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Chapter

Vitamin D and Autoimmune Diseases

Ifigenia Kostoglou-Athanassiou, Lambros Athanassiou and Panagiotis Athanassiou

Abstract

Vitamin D has many and profound effects on the immune system. Vitamin D deficiency is known to be related to the development of autoimmune diseases. In particular, vitamin D deficiency is related to the development and the severity of rheumatoid arthritis (RA). RA develops in patients with vitamin D deficiency, and the activity of the disease is related to vitamin D deficiency. Vitamin D deficiency is also related to the development of systemic lupus erythematosus (SLE). SLE develops in patients with vitamin D deficiency, and the activity of the disease is also greater in patients with vitamin D deficiency. Vitamin D deficiency is also related to the development and the severity of multiple sclerosis. Vitamin D should be administered to patients with multiple sclerosis, and this seems to mitigate the symptoms of the disease and to prevent disease progression. Vitamin D deficiency is also observed in patients with inflammatory bowel disease and may be related to disease severity. Low vitamin D levels have also been observed in patients with autoimmune Hashimoto's thyroiditis. Low vitamin D levels have been observed in patients with systemic sclerosis, especially in the diffuse form of the disease. Optimal vitamin D levels appear to be required for normal immune function and for the prevention and treatment of autoimmune diseases.

Keywords: vitamin D, autoimmunity, rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, inflammatory bowel disease, autoimmune Hashimoto's thyroiditis

1. Introduction

Vitamin D is a secosteroid hormone, which is known to be related to the regulation of the musculoskeletal system. It affects calcium and phosphate metabolism and is related to bone health. Recently, the extraskeletal effects of vitamin D are under intense research and have attracted the interest of the scientific community [1–6]. In particular, the relationship of vitamin D with the immune system is in the focus of scientific evaluation [7–9]. In the chapter herein, the effects of vitamin D on the immune system will be discussed, and the relationship of vitamin D deficiency with the development of autoimmune diseases will be reviewed.

2. Vitamin D and the immune system

The classic function of vitamin D is to enhance intestinal absorption of calcium by regulating several calcium transport proteins in the small intestine [4]. However, various cells express the vitamin D receptor (VDR) and the vitamin D activating enzyme 1-α-hydroxylase. Various cells of the immune system also express the VDR and harbor 1-α-hydroxylase [10, 11]. Thus, cells of the immune system respond to vitamin D and also activate vitamin D in a paracrine or autocrine fashion. The extra-renal 1-α-hydroxylase is not upregulated by PTH, and thus, production of $1,25(OH)_2D_3$ is dependent on concentrations of the substrate $25(OH)D_3$, and it may be regulated by inflammatory signals, such as lipopolysaccharide and cytokines [12, 13]. Cells of the immune system, which express the VDR and harbor 1-α-hydroxylase, are macrophages, T cells, dendritic cells, monocytes, and B cells (**Figure 1**) [9]. Vitamin D is involved in the regulation of the innate immunity as it enhances the defense system of the organism against microbes and other pathogenic organisms, and it modulates the adaptive immune system through direct effects on T-cell activation and on the phenotype and function of antigen-presenting cells, particularly dendritic cells.

2.1 Vitamin D and the innate immune system

The innate immune system is a first line of defense against infection. Vitamin D is a regulator of the innate immune system [1, 14]. The first data on the effect of vitamin D on the innate immune system have been generated on the treatment of diseases caused by mycobacteria, such as tuberculosis and leprosy [15–18]. Vitamin D has been used as a treatment of infections for more than 150 years. In 1849, Williams reported favorable results with the use of cod-liver-oil, an excellent source of vitamin D, in the treatment of patients with tuberculosis [19]. Fifty years later, Niels Finsen received the third Nobel Prize in Medicine for his description of using UV light, an effective method to increase vitamin D status, to treat lupus vulgaris, a cutaneous form of tuberculosis [20, 21]. Alfred Windaus contributed to the discovery of the chemical structure of vitamin D_2 and vitamin D_3 found in cod-liver-oil and received the Nobel prize [22–24]. Thereafter, several groups used vitamin D_2 and D_3 as a treatment for tuberculosis [22, 25]. Rook et al. [26] demonstrated in the 1980s that $1,25(OH)_2D_3$ inhibited the proliferation of *Mycobacterium tuberculosis* in culture. Vitamin D enhances the production of defensin β2 and cathelicidin in response to infection by macrophages, monocytes, and keratinocytes [12]. Humans have only

