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The Implication of Vitamin D and Autoimmunity: a Comprehensive Review

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Abstract Historically, vitamin D has been associated with the regulation of bone metabolism. However, increasing evidence demonstrates a strong association between vitamin D signaling and many biological processes that regulate immune responses. The discovery of the vitamin D receptor in multiple immune cell lineages, such as monocytes, dendritic cells, and activated T cells credits vitamin D with a novel role in modulating immunological functions and its subsequent role in the development or prevention of autoimmune diseases. In this review we, discuss five major areas in vitamin D biology of high immunological significance: (1) the metabolism of vitamin D; (2) the significance of vitamin D receptor polymorphisms in autoimmune diseases, such as multiple sclerosis, type 1 diabetes mellitus, and systemic lupus erythematosus; (3) vitamin D receptor transcriptional regulation of immune cell lineages, including Th1, Th17, Th2, regulatory T, and natural killer T cells; (4) the prevalence of vitamin D insufficiency/deficiency in patients with multiple sclerosis, type 1 diabetes mellitus, and systemic lupus erythematosus; and finally, (5) the therapeutic effects of vitamin D supplementation on disease severity and progression.

Keywords Vitamin D · Autoimmunity · Multiple sclerosis · Type 1 diabetes mellitus · Systemic lupus erythematosus

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Introduction

Vitamin D deficiency is an increasingly described phenomenon worldwide [1]. Compelling evidence from human disease associations and basic physiological studies demonstrated the significance of vitamin D deficiency in various physiological disorders including neuropathy [2], malignancy [3, 4], infertility [5], cardiovascular diseases [6, 7], kidney diseases [8], glucose metabolism [9], and immunological dysfunctions [10–13]. Vitamin D was first identified as a nutritional regimen for rickets in the early twentieth century and was broadly defined as a compound with curative effects on rickets. Chemically, vitamin D is the derivative of a steroid, 7-dehydrocholesterol, derived from cholesterol and is found in the sebaceous glands of the skin of animals. Upon exposure to sunlight, 7-dehydrocholesterol will absorb UVB light (~280 to 315 nm) and convert to precalciferol (also called previtamin D_3) in the skin. Much of the precalciferol eventually is isomerized into cholecalciferol (also called vitamin D_3) through thermal conversion [14]. Since sunlight is necessary for photosynthesis of previtamin D_3 in human skin, vitamin D is also commonly called "sunshine vitamin" (Fig. 1). In addition to 7-dehydrocholesterol in animals, ergosterol is another commonly occurring steroid in plants that can be activated by irradiation to produce ergocalciferol (also called vitamin D_2).

Both vitamin D_3 formed in the skin and vitamin D_3 absorbed from the digestive tract, travel to the liver, where they are hydroxylated at carbon 25 to form clacidiol (also called 25-hydroxy vitamin D_3, abbreviated as 25(OH)D) by liver 25-hydroxylase, CYP2R1 and CYP27A1. 25(OH)D is the major circulating vitamin D metabolite and a reliable indicator of vitamin D status. Following the hydroxylation in liver, calcidiol is further hydroxylated by 1-α-hydroxylase, CYP27B1, in the proximal convoluted tubule cells of kidney, forming calcitriol (also called 1,25-dihydroxy vitamin D_3, abbreviated as $1,25(OH)_2D$) which is considered the active form of vitamin D [15] (Fig. 1).

