Chapter

Vitamin D and Autoimmune Diseases

Ifigenia Kostoglou-Athanassiou, Lambros Athanassiou and Panagiotis Athanassiou

Abstract

Vitamin D has many and profound effects on the immune system. Vitamin D deficiency is known to be related to the development of autoimmune diseases. In particular, vitamin D deficiency is related to the development and the severity of rheumatoid arthritis (RA). RA develops in patients with vitamin D deficiency, and the activity of the disease is related to vitamin D deficiency. Vitamin D deficiency is also related to the development of systemic lupus erythematosus (SLE). SLE develops in patients with vitamin D deficiency, and the activity of the disease is also greater in patients with vitamin D deficiency. Vitamin D deficiency is also related to the development and the severity of multiple sclerosis. Vitamin D should be administered to patients with multiple sclerosis, and this seems to mitigate the symptoms of the disease and to prevent disease progression. Vitamin D deficiency is also observed in patients with inflammatory bowel disease and may be related to disease severity. Low vitamin D levels have also been observed in patients with autoimmune Hashimoto's thyroiditis. Low vitamin D levels have been observed in patients with systemic sclerosis, especially in the diffuse form of the disease. Optimal vitamin D levels appear to be required for normal immune function and for the prevention and treatment of autoimmune diseases.

Keywords: vitamin D, autoimmunity, rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, inflammatory bowel disease, autoimmune Hashimoto's thyroiditis

1. Introduction

Vitamin D is a secosteroid hormone, which is known to be related to the regulation of the musculoskeletal system. It affects calcium and phosphate metabolism and is related to bone health. Recently, the extraskeletal effects of vitamin D are under intense research and have attracted the interest of the scientific community [1–6]. In particular, the relationship of vitamin D with the immune system is in the focus of scientific evaluation [7–9]. In the chapter herein, the effects of vitamin D on the immune system will be discussed, and the relationship of vitamin D deficiency with the development of autoimmune diseases will be reviewed.

2. Vitamin D and the immune system

The classic function of vitamin D is to enhance intestinal absorption of calcium by regulating several calcium transport proteins in the small intestine [4]. However, various cells express the vitamin D receptor (VDR) and the vitamin D activating enzyme 1-α-hydroxylase. Various cells of the immune system also express the VDR and harbor 1-α-hydroxylase [10, 11]. Thus, cells of the immune system respond to vitamin D and also activate vitamin D in a paracrine or autocrine fashion. The extra-renal 1-α-hydroxylase is not upregulated by PTH, and thus, production of $1,25(OH)_2D_3$ is dependent on concentrations of the substrate $25(OH)D_3$, and it may be regulated by inflammatory signals, such as lipopolysaccharide and cytokines [12, 13]. Cells of the immune system, which express the VDR and harbor 1-α-hydroxylase, are macrophages, T cells, dendritic cells, monocytes, and B cells (**Figure 1**) [9]. Vitamin D is involved in the regulation of the innate immunity as it enhances the defense system of the organism against microbes and other pathogenic organisms, and it modulates the adaptive immune system through direct effects on T-cell activation and on the phenotype and function of antigen-presenting cells, particularly dendritic cells.

2.1 Vitamin D and the innate immune system

The innate immune system is a first line of defense against infection. Vitamin D is a regulator of the innate immune system [1, 14]. The first data on the effect of vitamin D on the innate immune system have been generated on the treatment of diseases caused by mycobacteria, such as tuberculosis and leprosy [15–18]. Vitamin D has been used as a treatment of infections for more than 150 years. In 1849, Williams reported favorable results with the use of cod-liver-oil, an excellent source of vitamin D, in the treatment of patients with tuberculosis [19]. Fifty years later, Niels Finsen received the third Nobel Prize in Medicine for his description of using UV light, an effective method to increase vitamin D status, to treat lupus vulgaris, a cutaneous form of tuberculosis [20, 21]. Alfred Windaus contributed to the discovery of the chemical structure of vitamin D_2 and vitamin D_3 found in cod-liver-oil and received the Nobel prize [22–24]. Thereafter, several groups used vitamin D_2 and D_3 as a treatment for tuberculosis [22, 25]. Rook et al. [26] demonstrated in the 1980s that $1,25(OH)_2D_3$ inhibited the proliferation of *Mycobacterium tuberculosis* in culture. Vitamin D enhances the production of defensin β2 and cathelicidin in response to infection by macrophages, monocytes, and keratinocytes [12]. Humans have only

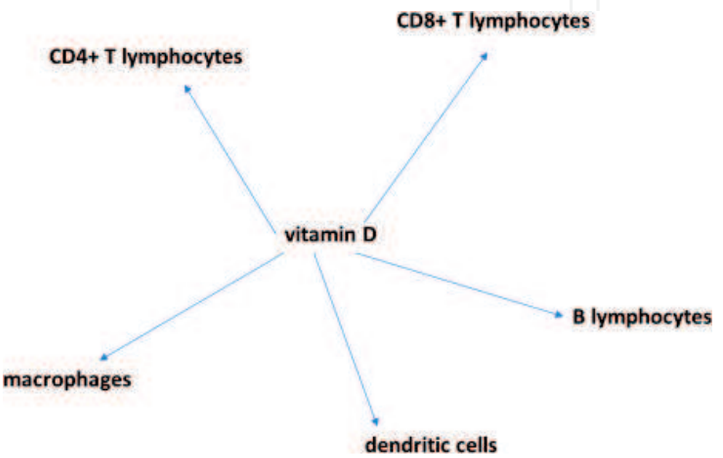

Figure 1.
Cells of the immune system regulated in part by vitamin D.

one cathelicidin, which is cleaved to form LL-37 [27]. Cells of the immune system including neutrophils and macrophages and cells lining epithelial surfaces that are constantly exposed to potential pathogens such as the skin, the respiratory, and the gastrointestinal tract produce cathelicidin [28–30]. Cathelicidin has broad antimicrobial activity against Gram-positive and Gram-negative bacteria, as well as certain viruses and fungi [31]. The killing mechanism of cathelicidin involves bacterial lysis by destabilizing cell membrane [32]. Treatment with $1,25(OH)_2D_3$ upregulates cathelicidin mRNA in several cell lines. Thus, it appears that $1,25(OH)_2D_3$ upregulates antimicrobial peptide production, primarily cathelicidin, on a variety of different cells [33]. Studies indicate that $25(OH)D_3$, the major circulating form of vitamin D to determine vitamin D status, is important for local production of $1,25(OH)_2D_3$ to upregulate cathelicidin production in the skin and macrophages. Exposing human monocytes to pathogens increases the expression of both $1,25(OH)_2D_3$ and VDR, thus increasing both the local production of $1,25(OH)_2D_3$ and the ability of the cell to respond to it [12]. Since keratinocytes also possess 25-α-hydroxylase, UV light may directly stimulate cathelicidin production by providing the substrate $25(OH)D_3$ directly from vitamin D_3 produced within the skin [34, 35]. Macrophages also respond to vitamin D increasing their antimicrobial activity, however, heterogeneously [36, 37]. Macrophages formed after interleukin-15 stimulus respond to vitamin D increasing their antimicrobial activity, whereas macrophages formed after stimulation by interleukin-10 respond to vitamin D stimulus weakly.

