Relationship between lupus erythematosus and vitamin D

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ABSTRACT

The review presents literature data on the frequency of hypovitaminosis D in systemic lupus erythematosus (SLE), analyzes the association of clinical and laboratory parameters of the disease and vitamin D levels, and considers the possibilities of therapeutic use of its metabolites. The anti-resorptive, anti-inflammatory and immunomodulatory effects of vitamin D metabolites substantiate the expediency of their use in chronic inflammatory diseases in combination with traditional basic agents.

Keywords: vitamin D; systemic lupus erythematosus; hypovitaminosis D.

Introduction . In the last decade, there has been increasing interest in the potential role of vitamin D in autoimmune diseases and the possibility of its therapeutic application. The results of numerous studies have formed a strong belief that vitamin D is not just a vitamin, but a steroid hormone that plays a huge role in human biology and is no less important for bone metabolism than calcium [1].

Main part . Vitamin D exists in two forms: vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol) . Sources of vitamin D for the body are food and endogenous synthesis. Vitamin D2 is produced by some types of fungi under the influence of ultraviolet light from ergosterol [2]. Humans synthesize vitamin D3 , its most natural form. The main part of vitamin D (more than 80%) is formed in the body by synthesis in the skin under the influence of sunlight - ultraviolet radiation (UVR). Ultraviolet waves with a length of 290-315 nm (B) upon contact with the skin convert 7-de-hydrocholesterol by breaking one of the cyclopentanper-hydrophenanthrene rings into provitamin D3 , which is converted into vitamin D3 . Only 20% of the vitamin D required by the body comes from food [3]. Vitamin D synthesized in the skin or ingested with food and drugs is metabolized in the liver to 25(OH)-vitamin D (calcidiol), the serum content of which determines the patient's vitamin D status [4, 5]. Then 25(OH)D in complex with vitamin D-binding protein is transported to the kidneys, where the final phase of vitamin D activation in 1,25-dihydroxyvitamin B (calcitriol) occurs. 1,25(OH)2B interacts with target organs in body tissues by binding to the nuclear vitamin D receptor (VDR), which belongs to the superfamily ligand -activated transcription factors [6, 7]

Table 1. Serum 25(OH)D levels and associated conditions

Status	Nmol/l	ng/ml
Deficiency (rickets, osteomalacia)	<30	<12
Failure	30-50	12-20
Norm	>50	>20
Surplus _	>125	>50

D intoxication	>374	>150

The main function of vitamin D is the interaction between the processes of resorption/formation of bone tissue and calcium homeostasis [8]. In recent years, additional effects of vitamin D have been discovered that are not related to the regulation of calcium homeostasis, primarily the effect on cell differentiation and proliferation. It has been established that 1a-hydroxylation of 25(OH)D occurs not only in the kidneys, but also in other tissues, while extrarenal produced 1,25(OH)D2 functions autocrine . The extrarenal activity of 1a-hydroxylase is influenced by cytokines and growth factors that optimize the level of 1,25(OH)D2 for their cell -specific action. Extrarenal 1,25(OH)D2-1a-hydroxylase activity is directly related to serum 25(OH)D levels. Most of the biological effects of 1,25(OH)D2 are due to interaction with BYN expressed on cell and nuclear membranes of various epidermal , hematopoietic, and immune system cells [9, 10].

The best indicator for assessing vitamin D status is considered to be its active component, serum 25-hydroxyvitamin D. Consensus regarding the optimal level of 25(OH)D in the blood serum has not yet been reached. According to most experts, vitamin D deficiency corresponds to its level in blood serum <20 ng /ml (Table 1). A level of 12–20 ng /mL is considered insufficient because it is inadequate for bone and does not correspond to the concept of “full health”. Vitamin D deficiency leads to the development of secondary hyperparathyroidism , resulting in loss of bone mineral density (BMD). The level of 25(OH)D in the blood serum required to maintain a normal concentration of parathyroid hormone (PTH) should be >75 nmol /l [11].

According to WHO, vitamin D deficiency occurs in approximately 50% of the world's population, i.e., about 1 billion people worldwide, of all nationalities and all age groups, suffer from hypovitaminosis D [12, 13]. Such a "pandemic" is mainly related to lifestyle (long stay indoors) and the influence of environmental factors (air pollution, etc.), which reduce the exposure to sunlight necessary for the production of vitamin D in the skin under the influence of UVR . This problem is of great social importance, since convincing evidence has been obtained for the possible role of vitamin D in the development of malignant neoplasms, cardiovascular pathology, autoimmune diseases, influenza, type 2 diabetes mellitus (DM), and depression [14].

