The Relationship Between the Coronavirus Disease 2019 (COVID-19) and Vitamin D: A Simple Review

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ABSTRACT

SARS-CoV-2, liable for the COVID-19 pandemic, is a worldwide public health issue with deadly consequences all over the world. A strong immune system is effective in reducing the spread of the virus and in the healing process. While many nutrients are essential for the immune system, vitamin D plays a huge part in strengthening immunity. It is assumed that vitamin D has immunomodulatory, anti-inflammatory, antifibrotic, and antioxidant assignments and that vitamin D may aid in infection of SARS-CoV-2. The fatal complications belonging to the SARS-CoV-2 virus are due to different mechanisms like acute respiratory distress syndrome, cytokine storms, and the disruption of the renin-angiotensin system. Vitamin D regulates all these mechanisms by suppressing cytokines of an inflammatory sort, thereby decreasing the severity of the disorder and the risk of death. Vitamin D is suggested both for protection against as well as part of the cure of COVID-19 since vitamin D diminishes the danger of the common cold, whilst increasing cellular immunity and modulating adaptive immunity along with giving rise to the expression of the genes that get involved in antioxidation. Nevertheless, there is insufficient evidence today regarding the relation between vitamin D levels, the severity of COVID-19, and mortality. Thereupon controlled trials of randomized sort and larger-scale cohort studies are needed to examine the very relationship. This review was made to examine the cause-and-effect relationship between the viral and immune response which affects the prognosis of COVID-19, and vitamin D.

Key Words: *COVID-19, SARS-CoV-2, Vitamin D, Cytokine storm*

eIJPPR 2023; 13(5):62-70

HOW TO CITE THIS ARTICLE: Sanlier N, Yasan N. The Relationship Between the Coronavirus Disease 2019 (COVID-19) and Vitamin D: A Simple Review. Int J Pharm Phytopharmacol Res. 2023;13(5):62-70. https://doi.org/10.51847/gtUAcbYfj5

INTRODUCTION

The coronavirus has been named COVID-19 by the WHO [1] and has been declared a pandemic [2]. Unfortunately, it has affected almost every country worldwide. Although there is no definitive treatment method against coronaviruses to date, preventive treatment strategies have been developed in the fight against the epidemic [3]. Known as RNA viruses, coronaviruses have four subfamilies which are alpha, beta, gamma, and delta [4]. Of these, alpha coronavirus and beta coronavirus can contaminate mammals, meanwhile, gamma coronavirus and delta coronavirus can contaminate both birds and mammals [5]. The coronaviruses that infect humans refer to the alpha coronavirus and beta coronavirus type [6]. The coronaviruses that affect the upper respiratory tract in human beings (HCoV-229E, HCoV-NL63, HCoV-HKU1, and HCoV-OC43) are generally droplet-spread causing slight cold-like symptoms, as well as SARS-CoV along with MERS-CoV which affect the lower respiratory system and cause death by triggering respiratory distress [6, 7].

The immune system is a very important factor in decreasing the rigor of the disorder [8]. It is known that adequate and balanced nutrition strengthens the immune system and provides serious protection against infections [9]. Inadequate and unbalanced nutrition affects the immune system negatively and increases the risk of disease. During the COVID-19 pandemic, it was mentioned that macronutrients such as protein,

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Received: 12 August 2023; **Revised:** 14 October 2023; **Accepted:** 19 October 2023

carbohydrates, and fat should be taken in balanced and adequate amounts and attention should be paid to micronutrient intake to strengthen immunity [10, 11]. Micronutrients like vitamins viz. vitamin A, C, D, E, iron, selenium as well as zinc hold a significant place in strengthening immunity [7]. Vitamin D, one of these micronutrients, protects against viral respiratory tract infections by regulating both congenital and adaptive immune systems [12].

As long as vitamin D deficiency, lung, cytokine levels, prevention of epithelial cell apoptosis, and epithelial cell repair are adversely affected. This weakens the immune system. Therefore, it is thought that it may be associated with lower mortality rates from COVID-19 due to a lack of vitamin D in communities regularly exposed to natural ultraviolet radiation from the sun. It has been observed that death rates from the COVID-19 epidemic are relatively lower in countries that are closer to the equator than in countries farther away. At the same time, a deficiency of vitamin D was observed in 76% of the patients ill with COVID-19 [13].

