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Potential benefits of vitamin D for patients with systemic lupus erythematosus

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Abbreviations: SLE, systemic lupus erythematosus; 25(OH)D, 25-hydroxyvitamin D; $1,25(OH)_2D$, 1,25-dihydroxyvitamin D; ECLAM, European Consensus Lupus Activity Measure; SLAM, systemic lupus activity measure; SLEDAI, Systemic Lupus Erythematous Disease Activity Index; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index; CVD, cardiovascular disease; PGA, Physician Global Assessment; DBP, Vitamin D binding protein; GN, glomerulonephritis; VDR, vitamin D receptor; IFNα, interferon-alpha; IL, interleukin; UVB, ultraviolet-B radiation

Systemic lupus erythematosus (SLE) is a complex multi-system autoimmune disease. Vitamin D deficiency has been proposed as an environmental trigger of disease onset and as a contributor to increased SLE activity. SLE patients are prone to develop vitamin D deficiency because of photosensitivity leading to sun avoidance and other sun protective measures. The impact of vitamin D on immune function previously seen in vitro and in cross-sectional studies has now been shown in prospective human studies, strengthening the evidence that there is a connection between SLE and vitamin D status. This review describes the role of vitamin D on immune function, prevalence of vitamin D deficiency in patients with SLE, identify risk factors for deficiency, describe the consequences of deficiency in SLE patients, and review current vitamin D recommendations for patients with SLE.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease with wide-ranging clinical manifestations and the potential to affect multiple organ systems in the body. Healthy immune responses help prevent or overcome harmful antigens and infections but immune dysfunction with loss of self-tolerance can lead to autoimmunity with self-antigens becoming the target of immune attack. Patients with SLE develop T and B cell-mediated autoimmune responses manifested by the production of autoantibodies. The actual mechanism of autoimmunity, and factors that contribute the progression to clinical autoimmune disease, is being extensively studied with a lot still unknown. Vitamin D deficiency has been implicated as one of the environmental factors contributing to the prevalence of several autoimmune diseases, including SLE.[1,2]

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Vitamin D is an essential steroid hormone with well-established effects on mineral metabolism, skeletal health, and more recently described effects on cardiovascular and immune health.[3-5] It has become recently apparent that vitamin D deficiency contributes to the morbidity and mortality of multiple chronic diseases.[6] Lifestyle factors have led to an increased prevalence of vitamin D deficiency in the general population, while improved availability and reliability of the serum 25-hydroxyvitamin D [25(OH)D] test have led to better awareness of the widespread deficiency.

Because patients with SLE are advised to avoid direct sunlight, a common trigger of disease flares but also the primary source of vitamin D_3, the risk of vitamin D deficiency is even higher among SLE patients than in the general population.[7] Without oral supplementation, the primary source of vitamin D_3 (cholecalciferol) is the skin upon exposure to ultraviolet-B radiation (UVB). Vitamin D_2 (ergocalciferol) from dietary sources is typically a minor contributor to overall vitamin D status.[8] Interestingly, solar radiation, particularly UVB (280–315 nm), is a risk factor for SLE and SLE-related mortality.[9-11] One study found over 90% of patients with SLE exposed to UV radiation had an abnormal reaction.[9]

Vitamin D and the immune system. The importance of vitamin D in immune regulation has gained increased interest over the past decade with the discovery of the vitamin D receptor (VDR) being expressed by cells of the immune system and manipulation of 1,25-dihydroxyvitamin D [$1,25(OH)_2D$] having downstream immune effects. The effects of $1,25(OH)_2D$ are mediated by complex nuclear receptor and the binding of the activated complex to regulatory DNA sequences of target genes. The VDR gene is a direct target of its own receptor, thus facilitating an upregulation of the VDR protein in certain target tissues.[12] Several hundred vitamin D-regulated genes have been identified, including multiple genes involved with the innate and adaptive immune system. The overall immunologic effects of $1,25(OH)_2D$ include downregulating Th1 immune responses, modulating the differentiation of dendritic cells (DCs), and lowering proliferation of activated B cells, while upregulating regulatory T cells and preserving innate immune responses.[2,13,14]

Each of the immune pathways influenced by $1,25(OH)_2D$ has profound potential implications for patients with SLE.

