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Vitamin D and autoimmunity

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Objectives: To review and evaluate the role of vitamin D in autoimmune diseases based on current studies.

Method: We searched PubMed using keywords such as ‘vitamin D’, ‘autoimmune disease’, and ‘autoimmunity’. We compiled and reviewed various studies including prospective cohorts, cross-sectional studies, longitudinal evaluations, genetic studies, and experimental models that investigated the role of vitamin D in autoimmune diseases.

Results: There is evidence based on these various studies that several key autoimmune diseases are modulated by vitamin D. These diseases include, but are not limited to, multiple sclerosis (MS), scleroderma or systemic sclerosis (SSc), autoimmune thyroid diseases, rheumatoid arthritis (RA), and primary biliary cirrhosis (PBC).

Conclusions: Although there is evidence for vitamin D as a factor in the pathophysiology of autoimmune diseases, the mechanism for this association has yet to be elucidated. Additional data are needed to corroborate these findings.

The functions of activated vitamin D are numerous. Vitamin D activates the absorption of calcium in the small intestine by binding to calcium transporting proteins (1). It also stimulates osteoclastic maturation, resulting in an increase in bone resorption and the release of calcium into the blood (2). Vitamin D also provides an important support in bone growth by aiding in the mineralization of the collagen matrix (3). For these reasons, vitamin D deficiency classically results in rickets in children and osteomalacia in adults.

Vitamin D may also have many functions apart from calcium homeostasis. Cells in the bone marrow, brain, colon, breast, and immune system have been shown to express the vitamin D receptor (VDR) (2). Thus, vitamin D may be able to regulate the growth and differentiation of these cell lineages, providing a potential tool for immune system modulation (4).

Overview of vitamin D

Vitamin D has two rudimentary forms, D2 (ergocalciferol) and D3 (cholecalciferol). While both may be ingested, vitamin D3 is produced primarily from the precursor protein 7-dehydrocholesterol found in the skin after exposure to ultraviolet B light. Moreover, less than 5% of vitamin D is obtained from the diet, as most is produced by the body (4). Cholecalciferol is hydroxylated in the liver to 25-hydroxycholecalciferol [calcifediol or 25-hydroxyvitamin D; 25(OH)D] by the enzyme D-25-hydroxylase (5, 6). 25(OH)D is then converted to its active form 1,25-dihydroxycholecalciferol [calcitriol or 1,25-hydroxyvitamin D; 1,25(OH)2D] in the kidney by the enzyme 1-α-hydroxylase, also known as CYP27B1 (5, 6).

As hydroxylation in the liver is loosely regulated, circulating levels of 25(OH)D accurately reflect the amount of cholecalciferol produced in the skin or absorbed in the diet, not produced by the body (2). Parathyroid hormone (PTH) and phosphate levels, however, tightly control hydroxylation in the kidney (5, 6). The activated form acts to regulate calcium equilibrium by modifying bone resorption, intestinal calcium absorption, and renal calcium reabsorption (5, 6). As a steroid hormone, activated vitamin D passes through the cytoplasmic membrane of cells and binds to the cytoplasmic vitamin D receptor (VDR). The 1,25(OH)₂D–VDR complex is then translocated into the nucleus to modulate gene expression by acting as a transcriptional factor (6).

Circulating 25(OH)D may also be activated within extrarenal cells containing the 1-α-hydroxylase function, with subsequent binding to vitamin D response elements on gene promoter segments (4). It has been suggested that over 500 genes may be modulated by these activities (4). Notably, cells of the immune system such as B lymphocytes, T lymphocytes, and macrophages have been shown to contain cytoplasmic...
VDR and can activate 25(OH)D into 1,25(OH)D with CYP27B1 (1). This is one example of how vitamin D might modulate the immune response in some individuals and under certain conditions. An important difference between renal and extrarenal sources of 1-α-hydroxylase is the lack of PTH regulation of the extrarenal enzyme (7). Instead, it may be regulated by cytokines such as interleukin (IL)-1, tumour necrosis factor (TNF), interferon (IFN)-γ, or circulating 25(OH) D (8). This regulation presents another facet of the interaction with the immune system and disease progression (7).

