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REVIEW PAPER

Role of 1,25-dihydroxycholecalciferol in immunological and molecular pathways involved in Multiple Sclerosis

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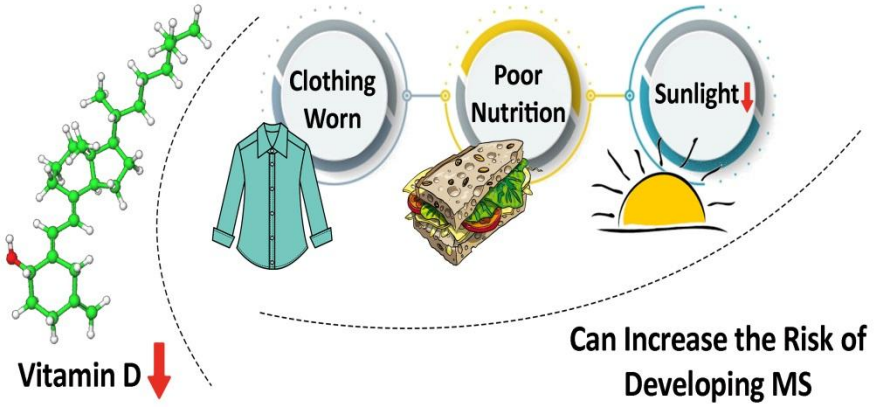
Highlights

- Multiple sclerosis is disorder of nervous system that is associated with oligodendrocytes destruction.
- Some genetic and environmental factors are associated with the risk of multiple sclerosis.
- Vitamin D could modulate the immune system and decrease the risk of multiple sclerosis.

Graphical Abstract



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Abstract

Multiple Sclerosis (MS) is a chronic disorder of central nervous system which is correlated with deformed axons and loss of oligodendrocytes. Many pathological factors, including genetic predisposition, smoking, exposure to EBV, and lack of sunlight which leads to reduced vitamin D intake are involved in MS occurrence. 1,25-dihydroxycholecalciferol or vitamin D is generally referred to a group of fat-soluble steroids. Its active form, 1,25 (OH) 2D, has a wide range of effects on human body which significantly affects the genetic predisposition and immune system. The observed evidence for the caring properties of MS supports the role of vitamin D in MS. It has been shown that low levels of vitamin D, or vitamin D in serum, increase the development of MS risk. Vitamin D works through its own receptor called VDR. The mentioned receptor is a cytosolic receptor as a member of the thyroid/steroid nuclear receptors, which is expressed in the brain, peripheral blood monocytes, on immune cells, and several other tissues. The presence of VDR in both peripheral T cells and thymus cells indicates the vital role of vitamin D in the function and development of T cells. VDR also interacts with many MS-related genes. This suggests that vitamin D can amplify or inactivate an important gene that regulates proteins in immune responses, and is therefore associated with the progression of MS. In the current narrative review, we describe the vitamin D role in multiple sclerosis disorder.

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Introduction

Multiple sclerosis (MS) is a chronic central nervous system (CNS) disease that occurs after a long period of weakness and numbness before the onset of a growing disability. From a pathological point of view, the swelling in the CNS is associated with deformed axons and the disappearance and reduction of oligodendrocytes (1). Nerve death occurs in the early stages of the disease, but over time is recognized and increased as a prominent feature of the disease. Some believe that the death of axons is the main mechanism in the development of weakness and disability (2).

Less than 200 out of every 100,000 people develop MS (3), but that number decreases to 100 per 100,000 in Canada and is higher in Western Europe. The prevalence of this disease is lower in countries near the equator due to exposure to sunlight (4). In some island communities, there is a high resistance to MS (5). In general, MS has a lower rate in Asian countries, and is more prevalent in countries with good social and economic status (6). The prevalence of this disease has been higher in recent decades (7). Early researchers estimated the prevalence of the disease to be the same among men and women, but in most subsequent studies the number of affected women has been reported to be higher (4). Some meta-analysis studies have also reported a decrease in the incidence rate among both sexes as they approach the equator (8). Cigarette use and distance to the equator can affect the prevalence rate (9). Another study found that women in the United States were three times more likely to be infected than men, and that the rate was reported to be higher among blacks than among whites, a data collected over a 60-year period (10). The impact of environmental factors on the increase in MS statistics is significant. In a review of migrants (11), two patterns were considered: moving migrants from a high-risk area to a low-risk area reduces the prevalence of MS, especially if migration occurs before the age of 15. This could be explained by effect of environmental factors on people. Second, migrants who moved from a low-risk area to a high-risk area still retained a low risk of infection, and the age factor did not have much of an impact. Newer studies continue to confirm these results (12, 13). Numerous pathological factors such as genetic predisposition, smoking (14), exposure to EBV (15) and lack of sunlight (which leads to reduced vitamin D intake) play a role in the prevalence of this disease (16). Genetic factors, also play an important role in the risk of MS disorder (17).

