



ASSOCIATION BETWEEN VITAMIN D DEFICIENCY AND ALLERGIC DISEASES

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"A vitamin is a substance that makes you ill if you don't eat it."

(Albert Szent-Gyorgyi, Nobel Prize winner in Physiology and Medicine, 1937)

Abstract

Vitamin D is important for the regulation of bone and muscle metabolism and other functions in the human body. The hydroxylated forms of vitamin D₂ and D₃ are the most important, however only 1,25(OH)₂D₃ is a fully active product. This hormone exerts its pleiotropic actions via the specific receptor VDR, an important transcription factor. The optimal vitamin D concentration in the blood is >20 ng/mL whereas insufficiency and deficiency are 10-20 ng/mL and <10 ng/mL, respectively. To maintain the optimal vitamin D status the total vitamin D intake in children should be at least 400 IU/day. Several studies have shown the effects of vitamin D on proinflammatory cytokines, regulatory T cells and immune response. Vitamin D is a very important activator of the immune response, and in hypovitaminosis D, T killer cells are not able to fight off serious infections. A negative correlation between IgE and vitamin D concentration and a positive relation between vitamin D and lung function was documented in children and teenagers with asthma. In asthmatic children the vitamin D deficiency is associated with a higher corticosteroid use. Vitamin D supplementation in patients with steroid resistant asthma can potentially increase the glucocorticoid therapeutic response. Recently, a new mediator in allergy pathogenesis was reported - IL-33 and its soluble receptor ST2. IL-33 promotes the Th₂ lymphocytes response as well as the activation of both mast cells and eosinophils via the ST2 receptor.

VITAMIN D METABOLISM

The classical effects of vitamin D concern bone and calcium-phosphorus metabolism. Vitamin D is also essential for muscle function. It exists in several forms among which ergocalciferol (D₂), cholecalciferol (D₃) and hydroxylation products are the most important. The sources of vitamin D₂ are limited (plants, fungi, external supplementation) whereas vitamin D₃ is produced in the skin during sun exposure (ultraviolet B), but can also be taken as supplements or from the diet (1), although its quantity in the food is low (2, 3). Circulating 25-hydroxyvitamin D [25(OH)D] hydroxylated in hepatocytes by 25-hydroxylase is further converted in kidneys to the active hormone 1,25

dihydroxyvitamin D [1,25(OH)₂D] by 1-hydroxylase. The second hydroxylation is tightly regulated, stimulated by PTH while inhibited by FGF23. Activity of this enzyme is also found in the mitochondria of proximal tubules and in intestine, prostate gland, osteoblasts, macrophages and immune cells. Active 1,25(OH)₂D operates through the cytosolic vitamin D receptor (VDR) found in almost all tissues and organs in the human body, which could explain its pleiotropic function. This action can be direct on genes (genomic response) or can be a non-gene action, which is faster, so-called a rapid response (4). VDRs are important nuclear transcription factors which allow to bind directly the DNA and then turn on or off specific genes (5).

The primary function of the 1,25(OH)₂D (calcitriol) is a regulation of calcium and phosphorus homeostasis by the impact on parathyroid glands and parathormone secretion which increases the Ca²⁺ mobilization from bones and calcium absorption in the intestine. In addition vitamin D regulates cell proliferation and differentiation via Ca²⁺ signals in osteoblasts. The calcium in osteoblasts comes from the endoplasmic reticulum by releasing through the inositol-1,4,5-phosphate (IP₃R) and ryanodine receptors (RyR) which are sensitive to Ca²⁺ concentration. Moreover, vitamin D in the bones is responsible for increased transcription of bone matrix proteins such as collagen type I, osteocalcin and osteopontin produced by osteoblasts in the process of bone formation. It is well established that vitamin D stimulates osteoblast's growth and differentiation (6). In the other tissues locally hydroxylated 25(OH)D is responsible for so called "non-classical" effects. Recently, it was demonstrated that non genomic actions of calcitriol are performed by a membrane-associated VDRs (7,8) and their activation facilitates L-type Ca²⁺ channel activity and increases [Ca²⁺] concentration (9).

