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Immunomodulatory Effects of Vitamin D: Bridging Cellular Defense and Inflammatory Control

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Abstract

Vitamin D, an evolutionarily conserved molecule essential for diverse life forms ranging from phytoplankton to mammals, plays a critical role in health beyond its classical functions. It promotes osteoclast differentiation indirectly via receptor activator of nuclear factor κB (RANKL) upregulation, facilitating intestinal calcium absorption, promoting renal calcium reabsorption, and stimulating the mineralization of the bone collagen matrix, thereby regulating calcium and bone homeostasis. Significantly, immune cells, including B lymphocytes, T lymphocytes, and antigen presenting cells express the vitamin D receptor (VDR) and possess the enzymatic to activate vitamin D. This locally produced vitamin D exert autocrine and paracrine immunomodulatory effects. Adequate vitamin D status influences both innate and adaptive immune responses, while deficiency is epidemiologically associated with increased susceptibility to infection and heightened risk of autoimmunity. Consequently, the immunomodulatory benefits of vitamin D supplementation in deficient individuals with autoimmune diseases extend beyond the regulation of calcium and bone metabolism.

Keywords Vitamin D, immune system, bone health, calcium absorption, autoimmunity

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List of abbreviations: DBP = Vitamin D-binding protein, IBD = Inflammatory bowel disease, IL = Interleukin, LPS = Lipopolysaccharide, LTA = Lipoteichoic acid, MHC-II = Major histocompatibility complex class II, MS = Multiple sclerosis, PTH = Parathyroid hormone, RA = Rheumatoid arthritis, SLE = systemic lupus erythematosus, TLR2 = Toll-like receptor 2, TNFα = Tumor necrosis factor alpha, UVB = Ultraviolet B, VDD = Vitamin D deficiency, VDR = Vitamin D, VDRE = Vitamin D response element, RXR = Retinoid X receptors

Introduction

The immune system achieves a critical balance between self-tolerance and defense against pathogenic microorganisms [(1)]. Research increasingly indicates that vitamin D deficiency significantly impacts immune function. Specifically, in genetically predisposed individuals, vitamin D insufficiency is associated with a heightened predisposition to autoimmune dysregulation and increased susceptibility to infections [(2)].

Vitamin D is obtained either through dietary intake or endogenous synthesis in the skin. The primary source is the photo conversion of 7-dehydrocholesterol within epidermal keratinocytes upon exposure to ultraviolet B (UVB) radiation (wavelength 280–320 nm), yielding vitamin D3 (cholecalciferol) [(3)]. Key factors modulating cutaneous vitamin D3 synthesis include latitude, season, sunscreen use, and skin melanin content, as melanin absorbs UVB photons, reducing precursor conversion efficiency [(4)].

This initial vitamin D form undergoes hepatic hydroxylation by 25-hydroxylase to form 25hydroxyvitamin D3 [25(OH)D3] (calcidiol) [(5)].

Circulating 25(OH)D3 concentration represents the most reliable clinical indicator of vitamin D status. This precursor is subsequently activated primarily in the kidneys by the mitochondrial enzyme 1α-hydroxylase (CYP27B1), whose activity is stimulated by parathyroid hormone (PTH), to produce the biologically active hormone 1,25-dihydroxyvitamin D3 [1,25(OH)2D3] (calcitriol). Conversely, 24-hydroxylase (CYP24A1) catalyzes the conversion of both 25(OH)D3 and 1,25(OH)2D3 into inactive metabolites, such as 1,24,25-trihydroxyvitamin D3 (6).

A tightly regulated negative feedback loop governs circulating 1,25(OH)2D3 levels. Elevated 1,25(OH)2D3 suppresses its synthesis by inhibiting renal CYP27B1 activity while simultaneously inducing CYP24A1 expression, thereby promoting catabolism and preventing excessive vitamin D signaling (7) (Figure 1).

