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The Impact of Vitamin D Deficiency on Susceptibility to Parasitic Infections: A Review

Rawa Faris Hussein Al-saeedi[1]; Noor Salih Hallab[1]; Ghassan Nissan[1]; Wasan Ghanem[1]; Shahad Mohammed Mustafa [1];Noor Issam Muzahim[1]

[1]Department of Microbiology, College of Science, Al-Karkh University of Science, Iraq

Correspondence:

Rawa Faris Hussein Al-Saeedi

Email: ruaa.faris@kus.edu.iq

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Abstract:

Vitamin D is one of the most important vital elements in regulating the immune system in the human body. This vitamin can support the body in confronting pathogenic agents. On the other hand, a deficiency of this vitamin makes the immune response to pathogenic agents low, and the incidence of parasitic diseases increases, especially in areas whose population suffers from malnutrition and poor health services. Vitamin D increases immune activity by regulating the work of immune system cells, lymphocytes such as macrophages and dendritic cells, where immune defense mechanisms depend mainly on these cells against pathogens. Many recent studies have indicated that there is a relationship between low vitamin D and infection with some parasites, including the Toxoplasma gondii parasite, which causes toxoplasmosis, and the leishmaniasis parasite, which causes cutaneous leishmaniasis. This review indicates, through its presentation of sources, that vitamin D deficiency affects the immune response and weakens the body's ability to defend and get rid of parasites, which leads to their development within it. Understanding the relationship between low levels of vitamin D and susceptibility to parasitic infection in a deeper way is an important step in scientific research because it can help devise new methods of prevention and treatment, aiming to strengthen immunity and reduce the spread of parasitic diseases.

Keywords: Vitamin D, Toxoplasma gondii, immune system, leishmaniasis.

Introduction

Vitamin D is now known to be an important supplement because it helps keep calcium levels in check and keeps bones healthy, but it also has an effect on the immune system. This may help explain how vitamin D can support immune system activity and enhance its response (1; 2). Studies indicate that low blood levels of vitamin D may increase the risk of various diseases, as well as the likelihood of autoimmune disorders and allergies (3; 4). Vitamin D plays a crucial role in regulating the immune system in multiple ways. It helps the body fight germs and regulates the body's chemical responses to infections. It also enhances the immune system's ability to adapt and cope with challenges without overreacting (5). The mechanisms of these pathways have been demonstrated in multiple scientific studies; however, it has been difficult to translate these findings into consistent clinical outcomes due to differences in study designs and populations (6). However, data from multiple studies consistently show respiratory infections, while nutritional

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supplements for individuals with vitamin D deficiency provide protective effects (7). Vitamin D strengthens the body's defenses while preventing excessive inflammation, highlighting its importance as a key regulator of immunity.

In addition to its role in regulating the immune system, vitamin D influences the body's susceptibility to parasitic infections and their progression. Parasitic infections remain a health problem and a constant concern for doctors and healthcare institutions worldwide, particularly in middle- and low-income countries. Parasitic infections not only cause chronic diseases but can also exacerbate immune disorders and malnutrition. Low vitamin D levels can reduce the immune system's ability to fight parasites, due to impaired production of the necessary defenses. Chronic parasitic infections can further lower vitamin D levels through malabsorption and systemic inflammation.

Experimental studies have provided a more profound understanding and revealed important aspects related to these interactions. Bezerra *et al*. (2019) demonstrated that highlighting the complex role vitamin D plays in regulating the parasite-host relationship. In humans, helminth infections are often accompanied by micronutrient deficiencies, which may affect immunity and the likelihood of further infection (4). A systematic review by Raj *et al*. (2022) has shown that parasitic worm infections in children often occur in conjunction with malnutrition, indicating that nutrients, and in particular vitamin D, have a clear effect on maintaining immune function and enhancing the body’s resistance to infection (5). Genetic factors also play a role in determining susceptibility to parasites. Salem *et al*. (2023) studied the relationship between VDR gene polymorphisms, serum vitamin D levels, and parasite load in patients with cutaneous leishmaniasis. The researchers found that specific vitamin D receptor variants were associated with higher parasite rates, suggesting that the severity of infection may be influenced by the interaction of two main factors: host genetic makeup and vitamin D levels (6).

