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·Minireview·

Role of vitamin D in immune responses and autoimmune diseases, with emphasis on its role in multiple sclerosis

Hong-Liang ZHANG, Jiang WU

Department of Neurology, The First Hospital of Jilin University, Changchun 130021, China

Abstract: Vitamin D is a seco-steroid involved in calcium and phosphorus metabolism, and bone formation and mineralization, through binding to a specific nuclear receptor, vitamin D receptor (VDR). Besides its well-established functions on bone health, multiple lines of evidence have indicated the immunomodulatory roles of vitamin D. Vitamin D can affect both innate and adaptive immunity, and prevent autoimmune responses efficiently. Vitamin D regulates the immune responses by suppressing T cell proliferation and modulating macrophage functions. Epidemiological studies have shown that vitamin D deficiency is associated with multiple diseases such as rickets and cancer. Moreover, associations between vitamin D and autoimmune diseases have been confirmed in multiple sclerosis (MS), rheumatoid arthritis (RA), *etc.* The present review mainly summarized the recent findings on the immunomodulatory role of vitamin D in various disorders, with special focus on its role in MS, an autoimmune disease of the nervous system.

Keywords: vitamin D; autoimmune disease; multiple sclerosis

1 Introduction

Vitamin D, a seco-steroid characterized by the breakdown of one bond in the steroid rings, acts on target tissues in a steroid hormone-like manner by binding to a specific nuclear receptor, vitamin D receptor (VDR). Vitamin D is produced *in vivo* mainly via skin exposure to ultraviolet (UV) radiation, with only a small amount from food sources (Fig. 1). In sunny countries such as Australia, humans receive 90%-95% of their vitamin D from the sun's UV radiation[1]. Under UV irradiation, cholecalciferol (vitamin D_3) is synthesized in the skin from 7-dehydrocholesterol. Then, 25-hydroxyvitamin D [$25(OH)D_3$] and 1, 25-dihydroxyvitamin D [$1,25(OH)_2D_3$], the main circulatory and physiologically active forms, are produced in the human body by hydroxylation of cholecalciferol[2]. In addition to the traditional role in bone health[3], the discovery of VDR on various tissue types has extended the roles of vitamin D. Vitamin D has been hypothesized to be an important environmental factor that is associated with a number of autoimmune diseases like multiple sclerosis (MS). MS is an autoimmune disease of the central nervous system (CNS), affecting more women than men[4]. Several lines of evidence have suggested that vitamin D can decrease the prevalence and severity, and improve the prognosis of autoimmune diseases including MS[5-8]. Moreover, epidemiological studies have suggested the association between the low vitamin D level and a higher MS risk, potentiating interventions targeting the low vitamin D levels in MS[7]. Moreover, vitamin D insufficiency would lead to autoimmune processes in animal models, while administration of vitamin D could attenuate immune-mediated symp-

