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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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