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REVIEW ARTICLE

To Supplement or not to Supplement? The Rationale of Vitamin D Supplementation in Systemic Lupus Erythematosus

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Abstract:

Background:

Systemic Lupus Erythematosus (SLE) is a systemic autoimmune disease characterised by abnormal activation of the immune system, chronic inflammation and organ damage. Lupus patients are more prone to be vitamin D deficient. However, current evidence is not conclusive with regards to the role played by vitamin D in SLE development, progression, and clinical manifestations.

Objective:

Here, we will summarise the current knowledge about vitamin D deficiency prevalence, risk factors, molecular effects, and potential pathogenic role in SLE. We will focus on the link between vitamin D deficiency and lupus clinical manifestations, and on the clinical trials assessing the effects of vitamin D supplementation in SLE.

Method:

A detailed literature search was performed exploiting the available databases, using "vitamin D and lupus/SLE" as keywords. The relevant interventional trials published over the last decade have been considered and the results are reported here.

Conclusion:

Several immune cells express vitamin D receptors. Thus, an immunomodulatory role for vitamin D in lupus is plausible. Numerous observational studies have investigated the relationship between vitamin D levels and clinical/serological manifestations of SLE with contrasting results. Negative correlations between vitamin D levels and disease activity, fatigue, renal and cardiovascular disease, and anti-dsDNA titres have been described but not conclusively accepted. In experimental models of lupus, vitamin D supplementation can improve the disease. Interventional trials have assessed the potential therapeutic value of vitamin D in SLE, but further larger studies are needed.

Keywords: Vitamin D, Lupus, Supplementation, Disease Activity, Immune System, Erythematosus.

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1. INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a chronic multifactorial systemic autoimmune disease affecting women more frequently than men, and with a peak of incidence in childbearing age [1]. Abnormal activation of the immune system, chronic inflammation, and tissue damage constitute the hallmark of the disease. SLE clinical manifestations are widely heterogeneous, ranging from mild symptoms of fatigue and oral ulcerations to life-threatening renal and neurologic disease complications. Typically, the disease fluctuates between clinical flares and quiescence; however, recurrent flares may ultimately lead to irreversible organ damage [2]. The aetiology of lupus has not been fully elucidated yet, but it has been associated with a variety of factors including genetic and epigenetic predisposition, female sex hormones, and environmental factors such as infections, Ultraviolet (UV) exposition and cigarette smoking [3]. Even if remarkable advances have been made in unravelling lupus pathogenesis, this remains not entirely defined. Increased production of type I interferon (IFN) by the innate immune cells, activation of T helper (Th) 1/Th17 with lowered interleukin (IL) 4 production [4], defects in the clearance of apoptotic debris, persistence of autoantigens, and release of autoantibodies are among the crucial events leading to SLE development. Eventually, damage to target organs and tissues is mediated by Immune Complexes (IC) deposition and complement activation. To date, treatment of lupus mostly depends on immunosuppressive agents; nonetheless, the complexity of the pathogenic mechanisms involved might offer several further options for immunomodulatory therap in the future [5].

Vitamin D is a steroid hormone, primarily known for its role in the regulation of the calcium and phosphorus homeostasis and bone protection but, more recently, a potential novel role for vitamin D as a modulator of the immune system has been described too. Once activated, vitamin D can exert its activity by binding Vitamin D Receptors (VDRs). In human, VDRs are widely expressed including numerous immune cells, suggesting that vitamin D may play an essential function in controlling immune system responses. This finding has encouraged several studies aiming at elucidating the immunomodulatory properties of the vitamin D/VDR axis [6, 7]. Defective signalling surely determines bone health and development's issues, but it could also associate with increased risk of multiple chronic diseases like autoimmune conditions, infectious diseases, and cancer [8]. In 1995, Muller *et al.* firstly described the link between low vitamin D levels and lupus [9]; since then, several subsequent reports confirmed a higher prevalence of vitamin D deficiency amongst SLE patients compared to the general population, often also observing a correlation with the disease severity [10 - 16].

Whether or not vitamin D deficiency could ultimately contribute to SLE onset, progression or clinical phenotype is still an unanswered question. Clinical trials assessing the therapeutic efficacy of vitamin D supplementation as an immunomodulatory agent in SLE have given contrasting results, but more extensive studies will hopefully help to shed light on this topic.

Here, we will summarise the current knowledge about vitamin D deficiency prevalence, risk factors and possible pathogenic role in SLE; also, critical molecular studies aiming at an in-depth characterisation of the immunomodulatory effects of vitamin D will be reviewed. Finally, we will focus on the link between vitamin D deficiency and clinical aspects of SLE and will recapitulate the results of the clinical trials assessing the effects of vitamin D supplementation in SLE.

2. VITAMIN D METABOLISM

Vitamin D is a steroid hormone essential for calcium metabolism and bone protection. It is partly obtained from the diet (vitamin D2 or ergocalciferol), but it predominantly derives from the photo-conversion of the 7-dehydroxycholesterol into vitamin D3 (or cholecalciferol) occurring in the skin in response to UV radiation [17]. Both ergocalciferol and cholecalciferol need to undergo chemical modifications to be biologically active. The activation requires two steps: i) in the liver, cytochrome p450 (CYP) hydroxylases, particularly CYP2R1, convert cholecalciferol into 25-dihydroxy-vitamin D3 [25(OH)D3]; ii) in the kidney, the 1α-hydroxylase CYP27B1 generates the active form 1,25-dihydroxy-vitamin D3 [1,25(OH)2D3], or calcitriol, which is around 10 times more effective than the 25(OH)D3. To maintain adequate levels of calcitriol, the 24-hydroxylase (CYP24A1) acts as a negative feedback on the vitamin D activation by hydroxylating both the 25(OH)D3 and the 1,25(OH)2D3 to generate less active molecules. The Parathyroid Hormone (PTH) is capable of modulating the equilibrium between the "activator" CYP27B1 and the "inhibitor" CYP24A1, shifting the system towards calcitriol formation. Low concentration of calcium in the serum up-regulates PTH; conversely, high levels of calcitriol can down-regulate and suppress it [18, 19]. More recently, the phosphaturic hormone fibroblast growth factor 23 (FGF23) emerged as a negative regulator of the 1,25(OH)2D3 generation [20].

Historically, 1,25(OH)2D3 was known for its ability to enable the absorption of calcium in the gastrointestinal tract to control the calcium homeostasis. Constant low levels of calcitriol impair intake of calcium from the intestine and favour the mobilisation of calcium from the bone ultimately leading to pathologies such as osteomalacia, osteoporosis and rickets [21, 22]. 1,25(OH)2D3 acts by binding its receptor VDR and mediating its conformational modification; VDR works as a transcription factor regulating the DNA-expression of the Vitamin D Response Elements (VDREs) [23]. Of notable importance in the context of autoimmune diseases as SLE the effect of the chronic use of corticosteroids, which can increment the activity of the calcitriol-inhibitor CYP24A1 while lowering the intestinal absorption of calcium [24, 25].

3. PREVALENCE AND RISK FACTORS FOR VITAMIN D DEFICIENCY IN SLE

3.1. Vitamin D Deficiency Definition

In current practice, the vitamin D status is evaluated by measuring the serum concentration of 25(OH)D3, a mirror of the most abundant pool sequestred in adipose tissue and muscles [26]. Analytical variability and discrepancies in epidemiologic studies raise the controversy on a universally accepted definition of vitamin D deficiency. Several techniques ranging from liquid chromatography and chemiluminescence to immunoassay have been developed, resulting in an intra-sample variability of up to 20% [27]. So far, liquid chromatography is probably the most reliable methodology as it is not influenced by the presence of other vitamin D species and metabolites [28]. In 2010, an international collaborative venture was launched by the National Institutes of Health aiming at promoting standardisation of the laboratory measurement of 25(OH)D3 and defining the appropriate concentration of plasmatic vitamin D [29]. Several international health and scientific organisations have approached this issue including the World Health Organization (WHO), the Institute of Medicine (IOM) and the Endocrine Society (ES), reaching different conclusions regarding the desirable level of circulating 25(OH)D3.

The ES sets the threshold to 30 ng/mL while the IOM to 20 ng/mL, discrepancy partially justified by the different target population considered. Nevertheless, both measures seem poorly representative for non-white ethnicities [27, 30, 31]. Despite using different criteria, both the ES and the IOM based their statements on a systematic review of the literature focusing mainly on ‘skeletal’ outcomes such as PHT inflexion point, calcium absorption, osteomalacia, rickets, Bone Mineral Density (BMD), and fractures [27, 30, 31]. In the absence of a universally accepted definition, most of the studies currently use a cut-off of 30 ng/mL to designate vitamin D insufficiency, and values under 20 ng/mL for vitamin D deficiency [17, 30, 32, 33]. Further studies focusing on non-musculoskeletal outcomes and representative of a more varied genetic background/ethnicity remain to be carried out [28].

3.2. Prevalence Of Hypovitaminosis D In Disease

Vitamin D deficiency is common in the general population and, as expected, its prevalence increases with higher latitudes [17]. Nonetheless, the still significant frequency of vitamin D deficiency in countries with high sun exposure suggests that other factors other than UV radiation influence the levels of 25(OH)D3, *e.g*. genetics, diet, cultural habits and clothing [17, 34]. A growing number of preclinical works is shedding light on the pleiotropic effects of vitamin D on virtually any cells. Thus, it is not surprising that a plethora of observational studies described altered levels of 25(OH)D3 in multiple conditions such as diabetes [35], atherosclerosis, cancer, and autoimmunity. Indeed, in most case-control studies on autoimmune diseases including SLE, patients had persistently lower vitamin D levels than controls [17, 36 - 39]. The inclusion of healthy controls as comparator group is mandatory to rightly interpret data on vitamin D deficiency/insufficiency because of its broad diffusion and the high variability of its prevalence worldwide. Among 14 controlled studies reviewed by Reynolds and Bruce in 2017 [40], 12 of them showed significantly lower levels of serum vitamin D in SLE, while only two failed to detect different average values between cases and controls [11, 41]. Hence, despite a prevailing consensus that SLE patients have significantly lower levels of vitamin D, variations in assay techniques, cut-off values, seasonality, ethnicity, age, sex, disease duration and latitude, all contribute to making the frequency of vitamin D deficiency/insufficiency challenging to compare between different studies. Overall, the rate of vitamin D deficiency/insufficiency considerably diverge across multiple cohorts, ranging from 8 to 30% [10, 42 - 47].

3.3. Risk Factors For Vitamin D Deficiency

Recurrently finding lower vitamin D levels in SLE patients raises a burning question still far to be answered: is vitamin D deficit a contributing factor to SLE development? Or, is it merely a consequence of the disease? Several

plausible hypotheses about this relationship have been advanced. *Reduced UV exposure* is indeed frequent in SLE patients. Active sun avoidance and use of high factor sunblock are recommended by clinicians worldwide due to the photosensitivity typical of the disease [14, 48]. Additionally, it is conceivable that symptoms such as fatigue and polyarthralgia may limit the outdoor activity of SLE patient impacting on the UV exposure and vitamin D metabolism. However, a recent study by Shoenfield *et al.* analysing *CYP24A1* polymorphisms showed that the photosensitivity and the sun exposure behaviour did not correlate with vitamin D levels, suggesting that the genetic background is a stronger driver of vitamin D status [49, 50]. *Renal involvement* typical of SLE may also affect the vitamin D metabolism by impairing its 1-hydroxylation occurring in kidneys. Epidemiological studies identified nephritis as one of the most influential predictors of vitamin D deficiency [14, 42, 51]. *Medications* could, in theory, participate to reducing the levels of vitamin D. Corticosteroids, for instance, may lower the intestinal calcium absorption and increase vitamin D catabolism; therefore, when prescribed for SLE treatment, steroids may contribute to vitamin D deficiency [51 - 53]. Though, even if plausible, this cannot fully explain the low level of vitamin D found in SLE patients, especially before the diagnosis when still steroids-naïve [48, 49]. *Genetic variations* also participate in regulating the absorption and metabolism of 25(OH)D3 [54]. For instance, intronic polymorphisms of the regulatory region of the gene encoding the negative regulator CYP24A1 [18] have been associated with SLE: in subjects with increased genetic risk for SLE development, the presence of two copies of the minor allele is able to increase 25(OH)D3 levels reducing the risk of having the disease [50].

Finally, 25(OH)D3 may also act as a *negative acute phase reactant*, dropping in consequence of acute or chronic inflammation. This relationship has been recently confirmed by a meta-analysis demonstrating that serum 25(OH)D3 levels decrease following traumatic events as orthopaedic surgery and acute pancreatitis and inversely correlate with C-Reactive Protein values [55].