Previous studies have shown that vitamin D has a complex role in the development of parasitic diseases, as its effect is not limited to being an essential nutrient, but extends to regulating the work of the immune system and supporting it in fighting parasites and reducing their impact on the body. Furthermore, vitamin D influences disease severity and outcome because it interacts with the host's genetics. Because the relationships between all these different diseases are complex, a comprehensive understanding and effective management strategy are essential in areas where parasitic infections are prevalent, as well as where vitamin and nutrient deficiencies are widespread. Treating low blood vitamin D levels is an effective and cost-efficient way to boost immunity (8). Therefore, this review aims to explore vitamin D deficiency and its relationship to increased susceptibility to parasitic infections, the impact of low levels on the body's immune response and susceptibility to parasitic infections, and treatment options.

Vitamin D and the Immune System

Vitamin D is a key regulator of immune function, with its receptors, called vesicular receptors (VDRs), located on various types of immune cells, including phagocytes, dendritic cells, and lymphocytes. These receptors help activate cells and regulate their reaction. Thanks to it, vitamin D contributes to directing the process of immune cell differentiation and increasing their number, and affects the way cytokines are produced. Ultimately, this helps achieve a healthy balance between innate and acquired immune response (9- 11). Low blood levels of vitamin D have been consistently associated with negative health Results, including increased susceptibility to infections and autoimmune disorders (12; 13). As well as being known for its role in boosting the immune system, vitamin D is also essential for maintaining a balanced immune

response. Its effect extends throughout a person's life, starting before conception until the period of pregnancy itself. Vitamin D has a clear effect on reproductive health and fetal growth, so it is considered a very important element in these sensitive periods (14). Research indicates that vitamin D can influence and precisely regulate immune activity. In the adaptive immune system, vitamin D performs a dual function, stimulating immune responses and modifying them as needed. However, applying these findings in clinical settings remains complex and difficult (Martins *et al*.,2020). Vitamin D plays an important role in its impact on COVID-19 infection outcomes and the effectiveness of vaccines (15). This topic deserves to be discussed in detail and extensively. Evidence suggests that sustainability is sufficient (16;17). Vitamin D enhances innate immunity by specifically enhancing the expression of antimicrobial peptides, cathelicidins, which enhance the body's defense against bacterial and viral pathogens (18; 19). Vitamin D- cathelicidin enhances the body's direct antibacterial response. It affects the body and stimulates the process of cleaning cells from the inside, which is a natural mechanism that helps get rid of germs that live inside cells. It also increases the body's ability to better resist infection (20).

Vitamin D plays a dual role in the adaptive immune system. It reduces the inflammatory responses of helper T cells, particularly in the Th17 and Th1 pathways. At the same time, it enhances the activity of regulatory T cells, which play a role in calming the immune system. This balance is very important because it prevents the body from attacking itself and also helps protect against autoimmune diseases. The presence of vitamin D receptors and the enzymes that convert it within immune cells allows the body to produce active vitamin D on its own (21). Also, the combination of vitamin D with vitamin A affects the balance of Th1 and Th2 cells, which encourages the immune system to adapt better. (22). Clinical and epidemiological studies support these mechanistic insights, as vitamin D deficiency has been associated with increased incidence of infections and autoimmune diseases, particularly among children (23). The therapeutic benefits of vitamin D are evident in specific disease states. For example, in multiple sclerosis, studies have shown that vitamin D supplementation enhances the production of anti-inflammatory cytokines such as IL-10 and TGF-β1, helping to reduce neuroinflammation and slow the progression of disability (24). In systemic lupus erythematosus, vitamin D reduces Th17-associated cytokines and expands regulatory T cells, thereby mitigating disease activity (25).

The importance of vitamin D in infectious disorders, particularly COVID-19, is demonstrated by its immunomodulatory effects, which may mitigate hyper-inflammatory conditions by reducing the secretion of pro-inflammatory cytokines (26). Furthermore, genetic research indicates that vitamin D modulates immune responses in autoimmune, microbial, and metabolic disease pathways, demonstrating its broad immunomodulatory impact (27). Based on these findings, vitamin D has multiple roles; it is not only preventative but also therapeutic. This highlights its importance in combating viral, inflammatory, and autoimmune diseases.

As a key component in regulating both the innate and adaptive immune systems, low levels of vitamin D can have effects that extend beyond typical infections and immune disorders. Research into the relationship between vitamin D levels and parasitic infections has become more important than ever, given the increasing impact of this vitamin on human health and current scientific trends in parasitic infections.