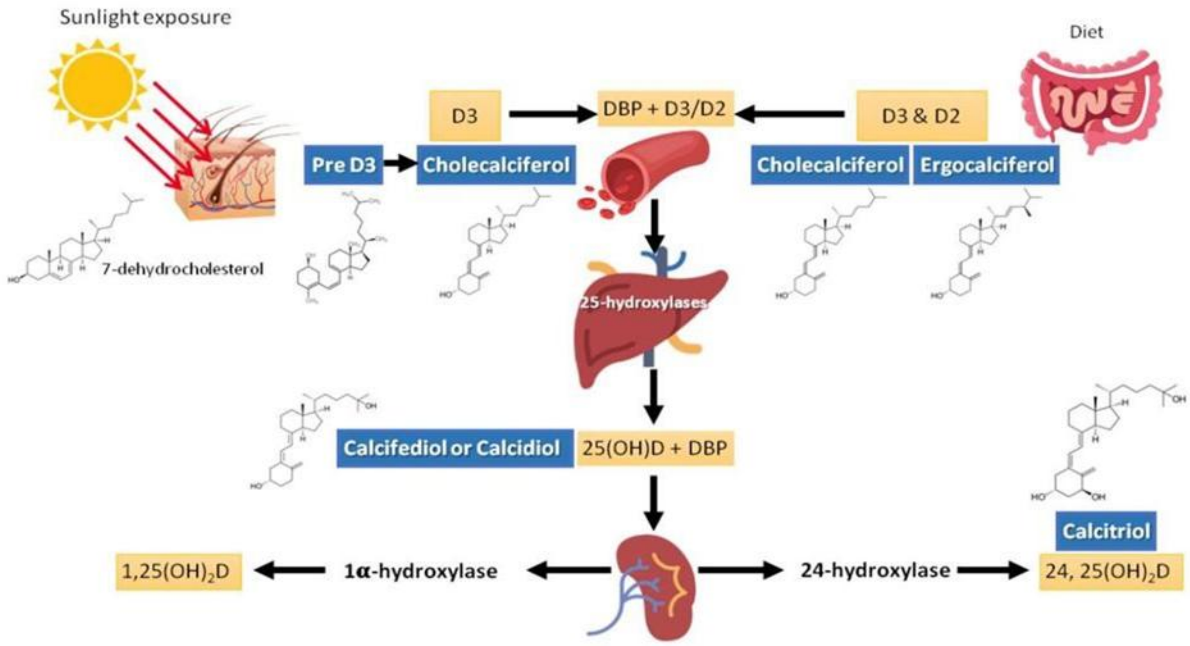

Figure 1. The metabolic pathway of vitamin D (6)

The physiological effects of 1,25(OH)2D3 on target tissues, such as promoting intestinal calcium absorption and osteoblast-mediated bone matrix mineralization, are mediated by its binding to the nuclear vitamin D receptor (VDR). The ligand-bound VDR heterodimerizes with the retinoid X receptor (RXR). This VDR-RXR complex translocate to the nucleus, binds to specific vitamin D response element (VDRE) in the promoter regions of target genes, and modulates their transcriptional activity (8).

The "critical balance between self-tolerance and defense against pathogenic microorganisms." While vitamin D's role in this balance is stated, the mechanism by which it achieves this is not fully elaborated. A critical analysis could delve into:

- How 1,25(OH)2D3 influences different immune cell types (T cells, B cells, macrophages, dendritic cells) to promote tolerance or enhance antimicrobial responses. For example, its known role in promoting regulatory T cells (Tregs) and suppressing T helper (Th) 1/Th17 responses could be discussed in the context of autoimmunity, while its ability to enhance innate immune responses (e.g., cathelicidin production) could be linked to infection defense.

- The specific molecular pathways beyond VDR binding through which vitamin D modulates immune cell function.

Vitamin D is a secosteroid hormone with increasingly recognized therapeutic potential [9]. Vitamin D deficiency (VDD) is now acknowledged as a significant global health concern, driven by heightened awareness of its critical role in maintaining overall health. The primary etiology of VDD is inadequate sunlight exposure. The biological actions of 1,25(OH)2D3 are mediated by the VDR, a nuclear receptor belonging to the steroid hormone receptor superfamily. Ligand-bound VDR regulates gene expression to maintain calcium homeostasis and influences diverse biological processes [10].