In general, $1,25(OH)_2D$ promotes the development of DCs with tolerogenic properties. $1,25(OH)_2D$ inhibits DC IL12 production and secondarily limits the development of Th1 helper cells shifting to a Th2 phenotype. Interferon α (IFNα), primarily produced by activated plasmacytoid DCs, plays a key role in SLE, with activation of the IFNα pathway being associated with increased anti-dsDNA antibodies and increased disease activity among patients with SLE. In vitro and ex vivo studies have shown the ability of $1,25(OH)_2D$ to inhibit DC maturation and the "IFNα signature" typical of active SLE.[5,15] Ritterhouse et al. showed that vitamin D deficient patients with SLE had higher serum IFNα activity.[16]

Vitamin D deficiency also contributes to B-cell hyperactivation and autoantibody production in genetically susceptible individuals. Linker-Israeli et al. showed that $1,25(OH)_2D$ and its analogs inhibit polyclonal and anti-dsDNA IgG production by stimulated peripheral blood mononuclear cells from patients with SLE.[17] Ritterhouse et al. compared 32 female patients with SLE to 32 healthy matched controls and found 25(OH)D deficiency to be associated with antinuclear antibody (ANA) positivity among controls and with increased B cell activation among patients.[16] Additional immune modulating actions of $1,25(OH)_2D$ of importance in suppressing autoimmunity include increasing Treg cells, decreasing autoantibody production, suppressing the release of inflammatory mediators and the potential reestablishment of immune tolerance.[18]

Prevalence of vitamin D deficiency in SLE. Vitamin D deficiency is a global health problem being detected at all ages, particularly among populations with darker skin pigmentation living further from the equator. African Americans have a 3-fold increased prevalence of SLE, develop SLE at an earlier age, and have increased SLE-related morbidity and mortality compared with Caucasians. It is notable that the same ethnic disparities seen in the prevalence of vitamin D deficiency are seen in the prevalence of SLE.[19] Multiple studies have shown that the majority of patients with SLE have insufficient levels of 25(OH)D, especially among African American and Hispanic patients with SLE.

To examine whether vitamin D deficiency is a potential environmental trigger of SLE, prospective studies and inception cohorts are needed. In the Nurses Health Study and Nurses Health Study II prospective analysis of over 180,000 women followed for up to 22 y found no significant evidence of association between dietary vitamin D intake and subsequent development of SLE. There were limitations which include use of self-reported exposure data without serum 25(OH)D measurements, observational study design and applicability of results to Caucasian female populations only. There was also limited power to detect a small effect of vitamin D intake on SLE development and the confidence intervals were relatively wide (0.5–1.4).[20] In the population-based Carolina lupus inception-cohort study it was noted that lower 25(OH)D levels were found in 123 cases with newly diagnosed SLE compared with 240 controls, which was statistically significant in Caucasians ($p = 0.04$), controlling for age, sex, season and smoking. Overall, 67% of the subjects were vitamin D deficient, with mean levels significantly lower among African Americans (15.9 ng/ml) compared with Caucasians (31.3 ng/ml). Critically low vitamin D levels ($\leq$ 10 ng/ml) were found in 22 of the SLE cases. These baseline results within an inception-cohort of SLE suggest vitamin D deficiency as a possible risk factor for the development of SLE.[21]

Many, but not all, studies of 25(OH)D among patients with established SLE have shown an association of 25(OH)D deficiency with increased SLE disease activity. A summary of the studies which have examined the relationship between SLE and vitamin D status is presented in **Table 1**.