Corresponding author: Hong-Liang ZHANG
Tel: 46-8-58585304; Fax: 46-8-58585470
E-mail: drzhl@hotmail.com
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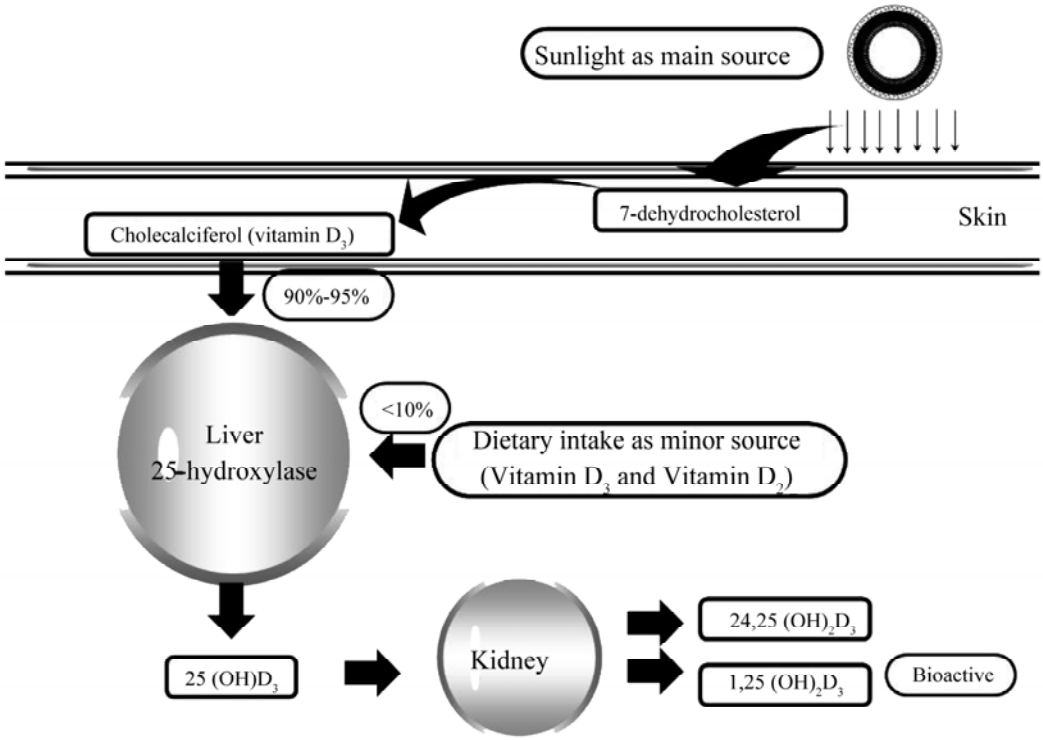

Fig. 1 Sources and metabolism of vitamin D in human. Vitamin D is produced *in vivo* mainly via exposure of the skin to ultraviolet (UV) radiation from sunlight (90%-95%), with only a small amount from food sources (<10%). Upon UV irradiation, 7-dehydrocholesterol (pre vitamin D_3) in the skin is photolyzed and transformed into cholecalciferol (vitamin D_3). In the liver, cholecalciferol is further hydroxylized into 25(OH)D_3 by 25-hydroxylase. 25(OH)D_3 bears bioactive properties of vitamin D. After the second hydroxylization by 1α-hydroxylase mainly in the kidney, the main circulatory and physiologically active form, 1,25-dihydroxyvitamin D [1,25$(OH)_2D_3$ or calcitriol] is produced.

toms[7]. The current review summarized multiple lines of evidence supporting the immunomodulatory role of vitamin D, with special emphasis on its role in MS.

2 General roles of vitamin D in physiological conditions and diseases

Vitamin D plays multiple roles in human physiological conditions and diseases, partly due to the wide distribution and identification of VDR in many tissue types. 1,25$(OH)_2D_3$, the most important gene regulator, enters the nucleus and regulates mRNA synthesis by binding to VDR. The principal physiological function of 1,25$(OH)_2D_3$ is enhancing the absorption of calcium and phosphate from the intestinal tract, therefore positively regulating bone formation[9-11]. To date, several lines of epidemiological and experimental findings have supported the links of vitamin D with various conditions or diseases beyond bone health[3], including muscle function[12,13], autoimmune diseases[14], cancer[15,16], cardiovascular diseases (CVD)[17-19], hypertension[20,21], diabetes[22], inflammatory diseases[23], and all-cause mortality[24], *etc.* (Table 1). Other roles of vitamin D, such as exerting antimicrobial effects via VDR-mediated innate immune response against mycobacterium tuberculosis, are also intriguing[25]. Promising as these findings are, interpretation of them should be with caution before a generalized conclusion is achieved.

3 Vitamin D and immune responses

The importance of vitamin D in regulating the immune system has been reported for decades. In 1984, Rigby *et al.* found that vitamin D could inhibit T cell proliferation[26]. Since then, accumulating findings have indicated an immunomodulatory role of vitamin D. The expression of VDR by multiple types of cells suggests an extensive role of vitamin D in the immune system and immune responses[27]. Although

the exact mechanism remains to be clarified, vitamin D affects immune responses by modulating functions of T cells, natural killer (NK) cells, B cells, and antigen presenting cells (APCs) (Fig. 2). High levels of VDR expression have been identified on dendritic cells, macrophages and monocytes, as well as on activated T and B lymphocytes[28]. In addition, 1α-hydroxylase is expressed by activated macrophages and dendritic cells[29].