With the onset of the pandemic, the trend towards vitamin D, which is valued for playing a part in upper respiratory tract infections, has increased and it is underpinned that vitamin D has the potential to inhibit or decrease the severity of COVID-19. Vitamin D acts on many genes expressed by immune cells. In addition, vitamin D has possible roles in reducing other acute respiratory tract infections and their severity [14].

This review was made to examine the cause-and-effect relationship between the viral and immune response which affects the prognosis of COVID-19, and vitamin D.

RESULTS AND DISCUSSION

Immune avoidance and cytokine storm

Although rigorous symptoms like acute respiratory distress syndrome, acute cardiac complications, multi-organ dysfunction syndrome, septic shock, and death are seen in most individuals with COVID-19, most of these complications that cause hyper-inflammation are thought to be caused by cytokine storms. A cytokine storm is defined as the uncontrolled release of cytokines that cause hyper-inflammation in infectious and non-communicable diseases [15]. At the same time, SARS-CoV-2 creates a cytokine storm by causing dysfunction in the renin-angiotensin system. The resulting cytokine storm is thought to induce acute lung damage and acute respiratory distress syndrome [16]. SARS-CoV-2 can evade the immune system by suppressing the activation of the innate immune system, inhibiting type I interferons (I IFN) production while inhibiting pathogen-associated molecular models (PAMPs) recognition through the relevant receptors namely pattern recognition receptors (PRRs) in double-membrane vesicles, and suppressing NF-Kb [17].

IFN plays a great role in effective congenital immune replications toward viruses and the regulation of adaptive immunity. Innate immunity and the host response to viral infections are largely dependent on the expression of type I IFNs. Viruses such as SARS-CoV-2 can escape from the congenital immune system by inhibiting type I IFN production whilst altering retinoic acid-inducible gene-I (RIG-I) like receptors. Immune cells detect viral RNAs as PAMP by 3 sensors which are PRR, cytoplasmic RNA sensors, and the cytoplasmic nucleotide-binding domain leucine-rich repeat (NLR) family of proteins. Toll-like receptors (TLR-) 3, TLR-7 alongside TLR-8, as well as PAMPs can be recognized by PRRs. Cytoplasmic RNA sensors include RIG-I along with melanoma differentiation-associated protein 5 (MDA5), while cytoplasmic NLR proteins include NLRP1, NLRP3, NLRP7, and NLRC4 [18]. Congenital immune cells are operated on they identify PAMPs with the help of PRRs. Recognition of RNA viruses activates several intracellular inflammatory signaling pathways by activating TLR3 and 7. In addition, unlike other RNA viruses, SARS-CoV-2 suppresses the activation of TRAF-3 and TRAF-6, factors associated with TNF receptors. While SARS-CoV-2 activates TLR3/7, it also suppresses TRAF-3 and TRAF-6. Thus, it causes inhibition of NF-kB and IRF-3/7 and suppresses early proinflammatory and antiviral responses via type I IFN [17]. Recognition of viruses by PRRs activates IRF-3 as well as IRF-7 and induces the secretion of type I IFNs. It activates IFN-stimulated genes (ISGs) by operating the JAK-STAT signaling pathway of type I IFNs [19]. Disruption of the JAK-STAT signaling pathway may improve the severity of SARS-CoV-2 and lead to impaired IFN-related antiviral response [20]. Nevertheless, at another phase, contracted cells resulted in cell death, resulting in the spread of virus particles and intracellular constituents. Thus, it causes an immune response. Recognition of these particles by PRRs on monocytes and macrophages arriving in the bloodstream activates NF-kB and IRF-dependent proinflammatory pathways.

Transcription factors cause the release of proinflammatory cytokines in higher levels like TNF-a, IL-1, and IL-6 and chemokines like CXCL10, CXCL9, CXCL8, CCL2, and CCL5 [21]. While some of the cytokines are beneficial (type I IFN, IL-7), some of them have harmful effects (IL-1β, -6, and TNF-α), especially in the context of cytokine storm and are of vital importance for the pathophysiology of COVID-19. Rapidly increasing cytokine and chemokine release attracts many cells of inflammatory sort like neutrophils as well as monocytes into the lung tissue and causes excessive infiltration of the lung tissue, causing damage to the lung

[22]. Delayed type I IFN increases the severity of the problem by causing inflammatory monocyte/macrophage accumulation. This situation contributes to the cytokine storm, causing damage to many tissues and causing pneumonia, ARDS, and intravascular coagulation [23].

