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Vitamin D Deficiency and Risk for Rheumatic Diseases

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An Update

Paul Gatenby, Robyn Lucas, Ashwin Swaminathan

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Abstract and Introduction

Abstract

Purpose of review: The role of vitamin D in situations other than calcium homeostasis and bone health has become very topical. It is apparent that vitamin D has significant effects on the immune system and as such may contribute to the pathogenesis of autoimmune disease. This review examines the evidence-to-date that vitamin D has a role in immune-mediated rheumatic disorders.

Recent findings: Low vitamin D status is reported in many inflammatory rheumatic conditions. In some this extends to an association with disease activity. Vitamin D acts on a number of cells involved in both innate and acquired immunity biasing the adaptive immune system away from Th17 and Th1, towards Th2 and Tregs. Deficiency accordingly could encourage autoimmunity. Direct evidence for this plausible mechanism in specific diseases remains largely to be demonstrated. To date, there is a dearth of controlled trials of vitamin D in prophylaxis or therapy.

Summary: Vitamin D deficiency may well be an important factor in autoimmune rheumatic disease, including initial disease development and worsening the disease once present. This is testable and there is a pressing need for therapeutic studies.

Introduction

The past decade has seen a growing realization that Vitamin D is no mere vitamin but a steroid hormone with a far wider role in human biology than calcium, bone, and mineral metabolism. Until 2007, all reviews including vitamin D in the journal were about metabolic bone disease. The immunological effects of vitamin D were first introduced in 2007 by Bikle[1] and in 2008 the role of vitamin D in systemic lupus erythematosus (SLE) was reviewed.[2] Environmental risk factors for rheumatoid arthritis (RA) were summarized in 2009, including a brief look at vitamin D by Liao *et al.* [3] Since then much work has been published in SLE, RA and other rheumatologic disorders. The breadth of this review is greater than the two previous reviews and will accordingly cover a time frame greater than is traditional for the Journal to deliver a current update. The potential role of vitamin D on disease susceptibility, severity and in therapy will be considered for several autoimmune rheumatological diseases. We focus on the recent literature about the role of vitamin D in regard to the actual immunological rheumatic diseases *per se*; the important issue of bone metabolism in these diseases will not be considered.

Where Vitamin D Comes From and How It Is Measured

Vitamin D may be acquired from dietary sources, including supplements, but most (over 80% in many countries) is derived from cutaneous exposure to ultraviolet B (UVB) radiation that causes sterol precursors to be converted to cholecalciferol (Vitamin D3). This, together with dietary vitamin D [either cholecalciferol or ergocalciferol (Vitamin D2)], is hydroxylated in the liver to 25-hydroxyvitamin D [25(OH)D] which in turn is converted to the most biologically active form 1,25-dihydroxyvitamin D [1,25(OH)D] by a 1α-hydroxylase enzyme, in a step now known to occur in cells of the immune system as well as the kidney. This active moiety has a short half-life and serum 25(OH)D is the best stable measure of vitamin D status. There is some controversy about what constitutes desirable levels of 25(OH)D. Various studies have used elevation of parathyroid hormone (PTH) levels as an indicator of deficiency, with highly variable results, possibly at least partly because of assay variability for both PTH and 25(OH)D.[4] Recent results suggest that a 25(OH)D level of less than 30 ng/ml (75 nmol/l) should be considered insufficient.[5] The level that is optimal for normal immune function is not clear.[5,6] The dominant role of UVB irradiation in providing adequate levels of vitamin D mandates consideration of UV radiation (UVR) exposure as an

independent factor in regard to rheumatic disease. Although the impact of UVB is dependent upon skin pigmentation, clothing, work, and leisure habits, the dominant variable is the latitude (and therefore the ambient UVR) at which patients reside.[7] Indeed, it was the recognition of the increased incidence of certain autoimmune diseases at high latitude, initially multiple sclerosis (MS) and then type 1 diabetes that triggered much of the interest in vitamin D and autoimmune disease.[7] Another important environmental observation is the influence of month of birth on the occurrence of immunological diseases. In a very large UK case–control study,[8] the risk of immunological diseases, including SLE and RA was correlated with second trimester UVB exposure and third trimester vitamin D status.