4. ROLE OF VITAMIN D IN THE IMMUNE SYSTEM REGULATION

As previously mentioned, the discovery of the expression of VDRs by a plethora of innate and adaptive immune cells [56 - 58] allowed to hypothesise a role for vitamin D in the immune system regulation and, potentially, in the pathogenesis/progression of conditions characterised by an impaired functioning of the immune response. *In vitro* studies have shown in multiple cell types that the vitamin D/VDR axis has important and broad immunomodulatory properties, overall mediating a negative regulation of several immunological abnormalities lupus-related. In the adaptive system, 1,25(OH)2D3 can decrease the proliferation of B cells by up-regulating their apoptosis, inhibit the B cells-to-plasma cells differentiation and the immunoglobulin (Ig) class switching, and limit the production of auto-antibodies including the anti-double strand (ds) DNA [59 - 61]. Since B lymphocytes are CYP27B1-expressing cells, an autocrine regulation of the response to calcitriol seems likely [61, 62]. Similarly, also in T cells the main effect of the vitamin D stimulation is a modulation of their activation. Numerous T cell populations like Th CD4+ and CD8+ cells express the VDR and can be targeted by vitamin D [57], and the VDR expression seems to be induced in response to an initial T-Cell Receptor (TCR) signalling [63]. On the one hand, vitamin D negatively regulates the release of pro-inflammatory cytokines, *e.g*. IL-17A and IL-12p70, and reduces the relative percentage of the Th17 subset [64, 65]. Contrariwise, it raises, at least temporarily, the number of the T-regulatory (Treg) cells and the expression of Treg-specific markers [66]. Among the innate immune cells, both DCs and monocytes/macrophages express the VDR and the activating enzyme CYP27B1 [67]. In monocytes, treatment with 1,25(OH)2D3 decreases MHCII and CD80/CD86 expression [68], inhibits monocytes differentiation [69] and limits the pro-inflammatory effects secondary to the activation of Toll-Like-Receptors (TLR), *e.g*. TLR 9 [70]. Vitamin D-treated macrophages show an M2-preferential phenotype [71], characterised by reduced production of Tumor Necrosis Factor (TNF)-α, IL-1β, IL-6, and nitric oxide but increased IL-10 [72], and have a limited ability to activate T cells [73]. Vitamin D can modulate the immune response also by inhibiting the maturation of DCs [69]: these immature and tolerogenic DCs have immunomodulatory properties and are able to promote Treg differentiation while restraining the proliferation of inflammatory T cells [74 - 76]. To note, when monocyte-derived DCs from lupus patients were treated with dexamethasone in combination with vitamin D3 they became able to promote IL10-expressing-Treg and to inhibit the pro-inflammatory T cell phenotype [77]. Neutrophils express VDRs too [78]; studies in SLE showed that, when bound by their ligand 1,25(OH)2D3, the activated VDR mediates an overall improvement of the endothelial damage secondary to the decreased generation of Neutrophils-Extracellular-Traps (NET) [79]. Some of the vitamin D effects observed *in vitro* were replicated in animal models of lupus, for instance, its ability to favour Treg differentiation and Foxp3 expression [80], to reduce IL-17/23, IFN-gamma and IL-6, and to decrease the titre of anti-dsDNA antibodies [80, 81]. A potential therapeutic role for vitamin D in improving clinical manifestations of lupus was hypothesised based on the decreased severity of the disease

observed in MRL/1 mice treated with 1,25(OH)2D3 [82]. Immunomodulatory properties of vitamin D were also confirmed in both controls and SLE patients treated with vitamin D supplementation; in healthy volunteers receiving 12-weeks of oral cholecalciferol supplementation (140000 IU/month) the number of Treg cells significantly increased [83]. Also, the pro-inflammatory cytokines production by cells isolated from vitamin D-deficient but otherwise healthy participants was reduced in subjects who corrected vitamin D levels following supplementation [84]. The chance that vitamin D could act as an immunomodulatory therapeutic agent prompted numerous studies assessing the role of vitamin D supplements in improving the immune and clinical responses in SLE. As it will be discussed afterwards, cholecalciferol administration to lupus patients seems to mediate a shift of the ratio between Th1/Th17 effector cells and Treg in favour of the latter [85 - 87], meanwhile decreasing the number of memory B cells and the production of anti-dsDNA antibodies [85 - 87]. Consistently, a negative correlation between 25(OH)D3 levels and the presence of anti-dsDNA antibodies was repeatedly observed [11, 90]. Finally, some [11, 88], however not all the studies [91] showed a negative correlation between the serum vitamin D values and the IFN signature in lupus patients.

5. DOES HYPOVITAMINOSIS D PLAY A ROLE IN SLE DEVELOPMENT?

As discussed above, although the high prevalence of vitamin D deficiency in lupus has been broadly demonstrated and accepted, its potential role in the development, progression and clinical manifestations of the disease is still under investigation. Several studies tried to establish a pathogenic function for impaired vitamin D levels in autoimmune diseases, though this sounds scientifically challenging. The body of evidence on the immunological and non-immunological disease-associated pathways potentially controlled by vitamin D is exponentially growing, but conclusive mechanistic correlations in human are elusive and hard to prove, particularly because most of the available data come from observational studies. Interestingly, significant lower vitamin D levels have been observed in subjects with anti-nuclear antibodies (ANA) positivity but not clinically proven SLE, hence suggesting that a breach of the immune tolerance may be more common in vitamin D deficient subjects [88]. A retrospective analysis of hospital admissions records in England related to diseases associated with vitamin D deficiency, including osteomalacia and rickets, revealed an increased future risk of developing immune-mediated conditions such as SLE, Rheumatoid Arthritis (RA) and systemic sclerosis in these patients [92]. However, due to the intrinsic limitations of this kind of study, confounders and reverse causality cannot be ruled out [92]. More recently, vitamin D deficiency in high-risk subjects (SLE siblings), along with *CYP24A1* polymorphisms, have been associated with higher prevalence of SLE onset within a follow-up period of 6 years [50]. In keeping with this, patients who progress from an undifferentiated Connective Tissue Disease (CTD) to a defined CTD seem more likely to have lower vitamin D levels than the non-progressors [93].

As it will be discussed later in this manuscript, experimental vitamin D administration (or deprivation) in animal models of SLE offers some insight on this topic. It seems indeed that the administration of 1,25(OH)2D3 to MRL/1 mice, a model of spontaneous SLE, prevents dermatological lesions such as alopecia and ear necrosis [82], and reduces the severity of proteinuria and arthritis, overall increasing the lifespan [94].

5.1. Vitamin D Receptor (VDR) Gene Polymorphisms Correlate With Risk of SLE

Genetics may further help to elucidate the link between vitamin D and SLE. Some of the numerous polymorphisms located within the VDR genes have been indeed associated with a higher risk of developing SLE in multiple studies. Meta-analyses of genetic studies confirmed the correlation for some of the SNPs in *VDR* in Asians but not in Caucasians. Among those, the most extensively studied mutations are TaqI(rs731236), BsmI(rs1544410), ApaI(rs7975232), and FokI(rs2228570) [95]. More specifically, the B allele in the *VDR* BsmI associates with a raised risk of SLE in the general population, with the strongest correlation in Asians and a lack of association in Caucasians. The association between the *VDR* FokI and the risk of SLE was confirmed too; though, a subsequent sub-analysis performed categorising patients for ethnicity again failed to identify any correlation in Caucasians. Data coming from the three genetic studies about ApaI revealed an association only in patients of African origin, and they should be taken anyway with some caution because of the limited sample size [96, 97]

6. CORRELATION BETWEEN VITAMIN D DEFICIENCY AND CLINICAL AND SEROLOGICAL MANIFESTATIONS IN SLE

In keeping with the above-described modulatory properties of 25(OH)D3 on the immune system cells, a considerable effort has been made over the last decades to investigate the association between vitamin D levels and lupus severity, disease progression, immunologic status, and comorbidities. To date, even if numerous studies have been published worldwide over the last decade (Table **1**), data in this field are not as yet conclusive: while some studies

reported an inverse correlation between vitamin D levels and lupus disease activity, disease flares, Cardiovascular (CV) involvement, renal disease, fatigue, and anti-dsDNA titre, these results were not constantly replicated. The interest in evaluating the correlation between vitamin D and clinical manifestations is not anyway limited to lupus but has been raised in other autoimmune conditions [98]. For instance, in two metanalyses lately published, a significant inverse correlation between serum 25(OH)D3 levels and disease severity has been found in both Crohn's disease and RA [37, 38].

Table 1. Relevant studies published over the last decade investigating the correlation between vitamin D levels and clinical and serological manifestations in SLE.

Reference	Patients/Ethnicity/Country	Main findings
Wang *et al*, 2017 [99]	113 premenopausal women with SLE (China)	25(OH)D3 lower level associated with increased metabolic syndrome prevalence, decreased HDL level and higher level of fasting glucose
Shahin *et al*, 2017 [100]	57 treatment-naïve SLE and 42 controls (Egypt)	25(OH)D3 lower levels associated with thrombocytopenia, no other clinical manifestations Negative correlation between vitamin D and ANA titre, IL-17 and IL-23
Garcia-Carrasco *et al*, 2017 [101]	137 women with SLE (Mexico)	No association between vitamin D and MEX-SLEDAI
Abdel-Galil *et al*, 2017 [102]	123 SLE and 100 controls (Egypt)	Negative correlation between vitamin D and SLEDAI in the high-disease activity group and patients with lupus nephritis Negative correlation between 25(OH)D3 and IFN-α serum level/gene expression (> in patients with lupus nephritis)
Eloi *et al*, 2017 [103]	199 SLE patients (Brazil)	Negative correlation between vitamin D and SLEDAI
Salman-Monte *et al*, 2016 [104]	102 female SLE patients (Spain)	Negative correlation between vitamin D insufficiency and fatigue 25(OH)D3 lower levels associated with more oral corticosteroids
Gao *et al*, 2016 [105]	121 SLE patients and 150 controls (China)	Severe vitamin D deficiency is prevalent in moderate/high disease activity (SLEDAI), but no correlation with organ damage (SDI)
Simioni *et al*, 2016 [106]	153 SLE patients and 85 controls (Brazil)	No correlation between vitamin D and SLEDAI Lower levels of vitamin D associate with leukopenia
Kokic *et al*, 2016 [107]	22 female SLE patients and 21 controls (Croatia)	Negative correlation between vitamin D levels and IFN-γ
Lin *et al*, 2016 [108]	35 pediatric-onset SLE (in active and inactive disease states) (Taiwan)	Lower levels of vitamin D associate with lupus nephritis Significant negative correlation between 25(OH)D3 and SLEDAI-2k
Yap *et al*, 2015 [109]	119 SLE patients (Australia)	Negative correlation between vitamin D and SLEDAI-2K Increase in serum 25(OH)D3 associated with reduced disease activity
Tay *et al*, 2015 [110]	61 SLE patients and 61 controls (Singapore)	25(OH)D3 lower levels independently predicted cognitive deficit in lupus patients.
Garf *et al*, 2015 [111]	70 juvenile-onset SLE patients, 40 controls (Egypt)	No correlation between vitamin D deficiency and SLEDAI
Dall'Ara *et al*, 2015 [112]	50 SLE patients, 30 SLE patients during disease flare; 170 healthy controls (Italy)	Measured 2 values, in winter and summer Lower vitamin D associated with disease flares during winter
Sabio *et al*, 2015 [113]	106 non-diabetic female SLE patients and 101 controls (Spain)	25(OH)D3 lower levels associated with insulin resistance and metabolic syndrome (trend) Negative correlation between vitamin D and insulin and C3
Sahebari *et al*, 2014 [114]	82 SLE patients and 49 controls (Iran)	No association between vitamin D deficiency and SLEDAI
Schoindre *et al*, 2014 [115]	170 patients treated with HCQ for 6 months (Plaquenil LUpus Systemic study) (France)	Negative correlation between 25(OH)D3 and SLEDAI score No association with flares during the six months following the measurement
Lertratanakul *et al*, 2014 [116]	890 patients SLE (North America, Europe and Asia)	Negative correlation between 25(OH)D3 and SELENA-SLEDAI score 25(OH)D3 lower levels associated with increased risk for hypertension and hyperlipidaemia but no correlation with other CV events
Mandal *et al*, 2014 [11]	129 SLE patients (79 treatment-naïve, 50 treated), 100 controls (India)	Negative correlation between 25(OH)D3 and SLEDAI, anti-dsDNA titre, plasma/gene expression of IFNα Higher levels of plasma IFN-α in treatment-naïve SLE patients compared to treated patients and controls
McGhie *et al*, 2014 [117]	75 patients with SLE (Jamaica)	Negative correlation between vitamin D and BILAG score (trend)

(Table 1) contd.....

