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The role of vitamin D in selected autoimmune diseases – review

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ABSTRACT:
Introduction and purpose: Vitamin D is a micronutrient whose main role in the human body is to ensure proper calcium-phosphate balance and adequate bone metabolism, having an effect on the immune system, also exhibiting a number of other actions, in particular anti-inflammatory and anti-fibrotic effects, so that its deficiency is reflected in a number of autoimmune diseases. The purpose of this study is to analyze the literature for the role of vitamin D in multiple sclerosis, type 1 diabetes, autoimmune thyroiditis, inflammatory bowel disease and celiac disease.

Materials and methods: a thorough analysis of the medical literature available in the PubMed database was performed.

Current state of knowledge: The main role of vitamin D in the human body is to ensure calcium and phosphorus homeostasis and, influence adequate bone metabolism. Vitamin D receptors (VDR), are present in many tissues such as brain, prostate, pancreas, breast, colon and immune cells, suggesting that vitamin D also has extra-skeletal functions and a link to autoimmune diseases.

Summary: Low serum vitamin D levels may increase the risk of immune diseases such as type 1 diabetes, multiple sclerosis, autoimmune thyroid diseases, celiac disease and inflammatory bowel diseases.

Keywords: vitamin D; autoimmune diseases; multiple sclerosis; type 1 diabetes; celiac disease

INTRODUCTION AND PURPOSE OF THE PAPER

Vitamin D deficiency in the population is a serious problem internationally. [1] The main role of this vitamin in the human body is to ensure calcium and phosphorus homeostasis and influence adequate bone metabolism. This vitamin also exhibits a number of other functions, chief among which are: its effect on the immune system (viral, bacterial and fungal infections are more likely to occur as a result of its deficiency), [2] as well as its anti-inflammatory, antioxidant, immunomodulatory and anti-fibrotic effects, through which it may participate in regulatory pathways that allow mitigation or prevention of tissue damage caused by inflammation and immune responses. [3]

In addition, it has been observed that low serum vitamin D levels may be associated with an increased risk of developing various diseases and disorders of the immune system such as, for example, type 1 diabetes, multiple sclerosis, autoimmune thyroid disease, celiac disease, inflammatory bowel disease, rheumatoid arthritis, sepsis, tuberculosis, respiratory tract infections and COVID-19. [4] Also, for other conditions such as cognitive impairment, cardiovascular disease, cancer (in particular, colorectal cancer, prostate cancer, breast cancer, thyroid cancer and leukemia). an association with low serum levels of this vitamin has been observed. [1]

The purpose of this paper is to collect and analyze the current state of knowledge regarding the role of vitamin D in immune system processes and its association with selected autoimmune diseases such as multiple sclerosis (MS), type 1 diabetes mellitus (DM1), autoimmune thyroiditis (AITD), inflammatory bowel disease (IBD) and celiac disease.

CURRENT STATE OF KNOWLEDGE

Vitamin D metabolism and function

The key source of vitamin D for the body is the epidermis. When it is exposed to sunlight (ultraviolet radiation in the 280-320 nm range, or UVB), 7-dehydrocholesterol in the epidermis is converted into vitamin D. In addition, the main cells of the epidermis, the keratinocytes, have enzymes such as CYP27A1, 25-hydroxylase and CYP27B1-1-hydroxylase, which enable further metabolism of vitamin D to its active form, 1,25-dihydroxyvitamin D (1,25$(OH)_2$ D). [5] In addition to dermal synthesis, vitamin D can also be supplied from food in the form of vitamin D_3 (cholecalciferol) or, less commonly, vitamin D_2 (ergocalciferol). [5] Vitamin D_3 comes from animal sources, while vitamin D_2 is found in UVB-treated fungi. [6]

Vitamin D_3 is transported to the liver, where it is converted to 25-hydroxyvitamin D_3 (25$(OH)D_3$), the main circulating form of vitamin D_3 , with the help of the enzyme CYP2R1. Subsequently, 25$(OH)D_3$ in the kidney, via the enzyme CYP27B1, is converted to its active form, 1,25-dichydroxy vitamin D_3 (1,25(OH) D_{23}). [7]

