

Vitamin D and the immune system: a comprehensive mini-review

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ABSTRACT

Vitamin D is classically recognized as a regulator of calcium and phosphate metabolism. It has also emerged as a crucial immunomodulator. Both innate and adaptive immune cells express the vitamin D receptor and possess the enzymatic machinery necessary to convert vitamin D into its biologically active form. Through genomic and rapid non-genomic actions, vitamin D can modulate antimicrobial peptide expression and cytokine secretion, and regulate epithelial and endothelial barrier integrity, thereby strengthening the first line of defense against external agents. In adaptive immunity, calcitriol promotes a shift toward a more tolerogenic phenotype by suppressing Th1/Th17 and B cell activity while promoting Th2 and regulatory T cell responses, thereby reducing the production of autoantibodies and ultimately limiting autoimmune responses. Epidemiological studies consistently associate vitamin D deficiency with increased susceptibility to infections, including respiratory tract diseases and sepsis, as well as autoimmune disorders such as multiple sclerosis, rheumatoid arthritis, and systemic lupus erythematosus. Although clinical trial results remain heterogeneous, maintaining 25(OH)D₃ serum levels above 30–50 ng/mL is essential for sustaining optimal immune system function. Given the high global prevalence of vitamin D insufficiency, strategies such as safe sun exposure, dietary fortification, and supplementation represent cost-effective interventions. Further mechanistic and clinical research is needed to elucidate the molecular basis of the immunomodulatory properties of vitamin D and to define optimal dosing and therapeutic applications in immune-related disorders.

KEYWORDS

Vitamin D3, immune system, innate immunity, adaptive immunity.

Introduction

Vitamin D deficiency is increasingly recognized as a major global public health problem. It has been estimated that more than half of the population have insufficient levels of vitamin D, especially during the darker months of the year when sunlight exposure is limited^[1]. Historically, the role of vitamin D has been understood primarily in the regulation of calcium homeostasis and phosphate metabolism, and it is essential in the prevention of defects of skeletal bone mineralization, such as rickets in children and osteomalacia in adults^[2–4].

The immune system defends against infectious agents and prevents excessive reactions that could lead to autoimmune diseases, maintaining a critical balance between the two functions. Vitamin D has recently been demonstrated to play a key role in this context by regulating the expression of genes involved in cellular homeostasis, differentiation, and innate and adaptive immune responses^[5]. Moreover, it has been shown to enhance antimicrobial peptide production, stabilize physical barriers, modulate T cell responses, and suppress excessive inflammation. Accordingly, as suggested by a growing body of evidence, vitamin D has a well-established role in musculoskeletal health, but its deficiency may represent a risk factor for immune dysfunction.

Article history

Received 26 Sep 2025 – Accepted 22 Oct 2025

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Vitamin D metabolism and genomic and non-genomic effects

The classical vitamin D metabolism pathway begins with either dietary intake or synthesis in the skin from 7-dehydrocholesterol in response to exposure to ultraviolet B radiation. Once produced as vitamin D₃ (cholecalciferol), it is transported to the liver where it undergoes a hydroxylation at position 25 by the enzyme 25-hydroxylase (CYP2R1) to form 25(OH)D₃ (calcifediol), which is the major circulating form and the most clinically useful marker of vitamin D status. In the kidneys, this compound is then further hydroxylated by the enzyme 1 α -hydroxylase (CYP27B1) to produce the biologically active form 1,25(OH)₂D₃, also known as calcitriol^[6].

Interestingly, the enzymatic machinery essential to convert calcifediol into calcitriol is present not only in proximal tubular cells but also in immune system cells, such as macrophages and dendritic cells, where it mediates the autocrine and paracrine

effects of vitamin D on the innate immune system, as well as on cell maturation and differentiation [7].

Vitamin D exerts its actions through binding to the vitamin D receptor (VDR), which can associate with the retinoid X receptor (RXR) to form a VDR:RXR heterodimer. This complex, in turn, binds to specific regions of DNA (repeated sequences typically positioned in the promoter region and known as vitamin D response elements), thereby modulating the expression of hundreds of genes involved in the regulation of calcium homeostasis, the immune response, inflammation, and barrier function [8-10].

