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The Influence of vitamin d on the immune system - A comprehensive review

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Abstract
Vitamin D, renowned for its pivotal role in immune system maintenance, exerts a profound influence on the body's immunological functions. It orchestrates a delicate balance between innate and adaptive immunity while modulating the inflammatory cascade. Vitamin D has garnered heightened attention in recent times due to its multifaceted effects on various chronic diseases. The significance of Vitamin D in regulating immune cell activity has experienced substantial growth in the past decade, owing to the discovery of the Vitamin D receptor and crucial Vitamin D-utilizing compounds expressed by immune cells. The present study explores the evidence demonstrating Vitamin D's pivotal role in orchestrating both innate and adaptive immunity, with a focus on the underlying molecular mechanisms.

Keywords: Vitamin D, immune system, T cells, B cells, innate immunity, adaptive immunity

Introduction
Vitamin D is widely recognized for its beneficial effects on calcium homeostasis and bone metabolism. However, more than three decades ago, researchers identified previously unknown aspects of Vitamin D, primarily related to its anti-proliferative effects on tumor cells expressing the Vitamin D receptor (VDR) [1]. Since then, Vitamin D deficiency has been associated not only with bone-related conditions like osteomalacia and rickets but also with various other pathological conditions. Emerging evidence suggests that Vitamin D plays an active role in regulating both innate and adaptive immune responses [2]. In fact, most studies support the idea that Vitamin D exerts extensive immunomodulatory effects in immune-mediated disorders, including infections, autoimmune diseases, and cancer [3]. Overall, these reports highlight the pleiotropic impacts of Vitamin D on immune response regulation; however, the underlying molecular and cellular mechanisms remain incompletely characterized. The interactions of Vitamin D with specific components of the immune response become even more intricate, considering that Vitamin D does not act exclusively through VDR's transcriptional effects inside the cell nucleus but also exerts rapid, non-genomic impacts when the VDR is localized on the cell membrane and cytoplasm [4]. This article aims to uncover the molecular activities of Vitamin D in various aspects of the immune system, with a particular focus on the innate and adaptive immune systems in relation to autoimmune diseases.

Sources and Metabolism of Vitamin D
In humans, Vitamin D can be obtained from two distinct sources: through dietary intake or via UV-mediated synthesis in the epidermal layer of the skin. Consequently, by definition, Vitamin D is not considered a genuine vitamin but rather a prohormone. Two forms of Vitamin D can be acquired through dietary consumption: Vitamin D2 (also known as ergocalciferol) is found in fungi/yeast, while Vitamin D3 (also known as cholecalciferol) is present in animal-derived foods. Only a few foods naturally contain significant amounts of Vitamin D. For instance, cod-liver oil and fatty fish are considered rich sources, whereas cream, butter, and egg yolk contain only small quantities. In contrast, human and cow's milk are poor sources of Vitamin D [5]. However, despite the availability of Vitamin D3 through nutrition, the skin remains the most crucial source of this prohormone, as it possesses a remarkable ability to produce Vitamin D3 upon exposure to sunlight.

In the skin, UV rays facilitate the photolytic cleavage of 7-dihydrocholesterol (7-DHC) into pre-Vitamin D3, which then undergoes spontaneous thermal isomerization into Vitamin D3 [6].

Vitamin D acquired from the diet and skin is subsequently transformed in the liver into 25hydroxyvitamin D (Figure 1). This metabolite is used to assess an individual's Vitamin D status. In the kidneys, the enzyme 25-hydroxyvitamin D-1 a-hydroxylase (CYP27B1) catalyzes the conversion of 25 hydroxyvitamin D into its active form, 1, 25-dihydroxyvitamin D. The renal production of 1, 25 dihydroxyvitamin D is tightly regulated by plasma parathyroid hormone (PTH) levels, as well as phosphorus and serum calcium levels. Fibroblast growth factor 23, released from bone tissue, induces the internalization of the sodium-phosphate cotransporter in the cells of the kidney and small intestine, concurrently suppressing the synthesis of 1, 25-dihydroxyvitamin D. This active form of Vitamin D enhances the absorption of renal calcium and intestinal calcium and phosphorus. It also triggers the expression of the enzyme 25-hydroxyvitamin D-24-hydroxylase (CYP24), which catabolizes both 25- hydroxyvitamin D and 1, 25-dihydroxyvitamin D into biologically inert, water-soluble calcitroic acid [7].