Data regarding other infections also exist. Thus, children with low vitamin D status may be more prone to urinary tract infections due to low production of cathelicidin and defensin β2 [38, 39]. Also, adults with asthma may be less prone to infection after treatment with vitamin D due to increased production of cathelidicin and modulation of inflammatory cytokines [40, 41]. Low levels of vitamin D may be related to chronic obstructive pulmonary disease severity [42]. Vitamin D may increase resistance to HIV infection. Low levels of vitamin D have been associated with disease progression and mortality [43]. The ability of the immune cells to hydroxylate $25(OH)D_3$ locally suggests that in patients with infections, it may be better to administer $25(OH)D_3$ rather than hydroxylated metabolites to allow for local production and the feedback system to function.

2.2 Vitamin D and autoimmunity

The natural history of autoimmunity remains largely unknown. However, the theory is that both genetic susceptibility and environmental factors play a role in the development of clinical autoimmune disease. Vitamin D has known immunomodulatory effects on a wide range of immune cells, including T and dendritic cells [44, 45]. Each of these immune cells expresses VDR and produces the enzymes 1-α-hydroxylase and 24-hydroxylase and is therefore capable of locally producing active $1,25(OH)_2D_3$ [46–49]. Activation of CD4+ T cells results in a significant increase in VDR expression enabling regulation of many genes responsive to $1,25(OH)_2D_3$ [50]. $1,25(OH)_2D_3$ suppresses T-cell receptor induced T cell proliferation and changes their cytokine expression. The overall shift is away from T helper Th1 phenotype toward a more tolerogenic Th2 response [51–53]. Vitamin D appears to directly inhibit Th1 cells and may additionally modulate a skewing toward a Th2 response [54]. Th17 cells are a subset of CD4+ T cells involved in organ-specific autoimmunity playing a role in maintaining inflammation, which can lead to tissue damage. $1,25(OH)_2D_3$ suppresses autoimmunity and tissue destruction by inhibiting the Th17 response at several levels [55, 56]. Altogether, the evidence suggests an important role for vitamin D in influencing T-cell responses and in tempering inflammation and tissue damage.

Vitamin D appears to have a direct effect on B cells and inhibits immunoglobulin production [57]. Additionally, differentiation of B cells is interrupted when exposed to $1,25(OH)_2D_3$. $1,25(OH)_2D_3$ also has effects on dendritic cells. Dendritic cells have important functions in maintaining both protective immunity and self-tolerance [58, 59]. Physiologic levels of $1,25(OH)_2D_3$ inhibit maturation of dendritic cells and maintain an immature and tolerogenic phenotype with inhibition of activation markers such as MHC class II, CD40, and others and upregulation of inhibitory molecules [60, 61]. Thus, it appears that the maturational state of dendritic cells can be modulated by $1,25(OH)_2D_3$, making it possible that the vitamin D status of an individual is likely to have important immunologic consequences.

3. Vitamin D and autoimmune diseases

There are several animal models of autoimmunity, in which disease could either be prevented or ameliorated with the administration of either $1,25(OH)_2D_3$ or one of its analogues. These animal models are models of autoimmune encephalomyelitis, collagen-induced arthritis, type 1 diabetes mellitus, inflammatory bowel disease, autoimmune uveitis, and lupus [44, 56, 62–76]. These studies show that treatment with active vitamin D is effective in modulating immune function and ameliorating autoimmune disease. Vitamin D deficiency is a risk factor for the development of some autoimmune diseases, such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), diabetes mellitus type 1, multiples sclerosis, inflammatory bowel disease, and Hashimoto's thyroiditis [49, 69, 74, 77–85] (**Figure 2**). Additionally, vitamin D deficiency has been observed in patients with systemic sclerosis [86].

3.1 Vitamin D deficiency and rheumatoid arthritis

A meta-analysis showed that low vitamin D intake is associated with the development of RA [87]. Thereafter, several studies performed in various areas all over the world showed that vitamin D deficiency is observed in patients with RA and that vitamin D deficiency is associated with disease activity [78, 82, 83, 88–97]. A meta-analysis of the good quality studies performed regarding the association between vitamin D deficiency and RA showed that vitamin D deficiency is observed in RA patients significantly more than in a control group and that vitamin D levels are inversely correlated with disease activity, meaning that low vitamin D levels are associated with high-disease activity [98]. Moreover, an

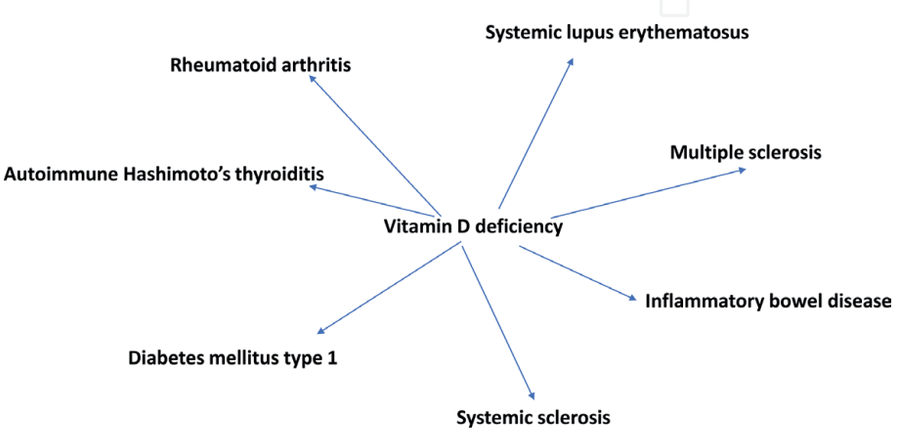

Figure 2.
Autoimmune diseases related to vitamin D deficiency.

association has been shown between VDR polymorphism and RA. Specifically, the FokI F allele of the VDR may be a risk factor for the development of RA [99]. Further studies are needed to unravel the exact association between vitamin D deficiency and RA and to determine the best method of vitamin D supplementation and whether it may be used for the prevention of RA or for the best management of the disease [77, 100]. In addition, it has been proposed that vitamin D may contribute to the management of pain in RA and may be used along with TNF-α inhibitors in RA treatment [77, 101].

