Hilla University College Journal For Medical Science

Volume 3 | Issue 2 Article 5

7-4-2025

# Vitamin D Receptor (VDR) and Autoimmune Diseases

Zahraa M. AL-Taee
*Department of Biology, College of Science, University of Babylon, Hilla, Iraq*,
sci.zahraa.mohammed@uobabylon.edu.iq

Noor Mahommoud Naji
*Department of Biology, College of Science, University of Babylon, Hilla, Iraq*,
sci.noor.mahmood@uobabylon.edu.iq

Zeena Hadi Obaid Alwan
*Department of Biology, College of Science, University of Babylon, Hilla, Iraq*,
sci.zeena.hadi@uobabylon.edu.iq

Anmar M. K. Al-Maamori
*Department of Biology, College of Science, University of Babylon, Hilla, Iraq*,
sci.anmar.mahdi@uobabylon.edu.iq

Rasha Kadhim Mahdi
*Department of Biology, College of Science, University of Babylon, Hilla, Iraq*, rashakadhim87@yahoo.com



## How to Cite This Article

AL-Taee, Zahraa M.; Naji, Noor Mahommoud; Alwan, Zeena Hadi Obaid; Al-Maamori, Anmar M. K.; and Mahdi, Rasha Kadhim (2025) "Vitamin D Receptor (VDR) and Autoimmune Diseases," *Hilla University College Journal For Medical Science*: Vol. 3: Iss. 2, Article 5.
DOI: https://doi.org/10.62445/2958-4515.1054

REVIEW ARTICLE

Hilla Univ Coll J Med Sci

# Vitamin D Receptor (VDR) and Autoimmune Diseases

Zahraa M. AL-Taee *, Noor Mahommoud Naji, Zeena Hadi Obaid Alwan, Anmar M. K. Al-Maamori, Rasha Kadhim Mahdi

Department of Biology, College of Science, University of Babylon, Hilla, Iraq

**Abstract**

**The vitamin_D_receptor (VDR) has great role in the regulates of expression of gene in several organs, responsive to vitamin D, after activation by physiologically active vit.D. There is strong evidence that vit.D is work in several physiological pathways, since vit.D-activating receptors and enzymes have been found in cell types that are unrelated to mineral and bone homeostasis. Many processes are affected by the so-called non-classic effects of VDR activation. These involve cell death, growth and reproduction of cells, and immune cell activity among many others. Moreover, immunity cells such as activated "CD4+ and CD8+ T cells, B cells, neutrophils, and antigen-presenting cells (APC) like dendritic cells and macrophages", were found to have vitamin D receptors. Resting "T and B" lymphocytes express very little VDR, whereas dendritic cells and monocytes express it intracellularly. On the other side, VDR expression in T cells rises fivefold with lymphocyte activation. Variants in the VDR gene may have effect on susceptibility to endocrine autoimmune diseases. Among the most prevalent VDR polymorphisms, "TaqI, *Bsm*I, *Apa*I, and F*ok*I" have been investigated. The risk of autoimmune thyroid sickness (ATS) is highly correlated with the *Bsm*I and *Taq*I polymorphism and the risk of systemic lupus erythematosus (SLE) is correlated with the *Bsm*I and *Fok*I polymorphism. The diabetic nephropathy may be affected by some VDR polymorphisms, such as *Fok*I, while the risk of rheumatoid arthritis (RA) has been detected in the polymorphism of *Apa*I, *Bsm*I, and *Taq*I. Vitamin D seems to be essential for immunological homeostasis, and research referred to the impact of this vitamin on the prevalence of autoimmune diseases.**

***Keywords:*** Vitamin D receptor, Autoimmune diseases, Polymorphism, SNP

## 1. Introduction

### *1.1. Receptor of vitamin D (VDR)*

Receptor of vitamin D, the transcriptional regulator and a one of the nuclear_receptor super-family was found to be essential to calcitriol signaling. Both hereditary and environmental variables influence VDR and the Vitamin D supplement efficacy may be affected by VDR gene variations [1].

Essential to the signaling mechanism of "calcitriol, or 1-alfa,25-dihidroxicolecalciferol (1$\alpha$,25(OH)2D)", is the superfamily of nuclear receptor transcriptional regulators, which includes VDR. The RXR and 1$\alpha$,25(OH)2D create a hetero-dimer, which leads to the binding and activation of the (VDR). While delivering the "1$\alpha$,25(OH)2D-VDR-RXR" complex to the nucleus, gene transcription regulates vitamin D effects. Some of the processes that are affected by these impacts include the control of the innate and adaptive immune systems, cell proliferation, and metabolism of phosphorus and calcium [1–3]. The VDR gene, which has over 900 documented allelic variations, is located in the VDR locus on chromosome 12 (12q13.11). The majority of research has been on VDR family polymorphisms affecting the Apal, BsmI, Taql, and Fokl genes (rs7975232, rs1544410). Messenger RNA stability is enhanced by three villainous genetic