Despite established roles in musculoskeletal health, mental health, and reducing the risk of chronic diseases (including cancer, autoimmune disorders, type 2 diabetes mellitus, neurocognitive disorders, and certain infectious diseases) and overall mortality, the precise mechanisms by which vitamin D and its metabolites contribute to gastric homeostasis remain incompletely understood. Consequently, optimizing vitamin D status represents a significant global public health objective, while further research is required to elucidate its specific functions within the gastrointestinal system [11].

The biological activity of vitamin D within a specific cell is contingent upon three key factors: the local metabolic generation or availability of the active ligand 1,25(OH)2D3, adequate expression levels of both the VDR and its RXR co-receptor protein, and cell-specific transcriptional programming that directs the regulation of genes encoding proteins responsible for mediating vitamin D effects [12]. Beyond its well-established roles in intestinal and skeletal tissues, VDR expression is also detected in diverse cell types, including those within the brain, bone marrow, colon, and malignant cells. This widespread distribution suggests physiological functions for vitamin D extending beyond calcium and bone homeostasis [13]. Furthermore, extra renal tissues possess the capacity for local 1,25(OH)2D3 synthesis, as they express the enzyme 1α-hydroxylase (CYP27B1), enabling the conversion of circulating 25-hydroxyvitamin D (25D) to active 1,25(OH)2D3 [14].

Consequently, vitamin D signaling may function not only systemically (endocrine) but also locally via autocrine or paracrine mechanisms [15]. Previous research has mentioned several non-classical actions of 1,25(OH)2D3, including modulation of cellular differentiation and proliferation, as well as significant immunomodulatory effects. These immunologic functions contribute to the maintenance of self-tolerance and the promotion of protective immune responses [16]. Key immune cells, such as T lymphocytes, B lymphocytes, and antigen-presenting cells, possess the necessary molecular machinery for both synthesizing and responding to 1,25(OH)2D3 [14]. Critically, the regulation of enzymes responsible for synthesizing (CYP27B1) and inactivating (e.g., CYP24A1) vitamin D metabolites differs substantially in peripheral tissues compared to the kidney. This differential regulation can lead to local tissue concentrations of 1,25(OH)2D3 that diverge significantly from systemic circulating levels. Unlike renal CYP27B1, the extra renal 1α-hydroxylase activity, particularly in macrophages, is not regulated by PTH [17].

Vitamin D and immune defense

Research indicates that vitamin D significantly modulates inflammatory and immune responses by inhibiting pro-inflammatory cell (Th1 and Th17) proliferation and regulating inflammatory cytokine production, processes central to the pathogenesis of inflammatory diseases [18]. Epidemiological studies consistently associate hypovitaminosis D with an elevated risk of acute infections and poorer clinical outcomes; conversely, vitamin D supplementation appears to enhance clinical responses during acute infection [19].

Beyond acute infection, lower vitamin D status is frequently observed in chronic inflammatory conditions, including asthma, inflammatory bowel disease, chronic kidney disease, and cardiovascular disease associated with atherosclerosis [20]. A key mechanism underpinning vitamin D's role in innate immunity against intracellular pathogens involves the induction of the antimicrobial peptide cathelicidin (LL37) [16]. Cathelicidin acts not only by directly binding and neutralizing diverse pathogens but also by facilitating vitamin D-mediated inflammatory processes during infection [13]. This antimicrobial function historically informed therapeutic strategies; prior to potent antibiotics, heliotherapy (sunlight exposure) in sanitariums and administration of vitamin D-rich cod liver oil were employed as treatments for tuberculosis (TB), leveraging sunlight-induced cutaneous vitamin D synthesis [21].

At the molecular level, VDR expression is documented in macrophages, critical innate immune cells. Activation of the toll-like receptor 2/1 (TLR2/1) heterodimer in human macrophages by *Mycobacterium tuberculosis* triggers the upregulation of both VDR and the 1α-hydroxylase enzyme CYP27B1. This cascade induces cathelicidin expression, leading to intracellular mycobacterial growth inhibition. Interleukin-15 (IL-15) links this vitamin D-dependent antimicrobial pathway to TLR2/1-induced macrophage differentiation [22].