Reference	Patients/Ethnicity/Country	Main findings
De Souza *et al*, 2014 [118]	45 SLE patients and 24 controls (Brazil)	No association between vitamin D deficiency and SLEDAI 25(OH)D3 lower levels associated with higher rate of haematuria and higher IL-6 level
Jung J *et al*, 2014 [119]	102 female SLE patients and 52 controls (Korea)	No correlation between vitamin D levels and subclinical markers of atherosclerosis
Abou-Raya *et al*, 2013 [89]	267 SLE patients (Egypt)	25(OH)D3 lower levels correlated with higher SLE disease activity (SLEDAI)
Chaiamnuay *et al*, 2013 [51]	101 SLE patients (Thailand)	Inverse correlation between 25(OH)D3 and creatinine levels and glucocorticoid doses
Attar *et al*, 2013 [90]	95 SLE patients (Saudi Arabia)	25(OH)D3 lower levels associated with active SLE, azathioprine treatment, low C3/C4 No correlation between vitamin D and SLEDAI-2K. 25(OH)D3: negative correlation with anti-dsDNA, positive correlation with C4
Kiani *et al*, 2013 [120]	200 patients followed up for 2 years Lupus Atherosclerosis Prevention Study - Hopkins Lupus Cohort (US)	No association between 25(OH)D levels and subclinical markers of atherosclerosis
Sumethkul *et al*, 2012 [42]	108 SLE patients (Thailand)	25(OH)D3 lower levels associated with urinary protein/creatinine index and nephritis with proteinuria
Mok *et al*, 2012 [43] Mok *et al*, 2012 [46]	290 Chinese patients with SLE (Hong Kong)	Negative correlation between 25(OH)D3 levels and SLEDAI scores and PGA 25(OH)D3 levels significantly lower in patients who experienced disease flares 25(OH)D3 lower levels associated with higher prevalence of aPL syndrome and higher total/HDL cholesterol ratio Negative correlation between 25(OH)D3 levels and anti-C1q/anti-dsDNA titres No correlation with complement levels, atherosclerosis, and organ damage
Yeap *et al*, 2012 [121]	38 premenopausal SLE (Malaysia)	Negative correlation between vitamin D levels and SLEDAI scores
Stockton *et al*, 2012 [41]	24 SLE 21 controls (Australia)	No correlation between vitamin D levels and fatigue
Birmingham *et al*, 2012 [122]	46 SLE patient (82 flares) (US)	25(OH)D3 levels decreased during flares (especially in non-African American)
Bogaczewicz *et al*, 2012 [123]	49 SLE 49 controls (Poland)	Vitamin D deficiency associated with renal disease and leukopenia
Munoz-Ortego *et al*, 2012 [124]	73 SLE (Spain)	No correlation between vitamin D and SLEDAI and SLICC/ACR scores
Fragoso *et al*, 2012 [125]	78 SLE 64 controls (Brazil)	No association between vitamin D and SLEDAI, fatigue and anti-dsDNA
Reynolds *et al*, 2012 [126]	75 SLE (United Kingdom)	25(OH)D3 lower levels associated with higher SLEDAI-2K, higher BMI and insulin resistance Negative correlation between serum 25(OH)D3 concentration and aortic stiffness (independent of BMI, insulin and other CVD risk factors) No association between vitamin D levels and carotid plaque area and intima media thickness.
Ravenell *et al*, 2012 [127]	51 SLE African-American patients	Negative correlation between vitamin D and age-adjusted total plaque area
Hamza *et al*, 2011 [45]	60 SLE 60 controls (Egypt)	Negative correlation between vitamin D levels and SLEDAI scores 25(OH)D3 lower levels associated with higher prevalence of photosensitivity
Souto *et al*, 2011 [44]	159 SLE patients (Brazil)	No correlation between vitamin D levels and disease activity score
Bonakdar *et al*, 2011 [128]	40 SLE (Iran)	Negative correlation between vitamin D levels and BILAG index score 25(OH)D3 lower levels associated with higher anti-dsDNA, lower Hb and albumin concentrations and higher LFTs
Szodoray *et al*, 2011 [129]	177 SLE (Hungary)	Negative correlation between vitamin D levels and SLEDAI score 25(OH)D3: negative correlation with anti-dsDNA, anti-Sm, and IgG levels; positive correlation with complement levels 25(OH)D3 lower levels associated with higher prevalence of pericarditis, neuropsychiatric diseases and deep vein thrombosis

(Table 1) contd.....

Reference	Patients/Ethnicity/Country	Main findings
Kim *et al*, 2011 [130]	104 SLE 49 controls (Korea)	No association between vitamin D levels and SLEDAI and SLICC Positive correlation between vitamin D and Hb and serum complement
Amital *et al*, 2010 [131]	378 European/Israeli patients	Negative correlation between vitamin D and disease activity (SLEDAI-2K/ ECLAM scales)
Ben-Zvi *et al*, 2010 [132]	198 SLE patients (US)	Negative correlation between vitamin D and disease activity
Ruiz-Irastorza *et al*, 2010 [133]	80 SLE (Spain)	No correlation between vitamin D levels and SLEDAI/SDI Negative correlation between 25(OH)D3 levels and VAS-fatigue
Toloza *et al*, 2010 [10]	124 SLE patients (Canada)	No correlation between vitamin D and disease activity Association between vitamin D and creatinine levels
Wu *et al*, 2009 [134]	181 female SLE (US)	Negative correlation between vitamin D levels and SLEDAI and SLICC scores. 25(OH)D3 lower levels associated with higher diastolic blood pressure, LDL cholesterol, lipoprotein-a, BMI and insulin resistance (significance lost if adjusting for BMI)
Borba *et al*, 2009 [135]	36 SLE, 26 controls (Brazil)	Inverse correlation between vitamin D level and SLEDAI, osteocalcin and bone-specific alkaline phosphatase
Cutolo *et al*, 2008 [136]	SLE patients from Estonia and Italy	Negative correlation between 25(OH)D3 levels and ECLAM and SLEDAI (in all patients)
Thudi *et al*, 2008 [137]	37 female SLE (US)	Vitamin D deficiency associated with lower disease global assessment scores Higher dsDNA titres associated with vitamin D > 47.7 nmol/L
Ruiz-Irastorza *et al*, 2008 [48]	92 SLE patients (Spain)	No association between vitamin D levels and disease duration, disease activity (SLEDAI, SLICC-ACR). Low vitamin D levels associated with self-rated fatigue VAS score
Orbach *et al*, 2007 [12]	138 SLE patients	No correlation between Vitamin D and ECLAM score
Kamen *et al*, 2006 [14]	123 recently diagnosed SLE 240 controls (US)	25(OH)D3 lowest levels (<10 ng/ml) associated with renal disease and photosensitivity

ANA, Anti-Nuclear Antibodies; SLE, Systemic Lupus Erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SLEDAI-2K, SLEDAI-2000; BILAG, British Isles Lupus Activity Group; SELENA, Safety of Estrogens in Lupus Erythematosus National Assessment; ECLAM, European Consensus of Lupus Activity Measurement; SDI, Systemic Lupus International Collaborating Clinics Damage Index; PGA, Physician Global Assessment; SLICC, Systemic Lupus International Collaborating Clinics; aPL, Anti-Phospholipid syndrome; HDL, High Density Lipoproteins; Hb, Haemoglobin; LFTs, liver function tests; VAS, visual analogue score; BMI, Body Mass Index; CV, Cardiovascular.

6.1. Vitamin D and SLE Disease Activity

Over the last decade, a considerable number of reports investigated the association between the serum concentration of vitamin D and the severity of the disease in lupus patients. Unfortunately, heterogeneous indexes have been used for assessing the disease activity (*e.g*. SLEDAI, SELENA-SLEDAI, BILAG, ECLAM) making somehow tricky the direct comparison between trials. Independently of the score used, a significant proportion of these observational studies showed the existence of an association between lower 25(OH)D3 serum concentration and higher disease activity [11, 42, 43, 45, 89, 103, 105, 108, 109, 121, 126, 128] [129, 131, 132, 135, 136]. However, this correlation was not confirmed in all the studies [10, 12, 44, 48, 90, 101, 106, 114, 118, 124, 130, 133]. The reasons beyond these discrepant results might be several; as mentioned, various indexes of disease activity have been used throughout the studies, as not a single standard measurement exists. Moreover, the different ethnicity of the subjects included could also play a substantial role. Despite the evidence of an association between vitamin D levels and disease activity, a direct causal relationship has not been found yet and cannot be driven as a conclusion from observational studies. On the one hand, in keeping with the effects of vitamin D/VDR on the immune system, deficit in vitamin D might represent a trigger for the development of autoimmunity and more aggressive disease. On the other hand, however, 25(OH)D3 concentration might be lowered secondary to the presence of systemic inflammation. Interestingly, even if a continuous high disease activity correlates with organ damage, most of the studies failed to show a correlation between low serum 25(OH)D3 and lupus-related organ damage [105]; in some circumstances, lower vitamin D levels have been associated with disease flares [42, 112, 122]. A more consistent consensus has been raised with regards to the negative correlation between vitamin D and ANA titres [11, 46, 88, 90, 100, 128, 129], in keeping with the *in vitro* ability of vitamin D of inhibiting B cells activation and autoantibodies production.

It is possible that some confounding factors could drive the link between low levels of 25(OH)D3 and severity/features of the disease. A meta-analysis published in 2014 analysed the results of 11 articles reporting a Pearson correlation coefficient between vitamin D levels and disease activity, more than 20 patients and at least one confounder factor for vitamin D serum concentration. Here the Authors showed that the most commonly identified confounding factors were renal function, proteinuria, BMI, and concurrent treatment including Disease Modifying Anti-Rheumatic Drugs (DMARDs), steroids and vitamin D supplementation [114]. Among the specific clinical manifestations lupus-related, nephritis [14, 42, 51, 108, 123] and CV involvement have been the more often associated with vitamin D deficiency (the correlation with CV manifestations will be discussed in details in the next paragraph).

6.2. Vitamin D and Cardiovascular Disease in Lupus Patients

With regards to CV disease, it is well accepted that patients affected by SLE have an increased CV risk, which especially manifests at an earlier age in comparison to the general population and translates into a higher mortality CV-related [138, 139]. The raised prevalence of CV events can be explained by the contribution of risk factors related to both the disease itself, such as chronic inflammation, and the disease treatment, including long-term use of steroids, both in association with traditional CV risk factors (*e.g*. smoking, hypertension, high low-density lipoprotein levels, obesity, impaired glucose metabolism) [140]. Accelerated atherosclerosis triggered by traditional and disease-related risk factors such as disease duration, raised homocysteine levels and pro-inflammatory cytokines [141], and the metabolic syndrome seem to be particularly important, the latter being present in almost half of lupus patients at the disease onset and being associated with the cumulative damage of organs and tissues [142, 143].

Since in the general population vitamin D deficiency has been described as a risk factor for the occurrence of CV disease [144 - 146], its association and role in the development of CV disease has also been assessed in the context of SLE. Once again, even if data in this field are somehow contradicting, there is substantial evidence that vitamin D deficiency associated with CV risk factors in lupus [42, 113, 116, 126, 134, 147, 148]. Some Authors have supported the direct correlation between low vitamin D levels and the age-adjusted total area of the carotid plaque in lupus patients [127]. This has not been confirmed in a different study [126], which, nonetheless, highlighted how vitamin D deficiency associated with increased aortic stiffness [126]. The relationship between low vitamin D and metabolic syndrome has been shown too [99]. Evidence from observational studies prompted interventional trials aiming at assessing the value of vitamin D supplementation for controlling/reducing CV risk factors. Results from the Women's Health Initiative (including 36282 post-menopausal women) did not support a role for vitamin D in modifying the CV risk in the general female population; however, the design of the study, which allowed a personal supplementation of vitamin D in the untreated arm might have constituted a fundamental confounding factor [149]. A metanalysis published by Chowdhury *et al.* in 2014 considering 73 observational studies and 22 randomised controlled trials concluded that a negative correlation between vitamin D levels and mortality rate (including for CV-related causes) exists in the general population and that the supplementation with 25(OH)D3 can decrease the overall mortality in adults (average age 56-85 years old) [150]. Thus, although in the absence of robust lines of evidence, vitamin D supplementation is encouraged in lupus patients [151] in keeping with the raised CV risk and related mortality.

6.3. Vitamin D and Fatigue Lupus-Related

Fatigue is one of the most common symptoms described by patients affected by SLE, being present in around 80% of all lupus patients and conferring disability in more than half of patients [152]. Vitamin D deficiency has been reported in several studies as a factor associated with fatigue in SLE, even when no other clinical correlations were found [48, 104, 133, 153]. Salman-Monte *et al.*, for instance, have recently shown that non-supplemented SLE female patients with insufficient vitamin D levels had significantly higher fatigue compared to subjects with normal vitamin D serum ranges [104]. Moreover, increased 25(OH)D3 levels secondary to supplementation seem to have a favourable influence on fatigue as suggested by the significant inverse correlation between changes in vitamin D levels and differences in the VAS fatigue score post-supplementation [133].

7. VITAMIN D SUPPLEMENTATION IN SLE: GOALS, REGIMENS AND THERAPEUTIC EFFECTS

At the time being, universally accepted guidelines about which categories of patients need to be tested for vitamin D deficiency have not been published yet, but recommendations come from diverse societies and organisations. For instance, the National Osteoporosis Society (NOS) suggested that only patients with bone or musculoskeletal symptoms should be tested [154] while the ES advised the measurement of vitamin D for patients affected by obesity, liver and chronic kidney disease and, more generally, subjects of Hispanic and African-American ancestry [30]. The controversy,

which was later discussed in two additional reports [155, 156], effectively exemplifies the difficulties in finding an international agreement in the field of vitamin D, already evident in the discrepancies of results reported in the observational studies listed above.

Similarly to the screening, no worldwide-accepted guidelines currently exist with regards to the supplementation of vitamin D (target levels and therapeutic regimes) in both the general population and in specific groups of patients, *e.g.* SLE. Cholecalciferol is the most common form of vitamin D used for supplementation in routine care [30]. The amount of vitamin D intake recommended hugely vary according to the different guidelines, from 600 IU/day (only dietary intake) advocated for the general population by the IOM [157] to 1500-2000 IU/day for subjects at high-risk as suggested by the ES [30]. The NOS proposed for patients with values < 30 nmol/l a loading dose of 300000 IU followed by a maintenance dose of 800-2000 IU/day [154]. Conversely, the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis recommended supplementation of 800 to 1000 IU/day for baseline 25(OH)D3 values below 50 nmol/L (20 ng/mL) [158]. A comprehensive metanalysis including 11 randomised trials of vitamin D supplementation concluded that treatment with ≥ 800 IU/day was helpful for preventing non-vertebral fractures in older adults [159], but there is no mention about any potential extra-skeletal effect of vitamin D.

Despite the favourable effects of vitamin D administration in murine models of autoimmunity, the efficacy of vitamin D supplementation as an immunomodulatory agent for treating lupus and other autoimmune diseases is currently under debate. A conventional therapeutic approach to SLE patients is missing; in routine care, the goal of the supplementation is the prevention of fractures and the protection of the bone, usually represented by values > 30-40 ng/ml [160]. The adjustment of the dose at individual levels should be made based on specific risk factors, in particular, the concurrent use of steroids in keeping with their known negative action on vitamin D absorption [33, 161, 162] [163]. A large inception study including 223 Spanish newly diagnosed SLE patients and assessing the nature of treatment during the first year of follow-up concluded that vitamin D supplementation was below the optimal dose required [164].