A series of *in vivo* animal studies have revealed that vitamin D can down regulate Th1 cell activity, and decrease cytokine release from macrophages and B cell antibody production. It can also reduce the release of interleukin (IL)-2 and interferon (IFN)-γ from $CD4^+$ T cells[30]. Nitric oxide (NO), an important effector of innate immunity, is inhibited

Table 1. Vitamin D deficiency and human diseases

Functions	Related disorders
Bone health	osteomalacia, osteoporosis[3]
Muscle function	muscle weakness[7,8]
Autoimmunity	multiple sclerosis, Crohn disease, diabetes mellitus, systemic lupus erythematosus, asthma, rheumatoid arthritis, *etc.*[49-59]
Cancer	breast, prostate, colorectal, lung, endometrial cancers, *etc.*[10,11]
Cardiovascular diseases	atherosclerosis, coronary heart disease, congestive heart failure, hypertension, diabetes, *etc.*[12-17]
Neurodegeneration	Alzheimer's disease, Parkinson's disease, *etc.*[66,67]
Others	schizophrenia, respiratory infection, all-cause mortality, *etc.*[18,19]

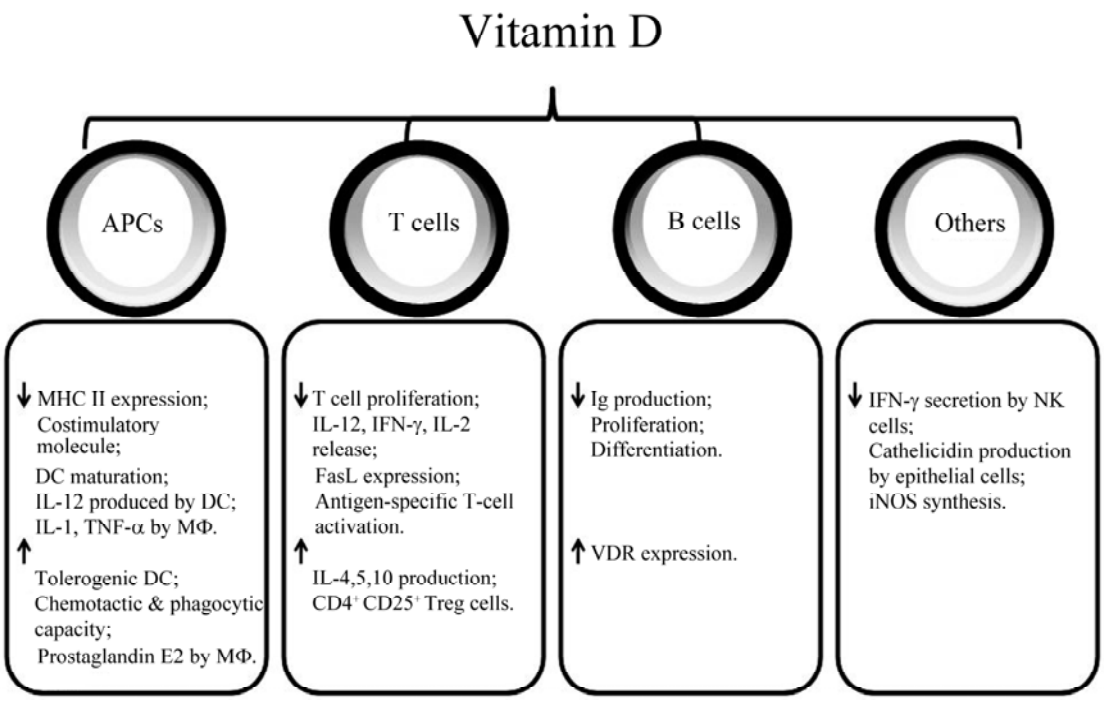

Fig. 2 The roles of vitamin D in the immune system and immune responses. Vitamin D affects immune responses at multiple levels, including function modulation of APCs, T, B and NK cells. ↑ denotes upregulation or induction, ↓ denotes downregulation or inhibition. MHC: main histocompatibility complex; IL: interleukin; TNF-α: tumor necrosis factor alpha; IFN-γ: interferon gamma; Ig: Immunoglobulin; MΦ: macrophage; DC: dendritic cells; NK cells: natural killer cell; iNOS: inducible nitric oxide synthase; VDR: vitamin D receptor.