Importance of vitamin D for the immune system

Vitamin D has been shown to play a significant role in the function of the immune system, in both innate and adaptive immunity (17–20). Many immune cells express VDRs and possess a mechanism to convert vitamin D into its active form (calcitriol) by utilizing the enzyme CYP27B1 (21). The role of vitamin D in the innate immune system has been elucidated by studies analysing its effect on macrophage killing of mycobacterium tuberculosis (Mtb) (21–23). For example, the gene transcription of the potent antibiotic cathelicidin is regulated by calcitrol (21). Increased expression of cathelicidin coincides with enhanced killing of Mtb by macrophages (21). These studies lend support to the findings that African Americans, who tend to have lower levels of vitamin D, are more susceptible to Mtb infection compared to Caucasians (24).

Of note, calcitriol has also been found to suppress antigen presentation by dendritic cells, therefore favouring T-cell tolerance (17). In addition, activated lymphocytes (both B and T cells) express VDRs (17). The function of three main types of T-helper (Th) cells has been found to be modulated by calcitriol. Cytokine production by Th1 cells, important in cell-mediated immunity, is suppressed by calcitriol (17). Conversely, cytokine production by Th2 cells, important in humoral-mediated immunity, is enhanced by calcitriol (17). The third type of Th cell influenced by vitamin D is the IL-17-producing Th17 cell (25). Inactive vitamin D and calcitrol have both been shown to suppress IL-17 production (25). Moreover, IL-17 appears to play a role in autoimmune disease, as its inhibition by vitamin D was found to suppress murine retinal autoimmunity (26).

VDR agonists also increase the immunosuppressive effect of T-regulatory cells (Tregs) and their recruitment to sites of inflammation (27). These cells function to decrease the immune response by regulating the activity of other T cells. Tregs are capable of inducing transplant tolerance and also arresting the development of autoimmune diabetes in mice (28). Therefore, this class of cells may be significant in the prevention of autoimmunity. This has been demonstrated with calcitriol, a VDR agonist, which has shown the ability to increase Tregs by directly inducing Treg lymphocyte differentiation (29, 30).

With regard to B-lymphocyte regulation, calcitriol suppresses B-cell proliferation, induces apoptosis in activated B cells, and decreases plasma cell generation and class-switched memory B-cells differentiation (31). In essence, vitamin D enhances the innate immune system and regulates the adaptive immune system in a way that appears to promote immune tolerance and thus acts to decrease the likelihood of developing autoimmune disease (32). In summary, the demonstrable ability of vitamin D to affect the immune system in these ways may have its impact on alleviating the detrimental effects of autoimmunity.
Autoimmunity and vitamin D

Epidemiological studies have shown an association between vitamin D deficiency and many autoimmune diseases including rheumatoid arthritis (RA), scleroderma or systemic sclerosis (SSc), systemic lupus erythematosus (SLE), multiple sclerosis (MS), and type 1 diabetes mellitus (T1DM) (27). Ishikawa et al (33) have shown that immunomodulation with vitamin D can impact RA. Of note, a study by Disanto et al (34) showed that autoimmune diseases are influenced by seasons, owing to differences in exposure to ultraviolet radiation, such that the month of birth may be of significance with regard to the risk and onset of an autoimmune disease. Moreover, murine models of MS, RA, T1DM, inflammatory bowel disease, and SLE all demonstrate disease improvement associated with vitamin D supplementation (31). A study in children by Zipitis and Akobeng (35) showed that vitamin D supplementation in early childhood decreased the incidence of T1DM. These studies illustrate the association between a lack of vitamin D and the progression of a number of autoimmune diseases, some of which are described below and shown in Table 1. The table summarizes the various autoimmune diseases, their relevance to vitamin D, disease severity, and the study design used.