Therapies for MS have been introduced since the 1980s, based on strategies to enhance and modulate the immune system. Although these treatments are effective, they do not stop the swelling process in the CNS, as evidenced by MRI images. If treatment is started in the early stages of the disease, treatment strategies will be more successful. The introduction of diagnostic criteria and disease characteristics has recently become more important for early diagnosis (18). In recent years, several drugs have been introduced in the CNS with the potential to increase, slow down or stop the swelling process. However, new solutions and drugs have serious side effects, such as nerve cell death. So far, no effective treatment has been found to stop the progression step of the disease (19).

There is a link between 1,25-dihydroxycholecalciferol (vitamin D) and risk of MS. Low levels of vitamin D increase the risk of MS. In women, an elevation in serum levels of 1,25 (OH) 2D for every 10 Nano-moles per liter is correlated with a 20% decrease in the risk of developing MS, indicating a protective influence high levels of vitamin D (20). Correlations between sunlight and fluids have been shown by a number of evidences, such as exposure to sunlight to be correlated with a reduced MS risk (21), a reverse association between prevalence MS and sunlight and reverse association between altitude as an indicator of intensity of sunlight and MS (22). The ethnical delivery of MS is associated with low occurrence in the tropics and increased prevalence with elevating latitude in two hemispheres. MS in areas far from the equator where sunlight is low indicating an correlation between vitamin D level and the MS risk (23, 24). One of the factors that affect the sensitivity to MS is the month of birth. People born in the spring are truly more likely to develop MS than those born in the fall (25). In fact, the month of birth is correlated with vitamin D exposure and latitude, indicating that mothers of infants born in the spring are less exposed to light than mothers of infants born in the fall (26). This reduction in vitamin D exposure in utero, together with the solar cycle and latitude differences, could be considered as an environmental factor for the MS development (27, 28). Vitamin D deficiency is very common in MS patients

(29). Vitamin D insufficiency in MS patients is probably because of a combination of low level of vitamin D intake and reduced outdoor activity in return for which vitamin D is produced in the skin (30). Vitamin D deficiency before birth or in early childhood may later in life elevate the developing risk of MS. Outdoor activities in early life (ages 16-20) in summer are correlated with a reduced MS risk. Studies have shown that women with consumption high doses of vitamin D supplementation have a 40% reduced MS risk than women who take 400 IU/day of vitamin D supplementation without additional vitamin D supplementation, at a dose of 1000 to 4000 IU/day to reach serum levels > 99 nmol/L is harmless and may decrease the MS risk by up to 62% (31). In this review, we describe the cellular, immunological, and environmental interactions of vitamin D with multiple sclerosis.

Vitamin D and its function

Vitamin D is generally referred to as a group of fat-soluble steroids. Its active form 1,25 (OH) 2D3 has a widespread range of influences on the human body, this factor greatly affects the genetic predisposition of individuals. The most well-known role in calcium homeostasis has been observed, where parathyroid hormone (PTH) and 1,25 (OH) 2D3 act to maintain steady-state blood calcium levels in bone (26). Recent evidence, however, supports the role of 1,25 (OH) 2D3 in the growth and function of the brain, heart, arteries, and musculoskeletal health. In addition, 1,25 (OH) 2D3 has anti-neoplastic characteristics that control insulin synthesize and has many impacts on the immune system (32).