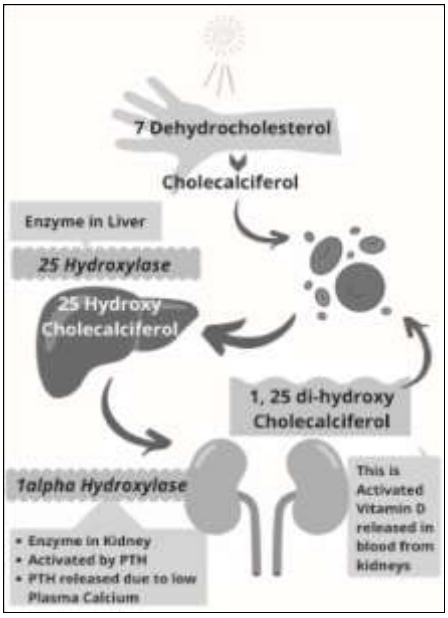

Fig 1: Vitamin D Metabolism

Definitions and Prevalence of Vitamin Deficiency

Although there is no consensus on the ideal levels of 25-hydroxyvitamin D as measured in serum, most experts define Vitamin D insufficiency as a 25-hydroxyvitamin D level of less than 20 ng per milliliter (50 nmol per liter) [8]. 25-Hydroxyvitamin D levels are inversely correlated with PTH levels until they reach 30–40 ng per milliliter (75–100 nmol per liter), at which point PTH levels begin to level off. Furthermore, intestinal calcium transport increased by 45–65% in women when 25hydroxyvitamin D levels were raised from an average of 20–32 ng per milliliter (50–80 nmol per liter) [9]. Given this data, a level of 25-hydroxyvitamin D between 21–29 ng per milliliter (52–72 nmol per liter) can be considered indicative of a relative Vitamin D deficiency, while a level of 30 ng per milliliter or higher can be considered indicative of sufficient Vitamin D [10]. Vitamin D intoxication is detected when serum levels of 25-hydroxyvitamin D exceed 150 ng per millilitre (374 nmol per liter). Using these definitions, it has been estimated that 1 billion people worldwide have either a deficiency or insufficiency of Vitamin D [11]. Over half of postmenopausal women taking medication for osteoporosis had inadequate levels of 25-hydroxyvitamin D below 30 ng per millilitre (75 nmol per liter). Children and young adults are also potentially at high risk for Vitamin D deficiency. Pregnant and lactating women, who were thought to be immune to Vitamin D insufficiency because they took a daily prenatal multivitamin containing 400 IU of Vitamin D (70% took a prenatal vitamin, 90% ate fish, and 93% drank around 2.3 glasses of milk per day), were also at risk; 73% of the women and 80% of their babies had insufficient levels of Vitamin D (25-hydroxyvitamin D level, <20 ng/ml) at the time of birth [12].

Vitamin D Regulation

The term "Vitamin D" refers to a group of fat-soluble secosteroids that are essential for the metabolic control of calcium, iron, magnesium, phosphate, and zinc. For humans, this group primarily consists of two active forms: animal-derived Vitamin D3, also known as cholecalciferol, and plant-derived Vitamin D2, known as ergocalciferol (Figure 2a and b). Both forms of Vitamin D can be obtained through the diet, while cholecalciferol can also be synthesized in the skin upon exposure to sunlight through UVB-mediated ring-opening electrocyclic reaction of its precursor molecule, 7-DHC. Since the term "vitamin" by definition refers to an essential element, organisms unable to produce Vitamin D should not consider it a vitamin but rather a hormone.

Vitamin D3 can undergo further metabolism in the liver, where it is hydroxylated to produce its pre-hormonal counterpart calcifediol, also known as calcidiol, 25-hydroxycholecalciferol, or 25 hydroxyvitamin D (25(OH) D) (Figure 2c). Circulating calcifediol serves as a marker for assessing an individual's Vitamin D status. It is further metabolized in the renal proximal.

