



A review of the role of vitamin d in autoimmunity

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Abstract

Introduction: The main function of vitamin D is to increase the intestinal absorption of calcium, participating in the stimulation of active transport of this ion in enterocytes. Extra-renal hydroxylation of vitamin D also occurs, originating the vitamin that would act in an autocrine and paracrine manner, with functions of inhibiting cell proliferation, promoting cell differentiation, and immune regulation. **Objective:** It was to review the scientific literature on the role of vitamin D in autoimmunity. **Methods:** A search was carried out on scientific articles centered on the proposed theme: "Role of vitamin D in autoimmunity". Several search engines that carried scientific information in the health area were used to carry out this study, such as Google Scholar and the Medical Publications database (PubMed), and Scientific Electronic Library Online (SCIELO). In collecting the information, the descriptors used to carry out this research were: vitamin D; vitamin D in preventing diseases; vitamin D and autoimmune diseases; vitamin D; autoimmune diseases. The inclusion criteria used in this study were publications of scientific articles available in full and with free electronic access, limited to a period between 2011 and 2022, and selected articles in Portuguese and English. **Results and Conclusion:** Based on this methodology, it was possible to analyze a population of 58 articles that were selected for the study and constituted the sample used in this review. Several studies point to the effects of vitamin D not related to calcium metabolism, such as antineoplastic activity (particularly concerning breast, colon, and prostate cancers, and lymphoproliferative

diseases), antihypertensive and immunomodulatory. Vitamin D deficiency and its use for treatment have been described in various autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, lupus, inflammatory bowel disease, myasthenia gravis, scleroderma, alopecia areata, psoriasis, vitiligo, autoimmune hepatitis, type 1 diabetes mellitus, autoimmune thyroiditis, etc. The effects of vitamin D on the immune system are related to the tolerance of self-antigens, exerting an inhibitory effect on the Th1 and Th17 type lymphocyte pattern, and a promoting effect on the expression of the Th2 and Treg pattern through the action of vitamin D in all cells of the system through the vitamin D receptor. More studies are needed to establish safe and effective doses in the management of these properties of vitamin D.

Keywords: Ocular immunity. Autoimmune uveitis. Vitamin D. 25-hydroxyvitamin D. Immunomodulation.

Introduction

The term vitamin D (VD) encompasses a group of secosteroid molecules derived from 7-dehydrocholesterol (7-DHC) interconnected through a cascade of photolytic and enzymatic reactions that take place in cells of different tissues. This broad name includes both the active metabolite (1 α ,25-dihydroxy-vitamin D or calcitriol) and its precursors (including vitamin D3 or cholecalciferol, vitamin D2 or ergosterol and 25-hydroxyvitamin D or calcidiol) and the degradation products [1].

Also, vitamin D occurs in two forms: ergocalciferol or vitamin D2, synthesized in the epidermis by the action of ultraviolet radiation from sunlight (UVB 290-315 nm)

on the vegetable steroid ergosterol, therefore, independent of enzymatic catalysis, and cholecalciferol or vitamin D₃, from cholesterol. The D₂ and D₃ forms differ only in the presence of an additional double bond and a methyl group incorporated into the long side chain of the biological form called D₂. After the first hydroxylation of these compounds in the liver, 25-hydroxyvitamin D (calcidiol or [25(OH) D₃]) is produced. The product of the second hydroxylation is known as calcitriol [1,25(OH)₂D₃]. Forms D₂, D₃, and 25-hydroxyvitamin D are considered prohormones, while calcitriol is the hormone activated in the kidneys [2].

Besides, vitamin D, or cholecalciferol, is a steroid hormone whose main functions are to regulate calcium homeostasis, bone formation, and reabsorption, through its interaction with the parathyroids, kidneys, and intestines. The main source of vitamin D is represented by the endogenous formation in skin tissues after exposure to ultraviolet B radiation, but 20% of the body's needs for this vitamin can be acquired through diet [1].

