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Review Article

Role of Vitamin D in Systemic Lupus Erythematosus

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Abstract

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Vitamin D is a steroid hormone that in addition to its well known role in the metabolism of calcium and phosphorus exerts immunoregulatory properties. Data from animal studies and from prospective clinical trials on patients with rheumatoid arthritis, multiple sclerosis and type 1 diabetes point to the potential role of vitamin D as important environmental factor in the development of autoimmune diseases. Such role of vitamin D in systemic lupus erythematosus (SLE) has not yet been sufficiently studied. This review shows the sources, metabolism and mechanism of action of vitamin D, its effect on the cells of the immune system, prevalence and causes of vitamin D deficiency in patients with SLE, the link between vitamin D status and disease activity as well as recommendations for vitamin D supplementation.

Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease of unknown etiology. Numerous genetic, hormonal and environmental factors are involved in the development of this disease. Lately, more attention is given to vitamin D as a potential environmental factor in pathogenesis of SLE. It is a steroid hormone that plays a key role in the metabolism of calcium, phosphorus and bone homeostasis. Also important is its role in the function of muscular, cardiovascular and immune system, as well as in the processes of reproduction, growth and cell differentiation. There is increasing evidence on the role of vitamin D deficiency in the development of autoimmune, neoplastic and cardiovascular diseases. In recent decades a significant increase in the prevalence of vitamin D deficiency in the general population has been evident. The reasons for this are insufficient exposure to sunlight, use of sunscreens, and insufficient intake of vitamin D through food [1]. Patients with SLE are particularly prone to developing a vitamin D deficiency. One explanation is a strict fotoprotection they are advised due to photosensitivity.

Sources, metabolism and mechanism of action of vitamin D

Vitamin D was discovered in 1913 by McCollum and Davis, along with many other vitamins, and the name is still retained although later research showed that vitamin D is actually prohormone [2]. The main source of vitamin D is an endogenous synthesis in the skin after exposure to ultraviolet B light (UVB 290-315 nm) (Figure 1). This process is influenced by numerous factors: season, latitude, skin pigmentation and sunscreen use. Smaller amounts of vitamin D come through food and supplements. The sun's UVB rays penetrate the skin and lead to the conversion of 7-dehydrocholesterol into previtamin D3, which is then spontaneously converted to vitamin D3 (cholecalciferol) which enters the circulation. Excess previtamin D3 or vitamin D3 is degraded under the influence of sunlight, so that even intense exposure to sunlight does not lead to vitamin D intoxication. Dietary vitamin D comes from foods and supplements in the form of vitamin D3 or vitamin D2. Few foods (e.g. salmon, tuna, sardines, egg yolk) naturally contain and some (e.g. milk, butter, orange juice, cheeses, infant formulas) are fortified with vitamin D. Vitamin D2 is produced through ultraviolet irradiation of ergosterol

from yeast and vitamin D₃ through ultraviolet irradiation of 7-dehydrocholesterol from lanolin. Both types of vitamins have identical metabolism. Vitamin D from foods or supplements is incorporated into chylomicrons and enters circulation through the lymphatic system. It becomes biological active after a gradual process of hydroxylation in the liver and kidneys, during which 1,25-dihydroxy-vitamin D (1,25(OH)₂D) is created. The production of 1,25(OH)₂D is regulated by concentrations of parathyroid hormone, calcium and phosphorus and 1,25(OH)₂D itself. A number of autocrine and paracrine actions of vitamin D are described too. In fact, the presence of the enzyme 1- α -hydroxylase (which catalyses the final stage of activation of vitamin D) has been shown in other tissues: lung, placenta, colon, β -cells of the pancreas, parathyroid gland and in many immune cells [3]. Majority of biological effects of 1,25(OH)₂D are achieved by binding to the widespread vitamin D receptor (VDR). Its presence has been identified in a number of cells: osteoblasts, cells of renal tubules and parathyroid glands, keratinocytes, promyelocytes, lymphocytes, epithelial cells of the colon, enterocytes, cells of the pituitary gland and ovary [1]. Binding of 1,25(OH)₂D to the VDR results in interreaction with the vitamin D responsive elements in the promoter region of vitamin D-responsive genes, thereby regulating the level of its transcription (slow genomic effects). By direct or indirect regulation of expression of over 200 genes, 1,25(OH)₂D regulates cell proliferation, differentiation, apoptosis and angiogenesis. Both, in normal cells and tumor cells vitamin D reduces cell proliferation and promotes terminal differentiation. Also, 1,25(OH)₂D inhibits renin synthesis, increases the production of insulin and myocardial contractility [4, 5]. An additional mechanism of action of 1,25(OH)₂D independent of gene transcription is assumed (fast non-genomic effects), which is achieved through modulation of intracellular signaling pathways [1, 6].