MS

There are several important studies that indicated that increased vitamin D levels have an impact on MS. Munger et al showed that high serum levels of 25(OH)D are correlated with a decrease in the likelihood of developing MS (48). Furthermore, Soilu-Hänninen et al (45) showed that serum vitamin D levels differed in individuals suffering from MS depending on whether an individual was in relapse or remission; remission was associated with higher serum levels of vitamin D when compared to periods of relapse (45).

More recently, Holmøy et al found that serum vitamin D levels in the high range of normal correlate with a decrease in the likelihood of relapse and a decrease in disease activity on magnetic resonance imaging (MRI) studies (46). Serum levels of vitamin D have also been shown to be important in the treatment of MS (47). IFN-β treatment, which is a standard of treatment in MS, has been shown to be only effective when vitamin D levels were high (47). MS patients treated with IFN-β when vitamin D levels were low had an increased risk of disease relapse (47).

SSc

While research linking vitamin D and SSc is limited, there are several studies that have shown a negative correlation between vitamin D and disease severity (43, 44, 49). One study showed that fibrosis of cutaneous tissue was correlated to low serum vitamin D levels (32).

However, this finding may be because vitamin D synthesis is affected by the skin pathology (32).

Oral calcitriol supplementation in scleroderma showed positive results in small open-label studies (50–53). However, in one follow-up randomized, double-blind study the effect of oral calcitriol supplementation was no more effective than placebo (54). Topical vitamin D analogues in other studies have shown positive results on cutaneous fibrosis (55, 56).

Studies suggest that the pathogenesis of SSc is related to the role of vitamin D in modulating cytokine transforming growth factor (TGF)-β, a key activator of fibroblast collagen production. For example, Zerr et al (57) analysed VDR expression in fibroblasts of SSc patients and murine models of SSc. They revealed that down-regulation of VDR expression in fibroblasts enhanced the sensitivity of VDR to TGF-β. By contrast, activation of VDR by paricalcitol reduced TGF-β stimulation of fibroblasts.

SLE

SLE disease activity has also been linked to serum levels of vitamin D; lower levels of vitamin D are associated with greater disease severity (40, 41, 58). Additionally, Birmingham et al further showed that SLE flare-up was triggered by large seasonal declines in vitamin D concentration (42). However, some studies are contradictory regarding the increased risk of flare-up. For example, Schoindre et al (59) have shown that lower vitamin D levels are associated with higher SLE activity but are not predictive of disease flare-up (59).

The clinical benefit of vitamin D supplementation in SLE has also been investigated. While some studies have shown no benefit with vitamin D supplementation (60, 61), others have shown that supplementation decreases disease activity (62), proteinuria (62), the amount of anti-DNA antibodies (63), and pro-inflammatory cytokines (64). Therefore, while future studies are warranted, there is a clear association between vitamin D levels and SLE severity.

Sjögren’s syndrome (SS)

Evaluation of vitamin D status in patients with SS had inconclusive results in two small case–control studies. One study showed that vitamin D levels were similar between SS patients and healthy controls (65) whereas the other study indicated that SS patients had an abnormal vitamin D3 metabolism (66). Agmon-Levin et al reinvestigated this uncertainty with a larger case–control study and demonstrated that levels of vitamin D were comparable between SS patients and healthy matched controls (67). Importantly, however, their investigation also revealed that low levels of vitamin D correlated with the presence of peripheral neuropathy and lymphoma in SS patients (67).

