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Review Article

Extraskeletal Immunomodulatory Roles of Vitamin D in Treatment-Resistant Disease Syndromes

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Abstract

Vitamin D is traditionally recognized for its role in calcium homeostasis and skeletal integrity; however, growing evidence highlights its broader immunomodulatory functions. This literature review examines the extra-skeletal importance of vitamin D and synthesizes current findings linking deficiency with treatment-resistant or immune-mediated disease states. Vitamin D influences both innate and adaptive immune pathways through widespread vitamin D receptor (VDR) expression and local activation in immune and epithelial tissues. These mechanisms contribute to its emerging relevance in neurological autoimmune disorders, metabolic dysfunction, chronic inflammatory conditions, and steroid-resistant airway disease. Clinical and translational studies consistently demonstrate that vitamin D deficiency is associated with dysregulated cytokine activity, impaired host defense, reduced glucocorticoid responsiveness, and heightened autoimmunity. Taken together, current evidence underscores vitamin D's role as a vital immunologic cofactor and supports continued investigation into its therapeutic potential across a range of disease processes.

Keywords: *Vitamin D; Extraskeletal Immunomodulatory; Treatment-Resistant Disease Syndromes*

Introduction

The physiological role of vitamin D has traditionally been framed within the context of skeletal health, particularly in the prevention of rickets and osteomalacia. The widely accepted serum threshold of 30 ng/mL has therefore been oriented toward avoiding these musculoskeletal complications [1]. However, emerging evidence suggests that serum concentrations in the 40-60 ng/mL range may be necessary for vitamin D's full extra-skeletal functions, including its increasingly recognized role as an immunomodulatory hormone [2].

A growing number of studies have demonstrated associations between vitamin D deficiency and a variety of immune-mediated or treatment-resistant conditions, including reactive airway disease, multiple sclerosis, recurrent infections, insulin resistance, and diabetes mellitus. These findings underscore the importance of examining vitamin D not merely as a nutrient affecting bone metabolism, but as a hormone-like regulator influencing numerous immunological pathways.

This literature review aims to further explore these interactions by integrating pathophysiologic insights, relevant case studies, and current clinical evidence surrounding vitamin D deficiency and its downstream immunologic effects.

Mechanisms of vitamin D immunomodulation

Vitamin D exerts widespread effects on both innate and adaptive immunity, although the precise causal mechanisms linking deficiency with autoimmune disease or infection are still being elucidated. The vitamin D receptor (VDR) is expressed in nearly all nucleated cells, and approximately 3% of the human genome is regulated directly or indirectly by the active form of vitamin D, 1,25-dihydroxyvitamin D [3].

Importantly, at least ten extrarenal tissues possess 1-α-hydroxylase-the enzyme responsible for converting vitamin D into its active form-allowing local autocrine and paracrine hormone production. Autocrine signaling enables cells to synthesize and respond to their own active vitamin D, while paracrine signaling allows nearby cells to be influenced. This decentralized activation highlights that vitamin D's biological role extends far beyond calcium and bone homeostasis, with the vitamin D-VDR system functioning analogously to nuclear receptor pathways seen with steroid or thyroid hormones.

Multiple immune cell types-including antigen-presenting cells (dendritic cells and macrophages), as well as T and B lymphocytes-express VDR and participate in vitamin D-mediated regulation. This means the vitamin D-VDR system influences broad aspects of both innate and acquired immunity (including mast cells). When vitamin D levels are profoundly deficient, innate immune responses such as monocyte and macrophage function become impaired, while adaptive immune activity becomes upregulated. This occurs because active vitamin D inhibits dendritic cell maturation, shifting the immune response toward tolerance and reducing inappropriate activation of T cells.

This mechanistic profile explains why deficiency may increase susceptibility to autoimmune conditions. Observational studies have demonstrated associations between low vitamin D levels and increased risk of type 1 diabetes mellitus, multiple sclerosis, and inflammatory bowel disease [3].

Vitamin D in immune-mediated neurological disorders

Literature has emphasized the role of vitamin D in both neuroprotection and immune system regulation. Vitamin D acts as an immunomodulator within the innate and adaptive immune responses. Its effects include, but are not limited to, influencing T-cell differentiation, reducing the activity of pro-inflammatory Th1 and Th17 cells, and promoting regulatory T cells. As a result, calciferol decreases the production of inflammatory cytokines such as IL-17 and IL-21, while increasing anti-inflammatory cytokines like IL-10 [4]. Understandably, these effects collectively contribute to preventing immune response dysregulation and reducing inflammation, processes that are implicated in immune-mediated neurological disorders (e.g. multiple sclerosis, Parkinson's disease, Alzheimer's disease).

