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Study on the Role of Vitamin D in Systemic Lupus Erythematosus

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ABSTRACT

Vitamin D is a hormone precursor with multiple biological effects. It binds to vitamin D receptors on target cells. It is an important participant in the metabolism of calcium and phosphorus in vivo. It is closely related to cell cycle, cell proliferation, differentiation, apoptosis, signal transduction and immune regulation. Its role in the treatment of infection, tumor and even immune diseases has been gradually recognized and studied. Patients with systemic lupus erythematosus generally have decreased levels of active vitamin D, and low levels of vitamin D are associated with disease occurrence, disease activity and complications. In the past ten years, a large number of studies have been carried out on it globally to explore the role of vitamin D in the occurrence and development of systemic lupus erythematosus. This paper summarizes its recent research progress.

1. Introduction

Systemic lupus erythematosus (systemic lupus erythematosus, SLE) is a connective tissue disease that is deficient in the ability to clear the deposited immune complex, to the extent that it causes damage to multiple important organs such as the brain, kidney, and heart. The pathogenesis is unclear, but it is generally believed that SLE pathogenesis is related to genetic, endocrine and environmental factors [1]. Studies such as Muller showed for the first time that low vitamin D levels may be linked to SLE development in 1995[2] .Since then, the study on the relationship between the two has never been interrupted, from the regulation of peripheral bone metabolism mechanism to the regulation of cell pleiotropic regulation, especially after the discovery of the expression of vitamin D receptor (vitamin D receptor, VDR) on the surface of immune cells, More studies on vitamin D and SLE immunomodulatory properties have been stimulated. Studies have confirmed that vitamin D deficiency in SLE patients is more obvious than in other immune diseases or healthy people, which may be related to light allergy and lack of light in SLE patients. And the use of glucocorticoids and other

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drugs in the treatment process accelerated the loss of vitamin D. Studies have also investigated differences in the prevalence of SLE races and regions, and found that the prevalence rate in high latitudes and non-white countries is higher, presumably because the vitamin D deficiency in these races is more significant, which is more likely to induce SLE[3]. So far, a large number of studies have tried to explore the relationship between vitamin D deficiency and SLE disease pathogenesis, disease activity, organ injury and laboratory parameters, but the results are still inconclusive. This paper reviews the research progress of active vitamin D physiology, deficiency related diseases, clinical application and its relationship with SLE.

2. Physiology of Vitamin D, Disease Related to Deficiency and Clinical Application

2.1 The Production and Mechanism of Vitamin D

The production and mechanism of vitamin D is a liposoluble ring-opening steroid. Its essence belongs to cholesterol. There are three main sources of production, namely, dietary source, skin production after sunlight exposure and drug supplement. Vitamin D in humans are synthesized mainly by skin exposure to ultraviolet light, while only a small fraction (<10%) is a dietary source[4]. Vitamin D mainly includes vitamin D2 and D3. Vitamin D2, also known as ergot calcitriol, is produced by ultraviolet radiation, mainly in yeast and plants. Vitamin D3, also known as cholecalciferol, is converted from 7-dehydrocholesterol in the skin after absorbing ultraviolet radiation. Vitamin D3 also comes from deep-sea fish oil and dairy products. The main source of human vitamin D is skin synthesis. Vitamin D2 and D3 are metabolized to form active vitamins D: ossified triols (1,25-dihydroxyvitamin-D, 1,25- $(OH)_2$-D)[5-6].Vitamin D metabolism is a complex process, including ultraviolet radiation and hydroxylation, synthesis and catabolism. The process of forming active vitamin D requires one hydroxylation in the liver and one in the kidney, and finally the synthesis of 1,25-(OH)2-D in the kidney. 1, 25-$(OH)_2$-D. In addition to kidney synthesis, Extracrenal synthesis also exists in many tissues, Like parathyroid glands, keratinocytes and immune cells, etc. Synthetic active vitamins must be linked to vitamin D receptors (vitamin D receptor,); and VDR) only after binding can play biological activity. VDR are expressed in a variety of body tissues, including brain, heart, skin, gut, gonad, prostate, mammary gland, immune cells, as well as bone, intestine, R kidney and parathyroid gland. Many immune cells containing VDR include monocytes, macrophages, dendritic cells and activated T and B cells, And these immune cells also have hydroxylase (25-hydroxyvitamin D-1alpha hydroxylase,) in them CYP27B1), Precursor vitamin D converted into active vitamin D[7] .

2.2 Vitamin D Deficiency Related Diseases

Vitamin D in addition to its classic function, the human body vitamin deficiency D also associated with many chronic diseases[5,6], These include immune diseases such as multiple sclerosis, rheumatoid arthritis, type 1 diabetes, inflammatory bowel disease, mixed connective tissue disease, autoimmune thyroid disease, scleroderma, systemic lupus erythematosus cardiovascular diseases such as coronary heart disease, hypertension, heart failure, sudden cardiac death, malignant tumors such as colon cancer, breast cancer, non-Hodgkin lymphoma and neurological diseases such as Alzheimer's disease[7,8].One Meta analysis suggests that lower and higher levels of 25-(OH)- D are associated with increased risk of disease mortality, and that ultraviolet radiation may affect many of the processes associated with vitamin D production in the body[2].As more and more research has been done on vitamin D in recent years, it has been found that it is more and more relevant to many diseases, especially in the field of immune diseases.

