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REVIEW

Role of vitamin D in COVID-19 and other viral infections

Muhammet Mesut Nezir Engin, Öner Özdemir

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Muhammet Mesut Nezir Engin, Private Outpatient Clinic of Child Follow-up Academy, Sakarya 54050, Türkiye

Öner Özdemir, Division of Allergy and Immunology, Department of Pediatrics, Sakarya Research and Training Hospital, Sakarya University, Faculty of Medicine, Sakarya 54100, Türkiye

Corresponding author: Öner Özdemir, MD, Full Professor, Division of Allergy and Immunology, Department of Pediatrics, Sakarya Research and Training Hospital, Sakarya University, Faculty of Medicine, Adnan Menderes Cad., Sağlık Sok., No. 195 Adapazarı, Sakarya 54100, Türkiye. onerozdemir@sakarya.edu.tr

Abstract

Vitamin D is a steroid hormone that is naturally produced in the body or obtained through dietary sources, primarily under the influence of UVB radiation. This essential nutrient has a vital role in numerous physiological processes, encompassing immune function, cell growth, differentiation, insulin regulation, and cardiovascular well-being, along with its pivotal role in sustaining the delicate equilibrium of calcium and phosphate concentrations in the body. Moreover, vitamin D reinforces mucosal defense and bolsters the immune system through immunomodulation, making it a critical component of overall health. Numerous studies have unveiled the profound connection between vitamin D and the predisposition to respiratory tract infections, including well-known viruses such as influenza and the novel severe acute respiratory syndrome coronavirus 2. Vitamin D deficiency has been consistently linked to increased severity of coronavirus disease 2019 (COVID-19) and a heightened risk of mortality among afflicted individuals. Retrospective observational studies have further substantiated these findings, indicating that levels of vitamin D are linked with both the occurrence and severity of COVID-19 cases. Vitamin D has its influence on viral infections through a multitude of mechanisms, such as promoting the release of antimicrobial peptides and fine-tuning the responses of the immune system. Additionally, vitamin D is intertwined with the intricate network of the renin–angiotensin system, suggesting a potential impact on the development of complications related to COVID-19. While further clinical trials and extensive research are warranted, the existing body of evidence strongly hints at the possible use of vitamin D as a valuable tool in the prophylaxis and management of COVID-19 and other viral infectious diseases.

Key Words: COVID-19; SARS-CoV-2; Vitamin D; Influenza virus; Viral infections

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INTRODUCTION

Unlike other vitamins, vitamin D is a hormone that can be produced by the body by the action of UVB radiation on the skin or can be obtained from fish, milk, cereal products, and dietary supplements[1]. Vitamin D has a familiar role in maintaining calcium and phosphate balance, but recent research has revealed that it also has a role in immune function, cell proliferation and differentiation, insulin release, and cardiovascular health[2-4]. Vitamin D enhances mucosal defense by increasing immunity by secreting antiviral peptides with its immunomodulatory role[5,6]. Nutritional elements, such as vitamin D, known for its pivotal role in immune function, emerge as key players in this context. Recent data has shown the antiviral properties of vitamin D, capable of directly inhibiting viral replication, while also operating in an anti-inflammatory and immunomodulatory capacity.

Studies have linked vitamin D deficiency to acute respiratory infections with viruses such as influenza and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[7-9]. A meta-analysis conducted in 2019 examining the relation between vitamin D deficiency and the incidence of community-acquired pneumonia revealed that individuals with serum vitamin D concentrations < 50 nmol/L (equivalent to < 20 ng/mL) faced a 64% elevated risk of developing pneumonia[10]. It is also predicted that vitamin D deficiency may endanger the function of the pulmonary immune system and increase the risk of coronavirus disease 2019 (COVID-19) severity and fatality[11]. Understanding the alterations in the severity and mortality of COVID-19 is crucial, with a strong emphasis on enhancing nutrition and fortifying the immune system.

Carpagnano *et al*[12] identified a significant prevalence of vitamin D deficiency among COVID-19 patients experiencing acute respiratory failure. It is essential to recognize that vitamin D deficiency is connected to a range of health conditions and diseases that elevate the long-term susceptibility to contracting COVID-19. There is also a suggestion that vitamin D deficiency may promote long-term complications following COVID-19, and vitamin D use could potentially have a role in treatment. Nevertheless, further research is imperative in this area.

To examine the role of vitamin D in the severity and fatality of COVID-19 and other viral infections, a comprehensive review of existing studies was carried out. Databases such as Scopus, Google Scholar, Web of Science, PubMed, Cochrane Central Register of Controlled Trials, and medRXiv were systematically investigated for pertinent literature, encompassing discussions on the function, severity, and fatality aspects of vitamin D in viral infections[1-6].

METABOLISM OF VITAMIN D AND ITS DEFICIENCY

For a considerable duration, vitamin D was primarily recognized as a nutritional element integral to bone metabolism. Yet, modern insights have redefined its categorization as a steroid hormone, exposing its crucial regulatory functions within diverse physiological systems and pathways inherent to the body. Newly emerging evidence highlights the connection between vitamin D deficiency and various infectious diseases, particularly noteworthy when inadequate responses to standard treatments coincide with viral infections. Numerous clinical trials have illuminated the relationship between vitamin D deficiency and an elevated vulnerability to pulmonary infections. This connection is further substantiated by a multitude of laboratory experiments that emphasize the inhibitory role of vitamin D within the renin-angiotensin signaling pathway. The synthesis of vitamin D occurs in the dermis, initiated by the action of ultraviolet radiation on 7-dehydrocholesterol. Following this, vitamin D is conveyed to the liver, where it associates with the vitamin D binding protein and undergoes a transformation into its primary circulating form, 25-hydroxycholecalciferol (25(OH)D), facilitated by at least one cytochrome P450 (CYP) hydroxylase enzyme. Subsequently, the converted 25(OH)D travels to the kidneys, where an additional CYP hydroxylase enzyme initiates the synthesis of its hormonally active form, 1,25-dihydroxycholecalciferol (1,25(OH)2D3). However, despite the widespread recognition of the importance of vitamin D, achieving optimal levels remains a challenging endeavor for many individuals across the globe. vitamin D deficiency is a pervasive universal health fear, affecting an estimated population of > 3 billion people, with half of these individuals experiencing a genuine and clinically significant vitamin D deficiency[7,13-21] (Table 1).

