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Review Article

Vitamin D Between Non-Skeletal Functions and Autoimmune Diseases: Pathophysiological Perspectives and Therapeutic Potential: A Literature Review of the Current Clinical Evidence

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Abstract

Vitamin D is increasingly recognized as a pleiotropic prohormone with extensive non-skeletal actions that shape immune, metabolic, neuroprotective, and barrier-tissue homeostasis. Immune cells, including macrophages, dendritic cells, monocytes, and lymphocytes, express both the vitamin D receptor (VDR) and 1α-hydroxylase (CYP27B1), enabling intracellular conversion of 25-hydroxyvitamin D into calcitriol and conferring direct control over the innate and adaptive immunity. Vitamin D deficiency is widespread, affecting 15.7% of the global population and exceeding 50% when insufficiency is included, with disproportionately high prevalence in autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, autoimmune thyroid disease, and type 1 diabetes, as well as metabolic disorders including type 2 diabetes and metabolic syndrome. Current evidence supports the concept of vitamin D as a threshold nutrient, with serum 25-hydroxyvitamin D concentrations above 40 - 50 ng/mL required to achieve full beneficial effects and prevent chronic diseases. Interindividual variability in responsiveness, captured by the vitamin D response index, reveals distinct high-, mid-, and low- responder phenotypes, with roughly one-quarter of individuals requiring substantially higher doses to elicit comparable biological responses of vitamin D. This literature review focuses on the non-skeletal functions of vitamin D and some autoimmune and metabolic diseases that are greatly associated with vitamin D deficiency. It aims to clarify the pathophysiological mechanisms that may link vitamin D deficiency to those diseases and to evaluate the therapeutic potential of vitamin D supplementation.

Keywords: *Vitamin D; Vitamin D Receptor (VDR); Autoimmune Diseases; Vitamin D Deficiency*

Introduction

In the late 19th and early 20th centuries, physicians noticed children exposed to more sunlight had lower rates of rickets. In 1922, Elmer McCollum identified a fat soluble factor distinct from vitamin A, B, and C that prevented rickets and named it vitamin D. Most of the vitamin D requirement is produced after exposure to ultraviolet B radiation by summer-like sunlight. Since most vitamin D should be derived from UVB rays from the sun, insufficient exposure is the most typical cause of vitamin D deficiency. Over 50% of the world's population suffers from either deficiency or insufficiency of vitamin D at a given time [1,2]. Vitamin D has traditionally been recognized for its essential role in calcium and phosphate homeostasis and prevention of skeletal diseases such as rickets in children and osteoporosis in adults. However,

increasing evidence has demonstrated that vitamin D exerts a wide range of extra-skeletal effects, particularly in the regulation of the immune system [2,3]. The presence of the vitamin D receptor (VDR) and vitamin D-hydroxylating enzymes, including 1α-hydroxylase (CYP27B1), in various immune cells such as macrophages, monocytes, dendritic cells, lymphocytes, and neutrophils highlights its direct involvement in immune function, including innate and adaptive immunity [1-3]. 1,25-dihydroxycholecalciferol (calcitriol) is the most active vitamin D metabolite and the form involved in all skeletal and non-skeletal functions. The circulating calcitriol does not affect the non-skeletal functions of vitamin D as those functions depend greatly on the calcidiol levels that penetrate the tissues and then produce calcitriol intracellularly. Calcitriol combined with its receptor translocates to the nucleus and regulates the transcription of multiple genes. In addition, Calcitriol has non-genomic and paracrine effects on neighboring cells [1,2].

Multiple epidemiological, systematic reviews, and meta-analysis studies in the last decades have shown consistently lower vitamin D levels in many autoimmune diseases, as well as diabetes mellitus. Many diseases, such as multiple sclerosis, autoimmune thyroid diseases, and rheumatoid arthritis, have shown a strong epidemiological link and immunological plausibility. Vitamin D deficiency has been shown to have an important role in the pathogenesis and immunomodulation of autoimmune diseases. This review focuses on high-quality evidence published within the past five years, identified through systematic searches of PubMed and Elsevier using keywords including vitamin D, autoimmune diseases, immunomodulation, vitamin D supplementation, and vitamin D deficiency.

Physiology of vitamin D

Vitamin D is a fat-soluble vitamin that is absorbed in the intestines along with bile and fats through micelle formation and chylomicron packaging, like the other fat-soluble vitamins, but some researchers prefer to call it a hormone because it is formed mainly in the body and it has extensive skeletal and non-skeletal functions. Besides the classical skeletal functions of increasing calcium absorption from the intestines and the kidneys and increasing bone mineralization, the non-skeletal function has attracted attention recently and has started to be studied extensively. The two major forms of vitamin D are cholecalciferol (vitamin D3), which is either formed in the skin or found in animal foods such as fatty fish like salmon, egg yolks, and liver. The other form is ergocalciferol (vitamin D2), which is found in mushrooms and fungi [4]. Infants and children with vitamin D deficiency and related disorders can take cereals or dairy products fortified with vitamin D. Cholecalciferol is produced in the epidermis from 7-dehydrocholesterol upon exposure to UVB radiation (290-315) by staying outdoors for about 20 minutes between 10 am and 2 pm with arms and legs exposed with no sunscreens. These conditions allow for excellent epidermal penetration that breaks the chemical bond between carbon atoms 9 and 10, forming previtamin D3, which is later converted into chemically stable vitamin D3 (cholecalciferol). Ergocalciferol can also be synthesized under the same conditions but from ergosterol as a precursor. Interestingly, excessive sun exposure does not result in intoxication of vitamin D [5]. Cholecalciferol is more potent, has a longer half-life, and binds with more affinity to the vitamin D receptor when compared to ergocalciferol, which is derived from ergosterol in the skin [6]. After cholecalciferol is synthesized or ingested, it binds to the transporting molecule, vitamin D-binding protein (VDBP) and to a lesser extent, albumin, before undergoing two sequential hydroxylation steps to become biologically active. The first hydroxylation occurs in the liver, where vitamin D is converted by 25-hydroxylase (CYP2R1) into 25-hydroxyvitamin D [25(OH)D], also known as calcidiol. This metabolite represents the major circulating form of vitamin D and the most reliable indicator of vitamin D status, mainly due to its long half-life of nearly three weeks as well as being a key player in the control of non-skeletal functions [3]. The second hydroxylation occurs primarily in the kidney, where 25(OH)D is converted by 1α-hydroxylase (CYP27B1) into the biologically active form, 1,25-dihydroxyvitamin D [$1,25(OH)_2D$], also known as calcitriol. While renal production accounts for the majority of circulating calcitriol, CYP27B1 has been found to be expressed in many tissues other than the kidney, including macrophages, monocytes, dendritic cells, lymphocytes, microglia, parathyroid glands, and epithelial cells of the breast, colon, and skin. This extra-renal synthesis of vitamin D depends on serum 25(OH)D levels and can be negatively regulated through the effect of VDR activation on upregulation of the 24-hydroxylase enzyme, causing degradation of calcidiol and calcitriol and preventing toxic accumulation [7]. On the