2.3 Clinical Application of Vitamin D

Most of the active vitamin D drugs commonly used in clinic are the third generation new vitamin D analogues. They are widely used in osteoporosis, hyperparathyroidism, chronic kidney disease, psoriasis and tumor.

3. Study on the Role of Vitamin D in SLE

3.1 Related Factors of Vitamin D Deficiency in SLE Patients

Serum 25-(OH)- D levels were clinically used as criteria for evaluating vitamin D levels in vivo. Studies have confirmed that levels of 25-(OH)-D in SLE patients are significantly inadequate or deficient, even if necessary vitamins are added D, this state of reduction or deficiency may still exist[9].The main reasons include the following. ① Lack of light: time, season, latitude of residence, light allergy, age and other factors may lead to reduced skin reception of ultraviolet B, as a result, vitamin D synthesis is inadequate, A significant increase in the probability of SLE. ② Application of Glucocorticoids: This drug promotes the metabolism of vitamin D, and so in the course of SLE treatment, A higher dose of vitamin D is needed to meet your balance. ③ Vitamin D activates and upregulates 24-hydroxylase to induce self-degradation, SLE activated B cells in patients upregulate the enzyme, the

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increase D vitamin degradation leads to its lack of [10]. ④ SLE VDR gene polymorphism, anti-antibody production, kidney damage, smoking, braking and other factors can also affect vitamin D levels and effects[11].

3.2 Relationship between VDR Gene Polymorphism and SLE Pathogenesis

The results of current research on the relationship between VDR gene polymorphisms and SLE risk, the difference of sample size, gene selection may lead to the emergence of different results. The results of a meta-analysis of VDR gene BsmI, FokI, ApaI or TaqI and the risk of SLE disease, BsmI B alleles are associated with SLE risk, FokI FF are susceptible genotypes of Asian SLE populations, FokI T /C and TaqI genetic polymorphisms were not associated with Caucasian disease, ApaI is not associated with SLE risk[12].Piantoni and other studies, The genotype appears more frequently ApaI AA SLE patients, Similar to Bb, BB BsmI B allele and FokI FF genotype, Also associated with SLE risk, ApaI AA, BsmI BB and FokI FF genotypes were also significantly associated with lupus nephritis and high activity of SLE diseases. Related studies have also found a significant correlation between Apa and BsmI gene polymorphisms, ApaAa-bb genotype was significantly associated with the onset of Han SLE in China, this genotype is mainly associated with polyplurisy, involvement of the blood system, and high titer antibody production[13-16].

3.3 Relationship between Active Vitamin D Level and SLE Disease Activity

Studies have shown a close relationship between low vitamin D levels and SLE disease activity[9,11,17]. Among them, Squance and other [18] found that patients with reduced or deficient vitamin D were more likely to express high titer anti-nuclear antibodies and anti-binary DNA antibodies, the results suggest that vitamin D may be associated with the pathogenesis of SLE. Schoindre and other [19] studies SLE initial treatment of patients found, Patients with SLE disease activity score (SLEDAI score)≥6 had lower levels of vitamin D, The result has certain clinical significance; Besides, Sahebari and other [20] also show that, Vitamin D levels were negatively correlated with SLEDAI scores, and identified glucocorticoids and other drugs, obesity and kidney involvement as risk factors for further vitamin D deficiency in patients.Nevertheless, the SLEDAI score did not include smooth muscle involvement and myocardial involvement in the scoring system, so McGhie and other [21] studied the relationship between vitamin D and the index score of British lupus assessment group. The results showed that low vitamin D level was negatively correlated with the score. AlSaleem and other [22] confirmed that vitamin D levels were negatively correlated with SLE disease activity, and given adequate vitamin D treatment in active children. The results showed that the disease activity decreased significantly and the renal and joint symptoms improved significantly. This conclusion is consistent with the results of cross-sectional studies in adults and young people [23-24].Combined with the above results, the mechanism mainly includes the following aspects: ① vitamin D can enhance cell chemotaxis, induce macrophage activation, inhibit dendritic cell maturation, and affect antigen presentation, attenuating helper T cells (T helper cell,); and Th11 and Th17 responses, Enhanced Th2 function, Promoting TGF β and forkhead transcription factor gene expression through CC chemokine receptor 4 expression, and increase the number T regulatory cells, Enhance its migration ability. But, uh, The balance in SLE patients with vitamin D deficiency is further disrupted, To make interleukin 6,10, excessive secretion of cytokines such as tumor necrosis factor α, α interferon, To promote disease progression[13,25-26], Imbalance of cytokine secretion mediates hyperactive B cells, Causing plasma cell differentiation to produce antibodies, Causes SLE multiple organs to be tired [27-29]. The study found, the disease activity of SLE patients with low vitamin D level was [30] with the expression of interferon in plasma. Aranow and other [31] have confirmed, Vitamin supplements may D reduce the secretion of α interferon, Improving disease activity and laboratory indicators. ② Vitamin D can induce early apoptosis of activated B cells and decrease the function of B cells, while vitamin D deficiency causes excessive activity of B cells and increase the level of autoantibodies, which leads to the damage of multiple organs[10]. ③ Vitamin D inhibits apoptosis of mononuclear cells in peripheral blood by up-regulating the Bax, FasL expression of B cell lymphoma / leukemia gene and down-regulating the apoptosis related gene[25]. ④ Vitamin D deficiency is significantly associated with shortening of SLE telomeres, while previous studies have confirmed that SLE patients have shorter telomeres and higher activity of anti-terminal antibodies, suggesting that anti-terminal antibodies are significantly associated with disease activity in SLE patients[32].None of these studies confirmed SLE relationship between disease recurrence and vitamin D deficiency, which may be responsible for the short follow-up period.