The association of vitamin D with neuropathy and lymphoma has also been investigated in other studies.
Table 1. Summary of clinical evidence of vitamin D and autoimmunity.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Relevance to vitamin D</th>
<th>Relevance to disease severity</th>
<th>Study design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 diabetes mellitus (T1DM)</td>
<td>Supplementing vitamin D (High)</td>
<td>Questionable decreased likelihood of developing disease</td>
<td>Systematic review and meta-analysis (35)</td>
</tr>
</tbody>
</table>
| Rheumatoid arthritis (RA)        | Low                    | Low vitamin D intake associated with increased risk of developing disease (36–38) | Prospective cohort study (36)  
54 Italian RA patients and 64 Estonian RA patients, vitamin levels in winter and summertime, as well as for DAS28 (37)  
850 RA men; multivariate logistic regression, adjusting for age, sex, season of enrolment, and race correlated with vitamin D levels (38)  
266 patients in the CLEAR Registry. Baseline plasma, and associations of 25(OH)D with disease status (39) |
| Systemic lupus erythematosus (SLE)| Low                    | Increased disease severity and increased flares of disease         | Cross-sectional study (40)  
Randomized clinical trial (41)  
Specimen bank and database of the longitudinal Ohio SLE Study (OSS) (42) |
| Systemic sclerosis (SSc)         | Low                    | Increased severity                                                  | Independent cohorts of patients (43)  
65 consecutive SSc patients: evaluation of vitamin D and disease severity correlation (44) |
| Multiple sclerosis (MS)          | Lower serum 25(OH)D concentrations in June to September compared with controls (45) | Serum vitamin D levels in the high range of normal correlate with decreased likelihood of relapses and decreased disease activity on MRI studies | Observational, experimental, and clinical studies. Repeated measurements of 25(OH)D in Norwegian patients with MS (46)  
Serum concentration of 25(OH)D at the time of MS diagnosis in 40 MS patients and 40 controls (45)  
Prospective cohort of 178 MS patients with serum 25(OH)D measured biannually, assessment by questionnaire for relevant factors, including IFN-β treatment (47) |

25(OH)D, 25-Hydroxyvitamin D; MRI, magnetic resonance imaging; IFN-β, interferon-β; DAS28, Disease Activity Score based on 28 joint counts; CLEAR, Consortium for the Longitudinal Evaluation of African Americans with Early Rheumatoid Arthritis.
For example, vitamin D has been reported to inhibit lymphoma cell line proliferation (68) and to have neuroactive and neuroprotective properties in the nervous system (69), and its deficiency has been correlated with diabetic neuropathy (70).

Autoimmune thyroid disease

Kivity et al studied vitamin D levels in individuals with autoimmune thyroid disease and compared them to individuals with non-autoimmune thyroid diseases and healthy controls (71). They found that vitamin D deficiency was more prevalent in patients with autoimmune thyroid disease when compared to those with non-autoimmune thyroid disease as well as healthy controls (71). Moreover, the study showed that vitamin D deficiency in patients with autoimmune thyroid disease correlated to abnormal thyroid function tests and the presence of antithyroid antibodies (71). However, other studies, such as the one by Effraimidis et al (72), showed no association between low serum vitamin D levels and autoimmune thyroid diseases. This discrepancy was addressed in a systematic review by Wang et al (73), who established that an association is indeed present. A number of studies have also evaluated the association between VDR gene polymorphism and autoimmune thyroid diseases but the results are inconclusive. To address this, Feng et al (74) meta-analysed eight relevant studies and determined that polymorphism in VDR genes (specifically BsmI and TaqI) were significantly associated with autoimmune thyroid diseases.

Antiphospholipid syndrome (APS)

Several studies have found low serum vitamin D levels to be prevalent among APS patients (75–79) and to be associated with an increased number of thrombotic events (75, 76, 79). Agmon-Levin et al investigated the effect of vitamin D on an in-vitro model of antiphospholipid-mediated thrombosis and showed that it decreased tissue factor induction by antiphospholipid antibodies (aPL) (75).

