Vitamin D, Autoimmune Diseases, and Systemic Lupus Erythematosus

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12.1 Introduction

Vitamin D is a steroid hormone (calcitriol – 1,25(OH)D3, D-hormone) that regulates not only bone metabolism, but like other steroid hormones such as glucocorticoids (GCs) and gonadal hormones, it also interferes with the immune system and estrogen-modulated cells. This occurs by reducing the aromatase activity and limiting the negative effects related to the increased peripheral estrogens (including B cell proliferation and overactivity). Consequently, serum vitamin D deficiency [25(OH)D] is considered a risk factor for several chronic/inflammatory or autoimmune conditions [1, 2].

The primary source of vitamin D is the synthesis of vitamin D3 in the skin upon exposure to UVB radiation. Any condition that potentially reduces sun exposure could further contribute to decreased serum levels of vitamin D, as observed in patients with systemic lupus erythematosus (SLE) [3–5].

Calcitriol (1,25(OH)D3, D-hormone) is the peripherally active endogenous metabolite of vitamin D originating from cholesterol. It is considered a true steroid hormone affecting the regulation of bone metabolism. Recently, the role of vitamin D has been investigated in several chronic pathological conditions including infectious diseases, type 1 diabetes, multiple sclerosis, and autoimmune rheumatic diseases (ARDs). In ARD such as rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE), the D-hormone seems to exert numerous immunomodulatory activities [6, 7].

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D. Roccatello, L. Emmi (eds.), *Connective Tissue Disease: A Comprehensive Guide-Volume 1*, Rare Diseases of the Immune System 5,
DOI 10.1007/978-3-319-24535-5_12

Eighty to 90 % of vitamin D synthesis is regulated by sunlight [8]. The hypothesis that vitamin D is linked to autoimmune disorders originally arose from the observation that people living near the equator are at decreased risk of developing common autoimmune diseases, as well as by the fact that there is a greater prevalence of RA in northern European countries as compared to the southern ones [9].

Patients with RA and SLE have multiple risk factors for vitamin D deficiency that seem to influence disease severity and, at least in RA, disease activity that shows a yearly rhythm (being more severe in winter) [10–13].

These observations suggest a pathophysiological and possibly therapeutic role for 1,25(OH)2D3 in clinical practice as a modulator of the immune system [14–16]. A recent study on vitamin D status in SLE patients analyzed the potential benefits of 2 years of supplementation and showed the results of different types of cholecalciferol regimens. It indicated that supplementation with an intensive dosage (300,000 IU initial bolus followed by 50,000 IU monthly for the first year) and then switching to the standard regimen (25,000 IU monthly, immediately after patient enrollment, throughout the study) in the second year is safe, and it allows to obtain a sufficient level of vitamin D. However, such a regimen does not seem to influence disease activity as compared to the standard regimen [17].
All these aspects will be discussed in this chapter.

12.2 Immune-Modulating Activities of Vitamin D

Vitamin D status influences the risk of developing several chronic/inflammatory conditions and immune-mediated rheumatic diseases. It exerts modulating effects on dendritic cells (DCs) and B cell and T cell functions, including regulatory T lymphocytes (T^{regs}) and Th17 cells, and acts on the self-tolerance and immune responses [5, 18–20].

In normal conditions, 1,25(OH)D3 regulates both innate and adaptive immunity, potentiating the innate response (antimicrobial activity of macrophages) but suppressing the adaptive immunity by acting on B lymphocytes and on Ig production [1, 2, 21, 22] (Fig. 12.1). In addition, 1,25(OH)2D3 has also been shown to inhibit the maturation of monocyte-derived DCs [1, 2, 21].

In previous studies, 1,25(OH)D3 was shown to inhibit the production of tumor necrosis factor (TNF)-alpha, interleukin-17 (IL-17), and interferon gamma (IFN-gamma). Conversely, it stimulates IL-4, IL-5, and IL-10 expression in peripheral blood mononuclear cells (PBMCs) and in CD4 T cells from healthy volunteers [23, 24].

Recently, 1,25(OH)D3 was found to reduce *in vitro* interleukin-17A (IL-17A) and IFN-gamma and to increase IL-4 levels in stimulated PBMCs from treatment-naive patients with early RA (Fig. 12.1) [12, 25].

