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MINI REVIEW

Protective role of vitamin D status against COVID-19: a mini-review

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Abstract

An outbreak of pneumonia caused by a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is called COVID-19 and has led to a pandemic worldwide. It is reasonable to investigate and control factors affecting disease severity and mortality. The relation between vitamin D and viral pneumonia has been previously reported. Vitamin D deficiency is common and may increase hospital admission and mortality rate in patients with COVID-19. This mini-review examines the pathways that show the association between vitamin D and COVID-19. On the other hand, it deals with the available evidence related to the relationship between vitamin D deficiency and the effect of vitamin D supplementation on the prevalence, severity, and mortality of COVID-19. Also, we described the pathophysiology of the organs' involvement in COVID-19 and the effect of vitamin D on these outcomes. Vitamin D strengthens the innate and adaptive immune system, modulates immune responses, prevents lung and cardiovascular system damage, and reduces thrombotic events. Vitamin D exerts these effects in several pathways. Vitamin D prevents virus entry and replication by maintaining the integrity of the body's physical barrier. Vitamin D reduces the damage to vital organs and thrombotic events by increasing the level of Angiotensin-converting enzyme 2 (ACE2), nitric oxide, and antioxidants or by reducing inflammatory cytokines and free radicals. Sufficient vitamin D may be reduced morbidity and mortality due to COVID-19. However, this issue should be investigated and confirmed by further research in the future.

Keywords COVID-19 · Vitamin D · Immune system · Respiratory · Cytokines

Introduction

At the end of 2019, pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported from Wuhan, China. The World Health Organization (WHO) called this pandemic disease as COVID-19. This disease had high morbidity and mortality and became a great challenge for governments and health systems. As of August 26, 2022, 596,873,121 definitive cases of COVID-19 have been reported to the WHO, of which 6,459,684 have died [1]. The incubation period of this disease is usually about 5–6 days. Most people infected with SARS-CoV-2 have mild to moderate symptoms of respiratory illness and recover with outpatient management and supportive measures. Symptoms such as fever, cough, fatigue, loss of taste or smell, sore throat, headache, myalgia, diarrhea, skin rash, and red eyes are common. However, some patients experience severe symptoms (such as shortness of breath, impaired consciousness, and chest pain) and require medical care. The severe form of the disease is more common in the elderly and those with underlying diseases such as cardiovascular disease, diabetes mellitus, chronic respiratory disease, and cancer. A small number of patients develop complications including acute respiratory distress, pulmonary thromboembolism, deep vein thrombosis, and vasculitis which may even lead to death [2–5].

Multiple treatment strategies are available for COVID-19. Treatment options vary depending on individual characteristics, disease severity, co-morbidities, and access of patients to health services. Treatment goals include preventing the disease

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progression, complications as well as reducing mortality. The National Institutes of Health (NIH) has published guidelines in this regard and its recommendations differ depending on whether it is outpatient or inpatient [6]. Antiviral agents such as remdesivir and immune system modulating drugs (such as dexamethasone and monoclonal antibodies) and antithrombotic drugs (such as low molecular weight heparin) can prevent disease progression and reduce mortality [7–10]. Five anti-SARS-CoV-2 monoclonal antibody products have received emergency use authorization (EUA) from the Food and Drug Administration (FDA) in the United States. The authorized anti-SARS-CoV-2 monoclonal antibody products which are currently available for use include Tocilizomab, Bebtelovimab, Tixagevimab plus Cilgavimab, Bamlanivimab plus Etesevimab, Casirivimab plus Imdevimab, and Sotrovimab [6, 11].

At present, COVID-19 control is performed by health measures, quarantine, and vaccination. New SARS-CoV-2 variants such as Delta and Omicron have appeared due to mutations in the virus genome. These new variants have also been able to create a pandemic [12]. The existing vaccines can probably prevent the severity of the disease and death caused by these new variants. However, there are still concerns about the effectiveness of existing vaccines against new variants of the virus [13–16]. The physicians and researchers continue to identify risk factors, common and rare signs and symptoms of COVID-19, and the complications to control the disease and to reduce the mortality rate of COVID-19 [17–20].

