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Review Article

THE ROLE OF VITAMIN D IN IMMUNE MODULATION: A REVIEW OF CLINICAL IMPLICATIONS

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Abstract: *Vitamin D, often celebrated for its crucial role in maintaining bone health, has garnered significant attention in recent years for its multifaceted contributions to immune modulation. The study aims to find Vitamin D's role in immune modulation. The innate immune system is the first line of defense against invading pathogens, and its leading roles are rapid responses, identification of the pathogen, and neutralization to avoid the aggravation of the disease. The role of Vitamin D in immune modulation extends across a spectrum of immune-related disorders, underscoring its significance in maintaining immune homeostasis and preventing disease. The immune modularity of vitamin D is mainly through the active form, 1,25-dihydroxyvitamin D [1,25(OH)2D]; this hormone binds to the Vitamin D receptor (VDR) inherent in several immune cells. This binding triggers the process of gene expression alterations that impact the abilities and duplication of these cells. For instance, in multiple sclerosis (MS), Vitamin D inhibits the production of Th1 and Th17, which are pro-inflammatory T-cells, while enhancing Tregs, which results in the curbing of inflammation and autoimmunity. Vitamin D is pivotal in immune modulation, influencing innate and adaptive immune responses. Its deficiency is linked to an increased risk and severity of various immune-related disorders, highlighting the importance of maintaining adequate Vitamin D levels.*

Keywords: Immune System, Vitamin D, Immune Modulation, Innate Immunity, Autoimmune Diseases.

Introduction

Vitamin D, often celebrated for its crucial role in maintaining bone health, has garnered significant attention in recent years for its multifaceted contributions to immune modulation. This fat-soluble vitamin, primarily synthesized through skin exposure to sunlight, extends far beyond its classical functions in calcium and phosphorus homeostasis. Emerging research highlights Vitamin D's involvement in modulating the immune system, influencing innate and adaptive immune responses (1). Knowledge of the way Vitamin D modulates the immune response expands the field for potential treatments and methods of preventing diseases. This introduction provides a brief review of the connection between Vitamin D and the immune system and a general overview of the role of Vitamin D in boosting human health (2). Vitamin D is a little different from other vitamins as it is produced in the body primarily by sunlight, particularly the UVB kind. Vitamin D comes in two types: D2, which is synthesized in the body from ergosterol, and D3, which is synthesized by the human body from 7-dehydrocholesterol. D2 is acquired from plant and enriched foods, while D3 is produced in the skin and is found in foods of animal origin. Both forms are metabolized in the liver to 25 hydroxyvitamin D or 25 (OH)D, which is the primary provision used to check the Vitamin D level of an individual. The last activation form occurs in the kidneys; 25(OH)D is further metabolized to the active form 1,25 dihydroxyvitamin D, popularly called calcitriol (3). This is the primary defense system in the body that tends to undertake the preliminary emergency response to pathogens. It encompasses the physical and damaged barriers, including skin and mucosa, and immune cells, including macrophages and dendritic cells (4). The immune response by vitamin D can be said to work through innate immunity as it directly increases the pathogen eradication ability of monocytes and macrophages, as well as reduces inflammation (5). Macrophages and dendritic cells also present the vitamin D receptor while synthesizing the enzyme 1α-hydroxylase necessary to activate 25(OH)D. Thus, such local synthesis of active Vitamin D enables the regulation of the innate immunomodulatory directly at sites of infection or inflammation. For example, taken from the article's contents, Vitamin D increases the synthesis of antimicrobial peptides, for instance, cathelicidin and defensins, that hinder the membrane of bacteria, viruses, and fungi, making these pathogens inactive. The adaptive immune system, characterized by its ability to remember past infections, involves lymphocytes such as T and B cells (6). Vitamin D modulates the adaptive immune system by affecting the function and proliferation of these cells. T cells, which play a critical role in cell-mediated immunity, express the VDR upon activation. The binding of active Vitamin D to the VDR inhibits the proliferation of pro-inflammatory Th1 and Th17 cells while promoting the development of anti-inflammatory Th2 and regulatory T cells (Tregs). This shift towards an anti-inflammatory profile is crucial in preventing excessive immune responses and maintaining immune tolerance (7). Additionally,

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Vitamin D influences B cell function by inhibiting their differentiation and the production of antibodies, further contributing to immune regulation. Vitamin D deficiency is a global health issue, affecting a significant portion of the population. Deficiency has been linked to an increased susceptibility to infections and a higher prevalence of autoimmune diseases (8).

