

# The Role of Vitamin D in the Pathogenesis of Allergic Rhinitis and Atopy

## *Alerjik Rinit ve Atopi Patogenezinde Vitamin D'nin Rolü*

Review  
Derleme

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Abstract

The aim of this work is to analyze and compare the discussions about the relationship between vitamin D and allergic rhinitis and the symptoms of atopy. Most investigators analyze its role as a mediator in the provision of an adequate immune response. Its effect, not only on allergic, but also on some neoplastic, autoimmune and cardiovascular disorders is widely discussed. However, many questions regarding its activity remain unclear and extensive research in this area will be crucial

for our understanding of both the physiological role and its potential therapeutic effect for a number of immune and inflammatory diseases. Undoubtedly proven is the influence of vitamin D on different cells of the immune system. Finally, the authors draw conclusions on current knowledge about the possibilities of influencing the vitamin D in the pathogenesis of allergic reactions.

**Key Words:** Vitamin D, allergic rhinitis, atopy, immune system

Özet

Bu çalışmanın amacı, vitamin D ile alerjik rinit ve atopi belirtileri arasındaki ilişki hakkındaki tartışmaları analiz etmek ve karşılaştırmaktır. Çoğu araştırmacı yeterli immün yanıt sağlamada bir mediatör olarak vitamin D'nin rolünü analiz etmektedir. Onun yalnızca alerjik değil, aynı zamanda bazı neoplastik, otoimmün ve kardiyovasküler hastalıklar üzerine etkisi yaygın olarak tartışılmaktadır. Ancak, aktivitesi ile ilgili birçok soru açıklık kazanmamıştır ve bu alanda kapsamlı bir araştırma hem birçok immün ve

inflamatuar hastalığındaki potansiyel terapötik etkisini hem de fizyolojik rolünü anlamamız için çok önemli olacaktır. Kuşkusuz kanıtlanmış olan immün sistemin farklı hücreleri üzerine vitamin D'nin etkisidir. Son olarak, yazarlar alerjik reaksiyonların patogenezinde vitamin D'nin etkisi ihtimali ile ilgili güncel bilgiler hakkında sonuçlar çıkarmaktadırlar.

**Anahtar Kelimeler:** Vitamin D, alerjik rinit, atopi, immün sistem

Vitamin D belongs to a group of fat-soluble vitamins. In nature, it is contained in large quantities in fish oil, liver, egg yolk, and less in some other products of animal origin. For a man, the main way to obtain it is by endogenous synthesis. Its active form-1 $\alpha$ ,25-dihydroxyvitamin D<sub>3</sub>/1.25(OH)<sub>2</sub>D<sub>3</sub>- is a product of biosynthesis, whose first reaction begins in the skin, and is catalysed by sunlight. UVB light (with a wavelength 270-300 Nm) is absorbed from the epidermal and dermal cells, and leads to the separation of the "B-ring" of the 7-dehydrocholesterol, leading to the production of pre-vitamin D<sub>3</sub>. The latter spontaneously isomerizes to vitamin D<sub>3</sub> (Figure 1), which leaves the skin and passes to the liver where it is converted to 25-hydroxyvitamin D of cytochrome P450 enzymes (25-hydroxylase). 25-hydroxyvitamin D is the circulating metabolite, which is converted to the active form 1.25-(OH)<sub>2</sub>D<sub>3</sub>, using the mitochondrial enzyme  $\alpha$ -1 hydroxylase (1, 2). The latter reaction is carried out in the kidney (Figure 2).

Some factors are distinctive for the environment, since reduced outdoor stay, increased skin pigmentation or use of sunscreen cream, can significantly reduce (by 99%) absorption of UV-rays and the subsequent production of vitamin D by the skin (3).

Although the active metabolite is 1.25-(OH)<sub>2</sub>D<sub>3</sub>, in order to determine the serum concentration of the vitamin, the measured form is 25 (OH)D (4-6). In the study they identified a low limit of serum concentration of vitamin D, while most authors accept 30 ng/mL (75 nmol/L) (4, 7, 8). Values lower than those are associated with an increased risk of occurrence of a pathologic process.

The main physiological action of vitamin D is related to the regulation of calcium and phosphorus homeostasis. It plays a primary role in increasing the absorption of calcium and inorganic phosphate in the intestines and reduces their excretion in the urine (9, 10). In the bones, vitamin D affects the activity of osteocytes and provides calcium and phosphorus for normal bone mineralisation (1).