The role of vitamin D in the control of pneumonia caused by viral agents such as influenza A and SARS has already been mentioned [21, 22]. COVID-19 is more prevalent and severe in higher latitude area and is more common in people who are more likely to have vitamin D deficiency, such as elderly and diabetics [23–25]. People with COVID-19 have a low serum level of 25 hydroxyvitamin D (13 ng/dl) and the prevalence of this vitamin deficiency is 45% in a study from Armenia [26]. There is an inverse relationship between serum 25 hydroxyvitamin D levels and the severity of COVID-19 [27, 28]. Vitamin D deficiency has increased hospital admission [odds ratio (OR) = 1.81, 95% confidence interval (CI) = 1.41–2.21] and mortality rate from COVID-19 (OR = 1.82, 95% CI = 1.06–2.58) in some studies [29]. Vitamin D supplementation may be reduced COVID-19 severity and mortality rate. In the clinical trials, vitamin D supplementation in hospitalized patients with covid-19 reduced the use of non-invasive ventilation and the level of inflammatory markers. Vitamin D supplementation also reduced the mortality rate in the case group by 50% compared to the control group [30–32]. Vitamin D can reduce the risk of viral infections and possibly COVID-19, its complications and mortality rate by various mechanisms. In this review, some of these mechanisms will be explained. A summary of these associations is shown in Fig. 1.

Vitamin D and body defense barrier and virus replication

The epithelial cells in the respiratory tract protects us as a physical barrier from pathogens invasions. The active metabolite of vitamin D (1, 25-dihydroxyvitamin D) upregulate genes that encode proteins such as Occludin, Connexin 43 and E-cadherin. These proteins are needed for tight junctions, as well as gap and adherent junctions, respectively. In this way, vitamin D can prevent the entry of pathogens and thus prevent lung infections [33].

The effect of vitamin D on the proliferation of respiratory viruses has been different in various studies. In the in vitro studies, replication and release of rhinovirus is reduced by 1, 25-dihydroxyvitamin D (1, 25(OH) $_2$ vitamin D). Downregulation of vitamin D receptor increases rhinovirus replication [34]. But in another study, 1, 25(OH) $_2$ vitamin D didn't decrease virus replication. Instead, 1, 25(OH) $_2$ vitamin D and 25 hydroxyvitamin D (25OHvitamin D) caused significant thickening of the cell layers and proliferation of cytokeratin-5-expressing cells in respiratory epithelium. Thus, vitamin D prevents the virus entry to the lung epithelium by strengthening the physical-defensive barrier and does not inhibiting the virus replication [35].

Vitamin D and immune system modulation

Immune responses to pathogens fall into two main categories: (a) intrinsic responses in which neutrophils, macrophages, and NK cells respond rapidly and specifically to the pathogen; and (b) adaptive responses in which T and B lymphocytes respond with a delay and slower but more specific to the pathogen. The effects of COVID-19 virus on the immune system have not been fully explained. Immune responses to COVID-19 have ceased in the innate immune phase and do not make sufficient progress toward adaptive immunity. Imbalances in the immune system reduce the innate immune response to pathogen and in turn disproportionately increase the production of cytokines and inflammatory factors. This imbalance intensifies the severity of the disease and consequently the mortality rate due to COVID-19 [36].

Vitamin D receptor (VDR) is expressed in almost all immune cells, including activated T cell with cluster of differentiation 4 ($CD4^+$ T cells) and CD8+ T cells, B cells, and antigen-presenting cells (such as macrophages and dendritic cells). Vitamin D has two important effects on the immune system. Strengthens the immune system against pathogens and reduces the rate of respiratory infections. It also prevents over-activation of the immune system and reduces autoimmune diseases as well as cytokine storms. First, the immunomodulatory role of vitamin D is applied to