other hand, renal CYP27B1 activity is regulated by the classical endocrine loop, stimulated by parathyroid hormone and fibroblast growth factor 23, and inhibited by calcitriol itself [7-9]. Like CYP27B1, the VDR is widely distributed in various body tissues such as renal tubules, parathyroid glands, skin keratinocytes, beta islet cells, thyroid glands, chondrocytes, neural cells, synoviocytes, and many other tissues, but the intestine is characterized by the highest expression of VDR. Activation of VDR by calcitriol allows VDR to translocate in the nucleus either with another VDR or with retinoid X receptor functioning as a transcription regulator by modulating the promoter regions in the vitamin D response elements in the DNA. Vitamin D can modulate about 1000 genes and, with the presence of its receptor and enzymes required for activation in most tissues of the body, can explain its tremendous skeletal and non-skeletal functions [4,10]. Additionally, vitamin D has rapid non-genomic effects, which are mediated mainly by binding to the membrane receptors (VDR and other receptors) and influencing downstream signals, second messengers, and other molecules such as MAPK and protein kinase C signaling, as well as regulating calcium influx. It also can promote endothelial nitric oxide production, improving vasodilation and reducing oxidative stress [1,4]. 25(OH)D and 1,25$(OH)_2$D are catabolized into inactive metabolites by CYP24A1 and excreted in bile.

Vitamin D status, deficiency, and supplementation

Current evidence suggests that the non-skeletal functions of vitamin D need higher serum 25(OH)D than skeletal functions and should be maintained above 50 ng/ml and up to 80 ng/ml [2,8]. Based on the data, we should consider a minimum serum concentration of 50 ng/ml of 25(OH)D as necessary to obtain all the non-skeletal functions and benefits of vitamin D. This serum concentration is also needed for 25(OH)D to diffuse into the target peripheral cells, such as the immune cells, in adequate quantities from the circulation [2].

According to the Endocrine Society guidelines, serum concentrations of 25(OH)D below 20 ng/mL (50 nmol/L) are classified as vitamin D deficiency, and levels between 20 - 29 ng/mL (50 - 75 nmol/L) are considered insufficient. Concentrations of 30 ng/mL (75 nmol/L) or higher are considered sufficient, with optimal levels typically ranging from 30 - 50 ng/mL (75 - 125 nmol/L) [3,5]. The global prevalence of vitamin D deficiency is 15.7% according to a recent analysis of approximately 8 million participants, while other studies indicate that the prevalence in Europe is 40%. This highlights the significance of the issue, considering its beneficial effects and the prevention of many diseases, as well as the need for worldwide screening and correction of deficiency [13]. There is no standard dose for the prevention and correction of deficiency because of the substantial interindividual variability in response. However, most individuals seem to benefit from a daily dose of 1000 IU to prevent deficiency, while a dosage of 40 IU/kg may be more effective for low responders (some suggest a maximum dose of 4000 IU/day for low responders), and a single bolus of 1000 IU/kg can be used to treat severe deficiency [14]. Cholecalciferol is the form that should be considered for supplementation because of its stability and efficacy [11]. The interindividual variability in vitamin D biology prompted the development of the vitamin D response index, which was derived from VitDmet and VitDbol studies that assessed the transcriptional responses to vitamin D supplementation using qPCR and RNA-seq, enabling the classification of the individuals as high, mid, and low responders (25% of the responders). The weak transcription response to vitamin D can reach 40%, highlighting how difficult it is to have a standard universal dose worldwide. Those low responders need the maximal daily doses of vitamin D to achieve its physiological benefits, and they are thought to be more susceptible to autoimmune diseases [14]. The interindividual variability in the response to vitamin D can be due to genetic variations or single-nucleotide polymorphisms in the vitamin D receptor, vitamin D binding protein, vitamin D response elements, and the hydroxylase enzymes involved in activation and degradation. Other factors affecting the vitamin D status can be the latitude, season, sun exposure, skin pigmentation, obesity, dietary intake, age, and comorbidities. These factors create substantial interindividual variability in baseline 25(OH)D and in the pharmacokinetics of supplementation [12]. In addition, evidence strongly suggests that there are thresholds of serum 25(OH) vitamin D to achieve full physiologic effects in target tissues, with 30 ng/ml recommended for skeletal functions and levels above 50 ng/ml for non-skeletal function and immunomodulatory protective effects [2,15]. Taken together, there can be different doses for prevention and treatment of vitamin D deficiency and autoimmune diseases, calling for individualized dosing for individuals guided by serum vitamin D status. Maintaining mean population serum 25(OH)D levels above 40 - 50 ng/mL leads to broader, better health outcomes and reduced healthcare costs. Vitamin D sufficiency should be adopted

before the development of the diseases associated with deficiency, as this approach is both cost-effective and linked to a reduced risk of many chronic diseases associated with vitamin D deficiency [2,16,17].

On the other hand, although vitamin D toxicity is relatively uncommon, healthcare providers should pay attention to this problem as it causes severe complications. The European guidelines reported that levels more than 100 ng/ml are toxicity, while in the USA, the levels considered toxic are higher than 150 ng/ml in some sources. The major complications of toxicity are hypercalcemia, renal stones, abdominal pain, QT interval shortening, constipation, and confusion. These risks emphasize the importance of appropriate dosing and monitoring during supplementation.

Vitamin D immunomodulatory effect

The roles of vitamin D in innate and adaptive immunity have been extensively studied in recent decades in experimental studies and animal models, confirming its crucial roles in enhancing immunity to pathogens, inducing immune tolerance, and fighting autoreactivity. Immune cells possess the necessary machinery to produce calcitriol, which supports these crucial roles. The activation of this machinery depends greatly on the vitamin D status, as well as some environmental factors such as pattern recognition receptors, cytokines, pathogen-associated molecular patterns, and activation of toll-like receptors [7,18]. This local production facilitates autocrine and paracrine signaling, allowing immune cells to regulate their own activity in response to environmental stimuli.