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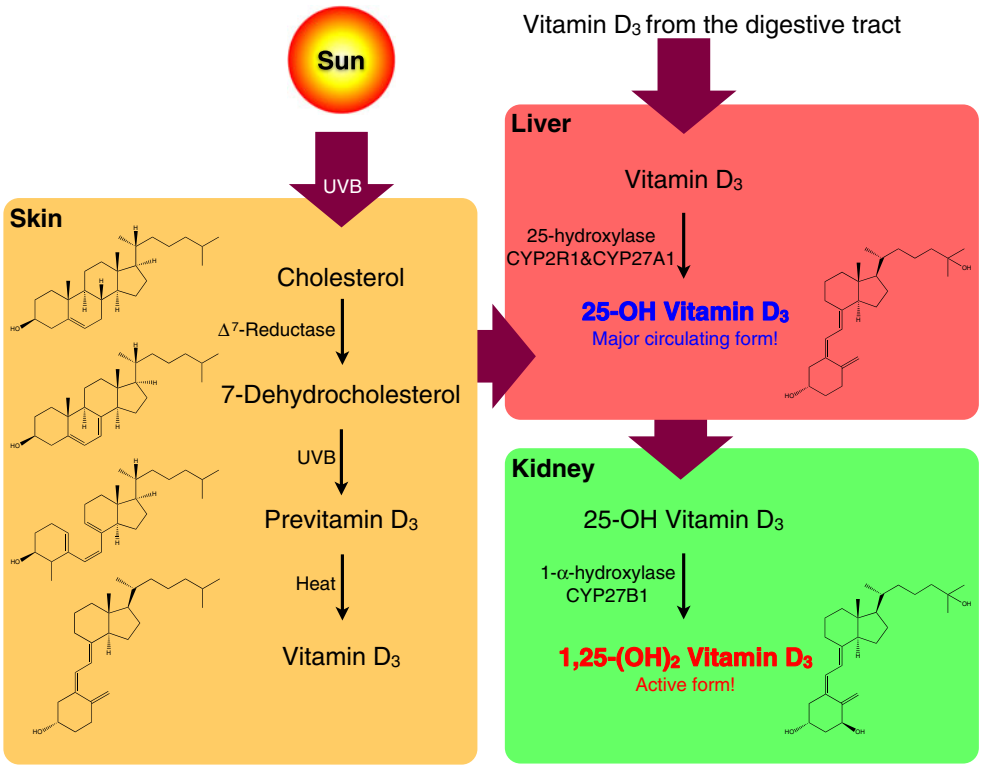

Fig. 1 The metabolism of vitamin D. 7-Dehydrocholesterol, the derivative of cholesterol in the skin, can be converted to previtamin D_3 via UVB irradiation from sunshine, and be thermally isomerized to vitamin D_3. Both vitamin D_3 spontaneously formed in the skin and absorbed from the digestive tract are further hydroxylated to a major circulating form, 25-OH vitamin D_3, in the liver, and finally hydroxylated to a biologically active form, 1,25-$(OH)_2$ vitamin D_3, in the kidney

At the cellular level, 1,25$(OH)_2$D interacts with nuclear vitamin D_3 receptor (VDR), which belongs to the superfamily of nuclear hormone receptors, to modulate gene transcription. Ligand binding initiates a conformational change that increases the receptor's affinity to the retinoid X receptor (RXR). Once the VDR-1,25$(OH)_2$D complex is heterodimerized with RXR, this complex will bind to vitamin D_3 response elements (VDREs) and recruit a number of nuclear coactivator or corepressor proteins. The transcription of genes for specific mRNA may be ultimately either enhanced or inhibited by this ligand-activated transcription factor [16] (Fig. 2).