There is a relationship between type B of beta coronaviruses, which cause serious diseases and even death, and COVID-19 [4]. The strength of the protective response of the body depends on other factors such as genetics, epigenetics, or lifestyle. Vitamin D can decrease the risk of viral infections as well as being able to prevent pneumonia and lung injury through several mechanisms, such as improving the concentration of cytokines of anti-inflammatory sort and lowering pro-inflammatory cytokine levels. Therefore, vitamin D is considered effective in decreasing the severity of COVID-19 disease [22, 23].

Vitamin D and covid-19 relationship

Vitamin D, where 90% of the requirement is met by ultraviolet-B (UVB) rays, is found in limited foods. Vitamin D receptor (VDR) and its vitamin D have effects of anti-inflammatory sort and are effective when it comes to immune system regulation [24]. Receptors of Vitamin D locate themselves in the vast majority of immune cells like dendritic cells, macrophages, or active T as well as B cells. Effective on innate as well as acquired immunity, vitamin D increases antimicrobial activity in conjunction with macrophages and monocytes. Vitamin D also affects the expression of genes, causing a decrease in proinflammatory cytokines (IL12 and IL23) and an increase in inhibitor molecules (IL10 and Tumor Necrosis Factor 5 [TNF]-alpha). It indeed is effective for T cell response through stimulation or inhibition of cytokines [25]. Since active vitamin D, dendritic cells, macrophages, and activated T as well as B lymphocytes express VDR together with 1α-hydroxylase, it modulates the immune response by regulating cytokine expression and interacting with adaptive and innate immune system cells [25, 26]. This immunomodulatory effect of vitamin D results in an increase in antimicrobial activity and a decrease in its pro-inflammatory action. VDRs on the surfaces of many immune cells promote monocytes' becoming different toward macrophages, increasing phagocytosis, reducing inflammatory cytokine production, and producing antimicrobial proteins. Thus, it helps to reduce the effect, including in the lungs. Vitamin D supplementation is announced to decrease some other infections like viral respiratory tract, particularly in individuals who are with vitamin D deficiency [26].

It has been stated that gene polymorphisms in vitamin D can affect the severity of COVID-19. To be more specific, the mutations in VDR, DBP, CYP27B1, and CYP24A1 are declared to adversely impact the activity that pertains to vitamin D. A relationship has been detected between VDR gene polymorphisms and acute respiratory tract infection. Toll-like receptor 2/1 increases VDR expression and CYP27B1 in monocytes while supporting the cellular production of cathelicidin and defensin 2. In addition, other immune cells, namely, dendritic cells as well as macrophages, T alongside B lymphocytes are also involved in VDR and CYP27B1 expression [27].

Vitamin D is an immunomodulatory hormone that is essential for immunity and it stimulates antimicrobial peptide production like cathelicidin and defensin, which suppress the production of proinflammatory cytokines originating from viruses, bacteria, and fungi [28]. TLR activation by human monocytes/macrophages increases VDR expression and vitamin D-1-hydroxylase genes, supports antimicrobial peptide cathelicidin expression, and ensures the intracellular killing of bacteria such as *Mycobacterium tuberculosis*. Likewise, a similar situation is observed in lung epithelial cells. It provides the expression of antimicrobial peptides by activating the VDR and $1,25(OH)_2D$ antimicrobial cathelicidin and defensin β2 genes. Human defensin-2 activates the innate immune system by expressing antiviral chemokines and cytokines that can recruit monocytes/macrophages, granulocytes, cells of the natural killer sort, known as NK, dendritic cells, T cells as well as leukocytes, such as cathelicidin, and antiviral IFN-γ, IFN-β, MxA increases the production of PKR and RNase L molecules [27-31]. LL-37, which is formed because of the cleavage of the cathelicidin peptide, shows an antimicrobial effect against various microbes such as viral, bacterial, parasitic, and fungal microorganisms. It also prevents viral entries to the cell by reducing the replication of viruses like SARS-CoV-2 [30]. Defensins, on the other hand, have anti-inflammatory effects on viruses such as SARS-CoV and influenza A [31]. Human α-defensin 5 inhibits cell entry of SARS-CoV-2 by binding to ACE2 [32].

