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VITAMIN D — ITS ROLE IN BRONCHIAL ASTHMA AND COMORBID CONDITIONS

Ibragimova Dilzoda Yunusovna
Central Asian Medical University Fergana, Uzbekistan

Abstract

Vitamin D is a steroid hormone that is synthesized in the skin under the influence of ultraviolet (UV) radiation and can also be obtained from food. The optimal blood level of vitamin D for maintaining normal calcium and parathyroid hormone levels is 30 ng/mL. Vitamin D includes several vitamers. Among them, two biological forms of vitamin D are most active — ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3) [48].

Vitamin D synthesized in the skin under the influence of ultraviolet radiation accounts for 90% of vitamin D in the body. The half-life of vitamin 25[OH]D in blood is 2–3 weeks [72].

The lifestyle of modern humans is characterized by predominantly indoor work, often irrational nutrition, and the use of sunscreens, which leads to low levels of vitamin D in peripheral blood [19]. Most foods contain insignificant amounts of vitamin D, with the exception of fatty fish varieties.

Under the influence of UV rays on human skin, 7-dehydrocholesterol is transformed into provitamin D3, with UV wavelength at 295 nm. Vitamin synthesis depends on skin pigmentation and age [10]. Subsequently, the provitamin, entering the bloodstream, binds with a specific transport protein synthesized in the liver. Conditions accompanied by hypoproteinemia lead to decreased blood vitamin D levels [15]. To become a biologically active form, vitamin D must first undergo hydrolysis in the liver, converting into calcidiol (25-hydroxyvitamin D).

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Calcidiol is the main circulating form but is biologically inactive. The active form is produced in the proximal tubules of the kidneys, converting 25-hydroxyvitamin D into 1,25-dihydroxyvitamin D (calcitriol). This process is regulated by parathyroid hormone [19, 38].

Currently, special interest is attracted by the study of non-alcoholic fatty liver disease (NAFLD) as one of the possible causes of vitamin D deficiency [13]. In 1980, J. Ludwig et al. identified NAFLD as an independent nosological form. NAFLD is detected in 58–74% of patients with excess body weight, and in 95% of cases with morbid obesity [31]. One of the main causes of NAFLD development is irrational nutrition. A sedentary lifestyle combined with high-calorie nutrition leads to pronounced postprandial hyperlipidemia and excessive formation of free fatty acids (FFAs) in genetically predisposed individuals. Postprandial hyperlipidemia and elevated FFA concentration stimulate glycogenolysis in the liver and exert a lipotoxic effect on pancreatic β-cells. Several authors have shown that weight reduction in patients with NAFLD leads to increased serum vitamin D levels [24].

Vitamin D concentration decreases in the central bloodstream in individuals with obesity due to its sequestration in adipose tissue. Normally, serum vitamin D concentration reaches a maximum within 24 hours after UV exposure or oral intake of tableted vitamin D. J. Worthman et al. (2016) showed that the time to reach maximum vitamin D serum concentration in patients with obesity increases compared to patients with normal body mass index [15, 11].

The effects of vitamin D can be divided into several components: influence on calcium metabolism, regulation of hormone secretion, regulation of immune function, and regulation of cellular proliferation and differentiation [26].

In 1920, the effect of vitamin D on calcium metabolism was established. Vitamin D can regulate the concentration of calcium and phosphorus ions in blood, acting as a synergist with parathyroid hormone and as an antagonist with thyrotropic hormone. Vitamin D increases the absorption of phosphorus and calcium ions

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through the small intestine epithelium. Together with parathyroid hormone, it stimulates calcium mobilization from bone tissue. It enhances reabsorption of phosphorus and calcium in renal tubules [39].

Calcitriol exerts its effect by interacting with vitamin D receptors, which are found in most cells of the body. Vitamin D receptors are nuclear receptors that, in the presence of vitamin D3, regulate gene transcription [30].