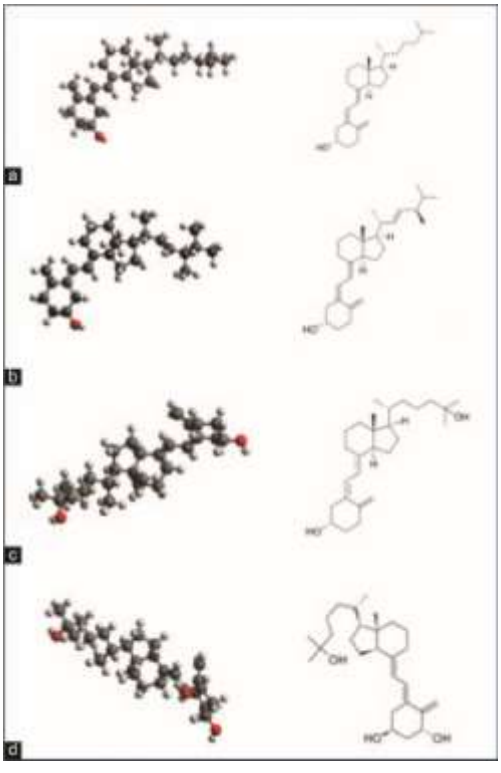

Fig 2: Structures of the Vitamin D Group

Components (a-d)

Tubules by the mitochondrial enzyme 25(OH) D-1a-hydroxylase (CYP27B1) to produce its active metabolite calcitriol (Figure 2d), also known as 1, 25-dihydroxycholecalciferol or 1, 25-dihydroxyvitamin D3 (1, 25(OH)2D3) [13]. Liver hydroxylation is a poorly controlled process directly proportional to the amount of ingested or synthesized Vitamin D3. Renal hydroxylation, on the other hand, is entirely regulated by PTH and calcitriol itself through a negative feedback mechanism [14]. Additional renal production of calcitriol occurs in numerous tissues expressing the CYP27B1 enzyme and the VDR, including epithelial cells of the skin, bone, lung, intestine, parathyroid gland cells, and various immune cells [15]. Calcitriol's established functions include promoting dietary calcium absorption from the gastrointestinal tract, increasing renal tubular reabsorption of calcium, upregulating osteoblastic activity, and inhibiting calcitonin, all of which lead to elevated serum calcium levels. Calcitriol has a short half-life of approximately 4 hours, is rapidly metabolized into calcitroic acid through the action of 24hydroxylase, and is excreted in the urine [16].

Vitamin D and Immunity

Within the various essential tissues and cells where the Vitamin D receptor (VDR) is found, we encounter immune system specialists: lymphocytes, monocytes, and dendritic cells (DCs). Consequently, the subsequent phase of development, particularly in the past decade, aimed to elucidate Vitamin D's role as a positive immune modulator on the immune system. The effects of Vitamin D deficiency in the pathogenesis of immune-mediated diseases and the pivotal role of pharmacological doses of Vitamin D in autoimmune diseases have been prominently emphasized. To date, more than 30 beneficial effects of Vitamin D on the immune system have been documented [3].

The intimate link between the creation of the active metabolite of Vitamin D upon exposure to UVB radiation has been well-established for many years. Vitamin D plays a role in the development of macrophages, encompassing the production of macrophage-specific surface antigens and the secretion of lysosomal enzymes such as acid phosphatase and hydrogen peroxide. These attributes of antimicrobial capacity are compromised in the context of Vitamin D deficiency [17]. Thus, Vitamin D plays a crucial role in enhancing the effects of innate immune processes while tempering the adaptive immune system, ultimately leading to improved outcomes in autoimmune diseases and a potential reduction in the risk of autoimmune disorders [18]. Furthermore, Vitamin D contributes to shaping the immune response by influencing T and B cells. For instance, the quantity of VDR on CD4+ T cells correlates with the degree of cell activation. The addition of 1, 25(OH)2D3 to CD4+ T cells restrains the proliferation of T-helper-1 cells and cytokine production. Additionally, there is a suppression of T-helper-1 cytokines, such as interleukin (IL)-2, IL-12, and interferon?, and an augmented production of T-helper-2 cytokines, such as IL-5 and IL-10, suggesting a predominance of T-helper-2 cells over T-helper-17 cells [19]. Vitamin D also exerts regulatory control over the responses of T-helper-17 cells, which are pivotal in immune system reactions. A nonhypercalcemic VDR agonist, elocalcitol, has been demonstrated to reduce T-helper-1-type and T-helper-17-type cytokine secretion while promoting the expression of T-helper-2-type cytokines. Additionally, 1, 25(OH)2D3 suppresses autoantibody production [20].

