

Vitamin D and Autoimmune Diseases: Is Vitamin D Receptor (VDR) Polymorphism the Culprit?

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ABSTRACT: Vitamin D deficiency is becoming an increasing problem worldwide. It should not be underestimated, not only due to the well-known consequences vitamin D deficiency has on bone health, but primarily because recent studies have shown how the biologically active form of vitamin D – 1,25(OH)₂D – is involved in many biological processes, including immune system modulation. Moreover, the presence of a vitamin D receptor was discovered in almost all immune cells and some of its polymorphisms were found to be associated with increased incidence of autoimmune diseases. This finding led to a proposed link between vitamin D deficiency and autoimmune diseases. Patients affected by various autoimmune diseases showed low levels of vitamin D. However, it is not always clear whether vitamin D deficiency is the cause or rather a consequence of the disease. Limitations of the studies, such as the small number of patients, heterogeneity of selected groups, environmental conditions, methods used to measure vitamin D serum concentration and other confounding factors do not lead to unequivocal results to demonstrate a direct link between low vitamin D levels and autoimmune disease. Therefore, randomized trials are needed to clarify conflicting results.

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25-hydroxy vitamin D, 25(OH)D, the major circulating form of vitamin D, with a half-life of 3 weeks. Due to its long half-life, 25(OH)D is the most reliable compound to assess individual vitamin D levels. Finally, the molecule is converted in the kidney to the biologically active form, 1,25-dihydroxy vitamin D – 1,25(OH)₂D – also known as calcitriol. 1,25(OH)₂D enters the target cells, binds to the vitamin D receptor (VDR) and induces a conformational modification that leads to its interaction with the retinoic acid receptor (RXR). The VDR is an intracellular polypeptide part of the steroid-thyroid-retinoid acid receptor superfamily. It binds as VDR/VDR homodimers or VDR/RXR heterodimers to target cell DNA, leading to special protein syntheses. Although the most well-known function of vitamin D is the role it plays in maintaining the right balance between calcium and phosphate serum levels, thus promoting bone health, binding of 1,25(OH)₂D to the intracellular VDR regulates more than 900 genes involved in many physiological processes. As such, vitamin D has recently started to be considered essential for the maintenance of physiological homeostasis, and its deficiency has been associated with a wide range of diseases and cardiovascular and metabolic disorders, including cancer, hypertension, and infectious and autoimmune diseases. Vitamin D deficiency is commonly defined as levels < 20 ng/ml [Table 1], and has been documented both in healthy and diseased populations worldwide, mainly in northern areas [1]. This new evidence is exposing vitamin D deficiency as a pandemic increasing problem.

Vitamin D, commonly defined as “the sunshine vitamin,” is a steroid hormone originating from cholesterol. Few foods naturally contain vitamin D, which is mostly synthesized in human skin through sun exposure. As vitamin D is absorbed by the skin after exposure to ultraviolet B light, its synthesis is influenced by latitude, season, lifestyle and skin pigmentation. Vitamin D is initially synthesized as a biologically inactive precursor, with a half-life of 12–16 hours. In the liver it is converted to

Binding of 1,25(OH)₂D to the intracellular vitamin D receptor (VDR) regulates more than 900 genes involved in many physiological processes, including both innate and adaptive immunity

VITAMIN D RECEPTOR AND IMMUNE CELLS

After stimulation by biologically active vitamin D, the VDR regulates the expression of genes in a variety of vitamin D responsive tissues. The discovery of VDR as well as of vitamin D-activating enzymes in cell types other than those involved in mineral and bone homeostasis strongly indicates the role of the hormone in other physiological conditions. Activation of VDR induces a wide variety of so-called non-classic effects, with mod-

Table 1. Vitamin D status according to 25(OH)D concentration

Definition	nmol/L	ng/ml
Deficiency	< 50	< 20
Insufficiency	50–75	20–30
Excess	> 250	> 100
Intoxication	> 375	> 150

ulation of cellular growth, proliferation, apoptosis, and immune cell activation [2]. Awareness of a the role vitamin D takes in the regulation of immune responses was prompted by the discovery of VDR in almost all immune cells, including activated CD4+ and CD8+ T cells, B cells, neutrophils, and antigen-presenting cells (APC) such as macrophages and dendritic cells. It has been shown that resting monocytes and dendritic cells express VDR intra-cellularly, while resting T and B lymphocytes express little to no VDR. However, VDR expression in T cells is increased fivefold upon lymphocytes activation [3].