3.2 Vitamin D deficiency and systemic lupus erythematosus

In SLE, the inflammatory milieu drives the development of T cells into proinflammatory pathways, defective function of Tregs, and survival and activation of B cells, which produce autoantibodies [78, 81]. Patients with systemic lupus erythematosus have lower $25(OH)D_3$ levels compared to controls, suggesting that vitamin D deficiency may be a risk factor for SLE [81, 84, 102–107]. The majority of studies have also found higher SLE disease activity associated with lower levels of $25(OH)D_3$ [84, 103]. As patients with SLE have often photosensitivity and are advised to avoid direct sun exposure, detecting vitamin D deficiency and replacing $25(OH)D_3$ with oral supplementation is critical and may impact disease activity [108].

3.3 Vitamin D deficiency and type 1 diabetes mellitus

Type 1 diabetes mellitus is one of the most prevalent chronic diseases with onset in childhood and is the result of immune-mediated destruction of pancreatic insulin producing β cells. There appears to be a geographic variation in incidence following a gradient in latitude, which is the inverse of the global distribution of ultraviolet B irradiation, critical for the production of vitamin D within the skin [109]. Studies have shown higher incidence of vitamin D deficiency in patients with type 1 diabetes [110–113]. One environmental factor thought to be protective against the development of type 1 diabetes mellitus is early supplementation with vitamin D [114]. A number of large case control studies showed that the risk of type 1 diabetes mellitus was significantly reduced in infants who were supplemented with vitamin D compared to those who were not supplemented [115–117]. Additionally, a lower incidence of type 1 diabetes was observed in infants born to mothers who were administered cod liver oil during pregnancy [118]. A birth cohort study in Finland, now more than 50 years ago, evaluated the effects of vitamin D supplementation on rickets and the development of type 1 diabetes mellitus [85]. All women due to give birth in 1966 were enrolled. There was an 80% reduction in the risk for type 1 diabetes mellitus in children having received >2000 IU vitamin D/day compared to those receiving less or not receiving supplementation with vitamin D. Evidence from both human and animal studies shows that vitamin D may be protective as far as the development of type 1 diabetes mellitus is concerned [68, 71, 76]. Thus, the administration of vitamin D may prevent diabetes mellitus type 1; however, once the destruction of pancreatic beta cells has taken place, it will not act therapeutically to reverse diabetes mellitus type 1.

3.4 Vitamin D deficiency and multiple sclerosis

Multiple sclerosis is characterized by inflammation, demyelination, axonal or neuronal loss, and astrocytic gliosis in the central nervous system, which can result in disability. Epidemiological studies have suggested that vitamin D insufficiency

may contribute to the risk of multiple sclerosis [62, 63, 75, 119, 120]. Moreover, several genetic studies in multiple sclerosis patients have shown that diverse abnormalities in vitamin D metabolism are related to the risk of the disease. It appears that vitamin D deficiency may interact with genetic and environmental protective and risk factors, such as the allele HLA BRB1*1501, infections, obesity, smoking, and sexual hormones and may modulate the risk of the disease [63, 74, 80]. Thus, vitamin D deficiency may be a risk modulating factor for the development of multiple sclerosis. Vitamin D acts as an immunomodulatory factor affecting T and B lymphocytes, and it may exert neuroprotector and neurotrophic actions within the central nervous system. Several studies have shown that vitamin D supplementation exerts multiple beneficial immunomodulatory effects in multiple sclerosis [121–124]. On the contrary, a Cochrane review states that there appears to be no benefit from vitamin D supplementation in patients with multiple sclerosis; however, the level of evidence is very low [125]. Nevertheless, it should be noted that robust statistical models used in association studies have already predicted a favorable vitamin D effect reducing relapses by 50–70% [121]. There is little doubt that vitamin D exerts a beneficial action on multiple sclerosis, the inflammatory component in particular, less so the degenerative. Until more information becomes available, vitamin D supplementation of multiple sclerosis patients, using a moderate physiological dose essentially correcting their vitamin insufficiency, is recommended.

3.5 Vitamin D and inflammatory bowel disease

Vitamin D deficiency has been observed in patients with inflammatory bowel disease, Crohn's disease, and ulcerative colitis [126]. It was found to be related to disease activity in Crohn's disease and ulcerative colitis. Vitamin D supports the integrity of the intestinal barrier and is related to microbiota homeostasis in this cohort of patients [127, 128]. Thus, vitamin D may contribute to the prevention of inflammatory bowel disease by supporting the integrity of the intestinal barrier, contributing to bacterial homeostasis and ameliorating disease progression via anti-inflammatory action. Vitamin D deficiency in inflammatory bowel disease is aggravated by decreased absorption of the vitamin via the gastrointestinal tract [128].

3.6 Vitamin D deficiency and autoimmune Hashimoto's thyroiditis

Studies have observed an association between autoimmune Hashimoto's thyroiditis and low vitamin D levels [79, 129]. These studies have not observed low vitamin D levels in patients with Graves' disease. A meta-analysis of 26 observational studies confirmed an association between vitamin D deficiency and autoimmune Hashimoto's thyroiditis [130]. The aforementioned meta-analysis found that although there was heterogeneity between the results of the various studies performed all over the globe, studies had similar results in populations from different countries and also in populations in different age ranges, in particular pediatric and adult populations.

3.7 Vitamin D deficiency and systemic sclerosis

Systemic sclerosis is a chronic, inflammatory, fibrotic disorder thought to be related to autoimmune etiology. Vitamin D deficiency has been observed in patients with systemic sclerosis [86, 131], especially in patients with the diffuse type of the disease [131].

4. Optimal levels of 25(OH)D_3

The molecule used to assess vitamin D sufficiency in a population is 25(OH)D_3 [9]. It appears that vitamin D has physiologic effects beyond those related to bone physiology and mineral homeostasis. It may be that the alarming prevalence of vitamin D deficiency observed all over the globe may be contributing to the development of autoimmune diseases. Based on bone-related biomarkers such as intact parathyroid hormone, calcium absorption, and bone mineral density, maintaining a 25(OH)D_3 level of at least 32 ng/ml appears sufficient.

5. Conclusions

It appears that vitamin D is a potent immunomodulator. It has multiple and diverse effects on the immune system. In particular, it potentiates the innate immune response enhancing the production of cathelicidin from human macrophages, monocytes, and keratinocytes, thus enhancing and potentiating the immune response against external pathogens. It affects the adaptive immune response shifting the phenotype of the adaptive immune response toward a more tolerogenic phenotype. Vitamin D deficiency is related to various autoimmune disorders. Vitamin D deficiency appears to be related to the development of RA and correlates with disease severity. Vitamin D deficiency is observed in patients with SLE. It was found to be related to disease severity and activity in some but not all studies. Vitamin D deficiency is observed in patients with multiple sclerosis, and vitamin D administration may ameliorate disease severity. Vitamin D deficiency is also observed in patients with inflammatory bowel disease, Crohn's disease, and ulcerative colitis, and it is related to disease activity. Vitamin D contributes to the integrity of the intestinal barrier and bacterial homeostasis. In addition, vitamin D absorption is decreased making supplementation important. Vitamin D deficiency is also observed in patients with autoimmune Hashimoto's thyroiditis. Vitamin D deficiency is found in patients with systemic sclerosis, especially the diffuse form of the disease. It appears that optimal levels of vitamin D are important for immune function and for the prevention of autoimmunity in the human organism.