Epidemiological studies consistently indicate a link between diminished plasma vitamin D levels and increased susceptibility to both acquiring and suffering from severe respiratory viral infections. These findings strongly indicate the potential utility of vitamin D intake in the realms of viral respiratory infection prevention and treatment. A meta-analysis

Table 1 Effects of vitamin D supplementation on the immune system and other different conditions[25]

Immune system component	Effect
T cells	↓ Th 1/Th 17 and ↑ Th 2
	↓ IL-8, IFN-γ, IL-12, IL-6, TNF-α, IL-17
	↑ IL-4, IL-5, IL-10
	Recognition of viral dsRNA by TLR - 3
B cells	↑ Apoptosis
Plasma cells	↓ Proliferation and immunoglobulin secretion
Neutrophils, monocyte-macrophages and dendritic cells	Reception to infectious areas, ↑ TLR
	↑ Intracellular killing of *Mycobacterium tuberculosis* (macrophages)
Infected cells	↑ Autophagy and apoptosis
Antimicrobial peptides (human cathelicidin peptide LL - 37 and β-defensin)	Augmented
Respiratory tract infections	Effect
Acute respiratory infections	↓ Proinflammatory cytokines in the lung through modulation of the activity of both macrophages and T lymphocytes
	↓ Risk of getting sick
VAP	↓ IL-6
	↓ Mortality rate
Autoimmune disease	Effect on disease
Type 1 diabetes	Prevention of onset, ↓ serum antibody levels, delayed β cell destruction in early stages of disease
Multiple sclerosis	Prevention of the onset
Rheumatic joint inflammation	Prevention of onset, reduced disease activity
Systemic lupus erythematosus	Prevention of onset, reduced disease activity
Crohn's disease	Prevention of the onset
Thyroiditis	Prevention of the onset
Psoriasis	Prevention of the onset
Polymyalgia rheumatica	Prevention of the onset
Autoimmune gastritis	Prevention of the onset
Systemic sclerosis	Downregulation of TGF-β/Smad signaling (putative antifibrotic effect in early stages of disease)
Pulmonary fibrosis	Effect
IL-1β	Decreased antagonism of pulmonary fibroblast cell activity in a murine model of bleomycin-induced lung fibrosis
Hydroxyproline, col1a1, col3a1, and α-smooth muscle actin mRNAs	Prevention of bleomycin-induced lung fibrosis in a mouse model

Th: T helper; IL: Interleukin; IFN: Interferon; TNF: Tumor necrosis factor; TLR: Toll-like receptor; VAP: Ventilator associated pneumonia.

revealed a reciprocal correlation between decreased serum 25(OH)D concentration and respiratory tract infections. According to this analysis, lower vitamin D levels were observed to be more efficacious in guarding against respiratory infections. Yet another meta-analysis identified a negative correlation between levels of circulating 25(OH)D and the risk as well as the severity of respiratory tract infections. Subjects with the lowest 25(OH)D concentrations < 15 ng/mL were determined to have the highest risk of respiratory tract infection[22-24].

The metabolism of vitamin D can be summarized as follows. In part A, how vitamin D regulates the immune system is discussed. In this section, vitamin D is specifically focused on T cells. The activity of T helper (Th)1 and Th17 cells is downregulated by vitamin D, while Th2 cells affect cytokine production. Proinflammatory type 1 cytokines [*e.g.*, interleukin (IL)-6, IL-8, IL-12, interferon (IFN)-γ, tumor necrosis factor (TNF)-α, and IL-17] decrease, while type 2 anti-inflammatory cytokines (*e.g.*, IL-4, IL-5, and IL-10) increase. Vitamin D has a function in regulation of the recognition of

viral double-stranded RNA (dsRNA) through Toll-like receptor 3. This regulatory function is pivotal in the immune response against viral infections. Vitamin D has a proapoptotic role by reducing the lifespan of B cells, the proliferation of plasma cells, and immunoglobulin production. Infected areas trigger the recruitment of neutrophils, monocytes, macrophages, and dendritic cells, which in turn enhance their intracellular pathogen-killing capabilities. This heightened immune response is especially critical in combating infections by pathogens such as *Mycobacterium tuberculosis*. Infected cells become more prone to autophagy and apoptosis. Finally, vitamin D may augment the production of antimicrobial peptides such as human cathelicidin peptide LL - 37 and β-defensin[25].

Part B deals with the influence of vitamin D on antiretroviral therapy. Vitamin D can mitigate the risk of disease development by participating in the reduction of proinflammatory cytokines. However, no clear effect on childhood pneumonia has been demonstrated. Decreased IL-6 levels and mortality rates have been reported in patients with ventilator-associated pneumonia (Table 1).

EFFECT OF VITAMIN D ON THE RENIN–ANGIOTENSIN SYSTEM

Vitamin D shows its effectiveness on the renin–angiotensin system (RAS) by inhibiting renin synthesis, reducing angiotensin-converting enzyme (ACE) and angiotensin (Ang) II production, and increasing ACE2/Ang-(1–7) axis activity. The active form of vitamin D (1,25(OH)2D3) directly inhibits renin synthesis. This effect is independent of Ang II feedback regulation. In *in vitro* studies, in cell lines with high renin expression levels, 1,25(OH)2D3 directly and comprehensively inhibits renin gene transcription. Vitamin D binds to vitamin D receptors (VDRs) in cells. This complex functions as a transcription factor that inhibits transcription of the renin gene. Binding of VDR to the promoter region of the renin gene directly reduces renin mRNA synthesis. 1,25(OH)2D3 supports the negative feedback mechanism on the RAS by reducing renin synthesis. This leads to lower levels of renin and Ang II, which in turn lowers blood pressure. Vitamin D may indirectly inhibit renin synthesis in the kidneys by reducing the production of inflammatory cytokines. Since inflammation is a factor that increases renin production, the anti-inflammatory effects of vitamin D may suppress renin synthesis[26,27].

