MEDICAL SCIENCES

VITAMIN D AND AUTOIMMUNITY

Shkiryak A.
CEO and chief medical officer "Shkiryak Clinic"
Ukraine
Neurosurgeon
MD, MsSc
ORCID: https://orcid.org/0000-0002-2282-8285
Khanenko S.
"Shkiryak Clinic"
Ukraine
Family doctor
MD, MBA
ORCID: https://orcid.org/0009-0000-4237-1158
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Abstract

Historically, vitamin D has been associated with the regulation of bone metabolism. However, increasing evidence demonstrates a strong association between vitamin D signaling and many biological processes that regulate immune responses. The discovery of the vitamin D receptor in multiple immune cell lineages, such as monocytes, dendritic cells, and activated T cells credits vitamin D with a novel role in modulating immunological functions and its subsequent role in the development or prevention of autoimmune diseases. In this review we, discuss five major areas in vitamin D biology of high immunological significance: (1) the metabolism of vitamin D; (2) the significance of vitamin D receptor polymorphisms in autoimmune diseases, such as multiple sclerosis, type 1 diabetes mellitus, and systemic lupus erythematosus; (3) vitamin D receptor transcriptional regulation of immune cell lineages, including Th1, Th17, Th2, regulatory T, and natural killer T cells; (4) the prevalence of vitamin D insufficiency/deficiency in patients with multiple sclerosis, type 1 diabetes mellitus, and systemic lupus erythematosus; and finally, (5) the therapeutic effects of vitamin D supplementation on disease severity and progression.

Keywords: Vitamin D, Autoimmunity, Multiple sclerosis, Type 1 diabetes mellitus, Systemic lupus erythematosus

Introduction

Vitamin D deficiency is an increasingly described phenomenon worldwide (1). Compelling evidence from human disease associations and basic physiological studies demonstrated the significance of vitamin D deficiency in various physiological disorders including neuropathy (2), malignancy (3, 4), infertility (5), cardiovascular diseases (6,7), kidney diseases (8), glucose metabolism (9), and immunological dysfunctions (10-13). Vitamin D was first identified as a nutritional regimen for rickets in the early twentieth century and was broadly defined as a compound with curative effects on rickets. Chemically, vitamin D is the derivative of a steroid, 7-dehydrocholesterol, derived from cholesterol and is found in the sebaceous glands of the skin of animals. Upon exposure to sunlight, 7-dehydrocholesterol will absorb UVB light (~280 to 315 nm) and convert to precalciferol (also called previtamin D_3) in the skin. Much of the precalciferol eventually is isomerized into cholecalciferol (also called vitamin D_3) through thermal conversion (14). Since sunlight is necessary for photosynthesis of previtamin D_3 in human skin, vitamin D is also commonly called "sunshine vitamin". In addition to 7-dehydrocholesterol in animals, ergosterol is another commonly occurring steroid in plants that can be activated by irradiation to produce ergocalciferol (also called vitamin D_2).

Both vitamin D_3 formed in the skin and vitamin D_3 absorbed from the digestive tract, travel to the liver, where they are hydroxylated at carbon 25 to form clacidiol (also called 25-hydroxy vitamin D_3, abbreviated as 25(OH)D) by liver 25-hydroxylase, CYP2R1 and CYP27A1. 25(OH)D is the major circulating vitamin D metabolite and a reliable indicator of vitamin D status. Following the hydroxylation in liver, calcidiol is further hydroxylated by 1-α-hydroxylase, CYP27B1, in the proximal convoluted tubule cells of kidney, forming calcitriol (also called 1,25-dihydroxy vitamin D_3, abbreviated as $1,25(OH)_2D$) which is considered the active form of vitamin D (15).

At the cellular level, $1,25(OH)_2D$ interacts with nuclear vitamin D_3 receptor (VDR), which belongs to the superfamily of nuclear hormone receptors, to modulate gene transcription. Ligand binding initiates a conformational change that increases the receptor's affinity to the retinoid X receptor (RXR). Once the VDR-$1,25(OH)_2D$ complex is heterodimerized with RXR, this complex will bind to vitamin D_3 response elements (VDREs) and recruit a number of nuclear coactivator or corepressor proteins. The transcription of genes for specific mRNA may be ultimately either enhanced or inhibited by this ligand-activated transcription factor (16).