The association of hypovitaminosis D with diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic scleroderma, ankylosing spondylitis, Behçet's disease , fibromyalgia , multiple sclerosis, allergic rhinitis and asthma in children, Graves' disease has been proven [15] . Hypovitaminosis D has been found to be an independent risk factor for overall mortality in the population [16, 17]. The first study on vitamin D in SLE appeared in 1995, and by 2013, about a hundred such studies had already been published [18]. Most of them mainly addressed the problems of the frequency of hypovitaminosis in SLE, the relationship of vitamin D levels with parameters of activity and damage [19, 20]. However, the question of the effect of vitamin D on the course and prognosis in patients with SLE remains open.

According to current data, vitamin D deficiency occurs in 2/3, and its deficiency occurs in every 5th SLE patient [21]. It is well known that insolation is the most important trigger of SLE. Avoiding sun exposure and using sunscreen is a component of SLE therapy, so it is not surprising that vitamin D deficiency is present in this disease. Other important factors contributing to the development of hypovitaminosis D in SLE are renal failure, long-term use of certain drugs (glucocorticoids — GCs, antiepileptic drugs), as well as the presence of antibodies to vitamin D that increase its clearance [22–24]. The literature provides conflicting information about the relationship between SLE and vitamin D (Table 2).

DL Kamen et al . [32] found a high incidence of vitamin D deficiency in 123 patients with a short duration of SLE compared with controls (n=140). Overall, 67% of SLE patients were

vitamin D deficient, with mean levels significantly lower in African Americans (16 ng /mL) compared with Caucasians (31 ng /mL). Critically low levels of vitamin D (<10 ng /ml) were found in 22 SLE patients , mostly patients with kidney damage and photosensitivity . Similar changes were noted in patients with a long history of SLE [18, 40]. AM Husiman et al. [41] studied the vitamin D status (hydroxyvitamin , dihydroxyvitamin and PTH levels) in 25 patients with SLE and in 25 patients with fibromyalgia . Hypovitaminosis D was registered in every 2nd patient of both groups, however, no statistical differences in the hormonal profile in patients with SLE and fibromyalgia were found [41]. At the same

A clear connection with SLE activity indicators was found by M. Mandai et al . [39] in 129 Indian patients. A feature of this group of patients was a high percentage (79 out of 129) of patients at the onset of the disease who did not receive immunosuppressive therapy. An inverse relationship was established between the level of 25(OH)D and the activity of the disease according to the SLEDAI scale (r=-0.42), the level of antibodies to dsDNA (r=-0.39), the level of α-interferon — IFN (r=-0. 43) and expression of the α-IFN gene (r=-0.45) regardless of the treatment. The main source of α-IFN in SLE patients are activated dendritic cells. In research in vitro demonstrated the ability of vitamin D to inhibit the maturation/activation of dendritic cells and the production of IFN; therefore, the found negative correlation between the content of IFN and 25(Off)D may reflect the involvement of this vitamin in the development and activation of SLE [44, 45].

A high frequency of hypovitaminosis D was noted by G. Ruiz-Irastoroza et al . [33]. Deficiency and deficiency of vitamin D were present in 75 and 15% of SLE patients, respectively. Higher levels of 25(OH)D were reported in female patients treated with aminoquinoline drugs (AP) and calcium supplements with vitamin D. Photosensitization was a predictor of vitamin D deficiency , and photoprotection was a predictor of deficiency . No relationship was found between hypovitaminosis D and the duration of the disease, but a higher frequency of weakness, as assessed by VAS , was noted . Patients were advised to take vitamin D orally, this recommendation was followed by 75% of them: the average level of vitamin D increased significantly, but in most cases it did not reach the optimal level. An increase in the level of dihydroxyvitamin D in the blood serum in patients with SLE was not accompanied by a decrease in activity and damage, determined by standard methods, however, a significant decrease in weakness was recorded [34].

In the SOLVABLE study (Study of Lupus Vascular and Bone long-term Endpoints) analyzed the relationship between vitamin D levels and risk factors for cardiovascular disease in patients with SLE (181 women with a reliable diagnosis of SLE, mean age 43 years). 35% of patients were postmenopausal, 30% had kidney damage, and 11% were smokers. Vitamin D deficiency (25(OH)D level <30 ng /ml) was registered in 62.2% of patients, and vitamin D deficiency (<15 ng/ml) — in 20%. A decrease in the level of hydroxyvitamin D was significantly associated with a high body mass index (BMI), arterial hypertension (AH), DM, fibrinogen levels, CRP, as well as with higher rates of SLE severity and activity [35].