VITAMIN D INSUFFICIENCY/DEFICIENCY

The optimal vitamin D concentration in blood is >20 ng/mL (20-60 ng/mL for children, 30-80 ng/mL for adults) (10). Insufficiency and deficiency is characterized by concentrations 10-20 ng/mL and <10 ng/mL, respectively (1). The definition of optimal vitamin D status is connected with the level of 25(OH)D that maximally suppresses the PTH secretion, in fact the major stimulus for PTH secretion is a low serum concentration of ionized calcium. However many studies have shown the connection between circulating 25(OH)D and PTH concentration, which demonstrate that there is a plateau in suppression of PTH when the concentration of 25(OH)D is around 30 ng/mL (11). An important limitation is that in children during puberty, physiologically elevated PTH concentration does not indicate an inadequate vitamin D as it is important for the bone's growth process. Low serum vitamin D does not increase the PTH secretion and higher concentration of vitamin D (> 30ng/mL) does not suppress PTH secretion (1).

The total vitamin D intake in children and adolescents from all sources (diet and/or supplements) should be at least 400 IU/day. In overweight/obese children/adults supplementation with higher doses of vitamin D up to 800-1000 IU/day should be considered because vitamin D is stored in fat tissue (12).

In pregnant and lactating women the supplementation is suggested only if there is inadequate intake from the diet and/or skin synthesis. However, some studies have shown conflicting data. At low maternal vitamin D concentration there is an increased risk of wheezing in children at age 3-5 years but also at the higher concentration of maternal vitamin D (> 30 ng/mL) increased risk for asthma in 9 years old children was shown (1). There is no consensus for recommended daily dosage to obtain the optimal vitamin D concentration however, the researches agree that the intake of vitamin D₃ and supplementation with vitamin D₃ is better than with vitamin D₂ because of the longer half life of the former (13).

Hypovitaminosis D is a prevalent disorder in many countries and varies widely by regions (14). It has been estimated that 1 billion of people worldwide have vitamin D deficiency. According to several studies 40 to 100% of U.S. and European elderly men and women which are living in the community and not in the nursing homes have hypovitaminosis D (15).

The NHANES researchers analyzed the data on more than 6,000 million children, aged one to 21 years, collected by the National Health and Nutrition Examination Survey (NHANES) between 2001-2004. They found that 9% of the study

sample were vitamin D deficient, while another 61% were vitamin D insufficient. Low vitamin D concentrations were especially common in children who were older, female gender, African-American, Mexican-American, obese, drank milk less than once a week, or spent more time indoor than outdoor with a sedentary life style (16) . These are also independent risk factors for accelerated atherosclerosis and metabolic syndrome (17) . The researchers also found that vitamin D deficiency was associated with poor bone health, lower calcium concentration, higher systolic blood pressure and lower HDL cholesterol values, which are key risk factors for heart disease (18).

Risk factors for hypovitaminosis D include extremes of age, sex, winter season, skin pigmentation, malnutrition, lack of sun exposure and obesity. During childhood, vitamin D deficiency can cause growth retardation, skeletal deformities (rickets) and may increase the risk of hip fracture in adulthood (15). Vitamin D deficiency has been linked to many disorders such as: increased risk for preeclampsia, multiple sclerosis, rheumatoid arthritis, types 1 and 2 diabetes, cardiovascular disease, dementia, some cancers and infectious diseases (1, 19). Moreover, recent studies suggested that children and adolescents who are vitamin D deficient are at higher risk for certain food and environmental allergies and low vitamin D level is associated with severity of asthma in children (20). Since the sources of vitamin D are limited, novel sources are being evaluated to improve the vitamin D status in the population. Fungi, such as yeasts and mushrooms, produce vitamin D₂ via UVB irradiation of ergosterol, which makes them naturally rich source of vitamin D. Vitamin D₂ from UV-treated mushrooms has been found to increase serum 25[OH]D and bone mineral density (BMD) in rats (21). Vitamin D₂-rich UV-treated yeasts can be used for baking bread, that is a widely consumed food item.

