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Review

Vitamin D in Prevention of Autoimmune Diseases

Valeria Dipasquale[1,*], Giovanna Lo Presti[1], Gregorio Paolo Milani[2,3], Antonio Corsello[2], Carlo Agostoni[2,3,†], Claudio Romano[1,†]

[1]Pediatric Gastroenterology and Cystic Fibrosis Unit, Department of Human Pathology in Adulthood and Childhood "G. Barresi", University of Messina, 98124 Messina, Italy
[2]Department of Clinical Sciences and Community Health, University of Milan, 20122 Milan, Italy
[3]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Pediatric Unit, 20122 Milan, Italy
*Correspondence: dipasquale.valeria@libero.it (Valeria Dipasquale)
[†]These authors contributed equally.

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Abstract

Vitamin D is essential for the regulation of the immune system. In recent years, the role of vitamin D in the control of several autoimmune conditions such as inflammatory bowel disease (IBD), celiac disease, type 1 diabetes mellitus (T1DM), and others has been investigated. The aim of this review was to define the level of knowledge on vitamin D's role in these disorders, as well as the preventive and therapeutic role of vitamin D supplementation. Relevant studies published over the last 20 years were identified via a PubMed/Medline (http://www.ncbi.nlm.nih.gov/pubmed/) search using the keywords: vitamin D, autoimmune disease, and prevention. Vitamin D deficiency or impaired function of the enzymes necessary for its activity has been shown to affect the onset and severity of the autoimmune diseases examined. Vitamin D supplementation appears useful in the support therapy of IBD. Its role in celiac disease, autoimmune hepatitis, T1DM, and autoimmune thyroiditis is unclear. In conclusion, further studies are needed to define whether vitamin D is a cause or a result of the most common autoimmune, extra-skeletal diseases, such as IBD. Vitamin D should be provided to all newborns during their first year of life. Afterwards, the vitamin D supplementation regimen should be tailored to the presence of risk factors for vitamin D deficiency and/or specific disease.

Keywords: autoimmune disease; vitamin D; prevention; prophylaxis; treatment

1. Introduction

Genetic, immunological, hormonal, environmental, or microbial factors can trigger the development of autoimmune diseases. It has been demonstrated that low vitamin D levels are associated with the development of many illnesses (including upper respiratory tract, enteric, and urinary infections), and that these concentrations may underpin the onset of autoimmune disease. Many autoimmune disorders, such as inflammatory bowel disease (IBD), celiac disease, and type 1 diabetes mellitus (T1DM), are more common in northern latitudes where sun exposure is limited, and vitamin D insufficiency is more prevalent [1]. This is because vitamin D promotes the function of immune cells and the generation of antimicrobial peptides in the immune system [2–6]. The aim of this study was to summarize knowledge regarding the relationship between low vitamin D levels and the most common autoimmune diseases and to investigate the possibilities of supplementing vitamin D in prevention or treatment.

2. Materials and Methods

Relevant studies published over the last 20 years were identified via a PubMed/Medline (http://www.ncbi.nlm.nih.gov/pubmed/) search using the keywords, or combinations of keywords: vitamin D, autoimmune disease, and prevention. The most common autoimmune diseases were afterwards used as search terms to review literature data regarding the role of vitamin D in their pathogenesis. Particular emphasis was placed on primary prevention studies, undertaken prior to any evidence of autoimmunity. Additional papers were identified by reviewing reference lists of relevant publications. Non-English publications were excluded. A systematic approach to study selection was not implemented. Instead, data were extracted based on their relevance to the topic.

3. Vitamin D Synthesis and Mechanisms of Action

Cholecalciferol, or vitamin D3, is primarily generated in the skin from a precursor, 7-dehydrocholesterol, via a photoconversion pathway mediated by ultraviolet B. This is the primary route of vitamin D3 production, although it may also be received from other sources, such as food (in conjunction with vitamin D2) (Table 1, Ref. [1]) or vitamin supplements [7].

Once synthesized, vitamin D attaches to vitamin D-binding protein (VDBP) and undergoes two successive hydroxylations: the first in the liver, mediated by cytochrome P450R1 and minimally by other enzymes, and the second

Table 1. Examples of foods containing vitamin D and relative average amounts (adapted from [1]).