The Immunological Effects of Vitamin D

The 'nonclassical' actions of 1,25(OH)D include a diverse range of influences on both innate and adaptive immune responses (reviewed in.)[9,10] Immunomodulation is mediated through the vitamin D receptor (VDR), a member of the nuclear receptor family of transcription factors found in almost all cell types, including macrophages, dendritic cells, B and T lymphocytes and neutrophils. VDR activation in immune cells leads to transcription of gene products that initiate a cascade of antiproliferative, prodifferentiating and immune-regulatory processes. Some immune cells (e.g. monocytes, macrophages) also express the 1α-hydroxylase enzyme, allowing local synthesis of 1,25(OH)D that can have autocrine and paracrine immunomodulatory effects.[11]

Dendritic cells are likely to be the primary immune target of 1,25(OH)D.[12] In-vitro models show that 1,25(OH)D inhibits maturation of monocyte-derived dendritic cells, impairing their ability to process and present antigen to T lymphocytes.[13] 1,25(OH)D-modulated dendritic cells also induce regulatory T lymphocytes [Treg, CD25 + FoxP3+; interleukin (IL) 10 producing][14] and downregulate the production of costimulatory molecules (HLA-DR, CD40, CD80, CD86) that activate T lymphocytes.[15] These critical influences promote a tolerogenic or regulatory role for dendritic cells.[16]

T lymphocyte expression of VDR increases upon antigenic activation.[17] 1,25(OH)D acts subsequently to reduce T lymphocyte proliferation (via [down arrow]IL-2) and affects differentiation into effector T-cell populations (via [down arrow]IL-12).[10] Although the conclusions of some studies[18,19] are conflicting, 1,25(OH)D appears to suppress Th1 (cell-mediated) and promote Th2 (humoral) immune processes. Development of Th17 cells, important for neutrophil function and inflammation, are suppressed by 1,25(OH)D via reduced IL-23 and IL-6 production.[20,21] In addition, 1,25(OH)D can also directly induce Treg lymphocyte differentiation.[22] Through autocrine or paracrine pathways,[11] 1,25(OH)D appears to have direct suppressive effects on B-cell proliferation, differentiation (including inhibition of plasma cells and postclass switching memory cell production) and antibody production.[23]

In summary, via multiple immunomodulatory influences acting in concert, 1,25(OH)D appears to suppress cell-mediated (Th1 and Th17) processes, and promote a regulatory or tolerogenic environment that may act to 'contain' autoimmune pathological mechanisms. Figure 1 summarizes the immunomodulatory influences of 1,25(OH)D on the adaptive immune system.[24]

