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Review Article

Significance of Vitamin D in Systemic Lupus Erythemetosus- A Mini Review

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Abstract:

Background: Vitamin D deficiency is more prevalent among SLE patients than the general population. Over the past decade, many studies across the globe have been carried out to investigate the role of vitamin D in SLE from various clinical angles. A possible explanation for this is the sun avoidance by SLE patients, which is an established trigger of lupus flares. Vitamin D also plays key roles as a natural immune modulator and has been implicated in the pathophysiology of autoimmune diseases, including systemic lupus erythematosus (SLE).

Conclusion: This study suggest that many people have inadequate levels of 25(OH)D, particularly patients with SLE, who have additional risk factors for deficiency inherent to SLE.

Keywords: Vitamin D, Systemic lupus erythematosus (SLE), Autoimmune disease, Multiple sclerosis.

Introduction

Systemic lupus erythematosus is a prototype of systemic autoimmune diseases, characterized by wide range of clinical manifestations, degrees of severity as well as alternating phases of remission and flares. In some tissues and organs, it also leads to persistent inflammation and damage. Systemic lupus erythematosus (SLE) affects several organs and systems of the body.

Since a variety of factors, including ethnicity, gender, genetics, and environmental factors are involved; its aetiology and incidence are unknown. The disease affects 30–50/10 000 people worldwide, with young women of reproductive age being most frequently affected (10–12 women for every man) [1,2]. Many studies have highlighted the role of vitamin D in the development of autoimmune diseases. Vitamin D deficiency seems to be associated with SLE activity, partly due to dysregulation in cytokine production balance. The photosensitivity and recommendation of sunscreen use, as well as other measures for less sun exposure, may favor the reduction of cutaneous vitamin D synthesis, which is an established trigger of lupus flares [3]. Therefore, due to the importance of the vitamin D-SLE binomial, this review was done to evaluate the role of vitamin D in autoimmune disease and consequences of deficiency in patients with SLE. It also describes/highlighted the effect of vitamin D supplementation on systemic lupus erythematosus, contributing to the increase of knowledge based on scientific evidence, considering that the subject is relevant, new and, therefore, requires more discussion to adequately guide the decision-making by health professionals.

This review will describe the role of vitamin D in autoimmune disease and consequences of deficiency in patients with SLE

Vitamin D and immune response

Vitamin D has a substantial impact on the innate and adaptive immune system activities. Vitamin D takes these modifications in its calcitriol form by interacting with nuclear vitamin D receptors (nVDR), which are expressed on immune cells such B and T lymphocytes, neutrophils, monocytes, and dendritic cells (DC) [9]. At different times during the immune system's development, vitamin

D is engaged in immunological regulation. Precursors of dendritic cells, monocytes move about in peripheral circulation. IFN-induced monocyte activation promotes the interaction of monocytes with T cells.

These immunological and inflammatory cells can also convert calcidiol into calcitriol, which is the active form of calcidiol [4,5], by up regulating the enzyme 1-hydroxylase (CYP27B1). Additionally, vitamin D stimulates the generation of antimicrobial peptides by keratinocytes, macrophages, monocytes, intestinal, lung, epithelial cells and corneal cell, including cathelicidin antimicrobial peptide (CAMP) [4, 6]. The function of the physical barrier is improved by keratinocytes and cells found in the intestines, lungs, and cornea. These antimicrobial properties work together to strengthen the body's defences against bacteria.

In addition, calcitriol reduces the synthesis of type 1 proinflammatory cytokines such IL-12, IFN-, IL-6, IL-8, TNF-, and IL-9, which slows down Th1 immune responses. Vitamin D affects the transition between humoral immunity (Th2) and cell-mediated immunity (Th1). Contrarily, calcitriol suppresses the growth of Th1 cells, promotes the development of T regulatory (Treg) cells, and up regulates Th2 cells and tolerogenic DC. The production of type 2 anti-inflammatory cytokines including IL-4, IL-5, and IL-10 is also increased by vitamin D [4, 6]. The main way that this cytokine modulation is carried out is by up regulating the NF-kB inhibitory and preventing NF-kB p65 activation [4-8]. Vitamin D and calcitriol also suppress the development of DCs by reducing the production of MHC class II molecules, co-stimulatory molecules, and IL-124 in immunoglobulin-producing B cells. Autoimmunity is avoided and self-tolerance is encouraged by inhibiting DC differentiation and maturation. Additionally, vitamin D causes apoptosis by causing macrophage polarisation to change from the proinflammatory M1 phenotype to the antiinflammatory M2 phenotype. This is due to the fact that immature DC only cause tolerance when an antigen is presented, while mature DC cause an immunological response [4]. When everything is considered, it is clear that vitamin D has a major anti-inflammatory role and can modulate at least certain immune responses. This may have clinical implications for future autoimmune disorders where antibodies play a significant role [4,7]. The overall effect of vitamin D is anti-inflammatory and aids in the prevention of autoimmunity (Fig 1)