Allelic variations within the VDR gene have been implicated in mediating susceptibility to endocrine autoimmune disease. The most studied VDR polymorphism are TaqI, BsmI, ApaI and FokI. Autoimmune thyroid disease risk was found associated with the BsmI or TaqI polymorphism, while the BsmI and FokI polymorphism are associated with increased risk of systemic lupus erythematosus (SLE) [4]. FokI polymorphism in the VDR gene might affect individual susceptibility to diabetic nephropathy [5], while the ApaI, BsmI and TaqI polymorphisms may be susceptibility risk factors for rheumatoid arthritis (RA) [6]. Taken together, these data show that there is a link between autoimmune diseases and vitamin D, which seems to be important to maintain immune homeostasis.

EFFECTS OF VITAMIN D ON THE IMMUNE SYSTEM

Vitamin D regulates both innate and adaptive immunity [Table 2]. The innate immune response is characterized by the activation of monocytes and macrophages, which are able to recognize pathogen-associated molecular patterns (PAMPs) and thus provide a first line of defense against outside agents, increasing the anti-microbial activity of macrophages and enhancing the chemotactic and phagocytic capacity of these cells [7]. Conversely, vitamin D deficiency impairs the ability of macrophages to mature, produce macrophage-specific surface antigens, produce the lysosomal enzyme acid phosphatase, and secrete hydrogen peroxide, which is essential to their antimicrobial function. In addition, the upregulation of VDR on toll-like receptor activation of monocytes and macrophages leads to the induction of cathelicidins, a family of polypeptides found in lysosomes of macrophages and polymorphonuclear leukocytes that have a

Genetic vitamin D receptor (VDR) mutations may result in an alteration of the effects produced by the binding of the receptor with 1,25(OH)₂D in the promoter regions of genes that respond to vitamin D

Table 2. Mechanisms of vitamin D action on the immune system

	Immune cells	Action/effect	Reference
Innate immune system		Chemotactic capacity	Xu et al. [7]
		Phagocytic capacity	Xu et al. [7]
		Ability to mature	Arnson et al. [15]
		Production of macrophage-specific surface antigens	Arnson et al. [15]
	macrophages	Production lysosomal enzyme acid phosphatase	Arnson et al. [15]
		Secretion hydrogen peroxidase	Arnson et al. [15]
		Induction cathelicidins	Liu et al. [8]
		IL-10	Almerighi et al. [9]
	dendritic cells	TNF- α , IL-1 α , IL-6	Almerighi et al. [9]
		Cell maturation	Cutolo et al. [11]
T cell activation		van Halteren et al. [13]	
Adaptive immune system	T cells	Antigen presentation	Cutolo et al. [11]
		T regulatory cells	Penna et al. [3]
		Th2	Peelen et al. [2]
		IL-4, IL-5, IL-10	Prieti et al. [12]
		Th1	Penna et al. [3]
	B cells	IL-2, IL-17, IL-21, INF- γ	Jeffery et al. [14]
		B cell apoptosis	Chen et al. [10]
		Cell proliferation	Chen et al. [10]
		Plasma-cell differentiation	Chen et al. [10]
		Ig secretion	Chen et al. [10]
Memory B cell generation	Chen et al. [11]		

critical role in innate immune defense. Cathelicidin production is enhanced after *Mycobacterium tuberculosis* (TB) infection, when macrophages recognize TB-PAMPs and upregulate VDR expression, inducing cathelicidin gene activation, thus killing the TB [8]. Monocytes activated in the presence of 1,25(OH)₂D show a decreased production of TNF- α , IL-1 α and IL-6, and an increased IL-10 production. Thus, vitamin D can modulate the immune response in a more anti-inflammatory and regulatory fashion [9].