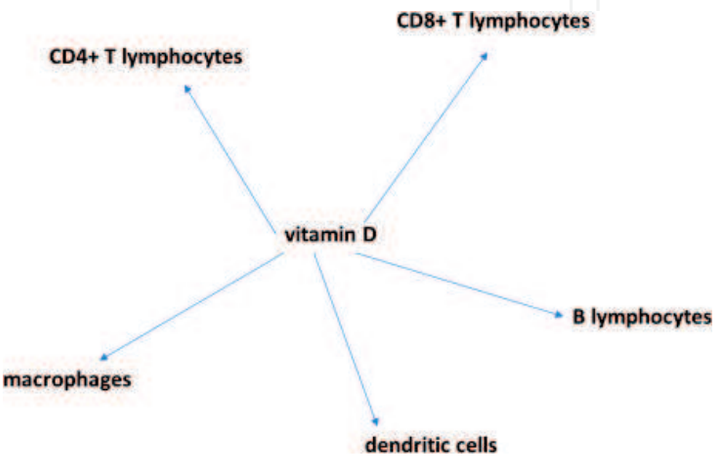

Figure 1.
Cells of the immune system regulated in part by vitamin D.

one cathelicidin, which is cleaved to form LL-37 [27]. Cells of the immune system including neutrophils and macrophages and cells lining epithelial surfaces that are constantly exposed to potential pathogens such as the skin, the respiratory, and the gastrointestinal tract produce cathelicidin [28–30]. Cathelicidin has broad antimicrobial activity against Gram-positive and Gram-negative bacteria, as well as certain viruses and fungi [31]. The killing mechanism of cathelicidin involves bacterial lysis by destabilizing cell membrane [32]. Treatment with $1,25(OH)_2D_3$ upregulates cathelicidin mRNA in several cell lines. Thus, it appears that $1,25(OH)_2D_3$ upregulates antimicrobial peptide production, primarily cathelicidin, on a variety of different cells [33]. Studies indicate that $25(OH)D_3$, the major circulating form of vitamin D to determine vitamin D status, is important for local production of $1,25(OH)_2D_3$ to upregulate cathelicidin production in the skin and macrophages. Exposing human monocytes to pathogens increases the expression of both $1,25(OH)_2D_3$ and VDR, thus increasing both the local production of $1,25(OH)_2D_3$ and the ability of the cell to respond to it [12]. Since keratinocytes also possess 25-α-hydroxylase, UV light may directly stimulate cathelicidin production by providing the substrate $25(OH)D_3$ directly from vitamin D_3 produced within the skin [34, 35]. Macrophages also respond to vitamin D increasing their antimicrobial activity, however, heterogeneously [36, 37]. Macrophages formed after interleukin-15 stimulus respond to vitamin D increasing their antimicrobial activity, whereas macrophages formed after stimulation by interleukin-10 respond to vitamin D stimulus weakly.

Data regarding other infections also exist. Thus, children with low vitamin D status may be more prone to urinary tract infections due to low production of cathelicidin and defensin β2 [38, 39]. Also, adults with asthma may be less prone to infection after treatment with vitamin D due to increased production of cathelidicin and modulation of inflammatory cytokines [40, 41]. Low levels of vitamin D may be related to chronic obstructive pulmonary disease severity [42]. Vitamin D may increase resistance to HIV infection. Low levels of vitamin D have been associated with disease progression and mortality [43]. The ability of the immune cells to hydroxylate $25(OH)D_3$ locally suggests that in patients with infections, it may be better to administer $25(OH)D_3$ rather than hydroxylated metabolites to allow for local production and the feedback system to function.