In the nervous system, calciferol supports neuroprotection by reducing immune cell trafficking across the blood-brain barrier (BBB). Vitamin D maintains the integrity of the BBB by upregulating tight junction proteins (e.g. zonula occluden-1, claudin-5) and downregulating adhesion molecules (e.g. ICAM-1, VCAM-1) [5]. Therefore, the barrier is less permeable to immune cells, preventing them from entering the brain and inducing inflammation. Activation of microglia and astrocytes in the central nervous system (CNS) is also suppressed. Additionally, vitamin D prevents neuronal apoptosis, promotes neurogenesis, and enhances cell survival in the nervous system [6]. Calciferol increases the expression of growth factors-most notably nerve growth factor-within oligodendrocytes, thereby promoting remyelination [7].

Among neurological disorders, multiple sclerosis (MS) is most strongly linked to vitamin D. MS is a chronic autoimmune condition of the CNS that is characterized by inflammation, demyelination, and neuron loss, presenting clinically with a variety of symptoms such as

muscle weakness, paresthesia, bladder and bowel dysfunction, and cognitive impairment [8]. Its pathophysiology involves macrophages and monocytes stimulating the migration of T-cells across the BBB, leading to barrier injury and immune cell infiltration. The resulting release of superoxide radicals by activated microglia, along with perivascular lymphocytic infiltrates, leads to the degradation of myelin sheaths and emergence of symptoms corresponding to the location of the CNS lesion [8].

Numerous studies have demonstrated that vitamin D deficiency is correlated with increased risk of MS, greater disease activity, and higher relapse rates [9]. For example, Munger., *et al*. found that women with a higher dietary intake of calciferol had both a reduced risk and incidence of MS in comparison to those with lower intake [10]. Similarly, a separate longitudinal study in the Netherlands reported that higher doses of vitamin D supplementation were associated with a significant reduction in the relapse risk of MS [11]. Moreover, neuro-ophthalmic complications of multiple sclerosis, such as acute optic neuritis (AON) and internuclear ophthalmoplegia (INO), may also benefit from calciferol supplementation. Malik., *et al*. found that lower vitamin D levels correlated with increased AON severity [12].

Beyond MS, vitamin D deficiency has been linked to increased risk and severity of other immune-mediated neurological disorders, including Parkinson's disease and Alzheimer's disease [13]. The underlying mechanisms of vitamin D deficiency are thought to parallel those in MS, involving reduced neuroprotective, immunomodulatory, and anti-inflammatory actions of calciferol in the CNS. Another theory in Parkinson's disease suggests that chronic vitamin D deficiency may contribute to the degeneration of dopaminergic neurons in the substantia nigra [13]. In Alzheimer's disease, low calciferol levels are associated with reduced cognitive function and increased neurodegeneration. Ultimately, in patients with either condition, vitamin D supplementation has been shown to improve cognitive performance and quality of life [13].

Vitamin D in endocrine and metabolic resistance

Diabetes mellitus (DM) is characterized as a metabolic disorder in which there is elevated blood glucose levels [14]. The main subtypes discussed in this review are Type 1 and Type 2 DM. The association of DM and vitamin D has been reviewed in several studies which will be referred to. In many observational studies, individuals who developed type 1 DM showed lower levels of vitamin D when compared to healthy controls [15].

In pancreatic beta cells, vitamin D receptor (VDR) expression has been found along with 1-hydroxylase expression [16]. There is also a vitamin D response element present on the human insulin gene promoter [16]. VDRs are also expressed in other cells such as osteoblasts, mononuclear cells, and B and T lymphocytes [16]. Vitamin D may play a protective role for beta cells in the pancreas from the immune system due to its regulatory effect on T-cells [16].

Studies have been conducted on non-obese diabetic mice (NOD) that have further shown the association of vitamin D with the development of type 1 DM [15]. These mice have long served as a model for human type 1 DM [15]. It was found that NOD that had low vitamin D levels growing up had a higher incidence of early-onset DM [15]. In the study, early supplementation with vitamin D in NOD showed prevention of diabetes [15]. Another study on NOD showed that short-term administration of calcitriol analogue prevented the formation of inflammatory cytokines such as IL-12 and IFN-gamma [15]. This led to lesser infiltration of T-helper 1 cells in pancreatic islet cells [15].

Low vitamin D levels have been correlated with insulin resistance, a finding associated with metabolic syndrome [17]. In a study conducted among vitamin D deficient and insulin-resistant South Asian women, supplementation with 4,000 IU/day of vitamin D for six months led to a marked improvement in insulin resistance [18]. In a recent randomized trial, daily supplementation with 4000 IU of vitamin D3 did not significantly reduce the risk of developing type 2 DM in high-risk individuals who were not selected for vitamin D deficiency [19]. In another literature review, it was mentioned that most studies focused on the association of type 2 DM and vitamin D revealed no improvement, except for one study which revealed an improvement of insulin resistance after vitamin D supplementation [20].