In the small intestine, the interaction of calcitriol with vitamin D receptors increases the synthesis of the vitamin D transport protein. Calcitriol, interacting with vitamin D receptors of osteoblasts, stimulates the synthesis of substances that promote the transition of preosteoclasts to osteoclasts, maintaining calcium homeostasis [16].

Vitamin D receptors belong to the superfamily of intracellular receptors [26]. Vitamin D, binding to the transport protein, enters the cell, where it first binds to VDR, and then forms a heterodimer with the retinoid X receptor (RXR), thereby acquiring the ability to bind to DNA [19]. Vitamin D, binding to the VDR-RXR complex, interacts with VDRE (vitamin D response elements — specific DNA sequences), which then initiates the transcription of target genes involved in immune response and calcium metabolism. VDRE can both activate and suppress protein transcription [13].

In the 1980s, vitamin D receptors were detected in immune system cells [9]. The first works demonstrating the non-classical influence of vitamin D on cells were conducted almost a quarter of a century ago, when an antiproliferative effect on cancer cells was established [28, 7]. In subsequent experiments, the influence of vitamin D on immune system cells was proven [18].

In the study by McGlade et al., it was shown that UV radiation or vitamin D supplementation can increase the regulatory influence of T cells. Thus, UV irradiation of the skin in patients with asthma reduced bronchial hyperreactivity to methacholine exposure [11].

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In an experiment involving patients with skin diseases, immune function and T cell count were analyzed depending on vitamin D levels. The study included 24 patients from Northern Scotland. After four weeks of dosed UV irradiation, the number of CD3 cells (regulatory T cells) increased, peripheral blood vitamin D levels also increased, and a decrease in proliferative activity and T cell cytokine response was observed [18].

Using new DNA technologies, a map of vitamin D receptors along the genome was created, and 2,776 loci were discovered that specifically bind vitamin D and express proteins [19]. Many of these loci are located near genes associated with autoimmune diseases and cancer [105].

Currently, there is no doubt that vitamin D plays a role not only in calcium metabolism but also has many other functions. Vitamin D is presumably involved in the pathogenesis of cancer, autoimmune diseases, obesity, metabolic syndrome, and type 1 and type 2 diabetes [26, 8].

A higher blood pressure level in patients with vitamin D deficiency may be associated with the influence of vitamin D on the renin-angiotensin system. Thus, mice with deleted VDR had higher levels of renin and angiotensin II, along with increased aldosterone [26].

In the study by A. Tanupriya et al., it was shown that vitamin D levels were lower in patients with diabetes mellitus compared to healthy controls. According to the study data, vitamin D intake in childhood may lead to a reduced risk of diabetes mellitus [28].

Metabolic syndrome includes increased visceral fat mass, arterial hypertension, decreased tissue insulin sensitivity, dyslipidemia, and hyperglycemia, associated with an increased risk of cardiovascular diseases and type 2 diabetes mellitus [12].

Excess body weight, according to several studies, is a risk factor for asthma development [14]. Prospective studies showed a positive correlation between increased BMI and asthma development. A significant correlational relationship

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was also established between increased BMI and the duration of asthma remission [12].

The NHANES III and NHANES 2003–2004 studies showed a significant inverse relationship between vitamin D levels and metabolic syndrome as one of the diagnostic criteria [13]. Vitamin D may play a role in glucose-induced insulin secretion, acting directly on β-cells through VDR receptors [85].

Two other studies are of interest, involving 15,088 and 6,810 patients, respectively. Analysis of the results revealed an association between high triglyceride levels and vitamin D deficiency [16, 17]. A direct correlation between vitamin D levels and apolipoprotein A-1 and an inverse correlation with the HDL/LDL ratio was demonstrated in 54 healthy patients [50]. In a weight loss program involving 63 overweight female patients, vitamin D supplementation allowed for better correction of the lipid profile. Thus, patients who received a dietary supplement of calcium 600 mg and vitamin D 200 IU/day for 15 weeks had lower total cholesterol and HDL/LDL ratio compared to the control group [28]. In another study, vitamin D supplementation in a weight loss program led to an even greater reduction in triglyceride levels, but, paradoxically, to an increase in total cholesterol and LDL levels compared to the control [17].