Adaptive immunity is also influenced by vitamin D in many ways. Vitamin D acts on cells of the monocyte-macrophage lineage preventing differentiation into dendritic cells [10] and reducing the expression of surface co-stimulatory molecules CD80 and CD86, thus affecting the T cell stimulatory capacity of these APC cells [10]. Moreover, 1,25(OH)₂D suppresses dendritic cell maturation, decreasing antigen presentation and T and B cells activity [10,11]. Dendritic cell-derived cytokine and chemokine expression are modulated by vitamin D, skewing the Th1/Th2 balance to a wider Th2 response and increasing the regulatory T lymphocyte compartment [3]. There is increas-

ing evidence from in vitro studies and animal models that 1,25(OH)₂D can suppress Th1 and Th17 responses while promoting the T regulatory cell and Th2 cell expression by enhancing the production of IL-4, IL-5 and IL-10 [12]. Moreover, after vitamin D stimulation, dendritic cells have a reduced capacity to trigger T cell proliferation [13]. In addition to dendritic cells, 1,25(OH)₂D has direct effects on T lymphocytes, and directly alters the cytokine profile of T cells, inhibiting pro-inflammatory cytokines production such as IL-2, INF- γ , IL-17 and IL-21 [14]. The B cell population is also influenced by the vitamin D pathway. Exposing B cells to 1,25(OH)₂D inhibits their proliferation, plasma cell differentiation and immunoglobulin secretion (IgG and IgM), and memory B cell generation as well as inducing B cell apoptosis [10].

VITAMIN D AND AUTOIMMUNE DISEASES

The pathogenesis factors of autoimmune diseases are a mosaic of genetic predisposition, hormonal effects and environmental factors. Low vitamin D status and VDR polymorphism have been suggested as important environmental risk factors in the development of autoimmune diseases. Growing evidence shows that VDR polymorphism (especially BsmI, ApaI, TaqI, and FokI polymorphism genotypes) are related to an increased incidence of autoimmune diseases, and it has been shown that the interaction between VDR and its ligand produces an anti-inflammatory effect on innate immunity and a regulatory and immunosuppressive action on adaptive immunity.

Low vitamin D levels have been reported in several autoimmune disorders, including multiple sclerosis (MS), type 1 diabetes mellitus (T1DM), SLE, RA, inflammatory bowel disease, thyroiditis and autoimmune gastritis [1,15-17]. However it is not always clear whether vitamin D deficiency is the cause or rather a consequence of the disease.

A well-designed study [18] investigated the association between vitamin 25(OH)D status and development of autoimmune disease in 12,555 individuals from three population-based studies. Relative risks of autoimmune disease were estimated by Cox regression and expressed as hazard ratio (HR) with 95% confidence interval (CI). There were 525 cases of incident autoimmune disease. The HR for a value of 10 nmol/l was 0.94 (95%CI 0.90-0.98) for any autoimmune disease, 0.83 (95%CI 0.72-0.96) for thyrotoxicosis, 0.95 (95%CI 0.88-1.02) for T1DM, 0.89 (95%CI 0.74-1.07) for MS, 1.00 (95%CI 0.86-1.17) for iridocyclitis, 0.95 (95%CI 0.80-1.13) for Crohn's disease, 0.88 (95%CI 0.75-1.04) for ulcerative colitis, 0.99 (95%CI 0.86-1.13) for psoriasis vulgaris, 0.97 (95%CI 0.89-1.07) for seropositive RA, and 0.94 (0.83-1.06) for polymyalgia rheumatica.

Sustaining the link between hypovitaminosis D and increased incidence of autoimmune diseases, Mathieu et al. [19] demonstrated that 1,25(OH)₂D supplementation alone was able to reduce incidence of insulinitis and prevent diabetes when administered to 3 week old non-obese diabetic mice. At 8 weeks it was efficient only if associated with an immune suppressor and was not therapeutic if given after lesion onset. These new results led to the speculative hypothesis that in genetically predisposed subjects living at high latitudes and presenting chronic insufficient or deficient hormone concentration, early vitamin D supplementation could control and/or block disease onset. Conversely, vitamin D supplementation, even at high dosage, after the immunological reaction may be able to reduce the severity of symptoms [20].