Role of vitamin D in innate immunity

This role was reported about 200 years ago, before the discovery of antibiotics, when sunlight exposure and rich cod liver oil were surprisingly found to be effective in tuberculosis management. That was long before the discovery of antibiotics, and the same treatment was then suggested for leprosy management. Vitamin D was found to be very effective in modulating innate immunity and improving chemotaxis, phagocytosis, intracellular killing, and attacking foreign bodies and pathogens, as well as strengthening epithelial and endothelial barriers [18]. Vitamin D enhances antimicrobial defenses, particularly in monocytes and macrophages, by activation of toll-like receptors and pattern recognition receptors by pathogen-associated molecular patterns, leading to upregulation of VDR and 1α-hydroxylase (CYP27B1) expression in immune cells, promoting local synthesis of calcitriol [7]. The genetic upregulation is caused by many transcription regulators such as STAT1, CEBP, and NF-kB response elements. The increase in calcitriol activates the VDR, which then translocates to the nucleus to upregulate specific genes in the DNA vitamin D response elements, such as Nucleotide-binding oligomerization domain-containing protein 2, hepcidin antimicrobial protein, cathelicidin, and β-defensin 2 [6]. This process can induce the differentiation of monocytes into macrophages and increase the production of antimicrobial peptides such as cathelicidin and defensin β2 [18]. Vitamin D also enhances intracellular killing of pathogens through the activity of nitric oxide synthase activity and increases autophagy. In addition, vitamin D can downregulate TLR2, TLR4, and TLR9 expression to control the activation of monocytes and macrophages and to prevent chronic responses. The reduced expression of TLR can decrease TH1 cells, IL6, and autoimmunity [1,2,8,11]. Finally, proinflammatory cytokines, including IL-1β, IL-6, IL-8, IFN-γ, and TNF-α, are all decreased with calcitriol by inhibiting the activation of p38 MAPK, NF-κB signaling, and other pathways in the monocytes, macrophages, and dendritic cells.

Vitamin D further influences innate immune responses by regulating dendritic cell differentiation, maturation, and function, which is a cornerstone in the activation of adaptive immunity and T cells. It also inhibits monocyte differentiation into dendritic cells. It acts on the myeloid-derived dendritic cells, shifting them into a tolerogenic phenotype. Dendritic cells can be either immunogenic or tolerogenic, controlling the production of T cell subpopulations which direct the body either to immune tolerance or to attack self-antigen in some instances [18]. Vitamin D reduces the expression of CD11c, CD40, CD80, CD86, CD1a, and MHC-II in dendritic cells and decreases antigen presentation. This antigen presentation also decreases in monocytes/macrophages [7,18]. The tolerogenic phenotype favors regulatory T cell (Treg) induction and reduction of proinflammatory T cell activation, like TH-1 and TH-17, which favor immune tolerance [18].

This tolerogenic phenotype increases the production of anti-inflammatory IL-10 and other inhibitory molecules like LILBR4 and TGF-B causing T-reg induction. It also decreases IL-12, and IL-23 which can have a role in autoimmunity [3,4,7,8].

Furthermore, multiple studies have shown various beneficial effects on the body's physical barriers, such as the epithelial, intestinal, and endothelial layers, thus contributing to innate immunity through a different mechanism. Vitamin D promotes the survival of intestinal epithelial cells as well as other epithelial layers by upregulating the tight junction proteins and increasing the secretion of antimicrobial peptides [2].

Role of vitamin D in adaptive immunity

Adaptive immunity leads to a rapid response to repeated exposure to specific pathogens by T and B cells compared to the response to the same pathogens at first exposure, with the production of specific B cells called memory cells that can produce neutralizing antibodies rapidly when the same pathogen is encountered [18]. It involves T and B lymphocytes that recognize antigens and coordinate targeted immune reactions. Autoimmune diseases are linked to persistent harmful activation of proinflammatory T cells and antibody-secreting B cells in the absence of the normal regulating cells of this vicious circle. Our immune system has special Treg cells, which are crucial in peripheral self-tolerance and suppressing T cell responses [7]. Vitamin D inhibits the conversion of CD4+ T cells to Th1 cells and Th17 cells and promotes the conversion of Th1 to Th2 cells. Thus, decreasing TH-1 and TH-17 proinflammatory cytokines like interferon gamma, tumor necrosis alpha, IL-17, IL-21, and interleukin 2, as well as stimulation of TH-2 cytokines such as IL-4, IL-10, and IL-5. Calcitriol also induces FOXP3 and CTLA-4 expression and Treg differentiation, increasing IL-10 and TGF-B and restoring the normal healthy balance of TH17/Treg [7-9,19].

B-cells, plasma cells, and memory cells can be key players in the pathogenesis of many autoimmune diseases, evidenced by the presence of many autoantibodies in those diseases. Vitamin D is known to decrease the activation, proliferation of B cells, differentiation into plasma cells and memory cells, as well as apoptosis of activated B cells through DNA hypomethylation [3]. Given the effects of vitamin D on both innate and adaptive immunity, supplementation can modulate immune responses and prevent many immune-mediated diseases [7]. Vitamin D's full immunologic benefits may need other cofactors and supplements such as Omega 3 fatty acids, which have been shown to decrease the incidence of autoimmune diseases more when added to Vitamin D in the Vital Trial.

Vitamin D neuroprotective effects

Both 25(OH)D and $1,25(OH)_2D$ cross the blood-brain barrier and act directly on neurons, oligodendrocytes, microglia, and astrocytes, all of which express the vitamin D receptor (VDR) and the activating enzyme CYP27B1. Vitamin D, through its receptor, mediates transcriptional regulation and upregulates genes involved in cell survival, myelin maintenance, antioxidant defense, and production of neurotrophins. Vitamin D increases expression of VDR in the neural stem cells (NSCs) and increases its differentiation into oligodendrocyte progenitor cell (OPCs), and that was studied in multiple experimental studies that show $1,25(OH)_2$ vitamin D increases OPCs, myelinating oligodendrocytes, and upregulating myelin proteins. These studies support the role of vitamin D in remyelination, particularly early disease stages when regenerative capacity remains intact [19]. Vitamin D also increases the expression of neurotrophins, such as BDNF, NT-3, CNTF, GDNF, and NGF. The neurotrophins support a repair microenvironment by supporting NSCs and OPCs to promote neuron survival, remyelination, oligodendrogenesis, neurogenesis, and synaptic maintenance [19,20].

The effects of vitamin D on microglia are crucial, particularly in multiple sclerosis, in which microglia differentiate into a pro-inflammatory M1 phenotype, causing antigen presentation and cytokine release as well as contributing to oxidative stress. Vitamin D surprisingly inhibits this phenotype by producing TNF-α, IL-1β, IL-6, IL-12, and inducible nitric oxide synthase. It also promotes a shift

towards the M2 phenotype with the secretion of anti-inflammatory cytokines and phagocytic clearance of myelin debris. This phenotypic shift reduces neurotoxicity and supports tissue repair [19,20].