Vitamin D has two chief types: cholecalciferol (vitamin D3) which is obtained from animal resources and ergocalciferol (vitamin D2) which is obtained from plant materials. Vitamin D3 is the primary vitamin D in the human body. This vitamin is made in the skin during the formation of B-ring (as pro-vitamin D3) and by sunlight at UVB wavelengths to form pro-vitamin D (29, 33); these pro-vitamins are spontaneously isomerized and produces vitamin D3. Vitamin D3 and vitamin D2 can be obtained from everyday food sources, but vitamin D2 is absorbed less effectively than D3 and is less biologically active (30). Circulating vitamin D (D2 and D3) is hydroxylated to a larger form and produces 25 (OH) D, after transporting to the liver. The 25 (OH) D forms strong bonds with vitamin D-binding protein (VDBP) in the kidneys and some other tissues of the body, converting to 1,25 (OH) 2D3 which is biologically active (31). The active form has a short shelf life, so 25 (OH) D itself is used as a constituent of vitamin D with a 30-day life cycle (31). Vitamin D plays its role via its receptor, VDR, (Figure 1).

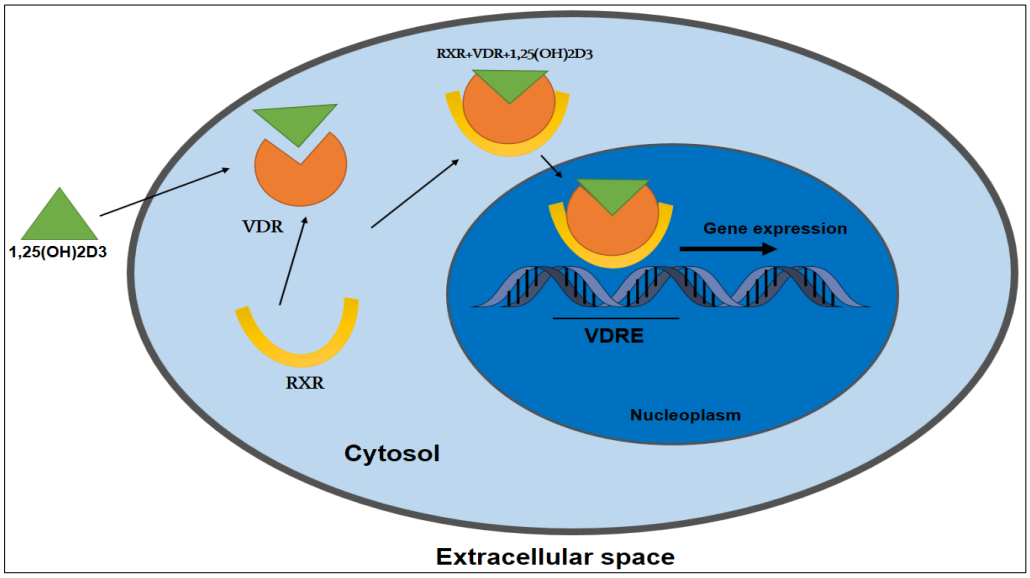

Figure 1. Role of vitamin D and its receptor in gene expression. The active form of vitamin D, 1, 25 (OH) 2D3, enters the cell and binds to its receptor (VDR). The complex then forms a larger complex with retinoid receptors (RXR) to regulate gene expression. The latter complex binds to vitamin D response elements (VDREs) on the genome and regulates gene expression.

In the endocrine apparatus, 1,25 (OH) 2D3 is made in the kidneys during the function of the enzyme 1-alpha hydroxylase which encoded via the CYP2B1 loci in chromosome 12. Also, the 25 (OH) D conversion to 1,25 (OH) 2D3 occurs in various cells and tissues where the enzyme 1-alpha hydroxylase is existent in mitochondria (34). Unlike the production of the endocrine system 1,25 (OH) 2D3, which is strongly controlled by calcium levels and parathyroid hormone, the construction of the region is largely related to the blood level of 25 (OH) D and the region of the cytokine milieu (35). One of the specific signs of the prevalence of MS is that 1-alpha hydroxylase is existent in the mitochondria organelle of numerous kinds of immune cells (22) as well as in glial neurons and CNS (34, 36). However, the presence of 1a-hydroxylase in immune cells, glial cells, and CNS tissue is not specific for MS.