Conflict of interest

The authors declare no conflict of interest.

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References

[1] Christakos S, Li S, Cruz J, Bikle DD. New developments in our understanding of vitamin metabolism, action and treatment. Metabolism. 2019;**98**:112-120. DOI: 10.1016/j.metabol.2019.06.010

[2] Bouillon R, Marcocci C, Carmeliet G, Bikle D, White JH, Dawson-Hughes B, et al. Skeletal and extraskeletal actions of vitamin D: Current evidence and outstanding questions. Endocrine Reviews. 2019;**40**(4):1109-1151. DOI: 10.1210/er.2018-00126

[3] Bikle DD. Extraskeletal actions of vitamin D. Annals of the New York Academy of Sciences. 2016;**1376**(1):29-52. DOI: 10.1111/nyas.13219

[4] Wacker M, Holick MF. Vitamin D-effects on skeletal and extraskeletal health and the need for supplementation. Nutrients. 2013;**5**(1):111-148. DOI: 10.3390/nu5010111

[5] Kostoglou-Athanassiou I, Pantazi E, Kontogiannis S, Kousouris D, Mavropoulos I, Athanassiou P. Vitamin D in acutely ill patients. The Journal of International Medical Research. 2018;**46**(10):4246-4257. DOI: 10.1177/0300060518792783

[6] Kostoglou-Athanassiou I, Athanassiou P, Gkountouvas A, Kaldrymides P. Vitamin D and glycemic control in diabetes mellitus type 2. Therapeutic Advances in Endocrinology and Metabolism. 2013;**4**(4):122-128. DOI: 10.1177/2042018813501189

[7] Illescas-Montes R, Melguizo-Rodríguez L, Ruiz C, Costela-RuizVJ.VitaminDandautoimmune diseases. Life Sciences. 2019;**233**:116744. DOI: 10.1016/j.lfs.2019.116744

[8] Murdaca G, Tonacci A, Negrini S, Greco M, Borro M, Puppo F, et al. Emerging role of vitamin D in autoimmune diseases: An update on evidence and therapeutic implications. Autoimmunity Reviews. 2019;**18**(9):102350. DOI: 10.1016/j.autrev.2019.102350

[9] Sassi F, Tamone C, D'Amelio P. Vitamin D: Nutrient, hormone, and immunomodulator. Nutrients. 2018;**10**(11)pii:E1656. DOI: 10.3390/nu10111656

[10] Morán-Auth Y, Penna-Martinez M, Shoghi F, Ramos-Lopez E, Badenhoop K. Vitamin D status and gene transcription in immune cells. The Journal of Steroid Biochemistry and Molecular Biology. 2013;**136**:83-85. DOI: 10.1016/j.jsbmb.2013.02.005

[11] Szymczak I, Pawliczak R. The active metabolite of vitamin D3 as a potential immunomodulator. Scandinavian Journal of Immunology. 2016;**83**(2):83-91. DOI: 10.1111/sji.12403

[12] Liu PT, Stenger S, Li H, Wenzel L, Tan BH, Krutzik SR, et al. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. Science. 2006;**311**(5768):1770-1773. DOI: 10.1126/science.1123933

[13] Stoffels K, Overbergh L, Giulietti A, Verlinden L, Bouillon R, Mathieu C. Immune regulation of 25-hydroxyvitamin-D3-1alpha-hydroxylase in human monocytes. Journal of Bone and Mineral Research. 2006;**21**(1):37-47. DOI: 10.1359/JBMR.050908

[14] Wei R, Christakos S. Mechanisms underlying the regulation of innate and adaptive immunity by vitamin D. Nutrients. 2015;7(10):8251-8260. DOI: 10.3390/nu7105392

[15] Oliveira ALG, Chaves AT, Menezes CAS, Guimaraes NS, Bueno LL,

Fujiwara RT, et al. Vitamin D receptor expression and hepcidin levels in the protection or severity of leprosy: A systematic review. Microbes and Infection. 2017;**19**(6):311-322. DOI: 10.1016/j.micinf.2017.03.001

[16] Cervantes JL, Oak E, Garcia J, Liu H, Lorenzini PA, Batra D, et al. Vitamin D modulates human macrophage response to *Mycobacterium tuberculosis* DNA. Tuberculosis (Edinburgh, Scotland). 2019;**116s**:S131-S1s7. DOI: 10.1016/j.tube.2019.04.021

[17] Singh I, Lavania M, Pathak VK, Ahuja M, Turankar RP, Singh V, et al. VDR polymorphism, gene expression and vitamin D levels in leprosy patients from North Indian population. PLoS Neglected Tropical Diseases. 2018;**12**(11):e0006823. DOI: 10.1371/journal.pntd.0006823

[18] Soeharto DA, Rifai DA, Marsudidjadja S, Roekman AE, Assegaf CK, Louisa M. Vitamin D as an adjunctive treatment to standard drugs in pulmonary tuberculosis patients: An evidence-based case report. Advances in Preventive Medicine. 2019;**2019**:5181847. DOI: 10.1155/2019/5181847

[19] Williams C. On the use and administration of cod-liver oil in pulmonary consumption. London Journal of Medicine. 1849;**1**:1-18

[20] Finsen N. Nobel prize presentation speech by professor the count K.A.H. Morner, Rector of the Royal Caroline Institute on December 10, 1903. 1903. Contract No: http://www.nobelprize.org

[21] Moller KI, Kongshoj B, Philipsen PA, Thomsen VO, Wulf HC. How Finsen's light cured lupus vulgaris. Photodermatology, Photoimmunology & Photomedicine. 2005;**21**(3):118-124. DOI: 10.1111/j.1600-0781.2005.00159.x

[22] Haas J. Vigantol–Adolf Windaus and the history of vitamin D. Würzburger Medizinhistorische Mitteilungen. 2007;**26**:144-181

[23] Wolf G. The discovery of vitamin D: The contribution of Adolf Windaus. The Journal of Nutrition. 2004;**134**(6):1299-1302. DOI: 10.1093/jn/134.6.1299

[24] Shampo MA, Kyle RA. Adolf Windaus–Nobel prize for research on sterols. Mayo Clinic Proceedings. 2001;**76**(2):119. DOI: 10.1016/s0025-6196(11)63115-7

[25] Brighenti S, Bergman P, Martineau AR. Vitamin D and tuberculosis: Where next? Journal of Internal Medicine. 2018. DOI: 10.1111/joim.12777. [Epub ahead of print]

[26] Rook GA, Steele J, Fraher L, Barker S, Karmali R, O'Riordan J, et al. Vitamin D3, gamma interferon, and control of proliferation of *Mycobacterium tuberculosis* by human monocytes. Immunology. 1986;**57**(1):159-163