Astrocytes are also modulated by vitamin D, and these cells become reactive in nerve injury and cause injury expansion. Vitamin D can reduce astrocyte activation and proliferation in demyelination models. Furthermore, vitamin D can stabilize the blood brain barrier (BBB) by reducing VEGF from astrocytes, upregulating claudin-5 and zonula occludens-1, and downregulating ICAM-1 and VCAM-1 adhesion molecules on the endothelial cells. These effects on the BBB can reduce the infiltration of the immune cells and CNS inflammation [19]. Vitamin D also plays a crucial role in upregulation of superoxide dismutase, catalase, and glutathione peroxidase, which strengthen the cellular defenses against oxidative injury.

Vitamin D also influences neurotransmitter systems within the CNS. It is involved in the regulation of dopaminergic, serotonergic, and glutamatergic pathways, which improve neuronal signaling and cognitive processes [19]. It is also involved in [20] neuroplasticity (formation of new synapses, the elimination of existing ones, or the modification of their properties) through regulation of synaptic remodeling, neurotransmitter systems, and calcium-dependent neuronal processes. Adequate levels have good effects on the management of depression and cognitive dysfunction [15]. Vitamin D regulates calcium uptake not only in bone cells but also in the brain and insulin B-cells [7]. Vitamin D further exerts immunomodulatory effects within the CNS by reducing the production of pro-inflammatory cytokines, including interleukin-2, interleukin-6, and interferon-γ, while promoting anti-inflammatory responses with attenuation of neuroinflammation. These neuroprotective functions of vitamin D are crucial in fighting many neurodegenerative diseases and autoimmune neurological disorders and need to be studied more in the future [19].

Vitamin D and gut microbiome

Gut microbiota are the complex microorganisms inhabiting the human gut, particularly the colon, and are composed of many commensal bacteria, viruses, fungi, and parasites that do not cause disease and live in symbiosis. The altered gut microorganism composition-also known as Dysbiosis-[4] disrupts the immune homeostasis and contributes to the pathogenesis of different autoimmune diseases. The normal gut microbiota is dominated by anaerobic bacteria with *Bacteroidetes* and *Firmicutes* (90% of the microbiota) [21]. Vitamin D increases the levels of beneficial bacteria, decreases pathogenic bacteria, and may restore the normal distribution of the gut microbiota. The effects of vitamin D on the gut microbiome are mediated through intestinal epithelial and immune cells, as the microorganisms do not express vitamin D receptors. Vitamin D upregulates the expression of antimicrobial peptides, mainly defensins and cathelicidins from Paneth cells and immune cells. The association between antimicrobial peptides and the gut microbiome is bidirectional; in other words, antimicrobial peptides can selectively damage pathogenic species while maintaining tolerance to other species, and the microbiota can produce specific short-chain fatty acids controlling their production and function [4]. The effects of Vitamin D are not limited to the microbiota but also enhance the expression of intestinal epithelial tight junction proteins, including claudin 2, 5, 12, and 15, which prevent the passage of pathogenic bacteria into the lamina propria and protect against the early pathogenic events in some autoimmune diseases [4].

Vitamin D and autoimmunity

In the last decades, there was a strong association between the worldwide prevalence of autoimmune diseases and vitamin D deficiency, and researchers started to link the role of vitamin D in immune modulation and immune tolerance with the pathogenesis of autoimmune diseases when there is a deficiency. Observational studies provided evidence that vitamin D deficiency can be linked to the risk, activity, and progression of multiple sclerosis, rheumatoid arthritis, autoimmune thyroid diseases, diabetes mellitus, inflammatory bowel diseases, and systemic lupus erythematosus, not only association and prevalence. Moreover, they started to study the role of vitamin D supplementation in the prevention of and clinical improvement of those diseases [18]. In addition, animal studies with vitamin

D receptor knockout have shown an increase in the incidence of autoimmune diseases. This was supported by Mendelian randomization studies that observed that some vitamin D receptor single-nucleotide polymorphisms (SNPs) were associated with altered risk of some autoimmune diseases, suggesting that vitamin D deficiency can be a possible causal factor. The most relevant SNPs are BsmI, ApaI, TaqI, and FokI, affecting VDR translation, mRNA stability, and consequently, the function of the vitamin D receptors and their response to vitamin D immunomodulatory benefits [7].

Several clinical trials and observational studies have demonstrated that vitamin D supplementation can reduce the development, progression, and disease activity of multiple autoimmune conditions. The VITAL randomized controlled trial was very promising and inspired the researchers to test the efficacy of vitamin D supplementation in many autoimmune diseases. The RCT included 25,871 patients from the USA and showed a reduced risk of autoimmune diseases by 22% in those who took vitamin D supplementation of 2000 IU/day for 5 years [12,13]. Similarly, many multiple meta-analyses also reported that vitamin D deficiency increases the risk of developing various autoimmune conditions. This remaining part of the review examines some of the diseases most commonly associated with vitamin D deficiency, with particular emphasis on autoimmune disorders. It aims to clarify the mechanistic role of vitamin D in disease pathogenesis, including its immunomodulatory effects. Furthermore, the review explores current evidence regarding the efficacy of vitamin D supplementation in those diseases.

Multiple sclerosis (MS)

MS is a progressive central nervous system (CNS) autoimmune disorder characterized by axonal demyelination, driven by self-reactive T and B cells activated in secondary lymphoid organs. After crossing the blood-brain barrier (BBB), these cells infiltrate the CNS, recognize self-antigens, and trigger an inflammatory response that leads to demyelination and neuronal damage. MS occurs more in high latitudes, and supplementation of vitamin D due to widespread deficiency has shown decreased incidence of the disease in recent decades. MS is predisposed to by genetic factors but environmental factors dominate. The genetic factors include approximately 200 MS-associated single nucleotide variants especially HLA-DRB*15:01 and environmental factors are high latitude, low sunlight exposure, EBV infection, vitamin D deficiency and adolescent obesity. Vitamin D emerges as a major environmental determinant of MS susceptibility. Several studies indicate that vitamin D deficiency is associated with MS progression, relapse, and severity [7,14]. Vitamin D's protective effects on MS pathogenesis are attributed both to its immunomodulatory properties and its neuroprotective functions on the CNS. It can cross the BBB, accumulate in the nuclei of the neurons and can have effects on oligodendrocytes, microglia, and astrocytes with modulation of the neurotransmitter levels. Microglia are the CNS immune cells whose activation impacts the survival of the neurons and has been associated with MS. Vitamin D can affect microglia function by decreasing proinflammatory cytokines and limiting free radical release, which is protective in MS [7,14]. Vitamin D is thought to maintain the integrity of the blood-brain barrier by supporting epithelial and endothelial layers, reducing self-reactive B and T cells, reducing proinflammatory cytokines, decreasing inflammation, and increasing neuronal regeneration, thus protecting against MS key pathogenic mechanisms. The details of the neuroprotective role of vitamin D in multiple sclerosis are mentioned earlier in the neuroprotective role of vitamin D.

