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Dolna 17, Warsaw,
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+48 226 0 227 03
editorial_office@rsglobal.pl

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HOW VITAMIN D AFFECTS THE IMMUNE SYSTEM: A REVIEW OF THE LITERATURE

Sandra Khiralla-Gawlik *(Corresponding Author, Email: sandrakhiralla@gmail.com)*
Wojewódzki Szpital Specjalistyczny im. Stefana Kardynała Wyszyńskiego SPZOZ w Lublinie, Poland
ORCID ID: 0009-0009-6894-9099

Konrad Strużek
Wojewódzki Szpital Specjalistyczny im. Stefana Kardynała Wyszyńskiego SPZOZ w Lublinie, Poland
ORCID ID: 0009-0000-3146-5132

Agnieszka Kwiatkowska
Wojewódzki Szpital Specjalistyczny im. Stefana Kardynała Wyszyńskiego SPZOZ w Lublinie, Poland
ORCID ID: 0009-0005-6598-9416

Ewelina Mączka
Uniwersytecki Szpital Kliniczny nr 1 w Lublinie, Poland
ORCID ID: 0000-0002-2597-2653

Wiktor Tracz
Uniwersytecki Szpital Kliniczny nr 1 w Lublinie, Poland
ORCID ID: 0009-0002-0192-2026

Patrycja Świercz
Wojewódzki Szpital Specjalistyczny im. Stefana Kardynała Wyszyńskiego SPZOZ w Lublinie, Poland
ORCID ID: 0009-0005-6389-2960

Kinga Teper
Uniwersytecki Szpital Kliniczny nr 1 w Lublinie, Poland
ORCID ID: 0009-0002-4326-5749

Aleksandra Anna Strzelecka
Uniwersytecki Szpital Kliniczny nr 1 w Lublinie, Poland
ORCID ID: 0009-0007-2361-5007

Aleksandra Ewa Basak
Uniwersytecki Szpital Kliniczny nr 1 w Lublinie, Poland
ORCID ID: 0009-0000-6769-7082

ABSTRACT

Vitamin D is essential for the proper functioning of the immune system, modulating the immune response through the activation of vitamin D receptors (VDR) in various immune cells. Vitamin D plays a crucial role in protecting against infections, particularly respiratory infections, and its deficiency is associated with an increased risk of autoimmune diseases. Although the results of studies on vitamin D supplementation in the treatment of autoimmune diseases are mixed, there is growing interest in its potential impact on the course of these diseases. This review discusses the mechanisms of vitamin D action in the context of the immune system and its significance in preventing infections and autoimmune diseases. Research indicates the need for further analysis to establish optimal supplementation doses of vitamin D and its effectiveness in different patient groups.

KEYWORDS

Vitamin D, Immunity, Infection, Autoimmune Disease, COVID-19

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1. Introduction

Vitamin D, often referred to as the "sunshine vitamin," belongs to a group of steroid compounds and exhibits hormone-like activity. It participates in the regulation of the expression of over 200 genes and plays a crucial role in the growth and development processes of the body. There are two main forms of this vitamin: vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol) [1]. Despite its name suggesting a vitamin compound, vitamin D is actually a prohormone because its primary source is not exclusively dietary. It can be synthesized in the skin under the influence of ultraviolet B radiation (with wavelengths of 290-315 nm) and is additionally provided to the body through food or dietary supplements [2]. Its active form, 1,25-dihydroxycholecalciferol (calcitriol), binds to vitamin D receptors (VDR) found in various immune system cells, including T and B lymphocytes, monocytes, and antigen-presenting cells, regulating the expression of numerous genes involved in immune responses [3].

An increasing number of scientific publications indicate that vitamin D deficiency is associated with the occurrence of various diseases affecting many organs and systems of the body, including autoimmune diseases, inflammatory conditions, infections, cancers, and neurological disorders [4,5].

The aim of this paper is to review the current scientific literature on the role of vitamin D in immune system function, with particular attention to biological mechanisms, its impact on susceptibility to infections, and its connections to autoimmune diseases.

2. Methodology of the Literature Review

The literature review was conducted based on publications from databases such as PubMed, Scopus, Oxford Academic, and other peer-reviewed scientific journals. Articles published between 2007 and 2023 were included, focusing on the impact of vitamin D on the immune system, infections, and autoimmune diseases. The search was based on keywords such as: vitamin D, immunity, infection, autoimmune disease, COVID-19. Priority was given to review articles, meta-analyses, and clinical studies.

3. Metabolism and Sources of Vitamin D

Vitamin D exists in two main forms: vitamin D_2 (ergocalciferol), which is primarily obtained from plant sources and fungi, and vitamin D_3 (cholecalciferol), which occurs naturally in animal products and is synthesized in human skin under the influence of ultraviolet B (UVB) radiation with wavelengths of 290-315 nm [1,2,6]. Although vitamin D can be obtained from food and supplements, its primary source in humans remains synthesis in the skin, initiated by exposure to sunlight. Under the influence of UVB radiation, 7-dehydrocholesterol present in the skin is converted to previtamin D_3, which is subsequently transformed into vitamin D_3 [7]. Both vitamin D_2 and D_3 lack biological activity and require two stages of enzymatic activation in the body. The first stage occurs in the liver, where vitamin D is converted to 25-hydroxyvitamin D (25(OH)D), the main metabolite present in the blood, used as a marker of vitamin D status. The second stage mainly occurs in the kidneys, where 1,25-dihydroxyvitamin D ($1,25(OH)_2D$, calcitriol) is produced, the active form with hormonal properties [8,9].