[27] Xhindoli D, Pacor S, Benincasa M, Scocchi M, Gennaro R, Tossi A. The human cathelicidin LL-37—A pore-forming antibacterial peptide and host-cell modulator. Biochimica et Biophysica Acta. 2016;**1858**(3):546-566. DOI: 10.1016/j.bbamem.2015.11.003

[28] Weber G, Heilborn JD, Chamorro Jimenez CI, Hammarsjo A, Torma H, Stahle M. Vitamin D induces the antimicrobial protein hCAP18 in human skin. Journal of Investigative Dermatology. 2005;**124**:1080-1082

[29] Bals R, Wang X, Zasloff M, Wilson JM. The peptide antibiotic LL-37/hCAP-18 is expressed in epithelia of the human lung where it has broad antimicrobial activity at the airway surface. Proceedings of the National Academy of Sciences of the United States of America. 1998;**95**(16):9541-9546. DOI: 10.1073/pnas.95.16.9541

[30] Gallo RL, Kim KJ, Bernfield M, Kozak CA, Zanetti M, Merluzzi L, et al. Identification of CRAMP, a cathelin-related antimicrobial peptide expressed in the embryonic and adult mouse. The Journal of Biological Chemistry. 1997;**272**(20):13088-13093. DOI: 10.1074/jbc.272.20.13088

[31] Ramanathan B, Davis EG, Ross CR, Blecha F. Cathelicidins: Microbicidal activity, mechanisms of action, and roles in innate immunity. Microbes and Infection. 2002;**4**(3):361-372

[32] Agerberth B, Charo J, Werr J, Olsson B, Idali F, Lindbom L, et al. The human antimicrobial and chemotactic peptides LL-37 and alpha-defensins are expressed by specific lymphocyte and monocyte populations. Blood. 2000;**96**(9):3086-3093

[33] Wang TT, Nestel FP, Bourdeau V, Nagai Y, Wang Q, Liao J, et al. Cutting edge: 1,25-dihydroxyvitamin D3 is a direct inducer of antimicrobial peptide gene expression. Journal of Immunology. 2004;**173**(5):2909-2912. DOI: 10.4049/jimmunol.173.5.2909

[34] Lehmann B, Rudolph T, Pietzsch J, Meurer M. Conversion of vitamin D3 to 1alpha,25-dihydroxyvitamin D3 in human skin equivalents. Experimental Dermatology. 2000;**9**(2):97-103

[35] Lehmann B, Tiebel O, Meurer M. Expression of vitamin D3 25-hydroxylase (CYP27) mRNA after induction by vitamin D3 or UVB radiation in keratinocytes of human skin equivalents—A preliminary study. Archives of Dermatological Research. 1999;**291**(9):507-510. DOI: 10.1007/s004030050445

[36] 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. Journal of Immunology. 2008;**181**(10):7115-7120. DOI: 10.4049/jimmunol.181.10.7115

[37] Kim EW, Teles RMB, Haile S, Liu PT, Modlin RL. Vitamin D status contributes to the antimicrobial activity of macrophages against *Mycobacterium leprae*. PLoS Neglected Tropical Diseases. 2018;**12**(7):e0006608. DOI: 10.1371/journal.pntd.0006608

[38] Deng QF, Chu H, Wen Z, Cao YS. Vitamin D and urinary tract infection: A systematic review and meta-analysis. Annals of Clinical and Laboratory Science. 2019;**49**(1):134-142

[39] Georgieva V, Kamolvit W, Herthelius M, Luthje P, Brauner A, Chromek M. Association between vitamin D, antimicrobial peptides and urinary tract infection in infants and young children. Acta Paediatrica. 2019;**108**(3):551-556. DOI: 10.1111/apa.14499

[40] Maes K, Serre J, Mathyssen C, Janssens W, Gayan-Ramirez G. Targeting vitamin D deficiency to limit exacerbations in respiratory diseases: Utopia or strategy with potential? Calcified Tissue International. 2019. DOI: 10.1007/s00223-019-00591-4. [Epub ahead of print]

[41] Talebi F, Rasooli Nejad M, Yaseri M, Hadadi A. Association of vitamin D status with the severity and mortality of community-acquired pneumonia in Iran during 2016-2017: A prospective cohort study. Reports of Biochemistry and Molecular Biology. 2019;**8**(1):85-90

[42] Zhu M, Wang T, Wang C, Ji Y. The association between vitamin D and COPD risk, severity, and exacerbation: An updated systematic review and meta-analysis. International Journal of Chronic Obstructive Pulmonary Disease. 2016;**11**:2597-2607. DOI: 10.2147/COPD.S101382

[43] Chokuda E, Reynolds C, Das S. Association of low vitamin D status with complications of HIV and AIDS: A literature review. Infectious Disorders Drug Targets. 2018. DOI: 10.2174/1871526519666181221122731. [Epub ahead of print]

[44] Deluca HF, Cantorna MT. Vitamin D: Its role and uses in immunology. The FASEB Journal. 2001;**15**(14):2579-2585. DOI: 10.1096/fj.01-0433rev

[45] Arnson Y, Amital H, Shoenfeld Y. Vitamin D and autoimmunity: New aetiological and therapeutic considerations. Annals of the Rheumatic Diseases. 2007;**66**(9):1137-1142. DOI: 10.1136/ard.2007.069831

[46] Norman AW. Minireview: Vitamin D receptor: New assignments for an already busy receptor. Endocrinology. 2006;**147**(12):5542-5548. DOI: 10.1210/en.2006-0946

[47] Veldman CM, Cantorna MT, DeLuca HF. Expression of 1,25-dihydroxyvitamin D(3) receptor in the immune system. Archives of Biochemistry and Biophysics. 2000;**374**(2):334-338. DOI: 10.1006/abbi.1999.1605

[48] van Etten E, Stoffels K, Gysemans C, Mathieu C, Overbergh L. Regulation of vitamin D homeostasis: Implications for the immune system. Nutrition Reviews. 2008;**66**(10 Suppl 2):S125-S134. DOI: 10.1111/j.1753-4887.2008.00096.x

[49] Correale J, Ysrraelit MC, Gaitan MI. Immunomodulatory effects of Vitamin D in multiple sclerosis. Brain. 2009;**132**(Pt 5):1146-1160. DOI: 10.1093/brain/awp033

[50] Mahon BD, Wittke A, Weaver V, Cantorna MT. The targets of vitamin D depend on the differentiation and activation status of CD4 positive T cells. Journal of Cellular Biochemistry. 2003;**89**(5):922-932. DOI: 10.1002/jcb.10580

[51] Bhalla AK, Amento EP, Serog B, Glimcher LH. 1,25-dihydroxyvitamin D3 inhibits antigen-induced T cell activation. Journal of Immunology. 1984;**133**(4):1748-1754