Epidemiological studies have convincingly demonstrated that hypovitaminosis D is an independent risk factor for cardiovascular complications, and there is an association between reduced levels of 25(OH)D and subclinical manifestations of atherosclerosis, such as thickening of the intima-media complex (IMC), calcification of the coronary arteries and endothelial dysfunction [46-53]. The point of view has long been expressed that a 50-fold excess in the incidence of cardiovascular diseases (CVD) in SLE cannot be explained only by traditional risk factors, therefore, special attention is paid to studying the atherogenic effect of the disease itself, comorbid conditions, and ongoing therapy [54, 55].

JA Reynolds et al . [36] assessed the possibility of association of hypovitaminosis D with early atherosclerosis in SLE patients (75 women aged 18–70 years), mostly Caucasians . Most of the patients were in remission of SLE. Vitamin D deficiency was present in 52% of patients.

Patients with active SLE had a significantly lower level of 25(OH)D compared with patients who had remission, however, associations between vitamin D levels and serological markers of disease activity (antibodies to dsDNA, C e and C4 complement components) did not discovered. Also, the content of vitamin D did not differ depending on GC therapy and the presence of nephritis. A statistically significant association of reduced vitamin D levels with some risk factors for CVD (high BMI, insulin resistance), as well as with a tendency to increase diastolic blood pressure (BP) was obtained. With regard to the subclinical manifestations of atherosclerosis, no relationship was found between vitamin D levels and IMT thickening and the presence of plaques. At the same time, vitamin D deficiency (regardless of BMI and insulin levels) was associated with arterial stiffness. IMT thickening and the development of atherosclerotic plaques occur over a number of years, while vascular resistance is a dynamic state and can change under the influence of therapy within a relatively short time [56]. Increased arterial stiffness is a predictor of cardiovascular outcomes in the population [57]. It has been suggested that the determination of arterial stiffness (resistance of the vascular wall) can serve as an earlier and dynamic marker , and further studies of the relationship between hypovitaminosis D and this indicator, as well as a possible predictor role of serum 25(OH)D levels in the development of early atherosclerosis and CVD in patients are required. SLE [36]. CC Mok et al . [37] obtained conflicting results when analyzing vitamin D levels and risk factors for the development of CVD in 290 patients with active SLE. An association of a low level of 25(OH)D with clinical and laboratory parameters of SLE activity, premenopause , dyslipidemia , and the presence of antibodies to phospholipids (aPL) was found, but there was no statistically significant relationship with subclinical signs of atherosclerosis, assessed by the thickness of the IMT. Also found lower levels of hydroxyvitamin D in patients with exacerbation of SLE.

In 2014, the results of a multicenter study of patients from North America, Europe, and Asia were published, which examined the relationship between vitamin D levels, SLE activity parameters, and risk factors for the development of CVD. Based on the data of a 6-year follow-up, conclusions were drawn about the inverse relationship between the level of 25(OH)D and the activity of SLE, the level of blood pressure, and hyperlipidemia . High levels of vitamin D had a protective effect on the development of coronary heart disease and stroke [58].

The involvement of vitamin D in the development and activation of SLE is of particular interest. First of all, the question about the role of UVI in SLE is natural: harm or benefit? On the one hand, insolation can lead to the development and exacerbation of the disease, on the other hand, an increase in vitamin D synthesis under the influence of sunlight can reduce SLE activity [59]. Representatives of the Negroid race are 3 times more likely to suffer from SLE, while the disease in them debuts at an earlier age and is characterized by a higher lethality compared to Caucasoids [60]. Differences in the incidence of SLE between blacks and Caucasians cannot be explained by genetic factors alone, as the disease is rare in blacks in West Africa. It has been suggested that the higher incidence of SLE in black patients in Western countries is associated with low sun exposure and decreased ultraviolet penetration through overpigmented skin, resulting in lower vitamin D levels.