Twenty years ago, the ability of immune cells to locally synthesize calcitriol was established, thereby exerting an immunomodulatory effect [26]. Immune cells capable of synthesizing calcitriol also possess vitamin D receptors (VDR) and enzymes necessary for the hydroxylation of provitamin D to vitamin D3 (1α-, 25-, and 24-hydroxylases) [14].

The conversion of 25-hydroxycalceferol to 1,25-dihydroxycalceferol occurs not only in the kidneys but also in the brain, intestine, and immune system cells. With sufficient amounts of 25-hydroxyvitamin D, immune system cells can synthesize calcitriol in a paracrine manner and modulate the immune response [18].

Vitamin D regulates the proliferation, differentiation, and function of immune cells. Vitamin D can accumulate in the microenvironment of lymphoid organs,

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where it performs specific autocrine or paracrine functions without inducing undesirable systemic effects such as hypercalcemia and increased bone resorption. Activated T cells can also participate in vitamin D synthesis by hydrolyzing 25(OH)D3 to 1,25(OH)2D3, provided that sufficient precursor 25(OH)D3 is formed in the liver, whereas macrophages and dendritic cells, possessing both enzymes, are capable of independently synthesizing 1,25(OH)2D3. Parathyroid hormone does not affect vitamin D production by immune cells; hydroxylation is regulated by IFN-γ and other cytokines [11].

Studies on cell cultures and animal models have shown the ability of vitamin D to directly or indirectly influence immunity, including T cells, B cells, and macrophages, thereby exerting its effect on both cellular and humoral immunity. The immunomodulatory effect of vitamin D is confirmed by epidemiological studies, where the relationship between vitamin D levels and autoimmune and chronic diseases is clearly traceable (rheumatoid arthritis, inflammatory bowel disease, type 1 diabetes, cardiovascular diseases, oncological diseases) [32].

A low vitamin D level has been associated with a more severe course of asthma and allergic manifestations in childhood, increased IgE levels, increased hospitalization rates due to asthma, as well as higher doses of glucocorticoids (GCs) [16, 36].

However, in the study by M.D. Griffin et al., it was shown that interacting with VDR through a ligand protein, vitamin D reduces the transcription of the gene responsible for IL-12 synthesis. Inhibition of IL-12 synthesis by dendritic cells leads to direct inhibition of the Th1 immune response [11].

Children with difficult-to-treat bronchial asthma have lower vitamin D levels compared to healthy controls [12]. In the study by T. Agrawal et al., it was shown that vitamin D supplementation in pregnant women reduces the risk of asthma development by 40% in children aged 3–5 years [38].

Vitamin D contributes to reduced production of pro-inflammatory cytokines, such as TNF-α, by inhibiting toll-like receptors [19]. Vitamin D also participates

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in the adaptive immune response, stimulating the synthesis of antimicrobial peptides: human antimicrobial peptide (cathelicidin) (hCAP-18) — the only protein of this class that humans are capable of synthesizing. It was described in macrophages, alveolar cells, neutrophils, keratinocytes, and epithelial cells [13]. The synthesis of this protein occurs during the interaction of vitamin D and a specific vitamin D receptor on the gene (VDRE) [11.

Vitamin D does not increase CD4+ lymphocyte levels. A study involving HIV-infected children was conducted: one group of patients received vitamin D at a dose of 800 IU/day, while the other group did not. An increase in CD4+ lymphocyte content was not established [11].

The optimal vitamin D3 content in peripheral blood should be no less than 30 ng/mL. Vitamin D is toxic at a dose of 50 ng/mL. When serum vitamin D levels fall below 20 ng/mL, macrophages and monocytes are unable to perform certain immune responses [13].