SYSTEMIC SCLEROSIS

Zerr et al. [21] analyzed the role of VDR signaling in fibrosis patients with systemic sclerosis (SSc), in which the levels of vitamin D3 are decreased. They characterized VDR as a negative regulator of TGF- β /Smad signaling. Impaired VDR signaling with reduced expression of VDR and decreased levels of

Low vitamin D status and vitamin D receptor (VDR) polymorphism have been thought to be important environmental risk factors in the development of autoimmune disease

its ligand may thus contribute to hyperactive TGF- β signaling and aberrant fibroblast activation in SSc. Vitamin D has been proposed as an anti-

fibrotic treatment option in the early onset of fibrosis in specific genotypes for VDR due to its known crosstalk with transforming growth factor (TGF)- β signaling. In primary human hepatic stellate cells vitamin D supplementation improved TGF- β -induced fibrogenesis through both VDR-dependents and VDR-independent mechanisms, while known polymorphisms of the VDR (A1012G single nucleotide polymorphisms) may influence the response to vitamin D treatment, abolishing the reduction of fibrogenic response.

MULTIPLE SCLEROSIS

Prevalence of MS in northern Europe strongly correlates with vitamin D deficiency and the risk of disease onset. It is known that vitamin D has immunomodulatory functions and suppresses an animal model of MS. Genome-wide association studies have identified more than 20 susceptible loci in MS, including the VDR gene and rs2248359. This last locus can increase MS risk by regulating the expression of nearby genes, for example CYP24A1, which encode the enzyme responsible for the degradation of 1,25(OH)₂D. rs2248359-C increases CYP24A1 expression in the human brain, thus showing a genetic connection between MS and vitamin D metabolism and indicates that the physiologic active form of vitamin D is protective. Some studies conducted in Iran, Japan, Australia and United Kingdom to find

the association between VDR polymorphisms (SNPs, TaqI and ApaI) and MS, have shown links between allelic and genotype frequencies and the disease. No correlation was found in other studies conducted in Greece, USA and the Netherlands. This discrepancy highlights the need for randomized trials.

SYSTEMIC LUPUS ERYTHEMATOSUS

In patients affected with SLE a significant inverse correlation was reported between disease activity and serum vitamin D concentration [22], and anti-vitamin D antibodies were found in a subset of patients with SLE and antiphospholipid syndrome [23]. The relation between VDR gene polymorphism and the risk of SLE is conflicting, A meta-analysis including 13 studies was conducted to evaluate the relationship between VDR BsmI (rs1544410), FokI (rs2228570), ApaI (rs7975232) and TaqI (rs731236) gene polymorphism and the risk of SLE. In this meta-analysis, the BsmI B allele and bb genotype, FokI f allele and ff genotype, and ApaI aa genotype were associated with the risk of SLE in the overall populations. In Asians, the BsmI B allele, BB genotype and bb genotype, FokI f allele and ff genotype were associated with the risk of SLE. In Africans, the BsmI B allele, BB genotype and bb genotype, FokI f allele and ff genotype, ApaI A allele, AA genotype and aa genotype were associated with the risk of SLE. However VDR BsmI, FokI, ApaI and TaqI gene polymorphism were not associated with the risk of SLE in Caucasians [24].

TYPE 1 DIABETES

Several studies suggested association between VDR polymorphisms and type 1 diabetes mellitus (T1DM) pathogenesis [25]. The interactions of genetic background with the development of T1DM are well documented in various populations as the incidence of childhood T1DM is known to vary widely between and within countries. A study conducted to investigate the relationship between VDR gene polymorphisms (at positions TaqI and ApaI) and the incidence of T1DM in Egyptians showed a significant association in diabetic patients compared with controls [26]. The results obtained in a study performed in an Iranian population demonstrated that genotypes frequency of the TaqI VDR polymorphism differed significantly between T1DM patients and controls [26]. The Diabetes Autoimmunity Study in the Young (DAISY) longitudinal study [27] explored the association between seven vitamin D metabolism gene single-nucleotide polymorphisms (SNPs) and the risk of islet autoimmunity (IA), the preclinical phase of T1DM. Two novel intronic variants for the association with T1DM, *DHCR7/NADSYN1* and *CYP27B1* were found to be significantly associated with the appearance of IA. Interestingly, these two variants were not found to be associated with progression to T1DM in IA-positive children. Six of the seven SNPs were significantly associated with

25(OH)D levels. These findings may offer insights concerning the complex role of vitamin D in the etiology of T1DM.

RHEUMATOID ARTHRITIS

A recent meta-analysis including 24 reports involving 3489 patients showed that RA patients had lower vitamin D levels than healthy controls and that a negative relationship exists between serum 25-hydroxyvitamin D (25OHD) levels and disease activity index [28].