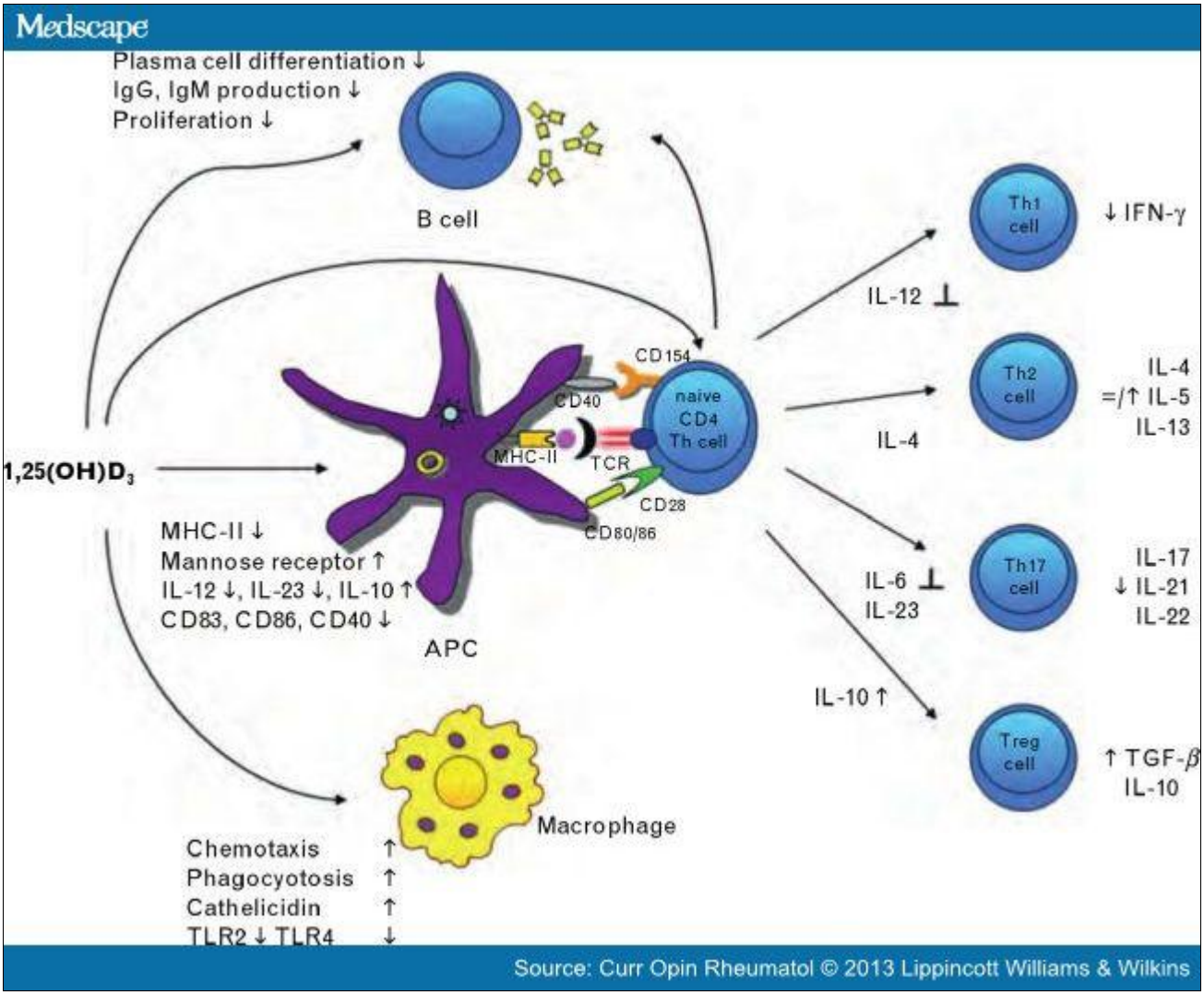

Figure 1.

The immunomodulatory influences of vitamin D on the adaptive immune system (Source: Figure 11.1 in [24]).

Systemic Lupus Erythematosus

SLE is a disease in which sun exposure is an important environmental risk factor for attacks in a substantial proportion of patients. Avoidance of sunlight and use of sunscreens are commonly advised as part of routine therapy so it is hardly surprising that vitamin D deficiency has been sought and found. Indeed, the contrary effects of UVR – to trigger disease but improve vitamin D synthesis, thus, potentially reducing disease – may cause confusion in some of the reported studies.[25] Most of the studies examining the relationship between SLE and vitamin D are cross sectional, so that there is a risk of reverse causality; to date there are no clinical trial data available. Several studies[26–33] have found low vitamin D status in lupus patients when compared with nonaffected individuals. In one study,[30] from Berlin, vitamin D deficiency was present throughout the year in lupus patients, whereas nonaffected participants normalized their vitamin D in summer. These studies are consistent with lupus patients avoiding the sun (and attendant UVB irradiation), and thus lowering their vitamin D levels. A particularly informative study included anti-nuclear antibody (ANA)-positive and negative disease-free patients and looked at patients with and without high B-cell activation. In patients, low vitamin D status was associated with ANA positivity and both high B-cell and IFN-α activity.[34] An association between lupus and vitamin D deficiency in children, stronger in the obese, was reported from Texas.[35] A very interesting study sought to compare a number of environmental factors in lupus-free young women from the Gullah population of the Sea Islands of South Carolina and Georgia, with matched young women from Sierra Leone, the African nation from where the Gullah originated. Vitamin D levels were much lower in the

African–American women, a population with a high incidence of lupus, compared with woman from Sierra Leone where lupus is relatively uncommon.[36] This study[36] at least is consistent with low vitamin D operating as a risk factor. Vitamin D intake was estimated by dietary questionnaire in the Nurses' Health Cohort Studies. Intake either as adults or in adolescence was not associated with the risk of SLE. However, no assessment of exposure to UVR or levels of 25(OH)D was made.[37,38]