Methodology And Results

The study's main objective is to find Vitamin D's role in immune modulation. The innate immune system is the first line of defense against invading pathogens, and its leading roles are rapid responses, identification of the pathogen, and neutralization to avoid the aggravation of the disease. Vitamin D plays an essential function in the operations of innate immunity as it activates the manufacture of pattern recognition receptors (PRRs), antimicrobial peptides, and cytokines in the cells (9). Besides, the differentiation of monocytes into macrophages and the maturation and activation of dendritic cells can also be suppressed by it. The proteins that form the major components of the immune system include cathelicidins, alpha- and beta-defensins, and other cationic antimicrobial peptides. Most current studies, especially those from relatively recent years, have identified the primary purpose of vitamin D signaling as regulating innate immunological interactions (10). Since the middle of the nineteenth century, it has been documented that vitamin D enhances the antibacterial properties of human monocytes and macrophages. Regarding macrophages, 1,25-(OH)2 D3 elevates their phagocytic and chemo-like effects. Antimicrobial cathelicidin peptides are produced when toll-like receptors are activated in monocytes and macrophages; they also facilitate positive expression of VDR and alpha one hydroxylase genes, which kills intrathecal M tuberculosis (11).However, 1,25-(OH)2 D3 consequently inhibits macrophages' TLR2 and TLR4 genes. This situation often takes control after 72 hours and negatively opposes TLR activation. During infection, cytokines such as interferon- γ (IFN- γ) and toll-like receptor signaling up-regulate CYP27B1 in infected macrophages and monocytes for converting 25-OH D3 to 1,25-(OH)2 D3. Its importance emanates from the fact that the 1,25-(OH)2 D3 is utilized to increase the antibacterial effects of macrophages and monocytes via the VDR-RXR signaling pathway (12). The result is that cathelicidin is produced in more significant amounts. This peptide inactivates invasive bacteria and fungi by disturbing their microbial membranes. Therefore,1,25-(OH)2 D3 modulates the immune system on Mycobacterium TB infection (13). Mammals cathelicidins examples are hCAP18 in neutrophils or the small inducible cationic peptide of 37 amino acids known as LL-37 isolated from large prepropeptides in non-immune tissue such as testes and functions in bacterial, fungal, and viral infections to breakdown microbial membranes (14). The data show that vitamin D signaling affects the physiological gut, promotes intestinal hemostasis, and establishes microbiota modulation within healthy individuals. Thus, the levels of ILCs and NK cells also get influenced by 1,25-(OH)2 D3 (15). Hence, while T cell and dendritic cell (DC) responses are important in immune response, another component of the innate immune system is described to regulate the cells. ILCs are part of the immune response and are indispensable to the species. These immune cells are resident in all mucosal tissues although they are most abundant in the colon (16). They also, shortly, as the first-line defenders, regulate cell division and differentiation, wound healing, the production of anti-inflammatory chemical substances in response to infections, and the synthesis of antimicrobial substances. The former stimulates the cytotoxic activity of NK cells and ILCs via their VDR receptors. Likewise, they have reduced concerted expression of their inflammatory cytokines (17).

Table 01: Role of Vit-D in immune modulation

Aspect of Immune System	Mechanism Involved	Role of Vitamin D
Mechanism of Action	Activation of Vitamin D receptor (VDR)	1,25(OH)2D binds to VDR in immune cells, initiating transcriptional changes affecting immune responses.
Innate Immunity	Antimicrobial Peptide Production	Induces production of cathelicidin and defensins, disrupting membranes of bacteria, viruses, and fungi.
	Inflammatory Response Regulation	It inhibits pro-inflammatory cytokines (IL-6, TNF-α) and promotes anti-inflammatory cytokines (IL-10).
Adaptive Immunity	T Cell Modulation	Inhibits Th1 and Th17 proliferation, promotes Th2 and regulatory T cells (Tregs), maintaining immune balance.
	B Cell Function	Inhibits B cell proliferation and differentiation, reducing antibody production.
Clinical Implications	Increased Susceptibility to Infections	Deficiency is linked to higher infection rates, including severe respiratory infections.
	Higher Prevalence of Autoimmune Diseases	It is associated with conditions such as multiple sclerosis, rheumatoid arthritis, and inflammatory bowel disease.
Therapeutic Potential	Supplementation Benefits	Potential to reduce the risk of acute respiratory infections and improve autoimmune disease outcomes.

Table 02: Vitamin D Function in Different Immune-Related Disorders

Immune-Related Disorder	Role of Vitamin D	Evidence and Implications
Multiple Sclerosis (MS)	Modulates T cell response reduces Th1 and Th17 proliferation and promotes regulatory T cells (Tregs).	Lower MS risk and disease activity in individuals with higher Vitamin D levels. Potential therapeutic role.