Fig 1: Regulation of cells of immune system by Vitamin D

Vitamin D and Systemic lupus erythematosus

Specifically, Systemic Lupus Erythematosus (SLE), Rheumatoid Arthritis (RA), Systemic Sclerosis (SSc), and Idiopathic Inflammatory Myopathies (IIM), as well as Multiple Sclerosis (MS), Inflammatory Bowel Diseases (IBD), type 1 diabetes, and other autoimmune diseases were associated with hypovitaminosis D from a clinical perspective [9]. It's noteworthy to note that vitamin D insufficiency has been associated with a greater autoimmune response even in healthy individuals. It was shown that in these cases, VD deficit was linked to increased interferon (IFN)-activity, a larger auto-immune response, and the presence of anti-nuclear antibodies (ANA).

Several autoimmune illnesses were also shown to have VDR mutations with impaired function. Many studies using animal model have demonstrated that

supplementation with VDR agonists is beneficial for the prevention and treatment of psoriasis, SLE, autoimmune diabetes, EAE, IBDs, and psoriatic arthritis [10-13].

Hypovitaminosis D and SLE was the subject of numerous clinical studies [14]. Since they are instructed to avoid the sun and to use sunscreen [15], SLE patients are, by definition, deficient in Vitamin D. A study by some authors have demonstrated that SLE reactivation was associated with lower VD serum levels in the winter which is also looked at the seasonality of disease flares [15].

A meta-analysis of eleven diverse articles found an inverse relationship between serum VD levels and SLE disease activity was reported by author [16]. Regarding organ-specific factors, several studies on SLE patients discovered a correlation between VD levels, overall cardiovascular risk, vascular stiffness, and endothelial dysfunction [17]. Additionally, hypovitaminosis D was linked to SLE, which had cognitive decline, exhaustion, and sleep disorders [18]. VD supplementation has been the subject of several prospective studies (each with a different treatment plan) in SLE patients, with varying degrees of success. Terrier et al. reported a rise in regulatory and naive T CD4+ cells and a fall in the numbers of Th1, Th17, and B memory cells [19]. Higher levels of Treg cells and Th2 were described by Andreoli et al. [20].

In SLE patients with inactive disease, an intensive supplementation regimen with VD produced sufficient serum 25(OH)D levels but had no impact on disease activity or serology [20]. In contrast, Aranow et al. in a 12-week double-blind, placebo-controlled study, the failure of a VD supplementation of up to 4,000 IU daily to reduce the IFN signature in VD-deficient SLE patients was described. The authors hypothesized that in order to influence immunologic outcomes, higher VD levels maintained for a longer period of time might be required 21. The individual response to VD appears to be explained by VDR polymorphisms, and it was discovered that some are linked to an increased risk of SLE development and disease phenotype [22].