Several studies[39–43] since 2008, from many parts of the world, have confirmed a relationship between low 25(OH)D levels and enhanced disease activity. A Canadian study[44] showed that cumulative steroid dose was associated with low 25(OH)D levels, suggestive of a link to higher disease activity. In a predominantly African–American population, there was an inverse correlation between 25(OH)D level and disease activity measured by the SLE Disease Activity Inventory (SLEDAI), and in-vitro work showed that this effect may be mediated via effects on dendritic cell differentiation and maturation that can be reversed by adding 1,25(OH)D.[45] In a related study,[46] disease flares appeared to be triggered by large seasonal declines in 25(OH)D concentration. Two reports demonstrate similar correlations between 25(OH)D levels and disease activity in pediatric patients with SLE.[47,48] In contrast, both Spanish[49] and Korean[31] studies showed no relationship between low 25(OH)D levels and disease activity (as measured by the SLEDAI), although fatigue was increased in the patients with low vitamin D status[50] leading one reviewer to question whether the SLEDAI, which does not include fatigue, is the most appropriate measure of activity.[51]

Evidence of a causal association between vitamin D and lupus risk or disease activity would be strengthened by the finding of an association with polymorphisms in vitamin D-related genes. A number of associations between VDR gene polymorphisms have been reported including a meta-analysis by Lee *et al.* [52] This, like other reports (e.g.),[53] showed a significant association between the *BsmI* polymorphism of the B allele and susceptibility to SLE in Asians, with odds ratio (OR) of 3.58 [95% confidence interval (CI) 1.41–9.13, $P = 0.007$]. Such relationships have not been detected in Whites.[54,55]

Vitamin D supplementation has been advocated for both prevention and treatment of SLE,[25] but as yet there is no high-level evidence to support this and it remains to be seen whether controlled trials with this widely available over-the-counter agent ever emerge.[56]

Rheumatoid Arthritis

At the time of the last review, it was apparent that there was a gradient of increasing prevalence of RA with increasing latitude.[57] Studies of vitamin D produced conflicting results, with the Iowa Women's Health study[58] suggesting a relationship between low dietary intake and increased susceptibility to RA. In contrast, the large Nurses' Health Cohort Studies found no association with dietary intake as measured by questionnaire.[37] These conflicting results raise the question of the utility of dietary questionnaire data without serum levels of 25(OH)D.[6] An interesting study found that, although there was no difference in 25(OH)D levels between RA patients and controls, there was an increased incidence of deficiency in undifferentiated arthritis. Assuming the latter is a frequent precursor to RA, this may be important.[59] Nevertheless, a report from Newcastle in the United Kingdom found no such association.[60] Similarly, no relationship was found between 25(OH)D and levels of rheumatoid factor or anti-cyclic citrullinated peptide antibodies, thought to predict risk of disease.[61] In a challenging commentary, Welsh *et al.* [62] review the literature to 2011 and raise the spectre of reverse causality in regard to many of the previous studies. Among their criticisms of the evidence, they raise the prospect that vitamin D is a phase reactant, but note that low 25(OH)D levels did not increase when remission and reduction of other phase reactants was seen with adalimumab[63] or rituximab[64] therapy.

A number of studies,[65–67] largely in Whites, reveal a link between disease activity and low vitamin D levels. However, in a study[68] involving African–Americans these observations could not be repeated. Similar results were obtained in a mixed-race golimumab trial.[69] The 2009 review in this Journal concluded that the situation with regard to RA and vitamin D was equivocal and this unsatisfactory situation remains.

VDR gene *FokI* polymorphisms of the B allele have been demonstrated in Whites (OR 1.50, 95% CI 1.16–1.95, $P = 0.002$)[52] and Native American populations to be associated with an increased incidence of RA.[70] Any interaction with 25(OH)D levels, for example, wherein a genetic effect in the VDR is apparent only when 25(OH)D levels are low, has not been explored.

Despite enthusiastic reviews postulating the benefits of vitamin D therapy there are few controlled trials.[71] Early RA responded in a controlled trial comparing triple disease-modifying antirheumatic drug (DMARD) therapy and 500 IU 1,25(OH)D_3 + calcium combination versus triple DMARD and calcium alone, in a study from India.[72] Two mechanistic studies[73,74] suggested a permissive role for vitamin D supplementation in developing immune changes that should be favorable. A study[75] of climatotherapy from the Dead Sea in Israel found a correlation between that treatment [that includes sun exposure and increased 25(OH)D levels] and reduced disease activity for a variety of rheumatological conditions including RA. The fact, however, remains that only controlled trials will provide suitable evidence for a therapeutic role of vitamin D alone, or in combination with calcium and disease modifying therapy in RA.[71]

Juvenile Idiopathic Arthritis

There are limited studies so far in this group of diseases. A role for vitamin D has been postulated based on a comparison with other autoimmune diseases.[76] In a US study,[77] although there was no overall relationship, a subset of new-onset patients had a nonsignificant negative correlation between 25(OH)D levels and disease activity.