While elevated levels of 1, 25(OH)2D3 do not hinder the generation of bone marrow dendritic cells (DCs), their development is slowed. In vitro, 1, 25(OH)2D3 inhibits IL-12 secretion and the differentiation of monocytes into DCs, as well as impeding the stimulatory effects that T cells have on their activity. While 1, 25(OH)2D3 enhances phagocytosis and the microorganism-killing ability of macrophages, it concurrently hampers the antigen-presenting capability of these cells, thereby creating dual responses within the innate and adaptive arms of the immune system. Moreover, 1, 25(OH)2D3 induces the differentiation of monocytes into macrophages and reduces the release of inflammatory cytokines and chemokines by these cells [19].

In light of this understanding of the mechanisms through which Vitamin D mitigates the risks of infection, it is worthwhile to examine the evidence supporting Vitamin D's role in reducing the risk of infectious diseases. In addition to tuberculosis, Vitamin D is known to protect against several bacterial diseases. One well-studied example is the prevention of dental caries due to the activity of oral bacteria. Studies conducted in the 1930s–1950s found that young people residing in sunnier areas in the United States had fewer dental caries compared to those living in less sunny regions [21].

The potential of Vitamin D to reduce the risk of acute respiratory infections has been a focal point of several recent studies. An investigation in Connecticut found that individuals with levels of 38 ng/ mL or higher were associated with a significant ($p<0.0001$) twofold reduction in the risk of developing acute respiratory tract infections and a marked decrease in the number of sick days [22].

In a supplementation study conducted in Sweden, involving 140 patients with recurrent respiratory tract infections (RTIs) using 4000 IU/day of Vitamin D3, participants in the supplementation group elevated their serum 25(OH)D level to 53 ng/mL, whereas those in the placebo group had 25(OH) D levels of 27 ng/mL [23]. Those taking Vitamin D3 experienced a 23% reduction in RTIs (95% confidence interval, 1–40%) and a 50% decrease in the number of days requiring antibiotics. There is mounting evidence supporting the notion that Vitamin D reduces the risk of sepsis [24]. Although the effects of Vitamin D have predominantly been observed in bacterial diseases, some reports have indicated benefits in viral infections such as influenza, HIV, and hepatitis C [25]. Furthermore, there is robust evidence that Vitamin D confers protection against autoimmune diseases, including multiple sclerosis, where Epstein Barr virus represents a significant risk factor [26].

In conclusion, it is apparent that Vitamin D may play an instrumental role in immune system homeostasis, offering protection against autoimmune diseases and lowering the risk of infections. Therefore, the routine prescription of Vitamin D in these conditions is highly recommended [19].

Functions of Vitamin D in Innate Immunity

Vitamin D has garnered considerable attention in recent years due to its unexpected and profound impact on the regulation of immune responses. Both in vivo and in vitro experimental studies have unveiled Vitamin D's influence on immune responses mediated by key innate immune cells, such as macrophages and dendritic cells (DCs) [16].

Mechanisms by Which 1, 25(OH)2D May Regulate Immune Cell Function

There is a general consensus that all types of immune cells are capable of responding to 1, 25(OH)2D. This discovery is grounded in the recognition of cell expression of the Vitamin D receptor (VDR), the identification of various essential 1, 25(OH)2D target genes in immune cells, and the revelation that many immune cells (including macrophages, DCs, T and B lymphocytes) possess the ability to convert 25(OH)D into 1,25(OH)2D through cytochrome P450 family 27 subfamily B member 1 (CYP 27B1). The quantity of 1, 25(OH)2D generated may depend on the immune cells' capacity to express CYP27B1 and other enzymatic components of the Vitamin D pathway, including the CYP24A1 deactivation enzyme. For example, in vitro studies have shown that stimulated macrophages produce more 1,25(OH)2D than DCs. DCs exhibit truncated CYP27B1 transcripts, resulting in lower CYP27B 1 protein levels, and express elevated levels of CYP24A1 mRNA [27]. Nevertheless, despite in vitro studies reporting significant biological effects of 1, 25(OH)2D on immune cells (often under ideal conditions using potentially supra-physiological concentrations of 1, 25(OH)2D), questions linger regarding the actual in vivo biological effects of 1,25(OH)2D.