Received 2 January 2025; accepted 19 March 2025.
Available online 4 July 2025

* Corresponding author.
E-mail addresses: sci.zahraa.mohammed@uobabylon.edu.iq (Z. M. AL-Taee), sci.noor.mahmood@uobabylon.edu.iq (N. M. Naji), sci.zeena.hadi@uobabylon.edu.iq (Z. H. O. Alwan), sci.anmar.mahdi@uobabylon.edu.iq (A. M. K. Al-Maamori), rashakadhim87@yahoo.com (R. K. Mahdi).

https://doi.org/10.62445/2958-4515.1054

variants: ApaI, TaqI, and BsmI. The protein is three amino acids shorter due to the FokI polymorphism, which is located on exon 2 [4–6]. Studies have linked these genetic variations to a wide range of long-term health problems, including T2DM, cancer, autoimmune diseases, cardiovascular changes, rheumatic arthritis, metabolic bone diseases, and autoimmune illnesses (7–10). Both genetic and environmental variables impact VDR control [11].

Some of the main environmental variables that have been linked to VDR regulation are diet, pollution, illness, and sun exposure [12–15]. Various environmental variables may influence vitamin D levels, which in turn control the receptor, according to certain theories. Despite the fact that researchers have postulated the involvement of epigenetic processes [16]. Vitamin D precursor consumption, ligand production, and activity are other variables that control VDRs. Environmental stimuli and genetic variables both have a moderating influence on the regulation of VDRs [11]. The effect of vitamin D supplementation on different people may fluctuate greatly due to individual genetic variations; one theory is that variations in the gene of VDR play a major role in this. Vit. D therapy responses could vary [4–6, 17] because of variations in VDR activity caused by polymorphisms in the gene of VDR. Numerous genetic association studies have looked at the correlation between vitamin D supplementation response and VDR gene mutations, but their results have been inconsistent [18–21].

A total of fourteen exons make up the VDR-gene, which may be found on chromosome 12q13.11. Six different variants (a–f) of exon 1, which is situated in the promoter region, are essential for alternative splicing, while exons two to nine are within the coding region [22]. So far, research has only identified three isoforms in human cells. With a molecular weight of forty-eight kilodalton, the VDR-A isoform is comprised of four hundred twenty-seven amino acids and starts at the second exon. Moreover, the VDR-B1 isoform (four hundred seventy-seven-amino-acid) has a molecular weight of 54 kilodalton and start-site at exon 1d. A single nucleotide polymorphism (SNP) in *Fok*I, that generates a translation of the start codon, gives a shorter isoform but with effective transcriptional activity: 424 amino acids and 47 kDa [23]. It is believed that some of the approximately 900 allelic variants in the VDR gene are interfere with vit.D action [24]. In previous research, three adjoining SNPs have been widely studied in related with various disorders within intron eight/exon nine, at the 3′ end of the *VDR*-gene, which involve: rs1544410, and rs731236. These SNPs identified initially by the means of the restriction fragment length polymorphism (RFLP) method based on the presence of the restriction-sites *Bsm*I, *Apa*I [25]. As mentioned earlier, another notable SNP was also identified in exon 2 is rs2228570. Base substitution (T to C) leads to decrease the protein length from four hundred twenty-seven amino acids to four hundred twenty-four amino acids due to the elimination of the first ATG translation start codon. However, this smaller size of protein is characterized by enhanced transcriptional activity [23, 26].

## 2. Role of VDR in immunity disorders

### *2.1. Multiple sclerosis (MS)*

Multiple sclerosis (MS) and other negative health outcomes are associated with vitamin D insufficiency [27–30]. Research on its immunomodulatory capabilities and its role in controlling calcium levels is ongoing. The synthesis of interleukin in antigen-presenting cells, the modulation of the Th17 immune response (which is critical in autoimmune illnesses), and the immunological regulation of mesenchymal stem cells are all impacted by vit. D, among other things [31–33]. The majority of vit.D's physiological effects are attributed to the vitamin D receptor (VDR), a nuclear receptor that has been well-preserved and functions as a flexible transcription factor [34]. But how the VDR gene contributes to multiple sclerosis is still unclear. Multiple sclerosis (MS) risk factors include environmental variables, genetics, and epigenetic pathways. An important epigenetic mechanism that regulates gene-expression and the structure of the chromatin is DNA methylation at CpG sites (CpGs). At gene promoters, for instance, methylation of CpG islands often suppresses gene production, while at active gene promoters, demethylation of CpG islands is common. Researchers are placing a greater emphasis on DNA methylation in the study of autoimmune and neurological diseases. Recent studies on multiple sclerosis have shown that DNA methylation controls several disease processes. As shown by hypomethylation of the promoter regions of FOXP3 and IL-17A, it is possible that untreated MS patients have an excess of circulating Tregs and Th17 cells [35, 36]. The fact that MS patients had 25% less PAD-2 promoter methylation than controls suggests that epigenetic mechanisms may govern demyelinizating processes. T lymphocytes identify myelin basic protein (MBP) as an antigen after PAD-2 destabilizes it [37]. In contrast to healthy persons, CD8+ and CD4+ T lymphocytes in RRMS exhibit distinct patterns in genome-wide DNA methylation profiles, according to recent research [38]. One potential marker for multiple sclerosis is the methylation patterns of cell-free plasma DNA [39]. Ayuso et al. studied the levels of

DNA methylation in two regulatory components of the VDR gene on T cells in RRMS patients and controls, controlling for age and gender. An alternate promoter located in exon 1c of the VDR gene showed a significant increase in DNA methylation levels, according to their findings [40].