In regard to metabolic syndrome, a meta-analysis examined the effects of vitamin D supplementation on lipid levels and insulin resistance in individuals with metabolic syndrome [21]. It was found that vitamin D supplementation led to early reductions in triglycerides, along with improvements in fasting glucose, insulin resistance, and systolic blood pressure, but it did not produce significant changes in LDL-C, HDL-C, or total cholesterol [21].

Studies show that low vitamin D is linked to both type 1 and type 2 diabetes. Taking vitamin D may help with blood sugar control in people with type 1 diabetes, but most research shows it does not significantly improve HbA1c in type 2 diabetes. More extensive research is needed to better understand this connection [20].

Vitamin D in steroid-resistant or infection-prone inflammatory conditions

Vitamin D plays an essential role in immune regulation, influencing inflammation, cellular communication, and the body's overall response to treatment. Its significance has become increasingly apparent in inflammatory conditions that are resistant to corticosteroids or prone to chronic infection. Reactive airway dysfunction syndrome (RADS) exemplifies such a disorder, an asthma-like condition that develops after exposure to a respiratory irritant and often fails to respond to standard steroid-based therapies.

A 51-year-old woman developed severe RADS after prolonged exposure to chlorine bleach and showed little improvement despite intensive steroid and bronchodilator treatment. Her symptoms persisted until clinicians identified and corrected a marked vitamin D deficiency (19 nmol/L), which was treated with high-dose ergocalciferol (50,000 IU weekly, then monthly). Following supplementation, her vitamin D levels rose to 200 nmol/L, and she experienced complete symptom resolution while discontinuing all other medications [22]. Although this is a single case report, it underscores vitamin D's potential to restore airway stability and improve recovery in disorders that respond poorly to conventional therapy.

The biological basis for these effects is increasingly supported by molecular and immunological evidence. Vitamin D acts as a steroid hormone that modulates both innate and adaptive immunity through its effects on immune cell differentiation and cytokine signaling. It downregulates pro-inflammatory mediators such as interleukin-2 (IL-2) and interferon-γ (IFN-γ), while promoting anti-inflammatory pathways and enhancing glucocorticoid receptor activity [23]. In addition, vitamin D suppresses nuclear factor-κB (NF-κB) activation and influences key immune cell types, including macrophages, dendritic cells, and Th17 lymphocytes, thereby promoting immune tolerance and reducing tissue injury. These mechanisms may explain why vitamin D supplementation can help re-establish corticosteroid sensitivity in resistant airway diseases.

A similar case described a healthcare worker who developed RADS after ammonia exposure and showed rapid improvement following high-dose vitamin D therapy [24]. While case studies are limited by their anecdotal nature, the consistency of such outcomes strengthens the hypothesis that vitamin D acts as an immunoregulatory agent capable of reducing airway inflammation and improving steroid responsiveness.

Beyond RADS, low vitamin D status has been linked to broader immune dysregulation and heightened infection susceptibility. A randomized placebo-controlled trial reported that vitamin D_3 supplementation significantly increased antimicrobial activity in the airway surface liquid of human participants, strengthening innate respiratory defense mechanisms [25]. This mechanism helps explain the increased incidence of infections in chronic inflammatory airway disorders when vitamin D levels are inadequate. By supporting both innate and adaptive immune pathways, vitamin D appears to play a dual role, attenuating inflammation while enhancing resistance to microbial triggers that perpetuate disease flares.

Taken together, current evidence suggests that vitamin D may serve as a valuable adjunctive strategy for steroid-resistant and infection-prone inflammatory conditions. While larger controlled trials are needed to establish causality and define optimal dosing, these

findings highlight the importance of monitoring and correcting vitamin D deficiency in patients with chronic or treatment-refractory airway inflammation.

Conclusion and Future Directions

Vitamin D is about more than just bone health. While current data and literature may support that sufficiency of vitamin D is anywhere above 30 ng/mL, there is now evidence to show that levels anywhere up to 60 ng/mL may be crucial for the necessary functions of the human body including immunological protection. As we uncovered, immune cells from both innate and adaptive forms including T cells, B cells, and dendritic cells all express VDR and are able to convert vitamin D into its active form. This means that our immune system often has an even greater need in times of infection. Through the diseases discussed, from neurological disorders such as MS as well as metabolic conditions like DM, vitamin D serves as a fuel for immune cells and the demand will only rise as these conditions become resistant to steroids and other forms of therapy.

Previous cutoffs described by guidelines for adequate vitamin D levels did not take into account the immune functionality it possesses. Prevention of bone breakdown in conditions such as rickets and osteomalacia were solely considered when making a decision on an adequate level of vitamin D in the human body. Though it may be seen as just a nutrient that supports physiological function such as any other vitamin would do, the recent discoveries of its immense gravity in immunologic support cannot be ignored and must be taken into consideration as a justification to reorganize and alter the previous standard set for adequate vitamin D levels.

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