Review

Vitamin D and systemic lupus erythematosus - The hype and the hope

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Abstract

Over the past 20 years, much has been written about the potential role of vitamin D in adverse health outcomes. In recent years, evidence has accumulated regarding the effect of vitamin D on the immune system, and its different cells. Some studies have noted lower vitamin D concentrations in patients with SLE. These epidemiological data still not answer the question: is vitamin D deficiency the cause or the effect? To answer this, we will discuss the association between vitamin D deficiency and SLE and review the evidence from intervention studies.

Keywords:
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1. Introduction

Our knowledge of the importance of vitamin D has grown rapidly in recent years, as its influences on different organ systems of the body have been studied. Many studies have focused on the active role of vitamin D in the homeostasis of different systems and...
more recently, highlighted its role in modulating the activity of the immune system [1–3]. Vitamin D may be considered as a pro-hormone which is obtained from 2 distinct sources; to a lesser extent diet, but principally by synthesis in the epidermal layer of the skin after UV exposure. In the skin, UV rays promote photolytic cleavage of 7-dihydrocholesterol into pre-vitamin D, which is subsequently converted by spontaneous thermal isomerization into vitamin D3 [4]. After synthesis, vitamin D and its metabolites are bound to a carrier molecule, known as the vitamin D binding protein (DBP), for systemic transport [5]. Vitamin D needs to be hydroxylated twice in order to become biologically active, firstly in the liver at the carbon 25-position by 25-hydroxylase and successively in the kidney generating the bioactive metabolite 1,25-dihydroxyvitamin D3 (1,25(OH)2D3) or calcitriol. 1,25(OH)2D3 acts through its cellular receptor, the vitamin D receptor (VDR), which is a member of the nuclear steroid hormones receptor superfamily. The VDR is a transcription factor which, after ligation with 1,25(OH)2D3, activates the vitamin D-responsive genes. The classical well known activity of vitamin D is to maintain extracellular calcium levels within narrow limits [6]. In the last decade different authors suggested a non-classical role of vitamin D in modulating the immune system [7–9]. This activity includes different functions in both innate and adaptive immune responses. In fact, the VDR is expressed in immune cells, such as macrophages, dendritic cells (DCs), B and T lymphocytes, neutrophils, and its expression is controlled by immune signals [10].

Whereas naïve T cells only display low vitamin D levels, this receptor is abundantly present upon T cell activation [11,12]. By contrast, the differentiation of monocytes, either into macrophages or myeloid DCs is accompanied by a decrease in VDR-expression, making these cells less sensitive to 1,25(OH)2D3, [13,14]. Vitamin D decreases the antigen-presenting activity of macrophages to lymphocytes, inhibits the differentiation of monocytes into myeloid DCs, B cell proliferation, plasma cell differentiation, antibody production, as well as the synthesis of a number of cytokines, including interleukin (IL)-12, IL-1, IL-6 and tumor necrosis factor α (TNFα). Conversely, vitamin D induces activation of T regulatory cells (Treg) and natural killer (NK) cells, increases the apoptosis induced by DCs and T lymphocytes as well as the production of IL-4, IL-5 and IL-10 [15]. Taken together these data shown that vitamin D may be considered an immunosuppressant [16]. The immunoregulatory effects of 1,25(OH)2D3 have also been investigated in different experimental models of autoimmunity. In the MRL-lpr/lpr mice, a spontaneous model of systemic lupus erythematosus (SLE), vitamin D supplementation improves longevity, reduces proteinuria, improves kidney function [17], and prevents dermatological lesions [18]. Administration of 1,25(OH)2D3 prior to the expression of the disease may prevent the development of the disease in this model [18]. In the same model, diet-induced vitamin D deficiency was associated with impaired endothelial function and a reduced capacity for angiogenesis and endothelial repair [19]. In a parallel human study where lupus patients with vitamin D deficiency were supplemented as part of routine care, an improvement in endothelial function in vitamin D deficient patients was observed with a correlation between the increment of 25(OH)D and change in endothelial function [20]. In the murine model of collagen-induced arthritis, vitamin D receptor agonists both prevent disease development and suppress established disease [18,21]. Furthermore, in a murine experimental autoimmune encephalomyelitis (EAE) model, 1,25(OH)2D3 analogs seem to protect against the development of disease, especially when combined with other immunosuppressive agents [22]. On the other hand, so far, it is still difficult to establish a strong relationship between vitamin D deficiency and autoimmune rheumatic diseases. Different cut-offs for vitamin D deficiency and insufficiency are used in different studies; some studies are based on the reported intake rather than on serum levels; as well as many confounding factors may be associated during these conditions, such as prednisone intake, photosensitivity and the decreased sun exposure.