## 3. Systemic lupus erythematosus (SLE)

Lupus Lupus Systematus The chronic autoimmune illness known as erythematosus may cause damage to more than one organ, like "skin, kidney, blood, and central nervous system" [41]. Although the exact mechanisms that cause SLE have not been fully understood, research has shown that environmental h factors, genetic predisposition, and epigenetics all play a role in the disease's progression [42]. Prior studies on SLE mostly examined alterations at the genomic, transcriptomic, and proteomic levels. Metabolomics' function in autoimmune illnesses, however, has just come to the fore. New information on the causes of SLE has been uncovered by metabolomics research [43]. For example, it has been shown that SLE patients and lupus-prone animals had greater levels of "CD4+ T cells" for both glycolysis and mitochondrial oxidative metabolism. By targeting these metabolic pathways, T cells may be normalized and potentially used as disease indicators [44]. The patho-physiology of SLE is heavily influenced by metabolism of the lipid. CD4+ T cells from SLE patients have altered glycosphingolipid profiles associated with lipid rafts, which are related with T cell receptor activation [45]. If these glycosphingolipids are not synthesized, active B cells will not produce as much anti-dsDNA antibody [46]. "CD4+ T-cells" derived from SLE infected peoples and lupus-prone animals have an abnormal activation of mTOR, leading to changes in glycolysis, lipid and fatty acid production, messenger RNA translation, sense amino acids, and growth factors [47, 48]. The pathophysiology of SLE has been associated with vit. D, a famous immunological modulator. In doing so, it controls how antigen-presenting cells (APCs) differentiate and function. Vitamin D inhibits the production of proinflammatory cytokines and the expression of tolllike receptors on monocytes. Inhibiting lymphocyte proliferation and regulating T cell development are two of vitamin D's functions. Active B and plasma cells also undergo apoptosis as a result [49]. Low vitamin D levels were associated with a more severe case of systemic lupus erythematosus (SLE) compared to healthy controls. Renal dysfunction and increased proteinuria were associated with low vitamin D levels. Lupus nephritis (LN) patients with systemic lupus erythematosus (SLE) had sig. lower vit. D levels than SLE infected people without LN or with inactive SLE [50, 51]. The VDR is a potential target for vit. D, which may affect the methylation of immune cells. Genes regulated by VDRs govern energy metabolism and the degradation of lipophilic intracellular molecules. Immune cells "(T cells, B cells, monocytes/macrophages, dendritic cells, etc.)" get their energy from glycolysis and oxidative phosphorylation, which it regulates. By affecting cellactivation,differentiation,and cytokine production, metabolic changes may influence immunity response in autoimmunity diseases [52, 53]. Vit. D impacts lipid metabolism by acting on nuclear hormone receptors including PPAR$\gamma$ and LXR, according to research. Among these impacts is a change in the cellular phospholipid profile. Taking vitamin D supplements has reduced oxidative stress and improved metabolic markers in MS patients and others. The precise effect of vit.D levels in the blood on these responses is unclear, although [54].

## 4. Type 1 diabetes (T1D)

Over the past two decades, research has focused on how autoimmune processes affect type 1 diabetes via genetic elements regulation that affect cytokine synthesis and immune response activation [55]. T1DM is a chronic multi-factorial illness that results from particular autoimmune damages of pancreatic beta cells. Global prevalence of T1DM has increased by nearly twofold in the last 40 years, with a rate of incidence of 9.5 per 1,000 individuals [56, 57]. Vitamin D is a significance contributor to the development of T1DM [58]. Many articles have looked at how VDR gene polymorphisms affect the risk of TD and vit. D levels among various groups of people. Study by Habibian and his group which found a link between polymorphic variants in the VDR gene, specifically BsmI and FokI, and a higher probability of T1DM [59]. Newly diagnosed type 1 diabetes patients with an adequate amount of "25(OH)D" in their serum ($\geq$30 ng/mL) and specific SNP genotypes (BsmI and TaqI) in the VDR gene can preserve the function of residual $\beta$-pancreatic cells [60]. Other studies found that SNPs in genes essential for the creation, action, and transportation of vitamin D could affect the possibility of developing T1D [61, 62]. As the global prevalence of diabetes mellitus rises and autoimmune diseases are still unclear, research into their immunoregulatory mechanisms is crucial. Based on multiple research projects, immune-mediated mechanisms have a major role in the T1DM development, which are subsequently established through different inducible elements, eventually causing aberrant immune regulation across the local and systemic degrees

with the emergence of the autoimmune defense pathways [63]. This disease is polygenic in nature, with multiple alleles that impact positively or passively when communicated with each other. For example, a meta-analysis research on VDR polymorphisms and T1D involving 23 papers concluded that: none of te" BsmI, ApaI, TaqI, or FokI SNPs" were found to be associated with T1D threat when examined separately. Whereas, the "BsmI-ApaI-TaqI b-A-T (T-A-T)" haplotype, was found to protect against T1D [64]. Study in the South Indian found that VDD is a major risk factor for T1D development. Furthermore, the FokI-FF genotype, as well as the "BsmI-B and ApaI-A alleles", were linked to T1DM. whereas, "the FokI-Ff genotype and the BsmI-b/ApaI-a/TaqI-T" haplotype had an adverse relationship with T1D [65].