An understanding of the causal relationship between vitamin D levels and SLE activity is also needed. Findings demonstrating an association of low levels of hydroxyvitamin D with clinical and laboratory manifestations of the disease do not answer the question: are the disorders primary or secondary? It is possible that the reason for the exacerbation of SLE may be not so much a low level of vitamin D, but a greater tendency to vitamin D deficiency in patients with active CLE due to the refusal of insolation, photoprotection , renal failure and medication that disrupt the metabolism of this hormone. Of interest are the results of the Ohio

SLE Study (OSS), which was conducted on the principle of regular monitoring (including clinical evaluation, registration of exacerbations and laboratory tests) in 106 patients with recurrent SLE of various ethnic origins (36% were blacks, 59% were Caucasians and 5% - Asians and Spaniards) [61]. The design of the study allowed us to consider one of the important aspects - the temporal relationship between serum levels of hydroxyvitamin D and exacerbations of SLE in patients with relapsing disease, adjusted for seasonal solar exposure and race (i.e., natural skin pigmentation). The main finding was the lowest hydroxyvitamin D level at the time of exacerbation (both renal and non-renal) in non-African Americans compared with vitamin D levels 4 and 2 months prior to the outbreak. This phenomenon was especially pronounced during exacerbations that developed in months with low insolation, while the decrease in the level of hydroxyvitamin D was about 3 times more significant compared to the usual decrease in the concentration of 25(OH)D in this season. Thus, the authors confirmed the hypothesis that during the winter months, a pronounced decrease in vitamin D levels can lead to the development of an exacerbation of SLE. In an analysis of 201 reported exacerbations in a cohort, there was a trend towards an overall higher exacerbation rate in non-African Americans during months of low insolation compared to seasons of normal insolation. In African Americans, these patterns were not found, possibly due to the initially lower level of hydroxyvitamin D and the relative insensitivity of this parameter to seasonal fluctuations due to physiological skin hyperpigmentation. It has been suggested that the role of vitamin D in the activation of SLE may depend on race [38].

However, racial differences are not the only explanation for the possible involvement of vitamin D in the pathogenesis of SLE. Thus, vitamin D deficiency is often observed in patients in India, regardless of social status [62]. At the same time, SLE is rare in Indians (approximately 3 cases per 100,000 population), but the survival rates of patients are significantly lower compared to European ones [63–65]. It is known that vitamin D is necessary for the normal functioning of phagocytes. It has been established that a low level of 25(OH)D causes impaired clearance of apoptotic cells, which may lead to the induction or exacerbation of CCA due to activation of the classical complement pathway [66].

Another possible mechanism for the development of hypovitaminosis D has been studied - hyperproduction autoantibodies to vitamin B. However, JF SaguaSho et al . [23], when examining 171 patients with SLE, found an elevated level of antibodies to vitamin D in only 4%, while the hyperproduction of these antibodies was not associated with a decrease in the serum level of 25(OH)D. A polymorphism in the VDR gene (Bsml) is considered as a possible genetic marker for SLE. In a genetic study of 58 Japanese, it was found that the BB genotype can serve as a trigger for the development of SLE, and the BB genotype can serve as a trigger for the development of lupus nephritis [67, 68]. In Taiwan, an analysis of 47 patients revealed an increase in the frequency of the VV genotype of VR in SLE, but no significant associations were found between allelic variations of VR and clinical and laboratory manifestations [69].

Conclusion . Thus, a direct link between low levels of vitamin D and the occurrence and activation of SLE cannot be ruled out, although the development of hypovitaminosis D due to the disease itself cannot be denied. To assess the status of the vitamin, it is necessary to determine the serum level of 25(OH)D, a decrease in this indicator <20 ng / ml (50 nmol / l) is regarded as hypovitaminosis B. In 2011, the US Institute of Medicine formulated recommendations that indicated the need to take 400 to 600 IU of vitamin D per day for people ages 1 to 70, and 800 IU for people over 70. There is no consensus on the tactics of using vitamin D in rheumatic diseases. Several studies have suggested that higher doses of vitamin D (>800 IU/ day) may be appropriate for patients with RA to achieve optimal levels of this hormone. There are no data on the effectiveness of vitamin D in patients with SLE. Experimental studies show increased survival

and decreased proteinuria in mice with vitamin B supplementation. About 30 years ago, it was found that the use of dihydroxyvitamin D in experimental lupus models led to a regression of alopecia , a decrease in proteinuria, and a decrease in the level of antibodies to dsDNA . The introduction of 1,25(OH)D/ before the onset of symptoms could even have a preventive effect in relation to the development of the disease. It was also noted that in mice with spontaneous development of lupus-like disease, the effectiveness of the prophylactic administration of vitamin D was comparable to that in the appointment of high doses of HA . A positive effect of vitamin D agonists on the prevention of disease expression and symptom severity was demonstrated in mouse models of collagen-induced arthritis. On experimental models of autoimmune encephalomyelitis (the prototype of multiple sclerosis), the protective effect of 1,25(OH) D e analogues on the development of the disease was shown , especially in the case of combined use with other immunosuppressive drugs.

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