response of parathyroid hormone. The 25(OH)D level required for optimal functioning of immune system is not known. There are several methods for measuring 25(OH)D level: radioimmunoassay (RIA), electrochemiluminescent immunoassay (ECLIA) and liquid chromatography, which many consider the gold standard [8].

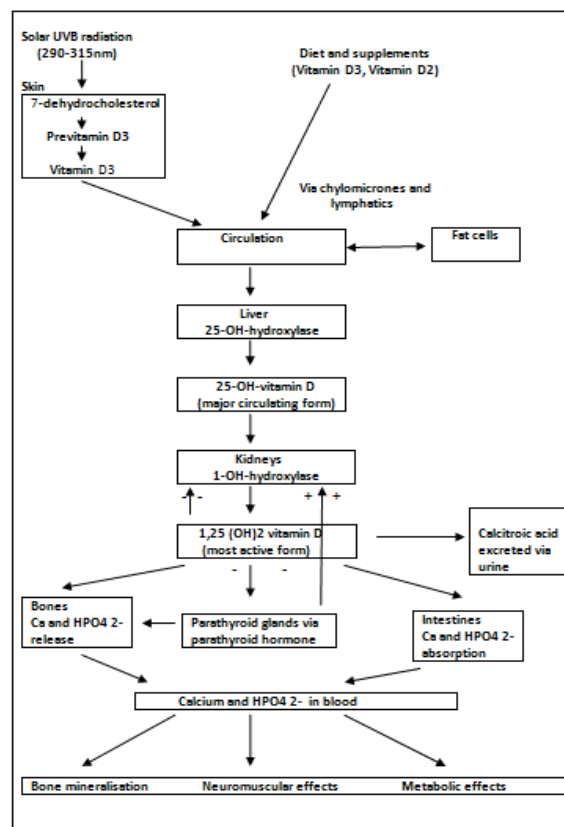


Figure 1: Sources and metabolism of Vitamin D.

Immunoregulatory properties of vitamin D

The potential role of vitamin D in the immune system functioning is assumed in the 1980s after the discovery that antigen-presenting cells (APC) such as macrophages and dendritic cells (DCs) constitutively express VDR, while lymphocytes express VDR only after activation. Activated macrophages possess the enzyme 1- α -hydroxylase, which allows them to synthesize and secrete 1,25(OH)₂D. However, unlike the 1- α -hydroxylase in the kidneys, which is regulated by parathormone and 1,25(OH)₂D, 1- α -hydroxylase in macrophages is controlled by the immune signals, primarily interferon gamma (IFN- γ). In addition, the hydroxylase in macrophages is not affected by the negative feedback of the 1,25(OH)₂D, thus explaining intermittent hypercalcemia in conditions of excessive macrophage activation (e.g. sarcoidosis). Monocytes and macrophages possess 24-hydroxylase, an enzyme that breaks down 1,25(OH)₂D. The activity of

Determination of vitamin D status

Vitamin D status is determined by measuring the serum level of 25(OH)D. This is the major circulating form of vitamin D with the half-life of approximately three weeks. In contrast, 1,25(OH)₂D has a short half-life and a very low serum level. There is no consensus on optimal 25(OH)D level. The majority of authors consider a serum level greater than 30ng/ml sufficient (conversion factor to nmol/l is 2.496). Vitamin D insufficiency is defined as a serum level of 25(OH)D between 21 and to 29 ng/ml, and values less than 20 ng/ml are considered as vitamin D deficiency [1, 6, 7]. These values are established in relation to the effects of vitamin D on calcium metabolism and bone homeostasis and the regulatory

