1, and vitamin D analogues were thus found to be protective against cardiac hypertrophy. Vitamin D deficiency in human was found to be associated with increased renin, hypertension, atherosclerosis, and cardiomyopathy.[10]

Of particular importance, vitamin D plays an important role in modulation of immunity and immune system response, and this role explains the association between vitamin D deficiency and atopy.[11] This role is expressed in detail in the next section.

Vitamin D deficiency

The most common cause of vitamin D deficiency is inadequate exposure to ultraviolet sunlight.[12] In infants and children, another very common cause is prolonged dependency on breast milk as the only source of diet in infants older than 6 months. Exclusively breast-fed infants after this age are often deficient in vitamin D.[13] Malabsorption and accelerated catabolism of vitamin D due to certain disorders or medications constitute less common etiologies for vitamin D deficiency.

In children, vitamin D deficiency may be asymptomatic. Severe and prolonged deficiency presents with delayed dentition and delayed motor developmental stones such as sitting, standing, or walking. Clinical examination of these children reveals leg bowing, knock-knees, head bossing, and rosary of costo-chondral junctions. In advanced states, bone fracture, spinal deformity, stunted growth, and intellectual disability occur. Older children and adults complain of muscle spasms, bone pains, and sleep disturbance. Hypocalcemia resulting from vitamin D deficiency may result in paresthesia, tetany, or seizures.[14] The main disorders of vitamin D deficiency in children are rickets and osteomalacia.[15,16]

Diagnosis of vitamin D deficiency depends on clinical presentation, laboratory investigations, and imaging. The laboratory test of choice for establishing the diagnosis of vitamin D deficiency is measurement of serum 25-hydroxyvitamin D [25(OH)D] level. Other tests include

calcium, phosphate, magnesium, and parathyroid hormone levels.[17] Because deficiency of bone mineralization and calcification is most evident at metaphysis of long bones, vitamin D deficiency result in widening of metaphyseal plates. This is visualized on plain x ray imaging of long bones such as distal ulna, distal femur, and proximal tibia. Anterior ends of ribs may also show rachitic rosaries. In advanced states, coxa vara, coxa valga, Harrison's sulcus at sternum may occur.[18]

ATOPY

Atopy is defined as the hereditary tendency of an individual to develop allergic diseases such as atopic dermatitis (eczema), bronchial asthma, and allergic rhinitis (hay fever). It refers to the exaggerated and inappropriate immune response to foreign antigen including intrinsic antigens and extrinsic allergens such as food or inhalants e.g. pollen, dust mites, dander, and chemical/physical irritants. Atopic syndrome refers to genetically-mediated predisposition to excessive production of immunoglobulin E (IgE) in response to exposure to these allergens.[19]

Hypersensitivity reactions are four types (I: IV), and atopy represents an exaggerated type I hypersensitivity response.[20] Type I hypersensitivity reactions are immediate IgE-mediated immune responses that involves binding of foreign antigen to the immunoglobulins. IgE-Antigen complexes bind to basophils and mast cells resulting in the release of inflammatory mediators such as cytokines, proteases, histamines, leukotrienes, prostaglandins, and chemotactic factors.[19]

These inflammatory mediators result in recruitment of eosinophils, type 2 helper T cells, and other inflammatory cells. Such inflammatory response had various effects on blood vessels, capillaries, smooth muscles, and secretory glands leading to vasodilation, increased capillary permeability, smooth muscle spasm, and mucous hypersecretion. This hypersensitivity reaction occurs in all atopic disorder such as eczema, urticarial, angioedema, allergic conjunctivitis, allergic rhinitis, bronchial asthma, and others.[20]

RELATIONSHIP BETWEEN VITAMIN D DEFICIENCY AND ATOPY

There is an established significant correlation between vitamin D deficiency and atopic diseases such as allergic rhinitis, allergic conjunctivitis, bronchial asthma, and eczema.[21]

This observation has been long studied to explore the exact pathophysiologic mechanism by which vitamin D influence atopy-mediated hypersensitivity reaction. With the recent discovery of VDR and CYP27B1 expressed in different tissues including myeloid cells, those mechanisms could be revealed.[22,23] Vitamin D plays its role in protection against and treatment of atopic disorders through modulating the immune system as will be discussed in this review.

