Vitamin D impact on immune functions: implications for preventive strategy of allergic disease?

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Abstract
Asthma and allergic diseases are substantial global health problems with a higher prevalence in the westernized countries. It has been proposed that vitamin D deficiency resulting from reduced exposure to sunlight and changes in lifestyle as well as dietary habits may contribute to a high prevalence of asthma and allergic diseases. This review examines the scientific evidence for pluripotent immunoregulatory actions of vitamin D in conjunction with nuclear actions as well as genetic and epigenetic determinants of the vitamin D effects. Findings of epidemiological and clinical studies on the potential association between vitamin D and allergic disease and asthma are reviewed.

Key words: vitamin D, immunity, asthma, allergy, children.

Introduction
Beyond its well-known effects on calcium homeostasis and bone mineralization, vitamin D has become recently recognized as a pluripotent immunoregulator of biological functions with a particular role in immune tolerance and antimicrobial immunity. Although extensive research has been carried out on the vitamin D action, its molecular and cellular mechanisms have not been fully elucidated thus far.

Humans obtain vitamin D in two different forms as prohormones, namely as cholecalciferol or vitamin D₃, a product of the photochemical reaction in keratinocytes from 7-dehydrocholesterol by exposure to sunlight as well as ergosterol or vitamin D₂, synthesized in plants exposed to UVB radiation. The former mechanism provides 80% of vitamin D to the human organism, although both cholecalciferol and ergosterol may also be obtained from animal and plant dietary products, respectively [1]. In the circulation, the precursor is complexed with the vitamin D-binding protein (VDBP) and transported to the liver where the first step of hydroxylation occurs by the mitochondrial cytochrome P-450 25-hydroxylase enzymes encoded by CYP27A1 and/or CYP2R1 genes giving rise to 25(OH)D₃. Subsequent renal hydroxylation at the 1α position by the cytochrome P450 enzyme encoded by CYP27B1 gene leads to the generation of the bioactive 1α,25-dihydroxyvitamin D (1,25(OH)₂D₃) [2]. The proximal kidney tubule is admittedly the primary place of the latter process, however many cell types, including monocytes/macrophages, dendritic cells and lung epithelial cells are capable of synthesizing 1,25(OH)₂D₃ [3-5]. These data in conjunction with expression of the vitamin D receptor (VDR) in many immune cells have led to the recognition of the associations between the vitamin D metabolism and chronic autoimmune, infectious, allergic, cardiovascular, neoplastic, and neurodegenerative disorders [6, 7].

The determinants of the vitamin status include exposure to the sunlight and time spent outdoors, diet rich in natural and fortified vitamin D-rich products and use of supplements, season of the year, latitude, atmospheric conditions, age, skin pigmentation as well as coverage with garments and the use of sunblocks. As both children and adults spend on average only 10% of daylight hours outside [8], the westernized lifestyle poses a high risk of vitamin D deficiency and increased incidence of related diseases.

Defining the vitamin D status
The major circulating form of vitamin D is 25 (OH)D₃, an inactive, relatively stable metabolite that has a half-life of approximately 2-3 weeks and most closely reflects vitamin D classical physiology and its supply to the organ-
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Molecular level of the vitamin D activity

The vitamin D receptor, encoded by the VDR gene, belongs to the nuclear hormone receptor superfamily and NRII subgroup [19]. The VDR mediates its action by first binding the ligand, 1α,25(OH)₂D₃, and then forming a heterodimer with the retinoid X receptor (RXR), which in turn binds to the vitamin D-responsive elements (VDRES) in the promoter regions of relevant target genes and either initiates recruitment of transcriptional complexes with nuclear proteins or downregulates transcription [20]. The VDR expression that has been identified in different cell types of all tissues in the human body and the regulation of approximately 3% of the human genome via the vitamin D pathway reflect its important role in biological processes [21].