Pre-vitamin D₃ can also undergo an isomerization process, originating biologically inactive products (lumisterol and tachysterol) and this mechanism is important to avoid the overproduction of vitamin D after periods of prolonged exposure to the sun. Sufficient exposure to sunlight or UVB radiation is up to 18IU/cm² in 3 hours. This process takes place in two stages: the first takes place in the deep layers of the dermis and consists of the photoconversion of 7-dehydrocholesterol into previtamin D or pre-calciferol [3].

Then, a chemical isomerization occurs depending on body temperature, and pre-vitamin D is slowly and progressively transformed into vitamin D₃, which has a high affinity for the vitamin D transporter protein (DBP) and vitamin D, with lower binding affinity, remains on the skin. Upon reaching the cutaneous capillary network, vitamin D is transported to the liver, together with DBP, where it begins its metabolic transformation [3].

The two types of VD undergo complex processing to be metabolically active and when they are ingested in excess, they settle in fatty deposits. In the blood, vitamin D circulates mainly bound to a vitamin D-binding protein, although a small fraction is bound to albumin. In the liver, it undergoes hydroxylation, mediated by a cytochrome P450-like enzyme, and is converted into 25-hydroxyvitamin D [25(OH)D] which represents the circulating form in greater quantity but is biologically inert. The hepatic hydroxylation step is poorly regulated, so that blood levels of 25(OH)D reflect the amount of vitamin D that enters the circulation, being proportional to the amount of vitamin D ingested and produced in the skin [2].

In the cells of the renal proximal convoluted tubules, an additional hydroxylation process occurs, forming 1,25 dihydroxy vitamin D [1,25(OH)₂D], also called calcitriol, the biologically active form of vitamin D. 1 α -hydroxylation increases with the elevation of parathyroid hormone (PTH) concentration, with hypocalcemia and hypophosphatemia, in the form of positive feedback, being inhibited by hyperphosphatemia, by the fibroblast growth factor and by 1,25(OH)₂D itself [3,4]. The final step in hormone production is the additional hydroxylation that takes place in the proximal convoluted tubule cells in the kidney, originating 1,25 dihydroxy vitamin D [1,25(OH)₂D], its biologically active form [4].

Therefore, the present study aimed to review the scientific literature on the role of vitamin D in autoimmunity.

Development

Classic functions of Vitamin D

The main function of vitamin D is to increase the intestinal absorption of calcium, participating in the stimulation of active transport of this ion in enterocytes. Vitamin D is important in several systems and has several actions: it mobilizes calcium from the bone, in the presence of PTH, it increases the renal reabsorption of calcium in the distal tubule, it inhibits the synthesis of type 1 collagen; induces osteocalcin synthesis; promotes the in vitro differentiation of monocyte-macrophage cell precursors into osteoclasts, stimulates the production of the RANK ligand (RANK-L), which results in an effect that facilitates the maturation of osteoclast precursors to osteoclasts, which, in turn, mobilize skeletal calcium deposits to maintain calcium homeostasis. When prolonged vitamin D deficiency occurs, we have rickets and osteomalacia and, in adults, when associated with osteoporosis, it leads to an increased risk of fractures [1].

Regulation of renal 1- α -hydroxylase activity is dependent on calcium and phosphate intake, circulating levels of 1,25(OH)₂D₃ metabolites, and PTH. On the other hand, the regulation of extrarenal hydroxylase is determined by local factors, such as the production of cytokines and growth factors, and by 25(OH)D levels, making this pathway more sensitive to vitamin D₁ deficiency. Extrarenal hydroxylation of vitamin D also occurs, originating the vitamin that would act in an autocrine and paracrine manner, with functions of inhibiting cell proliferation, promoting cell differentiation, and immune regulation [1].

Extrarenal Functions of Vitamin D

It is known about the extrarenal hydroxylation of vitamin D in the colon, breasts, lungs, prostate, keratinocytes, brain, smooth muscle of vessels, and macrophages with functions of inhibiting cell proliferation, promoting cell differentiation and immune regulation [4]. Studies have shown that individuals who routinely keep their bodies extensively covered by clothing and indoors during the day (a common situation in modern urban life) have mean circulating levels of 25(OH)D3 (calcidiol) of approximately 45 nmol/L (18 ng/mL), values lower than the minimum necessary (about 80 nmol/L or 32 ng/mL) to optimize the intestinal absorption of calcium and suppress the production of parathyroid hormone, preventing the loss of calcium by the bone tissue. In individuals whose daily activity routinely leads to higher sun exposure, the average level of calcidiol reaches average levels of around 120 nmol/L (48 ng/mL) [5,6].