A study conducted on a Tunisian cohort (108 patients with RA and 152 controls) to establish the associations of VDR gene polymorphisms FokI and BsmI with susceptibility to RA, demonstrated that FokI polymorphism alleles and genotype were significantly more common in the RA group than in controls ($P = 0.001$ and $P = 0.005$, respectively). In patients with RA, the FokI polymorphism was significantly associated with female gender ($P = 0.003$). No significant associations were found between the BsmI polymorphism and RA [29]. Moreover a case-control study including 106 RA Tunisian patients and an appropriate number of healthy control subjects showed no significant association for VDR ApaI and TaqI polymorphisms with RA risk ($P > 0.05$) [30].

Another study explored the role of vitamin D in RA pathogenesis by investigating enrichment of vitamin D response elements (VDREs) in confirmed RA susceptibility loci and testing variants associated with vitamin D levels for association with RA. SNPs in the *DHCR7/NADSYN1* locus showed evidence of positive association with RA ($P = 0.008$, OR 1.14 95%CI 1.03–1.24). The significant enrichment of VDREs at RA-associated loci and the modest association of variants in loci controlling levels of circulating vitamin D support the hypothesis that vitamin D plays a role in the development of RA [31].

AUTOIMMUNE THYROID DISEASES

Some studies have suggested an influence of vitamin D receptor polymorphisms on the development of autoimmune thyroid disease (AITD). One study investigated the distribution of VDR alleles (FokI, BsmI, ApaI TaqI polymorphisms) in a group of 111 Turkish patients with Hashimoto's thyroiditis and 159 healthy controls. It showed that the VDR gene TaqI TT and FokI FF genotypes were associated with increased risk of Hashimoto's thyroiditis. BbAaTtFf genotype seemed to be protective to Hashimoto's thyroiditis disease in the same population [32].

Another study tested whether the functional VDR polymorphisms (TaqI rs731236, ApaI rs7975232, FokI rs2228570 and BsmI rs1544410), group-specific component (GC) gene (rs7041 and rs4588), and CYP2R1 (rs10741657) are involved in the pathogenesis of AITD [33]. Using polymerase chain reaction-restriction fragment length polymorphism, 139 patients with Graves' disease, 116 HT patients and 76 control

subjects were genotyped. The frequency of the TT genotype for the TaqI polymorphism was higher in Graves' disease patients than in HT patients ($P = 0.0147$). The frequency of the C allele for the ApaI polymorphism was higher in Graves' disease patients than in control subjects ($P = 0.0349$). The frequency of the CC genotype for the FokI polymorphism was higher in HT patients than in control subjects ($P = 0.0174$) and Graves' disease patients ($P = 0.0149$). The frequency of the Gc1Gc1 genotype for the GC polymorphism and the AG genotype for the CYP2R1 polymorphism were lower in intractable Graves' disease than in Graves' disease in remission ($P = 0.0093$ and 0.0268 , respectively). This study showed how genetic differences in the VDR gene may be involved in the development of AITD and the activity of Graves' disease. Eight studies were identified and meta-analyzed to address the association of VDR gene FokI (rs2228570), TaqI (rs731236), BsmI (rs1544410), and ApaI (rs7975232) polymorphisms with AITD risk [34]. The result indicates that the BsmI or TaqI polymorphisms are significantly associated with AITD risk ($P_z = 0.001$ for B vs. b; $P_z = 0.010$ for t vs. T) while the ApaI or FokI polymorphism are not. In the subgroup analysis in Europeans, the decreased risk of AITD remained for the B or t variant. This gene-based analysis indicates that, based on current evidence from published studies, the cumulative effect of BsmI or TaqI polymorphisms in VDR is significantly associated with AITD.

Another recent meta-analysis investigated the association between vitamin D level and AITD through an accurate systematic literature review [35]. After identifying hundreds of references, the authors considered 20 papers that met their inclusion criteria. Analyzing the studies, Wang and co-authors [35] concluded that serum 25(OH)D was lower in AITD patients compared to healthy control individuals, and AITD was more likely to develop in individuals who showed low levels of serum 25(OH)D, which suggested that vitamin D deficiency may play a role in the pathological process of AITD.