Multiple interventional trials have been performed, but further will be needed to clarify the potential therapeutic effects of vitamin D in SLE beyond the bone protection. To date, only conventional doses of vitamin D have been used in trials, aiming to correct the deficiency but not to achieve predefined serum levels. Vitamin D supplementation is advantageously very well tolerated and only rarely toxic, and complications associated to vitamin D toxicity (*e.g.* hypercalcemia, hypercalciuria, calcifications) start appearing when levels are > 80 ng/ml [160]. Though, it would be interesting to evaluate the effects of higher doses of vitamin D in patients with lupus, trying to reproduce and enhance the immuno-modulation observed *in vitro* and animal models. Here, we have listed and discussed the most relevant interventional trials of vitamin D supplementation in lupus patients.

7.1. Interventional Clinical Trials

A large double-blind randomised controlled trial published in 2013 by Abou-Raya *et al.* included 267 SLE Egyptian patients with SLEDAI >1 and serum vitamin D level < 75 nmol/L randomised to receive cholecalciferol 2000 IU/day or placebo in a 2:1 ratio. At the end of the study (12 months), the SLEDAI was improved in the treatment arm; moreover, compared to the placebo group, cholecalciferol-treated patients had lower anti-dsDNA and inflammatory cytokines serum levels [89]. In the same year, Petri *et al.* assessed the effects of vitamin D supplementation in 1006 SLE patients (Hopkins Lupus Cohort). Lupus patients with baseline 25(OH)D3 levels < 40 ng/mL (around 80% of the recruited subjects) received 50000 IU/week of ergocalciferol in combination with a total of 400 IU calcium/cholecalciferol daily. Patients who corrected the vitamin D deficiency had a modest but significant improvement of the disease activity measured with the SELENA version of SLEDAI. Moreover, an amelioration of the urine-protein-to-creatinine ratio was observed too [165]. Ruiz-Irastorza *et al.* assessed the relationship between vitamin D supplementation and changes in clinical variables in 60 patients with SLE treated as per routine care for vitamin D deficiency and recruited in a previous observational study. Despite increasing the concentration of serum vitamin D, a remarkable proportion of patients still had low levels post-supplementation. The advantageous effect of increasing vitamin D levels was observed in the VAS fatigue. However, no significant effects were found on lupus disease activity or organ damage [133]. Similar conclusions, i.e. the absence of modifications in disease activity (assessed by SLEDAI) following vitamin D treatment were drawn in an open-label study enrolling 20 lupus patients and treating them with 100000 IU/weekly for one month followed by 100000 IU/monthly for six months. On the other hand, anti-dsDNA titres, memory B cells number, and the percentage of Th1/Th17 decreased while Treg increased. At the end of the trial, patients had reached significantly higher levels of vitamin D compared to baseline [85]. In 2015, Aranow *et al.* reported the results of a double-blind

randomised controlled trial evaluating the effects of vitamin D supplementation on the IFN signature response in SLE patients. 57 lupus patients with baseline vitamin D < 20 ng/ml and stable inactive disease were enrolled. Patients were required to have the presence of an IFN signature at baseline; this was quantified by gene expression of 3 IFN-related genes. Patients were randomised in 3 groups to receive 4000 IU/day of cholecalciferol, 2000 IU/day cholecalciferol and placebo for 12 weeks. At the end of the study, 16/33 patients receiving active treatment replenished vitamin D serum level, but no significant IFN-signature response was observed even in patients who achieved adequate vitamin D concentrations. The absence of IFN response might be explained by the relatively short time of the study and by the disease status at baseline (inactive) [91]. In another recent randomised trial, 34 female lupus patients received two different regimens of vitamin D supplementation for a total of 2 years. Patients were supplemented with one of the two schemes for 12 months and afterwards switched to the second therapeutic strategy. One scheme, standard, consisted of cholecalciferol 25000 IU/month; the other, more intensive, of 300000 IU initial loading followed by 50000 IU/month. Overall, the study failed to find clinical efficacy (disease activity and serology) of vitamin D supplementation in lupus patients independently of the regimen. It showed, however, favourable immunological variations such as enrichment of the Treg and increased release of Th2 cytokines. Remarkably, only the most intensive regimen allowed the achievement of adequate levels of vitamin D [86, 166]. The superiority of a high loading dose of cholecalciferol in correcting vitamin D deficiency has been previously observed [167]. In another randomised placebo-controlled study, 45 Vitamin D-deficient lupus patients were enrolled and received vitamin D (50.000 UI/week for 12 weeks followed by 50000 UI/month for three months); additional 45 patients were randomised to receive placebo. Even if the level of vitamin D significantly increased after the supplementation (but not in the placebo group), there was no difference in the SLEDAI between the two groups [168].

Lima *et al.* instead confirmed similar results as published by Abou-Raya *et al.* and Petri *et al.* in young adults affected by juvenile SLE. 40 patients were enrolled in a placebo-controlled trial and randomised 1:1 to receive cholecalciferol 50000 IU/week or placebo for 24 weeks. Vitamin D supplementation significantly improved the disease-related fatigue; moreover, a significant difference in SLEDAI and ECLAM was reported in favour of the treated group [169]. The beneficial effects of vitamin D on juvenile-onset SLE patients have also been established in the study of AlSaleem *et al.* in which 28 children (24 with low vitamin D levels) with lupus were recruited and received cholecalciferol 2000 IU/daily. After 12 weeks, a significant proportion of patients had improvement in SLEDAI score and autoantibodies titres [170].

The influence of vitamin D supplementation on the endothelial function, known to be impaired in patients with SLE [171], was evaluated in a pilot case-control study recently published by Kamen *et al.* Lupus patients vitamin D-deficient were randomised to receive oral vitamin D supplementation or placebo. In the absence of replenishment of the vitamin D levels (not reaching ≥32 ng/mL), the Flow-Mediated-Dilation (FMD), which is an indirect measure of the endothelial function, did not improve. Contrariwise, around 50% of the patients who increased vitamin D concentration had better values of FMD by the end of the trial [172]. Furthermore, in vitamin D-deficient patients treated with oral supplementation, a positive correlation between the improvement of the FMD values and the change in the vitamin levels post-treatment was proved [173]. Overall, these positive results call further larger studies assessing this aspect in lupus patients.

The potential favourable action of vitamin D supplementation on the endothelial function is not disease-specific; in fact, a single high dose of oral vitamin D was able to significantly improve FMD values in patients affected by type 2 diabetes mellitus in comparison with healthy controls [174]. *Ex vivo* studies corroborated the possible vitamin D ability of positively enhancing the endothelial repair mechanisms and the global endothelial function [173, 175], for example by reducing the NETosis [79]. Studies in experimental models of SLE (MRL/lpr) also showed that lower levels of vitamin D correlated with impaired endothelium-dependent vasodilation and defective neoangiogenesis in agreement with the human findings [176].

7.2. Conclusive Remarks on Interventional Trials

Overall, drawing definitive conclusions from the interventional studies discussed above is still not feasible because of the controversies of the results. Several reasons can explain the disagreement between findings: the limited number of patients included in some trials; a still relatively low number of double-blind randomised controlled trials; the heterogeneous features of patients enrolled (*e.g.*, different baseline vitamin D levels, various disease activity, concomitant treatment); and a non-univocal treatment regimen (dose/duration/final goal).

The central open question remains whether or not vitamin D might constitute a valuable therapeutic approach in modulating the immune response and the clinical/serological manifestations of lupus, potentially acting as sparing agent for other more harmful medications currently in use. Numerous revisions of the literature have been lately published, but rarely the Authors reached an incontrovertible consensus towards one or other conclusions [33, 40]. It is plausible that the lack of clinical effects vitamin D-related in some studies lies in an inadequate therapeutic approach regarding the dose, the duration and the patients' selection. Since it has been observed that patients with autoimmune diseases have persistently raised values of PTH, it is likely though that the goal of the supplementation should be the PTH suppression and not a "target" vitamin D plasmatic concentration [177]. The increasing interest for the therapeutic utility of vitamin D supplementation in the prevention and management of pathologic conditions is not limited to lupus but also involves other major chronic diseases, both autoimmune and not (type 1 diabetes, multiple sclerosis, and CV disorders) [178]. In conclusion, the promising results reported in some studies [89, 165] need to be confirmed, and further large clinical trials are therefore warranted in this field.

CONCLUSIONS AND TAKE HOME MESSAGES

1. Patients with SLE are more prone to be vitamin D deficient compared to the general population; however, vitamin D deficiency is common also in healthy individuals.
2. Potential determinants of vitamin D deficiency in SLE include reduced UV exposure, genetic variations, corticosteroid treatment, and renal disease.
3. Current knowledge is not conclusive with regards to the role of vitamin D deficiency in the development of autoimmunity and, specifically, SLE. Increased risk of SLE associates with polymorphisms of the VDR; higher incidence of vitamin D deficiency in ANA-positive non-lupus subjects and siblings of lupus patients (high-risk subjects) are in favour a causal relationship, but this has not been confirmed yet.
4. Immune cells express VDRs ubiquitously. Overall, vitamin D up-regulates anti-inflammatory responses, a shift towards Treg and Th2, reduced B cells activation and Ig production (including anti-dsDNA), and enhanced tolerogenicity of dendritic cells. In experimental models of lupus, vitamin D supplementation can improve the disease.
5. Numerous observational studies have investigated the correlation between vitamin D levels and clinical/serological manifestations of lupus with contrasting results. A negative relationship between vitamin D levels and disease activity, renal disease, CV risk factors and complications, fatigue, and anti-dsDNA titres have been described but not conclusively accepted.
6. Several interventional studies have tried to define the therapeutic value of vitamin D supplementation on disease activity, renal function, CV risk, fatigue, immunological profiles, and IFN-signature, however, once again, drawing controversial conclusions. Further large clinical trials with well-defined therapeutic protocols and goals are warranted to shed light on this topic.

LIST OF ABBREVIATIONS

ANA	=	Anti-Nuclear Antibodies
aPL	=	Anti-Phospholipid syndrome
BILAG	=	British Isles Lupus Activity Group
BMD	=	Bone Mineral Density
BMI	=	Body Mass Index
CTD	=	Connective Tissue Disease
CV	=	Cardiovascular
CYP	=	Cytochrome p450
DCs	=	Dendritic Cells
DMARDs	=	Disease Modifying Anti-Rheumatic Drugs
ds	=	Double-strand
ECLAM	=	European Consensus of Lupus Activity Measurement
ES	=	Endocrine Society
FGF	=	Fibroblast-Growth-Factor

FMD	=	Flow-Mediated-Dilation
Hb	=	Haemoglobin
HDL	=	High Density Lipoproteins
IC	=	Immune Complex
IFN	=	Interferon
Ig	=	Immunoglobulin
IL	=	Interleukin
IOM	=	Institute of Medicine
LFTs	=	Liver Function Tests
NET	=	Neutrophils-Extracellular-Traps
NK	=	Natural Killer
NOS	=	National Osteoporosis Society
PGA	=	Physician Global Assessment
PTH	=	Parathyroid Hormone
RA	=	Rheumatoid Arthritis
SDI	=	Systemic Lupus International Collaborating Clinics Damage Index
SELENA	=	Safety of Estrogens in Lupus Erythematosus National Assessment
SLE	=	Systemic lupus erythematosus
SLEDAI	=	Systemic Lupus Erythematosus Disease Activity Index
SLICC	=	Systemic Lupus International Collaborating Clinics
SNPs	=	Single Nucleotide Polymorphisms
TCR	=	T-Cell Receptor
Th	=	T Helper
TNF	=	Tumor Necrosis Factor
TLR	=	Toll-Like-Receptors
Treg	=	T regulatory
UV	=	Ultraviolet
VAS	=	Visual Analogue Score
VDRs	=	Vitamin D Receptors
VDREs	=	Vitamin D Response Elements
WHO	=	World Health Organization

CONSENT FOR PUBLICATION

Not applicable

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Lim SS, Drenkard C. Epidemiology of lupus: An update. Curr Opin Rheumatol 2015; 27(5): 427-32. [http://dx.doi.org/10.1097/BOR.0000000000000198] [PMID: 26196375]

[2] Klippel JH. Systemic lupus erythematosus: Demographics, prognosis, and outcome. J Rheumatol Suppl 1997; 48: 67-71. [PMID: 9150122]

[3] Podolska MJ, Biermann MH, Maueröder C, Hahn J, Herrmann M. Inflammatory etiopathogenesis of systemic lupus erythematosus: An update. J Inflamm Res 2015; 8: 161-71. [PMID: 26316795]

[4] Guimarães PM, Scavuzzi BM, Stadtlober NP, *et al.* Cytokines in systemic lupus erythematosus: far beyond Th1/Th2 dualism lupus: Cytokine

profiles. Immunol Cell Biol 2017; 95(9): 824-31.
[http://dx.doi.org/10.1038/icb.2017.53] [PMID: 28649995]

[5] Tsokos GC, Lo MS, Costa Reis P, Sullivan KE. New insights into the immunopathogenesis of systemic lupus erythematosus. Nat Rev Rheumatol 2016; 12(12): 716-30.
[http://dx.doi.org/10.1038/nrrheum.2016.186] [PMID: 27872476]

[6] Arnson Y, Amital H, Shoenfeld Y. Vitamin D and autoimmunity: New aetiological and therapeutic considerations. Ann Rheum Dis 2007; 66(9): 1137-42.
[http://dx.doi.org/10.1136/ard.2007.069831] [PMID: 17557889]

[7] Cutolo M. Further emergent evidence for the vitamin D endocrine system involvement in autoimmune rheumatic disease risk and prognosis. Ann Rheum Dis 2013; 72(4): 473-5.
[http://dx.doi.org/10.1136/annrheumdis-2012-202538] [PMID: 23440106]