Vitamin D and other autoimmune disease

The central nervous system is damaged by the immune system in multiple sclerosis (MS), a chronic inflammatory illness [23,22]. Although the exact cause of MS is unknown, it is possible that genetic predisposition or environmental factors are to blame, much like with other autoimmune diseases [24]. Epidemiological evidence suggests that MS has a geographic distribution: Although the disease is more prevalent in higher latitudes, it is less prevalent in tropical regions [25, 26]. Lack of sunshine in high-latitude areas, which is required for the cutaneous production of vitamin D, may contribute to vitamin D deficiency, which is a risk factor for multiple sclerosis (MS).. Many authors have demonstrated that MS patients had lower serum concentrations of 25(OH)D and 1,25(OH)2D than controls [27, 28]. Serum 25(OH)D levels varied seasonally in MS patients and controls, but during MS relapses, 25(OH)D levels were lower than in remission 29. This suggests that vitamin D may be involved in regulating the clinical disease progression and severity of MS. The majority of MS patients also lacked vitamin D, according to multiple studies [30, 31, 32]. In particular, MS patients' high rates of disability and relapse were linked to low serum 25 (OH)D levels [30, 31]. However, neither disability nor relapse rate were directly correlated with serum 1,25 (OH)2D, the biologically active form of vitamin D [31]. Munger and co. and Kragt, others reported that the risk of MS was strongly inversely related to the level of 25(OH)D in the blood [32, 33, 34]. However, the correlation was only evident among whites [32] and did not apply to blacks or Hispanics. It is possible that a combination of insufficient vitamin D intake and decreased outdoor activities as a result of lifestyle changes associated with increasing disability is the reason for MS patients typically has lower serum 25(OH)D levels than healthy controls. However, it is unclear whether the high prevalence of vitamin D deficiency among MS patients is the disease's cause or effect.

Several recent studies [35] have suggested that vitamin D insufficiency may enhance the incidence of MS. As a result, diagnosing vitamin D deficiency and re-establishing appropriate vitamin D status may be part of the therapeutic treatment of MS. In fact, vitamin D supplementation has been employed in various research [36, 37], 38. However, these clinical trials were unable to provide conclusive evidence for the therapeutic effects of vitamin D intervention, partly because of the incredibly small number of MS patients recruited. Due to the lack of a double-blind, placebo-controlled, randomised investigation with a significant number of patients [39], the favourable benefits of oral vitamin D supplementation on MS progression need to be further researched. The ideal dosage and duration of vitamin D administration, as well as its therapeutic effectiveness, are not clearly characterised. And may vary from patient to patient.

Type 1 Diabetes Mellitus (T1DM)

T1DM is an immune-mediated condition characterized by insulin deficiency as a result of autoimmune destruction of insulin-producing pancreatic cells40. As with other autoimmune disorders, environmental factors and/or genetic vulnerability may contribute to the development of T1DM [41]. Epidemiologic studies have showed a greater frequency of type 1 diabetes in regions with

less spontaneous vitamin D production and UV exposure [42]. This inverse relationship between T1DM prevalence and UV radiation shows that environmental UV exposure and cutaneous vitamin D production may affect the beginning of numerous autoimmune illnesses, which is consistent with the findings regarding MS.

A study using birth cohorts by Hypponen et al. demonstrated that taking vitamin D supplements as part of one's diet is linked to a lower risk of T1DM [43]. Nutritional vitamin D levels in T1DM patients have been the subject of renewed interest due to the possibility that ensuring adequate vitamin D levels could reduce the frequency of T1DM. In young adults and children, plasma 25(OH)D levels were found to be lower in T1DM patients than in control subjects [44, 45, 46]. In addition, T1DM children had a higher prevalence of vitamin D deficiency or insufficiency than controls [44, 45]. Surprisingly, male patients had lower 25(OH)D levels than female patients [46]. This suggests that the gender difference in plasma vitamin D status may be a factor in the high rate of T1DM in males. T1DM patients had lower levels of both plasma 25(OH)D and circulating 1,25(OH)2D than controls [47]. Before persistent microalbuminuria, T1DM's low serum 1,25(OH)2D levels indicated tubulo-interstitial dysfunction. It is interesting to note that in T1DM, there was no link between low levels of 1,25(OH)2D in the blood and an increased risk of microalbuminuria [48]. However, the local conversion of 25(OH)D into 1,25(OH)2D that produces beneficial effects may not be sufficient to match the levels of 1,25(OH)2D found in the blood. Vitamin D has been suggested as a means of preventing damage to pancreatic cells, restoring their function, and decreasing the prevalence of T1DM due to the strong correlation between vitamin D and T1DM. Pitocco et al. and Li and co. Vitamin D supplementation could only temporarily reduce the clinical insulin dose, which might be attributed to the low 1,25(OH)2D dose (0.25 g on alternate days) administered in T1DM [49]. Both studies demonstrated that vitamin D had a protective effect on preserving -cell function [49, 50], although the effect was not evident in the first study. The insulin and vitamin D treatment in Li's study (1-hydroxy vitamin D3; 0.5 g per day) group did not experience -cell failure, while 27.8 percent of the control group did; however, this randomized controlled trial has a very small number of patients. To determine the therapeutic value of vitamin D supplementation in T1DM, additional clinical studies are required.