In experimental studies conducted in rat models, the active form of vitamin D inhibits the production of renin, ACE and Ang II, while increasing the expression of ACE2. The active form of vitamin D directly inhibits ACE gene expression. This effect leads to decreased ACE levels and therefore decreased Ang II production. Vitamin D indirectly reduces Ang II production *via* ACE by reducing renin production. Decreased renin levels lead to decreased Ang I, which in turn leads to decreased ACE activity and Ang II production. Vitamin D may contribute to indirect inhibition of ACE and Ang II production by reducing the production of inflammatory cytokines. Inflammation is a factor that increases ACE and Ang II production. Vitamin D negatively regulates RAS by increasing the activity of the ACE2/Ang-(1–7) axis. This regulation provides a protective effect against acute lung injury[26-29].

BRIEF PATHOLOGY OF COVID-19

Chen *et al*[30] conducted a study using bronchoalveolar lavage samples from two patients exhibiting typical symptoms of COVID-19. They sequenced the complete genome of the SARS-CoV-2, comprising 29 881 nucleotides, utilizing a low-input metagenomic next-generation sequencing method. Their analysis unveiled a substantial 94.6% genetic resemblance between SARS-CoV-2 and SARS-CoV, suggesting their shared species origin. In previous years, it was established that SARS-CoV utilizes ACE2 as its primary receptor to infect host cells[26]. Building on this knowledge, Zhou *et al*[31] showed that SARS-CoV-2 similarly uses ACE2 as a cellular binding receptor in ACE2-expressing cells from humans, civets, pigs, and Chinese horseshoe bats (although not in mice). ACE2 acts as the cell fusion receptor, and its distribution in organs *e.g.* endothelium, lung, heart, kidney, and intestine aligns with the tropism of SARS-CoV-2. Preliminary investigations have associated SARS-CoV-2 infection with significant clinical manifestations, including acute respiratory distress, acute heart injury, acute renal failure, and gastrointestinal symptoms. ACE2, apart from its role in viral entry, serves as a second ACE, playing a vital role in regulating the RAS. The RAS system comprises numerous enzymes, peptides, and receptors critical for diverse biological functions like blood pressure and fluid balance in the body. Distinct from other RAS components such as ACE and Ang II, ACE2 has a protective role in mitigating lung injury. It counterbalances the effects of Ang II by converting it into Ang-(1–7), a peptide formed through ACE hydrolysis. Studies have indicated a connection between heightened ACE activity, linked to a deletion polymorphism in the ACE gene, and the development of ARDS and related fatality. Moreover, ACE2 has been shown to offer protection against sepsis-induced lung injury in mouse models. Therefore, ACE2 appears to be a pivotal factor both in facilitating the cellular entrance of SARS-CoV-2 and influencing the pathogenicity of the infection[30-38].

CURRENT STUDIES ON THE ROLE AND CONSEQUENCES OF VITAMIN D IN SARS-COV-2 INFECTION

Numerous retrospective observational studies have been undertaken to investigate the link between vitamin D levels and SARS-CoV-2 infection. Several of these studies have revealed substantial associations between vitamin D levels and the prevalence and severity of COVID-19. For instance, a study conducted in South Asian countries disclosed notable differences in vitamin D levels among mild, moderate, severe, and critical COVID-19 cases. Similarly, a cohort study in

Singapore demonstrated that patients receiving vitamin D, magnesium, and vitamin B12 supplements needed less oxygen therapy and exhibited protective effects against clinical deterioration. Other investigations have reported reduced vitamin D levels in cases with severe COVID-19 and those with predisposing medical disorders. A study from Belgium indicated that vitamin D levels in COVID-19 cases were meaningfully lower compared to a control group. Moreover, a study using data from diverse regions across the world suggested a 19% decrease in the number of severe COVID-19 cases in populations with normal vitamin D levels. A retrospective cohort study in Indonesia identified higher mortality rates among older COVID-19 male patients with low vitamin D levels and pre-existing medical conditions. Importantly, this study revealed a robust correlation between vitamin D levels and COVID-19 fatality, even after adjusting for potential confounding factors. A study done in the US mainland highlighted the link between sunlight exposure, vitamin D levels, and reduced risk of COVID-19 cases and mortality. While several observational research has indicated associations between vitamin D concentrations and COVID-19 incidence and severity, it is crucial to acknowledge that the results across these studies are not always consistent. A shortage of clinical trials and cohort research hinders the establishment of conclusive evidence concerning the function of vitamin D in the prophylaxis or management of COVID-19 (Table 2). Consequently, additional research is essential to provide more definitive insights into this matter[31-33,39-42].

POTENTIAL EFFECTS OF VITAMIN D ON COVID-19 COMPLICATIONS

Vitamin D may play an important role in the management of COVID-19 complications through its regulatory effects on the RAS. By reducing the production of renin, ACE, and Ang II and increasing the expression of ACE2, vitamin D may reduce the risk of ARDS, inflammation, vascular damage, and thrombosis. These mechanisms suggest that vitamin D may be used as a potential adjuvant in the treatment of COVID-19 (Table 2). However, more clinical research is needed to better understand these effects[25-28].

EVALUATION OF FINDINGS IN THE CONTEXT OF AGE, GENDER AND SYSTEMIC CONDITIONS

In the studies presented in Table 3, we addressed the effects of vitamin D deficiency and supplementation on viral infections in the context of various age groups, genders, and pre-existing systemic conditions[43-50].

Vitamin D deficiency increases susceptibility to respiratory infections. Adequate vitamin D levels may play an important role in reducing the risk of acute respiratory infections. It appears that vitamin D supplementation may reduce the incidence of respiratory infections, especially in at-risk groups such as children, the elderly, and individuals with chronic diseases.

Studies in children and adolescents reveal that vitamin D deficiency increases the risk of upper and lower respiratory tract infections. It is stated that vitamin D supplementation is effective in reducing the incidence of viral infections such as influenza. A significant association has been found between low vitamin D levels and an increased risk of respiratory infections in adults and elderly individuals. The protective effects of vitamin D supplementation were also supported in this group.