However, other studies failed to demonstrate a firm correlation. Effraimidis et al. [36] showed how vitamin D deficiency is not associated with early stages of thyroid autoimmunity, while an Asian Indian community-based survey found only a weak inverse correlation between serum 25(OH)D values and anti-thyroperoxidase antibody titers [37].

Thus, controversial opinions on the role of vitamin D in autoimmune disease onset are expressed by the scientific community [38]. Critical observers claim that many studies show strong limitations that impede the process of getting irrefutable and clear results. Although most of the observational studies reported moderate to strong inverse associations between vitamin D and autoimmune diseases, in most trials vitamin D supplementation had no effect on the disorders studied. This discrepancy between observational and interventional studies suggests that vitamin D deficiency could be the result and not the cause of the diseases. Additional co-factors may

affect the result of epidemiological studies, such as obesity, smoking, pregnancy, and sedentary lifestyle. For example, in SLE patients many factors can lead to vitamin D deficiency, including chronic steroid use, enzymatic problems due to renal involvement, anti-vitamin D antibodies and the need to avoid sun exposure [23]. Moreover, study designs are often conducted on small patient cohorts, with only partial case-control matching, with heterogeneity of the groups selected and environmental conditions. These contradictory data are further affected by the imprecision and variability of analytical methods for the measurement of blood levels of vitamin D, denying the possibility to have unequivocal results demonstrating a direct link between low levels of vitamin D and autoimmune diseases.

The heterogeneity of analytical methods used are reflected by a lack of concordance of the measured concentrations [39]. To make determinations of vitamin D performed in laboratories with different methodologies directly comparable, the US Office of Dietary Supplements of the National Institutes of Health launched a collaborative project among institutional organizations, scientific societies and industries in 2010, called Vitamin D Standardization Program (VDSP) [40]. The objective of this program, besides the compatibility of results obtained by different methods, was to ensure that the measured concentrations are accurate and consistent with the actual concentration of analyte contained in the sample to produce adequate information for clinical purposes and for health policy measures.

FUTURE PERSPECTIVES

Growing evidence proves that the increase in 25(OH)D attributable to vitamin D3 supplementation may vary according to functional common genetic differences in vitamin D 25-hydroxylase (CYP2R1), 24-hydroxylase (CYP24A1), and the VDR genes.

Some studies performed on representative case series found a statistically significant association between specific polymorphisms of VDR, single nucleotides, and autoimmune diseases. These mutations may result in a phenotypic change and an alteration of the biological effects produced by the binding of the receptor with 1,25(OH)₂D in the promoter regions of genes that respond to vitamin D, leading to ineffectiveness of regulatory actions produced by the hormone in the cells of the innate and adaptive immune systems.

Therefore, prospective studies designed to prove the link between vitamin D deficiency and autoimmunity will need to assess genetic differences and VDR polymorphisms, since these factors appear to influence the therapeutic strategy of intervention.