Vitamin D receptors (VDR) are present in many types of immune system cells, such as monocytes, macrophages, dendritic cells, and T and B lymphocytes [10]. The active form of vitamin D – 1,25-dihydroxyvitamin D_3 (calcitriol) – binds to VDR, influencing the expression of numerous genes involved in physiological processes, including mechanisms of the immune response [6,11]. In T lymphocytes, VDR activation modulates their proliferation, differentiation, and effector functions [11]. Additionally, VDR participates in maintaining the balance between subpopulations of T lymphocytes, which is important for limiting excessive inflammatory responses and the development of autoimmune diseases [10,11].

4. Mechanisms of Vitamin D Action on the Immune System

4.1 Activation of Macrophages and Monocytes and Regulation of Antibacterial Peptides

Vitamin D plays a key role in modulating the function of cells in the innate immune system, such as macrophages and monocytes. The active form of vitamin D, 1,25-dihydroxyvitamin D_3 (calcitriol), binds to the vitamin D receptor (VDR) present in these cells, leading to the regulation of gene expression involved in immune responses [3]. Calcitriol supports the antimicrobial properties of macrophages and monocytes through the activation of the VDR-RXR signaling pathway, which leads to increased synthesis of cathelicidins, including cathelicidin LL-37. These peptides bind to the membranes of microorganisms, aiding in their elimination, including bacteria and fungi. Cathelicidin also exhibits antiviral activity against respiratory pathogens by destabilizing their lipid envelope [12,13,14]. LL-37 has a broad antimicrobial spectrum, including against bacteria, viruses, and fungi. Additionally, LL-37 performs immunomodulatory functions, such as chemotaxis and modulation of the inflammatory response. Studies have shown that vitamin D supplementation can increase the level of LL-37 in the body, which enhances the immune response [14].

4.2 Regulation of Antibacterial Peptides

Vitamin D has the ability to suppress excessive inflammatory responses by inhibiting the production of pro-inflammatory cytokines, such as IL-1, IL-6, IL-8, IL-12, and TNFα. Calcitriol can reduce the expression of interleukin-6 (IL-6), interleukin-1β (IL-1β), and tumor necrosis factor-alpha (TNF-α) in immune cells such as monocytes and macrophages [15,16]. By doing so, vitamin D helps maintain the balance between defensive and inflammatory responses, which is important in preventing tissue damage during infections [15].

5. Vitamin D and Infections

5.1 Respiratory Infections

Vitamin D plays a significant role in modulating the immune response, which can influence susceptibility to respiratory infections. The active form of vitamin D, 1,25-dihydroxyvitamin D_3 (calcitriol), affects the functioning of immune cells, including macrophages and T lymphocytes, as well as the production of pro-inflammatory and anti-inflammatory cytokines [3,17,18].

Epidemiological studies suggest that low levels of vitamin D in the serum may be associated with an increased risk of respiratory infections [17]. However, the results of clinical studies regarding vitamin D supplementation for preventing such infections are mixed. Some studies indicate benefits, especially in individuals with vitamin D deficiency [17,18], while others show no significant effects.

5.2 Influenza

In the context of influenza, some studies suggest that vitamin D supplementation may reduce the risk of these infections, particularly in individuals with low vitamin D levels [18]. However, other studies do not confirm these benefits, indicating the need for further research in this area.

5.3 COVID-19

The COVID-19 pandemic has drawn attention to the potential role of vitamin D in preventing and treating SARS-CoV-2 infections. Some observational studies suggest that low vitamin D levels may be associated with a more severe course of COVID-19, including an increased risk of hospitalization and mortality [19,20]. However, the results of clinical studies regarding vitamin D supplementation in the context of COVID-19 are inconclusive, and some systematic reviews indicate insufficient evidence to support the effectiveness of such an intervention [19,20].

6. Vitamin D and Autoimmune Diseases

6.1 Introduction

Vitamin D plays a crucial role in regulating the immune system, influencing both innate and acquired immunity. The active form of vitamin D, 1,25-dihydroxyvitamin D_3 (calcitriol), modulates the functions of immune cells such as T and B lymphocytes, macrophages, and dendritic cells, which may impact the development and progression of autoimmune diseases [21].

6.2 Multiple sclerosis

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system, and its development may be linked to low vitamin D levels [1]. An updated Cochrane review from 2018, which included 12 clinical studies, did not conclusively confirm the effectiveness of vitamin D supplementation in the treatment of MS. The authors suggest that current data is insufficient to determine the impact of vitamin D on the course of the disease and recommend further research [21,22].

