RHEUMATOLOGY

The immunomodulatory potential of vitamin D on Th17 lymphocytes in systemic lupus erythematosus - a literature review

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Abstract

This review offers insight into the complex interplay between cytokines and vitamin D, with focus on its role in systemic lupus erythematosus (SLE) pathogenesis. It offers a helpful resource for researchers and clinicians seeking to better understand and treat SLE and related autoimmune conditions. The pathogenesis of SLE is complex and involves a wide range of cytokines, primarily of the Th2 type; these cytokines mediate hyperactivity in B lymphocytes and antibody production. Notably, vitamin D is found to suppress the activity of critical Th17-related cytokines like IL-23 and IL-6, which is pivotal for Th17 cell development and function. This ultimately leads to reduced IL-17 production, an increase in regulatory T lymphocytes, and subsequent secretion of IL-10. Supplementation with vitamin D is seen to have positive effects on SLE, leading to lower disease activity scores, decreased levels of autoantibodies, and a reduction of fatigue.

Keywords: systemic lupus erythematosus, vitamin D, immunomodulation

Introduction

Systemic Lupus Erythematosus (SLE) is a multifactorial autoimmune disease characterized by dysregulated immune responses against self-antigens, leading to chronic inflammation and tissue damage in multiple organ systems [1]. Among the diverse cellular components involved in SLE pathogenesis, T helper 17 (Th17) lymphocytes have emerged as key mediators, contributing to the inflammatory milieu through the secretion of pro-inflammatory cytokines such as interleukin-17 (IL-17) [2].

Vitamin D, traditionally recognized for its crucial role in calcium homeostasis and bone metabolism, has garnered increasing attention for its immunomodulatory properties. Epidemiological studies have highlighted an inverse association between vitamin D levels and the risk of developing autoimmune diseases, including SLE [3-5]. Moreover, experimental evidence suggests that vitamin D exerts regulatory effects on immune cell function, including the modulation of Th17 cell differentiation and activity [6].

Despite growing interest in the potential therapeutic implications of vitamin D supplementation in SLE management, the precise mechanisms underlying its immunomodulatory effects on Th17 lymphocytes remain incompletely understood.

In this narrative review, we aim to provide a comprehensive synthesis of the literature exploring the immunomodulatory potential of vitamin D on Th17 lymphocytes in SLE. We will examine the cellular and molecular mechanisms underlying vitamin D-mediated regulation of Th17 cell differentiation, effector functions, and cytokine production.

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Vitamin D and autoimmune diseases

In the case of innate immunity, vitamin D acts on the macrophage, which plays a key role in antimicrobial defense [7]. The regulatory mechanisms are multiple; 1,25(OH)2D3 or its analogs initiate the process of differentiation of myeloid cells into macrophages [8,9]. Simultaneously, vitamin D influences the expression level of IL-6, acting at the NF-kB level [10,11].

Chen et al. described the ability of vitamin D to modulate toll-like receptor (TLR) signaling via SOCS1 and miR-155. Recent findings related to the ability of vitamin D receptor (VDR) to interact with other nuclear receptors that exert anti-inflammatory action indicate the important role of vitamin D in initiating and propagating autoimmune phenomena [12].

Numerous studies have shown that vitamin D deficiency is associated with many autoimmune diseases, including rheumatoid arthritis [13], seronegative spondyloarthropathies, SLE, systemic sclerosis, Sjogren's syndrome, psoriatic arthropathy, inflammatory bowel diseases, multiple sclerosis, etc [14-18]. Although these diseases have different pathogenesis, the common link is the low level of vitamin D. The central role of the regulatory element of vitamin D is given by the presence of the VDR on all cell lines involved in immune defense [19].

An optimal level of vitamin D is also important in maintaining fertility and the development of a normal pregnancy [20,21]. One of the mechanisms by which vitamin D performs these functions is the prevention of endothelial cell activation by inflammatory cytokines such as TNF-alpha. A few studies in mice showed the modulatory role of vitamin D in angiotensin II production and its indirect role in vasomotricity [22-24].

Doubelt et al. showed in a study of 125 patients with ANCA-associated vasculitis that the vitamin D status correlates with the severity of the disease and male gender [25]. This draws attention to the fact that additional vitamin D intake in these patients may have an adjuvant effect in reducing the activation rate of endothelial cells.

Among autoimmune diseases, SLE has the highest potential to develop a vitamin D deficiency, primarily because these patients exhibit photosensitivity, which hinders exposure to UV radiation. Other factors contributing to a low level of vitamin D include lupus nephritis and chronic use of glucocorticoids. There are controversies discussing whether vitamin D deficiency is a cause or a consequence of triggering autoimmune processes in SLE. The consequence of vitamin D deficiency translates into creating an environment conducive to the production of pathogenic autoantibodies and excessive secretion of inflammatory interleukins: IL-17, IL-23, etc. [26-30].

Several studies, including a meta-analysis conducted by Franco et al., have highlighted the importance of the active form of vitamin D in reducing proinflammatory effects mediated by IL-17, IL-6, and IL-1beta. He also demonstrated that vitamin D supplementation reduces the titers of antinuclear antibodies in treatment-naive patients with SLE, as well as the SLEDAI score [31,32]. Vitamin D may have protective effects on renal function by reducing the inflammatory infiltrate at the glomerular level and immune complex deposition [33].