Vitamin D and musculoskeletal manifestations of SLE. Patients with SLE have a higher risk for osteoporosis and fragility fractures, compared with age-matched controls. The increased osteoporosis and fracture risk among young patients with SLE is attributed to systemic inflammation, frequent corticosteroids use, and more recently the high prevalence of vitamin D deficiency.[22] Low levels of 25(OH)D results in the calcium reserves in bone being depleted in an attempt to correct for the reduced calcium that will be absorbed from the gut. As 25(OH)D levels fall, absorption of dietary calcium declines to about 10% to 15%.[23] The reduction in intestinal calcium absorption associated with low levels of 25(OH)D triggers the release of parathyroid hormone (PTH), which stimulates the absorption of calcium through increased production of $1,25(OH)_2D$. PTH also mediates the mobilization of calcium from bone by stimulating bone resorption, which results in a reduction in bone mineral density.[24,25] Vitamin D deficiency is one of several osteoporosis risk factors common among patients with SLE, including high disease activity, renal disease, corticosteroid use, and premature ovarian failure from cytotoxic medications such as cyclophosphamide. Since most patients with SLE have multiple disease-associated and traditional osteoporosis risk factors, bone mineral density loss tends to run a rapid course, making vitamin D status even more important.[22]

Vitamin D and cardiovascular manifestations of SLE. SLE is associated with higher incidence of cardiovascular problems at a younger age. A leading cause of morbidity and mortality in women with SLE, including those who are premenopausal, is CVD.[26,27] Patients with SLE have an increased incidence of myocardial infarction up to 5 times that of the general population, with an age-specific incidence in young women up to 50 times higher. There is evidence to show that, like diabetes, SLE itself is an independent risk factor for the development of atherosclerosis.[28,29] The excess cardiovascular risk, which may be up to 52 times in SLE, is not explained by traditional cardiovascular risk factors. Excess mortality in SLE follows a bimodal pattern, with the early peak predominantly a consequence of active SLE or its complications, and the later peak largely attributable to atherosclerosis. Patients with SLE are also at increased risk of nonfatal ischemic heart disease.[30] As overall survival for patients with SLE improves with better, more targeted, immune suppression therapies, the prevention of morbidity and mortality from atherosclerosis becomes an increasingly critical need.

Table 1. Summary of observational studies of vitamin D status in patients with systemic lupus erythematosus (SLE)