2.2 Vitamin D and autoimmunity

The natural history of autoimmunity remains largely unknown. However, the theory is that both genetic susceptibility and environmental factors play a role in the development of clinical autoimmune disease. Vitamin D has known immunomodulatory effects on a wide range of immune cells, including T and dendritic cells [44, 45]. Each of these immune cells expresses VDR and produces the enzymes 1-α-hydroxylase and 24-hydroxylase and is therefore capable of locally producing active $1,25(OH)_2D_3$ [46–49]. Activation of CD4+ T cells results in a significant increase in VDR expression enabling regulation of many genes responsive to $1,25(OH)_2D_3$ [50]. $1,25(OH)_2D_3$ suppresses T-cell receptor induced T cell proliferation and changes their cytokine expression. The overall shift is away from T helper Th1 phenotype toward a more tolerogenic Th2 response [51–53]. Vitamin D appears to directly inhibit Th1 cells and may additionally modulate a skewing toward a Th2 response [54]. Th17 cells are a subset of CD4+ T cells involved in organ-specific autoimmunity playing a role in maintaining inflammation, which can lead to tissue damage. $1,25(OH)_2D_3$ suppresses autoimmunity and tissue destruction by inhibiting the Th17 response at several levels [55, 56]. Altogether, the evidence suggests an important role for vitamin D in influencing T-cell responses and in tempering inflammation and tissue damage.

Vitamin D appears to have a direct effect on B cells and inhibits immunoglobulin production [57]. Additionally, differentiation of B cells is interrupted when exposed to $1,25(OH)_2D_3$. $1,25(OH)_2D_3$ also has effects on dendritic cells. Dendritic cells have important functions in maintaining both protective immunity and self-tolerance [58, 59]. Physiologic levels of $1,25(OH)_2D_3$ inhibit maturation of dendritic cells and maintain an immature and tolerogenic phenotype with inhibition of activation markers such as MHC class II, CD40, and others and upregulation of inhibitory molecules [60, 61]. Thus, it appears that the maturational state of dendritic cells can be modulated by $1,25(OH)_2D_3$, making it possible that the vitamin D status of an individual is likely to have important immunologic consequences.

3. Vitamin D and autoimmune diseases

There are several animal models of autoimmunity, in which disease could either be prevented or ameliorated with the administration of either $1,25(OH)_2D_3$ or one of its analogues. These animal models are models of autoimmune encephalomyelitis, collagen-induced arthritis, type 1 diabetes mellitus, inflammatory bowel disease, autoimmune uveitis, and lupus [44, 56, 62–76]. These studies show that treatment with active vitamin D is effective in modulating immune function and ameliorating autoimmune disease. Vitamin D deficiency is a risk factor for the development of some autoimmune diseases, such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), diabetes mellitus type 1, multiples sclerosis, inflammatory bowel disease, and Hashimoto's thyroiditis [49, 69, 74, 77–85] (**Figure 2**). Additionally, vitamin D deficiency has been observed in patients with systemic sclerosis [86].

3.1 Vitamin D deficiency and rheumatoid arthritis

A meta-analysis showed that low vitamin D intake is associated with the development of RA [87]. Thereafter, several studies performed in various areas all over the world showed that vitamin D deficiency is observed in patients with RA and that vitamin D deficiency is associated with disease activity [78, 82, 83, 88–97]. A meta-analysis of the good quality studies performed regarding the association between vitamin D deficiency and RA showed that vitamin D deficiency is observed in RA patients significantly more than in a control group and that vitamin D levels are inversely correlated with disease activity, meaning that low vitamin D levels are associated with high-disease activity [98]. Moreover, an

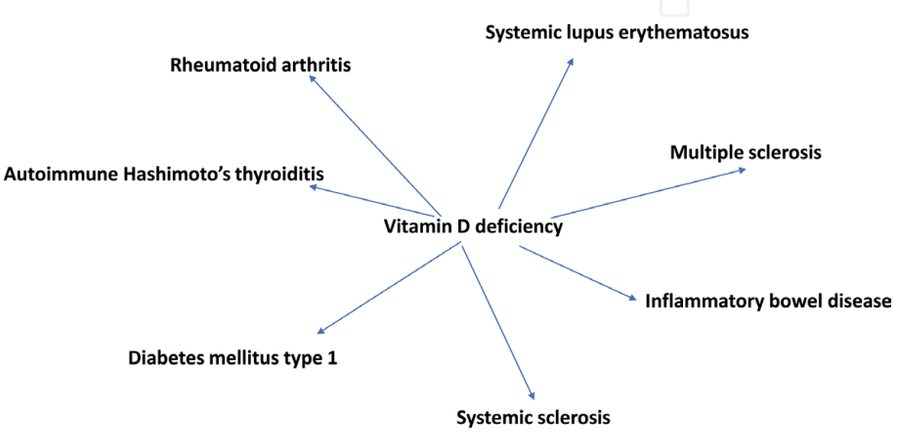

Figure 2.
Autoimmune diseases related to vitamin D deficiency.