Vitamin D deficiency and SLE

Lupus is uncommon autoimmune disorder where the immune system becomes hyperactive. If left untreated, the condition may lead to irreversible damage to major organs like kidneys, heart, lungs and brain. As photosensitivity is one of the key features in SLE, so avoiding exposure to sun, using high factor sun block agent and living in more northern countries may contribute to lower level of vitamin D in patients with lupus. Also those who are away from the equator are especially prone to deficiency and are at higher risk for developing SLE with more severe disease.

Vitamin D is known to have immunosuppressant properties and used as a therapeutic intervention in autoimmune disease. Vitamin D supplementation have a significant impact in the treatment of several autoimmune disease encephalomyelitis (EAE), SLE, type-1diabetes mellitus, collagen induced arthritis. Vitamin D deficiency is well known in lupus patients. Whether low vitamin D is a consequence of the inflammatory state or is responsible for high disease activity is a debatable matter [51]. Unfortunately, the uncontrolled disease can lead to kidney damage, characterized by heavy proteinuria.

DBP (vitamin D binding protein) or albumin (ten percent to fifteen percent) typically binds to vitamin D. A negligible amount (less than 0.03 percent) exists in free from call vitamin D [52]. Due to the excessive loss of DPB in the urine, lupus patients with kidney involvement may experience low vitamin D levels [53]. Since free vitamin D levels are not affected by hormonal levels, liver or kidney function, or hormonal levels, the measurement of free vitamin D in this group of patients may be a better marker to assess vitamin D bioavailability and may provide an explanation for the controversial data that have been reported so far regarding low levels of vitamin D and disease activity.

Vitamin supplementation in SLE

Measurement of circulating 25(OH) vitamin D is considered the best indicator of vitamin D status in humans, as it represents vitamin D stores gained from dietary intake and ultraviolet light [54]. Unlike other vitamins, very little of our vitamin D comes from food. Many experts are recommending increased vitamin D fortification of common foods to counteract the widespread deficiency. Oral supplementation of vitamin D is needed especially for patients with SLE. Since the 25(OH) D assay is quite expensive, so it seems reasonable to test once initially and then at 3 months following a change in vitamin D dosing. Vitamin D supplementation appears to lead to improvements in disease activity and fatigue in patients with systemic lupus erythematosus.

Vitamin D3 supplementation of 8000 IU per day for four weeks, followed by 2000 IU per day for maintenance, was recommended for patients lacking vitamin D. According to guidelines, patients with vitamin D deficiency should take 8000 IU of

vitamin D3 daily for eight weeks, followed by 2000 IU of maintenance55. After three months of taking vitamin D supplements, the serum 25-hydroxyvitamin D level and the calcium level should be checked to make sure the patients had enough vitamin D and didn't have hypercalcaemia. Patients should be contacted to check for compliance with vitamin D supplementation when the desired serum level of 25-hydroxyvitamin D (30 ng/mL) if not achieved, and the recommended dosage should be necessarily increased. After six and twelve months of vitamin D supplementation, the patients should be invited back for a second evaluation. The questionnaires and blood and urine tests should be repeated. This study suggests vitamin D may be low cost method of improving outcomes for some patients with SLE.

Conclusion

This study suggests that many people have inadequate levels of 25(OH)D, particularly patients with SLE, who have additional risk factors for deficiency inherent to SLE. Vitamin D plays an important role in the pathogenesis and progression of autoimmunity. Continued research will help us better understand the immunomodulatory role of vitamin D and determine the ideal range of serum 25(OH)D for immune health.

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Abbreviations

- SLE- systemic lupus erythematosus
- VDR- Vitamin D receptor
- DC- Dendritic cell
- IFN- Interferon
- CAMP- cathelicidin antimicrobial peptide
- IL- Interleukin
- NF- Necrosis factor
- MHC- Major histocompatibility complex
- RA- Rheumatoid Arthritis
- SSc- Systemic Sclerosis
- IIM- Idiopathic Inflammatory Myopathies
- MS- Multiple Sclerosis
- IBD- Inflammatory Bowel Diseases
- T1D- type 1 diabetes
- VD- vitamin D
- ANA- anti-nuclear antibodies
- EAE- Experimental autoimmune encephalomyelitis
- DBP- Vitamin D binding protein

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