[8] Agmon-Levin N, Theodor E, Segal RM, Shoenfeld Y. Vitamin D in systemic and organ-specific autoimmune diseases. Clin Rev Allergy Immunol 2013; 45(2): 256-66.
[http://dx.doi.org/10.1007/s12016-012-8342-y] [PMID: 23238772]

[9] Müller K, Kriegbaum NJ, Baslund B, Sørensen OH, Thymann M, Bentzen K. Vitamin D3 metabolism in patients with rheumatic diseases: Low serum levels of 25-hydroxyvitamin D3 in patients with systemic lupus erythematosus. Clin Rheumatol 1995; 14(4): 397-400.
[http://dx.doi.org/10.1007/BF02207671] [PMID: 7586974]

[10] Toloza SMA, Cole DEC, Gladman DD, Ibañez D, Urowitz MB. Vitamin D insufficiency in a large female SLE cohort. Lupus 2010; 19(1): 13-9.
[http://dx.doi.org/10.1177/0961203309345775] [PMID: 19897520]

[11] Mandal M, Tripathy R, Panda AK, *et al.* Vitamin D levels in Indian systemic lupus erythematosus patients: Association with disease activity index and interferon alpha. Arthritis Res Ther 2014; 16(1): R49.
[http://dx.doi.org/10.1186/ar4479] [PMID: 24507879]

[12] Orbach H, Zandman-Goddard G, Amital H, *et al.* Novel biomarkers in autoimmune diseases: Prolactin, ferritin, vitamin D, and TPA levels in autoimmune diseases. Ann N Y Acad Sci 2007; 1109(1): 385-400.
[http://dx.doi.org/10.1196/annals.1398.044] [PMID: 17785327]

[13] Kamen DL, Aranow C. The link between vitamin D deficiency and systemic lupus erythematosus. Curr Rheumatol Rep 2008; 10(4): 273-80.
[http://dx.doi.org/10.1007/s11926-008-0044-3] [PMID: 18662506]

[14] Kamen DL, Cooper GS, Bouali H, Shaftman SR, Hollis BW, Gilkeson GS. Vitamin D deficiency in systemic lupus erythematosus. Autoimmun Rev 2006; 5(2): 114-7.
[http://dx.doi.org/10.1016/j.autrev.2005.05.009] [PMID: 16431339]

[15] Cutolo M. Vitamin D or hormone D deficiency in autoimmune rheumatic diseases, including undifferentiated connective tissue disease. Arthritis Res Ther 2008; 10(6): 123.
[http://dx.doi.org/10.1186/ar2552] [PMID: 19090978]

[16] Pelajo CF, Lopez-Benitez JM, Miller LC. Vitamin D and autoimmune rheumatologic disorders. Autoimmun Rev 2010; 9(7): 507-10.
[http://dx.doi.org/10.1016/j.autrev.2010.02.011] [PMID: 20146942]

[17] Holick MF. Vitamin D deficiency. N Engl J Med 2007; 357(3): 266-81.
[http://dx.doi.org/10.1056/NEJMra070553] [PMID: 17634462]

[18] Christakos S, Ajibade D V, Dhawan P, Fechner A J, Mady L J. Vitamin D: Metabolism. Endocrinol Metab Clin North Am 2010; 39(2): 243-53.
[http://dx.doi.org/10.1016/j.ecl.2010.02.002]

[19] DeLuca HF. Overview of general physiologic features and functions of vitamin D. Am J Clin Nutr 2004; 80(6)(Suppl.): 1689S-96S.
[http://dx.doi.org/10.1093/ajcn/80.6.1689S] [PMID: 15585789]

[20] Liu S, Tang W, Zhou J, *et al.* Fibroblast growth factor 23 is a counter-regulatory phosphaturic hormone for vitamin D. J Am Soc Nephrol 2006; 17(5): 1305-15.
[http://dx.doi.org/10.1681/ASN.2005111185] [PMID: 16597685]

[21] Carmeliet G, Dermauw V, Bouillon R. Vitamin D signaling in calcium and bone homeostasis: A delicate balance. Best Pract Res Clin Endocrinol Metab 2015; 29(4): 621-31.
[http://dx.doi.org/10.1016/j.beem.2015.06.001] [PMID: 26303088]

[22] Bellan M, Pirisi M, Sainaghi PP. Osteoporosis in Rheumatoid Arthritis: Role of the vitamin D/parathyroid hormone system. Rev Bras Reumatol 2015; 55(3): 256-63.
[http://dx.doi.org/10.1016/j.rbr.2014.10.007] [PMID: 25582993]

[23] Pike J W, Meyer M B. The vitamin D receptor: new paradigms for the regulation of gene expression by 1,25-dihydroxyvitamin D(3). Endocrinol Metab Clin North Am 2010; 39(2): 255-69.

[24] Klein RG, Arnaud SB, Gallagher JC, Deluca HF, Riggs BL. Intestinal calcium absorption in exogenous hypercortisonism. Role of 25-hydroxyvitamin D and corticosteroid dose. J Clin Invest 1977; 60(1): 253-9.
[http://dx.doi.org/10.1172/JCI108762] [PMID: 874087]

[25] Hewison M. Vitamin D and innate and adaptive immunity. Vitam Horm 2011; 86: 23-62.
[http://dx.doi.org/10.1016/B978-0-12-386960-9.00002-2] [PMID: 21419266]

[26] Jones G. Pharmacokinetics of vitamin D toxicity. Am J Clin Nutr 2008; 88(2): 582S-6S.
[http://dx.doi.org/10.1093/ajcn/88.2.582S] [PMID: 18689406]

[27] Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium, A. C. Ross, C. L. Taylor, A. L. Yaktine, and H. B. Del Valle, "Dietary Reference Intakes for Calcium and Vitamin D," 2011.

[28] Fuleihan Gel-H, Bouillon R, Clarke B, *et al.* Serum 25-Hydroxyvitamin D Levels: Variability, knowledge gaps, and the concept of a desirable range. J Bone Miner Res 2015; 30(7): 1119-33.
[http://dx.doi.org/10.1002/jbmr.2536] [PMID: 25952470]

[29] Binkley N, Sempos CT, Vitamin D. Standardizing vitamin D assays: The way forward. J Bone Miner Res 2014; 29(8): 1709-14.
[http://dx.doi.org/10.1002/jbmr.2252] [PMID: 24737265]

[30] Holick M F, Binkley N C, Bischoff-Ferrari H A, *et al.* Weaver, Endocrine Society, Evaluation, treatment, and prevention of vitamin D deficiency: An Endocrine Society clinical practice guideline. J cli endo and meta 96(7): 1911-30.

[31] Ross AC, Manson JE, Abrams SA, *et al.* The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: What clinicians need to know. J Clin Endocrinol Metab 2011; 96(1): 53-8.
[http://dx.doi.org/10.1210/jc.2010-2704] [PMID: 21118827]

[32] Dawson-Hughes B, Heaney RP, Holick MF, Lips P, Meunier PJ, Vieth R. Estimates of optimal vitamin D status. Osteoporos Int 2005; 16(7): 713-6.
[http://dx.doi.org/10.1007/s00198-005-1867-7] [PMID: 15776217]

[33] Schneider L, Dos Santos ASP, Santos M, da Silva Chakr RM, Monticielo OA. Vitamin D and systemic lupus erythematosus: State of the art. Clin Rheumatol 2014; 33(8): 1033-8.
[PMID: 24573738]

[34] Nesby-O'Dell S, Scanlon KS, Cogswell ME, *et al.* Hypovitaminosis D prevalence and determinants among African American and white women of reproductive age: Third National Health and Nutrition Examination Survey, 1988-1994. Am J Clin Nutr 2002; 76(1): 187-92.
[http://dx.doi.org/10.1093/ajcn/76.1.187] [PMID: 12081833]

[35] Bellan M, Guzzaloni G, Rinaldi M, *et al.* Altered glucose metabolism rather than naive Type 2 Diabetes Mellitus (T2DM) is related to vitamin D status in severe obesity. Cardiovasc Diabetol 2014; 13(1): 57.
[http://dx.doi.org/10.1186/1475-2840-13-57] [PMID: 24618074]

[36] Duan S, Lv Z, Fan X, *et al.* Vitamin D status and the risk of multiple sclerosis: A systematic review and meta-analysis. Neurosci Lett 2014; 570: 108-13.
[http://dx.doi.org/10.1016/j.neulet.2014.04.021] [PMID: 24769422]

[37] Lin J, Liu J, Davies ML, Chen W. Serum vitamin D level and rheumatoid arthritis disease activity: Review and meta-analysis. PLoS One 2016; 11(1): e0146351.
[http://dx.doi.org/10.1371/journal.pone.0146351] [PMID: 26751969]

[38] Sadeghian M, Saneei P, Siassi F, Esmaillzadeh A. Vitamin D status in relation to Crohn's disease: Meta-analysis of observational studies. Nutrition 2016; 32(5): 505-14.
[http://dx.doi.org/10.1016/j.nut.2015.11.008] [PMID: 26837598]

[39] Holick MF. Vitamin D: Important for prevention of osteoporosis, cardiovascular heart disease, type 1 diabetes, autoimmune diseases, and some cancers. South Med J 2005; 98(10): 1024-7.
[http://dx.doi.org/10.1097/01.SMJ.0000140865.32054.DB] [PMID: 16295817]

[40] Reynolds JA, Bruce IN. Vitamin D treatment for connective tissue diseases: hope beyond the hype? Rheumatology (Oxford) 2017; 56(2): 178-86.
[http://dx.doi.org/10.1093/rheumatology/kew212] [PMID: 27179106]

[41] Stockton KA, Kandiah DA, Paratz JD, Bennell KL. Fatigue, muscle strength and vitamin D status in women with systemic lupus erythematosus compared with healthy controls. Lupus 2012; 21(3): 271-8.
[http://dx.doi.org/10.1177/0961203311425530] [PMID: 22004972]

[42] Sumethkul K, Boonyaratavej S, Kitumnuaypong T, *et al.* The predictive factors of low serum 25-hydroxyvitamin D and vitamin D deficiency in patients with systemic lupus erythematosus. Rheumatol Int 2013; 33(6): 1461-7.
[http://dx.doi.org/10.1007/s00296-012-2537-7] [PMID: 23179257]

[43] Mok CC, Birmingham DJ, Leung HW, Hebert LA, Song H, Rovin BH. Vitamin D levels in Chinese patients with systemic lupus erythematosus: relationship with disease activity, vascular risk factors and atherosclerosis. Rheumatology (Oxford) 2012; 51(4): 644-52.
[http://dx.doi.org/10.1093/rheumatology/ker212] [PMID: 21719424]

[44] Souto M, Coelho A, Guo C, *et al.* Vitamin D insufficiency in Brazilian patients with SLE: Prevalence, associated factors, and relationship with activity. Lupus 2011; 20(10): 1019-26.
[http://dx.doi.org/10.1177/0961203311401457] [PMID: 21646315]

[45] Hamza RT, Awwad KS, Ali MK, Hamed AI. Reduced serum concentrations of 25-hydroxy vitamin D in Egyptian patients with systemic lupus erythematosus: Relation to disease activity. Med Sci Monit 2011; 17(12): CR711-8.

[http://dx.doi.org/10.12659/MSM.882131] [PMID: 22129903]

[46] Mok CC, Birmingham DJ, Ho LY, Hebert LA, Song H, Rovin BH. Vitamin D deficiency as marker for disease activity and damage in systemic lupus erythematosus: A comparison with anti-dsDNA and anti-C1q. Lupus 2012; 21(1): 36-42.
[http://dx.doi.org/10.1177/0961203311422094] [PMID: 21993384]

[47] Sainaghi PP, Bellan M, Carda S, *et al.* Hypovitaminosis D and response to cholecalciferol supplementation in patients with autoimmune and non-autoimmune rheumatic diseases. Rheumatol Int 2012; 32(11): 3365-72.
[http://dx.doi.org/10.1007/s00296-011-2170-x] [PMID: 22045518]

[48] Ruiz-Irastorza G, Egurbide MV, Olivares N, Martinez-Berriotxoa A, Aguirre C. Vitamin D deficiency in systemic lupus erythematosus: Prevalence, predictors and clinical consequences. Rheumatology (Oxford) 2008; 47(6): 920-3.
[http://dx.doi.org/10.1093/rheumatology/ken121] [PMID: 18411213]

[49] Shoenfeld Y, Giacomelli R, Azrielant S, Berardicurti O, Reynolds JA, Bruce IN. Vitamin D and systemic lupus erythematosus - The hype and the hope. Autoimmun Rev 2017.
[PMID: 29108830]

[50] Young KA, Munroe ME, Guthridge JM, *et al.* Combined role of vitamin D status and CYP24A1 in the transition to systemic lupus erythematosus. Ann Rheum Dis 2017; 76(1): 153-8.
[http://dx.doi.org/10.1136/annrheumdis-2016-209157] [PMID: 27283331]

[51] Chaiamnuay S, Chailurkit L-O, Narongroeknawin P, Asavatanabodee P, Laohajaroensombat S, Chaiamnuay P. Current daily glucocorticoid use and serum creatinine levels are associated with lower 25(OH) vitamin D levels in Thai patients with systemic lupus erythematosus. J Clin Rheumatol 2013; 19(3): 121-5.
[http://dx.doi.org/10.1097/RHU.0b013e318289bd16] [PMID: 23519176]

[52] Kamen DL. Vitamin D in lupus - new kid on the block? Bull NYU Hosp Jt Dis 2010; 68(3): 218-22.
[PMID: 20969555]

[53] Akeno N, Matsunuma A, Maeda T, Kawane T, Horiuchi N. Regulation of vitamin D-1alpha-hydroxylase and -24-hydroxylase expression by dexamethasone in mouse kidney. J Endocrinol 2000; 164(3): 339-48.
[http://dx.doi.org/10.1677/joe.0.1640339] [PMID: 10694374]