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References

1. Agmon-Levin N, Theodor E, Segal RM, Shoenfeld Y. Vitamin D in systemic and organ-specific autoimmune diseases. *Clin Rev Allergy Immunol* 2013; 45: 256-66.
2. Peelen E, Knippenberg S, Muris AH, et al. Effects of vitamin D on the peripheral adaptive immune system: a review. *Autoimmun Rev* 2011; 10: 733-43.
3. Penna G, Amuchastegui S, Giarratana N, et al. 1,25-Dihydroxyvitamin D3 selectively modulates tolerogenic properties in myeloid but not plasmacytoid dendritic cells. *J Immunol* 2007; 178: 145-53.
4. Xiong J, He Z, Zeng X, Zhang Y, Hu Z. Association of vitamin D receptor gene polymorphisms with systemic lupus erythematosus: a meta-analysis. *Clin Exp Rheumatol* 2014; 32: 174-81.
5. Liu Z, Liu L, Chen X, He W, Yu X. Associations study of vitamin D receptor gene polymorphisms with diabetic microvascular complications: a meta-analysis. *Gene* 2014; 546: 6-10.
6. Mosaad YM, Hammad EM, Fawzy Z, et al. Vitamin D receptor gene polymorphism as possible risk factor in rheumatoid arthritis and rheumatoid related osteoporosis. *Hum Immunol* 2014; 75: 452-61.
7. Xu H, Soruri A, Gieseler RK, Peters JH. 1,25-Dihydroxyvitamin D3 exerts opposing effects to IL-4 on MHC class-II antigen expression, accessory activity, and phagocytosis of human monocytes. *Scand J Immunol* 1993; 38: 535-40.
8. Liu PT, Stenger S, Li H, et al. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. *Science* 2006; 311: 1770-3.
9. Almerighi C, Sinistro A, Cavazza A, Ciapriani C, Rocchi G, Bergamini A. 1 α ,25-dihydroxyvitamin D3 inhibits CD40L-induced pro-inflammatory and immunomodulatory activity in human monocytes. *Cytokine* 2009; 45: 190-7.
10. Chen S, Sims GP, Chen XX, Gu YY, Chen S, Lipsky PE. Modulatory effects of 1,25-dihydroxyvitamin D3 on human B cell differentiation. *J Immunol* 2007; 179: 1634-47.
11. Cutolo M, Paolino S, Sulli A, Smith V, Pizzorni S, Seriola B. Vitamin D, steroid hormones, and autoimmunity. *Ann N Y Acad Sci* 2014; 1317: 39-46.
12. Prietl B, Treiber G, Mader JK, et al. High-dose cholecalciferol supplementation significantly increases peripheral CD4⁺ Tregs in healthy adults without negatively affecting the frequency of other immune cells. *Eur J Nutr* 2014; 53: 751-9.
13. van Halteren AG, Tysma OM, van Etten E, Mathieu C, Roep BO. 1 α ,25-dihydroxyvitamin D3 or analogue treated dendritic cells modulate human autoreactive T cells via the selective induction of apoptosis. *J Autoimmun* 2004; 23: 233-9.
14. Jeffery LE, Burke F, Mura M, et al. 1,25-Dihydroxyvitamin D(3) and IL-2 combine to inhibit T cell production of inflammatory cytokines and promote development of regulatory T cells expressing CTLA-4 and FoxP3. *J Immunol* 2009; 183: 5458-67.
15. Arnson Y, Amital H, Shoenfeld Y. Vitamin D and autoimmunity: new aetiological and therapeutic considerations. *Ann Rheum Dis* 2007; 66: 1137-42.
16. Antico A, Tozzoli R, Giavarina D, Tonutti E, Bizzaro N. Hypovitaminosis D as predisposing factor for atrophic type A gastritis: a case-control study and review of the literature on the interaction of Vitamin D with the immune system. *Clin Rev Allergy Immunol* 2012; 42: 355-64.
17. Altieri B, Muscogiuri G, Barrea L, et al. Does vitamin D play a role in autoimmune endocrine disorders? A proof of concept. *Rev Endocr Metab Disord* 2017. DOI 10.1007/s11154-016-9405-9.
18. Skaaby T, Husemoen LL, Thuesen BH, Linneberg A. Prospective population-based study of the association between vitamin D status and incidence of autoimmune disease. *Endocrine* 2015; 50: 231-8.
19. Mathieu CH, Casteels K, Bouillon R. Vitamin D and Diabetes. In Feldman D (ed.) *Vitamin D*. New York: Academic Press, 1997: 1183-96.
20. Antico A, Tampoia M, Tozzoli R, Bizzaro N. Can supplementation with vitamin D reduce the risk or modify the course of autoimmune diseases? A systematic review of the literature. *Autoimmun Rev* 2012; 12: 127-36.
21. Zerr P, Vollath S, Palumbo-Zerr K, et al. Vitamin D receptor regulates TGF- β signalling in systemic sclerosis. *Ann Rheum Dis* 2015; 74:e20.