Although the studies generally included both genders, no significant difference was observed between genders. In both men and women, adequate vitamin D levels appear to have similar effects in reducing the risk of respiratory infections.

In individuals with chronic respiratory diseases such as asthma and chronic obstructive pulmonary disease, vitamin D deficiency can lead to more frequent respiratory infections. It is stated that vitamin D supplementation can reduce the frequency of infections in these individuals. Similar findings have been obtained in individuals with chronic diseases such as diabetes, hypertension and HIV infection. While vitamin D deficiency may increase the risk of respiratory infections in these individuals, it appears that this risk can be reduced with supplementation[45-54].

On the contrary, Murdoch *et al*[48] and Belderbos *et al*[55] show that the protective effect of vitamin D supplementation in all populations is not always clear. For example, Murdoch *et al*[48] found that vitamin D supplementation had no protective effect against upper respiratory tract infections in healthy adults. McNally *et al*'s study, conducted in children in intensive care, emphasized that vitamin D deficiency is associated with infections and the importance of improving vitamin D levels in these children[56].

As a result, vitamin D deficiency stands out as a factor that generally increases the risk of respiratory tract infections. It is supported by many studies that vitamin D supplementation may be effective in reducing the incidence of infection, especially in at-risk groups. However, some studies also show that protective effects are not always consistent, so more research is needed to better understand the effects of vitamin D supplementation.

CLINICAL EFFECTS OF VITAMIN D SUPPLEMENTATION ON VIRAL INFECTIONS AND DOSAGE CONTROVERSIES

The overall findings of the studies in Table 4 reveal the negative effects of vitamin D deficiency on viral infections, especially COVID-19. It is suggested that vitamin D supplementation may reduce the severity of infections and mortality, especially in high-risk groups (older people, those with chronic diseases). However, some studies also show that the effect of high-dose vitamin D supplementation on clinical outcomes is limited. Therefore, more research is needed to

Table 2 Correlation of vitamin D concentrations with severe acute respiratory syndrome coronavirus 2 infections and outcomes

Ref.	*n*	Population type	Study type	Vitamin D dosages	Results
Lau *et al*[111], 2020	20	Adults, average age 65.2 yr	Retrospective observational study	NA	Higher levels of vitamin D deficiency were observed in ICU patients (84.6%) compared to baseline patients (57.1%) (P = 0.29)
Hastie *et al*[115], 2020	449	Adults, age 37–73 yr	Cross-sectional study	NA	Vitamin D levels showed a significant association with SARS-CoV-2 infection in univariate analysis (P = 0.013)
Ilie *et al*[116], 2020	Cases and deaths/1 M population	Adults	Retrospective	NA	Negative correlation was observed between mean levels of vitamin D and COVID-19 cases (P = 0.050) and deaths (P = 0.053) per million population
Glicio *et al*[117], 2020	176	Adults, age ≥ 60 yr	Retrospective	NA	Severe patients are more likely than mild patients had a lower level of vitamin D
Tan *et al*[69], 2020	43	Adults, age ≥ 50 yr	Cohort observational	Vitamin D 1000 IU	Patients treated with vitamin D showed a significant protective effect against clinical deterioration after adjusting for age, sex and comorbidities (P = 0.041)
Darling *et al* [118], 2020	580 cases and 723 controls	Adults, average age 57.7 yr	Retrospective	NA	No significant difference was observed in vitamin D levels between COVID-19 cases and the control group
Raharusun *et al* [119], 2020	780 cases	Adults, average age 54.5 yr	Retrospective cohort study	NA	In univariate analysis, older and male cases with pre-existing medical conditions and below normal vitamin D levels were associated with higher mortality rates
Daneshkhah *et al* [120], 2020	5000 cases	Age ≤ 80 yr	As of March 21, 2020	NA	Approximately 15% reduction in the number of severe COVID-19 cases was observed in a population given a normal vitamin D status

NA: Not available; ICU: Intensive care unit; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; COVID-19: Coronavirus disease 2019.

better understand the effects of vitamin D supplementation and determine optimal dosage[57-66].

VITAMIN D AND MECHANISMS TO REDUCE VIRAL INFECTIONS

Most effects of vitamin D are intricately tied to the recruitment of calcitriol to the nuclear VDR. This receptor, located within the cell nucleus, orchestrates the assembly of active chromatin complexes that, in turn, instigate genetic and epigenetic modifications of transcriptional output. This occurs by the direct interaction of the receptor with regulatory sequences situated in proximity to the target genes. One of the most well-known functions of calcitriol, the active vitamin D, is its role in regulating serum calcium levels, forming a feedback loop with parathyroid hormone (PTH). In this intricate interaction, vitamin D ensures the harmonious absorption and utilization of calcium by counteracting the effects of PTH, ultimately serving to keep calcium concentration within a narrow range. Along with its role in calcium regulation, vitamin D boasts a plethora of other effects. It has a vital part in managing calcium and phosphate metabolism, overseeing the mineralization of bone, regulating the working of the immune system, and controlling the processes of cellular growth and differentiation. Through its genetic and epigenetic actions, vitamin D yields a far-reaching impact on health, influencing a wide array of biochemical and physiological processes within cells. This underscores the multifaceted role of vitamin D in sustaining overall healthiness[67-71].

Many studies have examined the mechanisms by which vitamin D reduces the risk of viral infections (Table 3). Vitamin D uses a variety of mechanisms to reduce the risk of microbial infections and associated mortality. A current review has categorized the role of vitamin D in reducing the risk of viral infections into three key categories.

Physical barrier enhancement

Vitamin D contributes to the maintenance of robust physical barriers that prevent the invasion of pathogens. It helps in preserving the integrity of tight junctions, gap junctions, and junctional complexes between cells, such as through E-cadherin. This maintenance of cell junctions acts as a protective physical barrier against infections. When these connections are compromised, it can elevate the risk of microbial invasion. Vitamin D has a function in preserving the integrity of these junctions, thereby reducing the susceptibility to infections.

