Vitamin D and Systemic Lupus Erythematosus: Myth or Reality?

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ABSTRACT: There is growing interest in the contribution of vitamin D deficiency to autoimmunity. Several studies have shown an association between low levels of vitamin D and autoimmune disorders, including multiple sclerosis, rheumatoid arthritis, type 1 diabetes, autoimmune thyroid diseases, celiac disease, and systemic lupus erythematosus (SLE). Vitamin D receptor ligands can mediate immunosuppressive effects. It has been suggested that low levels of this hormone contribute to the immune activation in lupus and other autoimmune diseases. This review updates and summarizes the literature on the association between vitamin D and SLE, and discusses the various correlations between vitamin D and SLE activity, clinical expressions, serology, and gene polymorphisms of vitamin D receptors.

IMAJ 2016; 18: 177–182

KEY WORDS: vitamin D, systemic lupus erythematosus (SLE), autoimmune disease, autoimmunity, immunomodulation, gene polymorphism, SLEDAI

Systemic lupus erythematosus (SLE) is a chronic autoimmune inflammatory disease affecting multiple systems of the body. The cause and epidemiology of SLE worldwide has been of interest for years since it is a combination of various factors, including gender, race, genetics and environmental influences [1,2]. Dancheko et al. [3] in 2006 reviewed studies from the National Library of Medicine to determine the incidence and prevalence of SLE in the United States, Europe, Asia and Australia. They discovered the highest prevalence of SLE in non-Caucasian populations in these countries. Since that study researchers have been eager to determine the potential cause. It was proposed that the high likelihood of vitamin D deficiency in these populations could have evoked the manifestation of SLE from within their genomes [3]. This idea was explored by Squance et al. in 2014 [4], who found that individuals with decreased levels of vitamin D were more likely to clinically express their serological autoimmunity as measured by antinuclear antibody (ANA) positivity.

Vitamin D was previously known solely as a hormone that regulates bone homeostasis via calcium and phosphorus metabolism. Recently, other important functions have been discovered, most notably its immunomodulatory properties. For example, studies have shown that vitamin D influences antigen-presenting cells and modulates the cytokines they secrete. In this manner, vitamin D can allow for increased tolerance by limiting the production of pro-inflammatory cytokines such as interleukin (IL)-12, which differentiates T cells into Th1 cells, and increasing the production of anti-inflammatory cytokines such as IL-10. This essentially decreases autoreactivity and is one of the many mechanisms whereby vitamin D can decrease the expression of autoimmune diseases [5]. Another mechanism by which vitamin D can influence the expression of autoimmune diseases is through polymorphisms of the VDR gene or the gene encoding the enzyme 1-alpha-hydroxylase as described in a study by Bizzaro and Shoenfeld [6]. Further studies on other autoimmune diseases, such as primary biliary cirrhosis, found that decreased levels of vitamin D correlate with disease manifestations and, more importantly, co-morbidity with other autoimmune diseases such as SLE, thus establishing the ability of vitamin D to modify the immune system [7].

LOW VITAMIN D LEVELS AND SLE ACTIVITY, FLARES AND CLINICAL EXPRESSION

Many studies have been conducted to define the relationship between low levels vitamin D levels and SLE activity. SLE is associated with overproduction of various cytokines. There is thought to be a shift in the balance of Th1 and Th2 cytokine secretion towards overproduction of Th2 cytokines in patients with SLE. These cytokines mediate B cell hyperactivity, which promote plasma cell differentiation and antibody production [8]. Increased autoantibody production and immune complex formation and deposition are believed to be the cornerstone of the clinical manifestations of SLE, such as nephritis, cytopenias and arthralgias [9]. Chen et al. [10] showed that vitamin D modifies B cell hyperactivity by inducing early apoptosis in active B cells. Normally, B cells stimulated with anti-IgM and anti-CD40 have decreased apoptotic activity compared to earlier

