

VITAMIN D IMMUNOMODULATORY EFFECT

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In addition to the classical role in the homeostasis of calcium and phosphorus, vitamin D shows a regulatory effect on a number of different cells, especially its anti-proliferative and pro-differential biological function. Through its own receptor in the immune cells, vitamin D increases the phagocytic activity of macrophages and NK cells. Also, by binding to the regulatory sequences of antimicrobial peptides genes, vitamin D increases the microbicidal activity of phagocytes. Inhibition of differentiation and maturation of antigen-presenting dendritic cells, as well as direct influence on their contact with T lymphocytes, it significantly influences the type of immune response. Dendritic cells under the influence of vitamin D induce a suppressor T cells, which can inhibit Th1 cell response and are critical in the regulation of immune tolerance. Vitamin D inhibits proliferation of Th1 and Th17 cells, as well their cytokine production, and suppresses the differentiation and maturation of B lymphocytes.

Due to all these functions, vitamin D has shown beneficial effects in the prevention and modification of a number of autoimmune diseases. On the other hand, immunity disorders with predominant Th2 response (asthma, allergies) did not show such good results after the use of hypocalcemic VDR agonists. *Acta Medica Medianae* 2012;51(4):58-64.

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Introduction

Following exposure to sunlight, vitamin D is synthesized in the skin from its precursor 7-dehydrocholesterol. Primarily created cholecalciferol goes through two conversions, a 25-hydroxylates in the liver (CYP27A1 enzyme) and 1 α -hydroxylates in the kidneys' mitochondrial cytochrome P450 (CYP27B1), before it becomes a hormonally active form - calcitriol (1 α ,25-dihydroxy-vitamin D₃, 1.25(OH)₂D₃) (1,2). Vitamin D exerts its effects by binding to its own receptor (vitamin D receptor - VDR), a member of the nuclear receptor superfamily of steroid hormone or ligand-activating transcription factor. Nuclear receptors act as ligand-inducible transcription factors that directly interact as monomers, homodimers or heterodimers with the retinoid X receptor (RXR). Vitamin D-VDR complex with RXR heterodimerises and initiates a cascade of macromolecular interactions, through the strong affinity association with the vitamin D responsive elements (VDREs) in the promoters of the target genes. Vitamin D induces expression of the gene encoding D-24-hydroxylase (CYP24A1), an enzyme that performs

its own signal loss and degradation of vitamin D in the cell (3,4).

The most familiar, classic role of vitamin D is to maintain calcium and phosphorus homeostasis through effects on the intestine, kidney, and bone, in conjunction with parathyroid hormone. It stimulates the differentiation of osteoblasts and deposition of calcified matrix, while in the case of hypocalcemia it stimulates the mobilization of calcium from bone, promoting the differentiation of osteoclast precursors. The physiological function of vitamin D in the CNS, heart, pancreas, mammary gland, skin and immune system are still poorly understood, but it can be said that its overall biological function is antiproliferative and pro-differential (2,5).

The potential role of vitamin D in the immune system is proposed after the discovery of VDR in macrophages, dendritic cells and activated T and B lymphocytes, and the ability of these cells to express CYP27B1. However, it is still unclear whether increasing the level of vitamin D in the circulation has an effect on the local, paracrine function (6,7). Also, despite the optimal level of vitamin D in circulation, the metabolism capacity can vary among individuals, as proposed in the case of certain genetic polymorphisms in VDR and vitamin D metabolizing enzymes. Four polymorphisms (FokI T_C, BsmI A_G, ApaI G_T and TaqI C_T) of VDR gene have been extensively studied in order to find their association with various diseases, including tumors of different

localization, as well as diseases associated with disorders of the immune response (8).

Vitamin D role in innate immune response

The current researches show that an important component of the monocyte-macrophage response to infection is intracrine induction of the antimicrobial activity of vitamin D (9). Activity of natural killer cells (NK) and phagocytic activity of macrophages is increased after the use of VDR ligands. However, at the same time, the stimulatory capacity of monocytes and macrophages is reduced, as determined by reduction of surface expression of MHC-II and co-stimulatory molecules (CD40, CD80 and CD86) (10). Differentiation of monocytes was accompanied by reduced expression of VDR, which makes the mature forms of these cells less sensitive to vitamin D (11). In contrast, the expression of VDR is prominent in activated T lymphocytes, whereas it is very weak in naive T cells (12). In dendritic cells, the levels of CYP27B1 are increased during the cell maturation (13), while in T and B lymphocytes the expression of these enzymes increases dramatically after their activation (Figure 1) (14).