Studies on the intracrine vitamin D pathway in monocytes revealed that enhancing the precursor 25(OH)D3 level boosts bacterial killing, suggesting that innate immune responses in monocytes are sensitive to subtle fluctuations in vitamin D status [23]. Other research has expanded this model, demonstrating that vitamin D's immune activity in monocytes involves mechanisms beyond LL37 induction. For instance, VDREs are present in the promoter region of the gene encoding the antimicrobial peptide β-defensin-2 (DEFB4/HBD2) [24].

Vitamin D metabolites elicit antibacterial activity not only in monocytes and macrophages but also in other cell types. Induction of LL-37 by vitamin D has been reported in placental trophoblasts, bronchial epithelial cells, and decidual myeloid cell lines. However, this response is not ubiquitous, and the underlying mechanisms may vary. For example, human keratinocytes exhibit reduced responsiveness to pathogen recognition receptor (PRR) ligands like TLR2 agonists, correlating with lower TLR-2 expression and consequently diminished IL-37 induction by vitamin D [25].

Vitamin D and autoimmune disease

Vitamin D plays a critical role in calcium and phosphate homeostasis and bone metabolism. Beyond its classical functions, the hormonally active metabolite 1,25(OH)2D3 exhibits significant immunomodulatory effects, influencing both innate and adaptive immunity, as well as endothelial membrane stability [26]. Epidemiologic studies consistently associate lower serum concentrations of 25(OH)D3 with an increased risk of immune related disorders, including multiple sclerosis (MS), autoimmune diseases, psoriasis, and type 1 diabetes mellitus [27]. Consequently, numerous clinical trials have investigated the therapeutic efficacy of vitamin D and its metabolites as supplements for managing these conditions, yielding variable outcomes [28,29].

This mechanistic basis supports the observed associations between vitamin D status and several autoimmune conditions, including MS, rheumatoid arthritis (RA), Crohn's disease, and juvenile-onset diabetes mellitus [30]. Although the immunomodulatory properties of vitamin D have been recognized for over two decades, its broader significance in human physiology is increasingly appreciated. This shift in perspective stems from two key factors: accumulating evidence linking vitamin D deficiency to prevalent immune disorders and a strengthening understanding of the molecular connections between vitamin D signaling and immune system regulation [31].

A growing body of epidemiologic evidence suggests a link between vitamin D deficiency and the incidence or severity of autoimmune diseases, including type 1 diabetes mellitus, MS, inflammatory bowel disease (IBD), and systemic lupus erythematosus (SLE) [32]. Notably, vitamin D deficiency is more prevalent in RA patients compared to the general population, although the causal direction (deficiency contributing to disease vs. disease causing deficiency) remains unclear [33]. Nevertheless, observational data, such as food frequency questionnaires, indicate that higher dietary vitamin D intake correlates with a reduced risk of developing RA. Genetic analyses further implicate vitamin D in autoimmunity; polymorphic variations in genes encoding components of the vitamin D metabolic and signaling pathways (e.g., certain VDR gene haplotypes) appear to confer protection against type 1 diabetes mellitus [34].

Serum levels of 25(OH)D3, the inactive precursor, demonstrate seasonal variation, reaching nadirs during winter months [21]. These levels inversely correlate with markers of immune system activation and with the prevalence and severity of autoimmune rheumatic diseases, such as MS, SLE, and RA [32]. Given that low serum 25(OH)D3 concentrations are recognized as a risk factor for these conditions, vitamin D3 supplementation is proposed to improve disease prognosis. Long-term supplementation may also potentially reduce the risk of developing RA [19]. Lower serum vitamin D levels are associated with MS and RA and may potentially predict future autoimmune disease onset [35]. Evidence also suggests that reduced prenatal vitamin D exposure, reflected by lower maternal intake during pregnancy, is associated with an increased risk of pancreatic islet cell autoimmunity in offspring of mothers at risk for autoimmune diabetes [36].

Furthermore, vitamin D deficiency is implicated in autoimmune gastrointestinal disorders, notably Crohn's disease, a major form of IBD. Experimental models, including murine inflammatory bowel disease, are utilized to investigate the mechanistic role of vitamin D in regulating immune responses within the gut [37].