Exposing differentiating DCs to 1, 25(OH)2D hinders their full maturation [28]. However, debates persist concerning the properties of these "tolerogenic" DCs and their ability to interfere with T cell division and the development and expansion of regulatory T cells (TRegs) [29]. Lymphocytes may also directly respond to 1, 25(OH)2D. Naïve T cells (Th0 cells) express low levels of the VDR, which is upregulated upon antigen-specific activation of T cell receptors, contributing to the education of naïve cells. Since VDR expression can also inhibit the transcription of the IL-2 gene, this may represent another mechanism of immune regulation by 1, 25(OH)2D. Additionally, 1, 25(OH)2D may modify homing receptors on T cells [30].

It has been observed that 1, 25(OH)2D prevents the accumulation of inflammatory cells in the central nervous system. However, 1, 25(OH)2D does not influence the activation of pathogenic interferon-g and IL-17-producing T cells in lymph nodes, spleen, or the immunization site. In essence, the robust primary immune response to myelin oligodendrocyte glycoprotein remains unaltered [31].

Circulating levels of 1, 25(OH)2D are significantly lower than those of 25(OH)D and are insufficient for immune regulation. It is generally recommended that 25(OH)D be converted locally to sufficient levels of 1,25(OH)2D to achieve biological activity. Recent research has identified mast cells, along with macrophages, DCs, and T and B lymphocytes, as capable of expressing CYP27B1 for local 1, 25(OH)2D production. Nevertheless, the level of Vitamin D binding protein (VDBP) and its affinity for 25(OH)D can also restrict the availability of 25(OH)D to DCs and potentially other cells. Studies involving individuals with various VDBP variants have shown that those with the high-affinity 25(OH)D binding variant experience limited availability of 25(OH)D to DCs, resulting in reduced interactions between dendritic cells and T cells [32].

The Role of Vitamin D in Autoimmune Disease

Although the precise etiology of autoimmunity remains largely unknown, the prevailing hypothesis suggests that both genetic susceptibility and environmental factors play a role in the development of clinical diseases. Both experimental observations and clinical investigations suggest a significant role for Vitamin D as a modifiable environmental factor in autoimmune diseases [33]. Vitamin D exerts well-documented immunomodulatory effects on a wide range of immune cells, including T lymphocytes, B lymphocytes, and DCs [34]. Each of these immune cell types expresses VDR and produces the enzymes 1a-OHase and 24-hydroxylase, which are capable of locally generating active 1, 25(OH)2D [35]. The autocrine and paracrine actions of 1, 25(OH)2D are subject to tight immune system regulation and depend on an adequate supply of circulating 25(OH)D, underscoring the critical importance of addressing Vitamin D deficiency for immune system health.

Specific Impacts on T and B Cells

Activation of CD4+ T cells leads to a five-fold increase in VDR expression, enabling the regulation of no fewer than 102 recognized genes responsive to 1,25(OH)2D [36]. 1, 25(OH)2D suppresses T cell receptor-induced T cell proliferation and alters their cytokine expression profile. The overall shift is away from a T helper (Th)1 phenotype towards a more tolerogenic Th2 phenotype. Exposure to 1, 25(OH)2D reduces the production of IFN? and IL-2 by T cells while increasing IL-5 and IL-10, indicating a shift towards a Th2 response. The production of the Th2 cytokine IL-4 is upregulated by 1, 25(OH)2D in most cases, though not all. Vitamin D appears to directly inhibit Th1 cells and may additionally promote a shift towards a Th2 response through its inhibitory effects on IL-12 [37].