by vitamin D via downregulation of inducible nitric oxide synthase (iNOS) expression[31]. Vitamin D plays a role in regulating T and B cell functions. Overexpression of VDR in activated $CD4^+$ T cells and inhibition of T cell proliferation by 1,25$(OH)_2D_3$ have been demonstrated[32,33]. The targets of 1,25$(OH)_2D_3$ in $CD4^+$ T cells involve multiple genes, including regulators of nuclear factor-κB, interleukin 2 (IL-2) receptor β gene and IgE binding factor[33]. 1,25$(OH)_2D_3$ can prevent recruitment of T cells via downregulation of IL-2 and IFN-γ production by $CD4^+$ T cells. Moreover, 1,25$(OH)_2D_3$ increases the productions of Th2 cytokines IL-4 and IL-5[34]. However, the direct effect of 1,25$(OH)_2D_3$ on $CD8^+$ T cells has not been found in experimental autoimmune encephalomyelitis (EAE) *in vitro*, although $CD8^+$ T cells express substantial amounts of VDR[35]. An alternative way by which 1,25$(OH)_2D_3$ suppresses immune responses is through inhibiting the Th17 response at several levels, including suppressing the ability of $CD4^+$ T cells to commit to the Th17 lineage, and inhibiting Th17-related IL-17 production[36]. Besides increasing Th2 cytokines IL-4 and IL-5, 1,25$(OH)_2D_3$ can also suppress immunoglobulin production and B cell proliferation and differentiation[37,38].

Vitamin D is responsible for the inhibition of monocyte differentiation into dendritic cells and the inhibition of differentiation, maturation, activation, and survival of dendritic cells, leading to reduced stimulatory activity of dendritic cells on T cells[39,40]. Vitamin D is also important for the interaction of monocytes with T cells, since 1,25$(OH)_2D_3$ reduces the CD40L-related production of proinflammatory cytokines such as IL-1 and TNF-α. Upon interaction between 1,25$(OH)_2D_3$ and CD40L, monocytes can reduce T cell proliferation and IFN-γ production, and elevate IL-10 synthesis[41]. Moreover, 1,25$(OH)_2D_3$ reduces expression of MHC II molecule, CD40, CD80, and CD86 in APC-like dendritic cells and macrophages, which is crucial for T cell activation by APCs. As shown by Daniel *et al.*[42], 1,25$(OH)_2D_3$ can promote dendritic cells to induce $CD4^+CD25^+$ regulatory T cells (Treg) via augmentations of FoxP3 expression and IL-10 production, which are decisive for Treg development. This is in line with previous findings that 1,25$(OH)_2D_3$ induces dendritic cells with a tolerogenic phenotype and an augmentation of the percentage of $CD4^+CD25^+$ Tregs in the spleen[43]. 1,25$(OH)_2D_3$ also induces the production of cathelicidin, a peptide involved in the activation of innate immune responses, by macrophages and epithelial cells[44-46].

Interestingly, apolipoprotein E (apoE), a plasma protein closely associated with a variety of human diseases including Alzheimer's disease[47], MS[48], *etc.*, resembles vitamin D in many aspects regarding the immunomodulatory roles[49,50]. The geographical differences in apoE allele frequency[51] and in serum vitamin D concentration[52] give some hints that there might be some correlations between apoE and vitamin D, although the evidence is not yet sufficient. When the lipid-related properties of apoE and the lipid origin of vitamin D are taken into consideration, the biosynthesis and bioactivities of vitamin D might be affected by polymorphism of apoE. As a receptor of apoE, megalin has been shown to be crucial for the activation of vitamin D[53]. Therefore, data concerning the association between vitamin D and MS should be interpreted with caution. Confounding factors like apoE polymorphism which may be also correlated with MS, would intervene the analysis of the association between vitamin D and MS, and thus should be prudently excluded during analysis.