Also, 1,25(OH)2D3 receptors are present in several cell types, including small intestinal and renal tubular epithelium, osteoblasts, osteoclasts, hematopoietic cells, lymphocytes, monocytes, epidermal cells, pancreatic cells, myocytes, and neurons. Several non-calcemic actions of vitamin D are being studied, such as cell proliferation and differentiation, in addition to immunomodulation [3]. The biological functions of vitamin D are exerted through its binding to nuclear receptors, the vitamin D receptors (VDR), which regulate the transcription of DNA into RNA, similar to receptors for steroids, thyroid hormones, and retinoids. These receptors are expressed by a variety of cell types, including small intestinal and renal tubular epithelium, osteoblasts, osteoclasts, hematopoietic cells, lymphocytes, epidermal cells, pancreatic cells, myocytes, and neurons [3].

After the discovery of the vitamin D receptor (VDR), which is expressed in a wide range of tissues, the role of vitamin D in the prevention and treatment of chronic diseases has become an important area of study. Vitamin D deficiency has been linked to some health problems, including cognitive decline, depression, cardiovascular disease, hypertension, type 2 diabetes, and cancer. During aging, the risk of vitamin D deficiency increases significantly due to reduced nutritional intake of vitamin D, increased adiposity, and decreased cutaneous vitamin D synthesis. This has led to considerable debate about vitamin D supplementation in the elderly and whether vitamin D deficiencies represent an indicator of poor health or increase susceptibility to chronic diseases [3].

Also, the non-calcemic actions of vitamin D, mediated by VDR, have been evidenced, particularly in

the immune system where the active form of vitamin D 1,25(OH)2D3 stimulates innate immune responses, increasing chemotactic and phagocytic responses of macrophages, as well as the production of antimicrobial proteins such as cathelicidin. On the other hand, 1,25(OH)2D3 also modulates adaptive immunity. At the level of the APC (antigen-presenting cell), 1,25(OH)2D3 inhibits the surface expression of the antigen linked to MHC-II and of costimulatory molecules, in addition to the production of cytokines IL-12 and IL-23, altering indirectly the polarization of T cells from a Th1 and Th17 phenotype to a Th2 phenotype. Furthermore, 1,25(OH)2D3 directly affects T cell responses, inhibiting the production of Th1 cytokines (IL-2 and IFN- γ) and Th17 cytokines (IL-17 and IL-21), and stimulating the production of Th2 cytokines (IL-4). Furthermore, 1,25(OH)2D3 favors Treg cell development by modulating DCs (dendritic cells) and directly targeting T cells. Finally, 1,25(OH)2D3 blocks plasma cell differentiation, production of IgG and IgM, and B6 cell proliferation [2].

The main components of the vitamin D system, notably the vitamin D receptor (VDR) and the vitamin D activating enzyme (1 α -hydroxylase) are present in a wide range of tissues, notably macrophages, dendritic cells and T lymphocytes (cells T) the immune system. Thus, serum 25-hydroxyvitamin D (25D) can be converted to hormonal 1,25-dihydroxyvitamin D (1,25D) within immune cells, and then interact with the VDR and promote transcriptional and epigenomic responses in the same or neighboring cells. These intracrine and paracrine effects of 1,25D have been shown to drive innate antibacterial or antiviral responses, as well as attenuate adaptive immunity from inflammatory T cells. In addition to these mechanistic observations, association studies have reported the correlation between low serum 25D levels and the risk and severity of human immune disorders, including autoimmune diseases such as inflammatory bowel disease, multiple sclerosis, type 1 diabetes, and rheumatoid arthritis. The proposed explanation for this is that decreased 25D availability compromises immune cell synthesis of 1,25D, leading to impaired innate immunity and overexuberant inflammatory adaptive immunity [7].