According to the estimates the direct and indirect costs of vitamin D deficiency are around 187 billions € in Europe, which can be saved annually by improving vitamin D status to at least 40 ng/mL in the population (22) . There is an agreement that increased intake of vitamin D in deficient children may be clinically useful but vitamin D supplementation in healthy children was not shown to have significant effects on total body bone mineral content (BMC) and hip or forearm BMD (23).

ASSOCIATION BETWEEN VITAMIN D DEFICIENCY AND ALLERGY

Allergy is a hypersensitivity of immune system activated by contact with common environmental allergens, molecules that in physiological conditions do not stimulate a specific defensive mechanism - hypersensitivity reaction type 1 [HR-T1] with the consequent abnormal production of IgE (24) . The pathogenic allergens can be found in different substances such as: plant pollens, some drugs, food, diagnostic reagents, insect toxins, dust mite excretion, animal fur and dander, parasites (Table 1).

Table 1. The most frequent causes of anaphylactic reaction (in descending order) (25)

Food	Peanuts, nuts, sea food, eggs, vegetables, fruits, milk
Insects toxins	Bee and wasp stings
Drugs latex rubber gloves used by medical and paramedical staff	Penicillin, sulfonamides, salicylates

HR-T1 process can be divided into two steps: the first allergen exposition and second allergen exposition.

- During the first allergen exposition, macrophages phagocytose the contact allergens, showing these molecules to Th2 cells. Activated Th2 lymphocytes release cytokines such as IL-4, IL-5, which allows the plasma cells, by cooperation between T and B cells (26), to release IgM. These IgM act immediately on antigens reducing their concentrations; in this step the clinical symptoms are weak because the concentration of allergens is quickly reduced by IgM before the increase in the concentration of IgE occurs (27, 24)

- The IgE released by B cells, get into contact with the mast cells surface, where, during the second allergen exposition, the formation of IgE “bridging” occurs (Fig.1) . This activate a cascade of reactions inside the mast cells with the purpose of degranulation and release of several inflammatory molecules. These preformed substances, such as histamine, cause the immediate allergic reaction (within minutes after contact with the allergen). In the late phase of this reaction (within 5 hours after contact with allergen) other, so called, generated mediators (prostaglandins, leukotrienes etc.) are involved (27, 24) .