Function of vitamin D in immunology

Over the past three decades, research has revealed a significant immunomodulatory role for the biologically active metabolite of vitamin D, 1,25(OH)2D3, extending beyond its classical function in calcium and bone homeostasis. Initial observations in 1983 identified macrophages as contributors to vitamin D metabolism and detected the VDR within activated human inflammatory cells. Subsequent findings in 1984 suggested that 1,25(OH)2D3 could inhibit T lymphocyte proliferation [38]. Evidence now robustly supports the involvement of vitamin D signaling in immune regulation.

1,25(OH)2D3 exerts diverse effects on immune cell populations. It suppresses B lymphocyte proliferation, differentiation, and immunoglobulin production. Furthermore, 1,25(OH)2D3 modulates T cell responses by inhibiting proliferation and shifting polarization away from the pro-inflammatory Th1 phenotype towards the Th2 phenotype [39]. It also promotes the induction of Tregs and inhibits the development of inflammatory Th17 cells. Collectively, these actions lead to an increased production of anti-inflammatory cytokines, such as IL-10, while reducing levels of proinflammatory cytokines like IL-17 and IL-21[35].

1,25(OH)2D3 also significantly influences antigen-presenting cells. It attenuates monocyte production of inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), IL-1, IL-6, IL-8, and IL-12 [40]. Additionally, 1,25(OH)2D3 inhibits dendritic cell differentiation and maturation, promoting retention of an immature phenotype characterized by reduced surface expression of major histocompatibility complex class II (MHC-II) molecules, decreased IL-12 production, and diminished expression of costimulatory molecules, as illustrated in figure (2) [41].

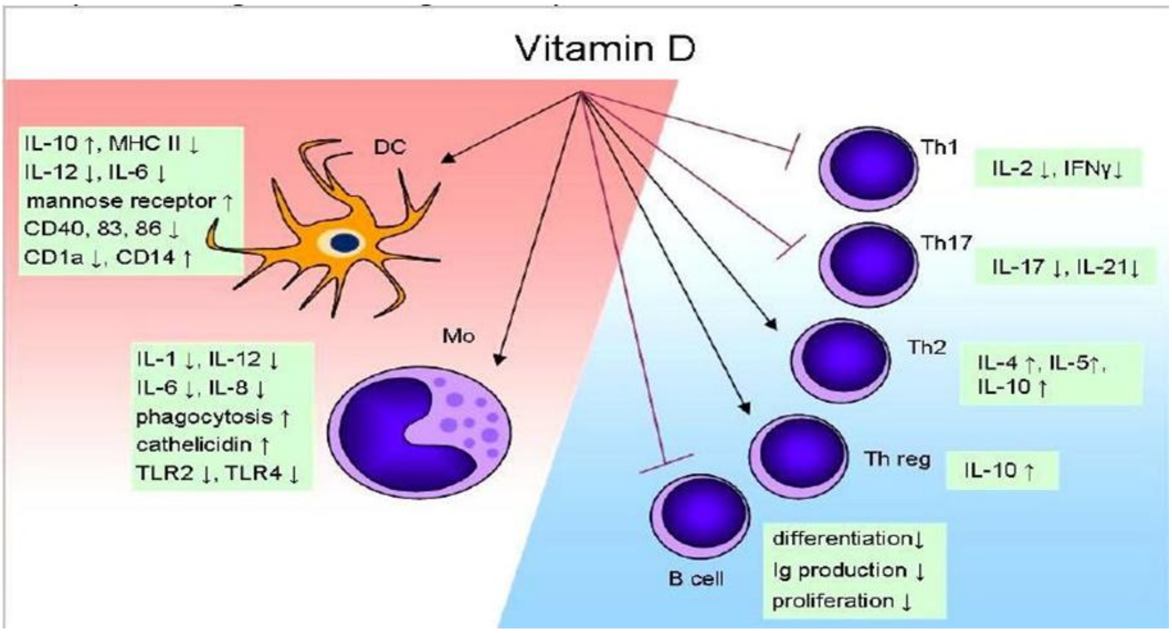

Figure 2. Immunomodulatory effects of vitamin D [41]

Vitamin D has immunomodulatory effects by either directly binding to vitamin D responsive elements in the promoters of cytokines' genes or regulating nuclear transcription factors. It also inhibits expression of pro-inflammatory cytokines (IL-1, IL-6, TNF-α, IL-8, IL-12, and interferon) in monocytes [23].