## 5. Celiac disease (CD)

A person's risk of developing autoimmune celiac disease (CD) increases if the disorder runs in their family. The most important genetic factor is the HLA-DQ2-HLA-DQ8 allele. In Celiac disease (CD), the body's immune system attacks certain gluten components and intestinal tissue, causing structural changes. The intestines aren't the only possible site of symptom perception [66]. Vit.D levels were lower and "1,25-(OH)2D3" levels were higher in CD infected people compared to HC individuals [67]. A compilation of data from four studies that looked at VDR SNPs in CD was published in a recent review [68]. The studies comprised 176 CD and 402 HC. While the ApaI, BsmI, and TaqI SNPs did not show any connection with CD incidence, the FokI T variant was associated with an elevated risk [69].

## 6. Rheumatoid arthritis (RA)

RA is a prevalent auto-immune disorder that involves the development of auto-antibodies, chronic synovial inflammatory processes, along with gradual deformation and damaging of joints [70]. In response to sunshine, the skin generates vitamin D, a pleiotropic hormone. To regulate bone turnover and keep calcium levels stable, it is necessary to start the growth of osteoblastic and osteoclastic cells [71]. Because it stimulates the production of cytokines, the maturation or activation of lymphocytes that possess the (VDR) [72], and the expansion of immune cells, calcitriol, the active form of vitamin D, is an effective immunoregulator. When it isn't working properly, it can't do its job of inhibiting Th1 and Th17 lymphocytes, which leads to the production of inflammatory cytokines [73]. A large body of research suggests that autoimmune illnesses are more common in those with low blood vitamin D levels [74]. Vitamin D insufficiency, for instance, is associated with an increased prevalence and severity of rheumatoid arthritis (RA) [75]. So, whether it's a hereditary trait or something more environmental, low vit.D levels could contribute to the development and worsening of autoimmune diseases. On chromosome 12, you'll find the VDR gene, which is essential for vitamin D's physiological effects [76]. Extensive research has shown that variations in the VDR gene affect its expression and function [77]. A number of autoimmune disorders have been linked to specific variations in the VDR gene, which include (RA), (MS), (SLE), (JIA), and (TD2) [78–82]. Patients with autoimmune illnesses frequently wind up taking vitamin D supplements because of the high frequency of vit.D insufficiency. According to research, calcitriol and a monoclonal_antibody targeting tumor necrosis factor-$\alpha$ together have a synergistic impact in RA. Combining vitamin D with TNF-$\alpha$ inhibitors may improve treatment outcomes for RA patients [83]. As consequently, VDR polymorphesms with fundamental roles may be correlated with clinical response and recovery in patients having TNF$\alpha$ therapy. Cusato et al. discovered that individuals with inflammatory bowel disease (IBD) who possessed the VDR rs1544410 SNP had reached clinical improvement after twelve weeks of TNF-$\alpha$ therapy [84]. Patients with axialspondyloarthritis introduce varying improvements in CRP and disease progression results after three and six months of TNF-$\alpha$ therapy, among the rs2228570, rs731236, and rs7975232 genotype of the VDR patients. Nevertheless, no studies have tested the potential role of rs11568820 SNP in TNF-$\alpha$ reaction to therapy. This particular variant is found in the promoter sequences and appears to be associated with modifying the VDR gene's transcription. Research by Arai and his group found the different allele of this SNP may enhance the expression of mRNA [4, 5].

## Ethical issue

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of Biology Department; document number B231002 and the date in 15-10-2023.

## Financial funding

This research received no external funding.

## Conflicts of interest

The authors declare no conflict of interest.