Innate cellular immunity activation

Vitamin D is involved in the activation of the innate cellular immune system. It enhances the antiviral activity of cells, thereby providing a protective effect against various microbes. This aspect of vitamin D contributes to the body's initial defense against pathogens, including viruses.

Table 3 Effect of vitamin D levels on viral infections according to age, gender and systemic conditions

Ref.	Age group	Gender	Preexisting conditions	Results
Martineau *et al*[43], 2017	0–95 yr	Both genders	Asthma, COPD	Vitamin D supplementation is effective in reducing the risk of acute respiratory infections
Ginde *et al*[9], 2009	≥ 20 yr	Both genders	Chronic diseases (DM, HT)	Vitamin D deficiency is associated with the prevalence of upper respiratory tract infections
Sabetta *et al*[44], 2010	20–89 yr	Both genders	Chronic diseases	The risk of respiratory tract infection is reduced in individuals with serum 25(OH)D levels above 38 ng/mL
Cannell *et al*[7], 2006	0–90 yr	Both genders	Various health conditions	Vitamin D deficiency may increase susceptibility to influenza and respiratory infections
Laaksi *et al*[45], 2007	18–28 yr	Male	Healthy individuals	Vitamin D supplementation may reduce incidence of respiratory infections
Urashima *et al*[46], 2010	6–15 yr	Both genders	Healthy children	Vitamin D supplementation is effective in reducing the incidence of influenza A
Berry *et al*[47], 2011	≥ 65 yr	Both genders	Chronic diseases	Vitamin D deficiency is associated with risk of respiratory infections
Murdoch *et al*[48], 2012	50–84 yr	Both genders	Chronic diseases (COPD)	Vitamin D supplementation has no protective effect on respiratory infections
Jolliffe *et al*[49], 2020	0–95 yr	Both genders	Asthma, COPD	Vitamin D supplementation is effective in reducing the risk of acute respiratory infections
Camargo *et al*[50], 2012	3–24 yr	Both genders	Healthy children	Vitamin D deficiency may increase risk of acute lower respiratory tract infections
Hollams *et al*[51], 2011	0–10 yr	Both genders	Asthma, allergy	Vitamin D deficiency is associated with asthma and respiratory infections
Majak *et al*[52], 2011	5–18 yr	Both genders	Asthma	Vitamin D supplementation may reduce infection frequency in children with asthma
Esposito *et al*[53], 2013	0–16 yr	Both genders	Healthy children	Vitamin D deficiency may increase risk of respiratory infections
Thornton *et al*[54], 2014	18–45 yr	Both genders	HIV positive individuals	Vitamin D deficiency is associated with risk of respiratory infections
Belderbos *et al*[55], 2011	0–1 yr	Both genders	Healthy babies	Vitamin D deficiency may increase the risk of respiratory syncytial virus bronchiolitis
McNally *et al*[56], 2009	0–17 yr	Both genders	Chronic diseases	Vitamin D deficiency associated with respiratory tract infection in intensive care
Le Goaziou *et al* [57], 2011	0–16 yr	Both genders	Healthy children	Vitamin D deficiency is associated with risk of upper respiratory tract infections
Liu *et al*[58], 2020	0–18 yr	Both genders	Chronic diseases (asthma, COPD)	Vitamin D deficiency associated with risk of viral respiratory infections
Grant *et al*[59], 2009	0–95 yr	Both genders	Various health conditions	Vitamin D deficiency may increase risk of influenza and pneumonia
Aloia *et al*[60], 2007	18–45 yr	Both genders	HIV positive individuals	Vitamin D deficiency is associated with risk of respiratory infections

COPD: Chronic obstructive pulmonary disease; DM: Diabetes mellitus; HT: Hypertension.

Support for adaptive immunity

Vitamin D also has a critical function in the adaptive immune system. It supports the proper functioning of immune cells and regulates inflammatory responses. By doing so, vitamin D aids in controlling the spread of microbial infections and moderating the body's immune responses, preventing excessive inflammation and tissue damage.

In summary, the multifaceted role of vitamin D in bolstering physical barriers, activating the innate cellular immune system, and regulating the adaptive immune system collectively contributes to lessening the risk of microbial infections and their associated consequences, underscoring the importance of sustaining satisfactory vitamin D levels for general well-being and immune function[71-74].

Vitamin D has a pivotal role in enhancing cellular innate immunity through several mechanisms, including the stimulation of antimicrobial peptides like human cathelicidin (LL-37) and defensins. These antimicrobial peptides display direct antimicrobial activity against a broad spectrum of pathogens, including Gram-positive and Gram-negative bacteria, enveloped and nonenveloped viruses, and fungi. They accomplish this by disrupting the cell membranes of pathogens

Table 4 Summary of current studies examining the use of vitamin D in coronavirus disease 2019 and other viral infections conditions

Ref.	*n*	Vitamin D type	Vitamin D dosage	Application method	Viral infection	Disease status	Results
Entrenas Castillo *et al* [61], 2020	76	Vitamin D3 (calcifediol)	0.532 mg on day 1, then 0.266 mg on days 3 and 7, and weekly thereafter	Oral	SARS-CoV-2	Mild–moderate	The need for intensive care and the mortality rate were lower in patients receiving vitamin D treatment
Murai *et al* [62], 2021	240	Vitamin D3 (cholecalciferol)	200000 IU loading dose	Oral	SARS-CoV-2	Mild–moderate	High-dose vitamin D treatment did not improve clinical outcomes of COVID-19 patients
Rastogi *et al* [63], 2020	40	Vitamin D3 (cholecalciferol)	60000 IU/d for 7 d	Oral	SARS-CoV-2	Light	Vitamin D treatment shortened the time to PCR negativity
Maghbooli *et al*[64], 2020	235	Vitamin D3 (cholecalciferol)	50000 IU/wk	Oral	SARS-CoV-2	Mild–moderate	Adequate vitamin D levels shortened hospitalizations and reduced rates of serious illness
Annweiler *et al*[65], 2020	77	Vitamin D3 (cholecalciferol)	80000 IU single dose	Oral	SARS-CoV-2	Moderate–severe	COVID-19-related mortality rates were lower in patients receiving vitamin D therapy
Cangiano *et al* [66], 2020	90	Vitamin D3 (cholecalciferol)	25000 IU/mo	Oral	SARS-CoV-2	Moderate–severe	Severity of COVID-19 symptoms decreased in older individuals with vitamin D deficiency
Giannini *et al* [67], 2021	100	Vitamin D3 (cholecalciferol)	100000 IU/mo	Oral	SARS-CoV-2	Mild–moderate	High doses of vitamin D were found to be effective in reducing complications due to COVID-19
Ling *et al*[68], 2020	50	Vitamin D3 (cholecalciferol)	400 IU/d	Oral	Respiratory tract infections	Mild–moderate	Vitamin D supplementation has been found effective in reducing the incidence of respiratory infections
Tan *et al*[69], 2020	43	Vitamin D3 (cholecalciferol)	1000 IU/d	Oral	SARS-CoV-2	Moderate–severe	Vitamin D supplementation was found to be effective in reducing hospital stay and complications