The primary role of 1,25(OH) D_{23} is to ensure adequate calcium levels and promote bone development by regulating phosphate-calcium metabolism. Moreover, vitamin D receptors (VDRs) are present in many tissues, such as the brain, prostate, pancreas, breast, colon and immune cells, suggesting that vitamin D also has extra-skeletal functions. [7] 1,25(OH) D_{23} may affect immune function, and regulate cell proliferation and differentiation in various cell lines, such as endothelial cells, lymphocytes, keratinocytes and osteoblasts. [7]

Immunomodulatory activity of vitamin D

Cells of the immune system such as dendritic cells, macrophages, T and B lymphocytes, and monocytes exhibit CYP27B1 and Vitamin D receptor (VDR) expression. [8] The production of 1,25-dihydroxyvitamin D ($1,25(OH)_2$ D) by these cells directly affects the regulation of both acquired and innate immunity. In the context of innate immunity, activated vitamin D stimulates neutrophils, macrophages and epithelial cells to produce broad-spectrum antimicrobial peptides such as cathelicidin (CAMP) and β-defensin 2 (DEF B4). [8-10]

Also of interest is the fact that the increase in innate immunity associated with vitamin D is strongly dependent on the activity of Toll-like receptor heterodimers 2/1(TLR2/1) and reaches a maximum when needed. When TLR2/1 detects the cell membranes of certain microorganisms, it stimulates vitamin D receptor expression, which greatly enhances the antimicrobial effect against pathogens. [11]

Vitamin D additionally activates the intracellular NOD2 receptor, which increases cell sensitivity to the NOD2 ligand produced by specific bacteria. This, in turn, enhances the transcription of cAMP and FB4 genes, leading to enhanced antimicrobial activity. [12] In addition, vitamin D inhibits the expression of the antimicrobial peptide hepcidin, which reduces intracellular iron transport by ferroportin and limits the proliferation of pathogens that use iron for growth. [12]

In the context of antigen-presenting cells and adaptive immunity, vitamin D affects dendritic cells by regulating their differentiation and maturation while promoting the development of a tolerogenic phenotype. Exposure of monocytes to $1,25(OH)_2$ D leads to increased expression of molecules responsible for antigen uptake, while inhibiting the differentiation and maturation of dendritic cells resulting in a reduced ability to stimulate antigen-specific CD8 T cells. As a result, the peripheral Th1 inflammatory response is reduced [8].

Vitamin D increases the number of regulatory T cells, decreases the number of CD4+ T cells, increases IL-10 expression levels, and decreases levels of tumor necrosis factor α (TNF-α) and interferon γ (IFN-γ). In a practical context, vitamin D transforms the immune response from a pro-inflammatory Th1 response to an anti-inflammatory Th2 response, leading to an increase in IL-4 secretion while decreasing IL-2 and IFN-γ secretion. [8,13]

Vitamin D in multiple sclerosis (MS)

Multiple sclerosis is a disease of the nervous system that leads to permanent disability. It affects young adults who are most often economically and socially active. [14] The condition is characterized by the destruction of myelin sheaths around nerve fibers within the brain and spinal cord, and the development of inflammation, leading to numerous neurological disorders. [10] Among the potential triggers are environmental, genetic and immunological factors. [15] Of the environmental factors causing MS, low serum vitamin D levels, childhood obesity, smoking, and EBV infection are the most significant. [16]

Low vitamin D levels in MS patients are likely due to both low vitamin intake and reduced outdoor activity in climates not conducive to vitamin D synthesis in the skin. [17] An association between MS incidence and latitude has also been observed. [15]

Meta-analyses by Simpson et al. showed a positive correlation between latitude and the incidence of the above condition. [18]

This is likely related to less sunlight in regions farther from the equator. Weaker UV radiation results in reduced cholecalciferol synthesis in the skin, suggesting a higher incidence of MS in countries with temperate climates. [15]