4 Vitamin D and autoimmune diseases

In general, the 25$(OH)D_3$ level in serum is lower with higher latitudes and with darker skin types. Vitamin D deficiency [serum 25$(OH)D_3$ < 25 nmol/L] is highly prevalent in India, China, Middle-East and Africa. In North America, this problem is much attenuated, since milk in human diet is usually supplemented with vitamin D and vitamin supplementation is relatively more common, although vitamin D insufficiency [serum 25$(OH)D_3$ concentration between 25-50 nmol/L] is still common. In Australia and New Zealand, poor vitamin D status is present in the elderly who are deficient in vitamin D. In Europe, vitamin D status is usually better in the Nordic countries than around the Mediterranean[54].

Both laboratory and clinical studies have provided evidence that vitamin D deficiency is an important environmental factor that can increase the prevalence of certain autoimmune diseases, such as MS[55-57], Crohn disease[58], diabetes

mellitus[59,60], systemic lupus erythematosus (SLE)[61,62], asthma[63], RA[64], Sjögren's syndrome, systemic vasculitis and antiphospholipid syndrome[65]. A correlation between reduced intake of vitamin D and prevalence of the diseases can be found, which raises the possibility that serum vitamin D level is important for the pathogenesis of autoimmune diseases. Besides, in some diseases, a lower $25(OH)D_3$ level in serum is correlated with higher disease activities[63]. Additional evidence supporting the role of vitamin D in autoimmunity is the finding of *VDR* gene polymorphism in patients with autoimmune conditions such as MS[66], inflammatory bowel diseases[67], RA[68], and juvenile diabetes mellitus[69]. However, besides the linkage of low serum levels of vitamin D with certain autoimmune diseases, and the effectiveness of vitamin D in treating autoimmune diseases, most conclusions are drawn based solely on the extrapolation of *in vitro* studies. The causal relation between vitamin D deficiency and autoimmune diseases still seems ambiguous. More intervention trials are needed to identify whether higher serum $25(OH)D_3$ level is protective against autoimmune diseases, or whether other confounding factors are also responsible for these positive associations. Considering the extensive effects of vitamin D on the immune system and immune responses, vitamin D has been suggested as a therapeutic agent in the treatment of immune-mediated diseases. The incidence and severity of autoimmune diseases are found to be reduced by vitamin D supplementation[44], suggesting that vitamin D is promising in the treatment of autoimmune diseases. Vitamin D also prolongs survival of allografts[70]. However, one question regarding its application is the dose of vitamin D in affecting autoimmune responses. Considering that 20 min of exposure in summer sunshine can be equivalent to an oral vitamin D intake of about 10 000 IU per day in an adult, the risks of high-dose administration of vitamin D are generally thought to be low. Recent studies suggest that long-term intake of 10 000-40 000 IU per day poses no risk for adults[71]. In this case, the most significant obstacle to its clinical use is the potential hypercalcemic effect of vitamin D, although the calcium status of the host may influence the effects of vitamin D on immunity[7]. Despite this, low to moderate doses of vitamin D seem to be promising in treating multiple immune disorders as a supplementary therapy.

5 Vitamin D and MS

MS is a chronic inflammatory demyelinating disorder in the CNS, characterized by focal inflammatory infiltration by lymphocytes and macrophages, and subsequent immune-mediated demyelination and neurodegeneration[72]. Aetiology of MS is multifactorial and pathogenesis of MS is still unclear. EAE, a T cell-mediated experimental disorder, serves as an animal model of MS. Virtually all mammalian species are susceptible to EAE[73].

Over 30 years ago, vitamin D deficiency was first proposed to be a risk factor for MS[74], evidence for which was accumulatively obtained after the discovery of the immunomodulatory effects of vitamin D[75]. The geographical difference of MS incidence can be partly explained by exposure to sunshine[76]. The UV-induced production of vitamin D in human body is an independent environmental factor that varies geographically in a pattern roughly the same as that of MS prevalence. Since the first report hypothesizing a link between low vitamin D levels or insufficient sunlight exposure and the development of MS[77], multiple lines of evidence have pointed to a close correlation between vitamin D and MS. MS patients are shown to have low levels of circulating vitamin D as compared with the controls[78]. The inverse association between serum $25(OH)D_3$ concentration and risk of MS could be explained by the direct immunosuppressive effect of UV. This is evidenced by animal studies which show that UV has a direct immunosuppressive effect on EAE[79]. Another explanation is the "hygiene hypothesis"[80], which states that the high rates of infection in third world countries explain the relatively low incidence of MS near the equator in comparison with near the 2 poles[80]. This is further supported by the experimental data from animal studies, which show that helminth infections protect from experimental autoimmune diseases, including EAE[81]. Besides, in the developed countries, physical activity and outdoor exposure have decreased, which may also help explain the high rates of MS.