this enzyme is highly dependent on the stage of activation/differentiation of monocytes and macrophages. The presence of the enzymes responsible for the metabolism of vitamin D in the cells of the immune system enables them to achieve high local 1,25(OH)₂D level in the microenvironment of the lymph tissues, while also limiting the undesired systemic effects such as hypercalcemia [6, 9, 10]. Quiescent CD4 + T cells express the VDR, and upon activation expression of VDR increases fivefold [11]. The overall effect of vitamin D on CD4 + T lymphocytes consists in the suppression of Th-1 and promoting Th-2 cellular response [12-14]. This is achieved through modulation of cytokine production and through direct effect on Th-1 lymphocytes. It has been shown that vitamin D facilitates the induction of Foxp3 + regulatory T cells [15]. Regarding B lymphocytes, vitamin D inhibits the production of immunoglobulins (direct effect) and interrupts the process of their differentiation [16, 17]. Examination of peripheral blood mononuclear cells (PBMCs) of patients with SLE showed that adding vitamin D to the culture of PBMCs significantly reduces the production of polyclonal antibodies and anti-ds-DNA antibodies [18].

The most significant effect of vitamin D on the immune system is achieved by affecting the DCs [19-22]. Its overall impact consists in promoting the creation of tolerogenic DCs. Kamen and Aranow showed that the MDCC in patients with SLE and in healthy individuals behave similarly in the presence of physiological concentrations of vitamin D. Lupus MDCC differentiated in the presence of vitamin D withhold immature phenotype with inhibited expression of costimulatory molecules HLA-DR, CD40 and CD86 [23].

Data collected by previous studies suggest that vitamin D has an overall inhibiting effect on the development of autoimmune diseases: suppresses the differentiation of DCs and Th-1 lymphocytes, stimulates T regulatory cells, reduces the production of autoantibodies and release of inflammatory mediators and possibly, leads to the re-establishment of autotolerance.

Vitamin D and autoimmune diseases

In numerous clinical studies a connection between vitamin D level and several autoimmune diseases is observed. Most data refers to the relationship between vitamin D level and multiple sclerosis, rheumatoid arthritis and inflammatory bowel disease [24, 25]. Large population studies (the Nurses' Health Study I and II) showed that women with the highest vitamin D intake had a 40% lower risk for developing multiple sclerosis [26]. The Women's

Iowa Health Study that included 29,368 women has demonstrated an inverse relationship between increased intake of vitamin D and the occurrence of rheumatoid arthritis [27]. Experimental studies on animal models have shown that vitamin D deficiency can lead to exacerbation of inflammatory bowel disease and multiple sclerosis [28]. Moreover, it has been demonstrated that the use of vitamin D suppresses the occurrence of multiple sclerosis and inflammatory bowel disease in experimental models in mice [29].

Vitamin D and SLE

Reduced concentration of vitamin D is found in the serum of patients with SLE. Possible causes of vitamin D deficiency in patients with SLE are photosensitivity, application of sunscreen with high sun protection factor, kidney damage, chronic use of glucocorticoids and antimalarials [30, 31]. Vitamin D deficiency is often asymptomatic. Symptoms, if they occur, are non-specific and usually manifest as musculoskeletal pain, paresthesia and cramps, which are often present in patients with SLE regardless of vitamin D deficiency.

Studies on several animal models of SLE have shown that vitamin D supplementation can lead to the improvement of various disease manifestations, including the reduction of proteinuria [32, 33] and even to the reduction of the risk for developing SLE [32]. Approximately 50% of patients with SLE show a specific pattern of gene expression called "interferon signature" which correlates with disease activity. The main source of interferon- α are plasmacytoid DCs, that release this cytokine upon stimulation by immune complexes containing nucleic acid. It is shown that plasma of patients with SLE may induce "interferon signature" in normal peripheral blood lymphocytes and that vitamin D suppresses the expression of "interferon signature" in MDCC of patients with SLE [23]. This finding suggests a possible application of vitamin D in therapy of SLE.

Prevalence of vitamin D deficiency in SLE

Literature data show a high prevalence of vitamin D deficiency in patients with SLE [31, 34-40]. One of the first studies which demonstrated the presence of low vitamin D levels in patients with SLE, dates from 1979. In this study, decreased concentration of 1,25(OH)₂D was found in 7 of 12 adolescents treated with glucocorticoid drugs [41]. Kamen and colleagues compared serum levels of 25(OH)D in 123 patients with newly diagnosed SLE with levels of 240 healthy controls, matched by age

and sex. The mean 25(OH)D level in a group of SLE patients was 21.6ng/ml and in the control group 27.4 ng/ml. Overall, it was found that 67% of patients with SLE have vitamin D deficiency. Critically low 25(OH)D level (< 10 ng/ml) was found in 22 patients, with presence of renal disease and photosensitivity being the strongest predictor [31]. The Israeli study that measured 25(OH)D level in a number of autoimmune diseases, showed that SLE patients had significantly lower levels (11.9 ng/ml) compared to European control (21.6 ng/ml) [43]. The group from Baltimore in a study from 2013 found reduced 25(OH)D levels in 76% of patients with SLE and the percentage was significantly higher in the population of African-Americans (85%) and those aged 30-50 years (79 %) [43].