It is now well established that vitamin D not only mediates classical genomic effects through the regulation of gene transcription but also elicits rapid non-genomic actions [11], which in turn help explain the wide spectrum of biological activities attributed to this secosteroid hormone. A peculiar characteristic of these actions is their extremely rapid nature; their occurrence within seconds to minutes clearly discriminates them from the slower genomic responses, which generally take hours to days to produce noticeable effects [12]. Furthermore, unlike genomic effects, non-genomic responses are not suppressed by pharmacological inhibitors of transcription and protein synthesis, such as actinomycin D and cycloheximide. Several studies suggest that the rapid non-transcriptional effects of $1,25(\text{OH})_2\text{D}_3$ may originate at the plasma membrane via a specific membrane-bound vitamin D receptor (mVDR) or through binding with a membrane-associated rapid response steroid-binding protein ($1,25(\text{OH})_2\text{D}_3$ -MARRS) [13-15]. It was subsequently hypothesized that, as a consequence of binding to protein disulfide isomerase family A member 3 (PDIA3), vitamin D is also able to promote the release of crucial secondary messengers (i.e., calcium and cAMP) and modulate several intracellular biological processes, such as the cell cycle, cell proliferation, and immune responses, via the sonic hedgehog (SSH), NF- κ B, wingless (WNT), and STAT1–3 signaling pathways [16].

Vitamin D and innate immunity

The innate immune system is the body's first line of defense following pathogen invasion. Vitamin D has been demonstrated to induce innate immune defenses by enhancing the production of antimicrobial peptides such as defensins and cathelicidin, pattern recognition receptors, and cytokines in cells. Antimicrobial peptides, produced by neutrophils, Paneth cells, intestinal epithelial cells, and monocytes/macrophages, are bacterial cell membrane-destabilizing molecules and constitute a particularly important defense mechanism against viral, fungal, and bacterial infections [17,18].

In addition to producing antimicrobial peptides, vitamin D has been recognized to preserve the integrity of epithelial and endothelial barriers through regulation of tight-junction gene expression [19]. By stabilizing tight junctions, this secosteroid hormone may reduce the risk of pathogen dissemination during infections, as in sepsis, where maintenance of vascular stability is crucial to prevent life-threatening complications.

Moreover, increased CYP27B1 expression in activated monocytes and macrophages during the onset of an infection

leads to conversion of calcifediol into the biologically active form of vitamin D, resulting in the reduction of pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor α , and interferon- γ (IFN- γ) [20]. In addition, calcitriol has been shown to upregulate IL-8 and IL-10, two cytokines with anti-inflammatory properties [21] that help prevent an excessive host immune response to pathogens, which can be harmful rather than affording protection against the infection itself [22].

Vitamin D and adaptive immunity

The effects mediated by T and B lymphocytes provide a plethora of protective mechanisms for responding to perturbations induced by pathogens and tissue damage, and they also play a pivotal role in inflammatory and autoimmune disorders. The responses mediated by these lymphocytes are collectively recognized as the core of adaptive immunity [23]. The adaptive immune system consists of cells, soluble mediators such as small peptides and proteins, and processes enabling identification of and, through specific receptors, responses to altered self-structures (e.g., tumor cells) and non-self-antigens (e.g., allergens and pathogens).

The biologically active form of vitamin D_3 has been demonstrated to inhibit synthesis of the pro-inflammatory cytokines IL-2 and IFN- γ , as well as T helper 1 (Th1)-mediated responses. Moreover, it increased production of T helper 2 (Th2) anti-inflammatory cytokines (such as IL-3, IL-4, IL-5, and IL-10), while decreasing production of T helper 22 (IL-22) and T helper 9 (IL-9) pro-inflammatory cytokines [24,25]. Overall, as demonstrated in both human and mouse models [26-29], calcitriol leads to suppression of acquired immune responses by inhibiting proliferation and differentiation into Th1 and Th17, instead promoting Th2 cell differentiation. This results in a more tolerogenic immune response, thereby limiting the manifestations of autoimmune diseases.

The biologically active form of vitamin D_3 has also been found to inhibit the proliferation and differentiation of B cells into memory and antibody-producing plasma cells, thus reducing their ability to produce antibodies. A reduced ability to produce immunoglobulins may have clinical relevance, given that the generation of autoantibodies represents a hallmark of autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis [30]. In this context, growing epidemiological evidence has revealed an association between vitamin D deficiency and the development and progression of autoimmune diseases [31].