Vitamin D and Th17 in Systemic Lupus Erythematosus

The dynamic interactions of cells in SLE are complex and involve components of both the innate immune system (macrophages, dendritic cells) and the adaptive immune system (lymphocytes).

Vitamin D acts on both pathways because the VDR is present on the surface of macrophages, Th1 lymphocytes, Th2 lymphocytes, Th17 lymphocytes, and natural killer (NK) cells. The binding of vitamin D to its receptor leads to the formation of a heterodimer with the retinoid X receptor (RXR), a complex that recruits histone acetylation enzymes. Thus, vitamin D has the ability to act specifically on genes [34]. One of these consequences is reflected in the blockade of dendritic cell maturation and differentiation. In parallel, 25(OH)D promotes the development of the M2 phenotype of IL-10-producing macrophages with anti-inflammatory effects, as opposed to M1 macrophages with a pro-inflammatory phenotype [35]. Efforts over the years to elucidate the role of vitamin D in regulating the immune response have concluded the importance of negative selection of hyperreactive lymphocytes. This effect is independent of the VDR gene polymorphism, which applies even to SLE patients with a vitamin D deficiency. Calcitriol acts intracellularly on the GATA 3 and STAT6 signaling systems of Th2 lymphocytes, negatively impacting the Th17 population, which expresses interferon-gamma [36-38].

The binding of vitamin D to its receptor interrupts the pro-inflammatory signal transmitted by NF-kB, resulting in reduced secretion of IL-6, IL-1beta, and IFN-gamma. In cases of SLE where peripheral blood mononuclear cells (PBMC) have reduced VDR expression, there is a more abundant population of T lymphocytes. Additionally, the absence of vitamin D is associated with a more abundant expression of MHC class II, CD40, and CD86, which are essential cellular markers for the interaction between Th1, Th2, and Th17 [34,39]. A meta-analysis involving 19,713 participants showed that both the pathogenesis of SLE and atopic dermatitis have Th1, Th2, and Th17 lymphocytes as the main effectors. As in SLE, in atopic dermatitis, patients have a Th2 cytokine profile, but also high concentrations of IL-12 and IL-22 as a result of Th17 activity [40,41].

The increased frequency of vitamin D deficiency demonstrated by Thudi et al. among SLE patients may explain the increased serum concentration of IL-17. IL-17 acts by promoting the recruitment and activation of various immune cells, including neutrophils, macrophages and B

cells, leading to increased production of autoantibodies and immune complexes that deposit in organs such as the kidneys, causing inflammation and organ damage [42,43]. The microenvironment created by IL-12, TNF-alpha, and IL-6 is conducive to the development and maturation of Th17. These cells are potent activators of synovial fibroblasts in SLE and rheumatoid arthritis, leading to a subsequent increase in the secretion of IL-6, IL-8, ICAM-1, and G-CSF [44-46]. It has also been observed that IL-23, an interleukin restricted to dendritic cells and macrophages, is decreased in SLE patients with lymphopenia and renal involvement. Other studies showed that active IL-23 can also be increased in SLE [47,48]. These contradictory results may suggest a mechanism of reciprocal potentiation between lymphocytes and antigen-presenting cells (macrophages or dendritic cells).

Vitamin D inhibits the development of Th17 and Th1, probably through a mechanism that occurs before the step involving STAT3 [40,49]. In parallel, vitamin D reduces the expression of genes encoding for IL-6, IL-17, and IL-23, thus preventing the conversion of CD4+ lymphocytes into Th17, a fact confirmed by an animal study in which the VDR was eliminated, and higher concentrations of IL-17 were expressed [27,50].

Regulatory T lymphocytes are CD4+ and FoxP3+CD25(high)CD127(low). Initially, only CD25 was considered the defining marker of the regulatory T lymphocyte phenotype [51]. Studies show contradictory results regarding the number of these cells in autoimmune diseases due to the lack of a precise marker for the Treg phenotype. There are hypotheses that some autoimmune diseases result from the conversion of Tregs into Th17 lymphocytes via IL-2, and in the case of SLE, the level of IL-17 is abnormally high. Dysfunction of these cells can be explained by the fact that cells expressing FoxP3+ lose CD25 expression [52,53].

The FoxP3+ gene has a VDR element in its promoter region [54]. Marinho et al. observed that vitamin D supplementation for 6 months increased FoxP3 expression in CD4+ T lymphocytes and increased the Treg/Th17 ratio, clinically proven by the improvement of the SLEDAI score [55-57]. Vitamin D also mediates communication between the innate and adaptive immune systems. It suppresses the activity of the promoter for the key transcription factor RelB in dendritic cell maturation [58,59]. As a result, a population of semi-mature dendritic cells is obtained, expressing fewer MHC class II molecules and costimulatory molecules. Dendritic cells derived from monocytes in SLE patients who received vitamin D have lower expression of genes for interferon-gamma [60].

An *in vitro* study on cell cultures, where dendritic cells were alternatively activated by treatment with dexamethasone for 5 days followed by dexamethasone and lipopolysaccharide (LPS) on the 8th day, showed that these cells had a different effect on naive T lymphocytes and memory T lymphocytes after vitamin D treatment. Naive T lymphocytes were polarized towards the IL-10-producing Treg phenotype, while memory T lymphocytes were directed towards a profile with reduced secretion of IL-17 and IFN-gamma [32].