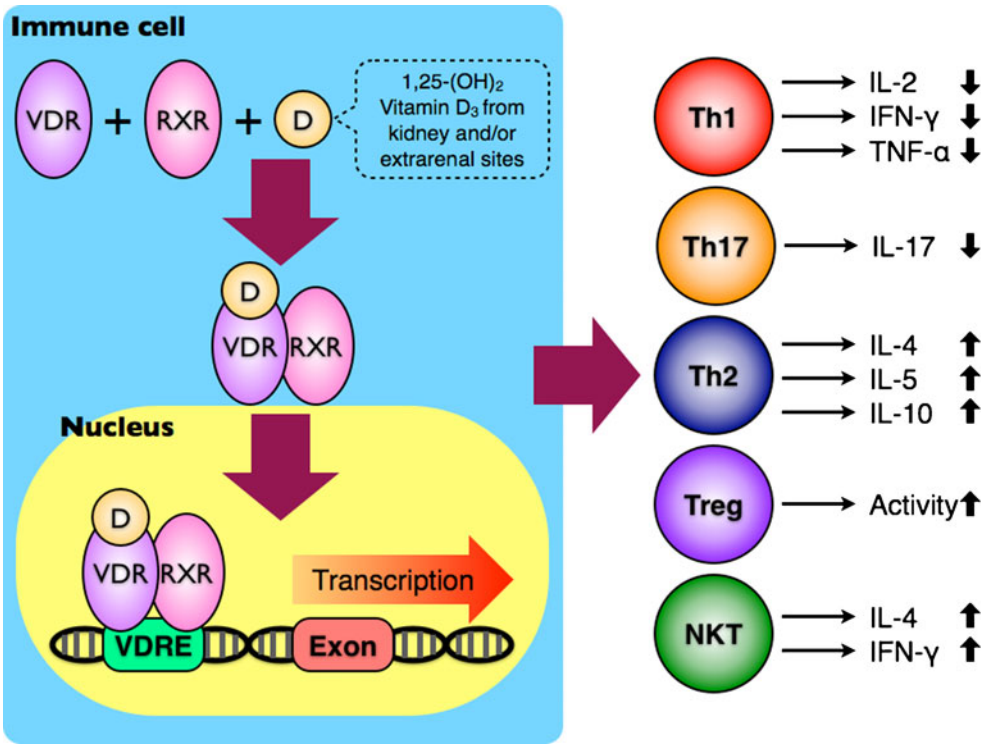

Fig. 2 The immunomodulatory effects of vitamin D on immune cells. After binding to VDR, the biologically active 1,25-$(OH)_2$ vitamin D_3 can induce a conformational change on VDR and increase its affinity to RXR. The VDR-RXR heterodimer becomes a transcriptional factor, interacts with VDREs in the promoter regions of different genes, and ultimately leads to functional changes in multiple immune cell lineages, including Th1, Th17, Th2, Treg, and NKT cells

Vitamin D_3 Receptor (VDR) Polymorphism

In humans, the VDR locus is located at chromosome 12q13.1. The gene encoding VDR spans over 100 kb and contains nine exons and eight introns. Four polymorphisms, ApaI (rs7975232), BsmI (rs1544410), TaqI (rs731236), and FokI (rs10735810) have been identified in the VDR gene. ApaI, BsmI (in the intron between exon 8 and 9), and TaqI (in exon 9) are located at the 3′ end of the gene, whereas FokI (in exon 2) is located near the translation start codon. The ApaI (G/T substitution), BsmI (A/G substitution), and TaqI (T/C substitution) single nucleotide polymorphisms (SNPs) do not produce any structural change on the VDR protein, but they are in strong linkage disequilibrium (LD), which occurs when genetic variations at different loci are dependent of another non-random associations of alleles at different loci. [17].

The FokI (T/C substitution) polymorphism on the other hand, introduces a second start codon in the VDR gene and yields two potential initiation sites. Therefore, two protein variants can be produced from the two translation initiation sites: a longer protein with three additional amino acids (f allele) and a shorter version (F allele) [18]. The actual structural change on the VDR protein caused by the FokI polymorphism suggests a potential functional consequence. Colin et al. demonstrated that peripheral blood mononuclear cells from subjects with the FF VDR genotype had a lower ED_{50} of 1,25 $(OH)_2D$ when compared with the Ff VDR genotype in an in vitro growth inhibition study [19]. In addition, van Etten et al. reported that monocytes and dendritic cells from subjects with the FF genotype expressed more interleukin (IL)-12 and proliferated more significantly after phytohemagglutinin stimulation than those with the homozygous ff genotype [20].

In addition to the effects of the FokI VDR polymorphism on functions of immune cells, FokI has also been associated with vitamin D status (serum levels of 25(OH)D) in twins with multiple sclerosis (MS) [21]. This correlation was also reported in unrelated MS patients and showed that the F allele corresponded with lower serum levels of 25(OH)D (circulating form) in both MS patients and controls, while the F allele was associated with higher serum levels of 1,25 $(OH)_2D$ (active form) in MS patients [22]. The similar association between serum 25(OH)D and the FokI polymorphism was also reported in systemic lupus erythematosus (SLE). Patients carrying the FokI ff genotype had significantly higher serum 25(OH)D concentrations compared with patients carrying the FF genotype [23]. The relationship between FokI polymorphism and vitamin D status in patients with type 1 diabetes mellitus (T1DM) was not reported; however, multiple studies yielded controversial results on the association between the FokI VDR polymorphism and T1DM [24–32], whereas the association between the FokI polymorphism and autoimmunity was not observed in MS and SLE [22, 23, 33–35]. Furthermore, SNPs of the VDR gene, especially BsmI and TaqI, are closely linked with disease risk of MS, T1DM, and SLE among different populations [25, 30, 32, 34, 36–43]. Other studies found only weak or no association between these SNPs and autoimmune diseases [23, 26, 29, 31, 35, 44–48] (Table 1). Although the inconsistent results make it difficult to conclude the functional consequences of these VDR polymorphisms, the three SNPs in LD with other polymorphisms within the VDR gene may underlie a potential effect on vitamin D status and disease risk of autoimmunity.