Th17 cells represent a specialized subgroup of CD4+ T cells deeply involved in organ-specific autoimmunity, playing a critical role in sustaining inflammation that can ultimately lead to tissue damage. In animal models of autoimmune conditions like uveitis and inflammatory bowel disease, 1, 25(OH)2D effectively dampens autoimmunity and curbs tissue destruction by inhibiting Th 17 response at multiple levels. This includes its capacity to interfere with dendritic cells' support for the maturation of Th17 cells and the ability of Th17 cells themselves to produce IL-17. Vitamin D also exerts control over the expression of IL-6, a cytokine that triggers Th17 cell generation, and it suppresses the production of IL-12p70, IL-23p19, IL-6, and IL-17. Furthermore, beyond its influence on CD4+ cells, Vitamin D aids in the recruitment of Foxp3+ TRegs, and a direct correlation exists between serum 25(OH)D levels and the capacity of T regulatory cells to restrain T cell proliferation. In essence, the body of evidence strongly supports the pivotal role of Vitamin D in modulating T cell responses and in mitigating inflammation and tissue damage.

Vitamin D also has a direct impact on B cells, effectively suppressing immunoglobulin production. Additionally, when exposed to 1, 25(OH)2D in vitro, the differentiation of B lymphocytes is disrupted, as demonstrated in the study conducted by Chen *et al*. [35]. Peripheral blood mononuclear cells (PBMCs) from patients with systemic lupus erythematosus (SLE) are particularly sensitive to the effects of Vitamin D. The addition of 1, 25(OH)2D to SLE PBMCs leads to a significant reduction in both spontaneous polyclonal antibody production and the generation of pathogenic anti-dsDNA autoantibodies by SLE B cells [20].

Vitamin D and Autoimmune Disease

Several animal models of autoimmunity have shown that the administration of either 1, 25(OH)2D3 or one of its analogs

can either prevent or ameliorate the disease. These animal models encompass autoimmune conditions like encephalomyelitis, collagen-induced arthritis, type-1 diabetes mellitus, inflammatory bowel disease, autoimmune uveitis, and lupus. These studies underscore the efficacy of hormonally active Vitamin D in modulating immune function and positively impacting autoimmune diseases.

Vitamin D deficiency stands as a significant risk factor in the development of various autoimmune diseases. Many clinical studies assess Vitamin D status primarily through dietary questionnaires, which represent an imperfect surrogate measure and often fail to consider sun exposure and skin pigmentation [39]. This limitation becomes especially apparent in recent studies due to increased awareness of skin cancer, resulting in greater overall sunscreen usage and sun avoidance. These methodological challenges help explain some of the inconsistencies observed in large epidemiological studies examining the relationship between Vitamin D intake and the incidence of rheumatoid arthritis.

Optimal Levels of 25-Hydroxy vitamin D

Clearly, 1, 25(OH)2D has physiological effects extending beyond those related to bone and mineral homeostasis. The alarming global prevalence of Vitamin D deficiency appears to contribute to immunemediated diseases. Based on bone-related markers such as intact PTH, calcium absorption, and bone mineral density, maintaining a 25(OH)D level of no less than 32 ng/ml appears sufficient. However, forthcoming studies aimed at determining whether similar levels are indeed necessary for optimal immune health remain ongoing. It is possible that higher thresholds of 25(OH)D will be required, and a more comprehensive understanding is likely to emerge as research progresses.

Conclusion

As delineated comprehensively in this paper, it becomes evident that 25(OH)VitD and 1, 25(OH)2VitD transcend their roles as mere participants within the autoimmune system. This unequivocally underscores that the cellular components of both arms of the immune system not only serve as targets for the active form of Vitamin D but also actively partake in the regulation of circulating 25(OH)VitD, engaging in intricate intracranial and paracrine interactions, all in addition to the well-established endocrine pathway.

Recent revelations have brought to light the robust immunomodulatory capabilities of Vitamin D, exerting significant influence on both innate and adaptive immunity. While Vitamin D bolsters innate immunity against "high-affinity" external antigens, it concurrently exerts a tempering effect on the processing of "low-affinity" self-antigens. While the precise mechanisms are still unfolding, it is imperative not to underestimate the pivotal role of Vitamin D in maintaining immune equilibrium.

To deepen our understanding of its therapeutic potential, interventional studies aimed at further elucidating the immunomodulatory effects of Vitamin D in humans should be diligently pursued.

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