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; COVID-19: Coronavirus disease 2019.

and can nullify the biological activities of endotoxins. For instance, in mouse models, LL-37 has demonstrated the capacity to reduce the replication of influenza A virus. Moreover, 1,25-dihydroxyvitamin D, the active vitamin D form, has been shown to diminish rotavirus replication both *in vitro* and *in vivo*. A clinical trial described that 4000 IU/day of vitamin D reduced the incidence of dengue disease. Vitamin D also exerts an influence on cellular immunity by mitigating the cytokine storm triggered by the innate immune system. When the innate immune system responds to viral and bacterial infections, it produces a mix of proinflammatory and anti-inflammatory cytokines. Vitamin D can decrease the synthesis of proinflammatory Th1 cytokines, *e.g.* TNF-and IFN-γ. Additionally, vitamin D administration increases the expression of anti-inflammatory cytokines by macrophages while concurrently declining the expression of proinflammatory cytokines. The ability of vitamin D to stimulate antimicrobial peptides, dampen pathogen replication, and modulate the cytokine response serves as a multifaceted approach in bolstering the innate and cellular immune systems, ultimately contributing to a more balanced and effective immune response to infections[11]. These mechanisms are illustrated in Figure 1.

Vitamin D functions as a modulator of adaptive immunity, and its active form, 1,25-dihydroxy vitamin D3 (1,25(OH)2D3), has several effects on immune responses.

Th1 suppression

1,25(OH)2D3 can suppress Th1-mediated responses, specifically by reducing the formation of inflammatory cytokines like IL-2 and IFN-γ. This leads to a dampened Th1 response, which is recognized for its proinflammatory properties.

Th2 promotion

Conversely, 1,25(OH)2D3 helps cytokine making by Th2 cells, which tend to produce anti-inflammatory cytokines. This balance helps in moderating immune responses.

T regulatory cell induction

1,25(OH)2D3 also plays a role in the stimulation of T regulatory cells (Tregs), which are crucial for controlling immune responses and preventing excessive inflammation.

In the context of COVID-19, it is worth noting that serum 25(OH)D levels are inclined to wane with age. Since case–fatality rates for COVID-19 rise with age, this age-related decline in vitamin D levels may be of implication. Reduced

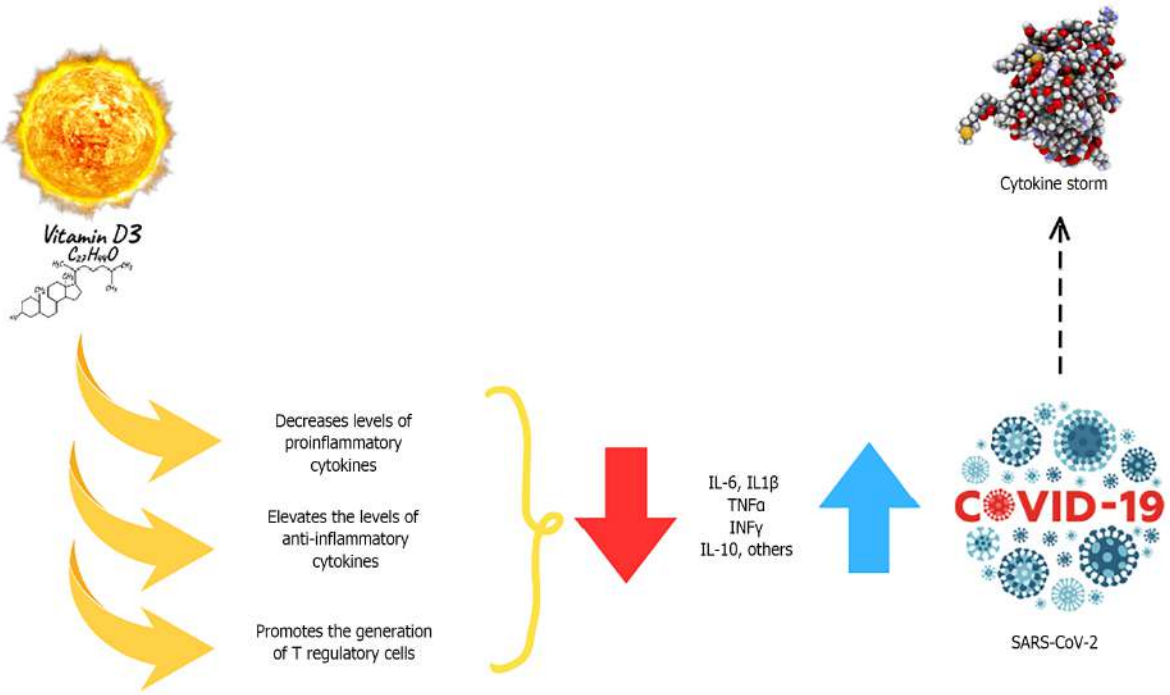

Figure 1 Mechanisms by which vitamin D may reduce the risk of cytokine storm. The blue up arrow indicates an increase and the red down arrow indicates a decrease. IL-6: Interleukin-6; IL-1β: Interleukin-1β; TNFα: Tumor necrosis factor α; INF-γ: Interferon γ; IL-10: Interleukin-10.