22. Amital H, Szekanecz Z, Szucs G, et al. Serum concentrations of 25-OH vitamin D in patients with systemic lupus erythematosus (SLE) are inversely related to disease activity: is it time to routinely supplement patients with SLE with vitamin D? *Ann Rheum Dis* 2010; 69: 1155-7.
23. Carvalho J, Blank M, Kiss E, Tarr T, Amital H, Shoenfeld Y. Antivitamin D, vitamin D in SLE: preliminary results. *Ann N Y Acad Sci* 2007; 1109: 550-7.
24. Zhou TB, Jiang ZP, Lin ZJ, Su N. Association of vitamin D receptor gene polymorphism with the risk of systemic lupus erythematosus. *J Recept Signal Transduct Res* 2014; 22: 1-7.
25. Mohammadnejad Z, Ghanbari M, Ganjali R, Afshari JT, Heydarpour M, Taghavi SM. Association between vitamin D receptor gene polymorphisms and type 1 diabetes mellitus in Iranian population. *Mol Biol Rep* 2012; 39: 831-7.
26. Kamel MM, Fouad SA, Salaheldin O, El-Rahman A, El-Razek A, El-Fatah AIA. Impact of vitamin D receptor gene polymorphisms in pathogenesis of type-1 diabetes mellitus. *Int J Clin Exp Med* 2014; 7: 5505-10.
27. Frederiksen BN, Kroehl M, Fingerlin TE, et al. Association between vitamin D metabolism gene polymorphisms and risk of islet autoimmunity and progression to type 1 diabetes: The Diabetes Autoimmunity Study in the Young (DAISY). *J Clin Endocrinol Metab* 2013; 98:e1845-e51.
28. Lin J, Liu J, Davies ML, Chen W. Serum vitamin D level and rheumatoid arthritis disease activity: review and meta-analysis. *PLoS One* 2016; 11: e0146351.
29. Karray EF, Ben Dhifallah I, Ben Abdelghani K, et al. Associations of vitamin D receptor gene polymorphisms FokI and BsmI with susceptibility to rheumatoid arthritis and Behçet's disease in Tunisians. *Joint Bone Spine* 2012; 79: 144-8.
30. Tizaoui K, Kaabachi W, Ouled Salah M, Ben Amor A, Hamzaoui A, Hamzaoui K. Vitamin D receptor TaqI and ApaI polymorphisms: a comparative study in patients with Behçet's disease and rheumatoid arthritis in Tunisian population. *Cell Immunol* 2014; 290: 66-71.
31. Yarwood A, Martin P, Bowes J, et al. Enrichment of Vitamin D response elements in RA associated loci supports a role for vitamin D in the pathogenesis of RA. *Genes Immun* 2013; 14: 325-9.
32. Yazici D, Yavuz D, Tarcin O, Sancak S, Deyneli O, Akalin S. Vitamin D receptor gene ApaI, TaqI, FokI and BsmI polymorphisms in a group of Turkish patients with Hashimoto's thyroiditis. *Minerva Endocrinol* 2013; 38: 195-201.
33. Inoue N, Watanabe M, Ishido N, et al. The functional polymorphisms of VDR, GC and CYP2R1 are involved in the pathogenesis of autoimmune thyroid diseases. *Clin Exp Immunol* 2014; 178: 262-9.
34. Feng M, Li H, Chen SF, Li WF, Zhang FB. Polymorphisms in the vitamin D receptor gene and risk of autoimmune thyroid disease: a meta-analysis. *Endocrine* 2013; 43: 318-26.
35. Wang J, Lv S, Chen G, et al. Meta-analysis of the association between vitamin D and autoimmune thyroid disease. *Nutrients* 2015; 7: 2485-98.
36. Effraïmidis G, Badenhoop K, Tijssen JG, Wiersinga WM. Vitamin D deficiency is not associated with early stages of thyroid autoimmunity. *Eur J Endocrinol* 2012; 167: 43-8.
37. Goswami R, Marwaha RK, Gupta N, et al. Prevalence of vitamin D deficiency and its relationships with thyroid autoimmunity in Asian Indians: a community-based survey. *Br J Nutr* 2009; 102: 382-6.
38. Bizzaro G, Shoenfeld Y. Vitamin D: a panacea for autoimmune diseases? *Can J Physiol Pharmacol* 2015; 4: 1-3.
39. Holmes EW, Garbincius J, McKenna KM. Analytical variability among methods for the measurement of 25-hydroxyvitamin D: still adding to the noise. *Am J Clin Pathol* 2013; 140: 550-60.
40. National Institutes of Health, Office of Dietary Supplements. Vitamin D Standardization Program (VDSP). <http://ods.od.nih.gov/Research/vdsp.aspx>.

“After you understand about the sun and the stars and the rotation of the earth, you may still miss the radiance of the sunset”

Alfred North Whitehead (1861–1947) English mathematician and philosopher best known as the defining figure of the philosophical school known as process philosophy