Vitamin D and IL-17 in Systemic Lupus Erythematosus

SLE is characterized by the interconnected activity of a wide range of cytokines, most of which originate from Th2 lymphocytes. The action of these cytokines mediates the hyperactivity of B lymphocytes and the production of autoantibodies [26,61,62].

Interleukin-17 is a cytokine that has recently gained attention in research regarding its contribution to the pathology of SLE [63]. The sources of IL-17 are multiple; the main subtypes of lymphocytes involved are Th17 lymphocytes, and to a lesser extent, T gamma-delta and alpha-beta double-negative lymphocytes. Th17 activity is potentiated by a multitude of cytokines: IL-6, IL-21, IL-1beta, TGF-beta, which in turn amplify the inflammation cascade and the effects of IL-17 [26,50].

Recently, the importance of intestinal dysbiosis in maintaining the inflammatory process in SLE has been highlighted, especially the alteration of the ratio between Firmicutes and Bacteroides species [64-66]. The causes of imbalance in the intestinal flora are multiple, including antibiotic consumption, viral infections with cytomegalovirus, Epstein-Barr, hormonal influences, hygiene, etc. vitamin D receptors (VDRs) in the gastrointestinal tract may influence microbial composition by modulating the immune response. VDR activation also stimulates the production of antimicrobial peptides such as cathelicidin and defensin, which are crucial for microbial homeostasis. The active form of vitamin D promotes the production of these peptides at the macrophage level, further contributing to the regulation of the gut microbiota and immune defense [67-69]. Experiments conducted on murine models have shown that the intestinal mucosa of female mice has a rich infiltrate of cells with the potential to secrete IL-17, IL-22, and IL-9 [70,71]. In addition, the alteration of the physiological microbiome leads to the impairment of intestinal barrier permeability, allowing the penetration of antigenic particles into the bloodstream. Supplementation with probiotics rich in Lactobacillus species and vitamin D contributes to the formation of tight junctions and maintains the integrity of the intestinal barrier [72-74].

The complexity of cellular and molecular interactions occurring in the autoimmune process necessitates the investigation of molecular targets that could underlie the immunological imbalance in SLE. It has been discovered that these patients exhibit alteration in the STAT3 signaling pathway, resulting in abnormal IL-17 production [75]. Additionally, certain non-coding messenger RNA

molecules, including lncRNA and miRNA, can influence STAT3 activity and signaling pathways mediated by interferon, TGF-beta, and NF-kB [76].

The reverberating effect of pathological phenomena in SLE is confirmed by oxidative stress resulting from the action of proinflammatory cytokines, which, in turn, activates caspases and cell death. IL-2 activates IL-17 production via Th17, which subsequently mediates the inflammatory cascade triggered by IL-6, IL-1, and TNF-alpha [77-79].

Vitamin D acts as a steroid hormone with multiple roles in cell proliferation and growth, as well as immunoregulatory properties. The activation of ubiquitously present VDR suppresses NF-kB activity, reduces IL-2 expression, decreases T lymphocyte proliferation, and reduces the production of IL-6, IL-1, and IL-17 [41,48,50]. Faraji et al. demonstrated that vitamin D administration in lupus murine models modulates cytokine production in favor of anti-inflammatory cytokines. Stimulation of IL-4 attenuates the aberrant activity of helper T lymphocytes [80,81]. Attenuation of the effects induced by IL-2 and interferon-gamma contributes to maintaining normal cognitive activity by neutralizing oxidative stress, thus providing neuroprotection [82].

At the level of Th17 lymphocytes, 1,25(OH2D3 has the ability to decrease interleukin-17 secretion and reduce the activity of other effector molecules such as CCR6, RORC, and ectonucleotidase CD39, while simultaneously stimulating IL-10 production [48,55].

Hypovitaminosis D in SLE patients creates a conducive environment for the pronounced expression of IL-17. This has been confirmed by studies on both animal and human models, showing that vitamin D supplementation promotes a tolerogenic status by enhancing the activity of regulatory T lymphocytes. IL-10 secreted by these lymphocytes tempers the proinflammatory action of IL-17 and IL-6 [26].

Today, it is well-known that SLE is associated with accelerated atherogenesis and cardiovascular risk [83]. Numerous opinions formulated in the literature on this topic have agreed on the roles of Th1, Th17 lymphocytes, and IL-17 via type I IFN in the activation of vascular endothelium and the promotion of oxidized LDL cholesterol deposition in the arterial wall. Imbalance in the ratio between regulatory T lymphocytes and Th17 lymphocytes results in reduced IL-10 production and abnormal increase in IL-17 concentration, accelerating the proatherogenic inflammatory process [36,84,85].

Although data regarding the role of cytokines IL-6, IL-17, and IL-1 beta in atherosclerosis genesis in SLE are still controversial, optimizing vitamin D levels in these patients is a measure that can slow down the formation and maturation of atheromatous plaques [86-88].