[54] Wang TJ, Zhang F, Richards JB, *et al.* Common genetic determinants of vitamin D insufficiency: A genome-wide association study. Lancet 2010; 376(9736): 180-8.
[http://dx.doi.org/10.1016/S0140-6736(10)60588-0] [PMID: 20541252]

[55] Silva MC, Furlanetto TW. Does serum 25-hydroxyvitamin D decrease during acute-phase response? A systematic review. Nutr Res 2015; 35(2): 91-6.
[http://dx.doi.org/10.1016/j.nutres.2014.12.008] [PMID: 25631715]

[56] Bhalla AK, Amento EP, Clemens TL, Holick MF, Krane SM. Specific high-affinity receptors for 1,25-dihydroxyvitamin D3 in human peripheral blood mononuclear cells: Presence in monocytes and induction in T lymphocytes following activation. J Clin Endocrinol Metab 1983; 57(6): 1308-10.
[http://dx.doi.org/10.1210/jcem-57-6-1308] [PMID: 6313738]

[57] Provvedini DM, Tsoukas CD, Deftos LJ, Manolagas SC. 1,25-dihydroxyvitamin D3 receptors in human leukocytes. Science 1983; 221(4616): 1181-3.
[http://dx.doi.org/10.1126/science.6310748] [PMID: 6310748]

[58] Brennan A, Katz DR, Nunn JD, *et al.* Dendritic cells from human tissues express receptors for the immunoregulatory vitamin D3 metabolite, dihydroxycholecalciferol. Immunology 1987; 61(4): 457-61.
[PMID: 2832307]

[59] Lemire JM, Adams JS, Sakai R, Jordan SC. 1 alpha,25-dihydroxyvitamin D3 suppresses proliferation and immunoglobulin production by normal human peripheral blood mononuclear cells. J Clin Invest 1984; 74(2): 657-61.
[http://dx.doi.org/10.1172/JCI111465] [PMID: 6611355]

[60] Linker-Israeli M, Elstner E, Klinenberg JR, Wallace DJ, Koeffler HP. Vitamin D(3) and its synthetic analogs inhibit the spontaneous *in vitro* immunoglobulin production by SLE-derived PBMC. Clin Immunol 2001; 99(1): 82-93.
[http://dx.doi.org/10.1006/clim.2000.4998] [PMID: 11286544]

[61] Chen S, Sims GP, Chen XX, Gu YY, Chen S, Lipsky PE. Modulatory effects of 1,25-dihydroxyvitamin D3 on human B cell differentiation. J Immunol 2007; 179(3): 1634-47.
[http://dx.doi.org/10.4049/jimmunol.179.3.1634] [PMID: 17641030]

[62] Geldmeyer-Hilt K, Heine G, Hartmann B, Baumgrass R, Radbruch A, Worm M. 1,25-dihydroxyvitamin D3 impairs NF-κB activation in human naïve B cells. Biochem Biophys Res Commun 2011; 407(4): 699-702.
[http://dx.doi.org/10.1016/j.bbrc.2011.03.078] [PMID: 21420936]

[63] von Essen MR, Kongsbak M, Schjerling P, Olgaard K, Odum N, Geisler C. Vitamin D controls T cell antigen receptor signaling and activation of human T cells. Nat Immunol 2010; 11(4): 344-9.
[http://dx.doi.org/10.1038/ni.1851] [PMID: 20208539]

[64] Wahono CS, Rusmini H, Soelistyoningsih D, *et al.* Effects of 1,25(OH)2D3 in immune response regulation of systemic lupus erithematosus (SLE) patient with hypovitamin D. Int J Clin Exp Med 2014; 7(1): 22-31.

[PMID: 24482685]

[65] Dankers W, Colin EM, van Hamburg JP, Lubberts E. Vitamin D in autoimmunity: Molecular mechanisms and therapeutic potential. Front Immunol 2017; 7(4): 697.
[PMID: 28163705]

[66] Banica LM, Besliu AN, Pistol GC, *et al.* Dysregulation of anergy-related factors involved in regulatory T cells defects in Systemic Lupus Erythematosus patients: Rapamycin and Vitamin D efficacy in restoring regulatory T cells. Int J Rheum Dis 2016; 19(12): 1294-303.
[http://dx.doi.org/10.1111/1756-185X.12509] [PMID: 25351606]

[67] Hewison M, Freeman L, Hughes SV, *et al.* Differential regulation of vitamin D receptor and its ligand in human monocyte-derived dendritic cells. J Immunol 2003; 170(11): 5382-90.
[http://dx.doi.org/10.4049/jimmunol.170.11.5382] [PMID: 12759412]

[68] Lerman M, Burnham J, Behrens E. 1,25 dihydroxyvitamin D3 limits monocyte maturation in lupus sera. Lupus 2011; 20(7): 749-53.
[http://dx.doi.org/10.1177/0961203310394542] [PMID: 21447602]

[69] Penna G, Adorini L. 1 Alpha,25-dihydroxyvitamin D3 inhibits differentiation, maturation, activation, and survival of dendritic cells leading to impaired alloreactive T cell activation. J Immunol 2000; 164(5): 2405-11.
[http://dx.doi.org/10.4049/jimmunol.164.5.2405] [PMID: 10679076]

[70] Dickie LJ, Church LD, Coulthard LR, Mathews RJ, Emery P, McDermott MF. Vitamin D3 down-regulates intracellular Toll-like receptor 9 expression and Toll-like receptor 9-induced IL-6 production in human monocytes. Rheumatology (Oxford) 2010; 49(8): 1466-71.
[http://dx.doi.org/10.1093/rheumatology/keq124] [PMID: 20435648]

[71] Zhang X, Zhou M, Guo Y, Song Z, Liu B. 1,25-Dihydroxyvitamin D_3 Promotes High Glucose-Induced M1 Macrophage Switching to M2 via the VDR-PPARγ Signaling Pathway. BioMed Res Int 2015; 2015(9): 157834-4.
[PMID: 25961000]

[72] Neve A, Corrado A, Cantatore FP. Immunomodulatory effects of vitamin D in peripheral blood monocyte-derived macrophages from patients with rheumatoid arthritis. Clin Exp Med 2014; 14(3): 275-83.
[http://dx.doi.org/10.1007/s10238-013-0249-2] [PMID: 23824148]

[73] Korf H, Wenes M, Stijlemans B, *et al.* 1,25-Dihydroxyvitamin D3 curtails the inflammatory and T cell stimulatory capacity of macrophages through an IL-10-dependent mechanism. Immunobiology 2012; 217(12): 1292-300.
[http://dx.doi.org/10.1016/j.imbio.2012.07.018] [PMID: 22944250]

[74] Piemonti L, Monti P, Sironi M, *et al.* Vitamin D3 affects differentiation, maturation, and function of human monocyte-derived dendritic cells. J Immunol 2000; 164(9): 4443-51.
[http://dx.doi.org/10.4049/jimmunol.164.9.4443] [PMID: 10779743]

[75] Jeffery LE, Wood AM, Qureshi OS, *et al.* Availability of 25-hydroxyvitamin D(3) to APCs controls the balance between regulatory and inflammatory T cell responses. J Immunol 2012; 189(11): 5155-64.
[http://dx.doi.org/10.4049/jimmunol.1200786] [PMID: 23087405]

[76] Sochorová K, Budinský V, Rozková D, *et al.* Paricalcitol (19-nor-1,25-dihydroxyvitamin D2) and calcitriol (1,25-dihydroxyvitamin D3) exert potent immunomodulatory effects on dendritic cells and inhibit induction of antigen-specific T cells. Clin Immunol 2009; 133(1): 69-77.
[http://dx.doi.org/10.1016/j.clim.2009.06.011] [PMID: 19660988]

[77] Wu HJ, Lo Y, Luk D, Lau CS, Lu L, Mok MY. Alternatively activated dendritic cells derived from systemic lupus erythematosus patients have tolerogenic phenotype and function. Clin Immunol 2015; 156(1): 43-57.
[http://dx.doi.org/10.1016/j.clim.2014.10.011] [PMID: 25463431]

[78] Takahashi K, Nakayama Y, Horiuchi H, *et al.* Human neutrophils express messenger RNA of vitamin D receptor and respond to 1alpha,25-dihydroxyvitamin D3. Immunopharmacol Immunotoxicol 2002; 24(3): 335-47.
[http://dx.doi.org/10.1081/IPH-120014721] [PMID: 12375732]

[79] Handono K, Sidarta YO, Pradana BA, *et al.* Vitamin D prevents endothelial damage induced by increased neutrophil extracellular traps formation in patients with systemic lupus erythematosus. Acta Med Indones 2014; 46(3): 189-98.
[PMID: 25348181]

[80] Lavi Arab F, Rastin M, Faraji F, *et al.* Assessment of 1,25-dihydroxyvitamin D3 effects on Treg cells in a mouse model of systemic lupus erythematosus. Immunopharmacol Immunotoxicol 2015; 37(1): 12-8.
[http://dx.doi.org/10.3109/08923973.2014.968255] [PMID: 25318538]

[81] Faraji F, Rastin M, Arab FL, *et al.* Effects of 1,25-dihydroxyvitamin D3 on IL-17/IL-23 axis, IFN-γ and IL-4 expression in systemic lupus erythematosus induced mice model. Iran J Basic Med Sci 2016; 19(4): 374-80.
[PMID: 27279980]

[82] Lemire JM, Ince A, Takashima M. 1,25-Dihydroxyvitamin D3 attenuates the expression of experimental murine lupus of MRL/l mice. Autoimmunity 1992; 12(2): 143-8.
[http://dx.doi.org/10.3109/08916939209150321] [PMID: 1617111]

[83] Prietl B, Treiber G, Mader JK, *et al.* High-dose cholecalciferol supplementation significantly increases peripheral $CD4^+$ Tregs in healthy adults without negatively affecting the frequency of other immune cells. Eur J Nutr 2014; 53(3): 751-9.
[http://dx.doi.org/10.1007/s00394-013-0579-6] [PMID: 23999998]

[84] Ojaimi S, Skinner NA, Strauss BJ, Sundararajan V, Woolley I, Visvanathan K. Vitamin D deficiency impacts on expression of toll-like receptor-2 and cytokine profile: A pilot study. J Transl Med 2013; 11(1): 176.
[http://dx.doi.org/10.1186/1479-5876-11-176] [PMID: 23875738]

[85] Terrier B, Derian N, Schoindre Y, *et al.* Restoration of regulatory and effector T cell balance and B cell homeostasis in systemic lupus erythematosus patients through vitamin D supplementation. Arthritis Res Ther 2012; 14(5): R221.
[http://dx.doi.org/10.1186/ar4060] [PMID: 23075451]

[86] Piantoni S, Andreoli L, Scarsi M, *et al.* Phenotype modifications of T-cells and their shift toward a Th2 response in patients with systemic lupus erythematosus supplemented with different monthly regimens of vitamin D. Lupus 2015; 24(4-5): 490-8.
[http://dx.doi.org/10.1177/0961203314559090] [PMID: 25801892]

[87] Boonstra A, Barrat FJ, Crain C, Heath VL, Savelkoul HF, O'Garra A. 1alpha,25-Dihydroxyvitamin d3 has a direct effect on naive CD4(+) T cells to enhance the development of Th2 cells. J Immunol 2001; 167(9): 4974-80.
[http://dx.doi.org/10.4049/jimmunol.167.9.4974] [PMID: 11673504]

[88] Ritterhouse LL, Crowe SR, Niewold TB, *et al.* Vitamin D deficiency is associated with an increased autoimmune response in healthy individuals and in patients with systemic lupus erythematosus. Ann Rheum Dis 2011; 70(9): 1569-74.
[http://dx.doi.org/10.1136/ard.2010.148494] [PMID: 21586442]

[89] Abou-Raya A, Abou-Raya S, Helmii M. The effect of vitamin D supplementation on inflammatory and hemostatic markers and disease activity in patients with systemic lupus erythematosus: A randomized placebo-controlled trial. J Rheumatol 2013; 40(3): 265-72.
[http://dx.doi.org/10.3899/jrheum.111594] [PMID: 23204220]

[90] Attar SM, Siddiqui AM. Vitamin d deficiency in patients with systemic lupus erythematosus. Oman Med J 2013; 28(1): 42-7.
[http://dx.doi.org/10.5001/omj.2013.10] [PMID: 23386945]

[91] Aranow C, Kamen DL, Dall'Era M, *et al.* Randomized, double-blind, placebo-controlled trial of the effect of vitamin D3 on the interferon signature in patients with systemic lupus erythematosus. Arthritis Rheumatol 2015; 67(7): 1848-57.
[http://dx.doi.org/10.1002/art.39108] [PMID: 25777546]

[92] Ramagopalan SV, Goldacre R, Disanto G, Giovannoni G, Goldacre MJ. Hospital admissions for vitamin D related conditions and subsequent immune-mediated disease: Record-linkage studies. BMC Med 2013; 11(1): 171.
[http://dx.doi.org/10.1186/1741-7015-11-171] [PMID: 23885887]

[93] Zold E, Szodoray P, Gaal J, *et al.* Vitamin D deficiency in undifferentiated connective tissue disease. Arthritis Res Ther 2008; 10(5): R123.
[http://dx.doi.org/10.1186/ar2533] [PMID: 18928561]

[94] Shoenfeld N, Amital H, Shoenfeld Y. The effect of melanism and vitamin D synthesis on the incidence of autoimmune disease. Nat Clin Pract Rheumatol 2009; 5(2): 99-105.
[http://dx.doi.org/10.1038/ncprheum0989] [PMID: 19182816]