B cells without stimulation. However, stimulated B cells had a significant increase in percentage of apoptotic cells with the addition of vitamin D compared to activated cells without the addition of vitamin D. Therefore, increased SLE disease activity in patients with inadequate levels of vitamin D may be due to fewer apoptotic B cells and subsequently increased production of autoantibodies. In addition, vitamin D induces its own degradation by activation and up-regulation of 24-hydroxylase. Up-regulation of this enzyme in activated B cells may be a possible cause of vitamin D deficiency in individuals with SLE along with decreased absorption of sunlight and disease-induced renal damage [10]. Schoindre and team [11] studied 170 patients with SLE categorized by their various SLEDAI scores (Systemic Lupus Erythematosus Disease Activity Index). Individuals with active disease, defined as SLEDAI scores ≥ 6 had lower levels of vitamin D with an odds ratio of 0.93, 95% confidence interval (CI) 0.87–0.99, $P = 0.02$. Interestingly, they did not find a correlation between disease flare-ups of SLE and 25(OH)D. However, this may be due to the fact that few individuals had flare-ups during the short period of the study [11]. A significant negative correlation between the serum concentration of vitamin D and the standardized values (z-scores) of disease activity scores as measured by the SLEDAI-2K and ECLAM (European Consensus Lupus Activity Measurement) scales was reported by Amital et al. [12].

A study involving Saudi children with SLE conducted by AlSaleem and team [13] agreed that 25(OH)D and SLE activity were inversely correlated. Furthermore, they showed that adequate vitamin D supplementation in children with active SLE disease can improve SLEDAI scores and renal impairment. These findings mirrored those found in a cross-sectional study conducted by Souza et al. [14]. Comparing a group of SLE patients with a control group, they confirmed a relationship between SLE and decreased levels of vitamin D: 55% of SLE patients lacked adequate levels of vitamin D versus 8% in the control group. In addition, within the group of SLE patients, those with vitamin D deficiency had higher levels of the inflammatory cytokine IL-6 than patients with sufficient levels of vitamin D [14]. Cytokines such as IL-6 and IL-10 have been useful regarding SLE activity. In a study by Chun et al. [15] serum levels of IL-6 were increased in SLE patients and correlated with other inflammatory markers of active disease such as SLEDAI, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Serum IL-10 was also elevated in patients with SLE and positively associated with SLEDAI and anti-dsDNA titers. They concluded that both IL-6 and IL-10 can be used as biomarkers for SLE disease activity [15]. The function of IL-6 in SLE activity is not simply that of a biomarker. Umare and collaborators [16] demonstrated a significant increase in renal involvement in patients with active SLE compared to inactive disease. Comparing serum IL-6 levels between these groups revealed that patients with active SLE and renal involvement had significantly increased levels of IL-6 in their serum, highlighting an association between IL-6 and renal disease in active SLE.

Vitamin D supplementation has been shown to improve the levels of inflammatory markers and autoantibodies in the blood of SLE patients. A clinical trial conducted by Abou-Raya and co-authors [17] tested the effect of vitamin D supplementation on specific inflammatory cytokines, including IL-1, IL-6, tumor necrosis factor-alpha, and ESR as well as production of certain autoantibodies including anti-dsDNA and anti-Sm in SLE patients with vitamin D insufficiency. The levels of these inflammatory mediators and autoantibodies decreased significantly over a 1 year period and improved the SLEDAI scores in SLE patients given vitamin D supplementation compared to the placebo group [17]. This further supports the immunomodulatory role of vitamin D, demonstrating that deficiency is associated with disease activity in autoimmune diseases including SLE. Patients with SLE had significantly shorter telomeres and higher anti-telomere antibody titers compared to age- and gender-matched unaffected controls. There was a positive correlation between anti-telomere antibody levels and disease activity among patients and a significant correlation of shorter telomeres with lower 25-hydroxyvitamin D levels in both patients and controls [18]. Low vitamin D levels cause reduced Treg migratory capacity in SLE patients and healthy people. This influence occurs through other factors rather than CCR4 expression [19]. Higher serum creatinine level and higher current daily glucocorticoid dose are associated with lower serum 25(OH) vitamin D levels [20].