Vitamin D Deficiency and Parasitic Infections

Studies indicate that vitamin D deficiency plays a crucial role in weakening the body's immunity

against parasitic infections, particularly by affecting immune regulation in the digestive system. Clinical observations indicate that individuals with malabsorption disorders, such as inflammatory bowel disease, are more likely to suffer from vitamin D deficiency than the general population. This deficiency weakens the intestinal lining's immunity, making it more susceptible to infections and parasitic infestations (28; 29).

Protozoan parasites, such as *Toxoplasma gondii, Giardia lamblia*, and *Entamoeba histolytica*, are important global pathogens, as they have a high capacity to adapt to different environmental conditions, in addition to exploiting the host's weak immune response, which increases their ability to spread and cause infection. (30; 31). Vitamin D deficiency could worsen the host's immune system function and, therefore, parasite persistence and pathogenicity. Changes of the vitamin D immune axis can induce aberrant synthesis of antimicrobial peptides, impaired epithelial barrier integrity, and an imbalance in protection in the context of invading protozoa, promoting chronic colonization with the host (32; 33). Vitamin D not only directly affects immunity but also contributes to maintaining a healthy gut microbiome, which is essential for resisting parasitic infections. In the intestines, a well-bounded and beneficial colonizing gut microbiota is a natural defense against colonization by protozoa; consequently, vitamin D deficiency is associated with dysbiosis, potentially favoring parasite survival and development of disease (34). The interaction can be seen in excessive rates of vitamin D deficiency in people infected chronically with *Helicobacter pylori*, leading to impairment of intestinal processes and favoring of pathogens, including protozoa (35). Moreover, vitamin D deficiency in immunocompromised populations (e.g., HIV patients) may render protozoan reactivation and its dissemination within the body more likely to occur. Long-time latent *Toxoplasma gondii* infections have been reported to be reactivated in these patients, and research has shown a potential role of vitamin D-mediated immune surveillance processes in this process (36). At the molecular level, several protozoan-specific proteins (e.g., proteasome complex involved in protozoan replication and growth) have been identified as potential therapeutic targets (37). An understanding of the connection of vitamin D with these biological pathways can help to guide future therapeutic development by designing new and highly targeted approaches. From a cross-sectional perspective, the available data indicate a possible relationship between vitamin D deficiency and the clinical course and chronicity of protozoan infections. In these cases, therefore, it could be possible to consider vitamin D deficiency treatment in populations most at risk of parasite exposure as a potential alternative in the prevention and treatment of protozoan disease. Therefore, immunology, parasitology, or the microbiome, included in future research, will greatly benefit the understanding of this intricate discipline and hopefully contribute to improved evidence-based treatment and prevention models. Vitamin D deficiency nowadays is progressively acknowledged as a critical factor affecting host susceptibility and immune responses to parasitic infections. Research has shown that vitamin D deficiency can alter disease course, parasitic infection severity, and immune polarization, although the results vary depending on the pathogen and host. Epidemiological studies demonstrate strong links between vitamin D deficiency and enteroprotozoal infections. Serum vitamin D levels lower than 20 ng/mL were associated with an almost twofold increase in the risk of infection by protozoa—namely, *Iodamoeba* and *Cyclospora*, demonstrating that low serum vitamin D levels can affect mucosal immunity (38).In leishmaniasis, altered vitamin D dynamics have been observed, with clinical studies reporting that vitamin D status correlates with disease recurrence and severity (39; 40).

Experimental models provide a future explanation for the mechanisms: Vitamin D-deficient mice infected with *Leishmania amazonensis* showed accelerated lesion healing, accompanied by enhanced Th1/IFN-γ responses and reduced IL-10 production. This suggests that vitamin D plays a role in directing immune responses and regulating the parasite-host interaction (41).

There is a growing body of research linking vitamin D deficiency to *Toxoplasma gondii* infection, showing that low vitamin D levels are associated with higher antibody levels in women of reproductive age. This suggests that vitamin D may play an important role in controlling the spread of infection, with potential implications for reproductive health and pregnancy (42). Vitamin D deficiency is also commonly observed in individuals with intestinal disorders (malabsorption syndromes), such as Crohn's disease, a disorder associated with impaired innate gut immunity and increased susceptibility to protozoal infections. (43; 44).