Last but not least, vitamin D has the capacity to express its protective effects, even in lupus nephritis, a major cause of mortality in these patients. Podocyte autophagy is implicated in the pathogenesis of lupus nephritis (LN) and is associated with both proteinuria and disease activity [89]. Additionally, vitamin D exerts a protective effect on podocyte injury in LN patients, mediated through the regulation of autophagic processes [90]. The glomerular filtration barrier, composed of podocytes, the glomerular basement membrane, and endothelial cells coated with a glycocalyx, exhibits a reduction in heparan sulfate (HS) in proteinuric patients [91]. This reduction is linked to elevated expression of the HS-degrading enzyme heparanase. vitamin D receptor (VDR) binds to the heparanase promoter, and treatment with 1,25-dihydroxyvitamin D3 (1,25-D3) inhibits heparanase promoter activity [92,93]. In vitamin D-deficient mice, proteinuria and increased heparanase expression were observed, both of which were reversed following 1,25-D3 treatment. Collectively, these findings suggest that vitamin D reduces heparanase expression in both in vitro and in vivo models of podocyte injury, likely through direct regulation of heparanase promoter activity [94,95].

The transient receptor potential cation channel C6 (TRPC6), a slit diaphragm protein expressed by podocytes, shows elevated expression in acquired proteinuric renal disease. Studies by Sonneveld indicate that 1,25-D3 downregulates TRPC6 expression in injured podocytes and animal models of focal segmental glomerulosclerosis (FSGS) and 1,25-D3 deficiency. In the angiotensin II nephritis (AN) rat model of FSGS, increased TRPC6 expression and proteinuria were significantly alleviated by 1,25-D3 treatment. Furthermore, vitamin D has been identified as a negative regulator of renin, and deficiency of VDR is associated with upregulated expression of angiotensinogen and AT1 receptors in renal tissues and podocytes [88,96-98].

Administration of 1,25(OH)2D3 reduced the level of deposited C3 at the glomerular level, anti-dsDNA antibody levels, probably through the stimulation of phagocytosis by macrophages. Its direct action on NF-kB inhibits the formation and deposition of circulating immune complexes and reduces the production of cytokines induced by IL-17 [99,100].

Vitamin D supplementation is often prescribed to address deficiencies and support bone health, but its long-term effects—both beneficial and adverse—extend beyond its traditional role in calcium homeostasis. Chronic vitamin D supplementation has been explored in autoimmune conditions like multiple sclerosis, type 1 diabetes, and rheumatoid arthritis. While some studies suggest that higher vitamin D levels are associated with reduced disease activity or lower risk of developing these conditions, long-term randomized controlled trials show mixed results, indicating that more research is needed. Researchers have not reached a consensus regarding the optimal dosing regimen for achieving these goals, and excessive supplementation

can lead to adverse effects, particularly related to calcium metabolism. Therefore, vitamin D supplementation should be personalized, based on the patient's needs and age.

In the last decade, research has focused on the gut microbiota, dysbiosis and its relationship with various conditions, including autoimmune diseases. Regarding SLE, it has not yet been determined whether the alteration of the gut microbiota is a cause or a consequence of the disease. There are many unanswered questions on this issue. We have yet to determine the optimal dose of vitamin D for modulating a healthy microbiota. In order to achieve this goal we also need to understand how vitamin D interacts with gut microorganisms and whether this interaction varies from individual to individual.

Conclusion

This review offers a detailed examination of the different mechanisms through which Th17 lymphocytes are involved in the pathogenesis of SLE and the impact of vitamin D through its immunomodulatory effects. Vitamin D emerges as a key player in immune regulation, acting as a steroid hormone that modulates cell growth, apoptosis, and the overall immune response.