A series of studies[82-86] with some exceptions[87,88] have shown an increased risk of MS relapse when vitamin D con-

centrations are at their lowest, but these findings could be confounded by infection[89,90]. After MS onset, serum $25(OH)D_3$ concentration declines[91], and hypovitaminosis D is observed throughout the course of the disease, even in a clinically isolated syndrome (CIS)[92-94]. Thus, the studies measuring $25(OH)D_3$ concentration in patients with MS are uninformative in deciding whether vitamin D can decrease the risk of MS[95,96]. In this case, longitudinal studies based on $25(OH)D_3$ concentration before the onset of MS are needed[95]. A nested case-control design to sample an underlying prospective cohort comprising 7 million individuals in the US showed that individuals in the top quintile of serum $25(OH)D_3$ levels had a 62% lower odds of MS than those in the bottom quintile, indicating that serum concentration of $25(OH)D_3$ in healthy young adults is an important predictor of developing MS[57].

The effects of vitamin D supplementation on immune responses have not been systematically investigated in human beings, and the evidence for a protective effect of vitamin D against MS largely comes from observational studies. Independent studies involving vitamin D in patients with MS have reached analogous conclusions. $CD4^+$ T cell proliferation is inhibited by $1,25(OH)_2D_3$ and more cells adopt a Treg phenotype[97]. The level of $25(OH)D_3$ or $1,25(OH)_2D_3$ in the blood is correlated with the suppressive activity of Tregs in MS patients[98,99], and the number of Tregs is correlated with the serum levels of $25(OH)D_3$ and $1,25(OH)_2D_3$[100]. Similarly, Tregs are increased in patients supplemented with vitamin D at the dose of 1 000 IU/day for 6 months[101,102]. Vitamin D is also proved to be effective in the prevention and treatment of EAE[103-107].

These findings suggest that vitamin D may be used for MS treatment[93], based on the finding that complications could be prevented by vitamin D[108]. However, further studies are still needed.

6 Conclusion

Vitamin D plays a role in several diseases including MS, through modulating the immune responses. The close associations between vitamin D status and the incidence and symptoms of MS have been proposed and confirmed. In addition, great achievements have been made on the cellular and molecular mechanisms underlying the effects of vitamin D on MS. Supplementation of vitamin D as a therapeutic strategy in the treatment of MS and other chronic diseases has been proposed and appears to be promising. However, since the evidence for the protective effect of vitamin D supplementation against MS largely comes from observational studies, large-scale randomized controlled trials on high-dose vitamin D supplementation are required to establish a protective effect and to rule out unexpected complications.

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维生素 D 在免疫反应和自身免疫性疾病特别是多发性硬化中的作用

张洪亮，吴江

吉林大学第一医院神经内科，长春 130021

摘要：维生素 D 是一种类固醇衍生物，其通过与特异性核受体结合，在钙磷代谢、骨质形成与矿化中发挥重要作用。除此之外，大量证据表明维生素 D 具有免疫调节作用。维生素 D 能调节天然免疫与获得性免疫，有效抑制自身免疫反应。研究表明，维生素 D 是通过抑制 T 细胞增殖和调节巨噬细胞功能来发挥免疫调节作用的。流行病学调查发现，维生素 D 缺乏与多种疾病相关。维生素 D 缺乏与自身免疫性疾病的关系在多发性硬化和类风湿性关节炎中得到证实。本文主要总结了维生素D在人类疾病中的免疫调节作用，尤其强调其在神经系统自身免疫性疾病——多发性硬化中的重要作用。

关键词：维生素 D；自身免疫性疾病；多发性硬化