exposure to sunlight, often due to aging, can lead to decreased vitamin D production, as the skin has lower levels of 7-dehydrocholesterol, a precursor necessary for vitamin D synthesis. Furthermore, some pharmaceutical drugs stimulate the pregnane-X receptor and, as a side effect, reduce serum 25(OH)D levels. These drugs include antibiotics, anti-inflammatory agents, antihypertensives, antiretrovirals, antiepileptics, antineoplastics, endocrine, and certain herbal drugs. It is important to note that pharmaceutical drug use naturally surges with age, potentially compounding the age-related decline in vitamin D levels. Vitamin D supplementation has been related to the amplified expression of antioxidation-related genes, which in turn can support the action of other antioxidants like vitamin C (ascorbic acid). Vitamin C is recognized to possess antimicrobial activity and is recommended for preventing and treating COVID-19. Prominent health figures have also suggested the probable function of vitamin D in addressing the COVID-19 pandemic. However, it is essential to emphasize that while these connections are noteworthy, more comprehensive research and clinical trials are required to demonstrate the precise function of vitamin D in COVID-19 prevention and treatment[75-85].

POTENTIAL MECHANISMS OF VITAMIN D TO REDUCE COVID-19 PROGRESSION

Numerous clinical and epidemiological studies have provided compelling evidence for a significant interplay between vitamin D and the complex network of RAS. In experimental studies involving rats, the active vitamin D form has been demonstrated to inhibit the creation of renin, ACE, and Ang II. Conversely, it increases the expression of ACE2, particularly in the context of lipopolysaccharide-induced acute lung injury (ALI). In essence, vitamin D appears to enhance the activity of the ACE-2/Ang-(1–7) axis by negatively regulating the RAS while concurrently reducing the activities of the renin and ACE/Ang II pathway. This modulation has been observed to have protective effects in animal models, where blocking the (pro)renin receptor led to a reduced inflammatory response in pulmonary cells, offering protection against lipopolysaccharide-induced ALI. Vitamin D has demonstrated the capacity to suppress renin production, and this effect appears to be independent of Ang II feedback regulation. In mice, vitamin D deficiency causes increased renin synthesis, whereas supplementation with 1,25(OH)2D3 inhibits renin expression. Moreover, *in vitro* studies have revealed that in cell lines characterized by high renin expression levels, 1,25(OH)2D3 directly and comprehensively inhibits the transcription of the renin gene through a VDR-mediated mechanism. This intricate relationship between vitamin D and the components of the RAS has implications for various aspects of health, including susceptibility to respiratory infections. Emerging data suggests that different RAS components have a role in the progress of complications associated with COVID-19, underscoring the importance of understanding the regulatory interplay between vitamin D and these elements. While it is not yet fully elucidated how poor vitamin D concentration contributes to the progress and aggravations of viral diseases, several hypotheses have been proposed. Research continues to elucidate these connections, emphasizing the relevance of vitamin D in respiratory health and its potential impact on viral infections[86-92].

The VDR is expressed at high levels in many immune system cells, including dendritic cells, as well as T and B lymphocytes. Once vitamin D interacts with VDR, it performs as a transcription factor, modifying the responses of these immune cells to viral infections. Importantly, VDR is also expressed in pulmonary tissue, and its role in lung health is

evident. *In vivo* studies involving rodents and VDR-knockout mice have provided valuable insights. These studies have indicated that VDR-knockout mice experience more severe LPS-induced ALI with higher mortality rates. The deficiency of VDR in lung cells leads to increased expression of Ang II, heightened alveolar permeability, pulmonary vascular leakage, elevated neutrophil infiltration, enhanced apoptosis, heightened respiratory inflammation, and increased expression of proinflammatory cytokines and chemokines. Additionally, a specific VDR polymorphism known as the FokI T allele has been related to an amplified susceptibility to viral infections caused by enveloped viruses. The FokI polymorphism involves genetic variations that alter the interaction between VDR and transcription factors, resulting in functional modifications of VDR. This polymorphism can lead to changes in the transcriptional activity of VDR, which in turn can impact the response to viral infections. In summary, the presence and function of VDR in immune cells and lung tissue underscore the vital role of vitamin D in regulating immune reactions and maintaining respiratory health. Variations in the VDR gene, such as the FokI polymorphism, can further influence an individual's susceptibility to viral infections, especially those caused by enveloped viruses. Understanding these genetic and immunological aspects provides valuable insights into the complex interplay between vitamin D and the immune system[39,90-96].

The study conducted by Hansdottir and colleagues sheds light on the expression of key genes in primary lung epithelial cells, providing valuable insights into the role of vitamin D in immune regulation. These cells were found to express high levels of the CYP27B1 gene and low levels of the CYP24A1 gene[18,22].

CYP27B1 is an enzyme responsible for converting the circulating vitamin D form, 25(OH)D3, into its active hormonal form, 1,25(OH)2D3. In contrast, CYP24A1 degrades the active vitamin D form. This active vitamin D, 1,25(OH)2D3, plays a pivotal role in the regulation of the immune system. Crucially, immune cells can convert the inactive form of vitamin D into its active form, facilitated by the CYP27B1 enzyme. This conversion is closely associated with the making and regulation of antimicrobial peptides. Among these peptides, defensins hold a significant role. They are produced by the human airway epithelium and are found in the respiratory tract, where they function in defending the respiratory mucosa. When vitamin D is activated locally, it can straightly stimulate the expression of cathelicidin peptides, particularly cathelicidins. In the context of viral infections, vitamin D can synergistically interact with the active form of viral RNA, leading to intensification in the expression of antimicrobial peptides, notably cathelicidins. Cathelicidins are a group of peptides that are part of the innate immune system in various vertebrates, and they possess direct and indirect antimicrobial activity against a range of pathogens, comprising enveloped viruses. The vitamin D–cathelicidin axis plays a crucial function in the control of the human immune system, modulating both innate and adaptive immunity. One member of the cathelicidin family, LL-37, is produced by respiratory epithelial cells and enhances the ability to combat microbes, particularly respiratory pathogens. Vitamin D can trigger the expression of the LL-37 gene (CAMP), contributing to this antimicrobial activity. In summary, the study underscores the significance of vitamin D in the regulation of immune responses, particularly through its role in the induction of antimicrobial peptides like cathelicidins, which are instrumental in defending against a range of pathogens, containing respiratory viruses[15,97-111].