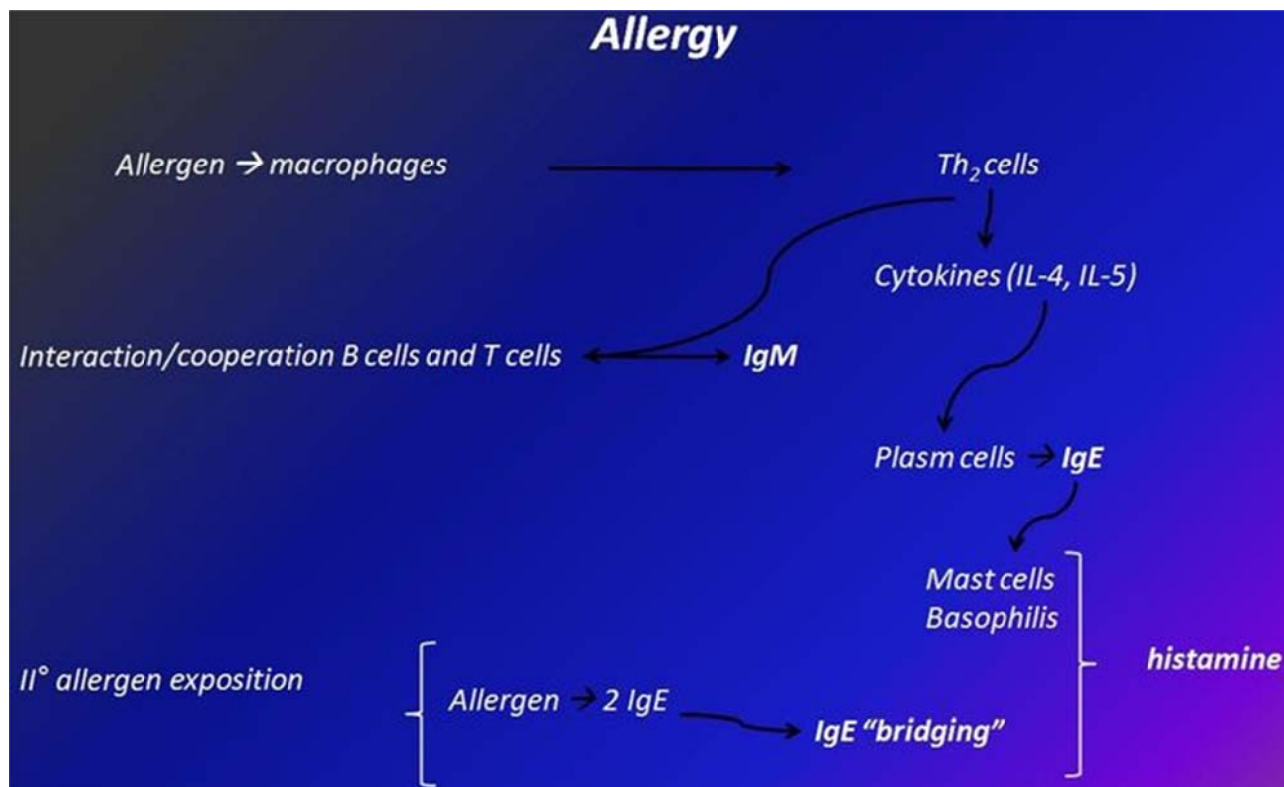


Figure 1. Scheme of hypersensitivity reaction type 1 (HR-T1).

The IgE-associated diseases are multifactorial complex disorders, which involve both genetic and environmental components. Several studies have shown the effects of vitamin D on proinflammatory cytokines, regulatory T cells and immune response. von Essen et al from Copenhagen University have discovered that vitamin D is very important to activate the immune response, and in cases of hypovitaminosis D, T killer cells are not able to react and fight off serious infections in the body. This study has shown that naive human T cells have very low expression of VDR and phospholipase C- γ 1 (PLC- γ 1). However the T cell receptor (TCR) signals induce the VDR expression which binds the 1,25(OH)₂D₃ and translocates it into the nucleus where vitamin D activates the gene encoding PLC- γ 1 (28) .

Negative correlation between IgE and vitamin D concentration and positive relation between vitamin D and lung function was documented in children and teenagers with asthma (29) . It was suggested that vitamin D supplementation may have anti-inflammatory and anti-atherogenic action, but the link between the incidents of allergies and CVD risk is not confirmed yet. Some recent in vitro studies have shown that 1,25(OH)₂D₃ inhibit directly the passively sensitized airway smooth muscle cells (30) and that in the bronchial smooth muscle cells it increases glucocorticoids bioavailability (31) . Hypovitaminosis D in asthmatic children have been observed to be associated with increased corticosteroid use (32) and investigations with T cells from patients with steroid-resistant asthma showed that vitamin D supplementation could potentially increase the glucocorticoid therapeutic response by restoring the compromised steroid-induced interleukin-10 response (33) . Recently, some data was reported on the novel mediator – IL-33 and its soluble receptor ST2 and their role in the pathogenesis of allergy and asthma as well as in atherosclerosis (34,35,36) . In humans IL-33 mRNA was found predominantly in the skin and lung tissues. The cellular mRNA expression has been described in human adipocytes, synovial fibroblasts, high endothelial venules and

endothelial cells. The cellular source of IL-33 protein in vivo have proved the vasculature as the dominant source, in particular the endothelial cells. IL-33 has been detected also in fibroblastic reticular cells of lymphoid tissues, skin keratinocytes, epithelial cells (of stomach, tonsillar crypts and salivary glands), cardiac fibroblasts and cardiomyocytes. It is interesting that the cellular location of IL-33 in the cells seems to be nuclear rather than cytoplasmic.

IL-33 is a member of the IL-1 family, which promote the Th2 response in lymphocytes as well as the activation of both mast cells and eosinophils via the ST2 receptors. Probably it is activated as the proinflammatory cytokines IL-1 β and IL-18, via caspase-1-dependent proteolysis, but this needs yet to be proven (37,38) .

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