References

1. D'Cruz DP. Systemic lupus erythematosus. BMJ. 2006;332:890-894.
2. Martin JC, Baeten DL, Josien R. Emerging role of IL-17 and Th17 cells in systemic lupus erythematosus. Clin Immunol. 2014;154:1-12.
3. Kamen DL, Aranow C. The link between vitamin D deficiency and systemic lupus erythematosus. Curr Rheumatol Rep. 2008;10:273-280.
4. Arnson Y, Amital H, Shoenfeld Y. vitamin D and autoimmunity: new aetiological and therapeutic considerations. Ann Rheum Dis. 2007;66:1137-1142
5. Yang CY, Leung PS, Adamopoulos IE, Gershwin ME. The implication of vitamin D and autoimmunity: a comprehensive review. Clin Rev Allergy Immunol. 2013;45:217-226.
6. Cutolo M. vitamin D and autoimmune rheumatic diseases. Rheumatology (Oxford). 2009;48:210-212.
7. Hewison M. Chapter two - Vitamin D and Innate and Adaptive Immunity. In: Litwack G, editor. Vitamins & Hormones. vol. 86: Academic Press; 2011. p. 23-62.
8. Fernandez GJ, Ramírez-Mejía JM, Urcuqui-Inchima S. vitamin D boosts immune response of macrophages through a regulatory network of microRNAs and mRNAs. J Nutr Biochem. 2022;109:109105.
9. Hewison M. vitamin D and the immune system: new perspectives on an old theme. Endocrinol Metab Clin North Am. 2010;39:365-379, table of contents.
10. Zhang L, Wang Z, Wang X, Zhang N, Ke J, Yang L. Study on the relationship between vitamin D level and macrophage typing in patients with type 2 diabetes mellitus. Int J Diabetes Dev Ctries. 2023;43:792-800.
11. Chen Y, Zhang J, Ge X, Du J, Deb DK, Li YC. vitamin D receptor inhibits nuclear factor κB activation by interacting with IκB kinase β protein. J Biol Chem. 2013;288:19450-19458.
12. Yin K, Agrawal DK. vitamin D and inflammatory diseases. J Inflamm Res. 2014;7:69-87.
13. Hiraki LT, Arkema EV, Cui J, Malspeis S, Costenbader KH, Karlson EW. Circulating 25-hydroxyvitamin D level and risk of developing rheumatoid arthritis. Rheumatology (Oxford). 2014;53:2243-2248.
14. Athanassiou L, Kostoglou-Athanassiou I, Koutsilieris M, Shoenfeld Y. vitamin D and Autoimmune Rheumatic Diseases. Biomolecules. 2023;13:709.
15. Ritterhouse LL, Crowe SR, Niewold TB, Kamen DL, Macwana SR, Roberts VC, et al. vitamin D deficiency is associated with an increased autoimmune response in healthy individuals and in patients with systemic lupus erythematosus. Ann Rheum Dis. 2011;70:1569-1574.
16. Cantorna MT. vitamin D and its role in immunology: multiple sclerosis, and inflammatory bowel disease. Prog Biophys Mol Biol. 2006;92:60-64.
17. Hausmann J, Kubesch A, Amiri M, Filmann N, Blumenstein I. vitamin D Deficiency is Associated with Increased Disease Activity in Patients with Inflammatory Bowel Disease. J Clin Med. 2019;8:1319.
18. Fletcher J, Cooper SC, Ghosh S, Hewison M. The Role of vitamin D in Inflammatory Bowel Disease: Mechanism to Management. Nutrients. 2019;11:1019.
19. Dankers W, Colin EM, van Hamburg JP, Lubberts E. vitamin D in Autoimmunity: Molecular Mechanisms and Therapeutic Potential. Front Immunol. 2017;7:697.
20. Pilz S, Zittermann A, Obeid R, Hahn A, Pludowski P, Trummer C, et al. The Role of vitamin D in Fertility and during Pregnancy and Lactation: A Review of Clinical Data. Int J Environ Res Public Health. 2018;15:2241.
21. Várbíró S, Takács I, Tűű L, Nas K, Sziva RE, Hetthéssy JR, et al. Effects of vitamin D on Fertility, Pregnancy and Polycystic Ovary Syndrome-A Review. Nutrients. 2022;14:1649.
22. Cyprian F, Lefkou E, Varoudi K, Girardi G. Immunomodulatory Effects of vitamin D in Pregnancy and Beyond. Front Immunol. 2019;10:2739.
23. Ajabshir S, Asif A, Nayer A. The effects of vitamin D on the renin-angiotensin system. J Nephropathol. 2014;3:41-43.
24. Jia J, Tao X, Tian Z, Liu J, Ye X, Zhan Y. vitamin D receptor deficiency increases systolic blood pressure by upregulating the renin-angiotensin system and autophagy. Exp Ther Med. 2022;23:314.
25. Doubelt I, Cuthbertson D, Carette S, Khalidi NA, Koening CL, Langford C, et al. vitamin D status in ANCA-associated vasculitis. Rheumatol Adv Pract. 2023;7:rkad021.
26. Shahin D, El-Farahaty RM, Houssen ME, Machaly SA, Sallam M, ElSaid TO, et al. Serum 25-OH vitamin D level in treatment-naïve systemic lupus erythematosus patients: Relation to disease activity, IL-23 and IL-17. Lupus.

2017;26:917-926.