INFLUENZA AND VITAMIN D

Influenza virus exerts its effect on the respiratory tract by direct infection or by impairing the immune system reaction. Pneumonia usually develops due to influenza infection and is one of the causes of death. The risk of pneumonia is higher in groups such as individuals < 5 years of age, > 65 years of age, white individuals and those living in nursing homes, those with chronic lung or heart disease, smokers, and those with weakened immune systems. Seasonal influenza infections are generally more common during the winter months. This has been linked to the season when the sun's UVB rays, and therefore vitamin D (25(OH)D) levels, are lowest in most mid- and high-latitude countries during the winter months. Serum 25(OH)D levels are around 21 ng/mL in winter and 28 ng/mL in summer in the northern and central USA, and around 24 ng/mL in winter and 28 ng/mL in summer in southern regions. The winter peak also concurs with weather conditions such as low temperature and relative humidity that permit the influenza virus to endure longer. Ecological research shows that higher 25(OH) D levels with vitamin D use during the winter months may decrease the risk of catching influenza. Results of randomized controlled trials confirm that vitamin D intake has beneficial effects in lessening the risk of influenza. However, some of these studies included vaccinated participants or did not measure baseline 25(OH)D levels, which may affect the evaluation of results. Evidence on the effects of vitamin D on the immune system suggests that vitamin D supplementation may decrease the risk of flu, but more studies are needed. Additionally, large population research would be helpful to establish whether vitamin D utilization is accompanied by variations in serum 25(OH)D levels[102-110].

An observational study performed in Connecticut during the fall and winter of 2009–2010 studied the association between serum 25(OH)D concentration and the incidence of acute respiratory tract infections (ARTIs). In the study, 198 healthy adults were examined. During the study period, only 17% of subjects with 25(OH)D levels above 38 ng/mL developed ARTI, whereas 45% of subjects with 25(OH)D concentrations below 38 ng/mL developed ARTI. Levels of 38 ng/mL or higher were linked with a significant (P < 0.0001) twofold decrease in the risk of developing ARTI and a significant reduction in sick days. Eight influenza-like illnesses happened during this time, seven of which were caused by the 2009 H1N1 influenza virus[44].

Vitamin D metabolism and magnesium

Magnesium is required for vitamin D metabolism. Magnesium functions as a cofactor of enzymes critical for the production of calcitriol (1,25-dihydroxyvitamin D), the biologically active form of vitamin D. Magnesium deficiency can negatively affect vitamin D metabolism and therefore reduce the effectiveness of the immune system. Therefore, optimal

magnesium levels may increase the effectiveness of vitamin D supplements and strengthen immune resistance to infections. For example, in the Zittermann[112] study, it was shown that vitamin D supplements are more effective if magnesium is at sufficient levels.

SUN EXPOSURE AND VITAMIN D

Sun exposure is a critical factor in vitamin D synthesis. The skin produces vitamin D when exposed to UVB rays. Adequate sun exposure can increase blood levels of vitamin D, which can have positive effects on the immune system. Not being exposed to enough sunlight, especially in winter months and in individuals working in closed environments, can lead to vitamin D deficiency. This may increase susceptibility to viral infections such as respiratory infections. It has been shown in many studies that sun exposure can reduce the risk of infection by increasing vitamin D levels. In the study of Holick[70], it was stated that exposure to sunlight reduces the risk of infection by increasing vitamin D levels.

PHYSICAL ACTIVITY

Physical activity is an important lifestyle factor for overall health and the immune system. Regular exercise can reduce inflammation, increase circulation of immune cells, and improve overall immune function. Exercise can also positively affect the metabolism of vitamin D, which is essential for muscle and bone health. Higher vitamin D levels and a stronger immune system have been observed in individuals who exercise. One study found that individuals who exercise regularly are more resistant to infections[113].

NUTRITION AND VITAMIN D

Apart from magnesium, other nutrients such as calcium, zinc and omega-3 fatty acids are also important for vitamin D activation and immune system functions. Zinc plays a critical role, particularly in antiviral immune responses, and may improve immune functions when used with vitamin D. Omega-3 fatty acids help regulate the immune system by reducing inflammation. Takeda *et al*'s study showed that the combination of zinc and vitamin D improved immune functions and reduced the risk of infection[114].

Vitamin D is a vitamin that is vital for immune system functions. However, it works effectively in conjunction with other nutrients such as magnesium and lifestyle factors such as sun exposure and physical activity. Having these factors together at optimal levels makes the immune system more resistant to viral infections. Vitamin D deficiency, combined with inadequacy of these nutrients and lifestyle factors, can increase vulnerability to infections. Therefore, it is important to take a holistic approach to ensure vitamin D levels are adequate.

CONCLUSION

We investigated the critical function of vitamin D in immune function, particularly in the context of viral infections such as SARS-CoV-2 and influenza. Once associated primarily with calcium and bone health, vitamin D is now known as a versatile steroid hormone with important effects on the immune system. We discuss vitamin D metabolism and the global concern regarding its deficiency and highlight the links between low vitamin D levels and amplified risk of respiratory infections. We also discussed several studies examining the connection between vitamin D levels and the severity and fatality of COVID-19, offering insights into the potential of vitamin D as a prophylactic and therapeutic agent. We think that meticulously investigating the mechanisms by which vitamin D can decrease viral infections, modulation of the RAS, and interactions with respiratory epithelial cells, sheds light on its versatile immune-boosting properties. We also examined the status of vitamin D in fighting influenza. In general, we wanted to provide a comprehensive overview of the important impact of vitamin D on the immune system and its potential effects in the context of viral infections.

FOOTNOTES

Author contributions: Engin MMN and Özdemir Ö have done everything.

Conflict-of-interest statement: All authors have no conflicts of interest to disclose.

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Country of origin: Türkiye

ORCID number: Öner Özdemir 0000-0002-5338-9561.

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