INTERVENTIONAL STUDIES

Several interventional studies were recently performed to evaluate vitamin D insufficiency and SLE [Table 1]. The previously mentioned study by AlSaleem et al. [13] in Saudi children with SLE was performed to assess 25-hydroxyvitamin D status and determine its association with clinical presentation, laboratory variables and disease activity. The study included 28 patients with a mean age of 9.7 years. All patients were treated with colecalciferol (vitamin D3, 2000 UI daily) and calcium supplement (caltrate 600 mg twice daily). The patients were evaluated both at enrolment and 3 months later for disease activity by SLEDAI, and for laboratory parameters including vitamin D profile and bone markers. The baseline assessment showed that 24 patients had low levels of vitamin D (mean 51.1 ± 33.6 nmol/L), 25 had high levels of autoantibodies, and 18 patients had high protein/creatinine. Bone density was subnormal, and mean disease activity was 6 ± 5.6. After 3 months of treatment with vitamin D and calcium, 17 patients showed improvement in their SLEDAI score and autoimmune markers [14]. With the objective of demonstrating dysfunction in T cell activation and anergy in SLE patients, Banica et al. [21] explored the expression of anergy-related factors in CD4+ T cells in relation to regulatory T cell frequency in SLE patients. Fresh CD4+T cells were

Tables 1. Low levels of vitamin D with SLE, 2014

Study [ref]	No. of SLE patients	Vit-D deficiency in SLE	No. of controls	Vit-D deficiency in controls	Correlation with activity	Correlation with other factors
Souza et al. [14] (cross-sectional)	45	55% of SLE patients	24	8% of controls	No	IL-6, hematuria
Squance et al. [4] (retrospective)	80	Vit-D levels 23.1 ng/ml	41	Vit-D levels 29.5 ng/ml	No flares	ANA positivity
Robinson et al. [26] (prospective)	201	30% of SLE patients			SLICC	hsCRP, BMI, LDL, minority status
Amital et al. [12] (retrospective)	378				SLEDAI-2K ECLAM	
Schoindre et al. [11] (prospective)	170	15.9% with deficiency, and 65% with insufficiency			High disease activity	No correlation with relapse-free survival
AlSaleem et al. [13] (prospective)	28	24 patients			SLEDAI	Antibodies
Sabio et al. [27] (cross-sectional)	106	Lower Vit-D levels than controls	101	Higher Vit-D levels than SLE	No	Vit-D inversely correlated with insulin, insulin resistance, C4
Jung et al. [30] (retrospective)	102		52		No	No correlation with carotid IMT or disease activity markers
Gholamrezaei et al. [28] (retrospective)	63		no			Sleep quality of SLE patients
Mcghie et al. [29] (retrospective)	75	56%			BILAG	
Mandal et al. [23] (cross-sectional)	129		100		SLEDAI	Anti-dsDNA, IFNα, IFNα gene expression
Lertratanakul et al. [32] (retrospective)	890				SLEDAI	Hypertension, hyperlipidemia, CRP
Kiani et al. [31] (retrospective)	200					CAC score, hsCRP, no correlation with subclinical atherosclerosis
Hoffecker et al. [18] (case-control)	59		59		Correlation between anti-telomere and disease activity	Shorter telomeres, higher anti-telomere
Handono et al. [19] (observational)	41	Vit-D level lower than controls	20			Treg cell migratory capacity
Petri et al. [25] (prospective)	1006				SLEDAI	Proteinuria
Chaiamnuay et al. [20] (cross-sectional)	101	41%			No association with disease activity	
Attar and Siddiqui [33] (retrospective)	95	43%			No correlation with SLEDAI	Positive correlation with C3, C4. Negative correlation with anti-dsDNA

N = number, Vit-D= vitamin D, ANA = antinuclear antibodies, hsCRP = high sensitivity reactive protein, BMI = body mass index, LDL = low density lipoprotein, SLICC = Systemic Lupus International Collaborative Clinics, IMT = intima-media thickness, PTH = parathormone, BILAG = British Isles Lupus Assessment Group index, CAC = coronary artery calcium, Treg = T regulatory, ECLAM = European Consensus Lupus Activity Measurement