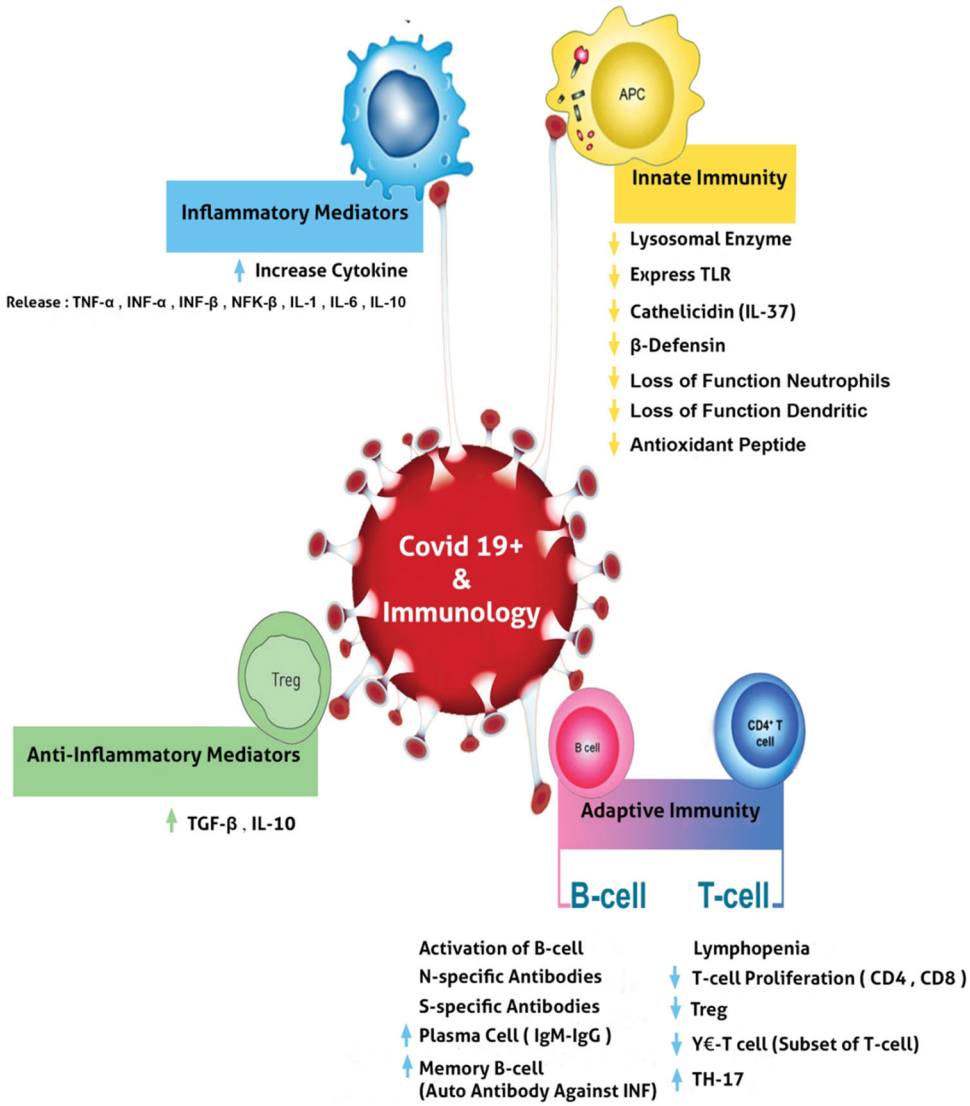

Fig. 1 Vitamin D deficiency and COVID-19 effects on different body system. ACE angiotensin-converting enzyme, An II angiotensin 2. ARDS acute respiratory distress syndrome, Ca calcium, PTH parathormone, ICU intensive care unit, IL interleukin, TNF tissue necrotizing factor