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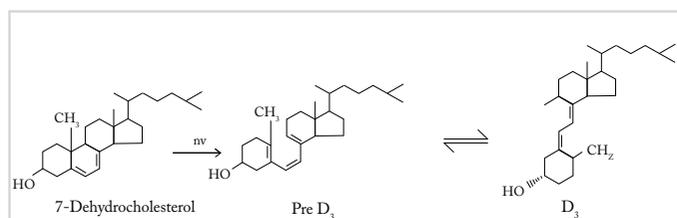


Figure 1. The latter spontaneously isomerizes to vitamin D3

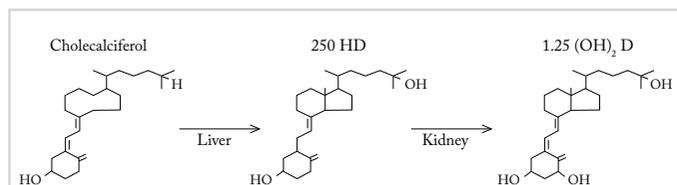


Figure 2. The latter reaction is carried out in the kidney

During recent years, epidemiological data indicate a relationship between vitamin D deficiency and a number of immune-mediated disorders. This has prompted many authors to focus their studies on the relationship between serum vitamin D and certain diseases. The most often mentioned diseases associated with a modulatory effect on fat-soluble vitamins are: cancer of the colon, lung, prostate, diabetes mellitus type I, MS and other autoimmune diseases, cardiovascular diseases and symptoms of atopy (1, 8).

The impact on the immune system and the use of vitamin D for the treatment of infections is known and has been practiced for over 150 years. In 1849, Williams reported favorable results with the use of fish oil, a rich source of vitamin D<sub>3</sub>, in the treatment of more than 400 patients suffering from tuberculosis (11). With the improvement of medical technologies data emerged showing its undeniable role in the regulation of the immune system, namely the discovery of receptors (VDRs) for vitamin D on nearly all cells of the immune system (IS), including T-lymphocytes, B-lymphocytes, neutrophils, macrophages, dendritic cells (DC) etc. (12).

### Vitamin D and T-helper cells

Th-lymphocytes have a central role in the antigen-specific response. The "Normal" response requires the existence of a balanced response between the two subtypes (Th1 and Th2). Th1 cells secrete interferon- $\gamma$  (IFN- $\gamma$ ), interleukin-2 (IL-2) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ). Th1 cell activation is essential for cell-mediated immune responses against neoplastic cells and intracellular pathogens (e.g., viruses). Th2 cells secrete IL-4, IL-5 and IL-13, which are important in the antibody-mediated immunity. Inflammatory responses against extracellular pathogens (mostly bacteria and parasites) require the active involvement of Th2 cells. Allergic rhinitis and the symptoms of atopy are Th2-mediated diseases. They occur when the balance between Th1/Th2 is disturbed in favor of the Th2 subset. As a result, the immune system responds with hyperergic response to certain antigens (allergens) from the environment (13). Currently, the mechanisms that predominantly trigger the response of one subclass Th, resulting in the emergence of various pathological conditions, remain unclear.

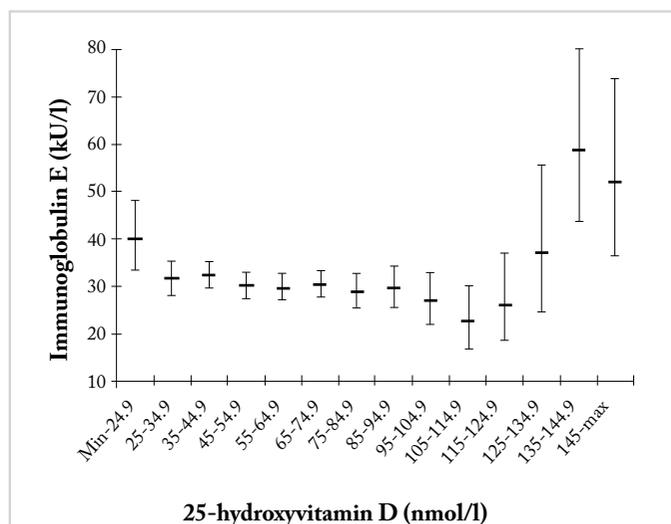


Figure 3. Hyponen E, Berry D, Wjst M, Power C: Serum 25-hydroxyvitamin D and IgE—a significant but nonlinear relationship

In their study Mahon et al. (14) reconfirmed that Th1 and Th2 lymphocytes are target cells for 1,25 (OH)<sub>2</sub>D<sub>3</sub>. Evidence for this can be found in the amount of expression of VDRs on the Th cell surface, whose activation is followed by a 5-fold increase in the number of receptors. The same authors reported a reduction in the IFN- $\gamma$ , IL-2 and IL-5, while the production of IL-4 was significantly increased by the vitamin's action (15). Confirmation was found in the works of Benson et al. (16), as well as Overbergh et al. (17), according to whom vitamin D has a suppressing effect on the production of IL-12, and as a result, reduces the production of the T helper type 1, potentially leading to enhanced formation of the allergy-associated T-helper type 2. They also found an increase in the production of IL-4, IL-5 and IL-10. However, its direct effect on Th2 cells remains incompletely understood. There are studies denying any influence of the vitamin on the function of helper cells (18, 19). Thus Kreindler et al. (20) confirmed the absence of induction of the Th2-response *in vivo* caused by vitamin D.

### Vitamin D and IgE

Immunoglobulin E (IgE) antibodies are the key effector molecules in type I allergic diseases, and CD40L, and IL-4 or IL-13 are conventional signaling molecules in inducing production of the B-lymphocytes (21). *In vitro*, vitamin D modulates the production of IgE, thus reducing the production of B-lymphocytes, suggesting that vitamin D deficiency could facilitate development of IgE-driven allergic reactions (22).