The non-classical immunomodulatory actions attributed to vitamin D are warranted by the VDR expression in immune cells – macrophages and their monocyte precursors, dendritic cells as well as T and B lymph cells. The initial observation of the 1α-hydroxylase activity and the ability of macrophages to produce 1,25(OH)₂D₃ upon stimulation with interferon gamma along with the endogenous VDR expression suggest both autocrine and intracrine mechanisms of the vitamin D action in these cells [22]. Subsequently, it was demonstrated that the vitamin D response elements are present in the promoter regions of CAMP (also known as HCAP18/LL-37/FALL37) and DEF4 genes encoding for the antimicrobial peptides (AMPs), cathelicidin and β-defensin 2, respectively [23, 24]. The ability to promote the synthesis of cathelicidin upon the macrophage Toll-like receptor (TLR) 1/2 activation by microbial PAMPs (pathogen-associated molecular patterns) is the most likely mechanism by which vitamin D interacts with the innate immune response. It is worth noting that regulation of antimicrobial peptides by 1,25(OH)₂D₃ has been shown in a variety of cells other than macrophages, such as keratinocytes [25, 26], lung epithelial cells [27, 28], and myeloid cell lines [29], thereby priming these cells for the innate immune response to pathogens.

In dendritic cells, 1,25(OH)₂D₃ regulates their maturation as well as impacts the phenotype and function of these cells. Preferentially, myeloid dendritic cells (mDC), which are effective antigen presenting cells, are the target of the vitamin D regulatory actions, leading to the increase of their tolerogenicity, whereas protolerogenic plasmacytoid dendritic cells (pDC) are less affected [30]. A key mechanism of this vitamin D pathway-related immunomodulation relies on downregulating expression of the costimulatory molecules, such as CD40, CD80, and CD86 as well as cytokine IL-12 along with upregulating cytokine IL-10. In myeloid DCs, 1,25(OH)₂D₃ inhibits intracellular signaling by nuclear factor-κB (NF-κB) pathway and regulates the T cell response, promoting generation of inducible Foxp3+ regulatory T cells at the periphery [31].

The VDR expression in the resting T cells is almost undetectable, but increases during their proliferation upon antigenic stimulation, resulting in vitamin D-dependent modulation of the T lymphocyte phenotype and shaping the cellular immune response. Downregulation of antigen-specific interferon γ (IFN-γ) and interleukin 17 (IL-17) responses in T lymph cells [32], resulting in predominating Th2-type immune processes may be a direct effect of 1,25(OH)₂D₃ on VDR expressing T lymphocytes or an indirect action via DCs in a paracrine fashion [33].

In the activated B cell, vitamin D exerts an inhibitory effect on development and functions, decreasing plasma cell differentiation and immunoglobulin production, contributing to B lymphocyte homeostasis [34, 35]. Detailed vitamin D effects on immune cells are displayed in Figure 1.

Genetic polymorphisms and epigenetic interactions in the pathogenesis of allergic diseases

There is growing evidence that diverse sensitivity to, and effects of the vitamin D actions may be due to genetic variability of the vitamin D pathway influencing activ-
ity of a wide number of related genes either directly or indirectly by epigenetic, gene-environmental interactions. Single nucleotide polymorphisms (SNPs) are genetic variants frequently occurring in the population and showing a functional impact on the immune system and contributing to the susceptibility to immune-mediated diseases. So far, three adjacent restriction fragment length polymorphisms for BsmI, ApaI, and TaqI at the 3’ end of the VDR gene have been most frequently studied [21].

Since the VDR is found in many different cell types, including immune cells, and mediates vitamin D-dependent effects on immune regulation by altering the differentiation and proliferation response, polymorphism of the VDR gene may be associated with intersubject predisposition to allergic diseases. So far, three adjacent restriction fragment length polymorphisms for BsmI, ApaI, and TaqI at the 3’ end of the VDR gene have been most frequently studied [21].

VDR maps to the centromeric region on the long arm of the chromosome 12, that has been linked to asthma and allergy-related phenotypes in genome-wide linkage analysis [36, 37]. Several polymorphisms of the VDR gene have been identified, which may be relevant to asthma and atopy. It is worth noting that FokI polymorphism was demonstrated to have a major impact on the immune system, resulting in VDR proteins with different structures and functional consequences in immune cells. The presence of the shorter F-VDR was associated with higher NF-κB and IL-12p40-driven transcription and more active inflammatory response [38]. In the Canadian asthma family-based cohort, an increased risk of asthma was shown to be associated with the Apal C allele of the VDR gene [39].