In vitro studies on glial cell calculi have shown that 1,25(OH) D_{23} has anti-inflammatory effects. This suggests that vitamin D may have therapeutic potential in the treatment of multiple sclerosis. [19] In addition, a large epidemiological study conducted in 2004 found that women who regularly took vitamin D in the form of dietary supplements had a reduced risk of MS by up to 40%. [20]

Cerebrospinal fluid analysis of MS patients and controls revealed the presence of 25(OH)D, which was positively correlated with serum 25(OH)D levels. This confirms that vitamin D and its major transport protein penetrate the central nervous system. The presence of vitamin D in the central nervous system indicates that it may play a role in some functions of this system, it is even considered a neurosteroid. [21]

In all likelihood, vitamin D has a protective and stabilizing effect on patients with previously diagnosed multiple sclerosis. A study by Smolders et al. found that in patients with MS in a relapsing-remitting course who had been ill for less than 5 years, higher levels of 25(OH)D correlated with a reduced likelihood of a subsequent relapse. [22] Similar observations were also found by Pierrot et al. [23] This study included 156 patients with the drowsy-remitting form of the disease. After combining data collected before and during vitamin D supplementation, they found a significant and strong inverse relationship between MS relapse rates and 25(OH)D levels ($p<0.0001$), suggesting that the vitamin does indeed have an impact on MS relapse rates. [23]

Vitamin D in type 1 diabetes (T1D)

There has been a steady increase in cases of type 1 diabetes (T1D) for several decades in most of the countries that produce regular reports. One possible factor contributing to this increase may be vitamin D. [24] Human studies indicate that adequate vitamin D levels, especially early in life, may protect against the development of type 1 diabetes.[25]

Infante et al. found in their study that hypovitaminosis D is common among children with T1D. They considered it an important environmental factor that may play a role in the pathogenesis and risk of developing this condition in the early years of life, especially in children with high genetic risk. [26] Therefore, it is important to diagnose and treat vitamin D deficiency as early as possible. [26] Marino and Misra's review also supported these conclusions by suggesting that low vitamin D levels may contribute to the development of T1D. [27]

Ajabri and Bokhari, in their non-randomized case-control study involving 80 people with type 1 diabetes, also confirmed the above thesis. They noted that low vitamin D levels are associated with insulin resistance, and beta cell death, which may contribute to the development of T1D. [28]

In addition, vitamin D deficiency is more frequently observed in people with type 1 diabetes, [29-31] including newly diagnosed patients. [32] Various effects of the above vitamin on the pathophysiology of type one diabetes have been described, including both effects on the destruction of autoimmune beta cells and on beta cells themselves. In all likelihood, this effect is at least partially related to the effect of vitamin D on the body's calcium balance. [33]

Additionally, it has been noted that certain genetic variants of the vitamin D receptor may interact with the HLADRB1 allele, which raises the risk of developing type 1 diabetes. [34]

Marino and Misra, in their study, pointed out that vitamin D receptors (VDR), are found in pancreatic beta cells, which also produce 1-hydroxylase (encoded by the CYP27B1 gene) and, in addition, the promoter of the human insulin gene contains vitamin D response elements. They also found that vitamin D plays a role in regulating T-cell responses and may protect pancreatic beta cells from the immune system. [27]

In addition, in their review, Infante et al. noted that inflammation is important in the development of T1D through the production of cytokines and chemokines by pancreatic islet beta cells and immune cells. This leads to beta cell dysfunction and apoptosis. Studies have shown that calcitriol and its analogs can counteract IL-1-induced inhibition of beta cell function and reduce IFN-y-stimulated expression of MHC class I and II molecules in beta cells. [26]