Experimental studies have shown that vitamin D has significant biological activities on the innate and adaptive immune systems. Animal studies have shown that the administration of vitamin D or its metabolites leads to changes in the occurrence and progression of several diseases related to the immune system. This supports clinical and epidemiological data linking vitamin D to the incidence and severity of many disorders such as psoriasis, multiple sclerosis, rheumatoid arthritis, type 1 diabetes, and infectious diseases [8].

Besides, vitamin D acts on the acquired immune response, influencing the function of T cells, through four possible mechanisms: 1) direct endocrine effects mediated by this substance, via the systemic route; 2) direct conversion of D3 [25(OH)D] into D3 [1,25(OH)2D] intracytoplasmic in T cells; 3) direct paracrine effects of 1,25(OH)2D by monocytes or dendritic cells; 4) indirect effects on antigen presentation to T cells, since D3 [1,25(OH)2D] affects localized antigen presenting cells [9]. Still, regarding the immune system, studies suggest a significant role of vitamin D in inducing immune tolerance and a potential role of vitamin D deficiency in the development of autoimmune diseases. It has been postulated that vitamin D resistance may be seen in some patients who require an individualized approach to treating vitamin D10 deficiency [9].

The *in vivo* effects of vitamin D on murine T cells include inhibition of T cell proliferation, inhibition of IFN- γ , IL-17, and IL-4 induction. Experiments in mice demonstrate that the effectiveness of 1,25(OH)2D requires NKT cells, IL-10, IL-10R, and IL-4. Comparisons of mouse and human T cells show that 1,25(OH)2D inhibits IL-17 and IFN- γ and induces regulatory T cells and IL-4. IL-4 was induced by 1,25(OH)2D in mouse and human iNKT cells. Activation for 72h was required for optimal expression of the vitamin D receptor (VDR) in human and mouse T cells and iNKT. Furthermore, T cells are potential autocrine sources of 1,25(OH)2D, but again only 48-72h after activation. Together, the data support the late effects of vitamin D in diseases such as inflammatory bowel disease and multiple sclerosis, where reducing IL-17 and IFN- γ , while inducing IL-4 and IL-10, would be beneficial. VDR has been identified in many other tissues including the immune system and it is now accepted that 1,25(OH)2D and vitamin D are important regulators of the immune system. All immune system cells have been shown to express the VDR, including T11 cells [9].

Genetic Mechanism of Resistance to the Actions of Vitamin D

At a genetic level, hypovitaminosis D has also been found to be associated with autoimmunity, due to mutations in genes involved in the transport, metabolism, or transcriptional activity of the vitamin D receptor (VDR), increasing the incidence and severity of many of these diseases. Genetic association studies have shown that up to 65% of serum vitamin D variation can be explained due to genetic origin. 90% of genetic variability occurs in the form of single nucleotide polymorphisms (SNPs), and SNPs in genes related to vitamin D metabolism have been associated with influencing serum calcidiol levels, such as in vitamin D

binding protein (VDBP; rs2282679 GC), 25-hydroxylase (rs10751657 CYP2R1), 1 α -hydroxylase (rs10877012, CYP27B1) and the vitamin D receptor (FokI (rs2228570), BsmI (rs1544410), ApaI (rs7975232) and TaqI (rs731236) VDR. Regarding VDR SNPs, the F allele, FF, and Ff genotypes of FokI (rs2228570) may provide a genetic risk for RA and SLE. The BsmI bb genotype (rs1544410) was associated with the genetic risk of MS and RA, while the B, BB, and Bb allele genotypes were associated with the genetic risk of SLE [10-12].

In general, the effect of vitamin D on the immune system translates into an increase in innate immunity associated with a multifaceted regulation of acquired immunity. A relationship has been demonstrated between vitamin D deficiency and the prevalence of some autoimmune diseases. It is suggested that vitamin D and its analogs not only prevent the development of autoimmune diseases but could also be used in their treatment. Vitamin D supplementation is therapeutically effective in several experimental animal models, such as allergic encephalomyelitis, collagen-induced arthritis, type 1 diabetes mellitus, inflammatory bowel disease, autoimmune thyroiditis, and systemic lupus erythematosus. Low serum levels of vitamin D may be related to other factors such as reduced physical capacity, less exposure to the sun, higher frequency of polymorphisms in VDR genes, and side effects of medications, in addition to nutritional factors [9].