Immunomodulatory effects of vitamin D occurs through the regulation of nuclear transcription factors, NF-AT and NF-kappaB, or direct binding to the vitamin D responsive elements in the promoters of cytokines' genes (15). Vitamin D inhibits the expression of interferon and proinflammatory cytokines in monocytes (IL-1, IL-6, TNF- α , IL-8 and IL-12) (16). The gene for TNF- α has VDR responsive elements in its promoter, while the gene for IFN- γ has a negative transcriptional regulatory elements for vitamin D. The regulation of granulocyte-macrophage colony stimulating factor is regulated by

VDR monomers, which bind to the repressive complex in the promoter of this gene, competing with the nuclear factor AT1. Vitamin D blocks the activation of NF-kB by increasing the expression of I κ B α and interfering with binding of NF-kB to the genes it regulates (IL-8, IL-12, etc.) (17).

The effect of vitamin D has been particularly investigated on the maturation, differentiation and migration of antigen presenting dendritic cells (DC). Vitamin D and its analogues inhibit the differentiation and maturation of DC, although these cells alone express CYP27A1 and are capable of creating 25OH-vitamin D. In vitro treatment of DC with calcitriol leads to down-regulation of CD40, CD80 and CD86 co-stimulatory molecules expression and decreased production of IL-12, while IL-10 production is increased. This contributes to the reduction of T cell activation level, in other words, vitamin D acts in creating a tolerogenic type of DCs (6,18,19).

It has been shown that the addition of calcitriol to the monocyte cell culture, on the first day, blocks DC differentiation from monocytes and inhibits the appearance of the characteristic cell surface molecules CD1a+, while increases the expression of monocyte-macrophage marker CD14+. Calcitriol treatment during DC maturation leads to the loss of CD1a marker and clear reinduction of CD14. In contrast, mature DC were CD1a+CD14- after addition of calcitriol. Obvious suppression of DC differentiation and phenotype inversion of immature DC may explain some of the immunosuppressive properties of vitamin D. Contrary to the anti-proliferative effects of vitamin D on some cell types, DC formation in the bone marrow is not suppressed. It is also significant that DC treated with vitamin D analogues have not progressed to a higher level of maturation after the end of the treatment, and that they clearly expressed weakened response to maturation signals (19).