Vitamin D exerts significant immunomodulatory effects, particularly on lymphocyte regulation. Microarray analyses have demonstrated that the active vitamin D metabolite, 1,25(OH)2D3, inhibits T cell proliferation and induces VDR overexpression in activated $CD4^+$ T cells [40]. Furthermore, 1,25(OH)2D3 modulates the expression of at least 102 genes within $CD4^+$ T cells, upregulating 45 and downregulating 57 [42]. Identified target genes include regulators of nuclear factor-Kappa B (NFκB), the IL-2 receptor β chain gene, and the Immunoglobulin E binding factor gene [40]. 1,25(OH)2D3 also suppresses the production of IL-2 and interferon-gamma (IFN-γ) by $CD4^+$ T cells, thereby inhibiting antigen presentation and subsequent T cell recruitment [43].

Given the frequent association of severe vitamin D deficiency with autoimmune disorders, its critical role in immune function, and the correlation between deficiency and increased disease activity, understanding the responsiveness of immune components within these diseases to vitamin D is essential [44].

For instance, in SLE, vitamin D partially corrects B cell abnormalities; pre-incubation of B cells from active SLE patients with 1,25(OH)2D3 significantly reduces both spontaneous and stimulated immunoglobulin production. This preincubation also markedly decreases the spontaneous production of anti-double-stranded DNA (anti-dsDNA) antibodies by approximately 60% [45].

In MS, vitamin D Impacts T cell function. Pre-incubation with increasing concentrations of vitamin D inhibits stimulated $CD4^+$ T cell proliferation in both MS patients and healthy controls. Furthermore, incubation with vitamin D reduces the production of IL-17 and IFN-γ by Th17 polarized T cells derived from MS patients and controls [46].

Vitamin D also modulates monocyte function, suppressing the production of pro-inflammatory cytokines TNF-α and IL-1 [47]. Monocytes from individuals with autoimmune diabetes mellitus and healthy controls exhibit significantly reduced cytokine production when exposed to vitamin D. Additionally, vitamin D exposure inhibits Toll-like receptor 4 (TLR4) activation triggered by lipopolysaccharide (LPS) or lipoteichoic acid (LTA) [48].

Vitamin D exhibits a wide range of effects on various immune cells, including B cells (reducing anti-DNA antibody production), T cells (inhibiting proliferation, decreasing Th17 cytokines like IL-17 and IFN-γ), and monocytes (reducing TNF-α and IL-1, inhibiting TLR4 stimulation). This suggests a generalized dampening of inflammatory and autoimmune responses. The consistent observation of Vitamin D's effects in conditions like MS and autoimmune diabetes mellitus underscores its potential therapeutic utility in these diseases. The mention of inhibiting TLR4 stimulation points to a potential mechanism by which Vitamin D modulates innate immune responses to bacterial components LPS (lipopolysaccharide) and LTA (lipoteichoic acid). According to therapeutic potential in autoimmune diseases, vitamin D3 is given its ability to reduce autoantibody production, inhibit pathogenic T cell responses (Th17), and suppress inflammatory cytokine production, Vitamin D supplementation or pharmacotherapy could be a valuable adjunctive or primary treatment strategy for autoimmune diseases. Also, the varying responses to vitamin D concentrations (e.g., in CD4 cell proliferation) suggest that optimal dosing might need to be individualized based on disease state, patient characteristics, and specific immunological targets [45].

There are no explicit contradictions, all the findings presented point towards vitamin D having an immunosuppressive and anti-inflammatory role across various immune cell types and in different autoimmune contexts.

In conclusion, beyond its established roles in calcium and bone homeostasis, vitamin D is a crucial regulator of both innate and adaptive immune responses. A deficiency in vitamin D is a common feature in autoimmune diseases. Immune cells possess the capability to both produce and respond to the active vitamin D metabolite. The observed beneficial effects of vitamin D on immune cell function in autoimmune contexts suggest that vitamin D supplementation may offer therapeutic benefits extending beyond the maintenance of skeletal health and calcium balance in these patients .

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