Immunomodulatory Effects of Vitamin D

Although historically vitamin D has been associated with the regulation of bone metabolism, it is now evident that vitamin D is involved in many biological processes that regulate immune responses [49–52]. There has been increasing interest in possible immunomodulatory effects of vitamin D since VDR was first discovered in monocytes [53, 54] and subsequently in dendritic cells and activated T cells [55, 56]. In vitro studies showed that vitamin D inhibits pro-inflammatory activity of CD4+ Th1 cells and their production of cytokines such as IL-2, interferon (IFN)-γ, and tumor necrosis factor-α [57–59]. $1,25(OH)_2D$ exerts an inhibitory effect on T cell proliferation, the expression of IL-2 [60, 61] and IFN-γ mRNA and protein in T cells [62], which could be caused by binding of the VDR–RXR heterodimer to the VDREs in the promoter regions of genes encoding IL-2 and IFN-γ [57]. In addition to its anti-inflammatory effects, vitamin D also promotes Th2 responses by enhancing IL-4, IL-5, and IL-10 production, thus skewing the T cell compartment from an inflammatory Th1 state to a more anti-inflammatory and regulated Th2 state [63]. Some studies reported that vitamin D could increase regulatory T (Treg) activity [64] and suppress Th17 responses [65]. Interestingly, vitamin D is not only required for the development of natural killer T (NKT) cells, but also increased IL-4 and IFN-γ production of NKT cells [66] (Fig. 2). Logically, these extensive effects of vitamin D on multiple immune cell lineages strongly suggest that vitamin D could play important roles in immune-mediated disorders in autoimmunity.

Vitamin D and Autoimmune Diseases

Multiple Sclerosis (MS)

MS is a chronic inflammatory disease characterized by immune-mediated damage of central nervous system [67]. The etiology of MS is not well understood but, like other autoimmune diseases, could be attributed to genetic