Food	Vitamin D amount (IU)
Cow's milk	5–40/L
Goat's milk	5–40/L
Butter	30/100 g
Yogurt	2.4/100 g
Cream	30/100 g
Pork	40–50/100 g
Salmon, trout, cod	30–1500/100 g
Cod liver oil	400/5 mL
Egg yolk	20/100 g

IU, international unit.

in the kidney, catalyzed by CYP27B1. Once activated, 1,25(OH)2D exerts its functions by binding to its nuclear receptor, the vitamin D receptor (VDR), which is found in a variety of tissues such as the skin, parathyroid, adipocytes, and the intestine [7]. It modulates plasma calcium content in the bloodstream by stimulating the development of osteoclast precursors into mature osteoclasts and enhancing the expression of calcium channels to promote dietary calcium absorption [7]. Recent studies have shown vitamin D-activating enzyme systems and VDRs in immune system cells such as dendritic cells, monocytes/macrophages, and lymphocytes [2,8]. Vitamin D downregulates major histocompatibility complex (MHC) class II and co-stimulatory molecules (such as CD40, CD80, and CD87) on dendritic cells, resulting in decreased activation of CD4+ T cells. Furthermore, vitamin D inhibits dendritic cell cytokine production, notably interleukin (IL) 23, which promotes T helper cell development into Th17 cells. Vitamin D also increases IL-10 expression [9]. Some Toll-like receptors are expressed on the surface of monocytes and macrophages and stimulate the expression of VDRs and CYP27B1 when they bind to microbial (bacterial, viral, or fungal) components. CYP27B1 enters the cell and transforms 25-hydroxyvitamin D (25(OH)D) into the active form of vitamin D. Within the cell, 1,25(OH)2D stimulates the formation of antimicrobial peptides such as cathelicidin and defensin 2, while also regulating the expression of the *DEFB4* gene via the transcription factor nuclear factor (NF)-κB [2,7,10]. Furthermore, 1,25(OH)2D promotes *DEFB4* transcription via NF-κB by inducing the expression of NOD2, a pattern recognition receptor (PRR) that identifies a common peptidoglycan among gram-negative bacteria [2]. It has also been demonstrated that 1,25(OH)2D promotes autophagy in macrophages via cathelicidin and its downstream proteins (p38, ERK, and C/EBP) [2,7,11]. Th1 differentiation and proinflammatory cytokine secretion (IL-2, IFN-γ, and TNF) are inhibited by 1,25(OH)2D, whereas Th2 differentiation and anti-inflammatory cytokine secretion (IL-4, IL-5, and IL-10) are increased [12]. Furthermore, 1,25(OH)2D suppresses Th17-type cytokine release (IL-17, IFN-γ, IL-21, and IL-22) and adversely regulates Th17-type differentiation, encouraging the development of regulatory T cells [11].

4. Vitamin D and Gut Microbiota

The gut microbiota has an increasingly recognized role in the genesis of autoimmune diseases. The microbiota is made up of bacteria, viruses, fungi, and other microbial agents and comprises the entirety of commensal, symbiotic, and pathogenic microorganisms found in the gut. There are approximately 2.8×10^{13} bacteria, with the most common phyla being *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, and *Actinobacteria* [13]. The microbiota aids in the breakdown of food into chemicals and nutrients that may be absorbed and used by the body [14]. The microbiota is established during pregnancy and is impacted by factors such as manner of birth, surrounding environment, nursing, and weaning, among others. Since the introduction of solid food, the microbiota has grown increasingly adult-like, attaining maturity in the first three years of life. The microbiota is required for immune system growth and maturation, including mucosal immunity [12]. Indeed, it has been demonstrated that dysbiosis, or an alteration in the composition of the microbiota, occurs in autoimmune diseases; additionally, specific bacteria differentially promote or inhibit the immune response, demonstrating the critical role of these microorganisms in regulating the immune system response [13,14].