In an experiment, it was proven that vitamin D is capable of inducing the synthesis of specific surface markers on keratinocytes, which are chemokines for T cells, thereby promoting T cell circulation [11].

In in vitro experiments, it was shown that vitamin D has a direct influence on T and B lymphocytes and modifies their response activity, thereby playing an important role in adaptive immunity. Inactive CD4+ T cells express vitamin D receptors at a low level; their activation is accompanied by a five-fold increase in receptor expression. Vitamin D affects T cells either indirectly, through dendritic cells, or directly, by inhibiting T cell proliferation [79].

Currently, 102 genes have been identified that are targets for vitamin D. These genes are localized in CD4+ T cells [50]. In mice with destroyed vitamin D receptors, T cells produce more IFN-γ and less IL-2, IL-4, IL-5 compared to wild-type mice [10].

In an in vitro experiment, the allergen response was analyzed at high calcitriol concentration (1×10^6 ng/mL) in whole blood, which showed a decrease in IFN-γ

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production and an increase in IL-5, IL-13 levels. At low calcitriol concentration (1×10^9 ng/mL), a decrease in cytokine levels produced by Th1 and Th2 lymphocytes was noted [13].

Vitamin D exerts an active influence on dendritic cells. By affecting dendritic cells, vitamin D promotes an increase in the synthesis of anti-inflammatory cytokines (IL-10) and a decrease in pro-inflammatory cytokines (IL-2). In an in vitro experiment, it was shown that under the influence of vitamin D, the proliferative activity of dendritic cells decreases, as does the differentiation of monocytes into dendritic cells [18, 16]. In another in vitro study, it was shown that dendritic cells after incubation with T cells and calcitriol induce the synthesis of cells with suppressive activity [11].

Vitamin D stimulates the differentiation of monocytes into macrophages, stimulates macrophages to produce the immunosuppressive prostaglandin E2, and reduces the expression of granulocyte-macrophage colony-stimulating factor (GM-CSF). It also reduces the synthesis of pro-inflammatory cytokines and chemokines by macrophages, decreases the maturation and production of specific membrane antigens, lysosomal phosphatases, and hydrogen peroxide necessary for antimicrobial activity, and increases chemotaxis and phagocytosis of macrophages [10]. The addition of 100 nM 1,25(OH)2D3 to a human monocyte culture inhibits the expression of immune receptors TLR2, TLR4, and TLR9 [10]. Vitamin D reduces the expression of major histocompatibility complex class II (MHC II) on the cell surface [15].

Two important aspects served as the basis for suggesting an association between vitamin D deficiency and asthma. The first is that vitamin D deficiency during the intrauterine period and infancy is associated with an increased risk of asthma development. The second aspect linking vitamin D deficiency and asthma manifestations is the direct correlation between treatment response, risk of exacerbations, and vitamin D levels. Thus, Brehm et al. found that vitamin D levels below 30 ng/mL increase the risk of severe asthma exacerbations [46]. In

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the study by Brehm et al., involving 616 children with asthma, vitamin D levels were inversely proportional to the severity of asthma, frequency of hospitalizations, and use of GCs. In the study by Brehm et al., involving 1,024 children from North America over 4 years, it was established that vitamin D deficiency increases the risk of bronchial asthma exacerbation [47].

Vitamin D may influence certain genetic factors that may lead to the development of asthma, such as — expression of vitamin D receptors, Toll-like receptors (TLR), and matrix metalloproteinase (MMPs) synthesis [11].