Higher percentages of IL-17A- and IL-22-expressing CD4 T cells and IL-17A-expressing memory T cells were observed in PBMCs from treatment-naive patients with early RA as compared to healthy controls. Interestingly, recent studies showed that TNF-alpha blockade alone does not suppress IL-17A and IL-22 and that the

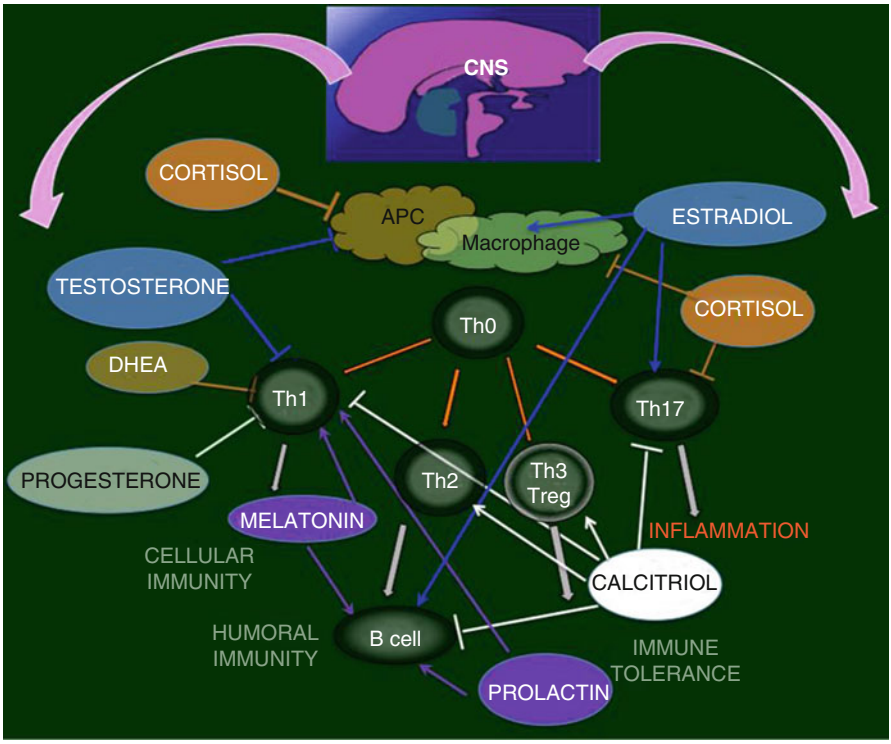

Fig. 12.1 Effects of 1,25(OH)D3 on immune response in normal conditions. Vitamin D (1,25(OH)D3) interferes with the neuroendocrine immune network which includes interactions between the central nervous system, the endocrine system, and the immune system. 1,25(OH)D3 regulates both innate and adaptive immunity, potentiating the innate response (antimicrobial activity of macrophages), decreasing antigen presentation and suppressing the adaptive immunity (B lymphocyte and selected T lymphocyte functions). However, in normal conditions, 1,25(OH)D3 increases the Th2 cytokines (i.e., IL-10) and the efficiency of regulatory T lymphocytes (Tregs). *CNS* central nervous system, *APC* antigen-presenting cell, *DHEA* dehydroepiandrosterone, *Th* helper T lymphocytes (Th0, Th1, Th2, Th3/reg, Th17)

addition of 1,25(OH)D3 on cultured synovial cells from early RA patients is needed to suppress cytokine production [26]. The combination of TNF-alpha blockade and 1,25(OH)D3 seems to control human Th17 activity and inhibit synovial inflammation. These observations might suggest a synergic effect of activating vitamin D receptor signaling and TNF neutralization strategies in patients with RA [24].

Severe serum 25(OH)D deficiency (<10 ng/ml) appears to be involved in the generation of characteristic symptoms of immune/inflammatory rheumatic diseases (i.e., with a negative correlation between 1,25(OH)2D3 and disease activity in RA), though supplementation seems to result in partial improvement [27–29].

Interestingly, it was found that a deficiency of vitamin D (less than 20 ng/ml) is not only present in patients with autoimmune diseases but is also observed in healthy subjects with a yearly rhythm, with lower levels in winter/spring [2, 19].

12.3 Synergic Effects of Vitamin D and Glucocorticoids

Literature dealing with vitamin D and glucosteroids suggests a synergic effect, supported by the observation that the combination of dexamethasone (DEX) and 1,25(OH)D3 is able to inhibit Th1 cytokine production and lymphocyte proliferation, thereby indicating immunosuppressive properties [28].