Systemic Vasculitis

The antineutrophil antibody associated vasculitides have been examined for a latitude gradient and an association with ambient UVR levels.[78] Granulomatous polyangiitis and to a lesser extent Eosinophilic granulomatous polyangiitis were more common at high latitude. As with MS, the effect was greater with ambient UVR than with latitude, and of the same order of magnitude as that seen for MS.[78] This is most plausibly a vitamin D effect, but there are no direct measurements of 25(OH)D levels reported to date in vasculitis.

Psoriatic Arthritis

Two studies,[79,80] one from Spain and one from Canada show low 25(OH)D levels in patients with psoriatic arthritis; the Spanish study suggested an association with activity and obesity. A study[81] from Israel did not replicate these findings; perhaps there is sufficient sun there. Alphacalcidol D3, a vitamin D3 analogue, appears to have positive immunological effects, paralleled by beneficial therapeutic effects, in psoriatic arthropathy.[82]

Scleroderma

A number of studies,[83–88] from France, Israel, Spain, Italy and Germany, have found low 25(OH)D levels in patients with scleroderma. The relationship with various measures of disease severity or extent varied and in two series there was none,[86,88] possibly reflecting the heterogeneity of the different case series. Two studies[83,85] showed a relationship with disease activity. The prospect that extensive skin disease impacts on vitamin D synthesis must be considered in this condition.[84,85] If vitamin D is involved in disease pathogenesis then this may allow for the possibility of disease-driven disease exacerbation.

Behcet's Disease

A Brazilian and a Tunisian study[89,90] both support an association between Behcet's disease and low vitamin D status, with the latter study also suggesting an association with disease activity. The *FokI* F allele and F/F genotype of the VDR gene were associated with Behcet's disease in Tunisian patients,[91] and particularly with the presence of vascular manifestations.

Spondyloarthropathies

A recent Chinese study[92] has demonstrated that, although patients with ankylosing spondylitis were no more likely to be vitamin D deficient than controls, there was an association between low 25(OH)D level and both clinical and laboratory measures of disease activity.

Connective Tissue Disease

A Hungarian study[93] in patients described as having undifferentiated connective tissue disease showed that seasonal variation in 25(OH)D levels was preserved but at lower levels than in controls and associated with worsening of disease and potential progression.

Prevention

There are no convincing studies showing decreases in disease risk following supplementation with vitamin D. Indeed, the ready availability of vitamin D and the clarion call for supplementation[71,94,95] make it unlikely that definitive studies will be carried out.

Treatment

This review documents a substantial number of observational studies demonstrating an association between low 25(OH)D levels and a variety of autoimmune inflammatory rheumatological conditions. A number of reviews have called for therapy with vitamin D. There is speculation that higher doses than appear adequate for bone health may be required.[71,94] A broader review of vitamin D supplementation in autoimmune diseases concluded that there were no clinical trials of vitamin D in rheumatological disorders.[95] Such trials must be carried out.

Conclusion

Many autoimmune rheumatological disorders appear to be associated with vitamin D deficiency and in some cases this extends to an association with disease activity. Genes involved in vitamin D metabolism are also associated. There are plausible immune mechanisms whereby this deficiency could contribute to the disease pathogenesis. At this time there is a paucity of treatment and preventive studies and an urgent need to carry them out.

Sidebar

Key Points

- Low vitamin D status is reported in many inflammatory rheumatic diseases, and has been inversely correlated with disease activity.
- The active form of vitamin D has immunomodulatory effects consistent with a beneficial effect on autoimmunity, that is, vitamin D deficiency is a plausible risk factor for autoimmune rheumatological diseases.
- Variation in measurement and definition of vitamin D status, and evidence arising predominantly from ecological and observational studies, limit confidence that there is a true causal association between vitamin D insufficiency and disease risk.
- Evidence is now required from well designed clinical trials to determine whether there is a causal relationship between vitamin D status and both disease risk and disease activity.

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*This systematic review of the literature on vitamin D and autoimmune disease, including studies from 1973–2011 concludes that the evidence from basic, genetic and epidemiological studies supports that vitamin D may have a potential role in the prevention of autoimmune diseases. However, clinical trials are now required to establish the clinical efficacy of vitamin D for these diseases.

Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest

** of outstanding interest

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