Vitamin D and Lupus

Vitamin D deficiency may be an environmental factor responsible for triggering systemic lupus erythematosus (SLE). Vitamin D has pluripotent effects on various organs and systems, including the immune system. Vitamin D enhances innate immunity and suppresses adaptive immunity; indirectly affects the polarization of T lymphocytes, promoting a shift of the immune response towards tolerance. Its role on B cells is to inhibit the secretion of antibodies and the production of autoantibodies [13].

In a cross-sectional, prospective study at the Rheumatology Service of the Hospital das Clínicas of the Federal University of Pernambuco, to determine the serum levels of 25-hydroxyvitamin D3 [25(OH)D] in 78 patients with SLE and verifying the association of 25(OH)D insufficiency/deficiency with clinical and laboratory parameters. The authors showed a high prevalence of 25(OH)D insufficiency/deficiency in SLE patients (57.7%) when compared to the healthy group. Given the results found, the authors emphasized the importance of determining serum levels of 25(OH)D in all patients with SLE, regardless of where they live and

the time since diagnosis of the disease [14].

A randomized placebo-controlled study conducted in 2013 concluded that vitamin D intake (2000 IU/day for 12 months) in SLE patients improved levels of inflammatory and hemostatic markers and reduced disease activity. The authors concluded that the beneficial effect of vitamin D in SLE may be due to its ability to expand regulatory T cells and its ability to reduce the frequency of Th1 cells, Th17 cells, B lymphocytes, and autoantibodies [15].

In another study, the prevalence of vitamin D deficiency in SLE and its association with the clinical, serological, and treatment profile, as well as with disease activity, were investigated in 153 patients with SLE and 85 control patients. The authors concluded that patients with SLE have more vitamin D deficiency than controls, but that this deficiency is associated with leukopenia (granulocytopenia) and not with disease activity [16].

Vitamin D and Rheumatoid Arthritis

Epidemiological studies suggest that vitamin D deficiency is common in patients with rheumatoid arthritis. However, its relationship with disease activity is not clear [17]. In a systematic review and meta-analysis, Hassan concluded that serum vitamin D levels in the rheumatoid arthritis group were significantly lower than those in the control group, and vitamin D levels play a role in rheumatoid arthritis susceptibility and activity. Furthermore, vitamin D deficiency was more observed in patients with neuropathic pain [18].

Vitamin D and Psoriasis

Calcitriol and its analogs exert anti-proliferative and pro-differentiative effects, which justifies their importance in psoriasis. Vitamin D analogs are used in the treatment of psoriasis and can be used in monotherapy or combination with corticosteroids, acting through the modulation of the immune system and the normalization of keratinocyte maturation [19].

The administration of vitamin D, in its inactive form (cholecalciferol), in doses much higher than those usually used, constitutes a safe and effective therapeutic resource for the autoimmune diseases psoriasis and vitiligo, in addition to being a cost-effective therapy. very low when compared with drugs made available by the pharmaceutical industry [5].

Vitamin D and Uveitis

The pathophysiology of noninfectious uveitis likely involves an autoimmune insult mediated by T lymphocyte responses to specific antigens in the uveal

tract. Studies have shown that interleukin (IL)-17-producing T cells are directly involved in the pathogenesis of systemic autoimmune diseases and experimental models of uveitis. This suggests the existence of common autoimmune mechanisms in which uveitis occurs as an ocular manifestation of underlying systemic diseases. In addition, the therapeutic potential of vitamin D and its relationship with various eye diseases have motivated scientific studies on its relevance to the immune regulation of the eye. Structures directly related to the action of vitamin D, such as its receptor (VDR), 1-alpha-hydroxylase (vitamin D activation enzyme), and its metabolites, have been identified in ocular tissues [20]. There is also evidence that vitamin D decreases ocular inflammation in experimental models. Oral administration of 1,25(OH)₂D₃ could prevent and partially reverse experimental autoimmune intraocular inflammation in mice by inhibiting Th17 cell activity. Low serum levels of 25(OH)D₃ have been detected in different types of autoimmune diseases, many of which have ocular involvement in the form of uveitis or scleritis [21]. Consequently, hypovitaminosis D has been associated with an increased risk of developing UAI [22].