## References


1. Bikle DD. Vitamin D: Production, metabolism and mechanisms of action. In Endotext, Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, *et al.*, Eds.; MDText.com, Inc.: South Dartmouth, MA, USA, 2021.
2. Pike JW. Vitamin D3 receptors: Structure and function in transcription. Annu. Rev. Nutr. 1991;11:189–216. [PubMed].
3. Christakos S, Raval-Pandya M, Wernyj RP, Yang W. Genomic mechanisms involved in the pleiotropic actions of 1,25-dihydroxyvitamin D3. Biochem. J. 1996;316(Pt 2):361–371. Correction in Biochem. J. 1996;318(Pt 3):1079. [PubMed].
4. Arai H, Miyamoto KI, Yoshida M, Yamamoto H, Taketani Y, Morita K, *et al.* The polymorphism in the caudal-related homeodomain protein Cdx-2 binding element in the human vitamin D receptor gene. J. Bone Miner. Res. 2001;16:1256–1264.
5. Bugaj B, Wieli´nska J, Swierkot J, Bogunia-Kubik K, G ´ órna K. VDR polymorphic variants are related to improvements in CRP and disease activity in patients with axial spondyloarthritis that undergo anti-TNF treatment. Genes. 2022;13:1873. [PubMed].
6. Bizzaro G, Antico A, Fortunato A, Bizzaro N. Vitamin D and autoimmune diseases: Is vitamin D receptor (VDR) polymorphism the culprit? Isr. Med. Assoc. J. IMAJ. 2017;19:438–443.
7. Haussler MR, Jurutka PW, Mizwicki M, Norman AW. Vitamin D receptor (VDR)-mediated actions of 1_,25(OH)2vitamin D3: Genomic and non-genomic mechanisms. Best Pract. Res. Clin. Endocrinol. Metab. 2011;25:543–559.
8. Hii CS, Ferrante A. The non-genomic actions of vitamin D. Nutrients. 2016;8:135.
9. Veldurthy V, Wei R, Oz L, Dhawan P, Jeon YH, Christakos S. Vitamin D, calcium homeostasis and aging. Bone Res. 2016;4:16041.
10. Muller V, de Boer RJ, Bonhoeffer S, Szathmary E. An evolutionary perspective on the systems of adaptive immunity. Biol. Rev. Camb. Philos. Soc. 2018;93:505–528.
11. Vanherwegen AS, Gysemans C, Mathieu C. Vitamin D endocrinology on the cross-road between immunity and metabolism. Mol. Cell. Endocrinol. 2017;453:52–67.
12. Cortes M, Chen MJ, Stachura DL, Liu SY, Kwan W, Wright F, *et al.* Developmental vitamin D availability impacts hematopoietic stem cell production. Cell Rep. 2016;17:458–468.
13. Zenata O, Vrzal R. Fine tuning of vitamin D receptor (VDR) activity by post-transcriptional and post-translational modifications. Oncotarget. 2017;8:35390–35402.
14. Agliardi C, Guerini FR, Zanzottera M, Bolognesi E, Meloni M, Riboldazzi G, *et al.* The VDR FokI (rs2228570) polymorphism is involved in Parkinson's disease. J. Neurol. Sci. 2021;428:117606.
15. Guerini FR, Bolognesi E, Chiappedi M, Mensi MM, Fumagalli O, Rogantini C, *et al.* Vitamin D receptor polymorphisms associated with autism spectrum disorder. Autism Res. 2020;13:680–690.
16. Arosio B, Guerini FR, Costa AS, Dicitore A, Ferri E, Mari D, *et al.* Vitamin D receptor polymorphisms in sex-frailty paradox. Nutrients. 2020;12:2714.
17. Mazur A, Fra¸czek P, Tabarkiewicz J. Vitamin D as a nutri-epigenetic factor in autoimmunity-A review of current research and reports on vitamin D deficiency in autoimmune diseases. Nutrients. 2022;14:4286.
18. Agmon-Levin N, Theodor E, Segal RM, Shoenfeld Y. Vitamin D in systemic and organ-specific autoimmune diseases. Clin. Rev. Allergy Immunol. 2013;45:256–266.
19. Almerighi C, Sinistro A, Cavazza A, Ciaprini C, Rocchi G, Bergamini A. 1Alpha,25-dihydroxyvitamin D3 inhibits CD40L-induced pro-inflammatory and immunomodulatory activity in human monocytes. Cytokine. 2009;45:190–197.
20. Piemonti L, Monti P, Sironi M, Fraticelli P, Leone BE, Dal Cin E, *et al.* Vitamin D3 affects differentiation, maturation, and function of human monocyte-derived dendritic cells. J. Immunol. 2000;164:4443–4451. [PubMed].
21. Bscheider M, Butcher EC. Vitamin D immunoregulation through dendritic cells. Immunology. 2016;148:227–236.
22. Guerini FR, Bolognesi E, Chiappedi M, Mensi MM, Fumagalli O, Rogantini C, *et al.* Vitamin D receptor polymorphisms associated with autism spectrum disorder. Autism Res. 2020;13:680–690.
23. Jehan F, d'Alésio A, Garabédian M. Exons and functional regions of the human vitamin D receptor gene around and within the main 1a promoter are well conserved among mammals. J. Steroid Biochem. Mol. Biol. 2007;103:361–367.
24. Jurutka PW, Remus LS, Whitfield GK, Thompson PD, Hsieh JC, Zitzer H, *et al.* The polymorphic N terminus in human vitamin D receptor isoforms influences transcriptional activity by modulating interaction with transcription factor IIB. Mol. Endocrinol. 2000;14:401–420.
25. Usategui-Martín R, De Luis-Román D-A, Fernández-Gómez JM, Ruiz-Mambrilla M, Pérez-Castrillón J-L. Vitamin D receptor (VDR) gene polymorphisms modify the response to vitamin D supplementation: A systematic review and meta-analysis. Nutrients. 2022;14:360.
26. Agliardi C, Guerini FR, Bolognesi E, Zanzottera M, Clerici M. VDR gene single nucleotide polymorphisms and autoimmunity: A narrative review. Biology. 2023;12:916. https://doi.org/10.3390/biology12070916.
27. Ascherio A, Munger KL, White R, KoÈchert K, Simon KC, *et al.* Vitamin D as an early predictor of multiple sclerosis activity and progression. JAMA Neurol. 2014;71:306–314. https://doi.org/10.1001/jamaneurol.2013.5993 PMID: 24445558.
28. Mokry LE, Ross S, Ahmad OS, Forgetta V, Smith GD, *et al.* Vitamin D and risk of multiple sclerosis: A mendelian randomization study. PLoS Med. 2015;12:e1001866. https://doi.org/10.1371/journal.pmed.1001866 PMID: 26305103.
29. Smolders J, Menheere P, Kessels A, Damoiseaux J, Hupperts R. Association of vitamin D metabolite levels with relapse rate and disability in multiple sclerosis. Mult Scler. 2008;14:1220–1224. https://doi.org/10.1177/1352458508094399 PMID: 18653736.
30. Mowry EM, Waubant E, McCulloch CE, Okuda DT, Evangelista AA, *et al.* Vitamin D status predictsnew brain magnetic resonance imaging activity in multiple sclerosis. Ann Neurol. 2012;72:234–240. https://doi.org/10.1002/ana.23591 PMID: 22926855.
31. Joshi S, Pantalena LC, Liu XK, Gaffen SL, Liu H, *et al.* 1,25-dihydroxyvitamin D(3) ameliorateSTh17 autoimmunity via transcriptional modulation of interleukin-17A. Mol Cell Biol. 2011;31:3653–3669. https://doi.org/10.1128/MCB.05020-11 PMID: 21746882.
32. Peelen E, Knippenberg S, Muris AH, Thewissen M, Smolders J, *et al.* Effects of vitamin D on the peripheral adaptive immune system: a review. Autoimmun Rev. 2011;10:733–743. https://doi.org/10.1016/j.autrev.2011.05.002 PMID: 21621002.
33. Duffy MM, McNicholas BA, Monaghan DA, Hanley SA, McMahon JM, *et al.* Mesenchymal stem cells and a vitamin D receptor agonist additively suppress T helper 17 cells and the related inflammatory response in the kidney. Am J Physiol Renal Physiol. 2014;307:F1412–1426. https://doi.org/10.1152/ajprenal.00024.2014 PMID: 25339699.
34. Saccone D, Asani F, Bornman L. Regulation of the vitamin D receptor gene by environment, genetics and epigenetics. Gene. 2015;561:171–180. https://doi.org/10.1016/j.gene.2015.02.024 PMID:25682935.
35. Suzuki MM, Bird A. DNA methylation landscapes: provocative insights from epigenomics. Nat Rev Genet. 2008;9:465–476. https://doi.org/10.1038/nrg2341 PMID: 18463664.
36. Janson PC, Linton LB, Bergman EA, Marits P, Eberhardson M, *et al.* Profiling of CD4+ T cells with epigenetic immune lineage analysis. J Immunol. 2011;186:92–102. https://doi.org/10.4049/jimmunol.1000960 PMID: 21131423.
37. Mastronardi FG, Noor A, Wood DD, Paton T, Moscarello MA. Peptidyl argininedeiminase 2 CpG island in multiple sclerosis white matter is hypomethylated. J Neurosci Res. 2007;85:2006–2016. https://doi.org/10.1002/jnr.21329 PMID: 17469138.