Vitamin D has been shown to influence the makeup of the microbiota. Previous research has demonstrated that a lack of vitamin D owing to dietary restriction, the absence of CYP27B1 or the VDRs stimulates the growth of *Bacteriodetes* and *Proteobacteria* [15,16]. In a cross-sectional study of healthy subjects, vitamin D consumption was linked to an abundance of *Prevotella* and *Bacteroides* [17]. In addition to *Prevotella*, lower amounts of *Haemophilus* and *Veillonella*, both from the phyla *Proteobacteria* and *Firmicutes*, were found [16,17]. In a study that compared biopsies obtained from endoscopic examinations in patients on vitamin D3 supplementation for 8 weeks, it was discovered that the upper gastrointestinal tract had a greater richness of different species, with a reduction in *Proteobacteria* and an increase in *Bacteroidetes*, whereas the lower gastrointestinal tract and feces had no difference in the composition of the microbiota before and after supplementation [14].

Bacteria can also impact vitamin D metabolism; for example, *Streptomyces griseolus* CYP105A1 converts vitamin D3 to 1,25(OH)D via two hydroxylation processes distinct from those discussed above [18]. *Ruminococcus torques* (*Firmicutes*) and *Mycobacterium tuberculosis* both have homologous CYP27A1 and CYP27B1 proteins [14].

Despite this, it remains unclear how vitamin D supplementation or deficiency impacts the microbiota of autoimmune disease patients. Genetic predisposition influences

Table 2. Vitamin D in pediatric inflammatory bowel disease patients [1].

Issue	Recommendation
Vitamin D status check	At diagnosis and at least yearly (serum 25(OH)D levels)
Vitamin D supplementation	Continuous and at least 1000–1500 IU/day (higher doses than those recommended for age) To be done after achieving vitamin D sufficiency (in case of deficiency)
Vitamin D treatment (deficiency)	Daily 2000–4000 IU/day vitamin D for ≥6–8 weeks
Vitamin D treatment (deficiency and poor compliance to daily treatment)	Intermittent bolus doses for a cumulative dose of ≥400,000 IU

IU, international unit.

all aspects of vitamin D activity, intestinal barrier integrity, and immune activation. A lack of vitamin D enhances permeability of the intestinal barrier and immunological activity.

5. Vitamin D and Autoimmune Diseases

It has been speculated that vitamin D, and particularly its insufficiency, is linked to the emergence of autoimmune diseases [1,11]. Below is reported the most recent evidence on the role of vitamin D in the genesis of some of the most frequent autoimmune diseases, such as IBD, celiac disease, autoimmune hepatitis, T1DM, and autoimmune thyropathy.

5.1 Inflammatory Bowel Disease

IBDs, which include Crohn's disease (CD), ulcerative colitis (UC), and IBD unclassified, are chronic inflammatory disorders with periods of activity and clinical remission. Given its function in immune system homeostasis, particularly at the intestinal level, vitamin D has been suggested to be capable of affecting the clinical activity of IBD [19].

The intestinal epithelium is the first line of defense, and its integrity is dependent on vitamin D, among other elements. It has been demonstrated that animals with VDR deletion at the intestinal epithelial level had clinically more severe colitis, with worsened apoptosis and enhanced mucosal response of Th1 and Th17 [13]. In contrast, vitamin D supplementation decreased the severity of colitis in both wild-type and Cyp knock-out mice, who are nonproducers of endogenous 1,25(OH)2D, in a model of acute colitis generated by sodium dextran sulfate. Furthermore, transgenic mice expressing human VDR in intestinal epithelial cells demonstrated better resistance to colitis induction than wild-type mice [20]. Du *et al.* [21] demonstrated that in inflammatory conditions, intestinal VDR is downregulated, which is related to elevated local CYP27B1 expression, as a protective effect for lowering inflammation and boosting VDR signaling. In fact, animals given antibiotics but unable to upregulate CYP27B1 suffered more severe colitis. Furthermore, elevated vitamin D levels appear to be associated with higher serum cathelicidin concentrations and decreased inflammation in UC patients. In a study conducted by Brandvayman *et al.* [19], no significant relationship was found between low vitamin D levels and seasonal patterns in disease onset in children; however, in the case of flares, a higher frequency was observed in June and a lower frequency in April ($p = 0.016$), with significantly lower vitamin D levels as compared to those tested during remission [19]. Low 25(OH)D levels have been linked to a higher incidence of active illness [22]. Notably, low vitamin D levels were seen even in IBD patients in clinical remission [23]. This might be owing to the effect of medicines on micronutrient absorption; for example, glucocorticoids diminish calcium, zinc, and phosphorus absorption and utilization and change vitamin D metabolism. Low or inadequate vitamin D levels are also connected with an increased requirement for admission and surgery in this group of subjects [13].