Vitamin D insufficiency and its risk factors

The well-known risk factors for deficiency of vitamin D are lack of sun, skin color, preterm delivery, obesity, weakness, race, age and environmental factors (37). Deficiency of vitamin D is higher in European population than in Asians and the Americas. In European ethnicity, the highest levels of serum 1,25 (OH) 2D3 were detected in the Nordic regions and the lowest in the Mediterranean regions, which might because of multivitamin use, and sun exposure, in the Nordic regions whereas a darker skin and shading are current in Mediterranean areas (38). High occurrence of vitamin D deficiency has also been observed in African Americans, as persons with skin of dark are less able to made vitamin D in the sun than those with light skin (39). Also, the occurrence of vitamin D insufficiency in immigrants of non-Western is high in the Netherlands (40) and in the Middle East (41), especially in Iran (42), in which lifestyle factors are vital. Due to the alterations that happen with aging, elder persons with other risk factor for deficiency of vitamin D may have insufficient storage of vitamin D. Older people produce a low level of vitamin D, often stay indoors, and are exposed to radiation of ultraviolet B (43). Persons that for a long time have been hospitalized and have not been helped with vitamin D supplementation, and persons who wear coverings and clothing for cultural or religious aims, might be at a high risk for deficiency of vitamin D (44). Supplementation with oil of fish liver plays a defensive role in a people with outdoor sports activities in summer (21). Vitamin D2 is not a good supplement for numerous issues such as absorption, differences in effectiveness in increasing levels of vitamin D, decreased binding of protein in the blood, shorter lifespan.

Immune and cellular functions

Vitamin D can act on two mechanisms in target cells: when 25 (OH) D binds to VDBP, which could pass inactively or actively across cellular membranes, and 1,25 (OH) 2D3 in the mitochondria become viable cells and so bound to the vitamin D receptor (VDR) and apply genetic impacts (45), or as free 1,25 (OH) 2D3 found in the kidneys (endocrine), in other cells it is produced in paracrine or autocrine forms (Figure 2), and could cross cell membranes and bind to VDR and rapidly produce interfering, rapid, and non-genetic effects. However, the role of VDR in the non-genomic effects of 1,25 (OH) 2D is controversial. The VDR is responsible for the faster impacts of 1,25 (OH) 2D3 (32), which begin in seconds of the 1,25 (OH) 2D3 bond to the receptor (45). These functions are primarily at the surface of the cell membrane and include interference with ion channels or ligand ion channels and the construction of AMP or inositol 1-4-5 triphosphate cycles in the cellular membrane that affect ion channels and signal transduction in the membrane. The 1,25 (OH) 2D3 has various interfering effects (46), which occur hours after appearance, such as protein kinases activation.

The 1,25 (OH) 2D3 regulates the immune response in vitro (47), as well as the construction of cytokines from T-helper type I (Th 1) during T-helper type II (Th 2) stimulation and affects the activity of regulatory cells (T reg) (48). In the CNS, 1,25 (OH) 2D3 blocks the production of precursor cytokines and nitric oxide with Microglia (49). In addition, 1,25 (OH) 2D3 is required for neuronal function and neurotransmission (50). Recently the 1,25 (OH) 2D3 has been shown to disrupt myelin degradation and oligodendritic cell destruction and activate oligodendritic receptors in adult cells (51).