isolated from four SLE patients via TCR/CD3 and CD28 receptors in the presence or absence of vitamin D. Results showed that SLE CD4+ T cells are characterized by reduced levels of anergy factors. Additionally, exposure of TCR/CD3 and CD28 to vitamin D led to the expansion of a cell population with a regulatory phenotype. A recent study investigated the effect of vitamin D on NETosis (a unique form of cell death characterized by the release of decondensed chromatin and granular contents to the extracellular space) in SLE patients with low levels of vitamin D. Neutrophils of five SLE patients with low levels of vitamin D were divided into four groups as cultured samples. Isolated neutrophils were incubated for 15 minutes and treated with different concentrations of 1,25(OH)2D3. Results showed a significant decrease in early apoptosis in the group treated with 10 nM of 1,25(OH)2D3 compared to the control group, as well as reduced endothelial damage by decreasing the NETosis activity [22]. Recently, a study by Mandal et al. [23] explored the association of vitamin D levels with SLE disease activity and interferon-alpha (IFNα). Of the 129 SLE patients enrolled, 79 were treatment-naïve, 50 were under treatment and 100 were healthy subjects. Plasma 25-OH vitamin D3 was significantly inversely correlated with SLEDAI scores, anti-dsDNA, plasma IFNα and levels of IFNα gene expression. Moreover, treatment-naïve SLE patients displayed significantly higher plasma levels of IFNα compared with SLE patients receiving treatment and controls, suggesting an important role for vitamin D in regulating disease activity and, therefore, the need to supplement vitamin D in their treatment [23]. Wahono et al. [24] investigated the effect of vitamin D in SLE patients and the effect of 1,25(OH)2D3 on dendritic cell maturation and Th17 and Treg cell activation in SLE patients with low vitamin D levels. Monocytes and lymphocytes of five SLE patients were divided

into four groups as cultured samples. The cells were treated with different doses of 1,25(OH)2D3, resulting in increased levels of Treg cells and transforming growth factor-beta (TGFβ), but not significantly. The study concluded that 1,25(OH)2D3 inhibited dendritic cell maturation and Th17 cell activation in SLE patients [24]. Petri and colleagues [25] reported an association between an increase in vitamin D levels and a decrease in the odds of having clinically significant proteinuria. This study included 1006 SLE patients who were monitored over 128 weeks. SLE patients with low 25-hydroxyvitamin D levels were given supplements of 500,000 units of vitamin D2 weekly plus 200 units of calcium/vitamin D3 twice daily. For those with 25(OH)D levels < 40 ng/ml, a 20-unit increase in the 25(OH) D level was associated with a mean decrease of 0.22 (95%CI 0.02–0.42) (P = 0.032) in the SELENA (Safety of Estrogens in Lupus Erythematosus National Assessment) version of the SLEDAI. Additionally, a 15% decrease in the odds of having clinically significant proteinuria was also noted [25].

Vitamin D levels affect numerous functions of the human body including insulin resistance, sleep quality, and atherosclerosis of arteries. A study conducted by Robinson et al. [26] on atorvastatin therapy for prevention of artherosclerosis in children and adolescents found that responses to atorvostatin on decreasing carotid intima medial thickness (CIMT) progression rate were enhanced in patients with sufficient levels of vitamin D.

Another study by Sabio et al. [27] observed that low levels of vitamin D were associated with increased insulin resistance in non-diabetic females with SLE, independent of BMI. Gholamrezaei et al. [28] studied the relationship between decreased vitamin D and the sleep quality of SLE patients. Although they concluded that more research is needed on the subject, it seems that vitamin D plays a role in sleep quality and sleeping disorders in patients with SLE. McGhie and co-researchers [29] reported an overall negative relationship between the total disease activity score using the BILAG (British Isles Lupus Assessment Group) index and vitamin D levels. Other studies aimed to find associations between low levels of vitamin D and other clinical aspects found among SLE patients. Various studies concluded the absence of a correlation between vitamin 25(OH)D3 levels and carotid IMT, plaque index, disease activity markers, or any measure of subclinical atherosclerosis [30,31]. Contending results were reported by other studies which showed that lower baseline 25(OH)D levels are in fact associated with a higher risk for cardiovascular disease [32]. Interestingly, it was reported that patients with SLE have a higher risk of developing 25(OH)D deficiency in the presence of low serum C3 and C4 levels, and high anti-dsDNA levels [33].