27. Abo-Shanab AM, Kholoussi S, Kandil R, Dorgham D. Cytokines, 25-OH vit D and disease activity in patients with juvenile-onset systemic lupus erythematosus. Lupus. 2021;30:459-464.
28. Meza-Meza MR, Muñoz-Valle JF, Ruiz-Ballesteros AI, Vizmanos-Lamotte B, Parra-Rojas I, Martínez-López E, et al. Association of High Calcitriol Serum Levels and Its Hydroxylation Efficiency Ratio with Disease Risk in SLE Patients with vitamin D Deficiency. J Immunol Res. 2021;2021:2808613.
29. Ding Y, Yang S, Fan S, Tang Y, Teng Y, Tao X, et al. Is vitamin D Deficiency the Cause or the Effect of Systemic Lupus Erythematosus: Evidence from Bidirectional Mendelian Randomization Analysis. J Immunol Res. 2022;2022:8689777.
30. Magro R, Borg AA. The effect of vitamin D on disease activity, fatigue and interferon signature gene expression in systemic lupus erythematosus. Mediterr J Rheumatol. 2017;28:127-132.
31. Franco AS, Freitas TQ, Bernardo WM, Pereira RMR. vitamin D supplementation and disease activity in patients with immune-mediated rheumatic diseases: A systematic review and meta-analysis. Medicine (Baltimore). 2017;96:e7024.
32. Wu HJ, Lo Y, Luk D, Lau CS, Lu L, Mok MY. Alternatively activated dendritic cells derived from systemic lupus erythematosus patients have tolerogenic phenotype and function. Clin Immunol. 2015;156:43-57.
33. Liu D, Fang YX, Wu X, Tan W, Zhou W, Zhang Y, et al. 1,25-$(OH)_2D_3$/vitamin D receptor alleviates systemic lupus erythematosus by downregulating Skp2 and upregulating p27. Cell Commun Signal. 2019;17:163.
34. Iruretagoyena M, Hirigoyen D, Naves R, Burgos PI. Immune Response Modulation by vitamin D: Role in Systemic Lupus Erythematosus. Front Immunol. 2015;6:513.
35. Nygaard RH, Nielsen MC, Antonsen KW, Højskov CS, Sørensen BS, Møller HJ. Metabolism of 25-Hydroxy-vitamin D in Human Macrophages Is Highly Dependent on Macrophage Polarization. Int J Mol Sci. 2022;23:10943.
36. Jha SB, Rivera AP, Flores Monar GV, Islam H, Puttagunta SM, Islam R, et al. Systemic Lupus Erythematosus and Cardiovascular Disease. Cureus. 2022;14:e22027.
37. Kaleta B, Bogaczewicz J, Robak E, Sysa-Jędrzejowska A, Wrzosek M, Szubierajska W, et al. vitamin D Receptor Gene BsmI Polymorphism in Polish Patients with Systemic Lupus Erythematosus. ISRN Endocrinol. 2013;2013:427818.
38. Ben-Zvi I, Aranow C, Mackay M, Stanevsky A, Kamen DL, Marinescu LM, et al. The impact of vitamin D on dendritic cell function in patients with systemic lupus erythematosus. PLoS One. 2010;5:e9193.
39. Mariz HA, Sato EI, Cardoso PRG, Gonçalves R, Duarte ALBP, de Melo Rego MJB, et al. vitamin D Presented In Vitro Immunomodulatory Property on T Lymphocyte-Related Cytokines in Systemic Lupus Erythematosus. Inflammation. 2023;46:730-738.
40. Yamamoto EA, Nguyen JK, Liu J, Keller E, Campbell N, Zhang CJ, et al. Low Levels of vitamin D Promote Memory B Cells in Lupus. Nutrients. 2020;12:291.
41. Partan RU, Hidayat R, Saputra N, Rahmayani F, Prapto H, Yudha TW. Seluang Fish (Rasbora Spp.) Oil Decreases Inflammatory Cytokines Via Increasing vitamin D Level in Systemic Lupus Erythematosus. Open Access Maced J Med Sci. 2019;7:1418-1421.
42. Zhang Z, Kyttaris VC, Tsokos GC. The role of IL-23/IL-17 axis in lupus nephritis. J Immunol. 2009;183:3160-3169.
43. Petrić M, Radić M. Is Th17-Targeted Therapy Effective in Systemic Lupus Erythematosus? Curr Issues Mol Biol. 2023;45:4331-4343.
44. Thudi A, Yin S, Wandstrat AE, Li QZ, Olsen NJ. vitamin D levels and disease status in Texas patients with systemic lupus erythematosus. Am J Med Sci. 2008;335:99-104.
45. Muhammad Yusoff F, Wong KK, Mohd Redzwan N. Th1, Th2, and Th17 cytokines in systemic lupus erythematosus. Autoimmunity. 2020;53:8-20.
46. Tanaka T, Narazaki M, Kishimoto T. IL-6 in inflammation, immunity, and disease. Cold Spring Harb Perspect Biol. 2014;6:a016295
47. Terrier B, Derian N, Schoindre Y, Chaara W, Geri G, Zahr N, et al. Restoration of regulatory and effector T cell balance and B cell homeostasis in systemic lupus erythematosus patients through vitamin D supplementation. Arthritis Res Ther. 2012;14:R221.
48. Wahono CS, Rusmini H, Soelistyoningsih D, Hakim R, Handono K, Endharti AT, et al. Effects of 1,25(OH)2D3 in immune response regulation of systemic lupus erithematosus (SLE) patient with hypovitamin D. Int J Clin Exp Med. 2014;7:22-31.
49. Català-Moll F, Ferreté-Bonastre AG, Godoy-Tena G, Morante-Palacios O, Ciudad L, Barberà L, et al. vitamin D receptor, STAT3, and TET2 cooperate to establish tolerogenesis. Cell Rep. 2022;38:110244.
50. Reihani H, Rastin M, Mahmoudi M, Ghoryani M, Abdollahi N, Tabasi NS, et al. Influence of 1 Alpha, 25-Dihydroxyvitamin D3 on T Helper 17 Cells and Related Cytokines in Systemic Lupus Erythematosus. Iran J Immunol. 2015;12:82-93.
51. Żabińska M, Krajewska M, Kościelska-Kasprzak K, Jakuszko K, Bartoszek D, Myszka M, et al. CD4(+)CD25(+) CD127(-) and CD4(+)CD25(+)Foxp3(+) Regulatory T Cell Subsets in Mediating Autoimmune Reactivity in Systemic Lupus Erythematosus Patients. Arch Immunol Ther Exp (Warsz). 2016;64:399-407.
52. Ferreira RC, Simons HZ, Thompson WS, Rainbow DB, Yang X, Cutler AJ, et al. Cells with Treg-specific FOXP3 demethylation but low CD25 are prevalent in autoimmunity. J Autoimmun. 2017;84:75-86.
53. Deknuydt F, Bioley G, Valmori D, Ayyoub M. IL-1β and IL-2 convert human Treg into T(H)17 cells. Clin Immunol. 2009;131:298-307.
54. Kang SW, Kim SH, Lee N, Lee WW, Hwang KA, Shin MS, et al. 1,25-Dihyroxyvitamin D3 promotes FOXP3 expression via binding to vitamin D response elements in its conserved noncoding sequence region. J Immunol. 2012;188:5276-5282.
55. Marinho A, Carvalho C, Boleixa D, Bettencourt A, Leal B,

Guimarães J, et al. vitamin D supplementation effects on FoxP3 expression in T cells and FoxP3+/IL-17A ratio and clinical course in systemic lupus erythematosus patients: a study in a Portuguese cohort. Immunol Res. 2017;65:197-206.