the both innate and secondary immune system. Vitamin D interacts with the innate immune system, by activating Toll-like receptors (TLRs) or increasing the levels of antimicrobial peptides (AMPs) such as cathelicidins and β-defensins by activating immune cells. Cathelicidins inactivate viruses such as Influenza A virus by destroying envelope proteins. A primary form of cathelicidins is known as LL-37, which prevents the virus from entering the cell. Also, LL-37 significantly increases H2O2 production within neutrophils in the response to virus entry. CD8+ T cells, which express high level of VDR, proliferate rapidly and kill infected cells by inducing apoptosis. Second, Vitamin D interacts with the adaptive immune system. Vitamin D reduces immunoglobulin which is secreted by plasma cells and pro-inflammatory cytokines production; thus, modulates T cells function. Vitamin D also promotes self-tolerance by shifting the differentiation pathway of helper T cells (TH) towards TH2 production, and the number of TH1 decreases. As a result, the production of inflammatory cytokines such as interferon-gamma (IFN-Y), tumor necrosis factor-alpha (TNF-α), interleukin 6 (IL-6), IL-8, IL-9, IL-12, and IL-17 reduces by decreasing $CD4^{+}$& $CD8^{+}$ T cells. Meanwhile, the production of anti-inflammatory factors such as IL-4, IL-5, and IL-10 from TH2 cells increases. CD8+ T cells, which express high level of VDR, proliferate rapidly and kill infected cells by inducing apoptosis [37–40]. These mechanisms are summarized in Fig. 2.

Vitamin D and lung injury in COVID-19

SARS-CoV-2 enters host lung cells through the angiotensin-converting enzyme (ACE) protein in the cell membrane. Binding of viral spikes protein to ACE2 receptor results in its downregulation and the level of ACE2