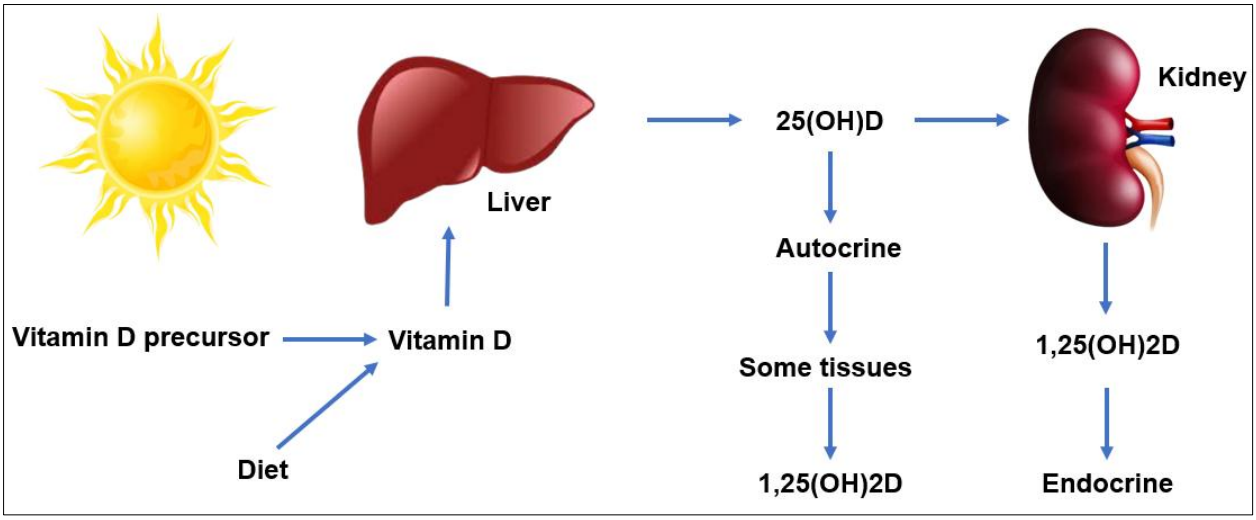

Figure 2. An overview of the production and uptake of vitamin D as well as the autocrine and endocrine function of this vitamin.

Genetic properties of vitamin D

Vitamin D applies genetic impacts in the mitochondria by converting 25 (OH) D to 1,25 (OH) 2D3, at higher stages involving chaperones and co-chaperones (46). These effects react happens with VDR. The D-VDR complex creates a hetero isoform with each of the 3 retinoid X-receptors (RXR) and binds to specific vitamin D response elements (VDRE) in the intended gene (46, 52). VDREs are specific sequences of DNA that are detected in the high presence of the complex 1,25 (OH) 2D3-VDR-RXR and cause structural changes (52). There are also many activators and inhibitors, which might be involved. These molecular complexes comprise acetyltransferase components that include members of family of the P160, including: steroid receptor coactivator-1 (SRC-1), transcriptional intermediate factor 2 (TIF2), RAC3, P300/CBP and DRIO205. The specific genetic, cellular, and regional functions of these activators, inhibitors, and chaperones together characterize whether the response to the complex combined with VDRE closes the structure of chromatin to reduce gene expression (53, 54, 55).

These genetic influences could control the metabolism of vitamin D (56, 57) but a range of genes involved in cell proliferation or differentiation (58, 59), as well as the immune system, including cytokines and its receptors (59, 60). Romagopalan et al. recently showed that the most genetically predisposed region of MS, the HLA-DR gene, is controlled by 1,25 (OH) 2D3, which is protected by VDRE (61).

Evidence showing vitamin D is involved in MS

Epidemiological evidence

The observed evidence for the caring properties of MS supports the role of vitamin D in MS. It has been found that low levels of vitamin D (62) or serum vitamin D (63) increased the MS risk. In a US study, few cases were observed to have high concentrations of 25 (OH) D (63). Serum level 25 (OH) D is lower in MS patients (64), but this clearly indicates a decrease in the activity of these substances during disease progression (65). Nevertheless, patients with MS have very low concentrations of vitamin D (66) and are at the highest risk (67).

Genetic evidence

Genetic variations in sequences encoding important peptides in function of vitamin D, such as VDR, as well as CYP27B1, which encodes 1 alpha hydroxylase, indicate signs of risk for MS. Variations in CYP27B1 gene are correlated with an elevated MS risk (68, 69), but this has not been confirmed by some research (70, 71, 72, 73). The evidence for the association between MS growth and polymorphisms in VDR is complex. The association between VDR and HLA-DR15 polymorphisms (74), sun exposure (72), or dietary vitamin D intake (71) has been detected but not yet established. Though, 1,25 (OH) 2D3 has pleiotropic impacts on the human genome. In

specific VDREs and genetic alterations and mutations, 80% of genes are involved and associated with MS. Vitamin D can amplify or inactivate an important gene that regulates proteins in immune responses, and is therefore correlated with the progression of MS. It has also been shown that genetic diversity in these genes might affect the way vitamin D affects MS (75). Other evidence proposes that low concentrations of 1,25 (OH) 2D3 could have a significant effect on MS risk (76). In all cases, these functions are associated with low concentrations of 1,25 (OH) 2D3 and indicate a strong correlation between low concentrations of 1,25 (OH) 2D3 and the MS risk (77).