Vitamin D supplementation in IBD patients may be compromised due to malabsorption; hence, substantial doses of vitamin D are typically necessary to attain optimum serological levels. The optimal dose strategy to treat vitamin D deficiency and maintain adequacy in IBD patients, however, is still being discussed [1]. In pediatric IBD patients, 2000 international unit (IU)/day of vitamin D3 for 6 months was found to be more effective than 400 IU/day or vitamin D2 dosages up to 2000 IU in raising blood 25(OH)D concentrations above 30 ng/mL [24,25]. Oral dosages of 2000 IU/day vitamin D3 and 50,000 IU/week vitamin D2 for 6 weeks were both well-tolerated and superior to 2000 IU/day vitamin D2 in boosting blood 25(OH)D concentrations in IBD patients with vitamin D insufficiency [26]. Simek *et al.* [27] discovered that two weekly vitamin D3 administration regimens for 6 weeks (5000 IU/10 kg/week, maximum weekly dose of 25,000 IU, and maximum cumulative dose of 150,000 IU versus 10,000 IU/10 kg/week, maximum weekly dose of 50,000 IU, and maximum cumulative dose of 300,000 IU) were safe and effective in correcting vitamin D status in IBD children with hypovitaminosis D. Current recommendations on vitamin D supplementation and status in pediatric IBD patients are summarized in Table 2 (Ref. [1]).

Supplementing with vitamin D has been shown to improve disease symptoms. It should be noted that if such individuals have genetic variants or VDR malfunction, supplementation may be changed [9].

Vitamin D supplementation and VDR's anti-inflammatory action are both linked to the gut microbiota. First, there is dysbiosis in IBD patients [28]. CD patients typically have a decrease in the phylum *Firmicutes*, particularly *Faecalibacterium prausnitzii*, and a rise in *Bacteroidetes* and *Proteobacteria*. The microbiota of UC patients is distinguished by a low number of butyrate-producing bacteria and an enhanced *Bacteroides fragilis/Faecalibacterium prausnitzii* ratio, which is linked with a poor anti-inflammatory response [28]. Low amounts of *Faecalibacterium prausnitzii* in the stool have been linked to flares; at normal quantities, they boost IL-10 production while decreasing IL-12 and interferon-γ [13]. In a study of adult CD patients in clinical remission, vitamin D administration for four weeks resulted in alterations in the bacterial makeup of the microbiome, that were not observed in healthy people. The microbiome was enriched in *Megasphaera* and *Lactobacillus* after four weeks [29,30]. Another study in adult patients with active and inactive UC found a significant increase in the abundance of *Enterobacteriaceae* following an 8-week vitamin D supplementation [31]. Zhang *et al*. [32] showed that VDR promotes the expression of the gene producing claudin-2. When VDR regulation at the intestinal epithelium level is missing in an inflamed gut, this tight junction protein hyperfunctions and the intestinal inflammatory response is amplified.

5.2 Celiac Disease

Celiac disease is a chronic autoimmune enteropathy caused by an immune response provoked by gluten in those who are genetically prone to it. It has been proposed that vitamin D insufficiency in childhood may contribute to the etiology of celiac disease by causing incorrect immunological responses, aberrant intestinal mucosal integrity, and reduced local defense against microbial pathogens [33]. A link between sun exposure and celiac disease pathogenesis has been proposed, suggesting that celiac disease is more frequent in northern than in southern latitudes in the United States [34]. Maternal vitamin D supplementation, as well as maternal and neonatal vitamin D status, were not found to be associated with the risk of celiac disease in children [35,36].