VITAMIN D AND SLE GENE POLYMORPHISM

In the last few years different studies have yielded conflicting results regarding the association between vitamin D receptor (VDR) gene polymorphisms and the risk of SLE. A recent meta-analysis included studies that associated the VDR gene BsmI, FokI, ApaI or TaqI polymorphism with SLE risk. This meta-analysis comprised 11 studies with 1621 cases and 1883 controls and showed that the BsmI B allele was associated with the onset of SLE for overall populations (OR 1.726, 95%CI 1.214–2.455) and Asians (OR 1.952, 95%CI 1.135–3.355). FokI FF genotype was correlated with the susceptibility of SLE for Asians (OR 1.469, 95%CI 1.005–2.148). FokI T/C and TaqI polymorphisms were not associated with SLE risk for Caucasians. There was no significant association between the ApaI polymorphism and SLE risk for overall populations, Asians and Caucasians [34]. Emerah and El-Shal [35] conducted a study to evaluate VDR (ApaI, BsmI, and FokI) gene polymorphisms and haplotypes as risk factors and/or activity markers for SLE. They found that the ApaI AA genotype, BsmI B allele, Bb, BB genotypes, FokI F allele and FF genotype frequencies of VDR were increased in the SLE group. There were significant associations of VDR ApaI AA, BsmI BB, and FokI FF genotypes with lupus nephritis and higher SLE activity scores. Moreover, serum 25(OH) D levels were increased in SLE patients carrying the FokI ff genotype compared with patients carrying the FF genotype. VDR haplotypes aBF and ABF were associated with SLE risk. The ABF haplotype was associated with higher SLE activity scores and lower serum 25(OH) D concentrations [35]. De Azevêdo Silva et al. [36] reported no association between VDR polymorphisms and SLE susceptibility.

Luo and co-authors [37] showed significant associations between the ApaI and BsmI gene polymorphisms, Aa-bb genotypes and the incidence of SLE in the Han population of China. The Aa-bb genotype is more involved in serositis, a hematological system disorder, and has a positive effect on production of antibodies [37]. A meta-analysis in 2011 investigated the association between the B allele, BB+Bb genotype, and BB genotype of the BsmI polymorphism and SLE, and showed significant associations with SLE and lupus nephritis in Asians. The overall ORs of the associations between the B allele and SLE and lupus nephritis were 3.584 (95%CI 1.407–9.130, P = 0.007) and 3.652 (95%CI 1.347–9.902, P = 0.011), respectively. In this meta-analysis associations were found between the VDR BsmI polymorphism and susceptibilities to SLE and lupus nephritis in Asians [38]. Another study in Taiwan noted that the vitamin D receptor Fok I start codon polymorphism is not related to patients with SLE [39]. Ozaki and group in 2002 [40] suggested that the BB genotype might trigger the development of SLE, and that the bb genotype is associated with lupus nephritis.

CONCLUSIONS

The exact relationship between vitamin D and SLE has been of interest for years. Vitamin D deficiency has been found in many patients with SLE due to a variety of causes such as

ethnicity, decreased sunlight, and physiological impairment. Vitamin D has an important role as an immunomodulator in the immune system and can influence the body's response to a variety of autoimmune diseases, including SLE. Multiple studies have shown that inadequate levels of vitamin D correlate with an increase in SLE activity, inflammatory markers and forms of clinical expression. This occurs through a variety of proposed mechanisms including modification of cytokines, as well as alteration in various immune cells activation, proliferation, and destruction. In addition, vitamin D supplementation to the regimen of SLE patients with vitamin D deficiency has proved beneficial in many aspects of SLE activity, including but not limited to SLEDAI scores and clinical manifestations such as proteinuria. VDR polymorphisms may also contribute to increased SLE susceptibility in certain populations. Although studies have supported this idea, other studies have shown no such association and this topic therefore warrants further research. Research has also shown that different VDR genes may be associated with higher SLE activity and lupus nephritis. Further research is needed to confirm the relationship between SLE susceptibility and VDR polymorphisms. Additionally, more studies are required to test the impact and optimal amount of vitamin D supplementation in the treatment of patients with SLE since adding vitamin D may significantly improve their lives.

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