2. The pros

2.1. Epidemiology first

The hypothesis that vitamin D may be related to autoimmune disorders is supported from some epidemiologic observations: i. people living near the equator show a decreased risk of developing autoimmunity [23]; and ii. decreased vitamin D levels are present in patients with a number of systemic autoimmune disorders [24]. At present, the definition of vitamin D deficiency is controversial, with a common recommended minimum of 20 ng/mL of calcifediol (25-hydroxy-vitamin D-25(OH)D), an indicator of vitamin D reserve [25]; however, the optimal level for the functioning of the immune system is yet to be determined. Vitamin D deficiency is relatively common in the general population, even in sunny countries [26]. Nevertheless, vitamin D deficiency is more prevalent among systemic lupus erythematosus (SLE) patients. When it comes to vitamin D and SLE, one thing seems to be a consensus – SLE patients display lower vitamin D levels than the general population. This result has been observed worldwide [27–31]. Another possible explanation for the association between vitamin D deficiency and SLE lies in genetics; different VDR polymorphisms were associated with higher risk for SLE in different ethnicities, notably in Asians and Africans [32]. As far as SLE disease activity and vitamin D are concerned, Borba et al. found lower levels of 25(OH)2D3 in 12 SLE patients with high disease activity when compared with 24 patients with low disease activity [33], and these results, were confirmed in another study where in 25 out of 57 SLE patients, lower 25(OH)2D3 levels significantly correlated with disease activity [34]. Furthermore, vitamin D deficiency was also previously linked to various comorbidities of SLE, such as cardiovascular diseases [35,36], insulin resistance [37], avascular necrosis [38] sleep disturbances [39] and fatigue [40]. Similar results in regards to vitamin D deficiency prevalence and association with disease manifestations and autoantibodies levels were also shown in regards to anti-phospholipid syndrome (APS) patients [41]. However, some studies reject this conclusion [27,42–44].

These epidemiological data still do not provide and answer to the question: is vitamin D deficiency the cause or the effect? This question has been debated in recent years. To answer this, we will review and address common explanations for this association, and current interventional studies.

2.2. Vitamin D deficiency in SLE patients is a result of medications use

It has been claimed that the association between low vitamin D and SLE is a result of the treatment for the disease, and steroids in particular. However, this association was found irrespective of steroid use [45,46]; therefore, steroids use cannot fully explain vitamin D deficiency in SLE patients. Furthermore, low levels of vitamin D seem to precede the diagnosis of the disease, and predict disease progression, making the disease’s treatment a less likely explanation. Low levels of vitamin D were associated with higher levels of anti-nuclear antibodies (ANA) in healthy controls [31], and in a cohort of undifferentiated connective tissue disease (UCTD) patients, vitamin D levels were lower in the patients who progressed into a connective tissue disease [47].

2.3. Vitamin D deficiency in SLE patients is a result of active sun avoidance

The existence of a genetic variance that links vitamin D deficiency and SLE can argue against the argument that vitamin D deficiency is the effect of active sun avoidance by SLE patients. In a cohort of individuals with a predisposition to develop SLE (individuals with a first degree relative with SLE), genetic variance in genes related to vitamin D and its
metabolism were investigated, and later correlated with the development of SLE. In this study it was suggested that vitamin D status and a polymorphism in the CYP24A1 gene, which is responsible for degradation of the active form of vitamin D (1,25(OH)2D), may have a role in the transition to SLE in these individuals [48]. The researcher also investigated whether sunlight avoidance in SLE patients was a confounder, as the main source of vitamin D in humans comes from UV-dependent synthesis in the skin, and SLE patients are advised to avoid exposure to the sun to prevent photosensitivity. In this study, although transitioned individuals had higher rates of vitamin D deficiency in the beginning, their vitamin D levels did not differ by their sun exposure behavior or by the presence of photosensitivity symptom [48]. This suggests that the vitamin D deficiency was driven by genetic factors rather than sunlight avoidance.