56. Mak A. The Impact of vitamin D on the Immunopathophysiology, Disease Activity, and Extra-Musculoskeletal Manifestations of Systemic Lupus Erythematosus. Int J Mol Sci. 2018;19:2355.
57. Izati AF, Mohd Shukri ND, Wan Ghazali WS, Che Hussin CM, Wong KK. Increased IL-23R+ Th Cells Population Exhibits Higher SLEDAI-2K Scores in Systemic Lupus Erythematosus Patients. Front Immunol. 2021;12:690908.
58. Griffin MD, Dong X, Kumar R. vitamin D receptor-mediated suppression of RelB in antigen presenting cells: a paradigm for ligand-augmented negative transcriptional regulation. Arch Biochem Biophys. 2007;460:218-226.
59. Dong X, Craig T, Xing N, Bachman LA, Paya CV, Weih F, McKean DJ, et al. Direct transcriptional regulation of RelB by 1alpha,25-dihydroxyvitamin D3 and its analogs: physiologic and therapeutic implications for dendritic cell function. J Biol Chem. 2003;278:49378-49385.
60. Wu H, Lo Y, Chan A, Law KS, Mok MY. Rel B-modified dendritic cells possess tolerogenic phenotype and functions on lupus splenic lymphocytes in vitro. Immunology. 2016;149:48-61.
61. Drozdenko G, Heine G, Worm M. Oral vitamin D increases the frequencies of CD38+ human B cells and ameliorates IL-17-producing T cells. Exp Dermatol. 2014;23:107-112.
62. Guimarães PM, Scavuzzi BM, Stadtlober NP, Franchi Santos LFDR, Lozovoy MAB, Iriyoda TMV, et at. Cytokines in systemic lupus erythematosus: far beyond Th1/Th2 dualism lupus: cytokine profiles. Immunol Cell Biol. 2017;95:824-831.
63. Ohl K, Tenbrock K. Inflammatory cytokines in systemic lupus erythematosus. J Biomed Biotechnol. 2011;2011:432595.
64. Li R, Meng X, Chen B, Zhao L, Zhang X. Gut Microbiota in Lupus: a Butterfly Effect? Curr Rheumatol Rep. 2021;23:27.
65. Yao K, Xie Y, Wang J, Lin Y, Chen X, Zhou T. Gut microbiota: a newly identified environmental factor in systemic lupus erythematosus. Front Immunol. 2023;14:1202850.
66. Hevia A, Milani C, López P, Cuervo A, Arboleya S, Duranti S, et al. Intestinal dysbiosis associated with systemic lupus erythematosus. mBio. 2014;5:e01548-14
67. Bellerba F, Muzio V, Gnagnarella P, Facciotti F, Chiocca S, Bossi P, et al. The Association between vitamin D and Gut Microbiota: A Systematic Review of Human Studies. Nutrients. 2021;13:3378.
68. Bakke D, Sun J. Ancient Nuclear Receptor VDR With New Functions: Microbiome and Inflammation. Inflamm Bowel Dis. 2018;24:1149-1154.
69. Krutzik SR, Hewison M, Liu PT, Robles JA, Stenger S, Adams JS, et al. IL-15 links TLR2/1-induced macrophage differentiation to the vitamin D-dependent antimicrobial pathway. J Immunol. 2008;181:7115-7120.
70. Mu Q, Zhang H, Luo XM. SLE: Another Autoimmune Disorder Influenced by Microbes and Diet? Front Immunol. 2015;6:608.
71. Ma Y, Xu X, Li M, Cai J, Wei Q, Niu H. Gut microbiota promote the inflammatory response in the pathogenesis of systemic lupus erythematosus. Mol Med. 2019;25:35.
72. Ma L, Morel L. Loss of Gut Barrier Integrity In Lupus. Front Immunol. 2022;13:919792.
73. Zhang L, Qing P, Yang H, Wu Y, Liu Y, Luo Y. Gut Microbiome and Metabolites in Systemic Lupus Erythematosus: Link, Mechanisms and Intervention. Front Immunol. 2021;12:686501.
74. Rahbar Saadat Y, Hejazian M, Bastami M, Hosseinian Khatibi SM, Ardalan M, Zununi Vahed S. The role of microbiota in the pathogenesis of lupus: Dose it impact lupus nephritis? Pharmacol Res. 2019;139:191-198.
75. Goropevšek A, Holcar M, Avčin T. The Role of STAT Signaling Pathways in the Pathogenesis of Systemic Lupus Erythematosus. Clin Rev Allergy Immunol. 2017;52:164-181.
76. Taheri M, Eghtedarian R, Dinger ME, Ghafouri-Fard S. Exploring the Role of Non-Coding RNAs in the Pathophysiology of Systemic Lupus Erythematosus. Biomolecules. 2020;10:937.
77. Yang J, Yang X, Zou H, Li M. Oxidative Stress and Treg and Th17 Dysfunction in Systemic Lupus Erythematosus. Oxid Med Cell Longev. 2016;2016:2526174.
78. Yan Z, Chen Q, Xia Y. Oxidative Stress Contributes to Inflammatory and Cellular Damage in Systemic Lupus Erythematosus: Cellular Markers and Molecular Mechanism. J Inflamm Res. 2023;16:453-465.
79. Shah D, Sah S, Nath SK. Interaction between glutathione and apoptosis in systemic lupus erythematosus. Autoimmun Rev. 2013;12:741-751.
80. Faraji F, Rastin M, Arab FL, Kalantari MR, Rabe SZ, Tabasi N, et al. Effects of 1,25-dihydroxyvitamin D3 on IL-17/IL-23 axis, IFN-γ and IL-4 expression in systemic lupus erythematosus induced mice model. Iran J Basic Med Sci. 2016;19:374-380.
81. Sun L, Su Y, Jiao A, Wang X, Zhang B. T cells in health and disease. Signal Transduct Target Ther. 2023;8:235.
82. Yan L, Wu P, Gao DM, Hu J, Wang Q, Chen NF, et al. The Impact of vitamin D on Cognitive Dysfunction in Mice with Systemic Lupus Erythematosus. Med Sci Monit. 2019;25:4716-4722.
83. Kurien BT, Fesmire J, Nath SK, Scofield RH. Increased carotid intima-media thickening and antioxidized low-density lipoprotein in an anti-Ro60 SLE autoantibody subset. Front Lupus. 2023;1:1197309.
84. Wilhelm AJ, Rhoads JP, Wade NS, Major AS. Dysregulated CD4+ T cells from SLE-susceptible mice are sufficient to accelerate atherosclerosis in LDLr-/- mice. Ann Rheum Dis. 2015;74:778-785.
85. Melano-Carranza E, Zambrano-Zambrano A, Valle-Uitzil W, Ezquerra-Osorio A, Rodriguez-Méndez A, Larios-Lara JH, et al. Coronary Artery Disease in Systemic Lupus Erythematosus: What Do the Facts Say? Cureus. 2023;15:e33449.