38. Maltby VE, Graves MC, Lea RA, Benton MC, Sanders KA, *et al.* Genome-wide DNA methylation profiling of CD8+ T cells shows a distinct epigenetic signature to CD4+ T cells in multiple sclerosis patients. Clin Epigenetics. 2015;7:118. https://doi.org/10.1186/s13148-015-0152-7 PMID: 26550040.
39. Liggett T, Melnikov A, Tilwalli S, Yi Q, Chen H, *et al.* Methylation patterns of cell-free plasma DNA in relapsing-remitting multiple sclerosis. J Neurol Sci. 2010;290:16–21. https://doi.org/10.1016/j.jns.2009.12.018 PMID: 20064646.
40. Ayuso T, Aznar P, Soriano L, Olaskoaga A, RoldaÂn M, Otano M, *et al.* Vitamin D receptor gene is epigenetically altered and transcriptionally up-regulated in multiple sclerosis. PLoS ONE. 2017;12(3):e0174726. https://doi.org/10.1371/journal.pone.0174726.
41. Bernatsky S, Boivin JF, Joseph L, *et al.* Mortality in systemic lupus erythematosus. Arthritis Rheum. 2006;54(8):2550-2557. https://doi.org/10.1002/art.21955.
42. Ameer MA, Chaudhry H, Mushtaq J, *et al.* An overview of systemic lupus erythematosus (SLE) pathogenesis, classification, and management. Cureus. 2022;14(10):e30330. https://doi.org/10.7759/cureus.30330.
43. Zhang T, Mohan C. Caution in studying and interpreting the lupus metabolome. Arthritis Res Ther. 2020;22(1):172. https://doi.org/10.1186/s13075-020-02264-2.
44. Yin Y, Choi SC, Xu Z, *et al.* Normalization of CD4+ T cell metabolism reverses lupus. Sci Transl Med. 2015;7(274):274ra18. https://doi.org/10.1126/scitranslmed.aaa0835.
45. McDonald G, Deepak S, Miguel L, *et al.* Normalizing glycosphingolipids restores function in CD4+ T cells from lupus patients. J Clin Invest. 2014;124(2):712–724. https://doi.org/10.1172/JCI69571.
46. Zhu Y, Gumlaw N, Karman J, *et al.* Lowering glycosphingolipid levels in CD4+ T cells attenuates T cell receptor signaling, cytokine production, and differentiation to the Th17 lineage. J Biol Chem. 2011;286(17):14787–14794. https://doi.org/10.1074/jbc.M111.218610.
47. Murray PJ, Rathmell J, Pearce E. SnapShot: Immunometabolism. Cell Metab. 2015;22(1):190–190el. https://doi.org/10.1016/j.cmet.2015.06.014.
48. Zhang CX, Wang HY, Yin L, *et al.* Immunometabolism in the pathogenesis of systemic lupus erythematosus. J Transl Autoimmun. 2020;3:100046. https://doi.org/10.1016/j.jtauto.2020.100046.
49. Charoenngam N. Vitamin D and rheumatic diseases: A review of clinical evidence. Int J Mol Sci. 2021;22(19). https://doi.org/10.3390/ijms221910659.
50. Sahebari M, Nabavi N, Salehi M. Correlation between serum 25(OH)D values and lupus disease activity: an original article and a systematic review with meta-analysis focusing on serum VitD confounders. Lupus. 2014;23(11):1164–1177. https://doi.org/10.1177/0961203314540966.
51. Wang XR, Xiao JP, Zhang JJ, *et al.* Decreased serum/plasma vitamin D levels in SLE patients: A meta-analysis. Curr Pharm Des. 2018;24(37):4466–4473. https://doi.org/10.2174/1381612825666190111145848.
52. Harrison SR, Li D, Jeffery LE, *et al.* Vitamin D, autoimmune disease and rheumatoid arthritis. Calcif Tissue Int. 2020;106(1):58–75. https://doi.org/10.1007/s00223-019-00577-2.
53. L. BE, Ismailova A, Dimeloe S, *et al.* Vitamin D and immune regulation: Antibacterial, antiviral, anti-inflammatory. JBMR Plus. 2021;5(1):e10405. https://doi.org/10.1002/jbm4.10405.
54. Yan Yunxia, Yu Fangyuan, Li Qi *et al.* Metabolic alterations in vitamin D deficient systemic lupus erythematosus patients, 22 January 2024, PREPRINT (Version 1) available at Research Square https://doi.org/10.21203/rs.3.rs-3861907/v1.
55. Hussein AG, Mohamed RH, Alghobashy AA. Synergism of CYP2R1 and CYP27B1 polymorphisms and susceptibility to type 1 diabetes in Egyptian children. Cell Immunol. 2012;279(1):42–45. DOI: 10.1016/j.cellimm.2012.08.006.
56. Atkinson MA, Eisenbarth GS, Michels AW. Type 1 diabetes. Lancet. 2014;383(9911):69–82. DOI: 10.1016/S0140-6736(13)60591-7.