[52] Mattner F, Smiroldo S, Galbiati F, Muller M, Di Lucia P, Poliani PL, et al. Inhibition of Th1 development and treatment of chronic-relapsing experimental allergic encephalomyelitis by a non-hypercalcemic analogue of 1,25-dihydroxyvitamin D(3). European Journal of Immunology. 2000;**30**(2):498-508. DOI: 10.1002/1521-4141(200002)30:2<498::AID-IMMU498>3.0.CO;2-Q

[53] Lemire JM, Archer DC, Beck L, Spiegelberg HL. Immunosuppressive actions of 1,25-dihydroxyvitamin D3: Preferential inhibition of Th1 functions. The Journal of Nutrition. 1995;**125**(6 Suppl):1704s-1708s. DOI: 10.1093/jn/125.suppl_6.1704S

[54] Boonstra A, Barrat FJ, Crain C, Heath VL, Savelkoul HF, O'Garra A. 1alpha,25-dihydroxyvitamin d3 has a direct effect on naive CD4(+) T cells to enhance the development of Th2 cells. Journal of Immunology. 2001;**167**(9):4974-4980. DOI: 10.4049/jimmunol.167.9.4974

[55] Eisenstein EM, Williams CB. The T(reg)/Th17 cell balance: A new paradigm for autoimmunity. Pediatric Research. 2009;**65**(5 Pt 2):26r-31r. DOI: 10.1203/PDR.0b013e31819e76c7

[56] Tang J, Zhou R, Luger D, Zhu W, Silver PB, Grajewski RS, et al. Calcitriol suppresses antiretinal autoimmunity through inhibitory effects on the Th17 effector response. Journal of Immunology. 2009;**182**(8):4624-4632. DOI: 10.4049/jimmunol.0801543

[57] Lemire JM, Adams JS, Sakai R, Jordan SC. 1 alpha,25-dihydroxyvitamin D3 suppresses proliferation and immunoglobulin production by normal human peripheral blood mononuclear cells. The Journal of Clinical Investigation. 1984;**74**(2):657-661. DOI: 10.1172/JCI111465

[58] Sallusto F, Lanzavecchia A. The instructive role of dendritic cells on T-cell responses. Arthritis Research. 2002;**4**(Suppl 3):S127-S132. DOI: 10.1186/ar567

[59] Lanzavecchia A, Sallusto F. Regulation of T cell immunity by dendritic cells. Cell. 2001;**106**(3):263-266. DOI: 10.1016/s0092-8674(01)00455-x

[60] Griffin MD, Xing N, Kumar R. Gene expression profiles in dendritic cells conditioned by 1alpha,25-dihydroxyvitamin D3 analog. The Journal of Steroid Biochemistry and Molecular Biology. 2004;**89-90**(1-5):443-448. DOI: 10.1016/j.jsbmb.2004.03.039

[61] Griffin MD, Kumar R. Effects of 1alpha,25(OH)2D3 and its analogs on dendritic cell function. Journal of Cellular Biochemistry. 2003;**88**(2):323-326. DOI: 10.1002/jcb.10335

[62] van Amerongen BM, Feron F. Effect of high-dose vitamin D3 intake on ambulation, muscular pain and bone mineral density in a woman with multiple sclerosis: A 10-year longitudinal case report. International Journal of Molecular Sciences. 2012;**13**(10):13461-13483. DOI: 10.3390/ijms131013461

[63] Kragt J, van Amerongen B, Killestein J, Dijkstra C, Uitdehaag B, Polman C, et al. Higher levels of 25-hydroxyvitamin D are associated with a lower incidence of multiple sclerosis only in women. Multiple Sclerosis. 2009;**15**(1):9-15. DOI: 10.1177/1352458508095920

[64] Van Etten E, Branisteanu DD, Overbergh L, Bouillon R, Verstuyf A, Mathieu C. Combination of a 1,25-dihydroxyvitamin D3 analog and a bisphosphonate prevents experimental autoimmune encephalomyelitis and preserves bone. Bone. 2003;**32**(4):397-404. DOI: 10.1016/s8756-3282(03)00030-9

[65] Van Etten E,Decallonne B, Verlinden L, Verstuyf A, Bouillon R, Mathieu C. Analogs of 1alpha,25-dihydroxyvitamin D3 as pluripotent immunomodulators. Journal of Cellular Biochemistry. 2003;**88**(2):223-226. DOI: 10.1002/jcb.10329

[66] Cantorna MT, Hayes CE, DeLuca HF. 1,25-dihydroxycholecalciferol inhibits the progression of arthritis in murine models of human arthritis. The Journal of Nutrition. 1998;**128**(1):68-72. DOI: 10.1093/jn/128.1.68

[67] Larsson P, Mattsson L, Klareskog L, Johnsson C. A vitamin D analogue (MC 1288) has immunomodulatory properties and suppresses collagen-induced arthritis (CIA) without causing hypercalcaemia. Clinical and Experimental Immunology. 1998;**114**(2):277-283. DOI: 10.1046/j.1365-2249.1998.00706.x

[68] Zella JB, McCary LC, DeLuca HF. Oral administration of 1,25-dihydroxyvitamin D3 completely protects NOD mice from insulin-dependent diabetes mellitus. Archives of Biochemistry and Biophysics. 2003;**417**(1):77-80

[69] Altieri B, Muscogiuri G, Barrea L, Mathieu C, Vallone CV, Mascitelli L, et al. Does vitamin D play a role in autoimmune endocrine disorders? A proof of concept. Reviews in Endocrine and Metabolic Disorders. 2017;**18**(3):335-346

[70] Lemire JM, Ince A, Takashima M. 1,25-dihydroxyvitamin D3 attenuates

the expression of experimental murine lupus of MRL/l mice. Autoimmunity. 1992;**12**(2):143-148

[71] Giulietti A, Gysemans C, Stoffels K, van Etten E, Decallonne B, Overbergh L, et al. Vitamin D deficiency in early life accelerates type 1 diabetes in non-obese diabetic mice. Diabetologia. 2004;**47**(3):451-462

[72] Froicu M, Cantorna MT. Vitamin D and the vitamin D receptor are critical for control of the innate immune response to colonic injury. BMC Immunology. 2007;**8**:5

[73] Froicu M, Weaver V, Wynn TA, McDowell MA, Welsh JE, Cantorna MT. A crucial role for the vitamin D receptor in experimental inflammatory bowel diseases. Molecular Endocrinology. 2003;**17**(12):2386-2392

[74] Cantorna MT. Vitamin D and its role in immunology: Multiple sclerosis, and inflammatory bowel disease. Progress in Biophysics and Molecular Biology. 2006;**92**(1):60-64

[75] Cantorna MT, Woodward WD, Hayes CE, DeLuca HF. 1,25-dihydroxyvitamin D3 is a positive regulatorforthetwoanti-encephalitogenic cytokines TGF-beta 1 and IL-4. Journal of Immunology. 1998;**160**(11):5314-5319