Recent epidemiological studies have shown a significant correlation between low serum 25-hydroxyvitamin D concentration and chronic lung diseases, such as asthma [31] and chronic obstructive pulmonary disease (COPD) [7]. A low vitamin D level was also associated with a more rapid decline in FEV_1 [31]. However, the molecular mechanisms underlying these phenomena are unknown. It is likely that vitamin D deficiency or vitamin D receptor damage can cause lung inflammation and alter lung function by influencing the protease/antiprotease balance. In a study, it was shown that mice with deleted vitamin D receptors had higher lung infiltration by inflammatory cells, phospho-acetylation of nuclear factor kappa-β (a transcription factor causing the synthesis of pro-inflammatory cytokines) [19]. In the study by Robert J. Freishtat et al., involving 92 patients with asthma and 21 patients without asthma, aged 6 to 20 years, vitamin D levels were significantly lower in the first group [10]. In the study by Felicia Montero-Arias et al. (121 patients with asthma), vitamin D levels were inversely proportional to the severity of bronchial asthma [17].

The definition of bronchial asthma reflects the high significance of the infectious component. Infectious agents often act as inducing factors for asthma exacerbation or the manifestation of the first signs of the disease [5]. Recent studies show that viruses are capable of stimulating selective proliferation of Th-2 lymphocytes, thereby provoking allergic inflammation in the bronchi [6]. At the same time, by damaging the bronchial epithelium, viruses facilitate the

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penetration of inhalation allergens through the bronchial mucosa. Several authors have proven the role of respiratory bacteria (*Chlamydia*, *Streptococcus pneumoniae*, *Haemophilus influenzae*) in the pathogenesis of asthma. Pathogenic bacteria are capable of disrupting the Th-1 immune response and stimulating the Th-2 inflammatory response [8]. In the study by A.A. Ginde et al., peripheral blood 25-hydroxycholecalciferol levels were inversely proportional to the frequency of upper respiratory tract infections [12]. In the study by J.M. Brehm et al., involving 1,024 children with asthma, it was established that children with vitamin D deficiency have more frequent disease exacerbations [36]. Similar results were obtained in another study published in 2012 by J.M. Brehm et al. The study included 560 children aged 6–14 years; vitamin D deficiency was associated not only with more frequent asthma exacerbations over the past year but also with a lower FEV_1/FVC ratio [8]. In the study by Stephanie Korn, conducted on 280 patients with asthma, a low vitamin D level was more characteristic of patients with severe asthma [49].

Vitamin D plays an important role in the prevention of infectious diseases and viral respiratory illnesses. Currently, a high risk of tuberculosis development has been established at low vitamin D levels in peripheral blood. As early as the 19th century, cod liver oil and sun baths were used in sanatoriums for tuberculosis treatment [11]. In an in vitro experiment, the influence of vitamin D on Mycobacterium tuberculosis was proven. Gentamicin and vitamin D were added to a culture of mononuclear cells obtained from whole blood by centrifugation. The study analysis was conducted based on the content levels of TNF-α, IL-6, IFN-γ, and IL-10. As a result of vitamin D exposure, the cytokine response to Mycobacterium tuberculosis decreased, and cathelicidin production increased [13].

Upon examination of British residents, a significant but non-linear relationship was identified between peripheral blood vitamin D levels and IgE levels. Thus, at low (< 25 nmol/L) or high (> 135 nmol/L) vitamin D levels, high IgE levels

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were determined. Scientists concluded that too low or too high vitamin D content may lead to the development of an allergic reaction.

Thus, it is obvious that vitamin D possesses immunomodulatory activity. However, the role of vitamin D in the pathogenesis of asthma remains debated. Most studies aimed at investigating the effect of vitamin D on the cytokine profile of asthma patients were conducted in vitro. Moreover, vitamin D was studied in isolation from other risk factors. A significant disadvantage of in vitro studies is the inability to reproduce processes occurring in vivo. According to the GINA 2016 expert consensus, asthma is recognized as a heterogeneous disease. Obviously, studying the effect of vitamin D on the course of asthma is advisable to conduct in combination with other risk factors (irrational nutrition, obesity, imbalance in the pro-inflammatory and anti-inflammatory cytokine system).

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