Immunomodulatory Effect of Vitamin D

Although historically vitamin D has been associated with the regulation of bone metabolism, it is now evident that vitamin D is involved in many biological processes that regulate immune responses (17-20). There has been increasing interest in possible immunomodulatory effects of vitamin D since VDR was first discovered in monocytes (21, 22) and subsequently in dendritic cells and activated T cells (23, 24). In vitro studies showed that vitamin D inhibits pro-inflammatory activity of CD4+ Th1 cells and their production of cytokines such as IL-2, interferon (IFN)-γ, and tumor necrosis factor-α (25-27). $1,25(OH)_2D$ exerts an inhibitory effect on T cell proliferation, the expression of IL-2 (28, 29)and IFN-γ mRNA and protein in T cells (30), which could be caused by binding of the VDR–RXR heterodimer to the VDREs in the promoter regions of genes encoding IL-2 and IFN-γ. In addition to its anti-inflammatory effects, vitamin D also promotes Th2 responses by enhancing IL-4, IL-5, and IL-10 production, thus skewing the T cell compartment from an inflammatory Th1 state to a more anti-inflammatory and regulated Th2 state . Some studies reported that vitamin D could increase regulatory T (Treg) activity and suppress Th17 responses. Interestingly, vitamin D is not only required for the development of natural killer T (NKT) cells, but also increased IL-4 and IFN-γ production of NKT cells. Logically, these extensive effects of vitamin D on multiple immune cell lineages strongly suggest that vitamin D could play important roles in immune-mediated disorders in autoimmunity.

Vitamin D and Autoimmune Diseases

Multiple Sclerosis (MS)

MS is a chronic inflammatory disease characterized by immune-mediated damage of central nervous system (31). The etiology of MS is not well understood but, like other autoimmune diseases, could be attributed to genetic predisposition and/or environmental factors. Epidemiologic evidence showed that MS has a geographical distribution: the prevalence of the disease is lower in equatorial regions and becomes higher with increasing latitudes (32). This phenomenon could be caused by the lack of sunshine in high-latitude regions that is required for the cutaneous synthesis of vitamin D and suggests that vitamin D insufficiency could be a potential risk factor for MS.

Soilu-Hanninen et al. and Correale et al. demonstrated that the serum concentration of 25(OH)D and 1,25(OH)2D were lower in MS patients than those in controls (33, 34). Seasonal variation of serum 25(OH)D levels were similar in MS patients and controls, but 25(OH)D levels were lower during MS relapses than in remission , suggesting that vitamin D could be involved in the regulation of the clinical disease progress and severity of MS. Multiple studies also demonstrated that most of the MS patients were deficient in vitamin D. In particular, low serum 25 (OH)D levels were associated with high disability and relapse rate in MS patients; however, serum 1,25 (OH)2D, which is the biologically active form of vitamin D, was not directly associated with both disability and relapse rate. Munger et al. and Kragt et al. reported that there was a strong inverse correlation between the level of serum 25(OH)D and MS risk; however, the correlation was only evident among whites but not blacks and Hispanics. The reason why MS patients generally have lower serum 25(OH)D levels than healthy controls could be a combination of insufficient vitamin D intakes and decreased outdoor activities caused by lifestyle changes associated with increasing disability. However, it is unknown whether the high prevalence of vitamin D deficiency found in MS patients is the cause or effect of the disease.

Recent studies showed that vitamin D deficiency might increase the risk of MS. As a result, detection of vitamin D deficiency and restoring vitamin D status to adequate levels may be considered as part of the clinical treatment of MS. In fact, vitamin D intervention has been implemented in several studies. However, these clinical trials were unable to provide definitive evidence to support the therapeutic effects of vitamin D intervention, mostly due to an extremely small number of MS patients recruited. Due to the lack of a double-blind, placebo-controlled, and randomized study with a large number of patients, the beneficial effects of oral vitamin D supplementation on MS progression need to be further investigated. In addition to clinical effectiveness, the optimal dose and duration of vitamin D supplementation are not well defined and may vary between patients.

Type 1 Diabetes Mellitus (T1DM)

T1DM is an immune-mediated disease that is caused by autoimmune destruction of pancreatic β cells that produce insulin, leading to insulin deficiency. Similar to other autoimmune diseases, environmental factors and/or genetic susceptibility could play roles in the onset and progression of T1DM. Epidemiologic studies also showed that the incidence rate of T1DM was higher in geographical regions with lower UV exposure that resulted in less spontaneous vitamin D synthesis. This inverse association of T1DM prevalence with UV radiation is consistent with that reported for MS, suggesting that the environmental UVexposure correlating with cutaneous synthesis of vitamin D could influence the development of multiple autoimmune disorders.

A birth-cohort study by Hypponen et al. demonstrated that dietary vitamin D supplementation is associated with reduced risk of T1DM. The possibility that ensuring sufficient vitamin D could decrease the frequency of T1DM has raised an interest of further investigating nutritional vitamin D levels in T1DM patients. It has been reported that the plasma 25(OH)D levels were lower in T1DM patients than in control subjects among young adults and children. Moreover, the prevalence of vitamin D deficiency/insufficiency was higher in T1DM children compared to controls. Interestingly, 25(OH)D levels were lower in male compared to female patients, suggesting that the gender difference in plasma vitamin D status might contribute to the high incidence of T1DM in males. In addition to plasma 25(OH)D, circulating 1,25(OH)2D levels were also lower in T1DM patients than in controls. The low serum 1,25(OH)2D levels were indicative of tubulo-interstitial dysfunction in T1DM before persistent microalbuminuria. Interestingly, low concentrations of circulating 1,25(OH)2D were not associated with increased risk of microalbuminuria in T1DM. However, the circulating 1,25(OH)2D levels may not be equal to the local conversion of 25(OH)D into 1,25(OH)2D that results in beneficial effects.