Altogether, these findings support the dual role of vitamin D in parasitic infections, both as an immune modulator and as a disease modulator and chronicity modulator. Despite being associated with increased vulnerability to protozoan parasites and worms in susceptible hosts with vitamin D deficiency, unanticipated protective effects in some populations have been noted. This illustrates the multi-dimensional mechanisms of vitamin D's role in immune function. Further trials are needed to elucidate this relationship so as to decide whether vitamin D supplementation is viable as a supportive treatment in those regions with common parasitic infections (45; 46).

Possible Mechanisms:

Vitamin D deficiency weakens the body's defenses by disrupting vital immune pathways that link innate and adaptive immunity. One of the key mechanisms for this is a reduced ability of immune cells. Which limits the efficiency of the immune response and weakens the body's resistance to pathogens. This disorder impairs immune communication within and between endocrine glands, weakening local immune regulation (47,48).

Two essential molecules that help the body fight viruses, bacteria, and intracellular pathogens. The active form of vitamin D also stimulates autophagy, an important cellular mechanism that eliminates intracellular microorganisms, such as the bacteria that cause tuberculosis. Vitamin D is shown not only to elicit general immunity but also to provide individual cellular defense against pathogens. Inadequate vitamin D reduces autophagy pathways and is responsible for enhancing pathogen survival and persistence (49). Vitamin D is important for antigen-presenting cells. More precisely, it helps to moderate dendritic cell maturation, preventing excessive inflammatory responses, and at the same time, it reinforces those traits that make them capable of supporting the formation of regulatory T cells, which help calm the immune system. Such a mediated interaction is a critical link between the innate and adaptive immunity that mediates the balanced immune response and prevention of autoimmune-induced insult (49). Vitamin D also works through genomic means, where VDR-mediated transcriptional control promotes pathogen resistance, but also through rapid non-genomic signaling pathways that are able to fine-tune an immune response in real time. Vitamin D deficiency thus hampers the body's ability to mount potent antimicrobial defenses, and it can also result in dysregulation of inflammatory responses, presenting susceptibility to developing infection, chronic inflammation, and immune-mediated diseases (50).

Public Health Perspective

Vitamin D deficiency (VDD) represents a major global public health challenge that transcends geographic and economic boundaries. A pooled analysis of approximately 8 million people from 81 countries showed that vitamin D deficiency is widespread, with 15.7% having levels below 30 nmol/L, 47.9% below 50 nmol/L, and 76.6% below

75 nmol/L during the period between 2000 and 2022 (Cui *et al*., 2023). Populations in low-income and lower-middle-income countries suffer a disproportionately high burden of vitamin D deficiency, particularly in the Eastern Mediterranean and South Asia. Systematic reviews have shown that the prevalence of vitamin D deficiency reaches 96.2% in Afghanistan, 94% in Pakistan, and approximately 68% among adults in South Asia overall (51). In urban Sri Lanka research, around 93.9% of people exhibited inadequate vitamin D levels, with approximately 67.5% experiencing severe deficiency (52). Approximately 18.5% of children in Africa have low vitamin D levels (less than 30 nmol/L). This percentage is significantly higher in the northern and southern regions, and among girls and urban populations, illustrating the influence of environmental and social factors on vitamin D levels across different age groups and regions (53).

Elderly populations worldwide also demonstrate high rates, with a median prevalence of 59.7% (<50 nmol/L) (54). Despite the availability of some data, approximately 65% of low- and middle-income countries still lack comprehensive national information that accurately reflects the population-level vitamin D status. This is mostly the case for Tunisia, India, Afghanistan, Pakistan, and Mongolia (55).

Conclusion

Vitamin D deficiency is associated with an increased risk and severity of parasitic infections, whereas parasitic diseases exacerbate vitamin D deficiency by impairing absorption and elevating levels of chronic inflammation. This intertwined relationship demonstrates the need to combine nutritional research with studies related to parasites, with the aim of understanding the biological mechanisms more accurately and assessing the effectiveness of vitamin D as a preventive or therapeutic measure in areas with a high prevalence of parasitic infections.

Recommendation

The critical importance of more thorough clinical and laboratory evidence of the association between vitamin D deficiency and higher susceptibility to parasitic infections, employing modern diagnostics to ensure accuracy, is highlighted in this review. The review also recommends the incorporation of vitamin D measurement and supplementation in preventive health programs in endemic regions and promotes multidisciplinary collaboration of those working in immunology, nutrition, and parasitology to enhance knowledge on the underlying mechanisms. Moreover, raising awareness about vitamin D's role in strengthening immunity and reducing parasitic infections among the wider public is also strongly supported.

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