Study Design	Study Population	Vitamin D Assessments	Disease-related Assessments	Comments	Reference
Case series	12 adolescent SLE patients	$1,25(OH)_2D_3$	Avascular necrosis (AVN) of bone	No association with AVN but 7 of 12 had low $1,25(OH)_2D_3$ and 9 had osteopenia	46
Cross-sectional case-control	25 SLE patients 25 fibromyalgia controls	PTH, 25(OH)D, $1,25(OH)_2D_3$	Hydroxychloroquine (HCQ), prednisone, and azathioprine use	No difference between groups in 25(OH)D, but lower $1,25(OH)_2D_3$ with HCQ use	47
Cross-sectional case-control	21 SLE patients 29 RA patients 12 OA patients 72 controls	25(OH)D, $1,25(OH)_2D_3$, DBP phenotype	Anti-dsDNA, ESR, CBC, LACC score	Lower 25(OH)D in SLE compared with OA and controls	48
Cross-sectional case-control	123 SLE patients 240 age and sex-matched population controls	25(OH)D	ACR criteria	Lower 25(OH)D in SLE compared with controls, associated with renal disease and photosensitivity	21
Cross-sectional case-control	57–112 SLE patients 29 RA patients 28 controls	25(OH)D $1,25(OH)_2D_3$	ANA, SLEDAI score	Lower 25(OH)D and $1,25(OH)_2D_3$ in SLE compared with controls and RA, inverse association of $1,25(OH)_2D_3$ with disease activity and ANA	49
Cross-sectional case-control	101 SLE patients 86 controls	25(OH)D	SLEDAI score	25(OH)D $<$ 30ng/ml in 95%, inverse association with disease activity	50
Cross-sectional case-control	46 SLE patients 35 controls	25(OH)D	ANA, anti-dsDNA, Hb, ESR, ECLAM and SLEDAI scores	Inverse association of 25(OH)D with disease activity	51
Cross-sectional case-control	38 pediatric SLE patients 207 controls	25(OH)D $1,25(OH)_2D$	SLEDAI score	Inverse association of 25(OH)D with disease activity and with BMI, and more severe deficiency in cases compared with controls	52
Cross-sectional case-control	32 SLE women, 32 age race and sex-matched controls	25(OH)D	ANA, IFNα activity and SLEDAI	More 25(OH)D deficiency in cases compared with controls, and inverse association between 25(OH)D and ANA positivity among controls and IFN-α activity among cases	16
Cross-sectional case-control	104 SLE women, 49 controls	25(OH)D	Anti-dsDNA, SLEDAI score	25(OH)D significantly lower in cases compared with controls, but no association with disease activity among cases	53
Cross-sectional case-control	60 SLE patients, 60 matched controls	25(OH)D	SLEDAI score	25(OH)D significantly lower in cases compared with controls, and inverse association between 25(OH)D and disease activity among cases	54
Cross-sectional cohort	165 SLE patients	25(OH)D	SLEDAI score	Inverse association with disease activity	55
Cross-sectional cohort	138 SLE patients	25(OH)D	ECLAM score	No association with disease activity	56
Cross-sectional cohort	25 SLE patients 12 incomplete lupus patients	25(OH)D	ANA, anti-dsDNA, autoantigen array, mHAQ, VAS global, VAS fatigue	65% deficient, associated with poorer functional status	57
Cross-Sectional cohort	36 SLE patients	25(OH)D	SLEDAI score	Inverse association with disease activity	58
Cross-Sectional cohort	378 SLE patients	25(OH)D	SLEDAI score, ECLAM score	Inverse association with disease activity	59
Cross- Sectional cohort	198 SLE patients	25(OH)D	SLEDAI score	Inverse association with disease activity	15
Cross- Sectional cohort	177 SLE patients	25(OH)D	SLEDAI score, anti-Sm antibody levels, C4 levels	Inverse association with disease activity, anti-Sm and C4 levels	60
Cross- Sectional cohort	37 SLE patients, ages 5–21 y	25(OH)D, Urinary DBP/ creatinine ratio	SLEDAI score, PGA	Low 25(OH)D associated with proteinuria and urinary DBP but not disease activity when proteinuria patients excluded	61

Table 1. Summary of observational studies of vitamin D status in patients with systemic lupus erythematosus (SLE) (continued)

Study Design	Study Population	Vitamin D Assessments	Disease-related Assessments	Comments	Reference
Cross-Sectional cohort	40 SLE patients	25(OH)D	BILAG score, anti-dsDNA	Inverse association with disease activity and anti-dsDNA antibodies	62
Prospective cohort	186,389 women from 1980–2002	Dietary intake questionnaire	190 incident cases of SLE	No association found with vitamin D intake	63
Prospective cohort	124 SLE women	25(OH)D	SLEDAI and SDI scores	No association found	64
Prospective cohort	75 SLE women	25(OH)D	SLEDAI score	Inverse association with disease activity	33
Prospective cohort	80 SLE patients	25(OH)D	VAS fatigue, SLEDAI and SDI scores	Inverse association with fatigue, but no association with SLEDAI or SDI	65

Vascular stiffness can be partly driven by inflammation, and better disease control in patients with inflammatory arthritis results in a reduction in pulse wave velocity (PWV) noted that inflammatory biomarkers in SLE were particularly associated with aortic PWV.[31,32] In study by Reynolds et al., the association between 25(OH)D and stiffness was at least in part accounted for by disease activity since in a regression model that includes SLEDAI score the association was no longer significant. The results suggest that the association between 25(OH)D and disease activity is strongest in those patients with the most active disease/lowest vitamin D. Vitamin D deficiency may therefore augment the inflammatory response in SLE, underpinning both increased disease activity and vascular stiffness.[33] A recent study by Zhao et al., has shown that concentrations of 25(OH)D were inversely associated with all-cause and CVD mortality among adults with hypertension in the United States.[4]