6.3 Type 1 Diabetes

In type 1 diabetes, vitamin D may modulate the autoimmune response against pancreatic β-cells. Some studies suggest that higher levels of 25(OH)D during childhood may be associated with a lower risk of developing type 1 diabetes, although it has not been conclusively confirmed whether supplementation can prevent it [23].

6.4 Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by joint inflammation and progressive joint damage. Vitamin D, through its immunomodulatory properties, may play a role in the pathogenesis and progression of RA. A meta-analysis of clinical studies showed that vitamin D supplementation may lead to improvements in disease activity indicators, such as DAS28, and reduce the number of painful joints, especially at doses exceeding 50,000 IU [24]. However, the results of studies are inconclusive, and further research is needed to definitively determine the effectiveness of vitamin D supplementation in the treatment of RA [25].

6.5 Psoriasis

Psoriasis is a chronic autoimmune skin disease in which vitamin D plays a significant role through its effects on keratinocyte differentiation and immune response. A review of studies indicates that its deficiency may exacerbate the symptoms of the disease, and supplementation, as well as the topical application of vitamin D analogs (e.g., calcipotriol), may improve the skin condition and reduce inflammation. However, there is a need for further research to determine the optimal supplementation doses and long-term effects of vitamin D therapy in the treatment of psoriasis [26].

6.6 Systemic Lupus Erythematosus (SLE)

SLE is a systemic autoimmune disease in which the immune system attacks the body's own tissues, leading to inflammation and damage to various organs. Vitamin D deficiency is often observed in patients with SLE and may be associated with increased disease activity. Vitamin D supplementation may help modulate the immune response and reduce disease activity in patients with SLE [27].

6.7 Inflammatory Bowel Disease (IBD)

Inflammatory bowel diseases, including Crohn's disease and ulcerative colitis, are chronic inflammatory diseases of the gastrointestinal tract with an autoimmune basis. Vitamin D plays a role in maintaining the integrity of the intestinal barrier and regulating the immune response. Studies suggest that vitamin D deficiency may be associated with increased disease activity and more frequent flare-ups. Vitamin D supplementation may provide benefits in reducing inflammation and improving the quality of life for patients with IBD [28].

7. Limitations and Controversies

7.1 Differences in Dosage and Reference Levels

One of the main challenges in assessing the impact of vitamin D on the immune system is the variability in recommended supplementation doses and reference levels of 25(OH)D in serum. Different health organizations propose varying values considered optimal for immune system functioning. For example, some guidelines suggest that a 25(OH)D level above 30 ng/ml is sufficient, while others recommend values above 40–50 ng/ml to achieve immunomodulatory effects [29].

Additionally, there is a lack of consensus regarding the optimal dosage of vitamin D supplementation for supporting the immune system. While some studies indicate benefits from daily intake of 1000–2000 IU, others suggest that higher doses may be more effective, especially in individuals with vitamin D deficiency. However, excessively high doses may lead to hypercalcemia and other adverse effects [30].

7.2 Insufficient Evidence in Some Areas

Although numerous observational studies suggest a link between vitamin D levels and immune system functioning, evidence from randomized clinical trials (RCTs) is often inconsistent or insufficient. For example, a meta-analysis involving over 60,000 participants did not show a statistically significant reduction in the risk of acute respiratory infections in individuals taking vitamin D supplements compared to a placebo [31].

Similarly, in the context of autoimmune diseases such as multiple sclerosis or rheumatoid arthritis, the results of studies on the effectiveness of vitamin D supplementation are mixed. Some studies suggest potential benefits, while others do not show significant therapeutic effects [32].

Additionally, there are methodological limitations in many studies, such as differences in dosage, duration of supplementation, study populations, and lack of standardization in measuring 25(OH)D levels. These factors complicate the clear interpretation of results and the formulation of universal recommendations regarding vitamin D supplementation for supporting the immune system.

8. Conclusions

Vitamin D plays a crucial role in the functioning of the immune system, influencing a range of immunological mechanisms, including the activation of immune cells such as T lymphocytes, B lymphocytes, macrophages, and monocytes. Its active form, calcitriol, modulates the immune response, supporting the body's defense against infections and helping maintain the balance between inflammatory and immunosuppressive responses. Vitamin D deficiency is associated with an increased risk of various diseases, including respiratory infections and the development of autoimmune diseases such as multiple sclerosis, type 1 diabetes, and rheumatoid arthritis.

Despite the growing number of studies indicating the beneficial effects of vitamin D on immune system function, the results regarding vitamin D supplementation in the prevention and treatment of infections and autoimmune diseases remain inconclusive. Many studies do not show clear benefits from vitamin D supplementation, suggesting the need for further analysis and clinical trials to better understand optimal doses, supplementation duration, and the effectiveness of such interventions.

Differences in recommended vitamin D dosages, 25(OH)D reference levels, and research methodologies complicate the formulation of clear recommendations for vitamin D supplementation. Therefore, it is essential to conduct further, more precise studies that will enable the development of specific guidelines for vitamin D supplementation in the context of improving immune system function and preventing infectious and autoimmune diseases.

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