2.4. “Vitamin D is a negative acute phase reactant”

Vitamin D was previously suggested to be a negative acute phase reactant, meaning its levels decrease in acute inflammatory conditions, which could explain its low levels in SLE. Furthermore, vitamin D deficiency is associated with high levels of inflammatory cytokines, such as IFN-α [31,49] and IFN-γ [50] as well as high auto-antibodies titers [43,42].

2.5. Testing the hypothesis: interventional studies

Vitamin D supplementation in SLE patients was associated with decrease in inflammatory cytokines and markers: IL-1, IL-6, IL-18, TNF-α, erythrocyte sedimentation rate (ESR) [30]; vitamin D supplementation was also associated with a reduction in autoantibodies and elevation in complement level [30,38]. Vitamin D treatment enhanced T-reg cells and production of T helper 2 cytokines [51]; a correlation was found between disease activity and change in 25(OH)D in deficient patients following treatment [52]; and vitamin D treatment even showed improvement in disease activity and fatigue among juvenile-onset SLE [53].

Taken together, vitamin D seems to play a role in the pathogenesis and progress of SLE disease. Vitamin D supplementation seems to have an ameliorating effect in SLE patients, and as suggested in our previous review [54], as this treatment is affordable and rarely toxic [55,56], a regular supplementation of the vitamin for all SLE patients might be recommended.

3. The cons

3.1. The other side of the coin: “reverse causation”

Over the past 20 years much has been written about the potential role of vitamin D deficiency on adverse health outcomes. Indeed, one recent review noted 137 different health outcomes linked in some way to lower vitamin D. Among this spectrum of poor health outcomes is the development of autoimmune disease. It is of course not only true for low vitamin D, but such “guilt by association” has also been levelled at an array of other nutrients including vitamins B, C, E, folic acid and selenium. Importantly, when treating populations with supplements in randomised trials, very few actually clearly demonstrate health benefits [57].

In the case of low vitamin D some studies have noted lower vitamin D concentrations in patients with SLE around the time of diagnosis. However, risk factors for lupus include fairer type I/II skin types [58] and even in early lupus, photosensitivity and active renal disease were particularly associated with severe vitamin D deficiency [59]. This suggests that rather than being directly causative, low vitamin D was a consequence of these particular factors, so called ‘reverse causation’.

It has been shown that the association between disease activity and low vitamin D is weak [60] and even in studies looking at the relationship longitudinally, a significant increment in vitamin D concentrations (20 mg/ml), over time, was only associated with very small changes in disease activity and urine protein excretion [52]. Such associations therefore may simply reflect vitamin D role as a reverse acute-phase reactant i.e. high disease activity being associated with low vitamin D rather than vitamin D causing changes in disease activity. In addition, such studies don’t fully adjust for other clear confounders such as steroid use, antimalarial use, body mass index and body fat distribution, nor do they consider that low vitamin D may simply be a marker of a ‘less healthy’ lifestyle with less outdoor activities etc. Even in the context of cardiovascular (CV) risk, where in SLE the Systemic Lupus International Collaborating Clinics (SLICC) group have shown associations between low vitamin D and a higher risk of hypertension and hyperlipidaemia [35], a meta-analysis of large population-based clinical trials have yet to demonstrate any actual benefit on overall CV risk [57]. In addition, some of the association between adverse CV outcomes and vitamin D may not be directly due to low vitamin D but may actually be related to other factors such as parathyroid hormone levels [61].

3.2. Is vitamin D a universally safe treatment?

Once again the lack of convincing data in lupus should not be a surprise as analysis of a wide range of different health outcomes concluded that there was convincing evidence for no clinical outcome being associated with vitamin D supplementation. ‘Probable’ evidence exists for certain endpoints including dental caries in children, birth weight after supplementing mothers with vitamin D and for parathyroid hormone reduction in patients with chronic kidney disease [57]. This analysis also highlighted potential “harms” of long-term vitamin D supplementation including hypercalcaemia, hypercalciuria/renal stones and falls in the elderly [57]. This again emphasises the point that medical interventions aimed at general population benefits must be weighed against potential inefficacy and also potential adverse effects.

3.3. Data from randomised control studies

The most rigorous way to demonstrate causation is not through observational cohort studies but by randomised controlled trials that demonstrate a meaningful effect size with any intervention.