57. Miettinen ME, Smart MC, Kinnunen L, Harjutsalo V, Reinert-Hartwall L, Ylivinkka I, *et al.* Genetic determinants of serum 25-hydroxyvitamin D concentration during pregnancy and type 1 diabetes in the child. PLoS One. 2017;12(10):e0184942. DOI: 10.1371/journal.pone.0184942.
58. Daskalopoulou M, Pylli M, Giannakou K. Vitamin D deficiency as a possible cause of type 1 diabetes in children and Adolescents up to 15 years old: A systematic review. Rev Diabet Stud. 2022;18(2):58–67. DOI: 10.1900/RDS.2022.18.58.
59. Habibian N, Amoli MM, Abbasi F, Rabbani A, Alipour A, Sayarifard F, Rostami P, Dizaji SP, Saadati B, Setoodeh A. Role of vitamin D and vitamin D receptor gene polymorphisms on residual beta cell function in children with type 1 diabetes mellitus. Pharmacol Rep. 2019;71(2):282–288. DOI: 10.1016/j.pharep.12.012.
60. Tapia G, Mårild K, Dahl SR, Lund-Blix NA, Viken MK, Lie BA, *et al.* Maternal and newborn vitamin D-binding protein, vitamin D levels, vitamin D receptor genotype, and childhood type 1 diabetes. Diabetes Care. 2019;42(4):553–559. DOI: 10.2337/dc18-2176.
61. Norris JM, Lee H-S, Frederiksen B, Erlund I, Uusitalo U, Yang J, *et al.* Plasma 25-hydroxyvitamin D concentration and risk of islet autoimmunity. Diabetes. 2018;67(1):146–154. DOI: 10.2337/db17-0802.
62. Ma X, Xie Z, Qin J, Luo S, Zhou Z. Association of vitamin D pathway gene CYP27B1 and CYP2R1 polymorphisms with autoimmune endocrine disorders: A meta-analysis. J Clin Endocrinol Metab. 2020;105(11):dgaa525. DOI: 10.1210/clinem/dgaa525.
63. Li M, Song L-J, Qin X-Y. Advances in the cellular immunological pathogenesis of type 1 diabetes. J Cell Mol Med. 2014;18(5):749–758. DOI: 10.1111/jcmm.12270.
64. Tizaoui K, Kaabachi W, Hamzaoui A, Hamzaoui K Contribution of VDR polymorphisms to type 1 diabetes susceptibility: Systematic review of case-control studies and meta-analysis. J. Steroid Biochem. Mol. Biol. 2014;143:240–249.
65. Thirunavukkarasu R, Chitra A, Asirvatham A, Jayalakshmi M. Association of vitamin D deficiency and vitamin D receptor gene polymorphisms with type 1 diabetes risk: A south indian familial study. J Clin Res Pediatr Endocrinol. 2024;16(1):21–30.
66. Taylor AK, Lebwohl B, Snyder CL, Green PHR. Celiac disease. In GeneReviews®, Adam MP, Mirzaa GM, *et al.*, Eds., University ofWashington: Seattle, DC, USA, 2008.
67. Corazza GR, Di Sario A, Cecchetti L, Tarozzi C, Corrao G, Bernardi M, *et al.* Bone mass and metabolism in patients with celiac disease. Gastroenterology. 1995;109:122–128.
68. Shree T, Banerjee P, Senapati S. A meta-analysis suggests the association of reduced serum level of vitamin D and T-allele of Fok1 (rs2228570) polymorphism in the vitamin D receptor gene with celiac disease. Front. Nutr. 2023;9:996450. [PubMed].
69. Agliardi C, Guerini FR, Bolognesi E, Zanzottera M, Clerici M. VDR gene single nucleotide polymorphisms and autoimmunity: A narrative review. Biology. 2023;12:916. https://doi.org/10.3390/biology12070916.
70. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N. Engl. J. Med. 2011;365:2205–2219.
71. Gil Á, Plaza-Diaz J, Mesa MD. Vitamin D: Classic and novel actions. Ann. Nutr. Metab. 2018;72:87–95.
72. Christakos S, Li S, De La Cruz J, Bikle DD. New developments in our understanding of vitamin metabolism, action and treatment. Metabolism. 2019;98:112–120. [PubMed].
73. Ooi JH, Chen J, Cantorna MT. Vitamin D regulation of immune function in the gut: Why do T cells have vitamin D receptors? Mol. Asp. Med. 2012;33:77–82. [PubMed].
74. Illescas-Montes R, Melguizo-Rodríguez L, Ruiz C, Costela-Ruiz VJ. Vitamin D and autoimmune diseases. Life Sci. 2019;233:116744. [PubMed].
75. Athanassiou L, Kostoglou-Athanassiou I, Koutsilieris M, Shoenfeld Y. Vitamin D and autoimmune rheumatic diseases. Biomolecules. 2023;13:709. [PubMed].
76. Miyamoto K, Kesterson RA, Yamamoto H, Taketani Y, Nishiwaki E, Tatsumi S, *et al.* Structural organization of the human