association has been shown between VDR polymorphism and RA. Specifically, the FokI F allele of the VDR may be a risk factor for the development of RA [99]. Further studies are needed to unravel the exact association between vitamin D deficiency and RA and to determine the best method of vitamin D supplementation and whether it may be used for the prevention of RA or for the best management of the disease [77, 100]. In addition, it has been proposed that vitamin D may contribute to the management of pain in RA and may be used along with TNF-α inhibitors in RA treatment [77, 101].

3.2 Vitamin D deficiency and systemic lupus erythematosus

In SLE, the inflammatory milieu drives the development of T cells into proinflammatory pathways, defective function of Tregs, and survival and activation of B cells, which produce autoantibodies [78, 81]. Patients with systemic lupus erythematosus have lower $25(OH)D_3$ levels compared to controls, suggesting that vitamin D deficiency may be a risk factor for SLE [81, 84, 102–107]. The majority of studies have also found higher SLE disease activity associated with lower levels of $25(OH)D_3$ [84, 103]. As patients with SLE have often photosensitivity and are advised to avoid direct sun exposure, detecting vitamin D deficiency and replacing $25(OH)D_3$ with oral supplementation is critical and may impact disease activity [108].

3.3 Vitamin D deficiency and type 1 diabetes mellitus

Type 1 diabetes mellitus is one of the most prevalent chronic diseases with onset in childhood and is the result of immune-mediated destruction of pancreatic insulin producing β cells. There appears to be a geographic variation in incidence following a gradient in latitude, which is the inverse of the global distribution of ultraviolet B irradiation, critical for the production of vitamin D within the skin [109]. Studies have shown higher incidence of vitamin D deficiency in patients with type 1 diabetes [110–113]. One environmental factor thought to be protective against the development of type 1 diabetes mellitus is early supplementation with vitamin D [114]. A number of large case control studies showed that the risk of type 1 diabetes mellitus was significantly reduced in infants who were supplemented with vitamin D compared to those who were not supplemented [115–117]. Additionally, a lower incidence of type 1 diabetes was observed in infants born to mothers who were administered cod liver oil during pregnancy [118]. A birth cohort study in Finland, now more than 50 years ago, evaluated the effects of vitamin D supplementation on rickets and the development of type 1 diabetes mellitus [85]. All women due to give birth in 1966 were enrolled. There was an 80% reduction in the risk for type 1 diabetes mellitus in children having received >2000 IU vitamin D/day compared to those receiving less or not receiving supplementation with vitamin D. Evidence from both human and animal studies shows that vitamin D may be protective as far as the development of type 1 diabetes mellitus is concerned [68, 71, 76]. Thus, the administration of vitamin D may prevent diabetes mellitus type 1; however, once the destruction of pancreatic beta cells has taken place, it will not act therapeutically to reverse diabetes mellitus type 1.

3.4 Vitamin D deficiency and multiple sclerosis

Multiple sclerosis is characterized by inflammation, demyelination, axonal or neuronal loss, and astrocytic gliosis in the central nervous system, which can result in disability. Epidemiological studies have suggested that vitamin D insufficiency

may contribute to the risk of multiple sclerosis [62, 63, 75, 119, 120]. Moreover, several genetic studies in multiple sclerosis patients have shown that diverse abnormalities in vitamin D metabolism are related to the risk of the disease. It appears that vitamin D deficiency may interact with genetic and environmental protective and risk factors, such as the allele HLA BRB1*1501, infections, obesity, smoking, and sexual hormones and may modulate the risk of the disease [63, 74, 80]. Thus, vitamin D deficiency may be a risk modulating factor for the development of multiple sclerosis. Vitamin D acts as an immunomodulatory factor affecting T and B lymphocytes, and it may exert neuroprotector and neurotrophic actions within the central nervous system. Several studies have shown that vitamin D supplementation exerts multiple beneficial immunomodulatory effects in multiple sclerosis [121–124]. On the contrary, a Cochrane review states that there appears to be no benefit from vitamin D supplementation in patients with multiple sclerosis; however, the level of evidence is very low [125]. Nevertheless, it should be noted that robust statistical models used in association studies have already predicted a favorable vitamin D effect reducing relapses by 50–70% [121]. There is little doubt that vitamin D exerts a beneficial action on multiple sclerosis, the inflammatory component in particular, less so the degenerative. Until more information becomes available, vitamin D supplementation of multiple sclerosis patients, using a moderate physiological dose essentially correcting their vitamin insufficiency, is recommended.