Due to the fact that numerous metabolic pathways may play a major role in complex multifactorial diseases, polymorphism in other genes involved in vitamin D system may be associated with asthma and atopy. In the German Asthma Family Study, Wjst et al. [40] identified SNPs in the IL-10, VDBP, CYP2R1 and CYP24A1 genes associated with asthma and IgE levels. Furthermore, a modest association with asthma or atopy was also confirmed in the study by Bossé et al. [41] with regard to SNPs in the IL-10 and CYP24A1 genes. In that report, the authors paid special attention to the fact that both single nucleotide polymorphisms as well as orientation of the risk alleles may differ between populations and the genetic effect of the VDR pathway may be overruled by other immune processes and be detectable in specific environments or age-related context.

Gene-environmental interactions, particularly these environmental exposures that act early in the postnatal period, as stated in the Barker’s hypothesis, may epige-
Vitamin D status and the risk of allergic diseases

The vitamin D effects on the immune phenomena have been translated into implications regarding the relationship between the vitamin D status and the risk of allergic diseases. The impact of 1,25(OH)₂D₃ on the fetal lung growth and development as well as surfactant production in alveolar type II cells [44] in conjunction with the effect on the developing immune system and promotion of the protolerogenic phenotype leads to questions about the role of vitamin D in the development of asthma.

Several studies showed a positive correlation between either the maternal serum 25(OH)D₃ during pregnancy or the higher vitamin D intake as well as the reduced risk of respiratory tract infections and early childhood wheezing in the offspring [45-47], the effect that might be owing both to the immunoregulatory activity of vitamin D and also to its antiviral actions [48]. Furthermore, in a study by Miyake et al. [49], the protective effect of maternal dairy food and vitamin D intake during pregnancy was not exclusively confined to respiratory symptoms, but the reduced risk of eczema in infants was also demonstrated.

However, it is worth noting that there is a considerable inconsistency regarding the results of the observational studies, notably because of influence of possible confounders. Morales et al. [50] admittedly showed the association between the higher maternal 25(OH)D₃ concentrations in pregnancy and the lower risk of respiratory tract infections, but not of wheezing and asthma in childhood. Moreover, contrary arguments that vitamin D excess may increase the risk of allergic diseases have also been proposed, based on the independent reports by Gale et al. [51] and Rothers et al. [52].

Another group of clinical studies was aimed at the assessment of the relationship between vitamin D status and allergic disease severity. The first epidemiological study demonstrating an association between low vitamin D levels and increased markers of asthma severity, including serum IgE, eosinophil count, the use of inhaled corticosteroids and hospitalization rate in the previous year was conducted among schoolchildren in Costa Rica [53]. Subsequently, higher odds of severe asthma exacerbations were shown by the same group of researchers in the Childhood Asthma Management Program Study in North American children [54]. In a study by Gupta et al. [55], the link between lower vitamin D levels with not only clinical manifestations but also with the decreased spirographic parameters as well as with histological features of the airway remodeling in children with severe, therapy-resistant asthma was demonstrated. This mechanistic approach to the relationships between serum vitamin D levels and asthma severity assessed based on the pulmonary function test was also reported by Alyasin et al. [56] and Tolppanen et al. [57], showing a positive correlation between 25(OH)D₃ status and the lung function.

The role of vitamin D as a possible preventive measure for asthma was explored in the study by Majak et al. [58]. The authors demonstrated that vitamin D supplementation during a period from September to July prevented decline of serum 25(OH)D₃, the effect that was associated with a reduced risk of asthma exacerbations triggered by acute respiratory tract infections. Assessment of the impact of vitamin D on atopic dermatitis as a possible therapeutic intervention was also investigated. A significant improvement in baseline score was noted in children receiving vitamin D supplementation, however, because of the small sample size comprising 5 patients, further trials on the effect of vitamin D on this entity are indispensable [59]. With a global increase in food allergy, the role of vitamin D supplementation and food allergy outcomes is a priority area of future research.

Concluding remarks

Given the potential for vitamin D to suppress inflammatory responses and enhance the antimicrobial pathway activity, it has been suggested that its deficiency might be blamed for the epidemic of allergic diseases. Therefore, the question whether implications regarding the adequate status of vitamin D as preventive strategy and treatment modality for asthma and other allergic disorders are being admitted as an endpoint of the aforementioned considerations, remains unanswered and requires further clinical controlled prospective studies.

References