Vitamin D and modulation of immune response

The modulation of immune responses is the central role of 1,25 (OH) 2D3 (78) so that several immune cells, such as macrophages, monocytes, dendritic cells, T and B active cells, contain VDR. In addition, it has a protective role against autoimmune disorders. The latter role is played by decreasing the MHC class II complex expression (79, 80). In addition, 1,25 (OH) 2D3 leads to B cell proliferation and their differentiation to plasma cells, immunoglobulins E and M secretion, memory B cell production and programmed cell death of activated B cells (81). It also promotes T-regulating cells, reduces the proliferation of effector T cells, and inhibits the production of cytokines as inflammatory molecules. In total, the available data show that 1,25 (OH) 2D3 boosts a number of immune system cascade players to produce a hormonal and anti-inflammatory secretion effect. The 1,25 (OH) 2D3 therapy has been revealed to reduce autoimmune diseases caused by Th1 (82, 83). In addition to treating mice with symptoms of MS with 1,25 (OH) 2D3, it eliminates the disorder in these animals. These outcomes could elucidate that this vitamin could alter the response of immune system even after disorder onset (82). T cells, and eventually B cells, may both serve as indirect or direct targets of 1,25 (OH) 2D3. However, various activation stimuli appear to increase the expression and synthesis levels of vitamin D receptors (VDR). Also, 1,25 (OH) 2D3 upregulates several genes including Osteocalcin, Calbindin, Osteopontin and hydroxylase-24 (84). Metabolites of vitamin D might also have a defensive against type 1 diabetes by downregulating dendritic cells and macrophages and Th1 cells, as well as promoting Th2 lymphocytes (85). Also, recent studies have linked deficiency of vitamin D to a variety of non-skeletal conditions including cancer, cardiovascular disease, cognitive impairment, stroke, and dementia. 1,25 (OH) 2D3 has been shown to provide a type of neuroprotection that involves clearing the nervous system of amyloid plaque. Plaque is a hallmark of Alzheimer's disease.

Vitamin D and autoimmune disorder

The vitamin D role in some autoimmune disorders, such as rheumatoid arthritis (RA), inflammatory bowel disease (IBD), type 1 diabetes, autoimmune thyroiditis, scleroderma, connective tissue disease, allergic encephalomyelitis, systemic lupus erythematosus (SLE), and MS has taken (36, 86). Vitamin D prevents the development of autoimmune diseases in animal models (87, 88). Some studies show that the risk of certain diseases including rheumatoid arthritis and type 1 diabetes is reduced in people with high vitamin D intake (89, 90). The best indicator of serum vitamin D status from all sources is 25 (OH) D. Serum concentrations less than 25 nmol/L are considered severe deficiencies, levels between 25-80 nmol/L are considered moderate and mild deficiencies, and levels above 80 nmol/L are considered sufficient. MS patients have low serum concentration of vitamin D than the standard level, and it is therefore proposed that this vitamin has a molecular immune role in the CNS, possibly via the response of Th1 (91). Vitamin D play an effective in vitro immunomodulator that can improve or even protect MS animal models (36). In other words, a poor vitamin D status can increase the risk of MS (92) and lead to severe MS (93). Several experiments have shown that the mentioned vitamin D reduces the pro-inflammatory status of the immune system (36, 94). This main role of vitamin D in avoiding immunodeficiency is argued that low concentration of vitamin D are correlated with risk of MS. Though, the causality of this correlation is not entirely obvious (95, 96, 97).

Conclusion

Multiple sclerosis is a multifactorial disorder in which different types of factors such as race, age, sex, smoking, and some other environmental factors are involved in the changing risk of MS. However, deficiency of vitamin D as a fat-soluble vitamin has a special role in increasing the risk of developing this disease. This vitamin works through its receptor, VDR, and can act as the immune response modulator. Factors that can reduce serum vitamin D, such as the type of clothing worn, exposure to sunlight, and poor nutrition, can increase the risk of developing MS.

Though the vitamin D and immune system interaction has been identified for many years ago, it is just in the past limited years that the physiological importance of vitamin D-mediated immunity has been developed obvious. Paper studying animal models and human cells have emphasized powerful impacts of vitamin D on responses of both adaptive and innate immunes in an extensive range of tissues. These notes support the total theory that vitamin D could play a main role in promoting removal of pathogens, while suppressing the possibly harmful influences of extended inflammation period. Also, vitamin D has the possible to impact a widespread series of immune illnesses, particularly autoimmune and infectious disorders. At a clinical level, related studies have extended functional information to indicate that the insufficiency of vitamin D is associated to many immune health complications.

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