Vitamin D as a modifiable predisposing factor in MS [23] was confirmed by two Mendelian Randomization (MR) studies. The first one showed that only one standard deviation reduction in the genetically determined 25(OH) D level results in a 100% increase in the risk of MS, and the second one used a compelling meta-analysis on the 25(OH)D-associated single nucleotide polymorphisms (SNPs) and showed that increased 25(OH) level was associated with a reduced risk [1]. Vitamin D receptor (VDR) FOKL and VDR TAQL polymorphisms were associated with a higher risk of multiple sclerosis, with the latter showing a weaker and less consistent association [22], but other studies showed an inconsistent association with a decreased risk of MS [24]. These findings are further studied in a meta-analysis that has shown that vitamin D deficiency < 50 nmol/L had a 54% higher risk of MS than those with sufficient vitamin D status [23]. Clinically, a recent

meta-analysis has shown that higher serum 25(OH)D was negatively associated not only with the incidence but also with disease severity, activity, and disability of multiple sclerosis, and there were low levels of vitamin D in MS, particularly with the clinical relapses [22]. Prospective cohorts and epidemiologic analysis have shown that each 20 ng/ml increase in 25(OH)D is associated with approximately a 40% decrease in risk of MS. Studies also confirm that vitamin D deficiency is highly associated with MS, and maintaining high levels of 25(OH)D can decrease relapse rate and new lesions. Specifically, that association was studied on 1000 MS patients with serum vitamin D above 50 ng/ml; the outcome was a 50-70% reduction of relapses. A recent systematic review suggested that each 25 nmol/L increase in 25(OH)D levels is linked to a 31%, 14%, and 19% decrease in the risk of relapse rate, gadolinium-enhancing lesions, and new active lesions, respectively, in individuals with multiple sclerosis [23,24]. Taken together, maintaining sufficient vitamin D may be an important modifiable risk factor for MS, and screening for deficiency is a very important step that should be standardized [23].

A recent meta-analysis has shown that integrating vitamin D supplementation in the management of MS could significantly reduce the annualized relapse rate, particularly with low and medium doses, but it did not significantly affect the expanded disability status scale (EDSS) score [25]. On the other hand, another recent meta-analysis has shown that high-dosage supplementation, not low-dose vitamin D, significantly reduces the annualized relapse rate of MS and improves fatigue, but has no effect on the relapse rate [22]. In a phase 3 randomized controlled trial, researchers tested high-dose vitamin D supplementation in patients with early MS, specifically those with clinically isolated syndrome (CIS). Patients in the treatment group were taking 100,000 IU every 2 weeks for 2 years. The results showed decreased disease activity as well as decreased occurrence of new or enlarged lesions, but there was no significant difference between the two groups in relapse rates and disability outcomes [7,26]. Despite no effects on the relapse rate, the study highlights the potential efficacy of supplementation of high-dose vitamin D to standard therapy due to improving disease activity and reduction of new and enlarging lesions, and these powerful RCTs suggest the crucial role of supplementation in early MS. The same frequency and dosage of vitamin D were used in the choline trial in relapsing-remitting MS patients on their standard IFN β-1a treatment, and showed significant reduction in new MRI lesions, disease activity, and disability progression [7].

Vitamin D protective effects may be more evident in 1) early stages of MS and 2) prevention of new lesions of MS, simply because the vitamin D protective effects play a major role in the pathogenesis of new MS lesions, but have no effects on permanently damaged neurons [14]. High doses for a longer duration of vitamin D supplementation are needed due to the high threshold needed to start the immunomodulatory effect and reset the already hyperactive immune system. More randomized controlled trials on vitamin D supplementation for MS are needed. Future research should put dose, frequency, duration, vitamin D response index, stage of the disease (early vs late), and patient genetics affecting vitamin D metabolism and transport into consideration.

Rheumatoid arthritis (RA)

RA is a chronic inflammatory disease characterized by autoimmune synovial inflammation causing symmetrical peripheral polyarthritis, affecting approximately 40 cases per 10,0000 people annually in the USA, with women being affected 2 - 3 times more often than men. Active RA destroys joints through destruction of cartilage and bone, causing disability and deformity. RA pathogenesis is thought to be due to autoreactive TH1, TH17, TH22, and dysfunctional Tregs. Like other autoimmune diseases, RA is linked with genetic and environmental factors. It can be associated with human leukocyte antigen (HLA) variable genes, but cigarette smoking is the only well-studied environmental risk factor [8]. Vitamin D is believed to have a significant role in the pathogenesis and disease activity of RA, and that is supported by the immunoprotective actions of vitamin D on TH1, TH17, and Tregs (the main immune cells involved in pathogenesis). Vitamin D not only causes immunomodulation but also can decrease chronic synovial inflammation and osteoporosis, which is very common in rheumatoid arthritis. The risk of rheumatoid arthritis (RA) is associated with vitamin D deficiency [1], and women in the highest tertile of vitamin D intake had a 24%-33% risk reduction in RA when compared to those in the lowest tertile, but other studies show inconsistent results including a recent meta-analysis [7], but other meta-analyses showed no association between vitamin D levels and RA risk but there were heterogeneity and lack of precision between studies [27]. The vitamin D intake that keeps

serum vitamin D status above 50 ng/ml is widely accepted to gain its protective skeletal and non-skeletal functions and to reduce the risk of autoimmune diseases [8]. Regarding the prevalence of vitamin D deficiency, several studies have shown that vitamin D deficiency has a high prevalence in RA [28] and that high disease activity is associated with low serum levels of 25[OH]D [6,27,28]. These associations were supported by a meta-analysis that included 3489 patients from 24 studies, which revealed a high prevalence of vitamin D deficiency in RA patients compared to healthy controls, and higher vitamin D levels were associated with lower disease activity and C-reactive protein levels [27].