Because of the strong correlation between vitamin D and T1DM, it has been suggested that vitamin D could prevent the damage, rescue the function of pancreatic β cells, and reduce the incidence of T1DM. Pitocco et al. and Li et al. both demonstrated that vitamin D had a protective effect on preserving β-cell function, although the effect was not evident in the former study and vitamin D supplementation could only temporarily reduce the clinical insulin dose, which might be attributed to the low 1,25(OH)2D dose (0.25 μg on alternate days) administered in T1DM. In Li's study, the insulin plus vitamin D treatment (1-α-hydroxy vitamin D3; 0.5 μg per day) group developed no β-cell failure, while 27.8 % in the control group developed β-cell failure; however, the number of patients in this randomized controlled study is very limited. Similar to MS, further clinical studies are necessary to determine the therapeutic value of vitamin D supplementation in T1DM.

Systemic Lupus Erythematosus (SLE)

SLE is a systemic autoimmune disease that can cause chronic inflammation and damage in multiple tissues and organs. Environmental factors and genetic susceptibility are both responsible for the pathogenesis of SLE. One of such factors is vitamin D deficiency. SLE patients tend to have inadequate vitamin D since most of them are photosensitive to UV radiation and unable to expose themselves to sunlight. The correlation between vitamin D deficiency/insufficiency and SLE has been documented in multiple studies. Ruiz-Irastorza et al. observed a high frequency of inadequate vitamin D status in SLE patients (75 % of them had insufficient vitamin D levels, serum 25 (OH)D<30 ng/ml, and 15 % of them had deficient vitamin D levels, serum 25(OH)D<10 ng/ml). Borba et al. reported the similar high prevalence of vitamin D insufficiency/deficiency in SLE; however, serum 25(OH)D levels were lower only in SLE patients with high disease activity, but not mild activity, than in controls. In another study by Kim et al., serum 25(OH)D titers were significantly lower in SLE than in controls. Although only 16.3 % of SLE patients had vitamin D insufficiency (serum 25(OH)D <30 ng/ml), the risk of vitamin D insufficiency was 4.6-fold increased in SLE.

Several observational studies yield inconsistent results on the correlation between vitamin D levels and disease severity. Some studies suggested that vitamin D concentrations were inversely related to SLE activity , while others claimed that no such relation was observed. In addition to 25(OH)D, $1,25(OH)_2D$ was also lower in SLE patients and the vitamin D deficiency was particularly associated with overweight SLE patients. Similar to other autoimmune diseases, seasonal variation of vitamin D status has been observed in SLE patients. In Bogaczewicz's study, the serum 25(OH)D levels in both SLE patients and controls during the cold season were lower compared to the warm season . Interestingly, serum 25(OH)D concentrations were lower in SLE patients than in controls only during the warm season but not the cold season. Furthermore, the cold season was found to be a risk factor for vitamin D deficiency, mainly due to the lack of sunlight exposure and/or the decrease in outdoor activities during the cold season of the year. In addition, there was no connection between serum concentrations of IL-17 and vitamin D status, whereas serum IL-23 was lower in SLE patients with vitamin D deficiency.

Ruiz-Irastorza et al. evaluated the therapeutic effects of oral vitamin D supplementation on SLE in an observational study. After around 2 years of oral vitamin D treatment, mean 25(OH)D levels in all treated patients were increased. However, the majority (71 %) of the SLE patients still had insufficient levels of vitamin D. Although it appears that there was no improvement of SLE severity after oral vitamin D supplementation in this study, the effect of vitamin D intervention in SLE has not been extensively investigated, probably because there are too many confounding factors that could affect vitamin D metabolism in clinical medications used to treat SLE.

Conclusion

Vitamin D, in addition to its crucial role in bone metabolism, has been associated with multiple autoimmune diseases in several epidemiological studies. Due to its unique capability to bind to VDR and serve as a transcriptional factor, vitamin D can regulate gene expression and further exert its immunomodulatory effects on immune cells. It has been shown to inhibit Th17 cytokine production, enhance Treg activity, induce NKT cell functions, suppress Th1, and promote Th2 cytokine production, and thus skew T cells toward Th2 polarization. Furthermore, accumulating evidence suggest that VDR polymorphisms and serum vitamin D status are both closely associated with disease risk of MS, T1DM, and SLE. Therefore, impaired vitamin D signaling and/or inadequate vitamin D intake caused by genetic predisposition (e.g. VDR polymorphisms) and/or environmental factors (e.g. insufficient sunlight exposure in high-latitude regions or during the cold season) may contribute to the onset and progression of autoimmunity. Because of the high prevalence of vitamin D insufficiency/deficiency in patients with MS, T1DM, and SLE, vitamin D supplementation has been considered a prospective candidate for the treatment of such autoimmune diseases. However, due to the lack of larger randomized trials, more well-organized studies with methodological design are essential in order to further confirm the potential of vitamin D to prevent and ameliorate autoimmunity.

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