Vitamin D and Autoimmune Thyroid Disease

In another systematic review, most of the studies reviewed indicated that vitamin D deficiency or insufficiency can increase the rate of autoimmune diseases such as Hashimoto's thyroiditis and Graves' disease. Randomized controlled trials with a longer follow-up period are needed to confirm the causal relationship between autoimmune thyroid disorder and vitamin D and to provide more reliable information on the relevance of treatment effects of vitamin D therapy or supplementation [23].

Vitamin D, Multiple Sclerosis, and Inflammatory Bowel Disease

Vitamin D regulates the development of the immune response and the development of inflammatory bowel disease and multiple sclerosis and may be useful in normalizing T-cell function and in the prevention and treatment of these diseases. Treatment with 1,25D₃ suppressed the development of experimental autoimmune encephalopathy, inflammatory bowel disease, and several other models where Th1 and Th17 cells were pathogenic. Vitamin D and 1,25D₃ were critical for the development of regulatory cells, including T reg, iNKT cells, and CD8αα/TCRαβ T cells. In the absence of vitamin D, the gastrointestinal tract was more susceptible to autoimmunity [24].

In a study in which 470 patients with inflammatory bowel disease were evaluated (272 with Crohn's disease and 198 with ulcerative colitis), the authors concluded that vitamin D levels were inversely associated with disease activity [25].

Vitamin D and Vitiligo

Also in vitiligo, there is a tendency to associate low levels of vitamin D with the severity of the clinical manifestation in vitiligo [26].

Vitamin D and Liver Autoimmune Diseases

The effects of vitamin D deficiency on hepatic autoimmune diseases have also been described. There are several potential implications of the action of vitamin D in autoimmune hepatitis, such as its effect on genomic and non-genomic functions, such as suppression of MCH-II antigen expression, and increased production of CTLA-4. As shown in a mouse model of autoimmune hepatitis induced by Concanavalin A (Con-A) in mice, calcitriol decreases serum ALT levels, attenuates histological liver damage, and decreases IFN- γ levels [27].

The hepatic immunomodulatory effect of vitamin D seems to be related to 25-hydroxylation, which creates negative feedback for local inflammation and leads to Th2 polarization, due to the inhibition of pro-inflammatory TNF- α , IL-2, IL-12, IL-17, IFN- γ and promotion of IL-4, IL-5 and IL-10 production. Furthermore, calcitriol may exert an antioxidant effect by increasing intracellular glutathione and neutralizing reactive oxygen species, which have been suggested to be involved in autoimmune hepatitis and primary biliary cirrhosis. Indeed, a diet low in vitamin D has been shown to increase NADPH in rat hepatocytes. Furthermore, a putative immunomodulatory role for vitamin D appears to be linked to its influence on the development of hepatic invariant natural killer T lymphocytes (iNKT). These are mainly found in the hepatic sinusoids and are capable of activating hepatic stellate cells as well as mediating the death of hepatocytes. Liver iNKT cells constitutively express OX40, which is involved in the induction of pro-inflammatory and pro-fibrotic liver damage [28].

Conclusion

Several studies point to the effects of vitamin D not related to calcium metabolism, such as antineoplastic activity (particularly concerning breast, colon, and prostate cancers, and lymphoproliferative diseases), antihypertensive and immunomodulatory. Vitamin D deficiency and its use for treatment have been described

in various autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, lupus, inflammatory bowel disease, myasthenia gravis, scleroderma, alopecia areata, psoriasis, vitiligo, autoimmune hepatitis, type 1 diabetes mellitus, autoimmune thyroiditis, etc. The effects of vitamin D on the immune system are related to the tolerance of self-antigens, exerting an inhibitory effect on the Th1 and Th17 type lymphocyte pattern, and a promoting effect on the expression of the Th2 and Treg pattern through the action of vitamin D in all cells of the system through the vitamin D receptor. More studies are needed to establish safe and effective doses in the management of these properties of vitamin D.

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Conflict of interest

The authors declare no conflict of interest.

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