3.5 Vitamin D and inflammatory bowel disease

Vitamin D deficiency has been observed in patients with inflammatory bowel disease, Crohn's disease, and ulcerative colitis [126]. It was found to be related to disease activity in Crohn's disease and ulcerative colitis. Vitamin D supports the integrity of the intestinal barrier and is related to microbiota homeostasis in this cohort of patients [127, 128]. Thus, vitamin D may contribute to the prevention of inflammatory bowel disease by supporting the integrity of the intestinal barrier, contributing to bacterial homeostasis and ameliorating disease progression via anti-inflammatory action. Vitamin D deficiency in inflammatory bowel disease is aggravated by decreased absorption of the vitamin via the gastrointestinal tract [128].

3.6 Vitamin D deficiency and autoimmune Hashimoto's thyroiditis

Studies have observed an association between autoimmune Hashimoto's thyroiditis and low vitamin D levels [79, 129]. These studies have not observed low vitamin D levels in patients with Graves' disease. A meta-analysis of 26 observational studies confirmed an association between vitamin D deficiency and autoimmune Hashimoto's thyroiditis [130]. The aforementioned meta-analysis found that although there was heterogeneity between the results of the various studies performed all over the globe, studies had similar results in populations from different countries and also in populations in different age ranges, in particular pediatric and adult populations.

3.7 Vitamin D deficiency and systemic sclerosis

Systemic sclerosis is a chronic, inflammatory, fibrotic disorder thought to be related to autoimmune etiology. Vitamin D deficiency has been observed in patients with systemic sclerosis [86, 131], especially in patients with the diffuse type of the disease [131].

4. Optimal levels of 25(OH)D_3

The molecule used to assess vitamin D sufficiency in a population is 25(OH)D_3 [9]. It appears that vitamin D has physiologic effects beyond those related to bone physiology and mineral homeostasis. It may be that the alarming prevalence of vitamin D deficiency observed all over the globe may be contributing to the development of autoimmune diseases. Based on bone-related biomarkers such as intact parathyroid hormone, calcium absorption, and bone mineral density, maintaining a 25(OH)D_3 level of at least 32 ng/ml appears sufficient.

5. Conclusions

It appears that vitamin D is a potent immunomodulator. It has multiple and diverse effects on the immune system. In particular, it potentiates the innate immune response enhancing the production of cathelicidin from human macrophages, monocytes, and keratinocytes, thus enhancing and potentiating the immune response against external pathogens. It affects the adaptive immune response shifting the phenotype of the adaptive immune response toward a more tolerogenic phenotype. Vitamin D deficiency is related to various autoimmune disorders. Vitamin D deficiency appears to be related to the development of RA and correlates with disease severity. Vitamin D deficiency is observed in patients with SLE. It was found to be related to disease severity and activity in some but not all studies. Vitamin D deficiency is observed in patients with multiple sclerosis, and vitamin D administration may ameliorate disease severity. Vitamin D deficiency is also observed in patients with inflammatory bowel disease, Crohn's disease, and ulcerative colitis, and it is related to disease activity. Vitamin D contributes to the integrity of the intestinal barrier and bacterial homeostasis. In addition, vitamin D absorption is decreased making supplementation important. Vitamin D deficiency is also observed in patients with autoimmune Hashimoto's thyroiditis. Vitamin D deficiency is found in patients with systemic sclerosis, especially the diffuse form of the disease. It appears that optimal levels of vitamin D are important for immune function and for the prevention of autoimmunity in the human organism.

Conflict of interest

The authors declare no conflict of interest.

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