[76] Takiishi T, Ding L, Baeke F, Spagnuolo I, Sebastiani G, Laureys J, et al. Dietary supplementation with high doses of regular vitamin D3 safely reduces diabetes incidence in NOD mice when given early and long term. Diabetes. 2014;**63**(6):2026-2036

[77] Adami G, Rossini M, Bogliolo L, Cantatore FP, Varenna M, Malavolta N, et al. An exploratory study on the role of vitamin D supplementation in improving pain and disease activity in rheumatoid arthritis. Modern Rheumatology. 2018:1-8. DOI: 10.1080/14397595.2018.1532622. [Epub ahead of print]

[78] Bae SC, Lee YH. Vitamin D level and risk of systemic lupus erythematosus and rheumatoid arthritis: A Mendelian randomization. Clinical Rheumatology. 2018;**37**(9):2415-2421

[79] Bozkurt NC, Karbek B, Ucan B, Sahin M, Cakal E, Ozbek M, et al. The association between severity of vitamin D deficiency and Hashimoto's thyroiditis. Endocrine Practice. 2013;**19**(3):479-484

[80] Cantorna MT. Vitamin D, multiple sclerosis and inflammatory bowel disease. Archives of Biochemistry and Biophysics. 2012;**523**(1):103-106

[81] Cutolo M, Otsa K, Paolino S, Yprus M, Veldi T, Seriolo B. Vitamin D involvement in rheumatoid arthritis and systemic lupus erythaematosus. Annals of the Rheumatic Diseases. 2009;**68**(3):446-447

[82] Cutolo M, Otsa K, Uprus M, Paolino S, Seriolo B. Vitamin D in rheumatoid arthritis. Autoimmunity Reviews. 2007;**7**(1):59-64

[83] Cutolo M, Otsa K, Laas K, Yprus M, Lehtme R, Secchi ME, et al. Circannual vitamin d serum levels and disease activity in rheumatoid arthritis: Northern versus southern Europe. Clinical and Experimental Rheumatology. 2006;**24**(6):702-704

[84] Guan SY, Cai HY, Wang P, Lv TT, Liu LN, Mao YM, et al. Association between circulating 25-hydroxyvitamin D and systemic lupus erythematosus: A systematic review and meta-analysis. International Journal of Rheumatic Diseases. 2019. DOI: 10.1111/1756-185X.13676. [Epub ahead of print]

[85] Hypponen E, Laara E, Reunanen A, Jarvelin MR, Virtanen SM. Intake of

vitamin D and risk of type 1 diabetes: A birth-cohort study. Lancet. 2001;**358**(9292):1500-1503

[86] Gupta S, Mahajan VK, Yadav RS, Mehta KS, Bhushan S, Chauhan PS, et al. Evaluation of serum vitamin D levels in patients with systemic sclerosis and healthy controls: Results of a pilot study. Indian Dermatology Online Journal. 2018;**9**(4):250-255

[87] Song GG, Bae SC, Lee YH. Association between vitamin D intake and the risk of rheumatoid arthritis: A meta-analysis. Clinical Rheumatology. 2012;**31**(12):1733-1739

[88] Kostoglou-Athanassiou I, Athanassiou P, Lyraki A, Raftakis I, Antoniadis C. Vitamin D and rheumatoid arthritis. Therapeutic Advances in Endocrinology and Metabolism. 2012;**3**(6):181-187. DOI: 10.1177/2042018812471070

[89] Grazio S, Naglić Đ, Anić B, Grubišić F, Bobek D, Bakula M, et al. Vitamin D serum level, disease activity and functional ability in different rheumatic patients. The American Journal of the Medical Sciences. 2015;**349**(1):46-49

[90] Hong Q, Xu J, Xu S, Lian L, Zhang M, Ding C. Associations between serum 25-hydroxyvitamin D and disease activity, inflammatory cytokines and bone loss in patients with rheumatoid arthritis. Rheumatology (Oxford, England). 2014;**53**(11):1994-2001

[91] Beyer K, Lie SA, Kjellevold M, Dahl L, Brun JG, Bolstad AI. Marine ω-3, vitamin D levels, disease outcome and periodontal status in rheumatoid arthritis outpatients. Nutrition. 2018;**55-56**:116-124

[92] Brance ML, Brun LR, Lioi S, Sánchez A, Abdala M, Oliveri B. Vitamin D levels and bone mass in rheumatoid arthritis. Rheumatology International. 2015;**35**(3):499-505

[93] Li D, Jeffery LE, Jenkinson C, Harrison SR, Chun RF, Adams JS, et al. Serum and synovial fluid vitamin D metabolites and rheumatoid arthritis. The Journal of Steroid Biochemistry and Molecular Biology. 2019;**187**:1-8

[94] Harrison SR, Li D, Jeffery LE, Raza K, Hewison M. Vitamin D, autoimmune disease and rheumatoid arthritis. Calcified Tissue International. 2019. DOI: 10.1007/s00223-019-00577-2. [Epub ahead of print]

[95] Khajoei S, Hassaninevisi M, Kianmehr N, Seif F, Khoshmirsafa M, Shekarabi M, et al. Serum levels of adiponectin and vitamin D correlate with activity of rheumatoid arthritis. Molecular Biology Reports. 2019;**46**(2):2505-2512

[96] Ramu R, Arya V, Chitkara A, Taneja RS, Ali M. Serum 25 hydroxy vitamin D levels in newly diagnosed rheumatoid arthritis and their correlation with disease activity. The Journal of the Association of Physicians of India. 2018;**66**(6):38-41

[97] Silva SSC, Kathurirathne G, Mahesh B, Sashikaran J, Jayasiri K. Prevalence of vitamin D deficiency and its associated factors among rheumatoid arthritis patients managed in a rheumatology unit of a tertiary care hospital in Sri Lanka. Clinical Medicine (London, England). 2019;**19** (Suppl 3):30

[98] Lee YH, Bae SC. Vitamin D level in rheumatoid arthritis and its correlation with the disease activity: A meta-analysis. Clinical and Experimental Rheumatology. 2016;**34**(5):827-833

[99] Song GG, Bae SC, Lee YH. Vitamin D receptor FokI, BsmI, and TaqI polymorphisms and susceptibility to rheumatoid arthritis : A meta-analysis. Zeitschrift für Rheumatologie. 2016;**75**(3):322-329

[100] Bragazzi NL, Watad A, Neumann SG, Simon M, Brown SB, Abu Much A, et al. Vitamin D and rheumatoid arthritis: An ongoing mystery. Current Opinion in Rheumatology. 2017;**29**(4):378-388

[101] Dankers W, Gonzalez-Leal C, Davelaar N, Asmawidjaja PS, Mus AMC, Hazes JMW, et al. 1,25(OH)2D3 and dexamethasone additively suppress synovial fibroblast activation by CCR6(+) T helper memory cells and enhance the effect of tumor necrosis factor alpha blockade. Arthritis Research & Therapy. 2018;**20**(1):212