Many studies have shown that vitamin D supplementation can increase Tregs and IL-10 and inhibit CD4+ T cell differentiation, restoring a normal TH17/Treg ratio, which is crucial to RA patients who already have low Tregs in their blood [7]. The current evidence suggests vitamin D supplementation can be added to the management of RA, given the mechanistic link to pathophysiology, association with the development, and protective immunomodulatory benefit [28]. A recent meta-analysis of 6 RCTs of 438 RA patients showed significant improvement in DAS28, tender joint count, and reduction of ESR with vitamin D supplementation, but the evidence was limited by a small number, short duration, and significant heterogeneity. The inconsistency of the findings and the outcomes, particularly regarding improvement in disease activity, necessitates future large multicenter RCTs.

Juvenile idiopathic arthritis (JIA)

Juvenile idiopathic arthritis (JIA) is a group of chronic arthritides that start before the age of 16 years and have seven subtypes. The symptoms are similar to adult RA but also involve axial joints as well as extra-articular structures such as uvea, skin, bursa, and internal organs [5]. Children with JIA exhibit lower baseline serum 25(OH)D levels compared with healthy controls, with a systematic review and meta-analysis showing that vitamin D deficiency/insufficiency is present in 82% of JIA patients [5,29]. Whether deficiency contributes to disease onset, severity, or progression remains unclear and inconsistent among studies, and further research is still needed [29].

Diabetes mellitus

Diabetes mellitus is a group of metabolic disorders characterized by chronic hyperglycemia resulting from absolute or relative insulin deficiency and/or insulin resistance. Its global prevalence has risen steadily over the past 15 years, highlighting a major public health concern. Diabetes mellitus prevalence is expected to grow to affect 12.2% of adults by 2045, rising from 10.5% in 2021 [30]. Multiple studies support an association between vitamin D deficiency and diabetes. VDRs are expressed in pancreatic β-cells, which also possess 1-α-hydroxylase, enabling local production of calcitriol within the pancreatic β-cells. The human insulin gene contains a vitamin D response element on the DNA promoter area, suggesting direct transcriptional regulation of insulin gene expression [31]. Vitamin D also regulates the genes needed for glucose transport and pancreatic β-cell survival. In addition, calcitriol can increase calcium intracellularly, leading to the release of insulin granules [32]. Finally, vitamin D modulates T-cell responses, antigen presentation, and B-cell maturation, reduces pro-inflammatory cytokines; and may protect β-cells from immune-mediated B-cell destruction, mechanisms particularly relevant to type 1 diabetes.

In the peripheral tissues, vitamin D is thought to decrease the chronic inflammation that drives the insulin resistance mainly through decreasing CRP, TNF, and IL-6 and increasing T-regs. It can also increase insulin expression (muscles, adipose tissue, liver) [34] and downstream signaling, as well as increase GLUT-4 translocation in the skeletal muscles [32]. In adipose tissues, vitamin D increases adiponectin and leptin and decreases resistin and other pro-inflammatory cytokines with improvement in metabolic balance. It can also modulate peroxisome proliferator-activated receptor-δ (PPARδ), which counteracts insulin resistance caused by hyperlipidemia [34]. Vitamin D reduces oxidative stress, which is a major driver of β-cell dysfunction and impaired insulin signaling in type 2 diabetes.

Furthermore, vitamin D can have some inhibitory effects on the renin-angiotensin-aldosterone system, which can increase insulin sensitivity [32].

Vitamin D is associated with diabetes mellitus and increases the risk of diabetic complications [33]. Vitamin D can also be associated with fatty liver and metabolic syndrome. Current evidence suggests the inverse association between vitamin D levels and insulin resistance [17,30,34]. These effects on insulin sensitivity are supported by epidemiologic observational studies showing that individuals with high levels of serum 25-hydroxyvitamin D exhibit substantially lower risk of developing type 2 diabetes, and Mendelian randomization analyses further support the reduced diabetes risk among individuals with genetically determined higher VitD status, reinforcing the crucial role of vitamin D in the onset of diabetes mellitus type 2 [12].

Vitamin D deficiency was also found in studies to be more prevalent in Latent Autoimmune Diabetes of the Adult (LADA). In a study that examined 90 patients with diabetes mellitus, vitamin D levels were low in 67% of the patients suffering from LADA, and those low levels were associated with anti-GADA titers; thus, vitamin D deficiency can have a crucial role in autoimmune attack on beta cells [31].

Type 1 diabetes (T1DM)

T1D is an autoimmune disorder in which immune-mediated destruction of pancreatic β cells leads to the loss of endogenous insulin production, thereby necessitating replacement therapy. Macrophages, CD8+ T, Th1, and Th17 cell infiltration in pancreatic islets, as well as Treg dysfunction, contribute to disease pathogenesis [7]. A 2024 systematic review, including 45 studies (n = 6995), estimated that the pooled prevalence of vitamin D deficiency in children and adolescents with type 1 diabetes was 45% [35]. The strongest epidemiologic evidence comes from the Finnish birth cohort, which showed that vitamin D supplementation during infancy was associated with a much lower risk of later T1DM. Subsequent meta-analysis of 8 observational studies showed 29% lower odds of developing T1DM among supplemented individuals. Furthermore, a recent meta-analysis provides robust evidence that lower circulating 25(OH)D levels are associated with higher T1DM risk and argues that there is a dose-response inverse association between vitamin D levels and T1DM risk [36]. Thus, screening for vitamin D deficiency in children and adolescents with T1DM should be considered because it is greatly prevalent and has been associated with the onset of the disease [35,36].

On the other hand, in a pediatric case-control study, severe deficiency was strongly associated with higher HbA1c, higher daily insulin requirements, and poor glycemic control in T1DM patients. Moreover, combined therapy with sitagliptin (a DPP-4 inhibitor) and vitamin D in newly diagnosed patients was associated with prolonged clinical remission in the honeymoon phase [31]. In T1DM, the honeymoon phase is a stage of clinical remission that occurs after the initial phase of the disease requiring insulin therapy, during which islet cell function may return partially or completely. Vitamin D may prolong this phase by its immunomodulatory effects and reduction of anti-inflammatory cytokines [33]. In the clinical world, a recent meta-analysis shows vitamin D supplementation significantly reduced insulin requirements, fasting blood glucose (FBS), and elevated 25(OH)D levels, but there was no positive impact on hemoglobin A1c (HbA1c) [38]. Furthermore, there was an unexpected decrease in fasting C-peptide levels, which may be due to variable B-cell functions [38]. Vitamin D supplementation appears to enhance β cell function [7], and a double-blind, randomized, controlled clinical trial showed that vitamin D supplementation improved β-cell function in patients with serum 25(OH)D levels below 12 ng/mL compared to placebo [33]. Therefore, growing evidence supports adding vitamin D to the standard treatment, but other large clinical trials gave inconsistent benefits and findings even in early disease, and large double-blinded RCTs are still needed [32,38].