Obstetric complications in pregnant women are known to be associated with APS. Most studies do not show a correlation between low serum vitamin D and obstetric APS (75, 76, 79). However, one study showed an increased odds of testing positive for aPL among vitamin D insufficient women with recurrent pregnancy loss (80). Mulla et al suggest that the mechanism of obstetric APS is mediated by an aPL-induced pro-inflammatory response in trophoblasts through the TLR4/MyD88 pathway, which compromises trophoblast survival (81). In addition, Gysler et al showed, in vitro, that aPL-induced trophoblast inflammation is attenuated in the presence of vitamin D (82).

Mixed connective tissue disease (MCTD)

Vitamin D levels in patients with MCTD have also been investigated. Hajas et al aimed to determine which endothelial cell markers, clinical symptoms, and laboratory parameters are associated with vitamin D levels (83). They found that patients with MCTD had lower vitamin D levels in comparison to the control group (83). They also determined that vitamin D levels are inversely correlated with the serum cytokines IL-6, IL-23, and IL-10, as well as endothelin levels (83). Importantly, vitamin D deficiency patients with MCTD have a greater chance of developing cardiovascular disease than those with normal vitamin D levels (83). Moreover, decreased vitamin D levels were associated with fibrinogen, total cholesterol, and carotid artery intima–media thickness (83).

Coeliac disease

Lerner et al studied serum levels of vitamin D in coeliac disease populations with the aim of challenging its routine supplementation (84). The investigation led to the finding that vitamin D levels correlated inversely with age; children with coeliac disease were found to have higher serum levels of vitamin D in comparison to adults with coeliac disease (84). Since vitamin D is known to have an effect on immune system regulation, Tavakkoli et al investigated whether low vitamin D levels among coeliac patients was a predictor of other autoimmune diseases (85). With the exception of psoriasis, their results revealed no difference in the overall prevalence of other autoimmune diseases in coeliac patients who had low vitamin D serum levels (85).

RA

With regards to vitamin D supplementation, the risk of developing RA is very controversial. While some studies found the risk of developing RA to be inversely correlated to vitamin D intake (36–38), others did not (39).

In an experimental RA model using rats, vitamin D supplementation was found to suppress the incidence of arthritis and inhibit hind paw swelling (86). In another investigation, fibroblast-like synoviocytes (FLS) purified from rats with arthritis and RA patients were studied in an in-vitro model of a collagen-rich barrier, in the presence or absence of calcitriol (87). In the presence of calcitriol, FLS invasion of the barrier was significantly reduced. Such studies suggest that vitamin D supplementation might have a role in treating RA. However, studies regarding vitamin D supplementation in RA are limited in number and the results conflicting. For example, in two open-label trials supplementation was found to have a positive effect on disease activity (88, 89). By contrast, supplementation did not have a positive effect on disease activity in two subsequent double-blind, placebo-controlled trials (90, 91).
Of interest, the onset, severity, and flares of RA have also been shown to be seasonal dependent (92). For example, Mouterde et al showed that when patients’ first symptoms of RA occurred in winter or spring, the progression of joint structural damage at 6 months was more severe than in those who first became symptomatic in summer (93).

Primary biliary cirrhosis (PBC)

Vitamin D deficiency is highly prevalent in patients with PBC (94). Vitamin D has been shown to have antiproliferative and antifibrotic effects on liver fibrosis (94). Furthermore, genetic studies have determined which proteins link vitamin D to the pathogenesis of PBC (95). These include, but are not limited to, major histocompatibility complex class II molecules, the VDR, toll-like receptors, apolipoprotein E, cytotoxic T lymphocyte antigen-4 (94), and Nramp1 (95). In addition, vitamin D can affect PBC through cell signalling pathways by altering proteins such as matrix metalloproteinases, prostaglandins, reactive oxygen species, and TGF-β (94). In conclusion, vitamin D may have a beneficial role in the treatment of PBC (95, 96).