vitamin D receptor chromosomal gene and its promoter. Mol. Endocrinol. 1997;11:1165–1179. [PubMed].
77. Ruiz-Ballesteros AI, Meza-Meza MR, Vizmanos-Lamotte B, Parra-Rojas I, de la Cruz-Mosso U. Association of vitamin D metabolism gene polymorphisms with autoimmunity: Evidence in population genetic studies. Int. J. Mol. Sci. 2020;21:9626.
78. 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. 2015;35:8–14.
79. Sentinelli F, Bertoccini L, Barchetta I, Capoccia D, Incani M, Pani MG, *et al.* The vitamin D receptor (VDR) gene rs11568820 variant is associated with type 2 diabetes and impaired insulin secretion in Italian adult subjects, and associates with increased cardio-metabolic risk in children. Nutr. Metab. Cardiovasc. Dis. 2016;26;407–413.
80. Scazzone C, Agnello L, Bivona G, Lo Sasso B, Ciaccio M. Vitamin D and genetic susceptibility to multiple sclerosis. Biochem. Genet. 2021;59:1–30. [PubMed].
81. Marini F, Falcini F, Stagi S, Fabbri S, Ciuffi S, Rigante D, *et al.* Study of vitamin D status and vitamin D receptor polymorphisms in a cohort of Italian patients with juvenile idiopathic arthritis. Sci. Rep. 2020;10:17550. [PubMed].
82. Latini A, De Benedittis G, Perricone C, Colafrancesco S, Conigliaro P, Ceccarelli F, *et al.* VDR polymorphisms in autoimmune connective tissue diseases: Focus on Italian population. J. Immunol. Res. 2021;2021:5812136. [PubMed].
83. van Hamburg JP, Asmawidjaja PS, Davelaar N, Mus AM, Cornelissen F, van Leeuwen JP, *et al.* TNF blockade requires 1,25(OH)2D3 to control human Th17-mediated synovial inflammation. Ann. Rheum. Dis. 2012;71:606–612.
84. Cusato J, Bertani L, Antonucci M, Tomasello C, Caviglia GP, Dibitetto S, *et al.* Vitamin D-related genetics as predictive biomarker of clinical remission in adalimumab-treated patients affected by crohn's disease: A pilot study. Pharmaceuticals. 2021;14:1230. [PubMed].