Patients with celiac disease have lower vitamin D levels than healthy people [1,37]. Furthermore, patients on a gluten-free diet (GFD) had greater vitamin D levels, with values more equivalent to those reported in healthy controls as compared to patients on a free diet. There is no difference in VDR genotypes between celiac disease patients and controls [38]. The microbiome, which may be important in the development of celiac disease, plays an important role. The microbiome of healthy adults varied from that of celiac patients who have not removed gluten from their diet, and patients on a GFD had a considerable drop in *Lactobacillus* and *Bifidobacterium* in the study by Nistal *et al*. [39]. Furthermore, another study found that pediatric celiac disease patients have a greater incidence of pro-inflammatory and gram-negative bacteria in the duodenum upon diagnosis than controls [40]. As previously stated, vitamin D regulates the gut flora, and a lack of it can increase the evolution of celiac disease through these changes. In addition, celiac disease is linked to gastrointestinal infections. *Rotavirus* infections in children and *Campylobacter* infections in adults, as well as antibiotic exposure and early childhood illnesses, are risk factors [38]. Vitamin D deficiency is known to enhance susceptibility to infections. It has also been demonstrated that chronic vitamin D and VDR deficiency might worsen celiac disease and influence prognosis [41].

Based on the research thus far, it is unclear if vitamin D is a contributing factor or a result of celiac disease. Bittker *et al*. [42] claimed that the high levels of 1,25(OH)2D (as opposed to 25(OH)D, which is low in patients with celiac disease) found in non-GFD patients may be considered a risk factor for celiac disease onset for a variety of reasons, including the association between prolonged oral vitamin D supplementation and an increased risk of celiac disease. The same cytokines, chemokines, and toll-like receptors are upregulated after high doses of vitamin D as well as throughout the disease [42].

5.3 Autoimmune Hepatitis

Autoimmune hepatitis is a disorder defined by an autoimmune reaction initiated by autoantibodies generated against the liver parenchyma, resulting in liver inflammation and, if not treated promptly, progression to cirrhosis and liver failure. In addition, Tao *et al*. [43] evaluated the relationship between low vitamin D levels and indicators of T-cell inflammation/subset in a retrospective study on a cohort of adult patients with autoimmune hepatitis. In this study, patients with low vitamin D levels had an increase in inflammatory response, oxidative stress, and a reduction in T cell subsets. These alterations were significantly different in patients with impaired liver function compared to those with autoimmune hepatitis but normal liver function. The amount of 25(OH)D in individuals with autoimmune hepatitis was found to correlate adversely with inflammatory factors (hs CRP, TNF, IL-6) and oxidative stress factor (malondialdehyde) and positively with CD3+ and CD4+ counts, superoxide dismutase, and total antioxidant capacity [43]. Furthermore, a mutation in the *FokI* gene at the beginning codon of vitamin D receptor exon 2 alters mRNA transcription and replication of VDR, reducing receptor function and leading to immunosuppression, which is the cause of autoimmune hepatitis.

5.4 Type 1 Diabetes Mellitus

T1DM is a polygenic autoimmune disease characterized by a total lack of insulin secretion. Several studies [1] have given light on the link between vitamin D and this condition. VDRs have been discovered at the pancreatic