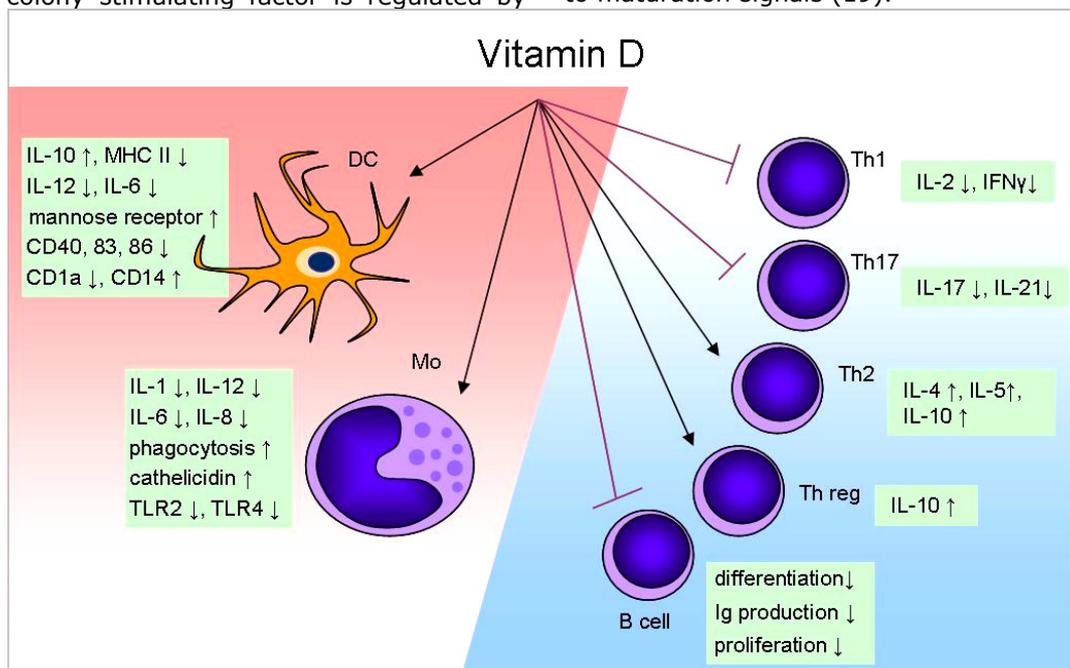


Figure 1. Immunomodulatory effect of 1,25(OH) $_2$ D $_3$

Protein profile in the DC changes significantly when exposed to VDR agonists. Major changes were observed in proteins involved in protein biosynthesis/proteolysis and cytoskeletal structure, which may have an impact on the formation of DC - T cell contacts and thereby T cells activation. Vitamin D also has the potential modulatory role in the binding of antigen to DC in the initiation phase of immune response. It enhances expression of mannose receptors, molecules involved in antigen binding, which correlates with higher endocytic capacity (20,21).

The vitamin D active form increases the expression of different endogenous antimicrobial peptides, with a broad spectrum of activity against bacteria, fungi and viruses (22). In response to innate immunity, the activation of Toll-like receptor (TLR) ligands results in direct antimicrobial response by polymorphonuclear cells, monocytes and macrophages. The resulting immune response consists in the production of reactive oxygen species and antimicrobial peptides, such as cathelicidins. Gene promoter of the human antimicrobial peptide cathelicidins contains functional vitamin D responsive elements (10). It has been shown that vitamin D treatment of human keratinocytes, monocytes and neutrophils induces the transcription of this peptide. Toll-like receptor-mediated up-regulation of VDR and CYP27B1 expression causes an intracrine, vitamin D-dependent, induction of cathelicidins and increased microbicidal activity of macrophages. Cathelicidin further stimulates the release of IL-6, IL-10, IL-18, expression of epidermal growth factor receptor, induces chemotaxis of neutrophils, monocytes, macrophages, T cells, and starts the proliferation and migration of keratinocytes (21). The above results show the importance of extra-renal expression of 1- α -hydroxylase (CYP27B1) in the vitamin D-mediated innate immunity. Extra-renal CYP27B1 enzyme is completely under the different type of control in comparison to the renal form of the enzyme, it is not influenced by parathyroid hormone, but can be stimulated by cytokines (1,6,11). CYP27B1 expression and production of calcitriol in monocytes-macrophages was strongly stimulated by IFN- γ , TNF- α , IL-1 and IL-2 (14), TLR4-ligand lipopolysaccharide and ligands that act on TLR2/1 complex (19kD mycobacterium tuberculosis lipoprotein and viral infection). However, no clear negative feedback was found between these factors and vitamin D. Activated macrophages are able to produce calcitriol, sometimes leading to hypercalcemia, as in situations with macrophage hyperactivation, as in sarcoidosis (12).

Since the mid 19th century, it is well known that vitamin D induces antimycobacterial activity of monocytes and macrophages, and reduces the production of proinflammatory cytokines, which is important in the treatment of tuberculosis and leprosy (12). The mechanism of its effect on tuberculosis was unknown to the research conducted by Liu et al. (23), who noted that activation of TLR2/1 via lipoproteins extracted from *M. tuberculosis*