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Rheumatoid Arthritis (RA)	Reduces pro-inflammatory cytokines (IL-6, TNF-α) and modulates immune cell function.	Vitamin D deficiency is linked to increased RA severity. Supplementation may alleviate symptoms.
Inflammatory Bowel Disease (IBD)	Enhances barrier function of the gut and reduces inflammation by modulating T cell responses.	Lower Vitamin D levels are associated with higher IBD activity, which has the potential to reduce flares and maintain remission.
Type 1 Diabetes (T1D)	Modulates immune response promotes regulatory T cells and reduces autoimmunity.	Higher Vitamin D levels are linked to lower T1D incidence—potential preventive and therapeutic benefits.
Systemic Lupus Erythematosus (SLE)	Reduces inflammatory cytokines, modulates B cell activity, and promotes regulatory T cells.	Deficiency associated with increased disease activity. Supplementation may improve outcomes.
Asthma	Reduces airway inflammation, enhances antimicrobial peptide production, and modulates the immune response.	Lower Vitamin D levels are linked to increased severity of asthma—potential to reduce exacerbations.
Chronic Obstructive Pulmonary Disease (COPD)	It enhances lung function, reduces inflammation, and modulates immune cell activity.	Vitamin D deficiency is associated with worse COPD outcomes. Supplementation may improve lung function.
Respiratory Infections	It enhances the production of antimicrobial peptides, modulates inflammatory response, and boosts innate immunity.	Higher Vitamin D levels are linked to reduced risk and severity of infections like influenza and COVID-19.
Psoriasis	Modulates keratinocyte proliferation reduces inflammatory cytokines and enhances regulatory T cells.	Topical and systemic Vitamin D treatments improve symptoms and reduce plaques.
HIV/AIDS	It enhances immune function, reduces inflammation, and improves CD4+ T cell count.	Deficiency is linked to faster disease progression. Supplementation may enhance immune recovery.
Tuberculosis (TB)	It enhances macrophage function, increases the production of antimicrobial peptides, and reduces inflammation.	Lower Vitamin D levels are associated with increased TB risk. Supplementation may support TB treatment.
Autoimmune Thyroid Disease (AITD)	Modulates T cell responses reduces inflammation and promotes immune tolerance.	Deficiency is linked to a higher risk of diseases like Hashimoto's thyroiditis and Graves' disease.

Discussion

The role of Vitamin D in immune modulation extends across a spectrum of immune-related disorders, underscoring its significance in maintaining immune homeostasis and preventing disease. The immune modularity of vitamin D is mainly through the active form, 1,25-dihydroxyvitamin D [1,25(OH)2D]; this hormone binds to the Vitamin D receptor (VDR) inherent in several immune cells. This binding triggers the process of gene expression alterations that impact the abilities and duplication of these cells (18). For instance, in multiple sclerosis (MS), Vitamin D inhibits the production of Th1 and Th17, which are pro-inflammatory T-cells, while enhancing Tregs, which results in the curbing of inflammation and autoimmunity. The same applies to RA and IBD, where Vitamin D acts on cytokine production and T-cells to lower disease severity and improve clinical status (19). There is sufficient evidence that Vitamin D deficiency is somewhat common globally and is associated with an elevated risk of several immune-related diseases. It has been proven that patients with Vitamin D deficiency are at a higher risk of experiencing higher disease activity and the severity of diseases like MS, RA, and IBD (20). For instance, patients with low levels of Vitamin D are more susceptible to MS, and they record more relapses. RA is associated with reduced levels of deficiency and is identified as aggrexone, which causes inflammation and joint destruction. Like in the case of HC, low Vitamin D levels are indicators of worse disease flares and unresponsiveness to treatment among patients suffering from IBD. The deficiency also proves to have an essential function in increasing infection rates. Tuberculosis and viral infections such as the flu and COVID-19 are worse in people with low Vitamin D. This is due to Vitamin D's immunomodulatory benefits that promote an increase in the synthesis of antimicrobial peptides and how it regulates inflammation, which is vital in pathogen elimination and management of infection. Since Vitamin D deficiency is manifested in various developed countries and immunological diseases are closely related, this supplement has become a possible therapeutic tool. Some research proponents found that Vitamin D supplementation can potentially lessen the incidences of acute respiratory infections and enhance the results of autoimmune disease patients.

Conclusion

Vitamin D is pivotal in immune modulation, influencing innate and adaptive immune responses. Its deficiency is linked to an increased risk and severity of various immune-related disorders, highlighting the importance of maintaining adequate Vitamin D levels. Supplementation holds promise as a therapeutic strategy, potentially reducing disease activity and improving clinical outcomes in conditions such as MS, RA, and IBD. As research continues to uncover the complex interactions between Vitamin D and the immune system, the potential for Vitamin D-based interventions in enhancing human health becomes increasingly evident.

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Declarations

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All data generated or analyzed during the study are included in the manuscript.
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