This more tolerogenic immune response is further supported by the influence of vitamin D on dendritic cells, whose differentiation and maturation it suppresses. This effect is particularly important for promoting self-tolerance and thereby reducing the risk of autoimmunity [32].

Epidemiological and clinical evidence

Several epidemiological studies have found a positive correlation between vitamin D deficiency and increased risk of in-

fectious diseases^[33,34]. Individuals with serum 25(OH)D₃ levels below 30 ng/mL (75 nmol/l) have been shown to be more susceptible to respiratory tract diseases^[35]. This issue is particularly relevant in newborns, as demonstrated by Belderbos *et al.*^[36], who found that neonates with cord blood 25(OH)D₃ levels above 30 ng/ml had a lower risk of developing respiratory syncytial virus infection during the first year of life than those with levels below 20 ng/ml.

Randomized controlled trials evaluating vitamin D supplementation for the prevention of infectious diseases have yielded inconsistent results, largely due to the absence of standardized dosing regimens for these conditions and to considerable interindividual variability in the response to supplementation^[37]. This inconsistency across studies makes it difficult to clearly determine the effect of vitamin D supplementation on infections.

Over recent years, the role of vitamin D has also been extensively investigated as a potential adjunctive strategy for mitigating COVID-19-related symptoms through modulation of both adaptive and innate immune responses. Several studies have highlighted that maintaining sufficient vitamin D levels may be crucial for enhancing viral clearance as well as reducing harmful inflammatory processes that contribute to lung injury^[38]. However, the association between hypovitaminosis D (< 20 ng/mL) and COVID-19 outcomes remains under debate due to potential confounding factors.

Public health and therapeutic implications

Epidemiological evidence shows vitamin D deficiency to be a major global public health concern, with prevalence rates varying by season, region, and age. Overall, approximately 30–80% of individuals, including children and adults, have suboptimal vitamin D levels. Based on the definitions of vitamin D status by several health agencies, serum 25(OH)D₃ concentrations below 20 ng/mL are considered suboptimal for musculoskeletal health, increasing the risk of associated disorders, such as rickets, osteomalacia, and secondary hyperparathyroidism^[6]. The worldwide prevalence of individuals with serum vitamin D concentrations below 20 ng/mL and 30 ng/mL is 47% and 75%, respectively, with higher rates reported in eastern Mediterranean and high-latitude regions, and among females^[39]. In view of the high prevalence of vitamin D deficiency across the global population and its implications for immune health, strategies aimed at improving vitamin D status are essential, including lifestyle changes such as regular safe sun exposure and vitamin fortification of foods.

For individual supplementation, a daily vitamin D intake of 2000–5000 IU is considered safe and effective to maintain optimal serum 25(OH)D₃ levels^[40].

Toxicity is rare when vitamin D supplementation is within the recommended ranges; adverse effects, such as hypercalcemia, generally occur only with daily intakes exceeding 10,000 IU^[41].

In addition, some common genetic variants in genes involved in vitamin D metabolism and action have been associated with vitamin status, bioavailability and functions^[42,43]. Re-

cent studies further support the association between VDR gene polymorphisms and an increased risk of autoimmune disease^[44]. Thus, understanding the molecular mechanisms underlying vitamin D signaling may help clarify the role of the vitamin D axis in the pathogenesis of autoimmunity.

Conclusion

There is increasing evidence that vitamin D-related metabolic enzymes are expressed in virtually all cells involved in both the adaptive and the innate immune systems. In particular, vitamin D has been shown to play a multifaceted role through different mechanisms, including induction of an immunosuppressive phenotype in neutrophils, reduction of pro-inflammatory cytokine production by monocytes/macrophages, inhibition of dendritic cell differentiation and maturation, suppression of B cell proliferation and autoantibody production, and downregulation of Th1/Th17 cell-related pro-inflammatory cytokines, together with polarization of T cells toward a Th2 phenotype.

Overall, preclinical and clinical data suggest a strong association between vitamin D status and susceptibility to infectious and autoimmune diseases. This evidence supports the need for greater efforts to improve vitamin D status through supplementation, safe sun exposure, and food fortification programs, with the aim of reducing the burden of several immune-related disorders.

Further studies should focus on elucidating the novel signaling mechanisms induced by vitamin D, in order to provide a deeper understanding of the cellular and molecular processes through which vitamin D metabolites regulate immunity. Such insights could pave the way for the identification of specific mechanisms that may serve as novel therapeutic targets.

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