More specifically, IFN-gamma production in lymphocyte cultures was significantly decreased with either DEX or 1,25(OH)D3 when compared with control culture media. Moreover, when both agents were added to the same culture, IFN-gamma production was further decreased compared to either agent alone [30]. In contrast, 1,25(OH)D3 significantly increased IL-5 and IL-13, whereas DEX significantly decreased these two cytokines. When 1,25(OH)D3 was combined with DEX, IL-5 and IL-13 production increased as compared to DEX alone [30].

Another study showed that the combination of 1,25(OH)D3 with DEX enhanced cell cycle arrest and apoptosis, at least on cultured carcinoma cells, and that vitamin D receptor (VDR) protein levels were higher due to the additive effect of 1,25(OH)D3 and DEX compared with 1,25(OH)D3 treatment alone [19]. Conversely, glucocorticoid receptor (GR) protein levels and ligand binding increased with 1,25(OH)D3 alone, but not with the combination with DEX [31].

The antiproliferative action of 1,25(OH)D3 on cell cycle and induction of apoptosis varies among cell types, and the effect depends on the levels of the VDR, a member of the steroid receptor superfamily that includes GR receptors, in which VDR acts as a ligand-inducible transcription factor [32].

The VDR-1,25(OH)D3 complex regulates transcription by binding the so-called vitamin D response elements/genes (VDREs) [32, 33].

1,25(OH)D3 is an important regulator of VDR both at the transcriptional and posttranscriptional levels [34, 35].

Recent data suggest vitamin D to stimulate GC-mediated anti-inflammatory effects in human monocytes [36]. Lower 25(OH)D serum levels in asthmatic children have been associated with increased GC use [37].

Lastly, in psoriatic patients, the combined use of calcipotriol, a vitamin D analog, and betamethasone has shown a combined effect on keratinocyte proliferation and differentiation, with clinical improvement and inflammation control [38, 39].

12.4 Deficit of Vitamin D and Autoantibody Production

Significant vitamin D deficiency has been reported in several immune-mediated or idiopathic inflammatory myopathies, like polymyositis, dermatomyositis, and inclusion body myositis, supporting the concept that low levels of vitamin D might be a risk factor for autoimmunity [20, 40]. Lower levels of serum 25(OH)D, as well as a higher frequency of anti-Jo-1 autoantibodies, were observed in patients with inflammatory myopathies as compared to controls [22].

The role of 25(OH)D as a risk factor for autoimmune diseases is also supported by the observation that vitamin D levels are lower in ANA-positive healthy controls

as compared to ANA-negative subjects. Furthermore, vitamin D may prevent autoimmune diseases by stimulating naturally occurring regulatory T cells [41].

Vitamin D deficiency plays a role in increased autoantibody production and in B cell autoimmunity [42, 43] (Fig. 12.1).

These observations may explain the potential role of vitamin D in B cell-related disorders such as SLE. In fact, the vitamin D concentration in the serum of SLE patients shows a negative correlation with clinical disease activity and anti-dsDNA titer. Besides, a reduction in the serum 25(OH)D levels has been found to be associated with the presence of autoimmune response, and a significant negative correlation between the titers of ANA and serum levels of 25(OH)D was observed [44].

12.5 Vitamin D Deficiency and Peripheral Metabolism of Estrogens in Autoimmunity

The role of vitamin D on estrogen-mediated cell proliferative activity has been shown, especially in cancer tissues where 1,25(OH)D3 decreases the expression of aromatase, the enzyme that catalyzes the peripheral synthesis of estrogens from androgens [45].

Notably, this effect is very important in breast and prostate cancer where aromatase and its intracrine activity are overexpressed [27].

In clinical practice, aromatase inhibitors, which are used in breast cancer treatment, inhibit enzymatic activity, while 1,25(OH)D3 reduces aromatase expression, inhibits estrogen synthesis and signaling and its anti-inflammatory action (see below), and consequently plays an important role in inhibiting estrogen receptor-positive breast cancer [46, 47].

Consequently, the inhibitory effect of 1,25(OH)D3 on aromatase and cytokine synthesis on cultures of human macrophages has also been observed [48, 49]. More specifically, 1,25(OH)D3 exerts its action by direct repression of aromatase transcription via promoter II and at the same time also by an indirect effect due to a reduction in the levels and biological activity of prostaglandins (especially PGE2), which are considered the main stimulators of aromatase transcription through promoter II [50].

