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 Erythematosus 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 manifest 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

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 D₃, 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 D₃ (cholecalciferol) is the skin upon exposure to ultraviolet-B radiation (UVB), Vitamin D₂ (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.

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.7,13,14

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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.18

Vitamin D deficiency also contributes to B-cell hyper-activation 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 (≤ 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.

www.landesbioscience.com Dermato-Endocrinology 147
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)$_2$D$_3$     | Avascular necrosis (AVN) of bone | No association with AVN but 7 of 12 had low 1,25(OH)$_2$D$_3$, 9 had osteopenia | 46        |
| Cross-sectional    | 25 SLE patients                               | PTH, 25(OH)D, 1,25(OH)$_2$D$_3$ | Hydroxychloroquine (HCQ), prednisone, and azathioprine use | No difference between groups in 25(OH)D, but lower 1,25(OH)$_2$D$_3$ with HCQ use | 47        |
| Cross-sectional    | 21 SLE patients                               | 25(OH)D, 1,25(OH)$_2$D$_3$, DBP phenotype | Anti-dsDNA, ESR, CBC, LACC score | Lower 25(OH)D in SLE compared with OA and controls | 48        |
| Cross-sectional    | 123 SLE patients                              | 25(OH)D               | ACR criteria                | Lower 25(OH)D in SLE compared with controls, associated with renal disease and photosensitivity | 21        |
| Cross-sectional    | 57–112 SLE patients                           | 25(OH)D, 1,25(OH)$_2$D$_3$ | ANA, SLEDAI score           | Lower 25(OH)D and 1,25(OH)$_2$D$_3$ in SLE compared with controls and RA, inverse association of 1,25(OH)$_2$D$_3$ with disease activity and ANA | 49        |
| Cross-sectional    | 101 SLE patients                              | 25(OH)D               | SLEDAI score                | 25(OH)D < 30ng/ml in 95%, inverse association with disease activity | 50        |
| Cross-sectional    | 46 SLE patients                               | 25(OH)D               | ANA, anti-dsDNA, Hb, ESR, ECLAM and SLEDAI scores | Inverse association of 25(OH)D with disease activity | 51        |
| Cross-sectional    | 38 pediatric SLE patients                     | 25(OH)D, 1,25(OH)$_2$D | 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    | 32 SLE women, 32 age race and sex-matched controls | 25(OH)D                   | ANA, IFN-α 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    | 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    | 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    | 165 SLE patients                              | 25(OH)D               | SLEDAI score                | Inverse association with disease activity                                  | 55        |
| Cross-sectional    | 138 SLE patients                              | 25(OH)D               | ECLAM score                 | No association with disease activity                                      | 56        |
| Cross-sectional    | 25 SLE patients                               | 25(OH)D               | ANA, anti-dsDNA, autoantigen array, mHAQ, VAS global, VAS fatigue | 65% deficient, associated with poorer functional status | 57        |
| Cross-Sectional    | 36 SLE patients                               | 25(OH)D               | SLEDAI score                | Inverse association with disease activity                                  | 58        |
| Cross-Sectional    | 378 SLE patients                              | 25(OH)D, SLEDAI score, ECLAM score | SLEDAI score                | Inverse association with disease activity                                  | 59        |
| Cross-Sectional    | 198 SLE patients                              | 25(OH)D               | SLEDAI score                | Inverse association with disease activity                                  | 15        |
| Cross-Sectional    | 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    | 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        |
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. 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. 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.

**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. 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 D₃ (cholecalciferol) rather than D₂ (ergocalciferol). Vitamin D₃ is preferred over vitamin D₂ due to vitamin D₂ being less efficacious in raising serum 25(OH)D, having diminished metabolite binding to vitamin D binding protein (DBP) and a shorter shelf life.

The dose of oral vitamin D₃ 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. The American College of Rheumatology published guidelines in 2001 recommending calcium and vitamin D supplementation for all patients starting corticosteroids. Corticosteroids accelerate the catabolism of 25(OH)D and 1,25(OH)₂D. Therefore patients on corticosteroids often require higher daily doses of vitamin D to maintain adequate levels. A phase I study of daily oral vitamin D₃ 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 D₃ 4,000 IU/day. Until further prospective trial results in patients with SLE are available, we recommend correcting vitamin D deficiency with 50,000 IU capsule of vitamin D₃ weekly for 8 weeks, followed by 2,000–4,000 IU of vitamin D₃ 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 D₃ required to raise the serum 25(OH)D level by 1 ng/mL. It takes approximately 3 mo to achieve steady-state once supplementation is started, but higher doses achieve steady-state sooner. Generally, rechecking a 25(OH)D is usually not necessary sooner than 3 mo. 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

| 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 |

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