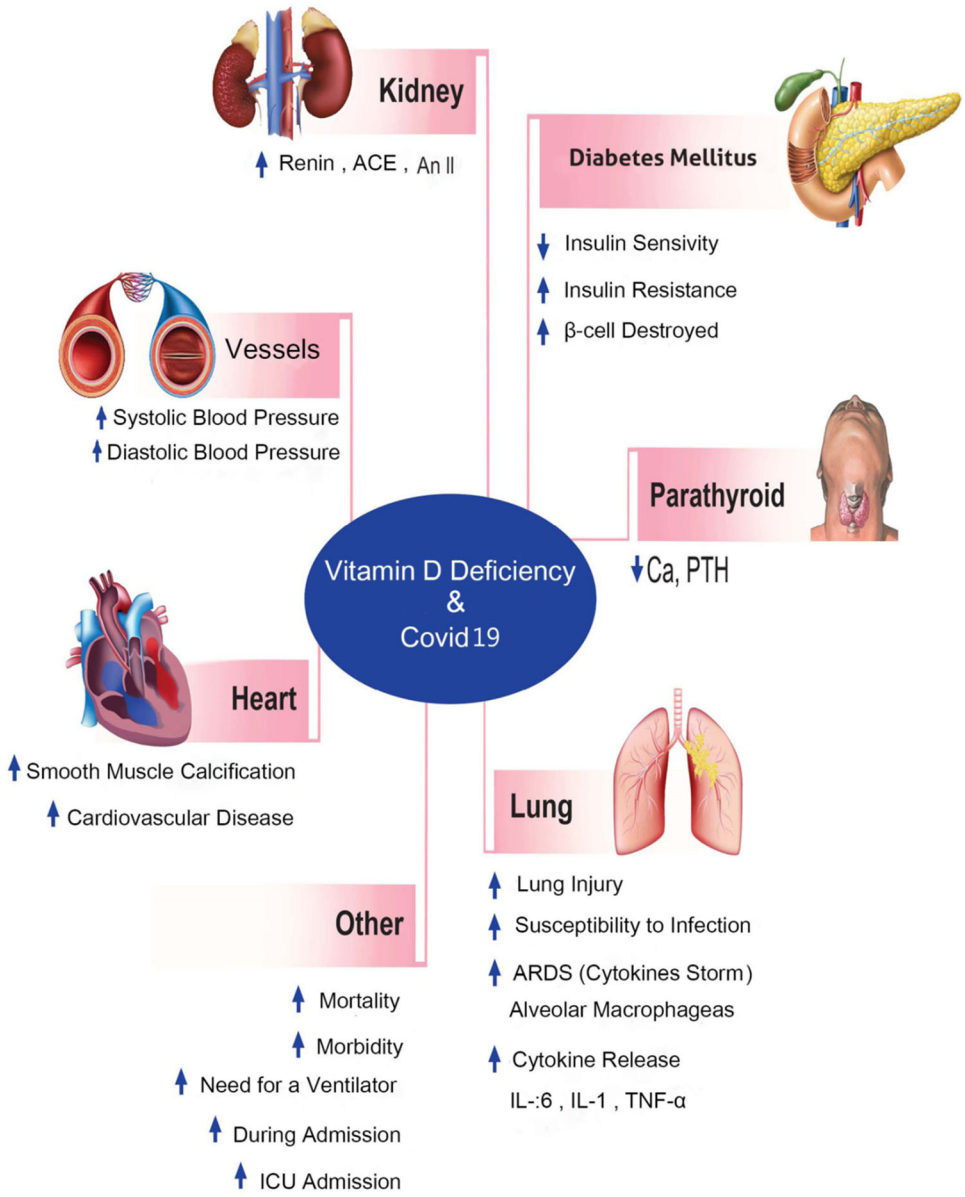

Fig. 2 SARS-Cov- 2 coronavirus effect on immune system. APC antigen-presenting cell, Ig immunoglobulin, INF interferon, IL interleukin, NFκB nuclear factor kappa-light-chain-enhancer of activated B cells, TH T helper cell, TLR toll-like receptor, Treg regulatory T cells, TNF tissue necrotizing factor, TGF-β transforming growth factor beta,TNF-α, tumor necrosis factor-alpha

level decreases. Because ACE2 protects the lungs from injury, ACE2 deficiency may expose patients to lung damage. Due to the protective effect of ACE2 receptor in preventing lung injury, deficiency of this receptor may expose the patient to lung damage. Several factors may affect the entry of SARS-CoV-2 into the cell through ACE2. There is evidence that the ACE inhibitors or angiotensin receptor blockers (ARBs) increase the risk of COVID-19 [41, 42]. Vitamin D can increase ACE2 levels by two mechanisms and may protect the lung from COVID-19-induced damage. Vitamin D independently increases ACE2 gene expression. In addition, vitamin D suppresses the compensatory increase in renin levels following inhibition of the renin-angiotensin system and causes an increases in ACE2 [43].

In COVID-19, ACE2 downregulation leads to unopposed inflammatory chain-reaction, cytokine storm (i.e. generation of both pro-inflammatory and anti-inflammatory cytokines by innate immune system) and lethal acute respiratory distress syndrome (ARDS). Vitamin D reduces lung permeability in animal models of ARDS by modulating renin-angiotensin system (RAS) activity and ACE2 gene expression [44].

Although most studies have suggested the role of ACE2 in COVID-19, but there are studies in which serum ACE levels are also low. In this study, the levels of vitamin D and ACE in patients with severe COVID-19 have been lower than in mild cases and have been associated with worse outcomes [45]. The score of lung involvement on computed tomography (CT) Scan of the Chest has an inverse

relationship with to the mean serum level of vitamin D in hospitalized patients with COVID-19 [46].

Another study examined the effect of vitamin D on hyperoxia-induced lung damage in newborn rats. Vitamin D has been able to reduce the lung damage caused by excessive oxygen administration by maintaining the integrity of the lung structure, reducing inflammation, reducing the deposition of extracellular matrix, and inhibiting lung cell apoptosis [47]. Vitamin D deficiency causes RAS overactivation and extracellular matrix deposition and resulting in pulmonary fibrosis and impaired lung function [48]. Vitamin D supplementation reduces the number of CD8+ and invariant mucosal T cells and may prevent the progression of lung damage associated with cystic fibrosis [49].