Interestingly, inflammatory cytokines (tumor necrosis factor alpha, interleukins 6 and 1) act as enhancers of aromatase activity, as observed in chronic inflammatory conditions such as RA synovitis or cutaneous lupus erythematosus [51, 52].

The higher incidence of autoimmune rheumatic diseases in women might be favored by possible links between 1,25(OH)D3 deficiency (with reduced aromatase downregulation) and the increase in the synthesis of peripheral estrogens [46, 53].

12.6 Vitamin D and Systemic Lupus Erythematosus (SLE)

Vitamin D has several effects on growth, proliferation, apoptosis, and cell functions. It shows pleiotropic action on various tissues as well as on the immune system on which it exerts an anti-inflammatory effect through the modulation of both cellular

proliferation and differentiation via the nuclear vitamin D receptor (also expressed on antigen-presenting cells) [1, 54].

In particular, vitamin D inhibits Th1 and Th17 cell proliferation, and it promotes Th2 response on T lymphocytes, thus influencing the transcription of several key cytokines and inhibiting the production of IFN-γ and IL-2.

Several studies have further suggested that vitamin D deficiency may play a role in the pathogenesis of systemic autoimmune diseases [24, 25, 55].

SLE is a chronic multisystem inflammatory autoimmune disease characterized by the presence of autoantibodies against intracellular antigens, by increased T cell activation and likely by an alteration of regulatory T cells [56].

Hypovitaminosis D is highly prevalent in SLE as a result of reduced exposure to sunshine caused by photosensitivity, use of photoprotection, alterations of the renal vitamin D metabolism, or the use of medications such as glucocorticoids or antimalarials [2].

A number of cross-sectional studies have examined the association of vitamin D deficiency with SLE disease activity in recent years. Most, but not all, have shown an association of 25(OH)D deficiency with increased SLE disease activity [57].

In addition, it is well established that seasonal variations in sun exposure influence 25(OH)D serum levels. Moreover, several data show the influence exerted by vitamin D levels on SLE activity, thereby supporting the notion that vitamin D deficiency in winter can be a risk factor for disease flares [10, 58].

Of note, low vitamin D concentrations have also been associated with complications of the disease such as osteoporosis, fatigue, and certain cardiovascular risk factors [55].

Therefore, since the active vitamin D metabolite 1,25(OH)D3 has been shown to modulate immunological pathways, its administration might affect SLE development and progression.

In this context, pharmacological supplementation of vitamin D results in a decrease in memory B cells and anti-DNA antibodies and an increase in naive CD4+ T cells and regulatory T cells together with a decrease in effector Th1 and Th17 cells [22].

A very recent study analyzed the effects of different monthly regimens of vitamin D supplementation on the circulating numbers of T cells and on cytokine production in SLE patients [59]. This study concluded that increasing vitamin D serum levels through long-term monthly cholecalciferol treatment increases Treg cells and promotes Th2 response [59].

Another recent 2-year study of SLE patients proposes supplementation with cholecalciferol using two different regimens: standard, 25,000 IU monthly, and intensive, 300,000 IU initial bolus followed by 50,000 IU monthly for the first year, switching to the standard regimen in the second year. The study shows that intensive vitamin D supplementation is needed to reach optimal vitamin D status. Notably, no effects were observed on SLE disease activity or laboratory parameters such as anti-DNA and complement levels [17].

Studies correlating low vitamin D serum levels with higher SLE activity reported controversial results [10, 60, 61]. However, it is generally accepted that vitamin D insufficiency represents a predisposing factor for the onset and perpetuation of autoimmune processes [1].

Conclusions

Calcitriol (1,25(OH)D3) is recognized as a true steroid hormone that exerts several biological activities, including regulation of the immune system, and that supports pathophysiological mechanisms for the development/risk of chronic/inflammatory autoimmune diseases [20, 62–64].

A possible synergism between 1,25(OH)D3 and glucocorticoids could represent a new approach for the management of chronic autoimmune diseases.

Supplementation with immediate-release cholecalciferol (especially in SLE patients) appears to induce sufficient serum levels of vitamin D in most subjects; however, it does not seem to influence disease activity, at least in short- to medium-term trials.

Conflicts of Interest The authors declare no conflicts of interest with the contents of the present manuscript.

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