Table 1 Association between VDR gene polymorphisms and autoimmune diseases

	Author	Year	Disease subject	Healthy control	Polymorphism	Association	Ref. no.
Multiple sclerosis	Cox et al.	2012	726	604	TaqI, FokI	Only weak association between TaqI and MS.	[48]
	Sioka et al.	2011	69	81	BsmI, TaqI	No.	[47]
	Simon et al.	2010	214	428	ApaI, BsmI, TaqI, FokI, Cdx2	No. But dietary intake of vitamin D was inversely related to MS risk in only the MS patients with the FokI ff genotype.	[35]
	Smolders et al.	2009	212	289	ApaI, TaqI	No.	[45]
	Smolders et al.	2009	212	289	FokI	No. But the F allele was associated with lower serum 25(OH)D levels in both MS patients and controls. However, the F-allele corresponded with higher 1,25 $(OH)_2D$ levels in MS patients.	[22]
	Tajouri et al.	2005	104	104	ApaI, TaqI, FokI	Yes. Only the frequency of the TaqI allele/genotype and the ApaI allele was different between MS patients and controls.	[34]
	Niino et al.	2000	77	95	ApaI	Yes. The ApaI A allele/AA genotype were more prevalent in MS patients than in controls.	[39]
	Fukazawa et al.	1999	77	95	BsmI	Yes. The BsmI b allele/bb genotype were more prevalent in MS patients than in controls.	[36]
Type 1 diabetes mellitus	Mohammadnejad et al.	2012	87	100	ApaI, BsmI, TaqI, FokI	Yes. Only the frequency of the TaqI T allele/TT genotype was higher in controls compared to T1DM patients.	[32]
	Gogas Yavuz et al.	2011	117	134	ApaI, BsmI, TaqI, FokI	No.	[31]
	Panierakis et al.	2009	100	96	ApaI, BsmI, TaqI, FokI	Yes. The ApaI A allele/AA genotype and the TaqI T allele/TT genotype were more frequent in T1DM patients, whereas the BsmI B allele/BB genotype and the FokI F allele/FF genotype were less frequent in T1DM.	[30]
	Shimada et al.	2008	774	599	BsmI	Yes. The BB genotype frequency was significantly higher in T1DM patients compared to controls.	[42]
	Lemos et al.	2008	207	249	ApaI, BsmI, TaqI, FokI	No.	[29]
	Capoluongo et al.	2006	246	246	BsmI, FokI	Yes. Only the frequency of the FokI ff genotype was higher in TIDM patients compared to controls.	[28]
	Audi et al.	2004	89	116	BsmI, FokI	Yes. The frequency of the FokI ff genotype was lower in T1DM patients compared to controls.	[27]
	Gyorffy et al.	2002	107	103	ApaI, BsmI, FokI, Tru9I	No.	[26]
	Fassbender et al.	2002	75	57	BsmI, TaqI, FokI	Yes. Only the frequency of the TaqI TT genotype was higher in T1DM patients than in controls.	[25]
	Taverna et al.	2002	101	99	TaqI	Yes. The frequency of the TT genotype was lower in T1DM patients compared to controls.	[41]
	Ban et al.	2001	110	250	Fok I	Yes. There was a higher prevalence of the F allele/FF genotype in T1DM patients compared to controls.	[24]
	Chang et al.	2000	157	248	ApaI, BsmI, TaqI	Yes. Only the allelic frequency of the BsmI B allele was higher in T1DM patients than in controls.	[37]
Systemic lupus erythematosus	Luo et al.	2012	337	239	BsmI	Yes. The alleic frequency of the B allele, but not the frequency of the BB genotype, was higher in SLE patients compared to controls.	[43]
	Monticielo et al.	2012	195	201	BsmI, FokI	No. But 25(OH)D concentrations were significantly higher in SLE patients carrying the FokI ff genotype compared with patients carrying the FF genotype.	[23]
	Abbasi et al.	2010	60	45	BsmI	No.	[46]
	Sakulpipatsin et al.	2006	101	194	BsmI	No.	[44]
	Huang et al.	2002	52	90	FokI	No.	[33]
	Huang et al.	2002	47	90	BsmI	Yes. The distribution of the B allele/BB genotype was increased in SLE patients.	[40]
	Ozaki et al.	2000	58	87	BsmI	Yes. The frequency of the BB genotype was significantly higher in SLE patients than in controls.	[38]

predisposition and/or environmental factors [68, 69]. Epidemiologic evidence showed that MS has a geographical distribution: the prevalence of the disease is lower in equatorial regions and becomes higher with increasing latitudes [70]. This phenomenon could be caused by the lack of sunshine in high-latitude regions that is required for the cutaneous synthesis of vitamin D and suggests that vitamin D insufficiency could be a potential risk factor for MS.

Soilu-Hanninen et al. and Correale et al. demonstrated that the serum concentration of 25(OH)D and $1,25(OH)_2D$ were lower in MS patients than those in controls [71, 72]. Seasonal variation of serum 25(OH)D levels were similar in MS patients and controls [73], but 25(OH)D levels were lower during MS relapses than in remission [71–73], suggesting that vitamin D could be involved in the regulation of the clinical disease progress and severity of MS. Multiple studies also demonstrated that most of the MS patients were deficient in vitamin D [74–76]. In particular, low serum 25(OH)D levels were associated with high disability and relapse rate in MS patients [74, 75]; however, serum $1,25(OH)_2D$, which is the biologically active form of vitamin D, was not directly associated with both disability and relapse rate [75]. Munger et al. and Kragt et al. reported that there was a strong inverse correlation between the level of serum 25(OH)D and MS risk [77, 78]; however, the correlation was only evident among whites but not blacks and Hispanics [77] (Table 2). The reason why MS patients generally have lower serum 25(OH)D levels than healthy controls could be a combination of insufficient vitamin D intakes and decreased outdoor activities caused by lifestyle changes associated with increasing disability. However, it is unknown whether the high prevalence of