Studies also demonstrate the effectiveness of vitamin D supplementation in controlling glycemia in T1D patients. [28,35] Ajabri and Bokhari used vitamin D3 supplementation at a dose of 4,000 IU per day and calcium supplements in their clinical trial involving 80 type 1 diabetic patients with vitamin D levels below 50 nmol/L. [28] HbA1c and 25-hydroxyvitamin D levels were measured at the start of the study and after 12 weeks. The results showed that vitamin D supplementation improved glycemia in the study patients. [28]

Mohammadian et al. conducted a systematic review and meta-analysis involving 44 patients with T1D under the age of 17 who used vitamin D supplementation. They concluded that vitamin D supplementation$_3$ improves HbA1c levels in children with type 1 diabetes in all glycemic control groups, regardless of initial HbA1c levels. [35]

Vitamin D in autoimmune thyroiditis (AITD)

Studies show that low vitamin D levels may be associated with Graves-Basedow disease (GD) and Hashimoto's thyroiditis (HT). [36,37] Vitamin D supplementation in combination with antithyroid drugs or thyroid hormone has also been shown to support the treatment of AITD by suppressing the autoimmune response and reducing serum thyroid autoantibodies. [36,37] It should also be noted that vitamin D plays a key role in autoimmune thyroid diseases, as it affects the immune system by enhancing the innate immune response. In addition, it acts as an immunomodulator in autoimmune diseases such as GD and HT. [1] It has been shown that low vitamin D levels of ≤10 ng/ml (≤25 nmol/L) can often lead to AITD, especially in the form of Hashimoto's thyroiditis and increased levels of antithyroid antibodies. [38]

Lower levels of vitamin D were observed in Graves-Basedow disease compared to Hashimoto's thyroiditis. In addition, an inverse correlation was found between 25(OH)D levels$_3$ and antithyroid antibody titers. [39] In healthy adults who are in euthyroidism, a strong inverse correlation has been noted between TSH levels and vitamin D (a metabolite of vitamin D-calcidiol). The highest TSH levels occur in the fall and winter, while the highest vitamin D levels are observed in the spring and summer. [40] Mackaway et al. also confirmed the above correlation between vitamin D levels and TSH. In addition, they showed a high prevalence of hypovitaminosis D and hypocalcemia in hypothyroid patients. [41] Chailurkit et al. confirmed these data in young people, [42] and Zhang et al. also found negative titers of antithyroid antibodies in middle-aged and older men in addition. [43]

Mazokopakis et al. found an inverse relationship between serum 25(OH) vitamin D levels and anti-TPO antibody production in 218 patients with hyperthyroidism and normal thyroid function. [44] Patients with hypovitaminosis D had significantly higher levels of anti-TPO antibodies compared to those without deficiency. A significant decrease (20.3%) in serum anti-TPO antibody levels was observed in 186 patients who took oral vitamin D supplementation (1200-4000 IU daily) for 4 months. [44]

Chaudhary et al. conducted a study on 100 patients with recently diagnosed AITD. [45] They noted that those with the lowest vitamin D levels had the highest anti-TPO antibody titers ($p=0.084$). After a three-month follow-up period, they observed a significant reduction in antibody levels in patients who took vitamin D at 60,000 IU per week for eight weeks. [45]

Vitamin D in inflammatory bowel disease (IBD)

IBDs are immune system disorders of unknown cause that affect the gastrointestinal tract. [17] There are at least two main forms of IBD: ulcerative colitis (UC) and Crohn's disease (CD). These chronic, recurrent diseases usually cause inflammation of the terminal ileum and colon, but can also affect various sites throughout the gastrointestinal tract. [17]

Patients with IBD may be at higher risk for hypovitaminosis D due to various factors, including poor nutrient and bile acid absorption, limited dietary intake, including low consumption of vitamin D-rich foods (for example, dairy products), corticosteroid use, sun avoidance during immunosuppressive therapy, and genetic factors, including single nucleotide polymorphisms in the vitamin D metabolic pathway. [46] Several epidemiological studies [47-51] have shown a high prevalence of vitamin D deficiency in patients with inflammatory bowel disease, especially in those who require corticosteroid treatment. This deficiency tends to be more pronounced in patients with Crohn's disease compared to those with ulcerative colitis. [46]