islet cell membrane, implying a function in glucose regulation [44]. Thus, vitamin D administration may slow the course of previously diagnosed T1DM by boosting pancreatic beta-cell secretion or by immunomodulatory actions. Maretzke *et al*. [45] examined meta-analyses, systematic reviews, and randomized controlled trials that found an inverse relationship between vitamin D supplementation in childhood and the likelihood of developing T1DM. According to these findings, supplementing with vitamin D during pregnancy has no influence on the risk of T1DM in children. However, all of the previous studies are of poor quality. There is insufficient evidence to support vitamin D supplementation as primary prophylaxis [45]. Data on supplementing during pregnancy are debatable, and no indication of protection has been demonstrated [46]. Epidemiological studies, on the other hand, have shown that patients geographically farther from the equator or in locations with longer winters had a higher risk of developing T1DM, indicating the protective role of vitamin D in the genesis of T1DM. Gregoriou *et al*. [47] conducted a high-quality systematic review that included seven randomized clinical trials in which alfacalcidol or vitamin D3 supplementation (0.25–0.5 μg per day) was shown to have beneficial effects on C-peptide levels by lowering daily insulin requirements; calcitriol supplementation had no effect. Polymorphisms in the *VDR* gene may be associated with T1DM. Several studies have linked an increased risk of T1DM to single nucleotide polymorphisms in VDR, particularly *BsmI* and *FokI*. According to Habibian *et al*. [48], serum levels of 25(OH)D greater than 30 ng/mL, as well as specific *TaqI* and *BsmI* SNPS genotypes in VDR, are significantly associated with higher levels of C-peptide (fasting and under stimulus) in patients with TDM1 onset, resulting in increased protection of residual beta-cell quantity and pancreatic function. Further research is needed to better understand the link between T1DM etiology and the aforementioned polymorphisms.

5.5 Thyropathies

Vitamin D is crucial in autoimmune thyroid disorders. Experiments in animal models have revealed that vitamin D insufficiency (25(OH)D $<$20 ng/mL) can control Graves' hyperthyroidism in BALB/c mice and that vitamin D supplementation, when combined with cyclosporine, prevents the development of autoimmune thyroiditis [49]. Vitamin D supplementation showed a protective effect against Graves' disease recurrence with a borderline significant recurrence rate reduction in individuals with Graves' disease and vitamin D deficiency [50]. Serum 25(OH)D levels are considerably lower in individuals with Graves' disease onset when compared to controls, with a clear link between vitamin D insufficiency and increased thyroid volume [51]. Furthermore, severe vitamin D deficiency has been observed in Hashimoto's thyroiditis patients, and the duration of the deficiency correlates with the severity of the deficiency. A case-control study on 90 pediatric patients with Hashimoto's thyroiditis (aged 12.32 $\pm$ 2.87 years) and 79 age-matched healthy controls (aged 11.85 $\pm$ 2.28 years) found a higher prevalence of vitamin D deficiency in cases (71.1%) than that in the control group (51.9%) (p = 0.025) [52]. Kivity *et al*. [53] investigated vitamin D levels in adult patients with thyropathies, as well as the relationship between vitamin D insufficiency and autoimmune thyroid disease, thyroid function, thyroid autoantibodies, and demographic variables. For the first time, a relationship between low vitamin D levels and anti-thyroid antibodies was reported. The latter were substantially more prevalent in vitamin D-deficient individuals than in those with normal levels. Furthermore, because low vitamin D levels and autoimmune thyropathies are more common in women, it is conceivable to propose a link between the two. Women have more autoantibodies, such as thyroglobulin antibody and thyroid peroxidase antibody, and lower 25(OH)D levels than males [54]. This has been confirmed in the pediatric population. In a study of 56 Egyptian children and adolescents with newly diagnosed autoimmune thyroiditis compared to a control group, a significant reduction in vitamin D was shown in subjects with autoimmune thyroiditis [55]. Vitamin D levels also correlated negatively with thyroglobulin antibody, thyroid peroxidase antibody, and thyroid stimulating hormone concentrations and positively with free T4. A lower value of vitamin D levels was shown in patients with overt hypothyroidism rather than in the subclinical disease group [56].

In summary, it is still unknown if vitamin D insufficiency is a cause or a result of autoimmune illness. The role of vitamin D supplementation and its consequent success in the therapy of autoimmune thyroid disease remains debatable.

6. Conclusions

The role of vitamin D has been thoroughly proven, not only in calcium-phosphorus metabolism but also in immune system modulation. More studies, particularly randomized clinical trials, are needed to determine if vitamin D has a causative or consequential role in these extra-skeletal autoimmune diseases since no clear evidence has been found yet. In the management of autoimmune diseases in terms of prevention or treatment, the role of vitamin D should be considered, especially in at-risk categories and/or in the presence of predisposing genetic factors.

Author Contributions

CA and CR designed the study. VD, GLP, GPM and AC performed the literature research. VD and GLP wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

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