Table 2 Serum vitamin D status in subjects with autoimmune diseases

	Author	Year	Disease subject	Healthy control	Result	Ref. no.
Multiple sclerosis	Hiremath et al.	2009	199	/	Large numbers (84 %) of MS patients had insufficient levels (≤100 nmol/L) of 25(OH)D.	[76]
	Correale et al.	2009	132	60	Serum 25(OH)D and $1,25(OH)_2D$ levels were lower in MS patients. The levels were lower during MS relapses than remission.	[72]
	Kragt et al.	2009	103	110	Higher circulating levels of 25(OH)D were associated with a lower incidence of MS.	[78]
	Smolders et al.	2008	267	/	Low serum 25(OH)D levels were associated with high disability and relapse rate in MS patients.	[75]
	Soilu-Hanninen et al.	2008	23	23	Seasonal variation of 25(OH)D was similar in MS patients and controls, but 25(OH)D serum levels were lower during MS relapses than in remission.	[73]
	van der Mei et al.	2007	136	272	Vitamin D insufficiency was only observed in MS patients with higher disability but not in those with lower disability.	[74]
	Munger et al.	2006	257	514	High circulating levels of 25(OH)D were associated with a lower risk of MS among whites but not blacks and Hispanics.	[77]
	Soilu-Hanninen et al.	2005	40	40	Serum 25(OH)D concentrations were lower in MS patients from June to September. The levels were lower during MS relapses than remission.	[71]
Type 1 diabetes mellitus	de Boer et al.	2012	1193	/	Low plasma concentrations of 25(OH)D and $24,25(OH)_2D$ were associated with increased risk of microalbuminuria in T1DM.	[79]
	Borkar et al.	2010	50	50	Plasma 25(OH)D levels were lower in T1DM children. Vitamin D deficiency was higher in T1DM children compared to controls.	[80]
	Singh et al.	2009	40	41	Serum $1,25(OH)_2D$ levels were lower in T1DM patients compared to controls.	[81]
	Bener et al.	2009	170	170	Vitamin D deficiency was higher in T1DM children compared to non-diabetic.	[82]
	Littorin et al.	2006	138	208	Plasma 25(OH)D levels were lower in T1DM patients than in control subjects. The levels were lower in men than in women with T1DM.	[83]
Systemic lupus erythematosus	Bogaczewicz et al.	2012	49	49	Serum 25(OH)D concentrations were lower in SLE patients only during the warm season. The cold season was found to be a risk factor for vitamin D deficiency.	[84]
	Kim et al.	2010	104	49	Serum 25(OH)D levels were lower and vitamin D insufficiency was more common in SLE patients. Vitamin D levels had no relation with SLE severity.	[85]
	Amital et al.	2010	378	/	Vitamin D serum concentrations were found to be inversely related to SLE activity.	[86]
	Wright et al.	2009	38	207	Severe deficiency (≤10 ng/mL) of 25(OH)D was more frequent among subjects with SLE. 25(OH)D and $1,25(OH)_2D$ were both lower in SLE.	[87]
	Borba et al.	2009	36	26	A high prevalence of 25(OH)D deficiency was observed in SLE patients. Low levels of 25(OH)D were present in patients in overt disease and negatively related to disease activity.	[88]
	Ruiz-Irastorza et al.	2008	92	/	Vitamin D insufficiency and deficiency were common in SLE patients. Vitamin D levels had no relation with SLE severity.	[89]

vitamin D deficiency found in MS patients is the cause or effect of the disease.

Recent studies showed that vitamin D deficiency might increase the risk of MS [90]. As a result, detection of vitamin D deficiency and restoring vitamin D status to adequate levels may be considered as part of the clinical treatment of MS. In fact, vitamin D intervention has been implemented in several studies [91–93] (Table 3). However, these clinical trials were unable to provide definitive evidence to support the therapeutic effects of vitamin D intervention, mostly due to an extremely small number of MS patients recruited. Due to the lack of a double-blind, placebo-controlled, and randomized study with a large number of patients, the beneficial effects of oral vitamin D supplementation on MS progression need to be further investigated [97]. In addition to clinical effectiveness, the optimal dose and duration of vitamin D supplementation are not well defined and may vary between patients.

Type 1 Diabetes Mellitus (T1DM)

T1DM is an immune-mediated disease that is caused by autoimmune destruction of pancreatic β cells that produce insulin, leading to insulin deficiency [98]. Similar to other autoimmune diseases, environmental factors and/or genetic susceptibility could play roles in the onset and progression of T1DM [99]. Epidemiologic studies also showed that the incidence rate of T1DM was higher in geographical regions with lower UV exposure that resulted in less spontaneous vitamin D synthesis [100]. This inverse association of T1DM prevalence with UV radiation is consistent with that reported for MS, suggesting that the environmental UV exposure correlating with cutaneous synthesis of vitamin D could influence the development of multiple autoimmune disorders.