[95] Lee YH, Bae S-C, Choi SJ, Ji JD, Song GG. Associations between vitamin D receptor polymorphisms and susceptibility to rheumatoid arthritis and systemic lupus erythematosus: A meta-analysis. Mol Biol Rep 2011; 38(6): 3643-51.
[http://dx.doi.org/10.1007/s11033-010-0477-4] [PMID: 21110115]

[96] Xiong J, He Z, Zeng X, Zhang Y, Hu Z. Association of vitamin D receptor gene polymorphisms with systemic lupus erythematosus: A meta-analysis. Clin Exp Rheumatol 2014; 32(2): 174-81.
[PMID: 24321519]

[97] Mao S, Huang S. Association between vitamin D receptor gene BsmI, FokI, ApaI and TaqI polymorphisms and the risk of systemic lupus erythematosus: A meta-analysis. Rheumatol Int 2014; 34(3): 381-8.
[http://dx.doi.org/10.1007/s00296-013-2898-6] [PMID: 24212677]

[98] Bellan M, Sainaghi PP, Pirisi M. Role of Vitamin D in Rheumatoid Arthritis. Adv Exp Med Biol 2017; 996(13): 155-68.
[http://dx.doi.org/10.1007/978-3-319-56017-5_13] [PMID: 29124698]

[99] Wang L-M, Zheng Z-H, Li T-F, *et al.* 25-hydroxyvitamin D is associated with metabolic syndrome among premenopausal women with systemic lupus erythematosus in China. Lupus 2017; 26(4): 403-9.
[http://dx.doi.org/10.1177/0961203316668040] [PMID: 27687025]

[100] Shahin D, El-Farahaty RM, Houssen ME, *et al.* Serum 25-OH vitamin D level in treatment-naïve systemic lupus erythematosus patients: Relation to disease activity, IL-23 and IL-17. Lupus 2017; 26(9): 917-26.
[http://dx.doi.org/10.1177/0961203316682095] [PMID: 27927883]

[101] García-Carrasco M, Mendoza-Pinto C, Etchegaray-Morales I, *et al.* Vitamin D insufficiency and deficiency in mexican patients with systemic lupus erythematosus: Prevalence and relationship with disease activity. Reumatol Clin 2017; 13(2): 97-101.
[http://dx.doi.org/10.1016/j.reuma.2016.02.013] [PMID: 27084269]

[102] Abdel Galil SM, El-Shafey AM, Abdul-Maksoud RS, El-Boshy M. Interferon alpha gene expression and serum level association with low vitamin D levels in Egyptian female patients with systemic lupus erythematosus. Lupus 2017; 23: 961203317716321.
[PMID: 28659049]

[103] Eloi M, Horvath DV, Ortega JC, *et al.* 25-hydroxivitamin D serum concentration, not free and bioavailable vitamin D, is associated with disease activity in systemic lupus erythematosus patients. PLoS One 2017; 12(1): e0170323.
[http://dx.doi.org/10.1371/journal.pone.0170323] [PMID: 28085957]

[104] Salman-Monte TC, Torrente-Segarra V, Almirall M, Corzo P, Mojal S, Carbonell-Abelló J. Prevalence and predictors of vitamin D insufficiency in supplemented and non-supplemented women with systemic lupus erythematosus in the Mediterranean region. Rheumatol Int 2016; 36(7): 975-85.
[http://dx.doi.org/10.1007/s00296-016-3497-0] [PMID: 27233506]

[105] Gao C-C, Liu S-Y, Wu Z-Z, *et al.* Severe vitamin D deficiency increases the risk for moderate to severe disease activity in Chinese patients with SLE. Lupus 2016; 25(11): 1224-9.
[http://dx.doi.org/10.1177/0961203316635289] [PMID: 26921268]

[106] Simioni JA, Heimovski F, Skare TL. On lupus, vitamin D and leukopenia. Rev Bras Reumatol Engl Ed 2016; 56(3): 206-11.
[http://dx.doi.org/10.1016/j.rbre.2015.08.008] [PMID: 27267638]

[107] Kokic V, Martinovic Kaliterna D, Radic M, Perkovic D, Cvek M, Capkun V. Relationship between vitamin D, IFN-γ, and E2 levels in systemic lupus erythematosus. Lupus 2016; 25(3): 282-8.
[http://dx.doi.org/10.1177/0961203315605367] [PMID: 26405019]

[108] Lin T-C, Wu J-Y, Kuo M-L, Ou L-S, Yeh K-W, Huang J-L. Correlation between disease activity of pediatric-onset systemic lupus erythematosus and level of vitamin D in Taiwan: A case-cohort study. J Microbiol Immunol Infect 2016.
[PMID: 27147283]

[109] Yap KS, Northcott M, Hoi AB-Y, Morand EF, Nikpour M. Association of low vitamin D with high disease activity in an Australian systemic lupus erythematosus cohort. Lupus Sci Med 2015; 2(1): e000064-4.
[http://dx.doi.org/10.1136/lupus-2014-000064] [PMID: 25893106]

[110] Tay SH, Ho CS, Ho RC-M, Mak A. 25-hydroxyvitamin D3 deficiency independently predicts cognitive impairment in patients with systemic lupus erythematosus. PLoS One 2015; 10(12): e0144149.
[http://dx.doi.org/10.1371/journal.pone.0144149] [PMID: 26636681]

[111] Garf KE, Marzouk H, Farag Y, Rasheed L, Garf AE. Vitamin D status in Egyptian patients with juvenile-onset systemic lupus erythematosus. Rheumatol Int 2015; 35(9): 1535-40.
[http://dx.doi.org/10.1007/s00296-015-3245-x] [PMID: 25773657]

[112] Dall'Ara F, Andreoli L, Piva N, Piantoni S, Franceschini F, Tincani A. Winter lupus flares are associated with low vitamin D levels in a retrospective longitudinal study of Italian adult patients. Clin Exp Rheumatol 2015; 33(2): 153-8.
[PMID: 25664429]

[113] Sabio JM, Vargas-Hitos JA, Martinez-Bordonado J, *et al.* Association between low 25-hydroxyvitamin D, insulin resistance and arterial stiffness in nondiabetic women with systemic lupus erythematosus. Lupus 2015; 24(2): 155-63.
[http://dx.doi.org/10.1177/0961203314551811] [PMID: 25216653]

[114] Sahebari M, Nabavi N, Salehi M. Correlation between serum 25(OH)D values and lupus disease activity: An original article and a systematic review with meta-analysis focusing on serum VitD confounders. Lupus 2014; 23(11): 1164-77.
[http://dx.doi.org/10.1177/0961203314540966] [PMID: 24961748]

[115] Schoindre Y, Jallouli M, Tanguy M-L, *et al.* Lower vitamin D levels are associated with higher systemic lupus erythematosus activity, but not predictive of disease flare-up. Lupus Sci Med 2014; 1(1): e000027.
[http://dx.doi.org/10.1136/lupus-2014-000027] [PMID: 25379192]

[116] Lertratanakul A, Wu P, Dyer A, *et al.* 25-hydroxyvitamin D and cardiovascular disease in patients with systemic lupus erythematosus: data from a large international inception cohort. Arthritis Care Res (Hoboken) 2014; 66(8): 1167-76.
[http://dx.doi.org/10.1002/acr.22291] [PMID: 24470118]

[117] McGhie TK, DeCeulaer K, Walters CA, Soyibo A, Lee MG. Vitamin D levels in Jamaican patients with systemic lupus erythematosus. Lupus 2014; 23(10): 1092-6.
[http://dx.doi.org/10.1177/0961203314528556] [PMID: 24644009]

[118] de Souza VA, Bastos MG, Fernandes NMDS, *et al.* Association of hypovitaminosis D with Systemic Lupus Erythematosus and inflammation. J Bras Nefrol 2014; 36(4): 430-6.
[http://dx.doi.org/10.5935/0101-2800.20140062] [PMID: 25517270]

[119] Jung J-Y, Koh B-R, Bae C-B, Kim H-A, Suh C-H. Carotid subclinical atherosclerosis is associated with disease activity but not vitamin D in Korean systemic lupus erythematosus. Lupus 2014; 23(14): 1517-22.
[http://dx.doi.org/10.1177/0961203314544185] [PMID: 25059488]

[120] Kiani AN, Fang H, Magder LS, Petri M. Vitamin D deficiency does not predict progression of coronary artery calcium, carotid intima-media thickness or high-sensitivity C-reactive protein in systemic lupus erythematosus. Rheumatology (Oxford) 2013; 52(11): 2071-6.
[http://dx.doi.org/10.1093/rheumatology/ket271] [PMID: 23955647]

[121] Yeap SS, Othman AZ, Zain AA, Chan SP. Vitamin D levels: its relationship to bone mineral density response and disease activity in premenopausal Malaysian systemic lupus erythematosus patients on corticosteroids. Int J Rheum Dis 2012; 15(1): 17-24.
[http://dx.doi.org/10.1111/j.1756-185X.2011.01653.x] [PMID: 22324943]

[122] Birmingham DJ, Hebert LA, Song H, *et al.* Evidence that abnormally large seasonal declines in vitamin D status may trigger SLE flare in non-African Americans. Lupus 2012; 21(8): 855-64.
[http://dx.doi.org/10.1177/0961203312439640] [PMID: 22433915]

[123] Bogaczewicz J, Sysa-Jedrzejowska A, Arkuszewska C, *et al.* Vitamin D status in systemic lupus erythematosus patients and its association with selected clinical and laboratory parameters. Lupus 2012; 21(5): 477-84.
[http://dx.doi.org/10.1177/0961203311427549] [PMID: 22065093]

[124] Muñoz-Ortego J, Torrente-Segarra V, Prieto-Alhambra D, Salman-Monte TC, Carbonell-Abello J. Prevalence and predictors of vitamin D deficiency in non-supplemented women with systemic lupus erythematosus in the Mediterranean region: A cohort study. Scand J Rheumatol 2012; 41(6): 472-5.
[http://dx.doi.org/10.3109/03009742.2012.697189] [PMID: 22830580]

[125] Fragoso TS, Dantas AT, Marques CDL, *et al.* 25-Hydroxyivitamin D3 levels in patients with systemic lupus erythematosus and its association with clinical parameters and laboratory tests. Rev Bras Reumatol 2012; 52(1): 60-5.
[http://dx.doi.org/10.1590/S0482-50042012000100007] [PMID: 22286646]

[126] Reynolds JA, Haque S, Berry JL, *et al.* 25-Hydroxyvitamin D deficiency is associated with increased aortic stiffness in patients with systemic lupus erythematosus. Rheumatology (Oxford) 2012; 51(3): 544-51.
[http://dx.doi.org/10.1093/rheumatology/ker352] [PMID: 22120462]

[127] Ravenell RL, Kamen DL, Spence JD, *et al.* Premature atherosclerosis is associated with hypovitaminosis D and angiotensin-converting enzyme inhibitor non-use in lupus patients. Am J Med Sci 2012; 344(4): 268-73.
[http://dx.doi.org/10.1097/MAJ.0b013e31823fa7d9] [PMID: 22222338]

[128] Bonakdar ZS, Jahanshahifar L, Jahanshahifar F, Gholamrezaei A. Vitamin D deficiency and its association with disease activity in new cases of systemic lupus erythematosus. Lupus 2011; 20(11): 1155-60.
[http://dx.doi.org/10.1177/0961203311405703] [PMID: 21680639]

[129] Szodoray P, Tarr T, Bazso A, Poor G, Szegedi G, Kiss E. The immunopathological role of vitamin D in patients with SLE: Data from a single centre registry in Hungary. Scand J Rheumatol 2011; 40(2): 122-6.
[http://dx.doi.org/10.3109/03009742.2010.507220] [PMID: 20977384]

[130] Kim H-A, Sung J-M, Jeon J-Y, Yoon J-M, Suh C-H. Vitamin D may not be a good marker of disease activity in Korean patients with systemic lupus erythematosus. Rheumatol Int 2011; 31(9): 1189-94.
[http://dx.doi.org/10.1007/s00296-010-1442-1] [PMID: 20352222]

[131] Amital H, Szekanecz Z, Szücs G, *et al.* Serum concentrations of 25-OH vitamin D in patients with systemic lupus erythematosus (SLE) are inversely related to disease activity: Is it time to routinely supplement patients with SLE with vitamin D? Ann Rheum Dis 2010; 69(6): 1155-7.
[http://dx.doi.org/10.1136/ard.2009.120329] [PMID: 20439290]

[132] Ben-Zvi I, Aranow C, Mackay M, *et al.* The impact of vitamin D on dendritic cell function in patients with systemic lupus erythematosus. PLoS One 2010; 5(2): e9193.
[http://dx.doi.org/10.1371/journal.pone.0009193] [PMID: 20169063]

[133] Ruiz-Irastorza G, Gordo S, Olivares N, Egurbide M-V, Aguirre C. Changes in vitamin D levels in patients with systemic lupus erythematosus: Effects on fatigue, disease activity, and damage. Arthritis Care Res (Hoboken) 2010; 62(8): 1160-5.
[http://dx.doi.org/10.1002/acr.20186] [PMID: 20235208]

[134] Wu PW, Rhew EY, Dyer AR, *et al.* 25-hydroxyvitamin D and cardiovascular risk factors in women with systemic lupus erythematosus. Arthritis Rheum 2009; 61(10): 1387-95.
[http://dx.doi.org/10.1002/art.24785] [PMID: 19790113]

[135] Borba VZC, Vieira JGH, Kasamatsu T, Radominski SC, Sato EI, Lazaretti-Castro M. Vitamin D deficiency in patients with active systemic lupus erythematosus. Osteoporos Int 2009; 20(3): 427-33.
[http://dx.doi.org/10.1007/s00198-008-0676-1] [PMID: 18600287]