Vitamin D and cardiovascular involvement in COVID-19

Cardiovascular diseases such as hypertension and ischemic heart disease have been reported as risk factors for COVID-19. Arrhythmias, myocardial infarction, and thromboembolic events are also important causes of mortality in COVID-19 patients. On the other hand, vitamin D has a protective role in cardiovascular diseases. Vitamin D exerts its protective effects on the cardiovascular system in several different ways. Activation of the vitamin D receptor by regulating the entry of calcium into myocytes causes myocardial contraction and affects the contractility of the heart. Vitamin D may inhibit the formation or progression of atherosclerotic plaques by inhibiting the conversion of macrophages to foam cells and by increasing cholesterol efflux, and thus, protects against atherosclerosis. 1, 25(OH) $_2$ vitamin D repairs vascular endothelium by producing vascular endothelial growth factor in vascular smooth muscle cells. Vitamin D reduces inflammation in the vascular endothelium by decreasing nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and IL-6. Vitamin D reduces vascular thrombosis by decreasing tissue factor 3 and increasing thrombomodulin in endothelial cells and macrophages. Vitamin D also increases nitric oxide in vascular endothelium and protects them. However, there is evidence that high levels of vitamin D increase vascular calcification and atherosclerotic disease [50].

Vitamin D deficiency is associated with hypertension, ischemic heart disease, diabetes mellitus and obesity. Both vitamin D deficiency and the above mentioned9 diseases are also associated with COVID-19 [51]. This relationship may be a simple, coincidental association, or in the context of an unknown pathophysiology that explains these relationships, or they may have a cause-and-effect relationship. These relationships are not well understood at present, and further fundamental and applied studies in the future may answer these questions.

Vitamin D supplementation and COVID-19

Vitamin D deficiency (25 hydroxyvitamin D < 50 nmol/L) is common and has affected more than one-third of the population worldwide [52]. Several systematic reviews and Meta-analyzes have evaluated the role of vitamin D Supplementation in the prevention of respiratory infections in randomized controlled clinical trials. Vitamin D had a protective effect against respiratory infections (OR = 0.64; 95% CI = 0.49–0.84). The protective effect of vitamin D in studies that used oral doses between 1000 and 4000 international unit (IU) per day was greater than the intramuscular bolus injection dose of 100,000 IU per month (OR = 0.51 vs. OR = 0.86, $P = 0.01$) [53]. In a clinical case series, the effect of vitamin D supplementation on patients with COVID-19 was evaluated in two groups, high dose group (Ergocalciferol 50,000 IU daily) and standard dose group (Cholecalciferol 1000 IU daily) for 5 days. In high dose group, vitamin D levels returned to normal earlier and they had better clinical outcome. The hospital length stays, oxygen requirements, and inflammatory markers were lower in this group [54]. At present, experts have different opinions in this regard. To reduce the risk of infection, they recommend that people at risk for influenza A and/or COVID-19 take 10,000 IU of vitamin D daily for a few weeks and then 5000 IU daily to increase vitamin D levels rapidly. The goal should be to increase the concentration of 25 (OH) D above 40–60 ng/ml (100–150 nmol/L). Higher doses of vitamin D3 may be helpful in treating people who become infected with COVID-19. However, to evaluate these recommendations, randomized controlled clinical trials and numerous population studies should be performed [55–58].

Conclusion

Vitamin D can protect body against COVID-19 through several main mechanisms. Vitamin D strengthens the innate and adaptive immune system, modulates immune responses, prevents lung and cardiovascular system damage, and reduces thrombotic events. Vitamin D deficiency can be a risk factor for COVID-19 infection and its severity. Vitamin D supplementation may be effective in improving the clinical outcome and reducing morbidity and mortality rate due to COVID-19. However, these issues should be investigated and confirmed by further research in the future.

Data availability

All the data obtained during this study are published in this article.

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Author contributions M.V. designed the project, searched, reviewed and selected different articles, wrote the initial draft of the article, wrote and edited the final format of the article. M.R. wrote and edited the immunology issue and drew figures 1 and 2. M.S. supervised the investigation. He reviewed and edited the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

Consent for publication The authors would like to submit this review article entitled "Protective role of vitamin D status against COVID-19: A Mini-Review" for consideration by the "Endocrine, International Journal of Basic and Clinical Endocrinology". The authors certify that this study is original and has not been published elsewhere, and is not currently under review elsewhere.

Ethics In this review article, the authors have referred to appropriate and relevant literature in support of the content presented in it.

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