A birth-cohort study by Hypponen et al. demonstrated that dietary vitamin D supplementation is associated with reduced risk of T1DM [101]. The possibility that ensuring sufficient vitamin D could decrease the frequency of T1DM has raised an interest of further investigating nutritional vitamin D levels in T1DM patients. It has been reported that the plasma 25(OH)D levels were lower in T1DM patients than in control subjects among young adults and children [80, 82, 83]. Moreover, the prevalence of vitamin D deficiency/insufficiency was higher in T1DM children compared to controls [80, 82]. Interestingly, 25(OH)D levels were lower in male compared to female patients [83], suggesting that the gender difference in plasma vitamin D status might contribute to the high incidence of T1DM in males. In addition to plasma 25(OH)D, circulating $1,25(OH)_2D$ levels were also lower in T1DM patients than in controls [81]. The low serum $1,25(OH)_2D$ levels were indicative of tubulointerstitial dysfunction in T1DM before persistent microalbuminuria. Interestingly, low concentrations of circulating $1,25(OH)_2D$ were not associated with increased risk of microalbuminuria in T1DM [79] (Table 2). However, the circulating $1,25(OH)_2D$ levels may not be equal to the local conversion of 25(OH)D into $1,25(OH)_2D$ that results in beneficial effects.

Because of the strong correlation between vitamin D and T1DM, it has been suggested that vitamin D could prevent the damage, rescue the function of pancreatic β cells, and reduce the incidence of T1DM. Pitocco et al. and Li et al. both demonstrated that vitamin D had a protective effect on preserving β-cell function [94, 95], although the effect was not evident in the former study and vitamin D supplementation could only temporarily reduce the clinical insulin dose, which might be attributed to the low $1,25(OH)_2D$ dose (0.25 μg on alternate days) administered in T1DM [95]. In Li's study, the insulin plus vitamin D treatment (1-α-hydroxy vitamin D3; 0.5 μg per day) group developed no β-cell failure, while 27.8 % in the control group developed β-cell failure; however, the number of patients in this randomized controlled study is very limited (Table 3). Similar to MS, further clinical studies are necessary to determine the therapeutic value of vitamin D supplementation in T1DM.

Table 3 Vitamin D supplementation and autoimmune disease severity and progression

	Author	Year	Disease subject	Result	Ref. no.
Multiple sclerosis	Wingerchuk et al.	2005	13	Four patients experienced a total of five clinical relapses during the 48 week study.	[93]
	Achiron et al.	2003	5	One patient improved, but another one patient had an acute relapse.	[92]
	Nordvik et al.	2000	16	Supplementation of vitamin D in combination with other nutriments reduced the exacerbation rate and disability in MS.	[91]
Type 1 diabetes mellitus	Li et al.	2009	35	1-α(OH)D plus insulin therapy preserved pancreatic β-cell function in patients with latent autoimmune diabetes.	[94]
	Pitocco et al.	2006	70	$1,25(OH)_2D$ had a modest effect on residual pancreatic β-cell function.	[95]
Systemic lupus erythematosus	Ruiz-Irastorza et al.	2010	80	Increasing 25(OH)D levels by oral vitamin D supplementation might have a beneficial effect on fatigue but not SLE activity.	[96]

Systemic Lupus Erythematosus (SLE)

SLE is a systemic autoimmune disease that can cause chronic inflammation and damage in multiple tissues and organs [102]. Environmental factors and genetic susceptibility are both responsible for the pathogenesis of SLE [103, 104]. One of such factors is vitamin D deficiency. SLE patients tend to have inadequate vitamin D since most of them are photosensitive to UV radiation and unable to expose themselves to sunlight [105]. The correlation between vitamin D deficiency/insufficiency and SLE has been documented in multiple studies. Ruiz-Irastorza et al. observed a high frequency of inadequate vitamin D status in SLE patients (75 % of them had insufficient vitamin D levels, serum 25(OH)D<30 ng/ml, and 15 % of them had deficient vitamin D levels, serum 25(OH)D<10 ng/ml) [89]. Borba et al. reported the similar high prevalence of vitamin D insufficiency/deficiency in SLE; however, serum 25(OH)D levels were lower only in SLE patients with high disease activity, but not mild activity, than in controls [88]. In another study by Kim et al., serum 25(OH)D titers were significantly lower in SLE than in controls. Although only 16.3 % of SLE patients had vitamin D insufficiency (serum 25(OH)D <30 ng/ml), the risk of vitamin D insufficiency was 4.6-fold increased in SLE [85] (Table 2).