[136] Cutolo M, Otsa K. Review: Vitamin D, immunity and lupus. Lupus 2008; 17(1): 6-10.
[http://dx.doi.org/10.1177/0961203307085879] [PMID: 18089676]

[137] Thudi A, Yin S, Wandstrat AE, Li Q-Z, Olsen NJ. Vitamin D levels and disease status in Texas patients with systemic lupus erythematosus. Am J Med Sci 2008; 335(2): 99-104.
[http://dx.doi.org/10.1097/MAJ.0b013e318134eeb6] [PMID: 18277116]

[138] Ward MM. Premature morbidity from cardiovascular and cerebrovascular diseases in women with systemic lupus erythematosus. Arthritis Rheum 1999; 42(2): 338-46.
[http://dx.doi.org/10.1002/1529-0131(199902)42:2<338::AID-ANR17>3.0.CO;2-U] [PMID: 10025929]

[139] Manzi S, Meilahn EN, Rairie JE, *et al.* Age-specific incidence rates of myocardial infarction and angina in women with systemic lupus erythematosus: Comparison with the Framingham Study. Am J Epidemiol 1997; 145(5): 408-15.
[http://dx.doi.org/10.1093/oxfordjournals.aje.a009122] [PMID: 9048514]

[140] Symmons DPM, Gabriel SE. Epidemiology of CVD in rheumatic disease, with a focus on RA and SLE. Nat Rev Rheumatol 2011; 7(7): 399-408.
[http://dx.doi.org/10.1038/nrrheum.2011.75] [PMID: 21629241]

[141] Roman MJ, Crow MK, Lockshin MD, *et al.* Rate and determinants of progression of atherosclerosis in systemic lupus erythematosus. Arthritis Rheum 2007; 56(10): 3412-9.
[http://dx.doi.org/10.1002/art.22924] [PMID: 17907140]

[142] Parker B, Urowitz MB, Gladman DD, *et al.* Impact of early disease factors on metabolic syndrome in systemic lupus erythematosus: Data from an international inception cohort. Ann Rheum Dis 2015; 74(8): 1530-6.
[http://dx.doi.org/10.1136/annrheumdis-2013-203933] [PMID: 24692585]

[143] Demir S, Artim-Esen B, Şahinkaya Y, *et al.* Metabolic syndrome is not only a risk factor for cardiovascular diseases in systemic lupus erythematosus but is also associated with cumulative organ damage: a cross-sectional analysis of 311 patients. Lupus 2016; 25(2): 177-84.
[http://dx.doi.org/10.1177/0961203315603140] [PMID: 26354963]

[144] Kendrick J, Targher G, Smits G, Chonchol M. 25-Hydroxyvitamin D deficiency is independently associated with cardiovascular disease in the Third National Health and Nutrition Examination Survey. Atherosclerosis 2009; 205(1): 255-60.
[http://dx.doi.org/10.1016/j.atherosclerosis.2008.10.033] [PMID: 19091317]

[145] Martins D, Wolf M, Pan D, *et al.* Prevalence of cardiovascular risk factors and the serum levels of 25-hydroxyvitamin D in the United States: Data from the Third National Health and Nutrition Examination Survey. Arch Intern Med 2007; 167(11): 1159-65.
[http://dx.doi.org/10.1001/archinte.167.11.1159] [PMID: 17563024]

[146] Kim DH, Sabour S, Sagar UN, Adams S, Whellan DJ. Prevalence of hypovitaminosis D in cardiovascular diseases (from the National Health and Nutrition Examination Survey 2001 to 2004). Am J Cardiol 2008; 102(11): 1540-4.
[http://dx.doi.org/10.1016/j.amjcard.2008.06.067] [PMID: 19026311]

[147] Sakthiswary R, Raymond AA. The clinical significance of vitamin D in systemic lupus erythematosus: A systematic review. PLoS One 2013; 8(1): e55275.
[http://dx.doi.org/10.1371/journal.pone.0055275] [PMID: 23383135]

[148] Wang TJ, Pencina MJ, Booth SL, *et al.* Vitamin D deficiency and risk of cardiovascular disease. Circulation 2008; 117(4): 503-11.
[http://dx.doi.org/10.1161/CIRCULATIONAHA.107.706127] [PMID: 18180395]

[149] Cauley JA, Chlebowski RT, Wactawski-Wende J, *et al.* Calcium plus vitamin D supplementation and health outcomes five years after active intervention ended: the Women's Health Initiative. J Womens Health (Larchmt) 2013; 22(11): 915-29.
[http://dx.doi.org/10.1089/jwh.2013.4270] [PMID: 24131320]

[150] Chowdhury R, Kunutsor S, Vitezova A, *et al.* Vitamin D and risk of cause specific death: systematic review and meta-analysis of observational cohort and randomised intervention studies. BMJ 2014; 348(1): g1903-3.
[http://dx.doi.org/10.1136/bmj.g1903] [PMID: 24690623]

[151] Iaccarino L, Bettio S, Zen M, *et al.* Premature coronary heart disease in SLE: Can we prevent progression? Lupus 2013; 22(12): 1232-42.
[http://dx.doi.org/10.1177/0961203313492871] [PMID: 24097995]

[152] Iannuccelli C, Spinelli FR, Guzzo MP, *et al.* Fatigue and widespread pain in systemic lupus erythematosus and Sjögren's syndrome: Symptoms of the inflammatory disease or associated fibromyalgia? Clin Exp Rheumatol 2012; 30(6)(Suppl. 74): 117-21.
[PMID: 23261010]

[153] Ahn GE, Ramsey-Goldman R. Fatigue in systemic lupus erythematosus. Int J Clin Rheumatol 2012; 7(2): 217-27.
[http://dx.doi.org/10.2217/ijr.12.4] [PMID: 22737181]

[154] Francis RM, Aspray TJ, Bowring CE, *et al.* National Osteoporosis Society practical clinical guideline on vitamin D and bone health. Maturitas 2015; 80(2): 119-21.
[http://dx.doi.org/10.1016/j.maturitas.2014.11.018] [PMID: 25510660]

[155] Rosen CJ, Abrams SA, Aloia JF, *et al.* IOM committee members respond to Endocrine Society vitamin D guideline. J Clin Endocrinol Metab 2012; 97(4): 1146-52.
[http://dx.doi.org/10.1210/jc.2011-2218] [PMID: 22442278]

[156] Holick MF, Binkley NC, Bischoff-Ferrari HA, *et al.* Guidelines for preventing and treating vitamin D deficiency and insufficiency revisited. J Clin Endocrinol Metab 2012; 97(4): 1153-8.
[http://dx.doi.org/10.1210/jc.2011-2601] [PMID: 22442274]

[157] Ross AC. The 2011 report on dietary reference intakes for calcium and vitamin D. Public Health Nutr 2011; 14(5): 938-9.
[http://dx.doi.org/10.1017/S1368980011000565] [PMID: 21492489]

[158] Rizzoli R, Boonen S, Brandi M-L, *et al.* Vitamin D supplementation in elderly or postmenopausal women: A 2013 update of the 2008 recommendations from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). Presented at the Current medical research and opinion. 29(4): 305-13.

[159] Bischoff-Ferrari HA, Willett WC, Orav EJ, *et al.* A pooled analysis of vitamin D dose requirements for fracture prevention. N Engl J Med 2012; 367(1): 40-9.
[http://dx.doi.org/10.1056/NEJMoa1109617] [PMID: 22762317]

[160] Souberbielle J-C, Body J-J, Lappe JM, *et al.* Vitamin D and musculoskeletal health, cardiovascular disease, autoimmunity and cancer: Recommendations for clinical practice. Presented at the Autoimmunity reviews. 9(11): 709-15.

[161] Zhou C, Assem M, Tay JC, *et al.* Steroid and xenobiotic receptor and vitamin D receptor crosstalk mediates CYP24 expression and drug-induced osteomalacia. J Clin Invest 2006; 116(6): 1703-12.
[http://dx.doi.org/10.1172/JCI27793] [PMID: 16691293]

[162] Mok CC. Vitamin D and systemic lupus erythematosus: An update. Expert Rev Clin Immunol 2013; 9(5): 453-63.
[http://dx.doi.org/10.1586/eci.13.19] [PMID: 23634739]

[163] Grossman JM, Gordon R, Ranganath VK, *et al.* American College of Rheumatology 2010 recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. Arthritis Care Res (Hoboken) 2010; 62(11): 1515-26.
[http://dx.doi.org/10.1002/acr.20295] [PMID: 20662044]

[164] Ruiz-Irastorza G, García M, Espinosa G, *et al.* Patterns of drug therapy in newly diagnosed Spanish patients with systemic lupus erythematosus. Clin Exp Rheumatol 2016; 34(3): 466-72.
[PMID: 26940538]

[165] Petri M, Bello KJ, Fang H, Magder LS. Vitamin D in systemic lupus erythematosus: Modest association with disease activity and the urine protein-to-creatinine ratio. Arthritis Rheum 2013; 65(7): 1865-71.
[http://dx.doi.org/10.1002/art.37953] [PMID: 23553077]

[166] Andreoli L, Dall'Ara F, Piantoni S, *et al.* A 24-month prospective study on the efficacy and safety of two different monthly regimens of vitamin D supplementation in pre-menopausal women with systemic lupus erythematosus. Lupus 2015; 24(4-5): 499-506.
[http://dx.doi.org/10.1177/0961203314559089] [PMID: 25801893]

[167] Sainaghi PP, Bellan M, Nerviani A, *et al.* Superiority of a high loading dose of cholecalciferol to correct hypovitaminosis d in patients with inflammatory/autoimmune rheumatic diseases. J Rheumatol 2013; 40(2): 166-72.
[http://dx.doi.org/10.3899/jrheum.120536] [PMID: 23242183]

[168] Karimzadeh H, Shirzadi M, Karimifar M. The effect of Vitamin D supplementation in disease activity of systemic lupus erythematosus patients with Vitamin D deficiency: A randomized clinical trial. J Res Med Sci 2017; 22(1): 4.
[http://dx.doi.org/10.4103/1735-1995.199089] [PMID: 28400826]

[169] Lima GL, Paupitz J, Aikawa NE, Takayama L, Bonfa E, Pereira RMR. Vitamin D Supplementation in Adolescents and Young Adults With Juvenile Systemic Lupus Erythematosus for Improvement in Disease Activity and Fatigue Scores: A Randomized, Double-Blind, Placebo-Controlled Trial. Arthritis Care Res (Hoboken) 2016; 68(1): 91-8.
[http://dx.doi.org/10.1002/acr.22621] [PMID: 25988278]

[170] AlSaleem A, AlE'ed A, AlSaghier A, Al-Mayouf SM. Vitamin D status in children with systemic lupus erythematosus and its association with clinical and laboratory parameters. Clin Rheumatol 2015; 34(1): 81-4.
[http://dx.doi.org/10.1007/s10067-014-2811-z] [PMID: 25367346]

[171] Mauro D, Nerviani A. Endothelial Dysfunction in Systemic Lupus Erythematosus: Pathogenesis, Assessment and Therapeutic Opportunities. Rev Recent Clin Trials 2018; 13(3): 192-8.
[http://dx.doi.org/10.2174/1574887113666180314091831] [PMID: 29542419]

[172] Kamen DL, Oates JC. A Pilot Study to Determine if Vitamin D Repletion Improves Endothelial Function in Lupus Patients. Am J Med Sci 2015; 350(4): 302-7.
[http://dx.doi.org/10.1097/MAJ.0000000000000556] [PMID: 26351776]

[173] Reynolds JA, Haque S, Williamson K, Ray DW, Alexander MY, Bruce IN. Vitamin D improves endothelial dysfunction and restores myeloid angiogenic cell function via reduced CXCL-10 expression in systemic lupus erythematosus. Sci Rep 2016; 6(1): 22341.
[http://dx.doi.org/10.1038/srep22341] [PMID: 26930567]

[174] Sugden JA, Davies JI, Witham MD, Morris AD, Struthers AD. Vitamin D improves endothelial function in patients with Type 2 diabetes mellitus and low vitamin D levels. Diabet Med 2008; 25(3): 320-5.
[http://dx.doi.org/10.1111/j.1464-5491.2007.02360.x] [PMID: 18279409]

[175] Reynolds J, Ray D, Alexander MY, Bruce I. Role of vitamin D in endothelial function and endothelial repair in clinically stable systemic lupus erythematosus. Lancet 2015; 385: S83.
[http://dx.doi.org/10.1016/S0140-6736(15)60398-1] [PMID: 26312905]

[176] Reynolds JA, Rosenberg AZ, Smith CK, *et al.* Brief Report: Vitamin D Deficiency Is Associated With Endothelial Dysfunction and Increases Type I Interferon Gene Expression in a Murine Model of Systemic Lupus Erythematosus. Arthritis Rheumatol 2016; 68(12): 2929-35.
[http://dx.doi.org/10.1002/art.39803] [PMID: 27390112]

[177] Sainaghi PP, Bellan M, Antonini G, Bellomo G, Pirisi M. Unsuppressed parathyroid hormone in patients with autoimmune/inflammatory rheumatic diseases: implications for vitamin D supplementation. Rheumatology (Oxford) 2011; 50(12): 2290-6.
[http://dx.doi.org/10.1093/rheumatology/ker314] [PMID: 22019806]

[178] Cianferotti L, Bertoldo F, Bischoff-Ferrari H A, *et al.* Vitamin D supplementation in the prevention and management of major chronic diseases not related to mineral homeostasis in adults: research for evidence and a scientific statement from the European society for clinical and economic aspects of osteoporosis and osteoarthritis (ESCEO). Endocrine 56(2): 245-61.