[102] Cutolo M, Otsa K. Review: Vitamin D, immunity and lupus. Lupus. 2008;**17**(1):6-10

[103] Amital H, Szekanecz Z, Szucs G, Danko K, Nagy E, Csepany T, 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? Annals of the Rheumatic Diseases. 2010;**69**(6):1155-1157

[104] Watad A, Neumann SG, Soriano A, Amital H, Shoenfeld Y. Vitamin D and systemic lupus erythematosus: Myth or reality? The Israel Medical Association Journal. 2016;**18**(3-4):177-182

[105] 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**(4):644-652

[106] Ruiz-Irastorza G, Egurbide MV, Olivares N, Martinez-Berriotxoa A, Aguirre C. Vitamin D deficiency in systemic lupus erythematosus: Prevalence, predictors and clinical consequences. Rheumatology (Oxford). 2008;**47**(6):920-923

[107] Bogaczewicz J, Sysa-Jedrzejowska A, Arkuszewska C, Zabek J, Kontny E, McCauliffe D, et al. Vitamin D status in systemic lupus erythematosus patients and its association with selected clinical and laboratory parameters. Lupus. 2012;**21**(5):477-484

[108] Dankers W, Colin EM, van Hamburg JP, Lubberts E. Vitamin D in autoimmunity: Molecular mechanisms and therapeutic potential. Frontiers in Immunology. 2016;**7**:697

[109] Xia Y, Xie Z, Huang G, Zhou Z. Incidence and trend of type 1 diabetes and the underlying environmental determinants. Diabetes/Metabolism Research and Reviews. 2019;**35**(1):e3075

[110] Littorin B, Blom P, Scholin A, Arnqvist HJ, Blohme G, Bolinder J, et al. Lower levels of plasma 25-hydroxyvitamin D among young adults at diagnosis of autoimmune type 1 diabetes compared with control subjects: Results from the nationwide diabetes incidence study in Sweden (DISS). Diabetologia. 2006;**49**(12):2847-2852

[111] Greer RM, Portelli SL, Hung BS, Cleghorn GJ, McMahon SK, Batch JA, et al. Serum vitamin D levels are lower in Australian children and adolescents with type 1 diabetes than in children without diabetes. Pediatric Diabetes. 2013;**14**(1):31-41

[112] Greer RM, Rogers MA, Bowling FG, Buntain HM, Harris M, Leong GM, et al. Australian children and adolescents with type 1 diabetes have low vitamin D levels. The Medical Journal of Australia. 2007;**187**:59-60

[113] Daga RA, Laway BA, Shah ZA, Mir SA, Kotwal SK, Zargar AH. High prevalence of vitamin D deficiency among newly diagnosed youth-onset diabetes mellitus in North India. Arquivos Brasileiros de Endocrinologia e Metabologia. 2012;**56**(7):423-428

[114] Zella JB, DeLuca HF. Vitamin D and autoimmune diabetes. Journal of Cellular Biochemistry. 2003;**88**(2):216-222

[115] Dong JY, Zhang WG, Chen JJ, Zhang ZL, Han SF, Qin LQ. Vitamin D intake and risk of type 1 diabetes: A meta-analysis of observational studies. Nutrients. 2013;**5**(9):3551-3562

[116] Zipitis CS, Akobeng AK. Vitamin D supplementation in early childhood and risk of type 1 diabetes: A systematic review and meta-analysis. Archives of Disease in Childhood. 2008;**93**(6):512-517

[117] Stene LC, Joner G. Use of cod liver oil during the first year of life is associated with lower risk of childhood-onset type 1 diabetes: A large, population-based, case-control study. The American Journal of Clinical Nutrition. 2003;**78**(6):1128-1134

[118] Stene LC, Ulriksen J, Magnus P, Joner G. Use of cod liver oil during pregnancy associated with lower risk of type I diabetes in the offspring. Diabetologia. 2000;**43**(9):1093-1098

[119] Gianfrancesco MA, Stridh P, Rhead B, Shao X, Xu E, Graves JS, et al. Evidence for a causal relationship between low vitamin D, high BMI, and pediatric-onset MS. Neurology. 2017;**88**(17):1623-1629

[120] Cantorna MT, Hayes CE, DeLuca HF. 1,25-dihydroxyvitamin D3 reversibly blocks the progression of relapsing encephalomyelitis, a model of multiple sclerosis. Proceedings of the National Academy of Sciences of the United States of America. 1996;**93**(15):7861-7864

[121] Pierrot-Deseilligny C, Souberbielle JC. Vitamin D and multiple sclerosis: An update. Multiple Sclerosis and Related Disorders. 2017;**14**:35-45

[122] Pierrot-Deseilligny C, Souberbielle JC. Widespread vitamin D insufficiency: A new challenge for primary prevention, with particular reference to multiple sclerosis. Presse Médicale. 2011;**40**(4 Pt 1):349-356

[123] VanAmerongen BM, Dijkstra CD, Lips P, Polman CH. Multiple sclerosis and vitamin D: An update. European Journal of Clinical Nutrition. 2004;**58**(8):1095-1109

[124] Mark BL, Carson JA. Vitamin D and autoimmune disease—Implications for practice from the multiple sclerosis literature. Journal of the American Dietetic Association. 2006;**106**(3):418-424

[125] Jagannath VA, Filippini G, Di Pietrantonj C, Asokan GV, Robak EW, Whamond L, et al. Vitamin D for the management of multiple sclerosis. Cochrane Database of Systematic Reviews. 2018;**9**:Cd008422

[126] 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. Journal of Clinical Medicine. 2019;**8**(9):pii: E1319. DOI: 10.3390/jcm8091319

[127] de Souza HS, Fiocchi C. Immunopathogenesis of IBD: Current state of the art. Nature Reviews. Gastroenterology & Hepatology. 2016;**13**(1):13-27

[128] Fletcher J, Cooper SC, Ghosh S, Hewison M. The role of vitamin D in inflammatory bowel disease: Mechanism to management. Nutrients. 2019;**11**(5)pii: E1019. DOI: 10.3390/nu11051019

[129] Ke W, Sun T, Zhang Y, He L, Wu Q, Liu J, et al. 25-hydroxyvitamin D serum level in Hashimoto's thyroiditis, but not Graves' disease is relatively deficient. Endocrine Journal. 2017;**64**(6):581-587

[130] Stefanic M, Tokic S. Serum 25-hydoxyvitamin D concentrations in relation to Hashimoto's thyroiditis: A systematic review, meta-analysis and meta-regression of observational studies. European Journal of Nutrition. 2019. DOI: 10.1007/s00394-019-01991-w. [Epub ahead of print]

[131] An L, Sun MH, Chen F, Li JR. Vitamin D levels in systemic sclerosis patients: A meta-analysis. Drug Design, Development and Therapy. 2017;**11**:3119-3125