Several observational studies yield inconsistent results on the correlation between vitamin D levels and disease severity. Some studies suggested that vitamin D concentrations were inversely related to SLE activity [86–88], while others claimed that no such relation was observed [85, 89]. In addition to 25(OH)D, $1,25(OH)_2D$ was also lower in SLE patients and the vitamin D deficiency was particularly associated with overweight SLE patients [87]. Similar to other autoimmune diseases, seasonal variation of vitamin D status has been observed in SLE patients. In Bogaczewicz's study, the serum 25(OH)D levels in both SLE patients and controls during the cold season were lower compared to the warm season [84]. Interestingly, serum 25(OH)D concentrations were lower in SLE patients than in controls only during the warm season but not the cold season. Furthermore, the cold season was found to be a risk factor for vitamin D deficiency, mainly due to the lack of sunlight exposure and/or the decrease in outdoor activities during the cold season of the year. In addition, there was no connection between serum concentrations of IL-17 and vitamin D status, whereas serum IL-23 was lower in SLE patients with vitamin D deficiency.

Ruiz-Irastorza et al. evaluated the therapeutic effects of oral vitamin D supplementation on SLE in an observational study [96] (Table 3). After around 2 years of oral vitamin D treatment, mean 25(OH)D levels in all treated patients were increased. However, the majority (71 %) of the SLE patients still had insufficient levels of vitamin D. Although it appears that there was no improvement of SLE severity after oral vitamin D supplementation in this study, the effect of vitamin D intervention in SLE has not been extensively investigated, probably because there are too many confounding factors that could affect vitamin D metabolism in clinical medications used to treat SLE [106].

Conclusion

Vitamin D, in addition to its crucial role in bone metabolism, has been associated with multiple autoimmune diseases in several epidemiological studies. Due to its unique capability to bind to VDR and serve as a transcriptional factor, vitamin D can regulate gene expression and further exert its immunomodulatory effects on immune cells. It has been shown to inhibit Th17 cytokine production, enhance Treg activity, induce NKT cell functions, suppress Th1, and promote Th2 cytokine production, and thus skew T cells toward Th2 polarization. Furthermore, accumulating evidence suggest that VDR polymorphisms and serum vitamin D status are both closely associated with disease risk of MS, T1DM, and SLE. Therefore, impaired vitamin D signaling and/or inadequate vitamin D intake caused by genetic predisposition (e.g. VDR polymorphisms) and/or environmental factors (e.g. insufficient sunlight exposure in high-latitude regions or during the cold season) may contribute to the onset and progression of autoimmunity. Because of the high prevalence of vitamin D insufficiency/deficiency in patients with MS, T1DM, and SLE, vitamin D supplementation has been considered a prospective candidate for the treatment of such autoimmune diseases. However, due to the lack of larger randomized trials, more well-organized studies with methodological design are essential in order to further confirm the potential of vitamin D to prevent and ameliorate autoimmunity.

Take-Home Messages

1. Vitamin D can be spontaneously synthesized from cutaneous cholesterol upon UVB exposure and has pleiotropic effects on the immune system.
2. Vitamin D, after metabolized into a biologically active form, $1,25(OH)_2D$, and bound to VDR/RXR, can initiate gene transcription and exert its immunomodulatory effects.
3. Both environmental trigger (insufficient sunshine exposure) and genetic factor (VDR polymorphism) could contribute a poor vitamin D status.
4. Vitamin D deficiency (low serum levels of 25(OH)D) is prevalent in multiple autoimmune diseases, e.g. MS, TIDM, and SLE.
5. Because the vitamin D status is highly associated with the risk of autoimmunity, vitamin D has been implicated in prevention and protection from autoimmune diseases.

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