reduced the viability of intracellular mycobacteria in human monocytes and macrophages, along with increased expression of VDR and CYP27B1. Efficient elimination of mycobacteria existed only in the presence of adequate levels of 25-hydroxy vitamin D, the substrate of the enzyme CYP27B1. This demonstrated the key role of endogenous production of active vitamin D in antimycobacterial capacity of macrophages. Formation of cathelicidins in macrophages also helps in the fight against mycobacteria. Vitamin D is able to induce autophagy and mediates the co-localization of mycobacteria and antimicrobial peptides within autophagosomes, accelerating the destruction of bacteria. It is significant that this hormone also inhibits TLR2 and TLR4 expression on monocytes, inducing condition of hyporesponsiveness to pathogen-associated molecular pattern (PAMPs) (24). This effect is mostly expressed after 72 hours and was nominated for a negative feedback mechanism that prevents excessive TLR activation and inflammation in the late infection phase. At the same time, vitamin D significantly reduces mycobacterial-induced expression of matrix metalloproteinases in monocytes. Metalloproteinases can degrade all components of pulmonary extracellular matrix and is thought to participate in the pathogenesis of pulmonary tuberculosis cavitation. In activated monocytes, vitamin D stimulates the secretion of IL-10 and prostaglandin E2, transcription regulator that suppresses the expression and secretion of metalloproteinases (25).

The recent studies have indicated that the antimicrobial vitamin D activity is VDR-mediated and accompanied with the strong induction of antimicrobial peptides, cathelicidins and defensins b2, in various cells, including myeloid cells, keratinocytes, neutrophils, and bronchial epithelial cells (24). The epithelium is a key factor in the innate immune response initiation. It contains the largest number of cells that express CYP27B1, and it is believed that UVB radiation is sufficient to create the active form of vitamin D in them. Keratinocytes express CYP24A1 and thus regulate the concentration of 1,25(OH)2D3 (26), so they can modulate the immune response. It has been shown that keratinocytes treated with calcitriol are significantly more effective in killing *Staphylococcus aureus* (27).

Vitamin D role in adaptive immune response

Immunomodulatory effects of vitamin D in the acquired immune system are the result of its direct effect on cell proliferation, differentiation and apoptosis of T lymphocytes (especially T-helper) and B-lymphocytes (16). Vitamin D inhibits proliferation and cytokine response of Th1 and Th17 cells, induces the formation of regulatory T-cells (Treg or Th3) and the production of IL-4. Differentiation and maturation of B cells is inhibited by the use of 1,25(OH)2D3 (15). Also, by slowing the maturation of DC and inhibiting

the expression of MHC II molecules and co-stimulating molecules on antigen presenting cells, vitamin D reduces the ability of these cells to present antigens and activate T cells (10). In addition, vitamin D modulates the expression of cytokines in DC, inhibiting the production of key cytokines of Th1 and Th17 differentiation (IL-12 and IL-23), but enhancing the release of IL-10, and chemokines MIP-3a (CCL22) involved in the recruitment of regulatory CCR4+ T cells (11, 28).

Overall, vitamin D exerts an inhibitory effect on the acquired immune system. By suppression of IL-12 production, an important factor for T-helper cells development, it inhibits the development of Th1 cells, and thus the production of IFN- γ and IL-2. Also, by reduced secretion of IL-23 and IL-6, vitamin D inhibits Th17 development and function of these cells, as well the secretion of Th17 cytokines, IL-17 and IL-21. Decrease in IFN- γ reduces the recruitment of T cells, and a decrease of IL-2 reduces their proliferation. At the same time, suppression of IL-12 promotes the development of Th2 cells, which leads to increased production of IL-4, IL-5 and IL-10, which further suppresses Th1 cells, and shifts the balance towards Th2 phenotype (7, 29).

Treatment of dendritic cells with vitamin D may induce a formation of CD4+/CD25+ suppressor T cells, due to reduced expression of co-stimulatory molecules and production of IL-10. These cells inhibit Th1 cell responses and are critical in the regulation of immune tolerance. Ability of VDR agonists to enhance Treg activation in vitro was observed in a number of studies. In addition, VDR agonists enhance the suppressive capacity of Treg cells (30). It has been shown that vitamin D regulates a set of genes in the DC cells, which increases the potential of these cells to induce Treg cells, independently of vitamin D effect on DC differentiation and maturation. However, the role of tolerogenic DC does not seem to prerequisite the Treg cells induction with vitamin D, as evidenced by the very action of vitamin D, or in combination with dexamethasone, for the creation of IL-10 producing Treg cells in in vitro system, in the absence of antigen presenting cells (31).

VDR expression dramatically increases in T lymphocytes following their activation. High VDR expression can be induced by various T cell activation stimuli, such as anti-CD3/anti-CD28, creating two necessary activation signals. The expression level and dynamics depend on the stimulus, so that the different effects of vitamin D on T cells can be registered (12,28,31).