Very intriguing results have been produced by Hyponen et al. (23) they reported elevation of the levels of IgE in their study participants with lower 25(OH)D (<25 nmol/L) and very high 25(OH)D serum levels (>135 nmol/L). Figure 3 shows a graph of the results of this study, demonstrating the existence of small changes in the levels of IgE at concentrations of vitamin D between 30 and 120 nmol/L. This „U-shaped“ relationship supports the thesis of the unambiguous effect of vitamin D on the atopic processes.

### Influence on the Antigen Presenting Cells

The value and nature of the T cell response is dependent on the context in which the antigen is presented to T cells by specific antigen-presenting cells (APC). The dendritic cells (DC) have a central role in this process and are considered as the main link between non-specific and specific immune response. In collaboration with the MHC, molecules expressed on the APC surface fragments phagocytose antigens, thus making them accessible to T cells. Congenital models and some local cytokines modulate further immune response-e.g. T-helper type 1-Th1, Th2, Th17 etc. (2). The modulating effect of 1,25-(OH)<sub>2</sub>D<sub>3</sub> in this phase of reaction is also allowed. In tests carried out, the use of 1,25-(OH)<sub>2</sub>D<sub>3</sub> on human DC *in vitro* results in a reduction of the expression of co-stimulatory molecules CD80 and CD86 and a decrease of expression of HLA-DR molecules and maturation markers-CD83, all related phenotypically to immature DC. The active metabolite of the vitamin is involved in the regulation of the maturation of monocytes by inhibiting the production of IL-12 p70 and an increased secretion of IL-10 (24, 25). It has been found that vitamin D inhibits effector T-cell responses by modulating the function of APC and by direct inhibition of T-cell responses. The active form of vitamin D also decreases the production of autocrine T-cell growth factor-IL-2 by inhibition of transcription factors known as the nuclear factor of activated T-cells, and this leads to a significant reduction of the proliferation of CD4+ T-cells (26).

### Interaction at the Genetic Level

The opportunity to participate in the pathogenesis of atopic diseases also exists at the genetic level. Vitamin D is a metabolite which is directly or indirectly involved in the regulation of the expression of more than 900 genes (27). Some of them, associating with an allergic phenotype, are more or less involved in its regulating effect. In an article published in 2006, Wjst presented a list of 17 genes, and cytokines (TNF, IFN, IL-8, IL4RFLG) participating in the pathogenesis of allergic reactions that fall under the control of vitamin D (28). Vimalaswaran et al. (29) have examined possible links between 27 genes and production of total IgE (IgEt) and specific (IgEs) among Europeans with white skin color. They reached the conclusion that vitamin D deficiency is associated with high concentrations of IgEt only as holders of allele "C" of the IL-4.

The correlation between serum vitamin D concentration, and the appearance of symptoms of AR and atopy, represent a broadly discussed topic. Published data from studies on this issue are very multifaceted and have ambiguous and even contradictory results. Some of them establish a link between vitamin D deficiency and the presence of allergic rhinitis and atopy, with poor control and/or frequent exacerbations of concomitant symptoms (30-32). Other authors, however, deny the existence of a relationship, and even maintain the contrary proposition, namely an increase in the incidence of allergic rhinitis suffers with increased serum vitamin D (33). Some previous human studies indicate a high incidence of allergic rhinitis and asthma in higher levels of maternal 25(OH)D, and high-dose vitamin

D added at the beginning of the life, while others suggest that the risk of allergy is reduced in the offspring of mothers with a high dietary intake of vitamin D (34-39).

The results of a study on the status of vitamins D in Bulgaria involving 3,450 people aged between 20 and 80 years were published recently (40). The data by the authors show that 75.8% of the population have a low serum level of adoption, with a low limit level (50 nmol/L). These results only confirm the world trends (41). Simultaneously, the frequency of patients with allergic rhinitis, asthma and other symptoms of atopy is continuously increasing. This relationship is subject to further thorough, impartial and objective analysis, in view of the unclear results obtained from the present analysis.

### Question

1. vitamin D is a hormone affecting all body cells, and particularly cells of the immune system.
2. Conflicting and ambiguous results of studies on the influence of vitamin D in the pathogenesis of allergic rhinitis indicate a need for further studies in this area, involving large groups of participants using more objective methods for tracking.
3. On this problem collaboration with various specialists is indicated, as it seems that it is multidisciplinary.
4. Recently announced data on the status of the Bulgarian nation only confirm the global trend towards low serum concentrations of vitamin D while ever-increasing levels indicate the prevalence of allergic rhinitis as a prerequisite for a more detailed discussion and study of the problem.
5. At this stage, it is suggested that the standards established for the application of vitamin D during infancy for prevention of a serious diseases, such as rickets, be corrected.

### Conflict of Interest

No conflict of interest was declared by the authors.

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### Author Contributions

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Yazarlar herhangi bir çıkar çatışması bildirmemişlerdir.

**Hakem değerlendirmesi:** Dış bağımsız.

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