Type 2 diabetes (T2DM)

In T2DM, the body has less response to insulin, and, over time, the pancreas does not make enough insulin to compensate for this. Insulin resistance is the primary pathogenic mechanism, contributing to impaired glucose tolerance, disease progression, and complications. Insulin resistance is also the pathophysiological mechanism of metabolic syndrome, which is a very important risk factor for Type 2

diabetes [30]. Although insulin resistance is well known to be linked with specific unhealthy fats and carbohydrates, vitamin D is gaining popularity in insulin sensitivity (as mentioned earlier), as well as T2DM. The role of vitamin D deficiency in insulin resistance has been described in many studies. Cross-sectional studies link low VitD to higher fasting glucose, higher HbA1c, greater insulin resistance, and more adverse cardiometabolic profiles [12]. The studies have shown a very high prevalence of vitamin D deficiency among prediabetic and T2DM patients. In a large prospective population cohort in Denmark with 29 years of follow-up and about 10000 participants, they found that lower vitamin D was associated with a higher incidence of T2DM with a strong dose-response relationship. Another meta-analysis of 21 prospective studies showed that participants in the highest vitamin D group were associated with a 38% lower risk of T2DM. In a univariate regression analysis on 126 glucose-tolerant patients, patients with vitamin D deficiency were found to have a higher risk of developing insulin resistance, suggesting a protective role of vitamin D in insulin resistance and that deficiency can be a modifiable risk factor [32]. Additionally, individuals with prediabetes and low vitamin D progress more rapidly to T2DM. Several studies have shown that vitamin D supplementation not only reduces the risk of T2DM but also may protect prediabetes patients from developing T2DM and can even normalize their glucose tolerance [32,33]. Moreover, observational studies have shown a negative correlation between vitamin D levels and other metabolic disorders linked to insulin resistance [30]. Thus, Vitamin D deficiency should be considered as a modifiable risk factor for these metabolic disorders. Regarding Vitamin D supplementation, many studies have tried to elucidate the efficacy of vitamin D supplementation in T2DM. On insulin resistance, supplementation significantly relieved insulin resistance compared to controls in a recent meta-analysis [30]. On clinical parameters, a modest reduction was noted in HbA1C, insulin resistance (HOMA-IR), and no difference in FBG (fasting blood glucose) after vitamin D supplementation in T2MD [30]. The current evidence supports that prevention of vitamin D deficiency and maintaining sufficient levels by supplementation of moderate doses of vitamin D should be a standard guideline in health care practice in Type 2 diabetes and can decrease the risk, the progression and even the complications of T2DM [33,34], and can be used as an adjunct but large randomized controlled trials are still needed because other trials and patients showed inconsistent findings and clinical outcomes [34].

Autoimmune thyroid disease (AITD)

AITD is the most frequent autoimmune disease with an estimated prevalence of 5%. Adult women have a higher risk of developing thyroid autoimmunity than men [39]. The most common AITDs are Hashimoto's thyroiditis (HT) and Graves' disease (GD), with more evidence linking vitamin D to HT. HT has infiltration of CD4 T helper cells, cytotoxic T cells, B cells, macrophages, and plasma cells with production of autoantibodies, while GD has a stronger TH2 component and B-cell activation with autoantibody production. In addition, thyroid follicular cells can increase MHC-II expression and perpetuate the autoimmune response. Vitamin D was found to have very beneficial suppressive effects on B cells, T cells, dendritic cells, and inflammatory cytokines such as IL-17, as well as decreasing MHC-II expression on thyroid follicular cells and increasing IL-10 and TGF-β, breaking the autoimmune loop [1,2,16,39]. The effects of vitamin D on B cells are protective and can decrease thyroid autoantibodies, particularly in Hashimoto's thyroiditis, as it reduces B cell maturation and plasma cell formation [3]. Vitamin D can also modulate the gut microbiota and decrease the incidence of thyroid diseases. Vitamin D deficiency is increasingly recognized as a risk factor for autoimmune thyroid disorders, and meta-analysis and systematic reviews showed that vitamin D deficiency was greatly associated with Hashimoto's thyroiditis (HT), hypothyroidism, and Grave's disease (GD) when compared to healthy controls [4,10,40,42]. Moreover, a recent Mendelian randomization study showed a decreased risk of autoimmune thyroiditis with higher genetically predicted vitamin D, suggesting a possible vitamin D deficiency can be a causal factor [4]. Other studies showed no association of AITD with VDR polymorphisms [11]. Therefore, vitamin D deficiency can be considered a modifiable risk factor [26,39]. Furthermore, vitamin D status has been correlated with thyroid function and was inversely associated with TSH levels, suggesting that deficiency can have a role in hypothyroidism. Thus, screening for vitamin D deficiency in the management of AITD should be performed and corrected if present because of the strong association with pathogenesis and risk of the disease [41].

HT is the most common cause of hypothyroidism worldwide and is characterized by the presence of circulating anti-thyroid peroxidase antibodies (TPOAb) or anti-thyroglobulin antibodies (TgAb). The disease is primarily driven by a CD4+ Th1-mediated immune

response, causing damage to the thyroid follicles. Vitamin D levels are inversely associated with the development and progression of HT [9], and it is prevalent in 60% of patients [9]. This association with the disease was greatly documented in multiple meta-analyses and systematic reviews [13]. Vitamin D supplementation in HT patients has shown beneficial immunomodulatory effects in HT patients, but furthermore, more powerful randomized controlled trials are still needed [13]. Most of the randomized controlled trials showed positive results in HT with a significant reduction in TgAB and TPOAB when different doses and frequencies of vitamin D were administered [41]. Additional RCTs testing higher doses and longer duration showed that daily doses of 2000 - 4000 IU or weekly doses of 50,000 - 60,000 IU over 8 - 12 weeks showed reductions in thyroid autoantibodies. Meta-analyses further support these findings, indicating that vitamin D supplementation can reduce TPOAb titers by 15 - 30%, particularly in individuals with euthyroidism or subclinical hypothyroidism. Conversely, this immunological benefit appears to be attenuated in patients with overt hypothyroidism, suggesting that early correction of vitamin D deficiency may help limit antibody production before irreversible thyroid damage occurs. On the other hand, certain patients exhibit a lack of response to vitamin D supplementation, potentially attributable to polymorphisms in the VDR gene, such as FokI, BsmI, ApaI, and TaqI, which are recognized to affect receptor function [11] and may affect both susceptibility to HT and the efficacy of vitamin D supplementation [9]. Taken together, vitamin D deficiency should be screened for and corrected to sufficient levels, as it can serve as an adjuvant to the standard treatment of HT and shows promise [13], given the beneficial immunomodulatory effects of supplementation and its association with the risk of developing HT [41].