It is still not clear whether vitamin D deficiency precedes the occurrence of SLE or the disease itself contributes to vitamin D deficiency. Is vitamin D an environmental factor important in the emergence and further course of SLE that we can influence?

Vitamin D as a potential biomarker of SLE

Several studies showed a trend of higher SLE activity in patients with vitamin D deficiency. According to the study that included 165 SLE patients in three centers, a significantly higher level of disease activity was found in those with severe vitamin D deficiency ($25(\text{OH})\text{D} \leq 10$ ng/mL) compared to those with less severe deficiency [44]. A significant negative correlation between 25(OH)D level and disease activity was found in the group of 46 patients from northern and southern Europe [24]. Chinese study on 88 SLE patients showed a significant correlation between lower 1,25(OH) $_2$ D levels, but not the 25(OH)D levels and disease activity [17]. Of particular interest are results of a study that included 378 patients with SLE from Europe and Israel, where disease activity was measured using two scoring systems - SLEDAI and ECLAM in which significant negative correlation between disease activity and 25(OH)D levels was found. In this study, patients with active disease (SLEDAI > 3 or ECLAM > 1) had significantly lower vitamin D levels. In those with inactive SLE serum 25(OH)D level was 62 nmol/L and it is assumed that this 25(OH)D level may have protective effect on the occurrence of relapse of SLE [46]. Mok et al. found a significant negative correlation between 25(OH)D level and clinical activity of SLE, the titer of anti-C1q and anti-dsDNA antibodies [46]. However, in a few studies, a connection between vitamin D level and SLE activity has not been demonstrated [42, 47, 48].

Vitamin D as a potential therapeutic agent in SLE

The possible use of vitamin D and its synthetic analogues in the treatment of various autoimmune diseases, including SLE has been investigated in several studies. Ruiz-Irastorza and associates have examined the effects of application of oral supplements of vitamin D3 (600 IU/day and 800 IU/day) in the SLE. After the second year of therapy, although all patients had higher 25(OH)D level, 71% of them were still vitamin D insufficient and there was no decrease in disease activity [47]. On the other hand, large randomized placebo-controlled study with 267 patients with SLE, showed a significant improvement in the inflammatory and hemostatic markers, as well as in the disease activity after 12 months of use 200 IU/day of vitamin D3 [49]. There are ongoing studies that examine the efficacy and safety of different doses (800 IU, 2000 IU, 4000 IU/day) of vitamin D in SLE patients [50, 51].

Recommendations for vitamin D supplementation in SLE patients

There is no international consensus on optimal dose of supplements for correction of vitamin D deficiency. Oral supplements of vitamin D may be in the form of vitamin D3 (cholecalciferol), or in the form of vitamin D2 (ergocalciferol). The dose of vitamin D supplement required to achieve adequate 25(OH)D level depends on the initial serum concentration of 25(OH)D and the presence of additional risk factors (use of glucocorticoids, antimalarials, renal lesions, malabsorption). For each 1ng/ml of deficit of 25(OH)D, a 100 IU/day of vitamin D should be added. In patients with severe vitamin D deficiency and additional risk factors application of loading dose (50,000 IU of vitamin D3 per week for 6-8 weeks) is advised, followed by maintenance dose (2000-4000 IU/day) [52-57]. A stable serum 25(OH)D level is expected to be achieved in about 3 months, when first control measurement is recommended, and then it should be controlled every 6 to 12 months. In recent years, there are attempts of personalized approach which involves the use of a certain formulas to calculate the required dose of supplements [57].

Conclusion

Vitamin D deficiency is common in patients with SLE. The evidence from basic, genetic and epidemiological studies are still insufficient to

establish a causal connection between vitamin D deficiency and the development of the SLE, as well as its role in the further disease course. Randomized controlled studies on a large number of subjects and with sufficiently long follow-up are necessary in order to demonstrate the credibility of this connection and to determine the best formulation, dosage, and duration of supplementation, as well as potential side effects.

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