Direct effects of vitamin D on the production of Th2 cytokines are currently less well known. According to some studies, vitamin D potentiates the formation of Th2 cells with up-regulation of specific transcription factor GATA-3 and c-maf expression, and associated cytokines (IL-4), while other studies contraindicated these findings (32,33). T cells of VDR knock-out (KO) mice produced more IFN- γ and less Th2 cytokines (IL-4 and IL-5) compared to T cell of normal animal type (wild type - WT) (34).

Influence of vitamin D on B cells is less known. Although the modulation of Th responses inevitably

affects a B cell compartment, these cells are also directly affected by vitamin D. Exposure of B cells to the active form of the vitamin inhibits their proliferation, plasma cell differentiation and secretion of immunoglobulins (IgG, IgM and IgE), the creation of memory B cells, and induces B cell apoptosis (7).

The downside of acquired immunity suppression is susceptibility to development of a number of infections. In an experimental model of mice has been shown that 1,25(OH)2D3 predisposes infection with *Leishmania major* and toxoplasmosis, while VDR-null mice were relatively protected (8). This is partly explained by the reduction of IFN- γ , which is required for the stimulation of macrophages and production of reactive oxygen species and NO.

Effect of vitamin D on autoimmune diseases

Although there is still no large-scale prospective studies, the results of epidemiological studies suggest an association between a number of diseases with a concentration of vitamin D in the blood (7). Due to the ability to induce innate and suppress acquired immune response, vitamin D has a beneficial role in the prevention and treatment of various autoimmune diseases, and the prevention of transplant rejection (6, 28). There is an inverse correlation between serum vitamin D concentration and the incidence and severity of autoimmune diseases, such as type 1 diabetes mellitus (DM), systemic lupus erythematosus, multiple sclerosis (MS), inflammatory bowel disease (IBD), rheumatoid arthritis, psoriasis, fibromyalgia and other (12,18,35). In contrast, vitamin D does not exhibit the same beneficial effects in a number of diseases in which the immune system plays a key role, such as asthma and infection. Some authors draw attention to vitamin D enriched foods, which seems to cause a higher incidence of allergic diseases (28). In the study of Hypponen et al. (36), the prevalence of atopy, allergic rhinitis and asthma was higher in people who were regularly taking vitamin D supplements during the first year of life.

Examples of Th1 autoimmune diseases are MS, type 1 DM and IBD, while allergy and asthma are influenced by Th2 lymphocytes (28). In various experimental models (inflammatory arthritis, autoimmune diabetes, tieroiditis) VDR agonist administration prevented and/or attenuated the disease, through the inhibition of Th1 response. It was found that children with vitamin D deficiency have a higher risk of type 1 diabetes development, and vitamin D supplementation in infancy reduced the development of this disease (29). Similarly, diseases and conditions with active Th17 immune response (arthritis, psoriasis, experimental allergic encephalitis) respond positively to VDR agonist treatment. The active form of vitamin D has a direct repressive effect on the transcription of IL-17 in T cells (37).

The prevalence of MS is highest in countries where sun exposure is lowest, and vice versa. Also, the incidence of MS is higher in people who have low levels of 25-OH-vitamin D in the blood. It is believed that the mechanism of vitamin D effects on MS is

associated with paracrine and autocrine 25-OH-vitamin D metabolism in immune and nerve cells, which express CYP27B1. It has been shown that vitamin D treatment of experimental autoimmune encephalomyelitis (a mouse model of MS) eliminated paralyzes and disease progression, with a clear reduction in the number of Th17 cells (37).

Vitamin D deficiency is often seen in Crohn disease (38). In an animal model of enterocolitis, IL-10 knock-out mice develop disease within 9-12 weeks of age. Vitamin D deficiency in these mice accelerated the development of IBD symptoms, while vitamin D deficit delayed the disease onset. Mice negative for VDR and IL-10 developed severe colitis. It was also noted that the presence of calcium in the diet further affects the efficiency of vitamin D treatment in IBD. Such treatment of KO mice reduced the number of lymphocytes in the lymph nodes, and increased levels of IL-4 and TGF- β 1 transcription (18).