VDRs and immunomodulation

Agonists specific to the VDR have immunomodulating characteristics, such as anti-inflammatory effects (97). For example, it has been shown that suppression of inflammatory processes by VDR agonists resulted in a switch in the immune response from Th1 to Th2 dominance (97). In addition, an antagonism of the self-enhancing inflammatory loop between immune and resident cells can be observed (98). This antagonism is also associated with cytokine release impairment (97–102). Those molecules are able to inhibit the release of the IFN-γ-induced protein IP-10/CXCL10, a powerful chemokine driving Th1-mediated inflammation (103). Giacomet et al performed a randomized controlled trial consisting of HIV-infected patients with low levels of 25(OH)D who received oral cholecalciferol or placebo (97). They showed that while cholecalciferol supplementation had no effect on CD4 + T-cell counts, there was an associated decrease in the Th17:Treg ratio (97).

It has also been shown that 1,25-dihydroxyvitamin D3 [1,25(OH)2D3] modulates the innate immune response, but the mechanism is not yet understood. Chen et al showed that VDR signalling enhances negative feedback regulation of Toll-like receptors, which play a role in the innate immune system (104). In addition, Chen et al demonstrated that VDR inactivation could lead to a hyperinflammatory response in mice and macrophage cultures when challenged with immunogenic lipopolysaccharides (LPS). This occurred due to the overproduction of microRNA-155 (miR-155), leading to excessive suppression of cytokine signalling 1 (104). Cytokine signalling 1 is a key regulator that enhances the negative feedback loop where the deletion of miR-155 causes an attenuation of vitamin D suppression of LPS-induced inflammation (104). According to Chen et al, this provides corroborating evidence that 1,25(OH)2D3 suppresses cytokine signalling 1 by down-regulating miR-155 (104).

Targeted drug delivery of vitamin D

In countries where there is ample sunlight and vitamin D consumption may be expected to reach acceptable levels, vitamin D deficiency does still persist (105, 106). This, therefore, requires supplementation with vitamin D. However, supplementation has its limits. It should be questioned whether targeted drug delivery could allow a more effective treatment for this deficiency, particularly for autoimmune diseases (107, 108).

Goff et al demonstrated that targeted vitamin D delivery in a murine colitis-induced model could be achieved using β-glucuronides of vitamin D (107). This would allow 25(OH)2D delivery while reducing the risk of hypercalcemia, which could be seen using a native form of 25(OH)2D (107). Goff et al continued to show that bacteria residing in the lower intestinal tract are capable of liberating 1,25(OH)2D from β-gluc-25(OH)D in mice that are hypercalcemic at the time of death. Additional studies showed that using β-glucuronide forms of 1,25(OH)2D and 25(OH)D allows delivery of 1,25(OH)2D and 25(OH)D to the colon in amounts that stimulate colon gene expression and the upregulation of the vitamin D-dependent 24-hydroxylase gene (Cyp24) to a much higher degree than the native hormone, 1,25(OH)2D (108). This may open up the possibility of a future drug delivery system that may address vitamin D deficiency even in areas that are rich in sunlight (107, 108).

Vitamin D target levels and supplementation in autoimmune diseases

Investigations such as those discussed in this review have shown a correlation between low serum vitamin D levels and the incidence of autoimmune diseases. However, there are insufficient significant studies that show that supplementation of vitamin D can help to reduce the risk or severity of autoimmune diseases. The studies that are available are mostly experimental models and only a few studies have been conducted in humans. Furthermore, there is no agreement as to what serum level of vitamin D is required for immune homeostasis (109).

Conclusions

This review has assessed the relevance of vitamin D in different diseases with autoimmune mechanisms. As
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noted, there is mounting evidence that vitamin D has an impact on the pathophysiological mechanisms of autoimmunity, although the mechanisms have yet to be elucidated. Furthermore, additional clinical data are needed to corroborate these findings. The delivery of vitamin D is also important as supplementation using traditional methods has not impacted autoimmunity as expected. Moreover, vitamin D supplementation, particularly with the use of targeted drug delivery systems that are absorbed locally in the gastrointestinal system such as in the colon, may act as an important immunomodulatory medium (17).

References