Vitamin D recommendations for patients with SLE. Due to the high prevalence of vitamin D deficiency seen worldwide and the conditions associated with deficiency, we recommend all patients at risk for SLE or with established disease be screened for vitamin D deficiency. The only lab test usually required to ascertain the patient's status is the 25(OH)D level. Current guidelines give conflicting recommendations for what is considered an "ideal" level of 25(OH)D for the general population and in subpopulations with certain health conditions such as SLE. As our knowledge expands, we may find out that higher thresholds are needed for optimal health, however at this time the minimally adequate level of 25(OH)D is 30 ng/ml.

Achieving sufficient levels of vitamin D is a particularly complex issue for patients with SLE because they are told to avoid the sun, the primary source of vitamin D. There is good evidence that even "sensible" sun exposure of 1 minimal erythema dose daily could trigger a disease flare.[34] For that reason, there will be an even greater dependence on adequate dietary vitamin D intake. Unlike other vitamins, currently very little of our daily vitamin D comes from food. Many experts are recommending increased vitamin D fortification of common foods to help counteract widespread deficiency. But for now, oral vitamin D supplementation is needed for most, if not all, patients with SLE. Oral vitamin D supplementation is recommended in the form of vitamin D_3 (cholecalciferol) rather than D_2 (ergocalciferol). Vitamin D_3 is preferred over vitamin D_3 due to vitamin D_2 being less efficacious in raising serum 25(OH)D, having diminished metabolite binding to vitamin D binding protein (DBP) and a shorter shelf life.[35,36]

The dose of oral vitamin D_3 required to achieve adequate 25(OH)D levels can be difficult to predict and will depend on the patient's baseline serum level and the presence of other risk factors for deficiency, such as obesity and corticosteroid use.[37,38] The American College of Rheumatology published guidelines in 2001 recommending calcium and vitamin D supplementation for all patients starting corticosteroids.[39] Corticosteroids accelerate the catabolism of 25(OH)D and $1,25(OH)_2D$.[40] Therefore patients on corticosteroids often require higher daily doses of vitamin D to maintain adequate levels. A phase I study of daily oral vitamin D_3 showed that doses up to 4,000 IU/day for 3 mo was safe and well-tolerated among African American patients with SLE, and other trials among non-SLE patients have shown similar safety of vitamin D_3 4,000 IU/day.[41,42] Until further prospective trial results in patients with SLE are available, we recommend correcting vitamin D deficiency with 50,000 IU capsule of vitamin D_3 weekly for 8 weeks, followed by 2,000–4,000 IU of vitamin D_3 daily. The dose required to achieve and maintain adequate levels of 25(OH)D depends on the starting level, with roughly 100 IU of additional daily oral vitamin D_3 required to raise the serum 25(OH)D level by 1 ng/ml.[43] It takes approximately 3 mo to achieve steady-state once supplementation is started, but higher doses achieve steady-state sooner.[44] Generally, rechecking a 25(OH)D is usually not necessary sooner than 3 mo.[45] Individual responses may vary and known risk factors for deficiency should be taken into account.

Conclusions

It is well established that many people worldwide have inadequate levels of 25(OH)D, particularly patients with SLE who often have additional risk factors for deficiency inherent to their disease. There is mounting evidence that vitamin D plays a key role in the pathogenesis and progression of autoimmunity. The hope is that something as nontoxic, inexpensive and widely available as vitamin D turns out to be effective as a

disease suppressing intervention for patients with SLE. In addition to the potential benefit of vitamin D replacement on SLE activity, patients will also avoid the excess morbidity and mortality associated with long-term deficiency of vitamin D. 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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