In Grave's disease (GD), vitamin D has a great immunomodulatory effect that can affect its pathogenesis, particularly decreasing the level of inflammatory Th1 cytokines and reducing thyroid receptor antibodies (TRAb) production [26]. There is growing evidence that low serum 25(OH) may increase the risk of GD in a recent meta-analysis [26,43]. But trials of vitamin D supplementation have not shown a consistent effect on thyroid receptor antibodies or thyroid hormone levels and function [9]. The existing data show only an association of vitamin D deficiency with GD, but whether supplementation is beneficial or not is still an unresolved issue and needs further research and large RCTs [43].

Inflammatory bowel diseases (IBD)

There is a strong association between the altered gut microbiome (gut dysbiosis) and IBD. This gut dysbiosis shifts more towards pathogenic bacteria instead of commensal bacteria that can be detected by the immune system as a foreign antigen, attacking self-antigens by the molecular mimicry concept, thus causing autoimmunity. In addition, the presence of an intact mucosal layer and intestinal epithelium prevents the entry of this pathogenic bacterium into the interstitium thus damage of these layers and the presence of pathogenic organisms in the microbiome are closely related to the pathogenesis [21]. Thus, barrier dysfunction with microbial exposure leads to innate and adaptive immunity activation with TH1, TH2, and TH17 activation. Vitamin D can have very useful functions in IBD, not only related to immunomodulation but also to modulating the gut microbiome, increasing the tight junction expression, and strengthening the intestinal epithelium and mucosal barrier. It can stimulate Treg formation, anti-inflammatory cytokines, antimicrobial peptides release, and decrease TH1 and TH17 [1]. A recent meta-analysis of 55 observational studies showed that vitamin D deficiency was greatly associated with IBD. Evidence supports the inverse correlation between disease activity and vitamin D levels. In addition, a large prospective cohort study with a 22-year follow-up period and 22000 women without IBD showed that women who were in the highest predicted vitamin D category had a 46% reduction in risk of Crohn's disease, but the results of ulcerative colitis were statistically insignificant. Vitamin D deficiency in IBD is caused greatly by malabsorption due to loss of intact absorptive surface as well as corticosteroids and reduced outdoor activity. There is growing evidence suggesting that vitamin D supplementation is associated with clinical improvement and decreased disease activity [21]. Therefore, these patients should be screened and treated for vitamin D deficiency. Studies have shown that oral vitamin D supplementation is associated with a positive change in gut microbial composition in patients with IBD, as mentioned earlier, which can decrease the overall gut inflammation in both CD and UC. Various clinical trials reported that vitamin D supplementation was beneficial in patients with IBD by decreasing the relapse rate, but most of them were of low quality and power. Further RCTs are needed with a large sample size, long follow-up, and uniform dose, frequency, duration, and standard clinical outcomes measured.

Systemic lupus erythematosus [SLE]

SLE is a chronic, destructive autoimmune disease, with women being affected 9 times more than men. The etiology is not clear, but genetic and environmental factors have a role in disease pathogenesis, which disrupts the self-tolerance and induces autoimmunity against self-antigens. Clinically, SLE manifests with different symptoms, which range from mild to severe. The disease commonly presents itself with cutaneous, joint, serosal, and renal involvement. SLE patients suffer from photosensitivity, which decreases sunlight exposure, and renal disease, which can cause vitamin D deficiency. Corticosteroids are the mainstay of treatment, which can also cause vitamin D deficiency [7]. SLE can increase TH17 and disrupt Treg formation with various effects on other T cells. The most common autoantibodies in SLE are anti-dsDNA, ANA, anti-Sm/RNP, and anti-Ro/La [8].

Vitamin D deficiency has been widely associated with SLE patients and has been linked to disease activity, flares, and pathophysiologic mechanisms. Moreover, there was decreased vitamin D receptor expression in lupus nephritis on renal biopsy [8]. Observational studies have shown a consistent inverse association between vitamin D levels and SLE and the systemic lupus erythematosus activity index scores (SLEDAI). Vitamin D deficiency is also associated with increased anti-dsDNA. That can be explained by the effects of vitamin D on B cell maturation and apoptosis, plasma cells, monocytes, dendritic cells, and T cell differentiation, which favor immune tolerance [7]. The observational and cross-sectional studies showed inconsistent findings related to the association between vitamin D deficiency and the risk of developing SLE, but they showed a strong correlation to anti-dsDNA positivity and remission. In a recent meta-analysis of ten randomized controlled trials with a total of 800 patients with SLE, vitamin D3 supplementation was found to decrease disease severity (SLEDAI) in patients with SLE in the majority of the included studies. Moreover, a cross-sectional study reported that vitamin D deficiency is highly associated with juvenile systemic sclerosis (jSLE) as well as disease activity and biomarkers. Two RCTs were performed in 2016 and 2017, investigated vitamin D's influence on jSLE, and both used a high dose of 50000 IU/week for 24 weeks. The first RCT showed significant improvements in disease activity and fatigue scores. The second RCT showed significant improvement in bone microarchitecture [5].

Further research is still needed to further study vitamin D supplementation in SLE patients despite those promising results and its protective role in SLE. The bottom line is that vitamin D deficiency is very common in SLE and should be screened for and treated to prevent skeletal and non-skeletal complications.

Conclusion

The roles of vitamin D in immune modulation, immune tolerance, insulin sensitivity, pancreatic β-cell function, and other non-skeletal functions are widely reported and increasingly studied in recent decades. The prevalence of vitamin D deficiency is about 15% worldwide, with supplementation more common in developed countries compared to developing countries. Vitamin D deficiency is associated with the onset, progression, and activity of many autoimmune diseases. Some studies showed that vitamin D deficiency can be a causal factor in some of these diseases. The vital trial and the non-skeletal functions of vitamin D have paved the way for the use of vitamin D supplementation in the prevention and treatment of various diseases, with a specific focus on preventing vitamin D deficiency, which can be considered as a form of primary prevention for many diseases. Further research is needed to elucidate the direct implication of vitamin D in many disease pathogeneses, such as autoimmune diseases and diabetes mellitus, and to optimize vitamin D supplementation in these diseases through future large, long-duration randomized controlled trials. The existing literature has weak points, which include the predominance of cross-sectional and observational studies, heterogeneity of vitamin D assays, cutoffs of deficiency, confounding by disease severity, comorbidities, obesity, lifestyle factors, medications, small, short randomized controlled trials, and lack of stratification of patients based on baseline vitamin D status, suggested dosage and frequency, disease phenotype, and genetic variations between patients.

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