VITAMIN D AND THE IMMUNE SYSTEM

Basically, there are two types of immunity that interact together for proper function of the immune system: the innate and the adaptive immunity, and vitamin D is closely correlated with the two types.[11] The innate immunity involves the interaction between Toll-like receptors (TLRs) on the surface of different antigen-presenting cells (e.g. mast cells, monocytes, macrophages, and polymorphonuclear cells) with pathogen-associated molecular pattern (PAMP) that are released by foreign antigens. This interaction triggers the immune response by inducing various antimicrobial peptides (AMP) e.g. reactive oxygen species (ROS) and Catheliciden which consequently damage the antigens. Vitamin D role comes here in this step through inducing the expression of cathelicidin in antigen-presenting cells and epithelial cells. This action is further facilitated by the increased expression of CYP27B1 and VDR by the stimulated TLRs. Therefore, adequate vitamin D levels are essential for promoting the innate immunity.[24,25] As regards the adaptive immunity, it involves activation of antigen presenting cells when exposed to foreign antigens after recognizing them. The most important cells here are T helper cells class Th1, Th2, and Th17. Vitamin D facilitates the adaptive immune response through activating T helper cells both directly and indirectly by acting on cytokines e.g. IL-2, IL-6, IL-12, IL-23, and IFN-γ.[3,24]

The recognized effect of vitamin D on immune modulation was the basis for its use in treatment of autoimmune disorders and in immunosuppression after organ transplantation.[26,27] Furthermore, this close interaction between vitamin D and immune system were the main focus of studying the correlation between vitamin D and atopy.

VITAMIN D AND ATOPY

Antigen-presenting cells, particularly mast cells, play a vital role in the pathogenesis of atopy and allergy.[3,21] Mast cells produce cytokines (such as tumor necrosis factor) that stimulate T helper cells recruitment. This recruitment subsequently activates an immune response to the recognized antigen. Vitamin D was found to possess an inhibitory effect on mast cells. It suppresses mast cell action and reduce the final production of immunoglobulin E in the immune pathway. Simultaneously, vitamin D is converted by human mast cells to active metabolites that inhibit the IgE-mediated release of inflammatory mediators.[28] The interaction between vitamin D and mast cells is carried out through CYP27B1. Many authors have noted that the mast cells express higher levels of basal reactivity in cases of low or absent vitamin D. Adequate vitamin D levels increase the

expression of VDRs which consequently inhibit IgE synthesis and prevent the degranulation of mast cells.[3,28]

Additionally, vitamin D has a direct effect on interleukin 33.[28] Interleukin 33 is involved in activation of allergic inflammation and is considered a danger signal for atopy. It has a synergistic action with neuropeptide substance P in stimulating mast cell action. Vitamin D inhibits its action and stimulates the production of soluble interleukin-33 receptors. Several studies demonstrated that low levels of active vitamin D3 were associated with high levels of IgE and eosinophils count. Given those multiple mechanisms of action of vitamin D on immune system, it is reasonable that vitamin D deficiency in encountered in many atopic diseases.[3,24]

VITAMIN D DEFICIENCY AND ATOPIC DISEASES

Vitamin D was linked to many atopic diseases.[22] Various studies reported that vitamin D levels were significantly low in patients with atopic diseases. Researchers noted a link between atopic dermatitis in children and vitamin D deficiency.[29,30] The mechanism by which vitamin D level prevents atopic dermatitis is through inhibition of proliferation and induction of terminal proliferation of keratinocytes, along with its aforementioned effect on mast cell suppression. Similarly, vitamin D deficiency was found to be a risk factor for contact hypersensitivity response. In contrast, high maternal serum levels of 25(OH)D were associated with higher prevalence of infantile eczema at the age of 9 months.[31]

Vitamin D deficiency was also reported to be significantly associated with bronchial asthma in children.[32-34] Additionally, one cross-sectional study noted that low vitamin D levels were significantly correlated with the use of anti-inflammatory drugs and with asthma-related hospitalizations.[35] Furthermore, low maternal serum vitamin D levels during pregnancy were associated with higher prevalence of childhood wheezing around the age of 5 years.[31] Children and adults with allergic rhinitis were found to have considerably lower serum levels of vitamin D in comparison to normal healthy individuals.[36] A systematic review referred to a significant correlation between the severity of rhinitis and vitamin D levels.[37] Low vitamin D levels were also reported to be significantly associated with atopy, food allergens, and other types of allergies.[38] Despite the established correlation between vitamin D and atopic disorders, double-blinded randomized controlled studies are still lacking to approve this relationship and to provide clear consensus guidelines for the recommended supplementary doses of vitamin D to prevent or treat these conditions.

CONCLUSION

In conclusion, vitamin D is an essential immunomodulatory vitamin that interact with the immune system in response to foreign antigens. This interaction is mediated by the vitamin D receptors (VDR) expressed on the surface of various immune cells. Vitamin D has an inhibitory effect on synthesis and release of immunoglobulin E and thus is closely related to atopic disorders. Vitamin D deficiency is a risk factor for bronchial asthma, and it increased asthma-related exacerbation. Low vitamin D levels are encountered in patients with allergic rhinitis and increase the severity of the disease. Other allergic conditions such as atopic dermatitis, contact dermatitis, and food allergy were reported to be significantly correlated with vitamin D serum levels. Despite the established correlation between vitamin D and atopic disorders, double-blinded randomized controlled studies are still lacking to approve this relationship and to provide clear consensus guidelines for the recommended supplementary doses of vitamin D to prevent or treat these conditions.

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