Th2 cells play a dominant role in the inflammatory response in allergic respiratory diseases. In animal allergic asthma model, the development of the disease was examined in VDR KO, WT or WT mice, treated with active vitamin D. Asthma developed in WT mice, in contrast to the VDR KO mice, despite the formation of antigen-specific Th2 cell responses in the periphery and high concentrations of IgE (39). Vitamin D treatment in WT mice did not affect the severity of the disease, although in a similar study of Th2 dependent animal model of asthma, the active form of vitamin D had anti-inflammatory effects (40). Also, when VDR KO splenocytes were transferred into WT mice they were able to cause bronchial inflammation in WT mice, while in the opposite case the disease did not develop. Presently, there is no clear explanation of these results. It is assumed that Th2 cells do not infiltrate the lungs at all, or that VDR KO mice epithelial cells are unable to respond to inflammation by the experiment.

The positive effects of VDR agonists in combination with immunosuppressive agents have

been observed in transplant procedures, which require the inhibition of the acquired immune response. In an experimental model of aortic allograft, bone, bone marrow, kidney, liver, pancreatic islets, skin and small intestine, VDR agonists had a beneficial effect (30). Favorable effects consisted in reduced infiltration of Th1 cells, macrophages and dendritic cells in the graft tissue, decreasing the production of Th1 cytokines.

Unfortunately, the clinical applications of vitamin D for the modulation of immune responses are limited by its toxicity, especially hypercalcemic side effects. There is also a problem with hypercalcemia, in some diseases with immune system disorders, due to elevated values of active vitamin D in the blood (sarcoidosis, tuberculosis, Crohn's disease, T cell lymphoproliferative disorders), which can be explained by stimulation of cytokine expression of CYP27B1 and CYP24A1 dysfunction. To overcome this limitation, VDR agonists are to be designed, which should not cause hypercalcemic effects but have an immunoregulatory activity similar to that of the active vitamin D (12).

Conclusion

Vitamin D can be designated as a selective immune system regulator and modulator of growth, differentiation and function of immune cells. It affects both types of immune response, by emphasizing the innate and suppressing the acquired immunity, contributing to immune tolerance. Vitamin D directly regulates the expression of antimicrobial peptides and improves the function of macrophages in defense against mycobacteria. Also, vitamin D shows a useful role in the prevention and treatment of various autoimmune diseases and the prevention of transplant organ rejection. Vitamin D receptor agonists, particularly hypocalcemic analogues, are eligible candidates for the prevention and treatment of infections and some autoimmune disorders.

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IMUNOMODULATORNO DEJSTVO VITAMINA D

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Pored klasične uloge u homeostazi kalcijuma i fosfora, vitamin D pokazuje regulatorni uticaj na veći broj različitih ćelija, pre svega svojom antiproliferativnom i prodiferencijacionom biološkom funkcijom. Vezivanjem za sopstveni receptor u imunskim ćelijama vitamin D povećava fagocitnu aktivnost makrofaga i NK ćelija. Takođe, vezivanjem za regulatorne sekvence gena antimikrobnih peptida, vitamin D povećava mikrobicidnu aktivnost fagocita. Inhibicijom diferencijacije i maturacije antigen prezentujućih dendritičnih ćelija, kao i direktnim uticajem na kontakt ovih ćelija sa T limfocitima, on značajno utiče na vrstu imunološkog odgovora. Dendritične ćelije pod uticajem vitamina D indukuju stvaranje supresornih T ćelija, koje mogu inhibirati Th1 ćelijski odgovor i kritične su u regulaciji imunološke tolerancije. Vitamin D suprimira proliferaciju Th1 i Th17 ćelija kao i produkciju njihovih citokina, a inhibitorno utiče na diferencijaciju i maturaciju B limfocita.

Usled navedenih funkcija, vitamin D je pokazao povoljne efekte u prevenciji i modifikaciji određenog broja autoimunoloških bolesti. S druge strane, poremećaji imuniteta sa dominantnim Th2 odgovorom (astma, alergije) nisu pokazali tako dobre rezultate posle primene hipokalcemičnih VDR agonista. *Acta Medica Medianae* 2012;51(4):58-64.

Ključne reči: vitamin D, imunomodulatorno dejstvo, urođeni imunitet, katelicidin