3.4 Relationship between Vitamin D Deficiency and SLE Complications

Studies have shown that SLE patients with low vitamin

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D have a higher percentage of bone mineral content and a higher risk of fracture[33], The deficiency of active vitamin D in vivo destroys the bone metabolism balance between osteoblasts and osteoclasts, affects the secretion of osteoprotegerin/nuclear factor kB receptor activator ligand and the establishment of bone transformation microenvironment involved in it[34-36].Recently, it has been found that SLE mesenchymal stem cells have differentiation defects, which may be another cause of SLE related osteoporosis[37], There is no correlation between active vitamin D and SLE defective mesenchymal stem cells. Low levels of vitamin D are associated with SLE with insulin resistance, dyslipidemia, cardiovascular risk and mental state, and reduced levels of vitamin D in non-diabetic patients increase insulin resistance and hyperlipidemia[38].Also, vitamin D can reduce cardiovascular risk by reducing the expression of chemokine ligand 10, improving endothelial cell function and repairing angiogenesis cells [39-41]. A study of neuropsychiatric lupus found that vitamin D deficiency is an important factor in sleep quality decline, fatigue and cognitive impairment[42-43].

3.5 Intervention Therapy for Vitamin D

There are many studies on vitamin D intervention SLE at home and abroad, the differences of disease activity, inflammatory factors, autoantibodies and prognosis before and after vitamin D supplementation in SLE patients were compared. Research on vitamin D3 in SLE children with low vitamin D 2000U, 1 daily and 600 mg, calcium Two interventions per day, We found kidney damage three months later, SLEDAI scores and autoimmunity markers were improved[22].The findings are consistent with the findings of another cross-sectional study of young people and adults[44-45].Studies have shown that the combination of different doses of vitamin D in SLE patients can reduce the level of urine protein, the expression of interleukin-1, tumor necrosis factor α, anti- dsDNA antibody in serum, and reduce the disease activity of patients[11,17].Lima and other [46] conducted a 24-week randomized, double-blind, controlled trial of SLE patients with juvenile onset. the results showed that after the patients were treated with active vitamin D, the disease activity and fatigue score decreased compared with before treatment, and the symptoms of fatigue and fatigue were also improved. Nevertheless, a prospective study that treated premenopausal SLE patients with different vitamin D supplementation regimens found that although vitamin D levels were elevated and the treatment was safe and effective, no significant improvement in SLE disease activity and serological indicators was observed [47] either regimen.In addition, the following findings were found in the in vitro intervention test: ① The increase of CD T cell ratio in ① SLE patients can improve the degree of T cell dysfunction and cause phenotypic amplification. Active vitamin D may participate in the of immune tolerance mechanism of lymphocytes[48]. ② Vitamin D may be associated with a particular mode of cell death NETosis White blood cells isolated from peripheral blood were treated with different concentrations of vitamin D. The results showed that the number of early apoptosis of white blood cells in the treated samples was significantly reduced and the damage of endothelial cells was reduced by NETosis methods[49]. ③ such as Wahono and Wu found that low active vitamin D levels affected dendritic cell maturation and Th17, regulatory cell activation. Treatment of isolated cultured peripheral blood monocytes and lymphocytes with different concentrations of active vitamin D, The results showed that the treated cells could slightly upregulate the β, of regulatory T cells and TGF and inhibit dendritic cell maturation and Th17 activation[51-52].

4. Conclusion

While there are many studies on the relationship between vitamin D and SLE, it is difficult for most studies to clarify the true significance of long-term vitamin D deficiency in the process of SLE disease. While vitamin D, as an immunomodulator, can inhibit the secretion of inflammatory factors, reduce SLE antibody titer, reduce renal damage and reduce disease activity, and play a regulatory role in many immune pathways, the above effects are inevitably controversial. Moreover, in clinical work, the best time for vitamin D supplementation in SLE patients and the choice of supplementary dose are not clear, and more research is needed. Whether active vitamin D and its analogues can become the third kind of drugs to treat SLE or improve its complications in addition to hormones and immunosuppressants in the future will become a new direction for researchers to understand the mechanism of rheumatism and treat immune diseases.

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