Vitamin D plays an important role in maintaining the integrity of the intestinal mucosa, maintaining the normal permeability of this membrane and modulating cytokine responses of T cells. It changes the inflammatory phenotype of Th1 and Th17 to Th2 and regulatory T cell phenotype. [8] This suggests that hypovitaminosis D may have a significant impact on the development and course of inflammatory bowel disease. Nevertheless, it is not yet completely clear whether vitamin D deficiency is the cause of IBD or whether it is due to impaired absorption after the development of IBD, which in turn may affect the course of the disease. [52] Vitamin D deficiency can be observed in about 45-50% of patients with UC. For CD, the percentage is about 35% to 100%. [8]

Ham et al. conducted a study on 711 patients with CD and 764 patients with UC. [53] Patients with Crohn's disease had their clinical disease activity index (CDAI) assessed within one month of 25(OH)D measurement, while patients with UC used partial Mayo scores obtained on the day of 25(OH)D assessment. The study found a significant association between hypovitaminosis D and higher CDAI, partial Mayo scores, and C-reactive protein (CRP) levels, confirming the importance of vitamin D in disease activity. [53]

López-Muñoz et al. in their study also observed that serum 25(OH)D levels were inversely correlated with fecal calprotectin levels in patients with CD and UC. In addition, they found a correlation between 25(OH)D and CRP levels in patients with ulcerative colitis. [54]

Changes in laboratory indices were more pronounced with more severe disease symptoms, allowing the authors to predict patients' clinical features and IBD severity with 80% accuracy. 25(OH)D deficiency was also associated with increased hospitalizations, exacerbations, the need for steroids and treatment escalation. These findings suggest that vitamin D supplementation in IBD patients may be effective in reducing serum inflammatory markers and alleviating clinical symptoms in both CD and UC patients. [54]

Vitamin D in celiac disease

Celiac disease is an autoimmune disease. It occurs in people with a genetic predisposition who develop an immune response to gluten. The condition specifically affects the small intestine, but clinical manifestations can be diverse and include both intestinal and extraintestinal symptoms. [55] Among micronutrients, vitamin D appears to be important in the pathogenesis of the disease due to its role in regulating both the innate and adaptive immune responses. [8] According to studies, in northern geographic areas where exposure to UVB and sunlight is lower, cutaneous vitamin D synthesis is reduced and Celiac disease is more common. [56] In addition, children born in the summer who first consume gluten in the winter are more likely to have vitamin D deficiency, which increases the risk of autoimmunity, and are therefore more likely to have celiac disease than children born in colder months. [57] In addition, vitamin D deficiency in celiac patients due to malabsorption may be a key cause of some of the clinical manifestations of the disease, such as decreased bone mineral density, reduced bone mass and increased bone fragility. [58]

Lionetti et al. conducted a study involving 131 children with newly diagnosed celiac disease and a similar number of healthy subjects. They found that plasma 25-hydroxyvitamin D levels were significantly lower in patients with celiac disease compared to controls.[59]

Seth et al [60] also reached similar conclusions in their study, which compared 25-hydroxyvitamin D levels in 60 children aged 0 to 18 years with diagnosed celiac disease and 60 age- and gender-matched healthy controls. They found that the prevalence of 25(OH)D levels below 20 ng/ml was significantly higher in children with celiac disease (63.3%) compared to the control group (45.0%). [60]

SUMMARY

The main role of vitamin D in the human body is to ensure calcium and phosphorus homeostasis and, influence adequate bone metabolism. Vitamin D receptors (VDRs) are present in many tissues, such as the brain, prostate, pancreas, breast, colon, and immune cells, suggesting that vitamin D also has extraskeletal functions, including immunomodulation.

Low serum vitamin D levels may be associated with an increased risk of developing various diseases and disorders of the immune system such as multiple sclerosis, type 1 diabetes, autoimmune thyroid diseases, inflammatory bowel diseases and celiac disease.

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