In a trial of juvenile SLE, 40 patients were randomised to cholecalciferol 50,000 IU weekly or placebo after a 3-month washout from any previous vitamin D supplements. After 6 months follow-up there was a significant difference in the change in Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score between vitamin D and placebo groups. This change was driven by a median (range) 1 (−12, 6) point increase in the SLEDAI in the placebo group versus 0 (−4, 5) in those on vitamin D [53]. On the other hand, Aranow et al. randomised patients with lupus to placebo, or vitamin D supplementation at either 4000 IU or 2000 IU per day. The results showed no effect of vitamin D supplementation on the interferon signature: which was used as a biomarker of lupus response [26]. Another trial randomised Egyptian lupus patients to placebo or 2000 IU per day plus calcium supplements. The primary outcome was changes in pro-inflammatory and haemostatic biomarkers (including ESR, serum C4 complement and anti-double-stranded (ds) DNA antibodies) and all 10 biomarkers improved over the 12 month period. In a subset analysis, patients with vitamin D insufficiency or deficiency who got vitamin D replacement had a reduction in their SLEDAI score at 12 months [30]. Some criticism arises from this study. Whilst patients were reported to be on stable background concomitant therapy throughout the study period there is no report in the trial of flare rates, changes in clinical features, background medication or adjustments in steroid dose that patients may have had over the 12 months of follow-up. It is also not clear from the trial whether disease activity was reduced due to improvements in serology (anti-ds DNA and serum complement) or whether actual clinical disease
activity improved in the trial [30]. One can therefore conclude that even if there is an effect of ongoing vitamin D supplementation, it is a very small effect size.

At present, there is no international consensus as to the ideal target dose to use, or target levels of vitamin D that are deemed ‘sufficient’. Such ‘optimal’ levels vary according to country and many opinion leaders believe that an optimal level of vitamin D concentration may be 20–30 ng/ml. Also at an international level, there are virtually no recommendations for vitamin D supplementation beyond those required for maintenance of bone health [62]. The other major issue is that many vitamin D supplements are not prepared to good medical practice (GMP) standards and it is therefore difficult to recommend over-the-counter supplementation or product to guarantee the dose that the patient may receive. There are other unknowns when it comes to vitamin D including whether there is a threshold effect above which no additional benefit occurs and also whether individual variations in response are driven in part by for example vitamin D binding protein, cytochrome polymorphisms etc. We also need better data on long-term safety and whether indeed we need to monitor levels rather than simply recommending chronic supplementation.

4. Conclusion

In conclusion, the knowledge about vitamin D is rapidly increasing: new genes, new targets, new physiological mechanisms. Although the potential role of vitamin D supplementation in SLE remains controversial, the wide variety of effects of this molecule on the immune system, might suggest a role of vitamin D in the future therapeutic strategies. Conflicting results have been published in the clinical setting: adding vitamin D to the traditional pharmacological regimen has been found beneficial in some study, whereas other studies failed to replicate these results. Further studies, improving our knowledge in this field are still an important unmet need to evaluate on one hand, the relationship between vitamin D and the pathogenesis of several autoimmune diseases and, on the other hand, the real efficacy of vitamin D treatment in the same patients. Finally, in order to move association studies to general recommendations, significant clinical improvement must be demonstrated in unbiased randomised controlled clinical trials that consistently demonstrate a clear effect size to warrant screening and intervention.

Take-home messages

- Vitamin D is important in modulating the immune system, both in innate and adaptive pathways;
- Vitamin D supplementation in SLE patients was associated with decrease in inflammatory cytokines and ESR;
- Vitamin D treatment is affordable and rarely toxic, a regular supplementation of the vitamin for all SLE patients might be recommended;
- There is no consensus as to the ideal vitamin D ideal target dose or its target level in SLE patients;
- Is difficult to establish a strong correlation between vitamin D and SLE disease activity;
- Rather than being directly causative low vitamin D levels could be the consequence of SLE patients characteristics;
- Results from RCTs are controversial and further studies are needed to demonstrate a clear effect size to warrant screening and intervention.

Conflict of interest statement

Professor Bruce and Dr. Reynolds live in Manchester, UK which is 53.4808° N, 2.2426° W. As such we really want everything they say to be true!

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