86. Medeiros PBS, Salomão RG, Teixeira SR, Rassi DM, Rodrigues L, Aragon DC, et al. Disease activity index is associated with subclinical atherosclerosis in childhood-onset systemic lupus erythematosus. Pediatr Rheumatol Online J. 2021;19:35.
87. Mok CC, Birmingham DJ, Leung HW, Hebert LA, Song H, Rovin BH. vitamin D levels in Chinese patients with systemic lupus erythematosus: relationship with disease activity, vascular risk factors and atherosclerosis. Rheumatology (Oxford). 2012;51:644-652.
88. de la Guía-Galipienso F, Martínez-Ferran M, Vallecillo N, Lavie CJ, Sanchis-Gomar F, Pareja-Galeano H. vitamin D and cardiovascular health. Clin Nutr. 2021;40:2946-2957.
89. Jin J, Ye M, Zhao L, Zou W, Shen W, Zhang H, et al. The novel involvement of podocyte autophagic activity in the pathogenesis of lupus nephritis. Histol Histopathol. 2018;33:803-814.
90. Yu Q, Qiao Y, Liu D, Liu F, Gao C, Duan J, et al. vitamin D protects podocytes from autoantibodies induced injury in lupus nephritis by reducing aberrant autophagy. Arthritis Res Ther. 2019;21:19.
91. Borza DB. Glomerular basement membrane heparan sulfate in health and disease: A regulator of local complement activation. Matrix Biol. 2017;57-58:299-310.
92. Yang S, Li A, Wang J, Liu J, Han Y, Zhang W, et al. vitamin D Receptor: A Novel Therapeutic Target for Kidney Diseases. Curr Med Chem. 2018;25:3256-3271.
93. Mayfosh AJ, Nguyen TK, Hulett MD. The Heparanase Regulatory Network in Health and Disease. Int J Mol Sci. 2021;22:11096.
94. Garsen M, Sonneveld R, Rops AL, Huntink S, van Kuppevelt TH, Rabelink TJ, et al. vitamin D attenuates proteinuria by inhibition of heparanase expression in the podocyte. J Pathol. 2015;237:472-481.
95. Huang HY, Lin TW, Hong ZX, Lim LM. vitamin D and Diabetic Kidney Disease. Int J Mol Sci. 2023;24:3751.
96. Chandel N, Ayasolla K, Wen H, Lan X, Haque S, Saleem MA, et al. vitamin D receptor deficit induces activation of renin angiotensin system via SIRT1 modulation in podocytes. Exp Mol Pathol. 2017;102:97-105.
97. Sonneveld R, Ferrè S, Hoenderop JG, Dijkman HB, Berden JH, Bindels RJ, et al. vitamin D down-regulates TRPC6 expression in podocyte injury and proteinuric glomerular disease. Am J Pathol. 2013;182:1196-1204.
98. Al-Ishaq RK, Kubatka P, Brozmanova M, Gazdikova K, Caprnda M, Büsselberg D. Health implication of vitamin D on the cardiovascular and the renal system. Arch Physiol Biochem. 2021;127:195-209.
99. Li X, Liu J, Zhao Y, Xu N, Lv E, Ci C, et al. 1,25-dihydroxyvitamin D3 ameliorates lupus nephritis through inhibiting the NF-κB and MAPK signalling pathways in MRL/lpr mice. BMC Nephrol. 2022;23:243.
100. Kraemer AN, Schäfer AL, Sprenger DTL, Sehnert B, Williams JP, Luo A, et al. Impact of dietary vitamin D on immunoregulation and disease pathology in lupus-prone NZB/W F1 mice. Front Immunol. 2022;13:933191.