Vitamin D can also prevent the release of cytokines by balancing the responses of Treg (T) cells. Vitamin D suppresses Th1 cells, which are thought to cause ARDS, and decreases proinflammatory cytokine production e.g., IFNγ and TNF-α. It was pinpointed that supplementation that is pertinent to vitamin D increases the number of $CD11c^+$ cells, suppresses proinflammatory cytokine production (TNF-α, IFN-γ, and IL-6), regulates the expression of some antioxidant genes such as glutathione reductase, and increases the expression of antimicrobial peptides and genes related to autophagy [33]. It has been shown that peripheral CD4 + T cell and CD8 + T cell numbers are considerably reduced in SARS-CoV-2 patients, and CCR6 + Th17 concentration increases in CD4 + T cells [34]. In addition, low lymphocyte count, high leukocyte count, and neutrophil-lymphocyte ratio, as well as fewer monocytes, eosinophils, and basophils,

were found in severe COVID-19 patients [35]. Therefore, innate, and adaptive immune responses are important in these harmful biological systems that cause the cytokine storm to occur. It was shared that vitamin D regulates adaptive and innate immune responses by modulating CD4 + T as well as CD8 + T cells, neutrophil counts, B cells, macrophages, and monocytes along dendritic cells through the VDR. Vitamin D suppresses Th1 and Th17 cell differentiation by increasing VDR expression in CD4 + T cells and supports Th2 cell differentiation, and changes in the T cell subset affect cytokine storm [36].

SARS-CoV-2 accelerates inflammation by stimulating the expression of IL-6 from $CD14^+$ and $CD16^+$ monocytes of Th1 cells [37]. TNF-α, IFN-γ, as well as IL-2 of Th1 cells along with IL-13, IL-9, IL-5, and IL-10 cytokines of Th2 cells, have been detected in individuals with COVID-19. Proinflammatory cytokines of Th1 and Th2 cells are high in individuals with severe COVID-19, and this is seen as the cause of cytokine storm, infection, immune system disorder, pneumonia, and acute respiratory distress syndrome [37, 38]. Vitamin D suppresses proinflammatory cytokine production like TNF-α, IFN-γ, IL-2, IL-1, IL12, IL-17, IL-23, and IL-22 produced by Th1 and Th17 cells, respectively, and cytokine production like IL-4 whilst activating and adapting the immune response, thus shifting the immune response to Th2 responses [36, 39]. M1 and M2 macrophages are induced in response to T helper cells Th1 and Th2 responses, respectively. M1 macrophages contain some proinflammatory cytokines like TNF-α, IL-1β, IL-8, IL-6, IL-12, IL-23, IL-18 and CXCL1, CXCL8, CXCL3, CXCL9, CXCL5, CXCL11, CXCL10, CXCL13 and it synthesizes some chemokines such as CXCL16. M2 macrophages, on the other hand, prevent tissue damage by phagocytic effects by producing anti-inflammatory cytokines such as TGF-*β,* IL-13, IL-4, and IL-10. $1,25(OH)_2D$ can reduce proinflammatory cytokine production like IL-12p40, IL-6, IL-1b produced from M1 macrophages and some chemokines such as TNF-a and CXCL9, CXCL10, CXCL11. The switch of macrophage polarization from pro-inflammatory phenotype M1 to anti-inflammatory phenotype M2 is supported by $1,25(OH)_2D$ [40].

Modulating the immune balance and preventing the proinflammatory cytokine storm are among the possible beneficial effects of vitamin D in combating the severity of COVID-19. Vitamin D may play a dual role in inflammation, initially controlling viral replication and later alleviating hyperinflammation [36, 39-41]. Therefore, it is important to keep vitamin D at an adequate level.

Vitamin D modulates the renin-angiotensin system as well as increasing angiotensin-converting enzyme 2 ACE2 levels. SARS-CoV-2 gets into the host cells by binding with ACE2, a member of the renin-angiotensin system, thereby reducing ACE2 levels in the body. ACE2 is found in high levels in respiratory epithelial cells, lung alveolar cells, heart, kidney, blood vessels, and gastrointestinal system [42]. At the same time, as SARS-CoV-2 binds to ACE2, it increases ACE levels and causes more angiotensin II production. This situation increases the severity of the disease [43]. ACE2 reduces the effect of ACE by converting angiotensin II, which has a pro-inflammatory effect, to angiotensin [44]. ACE2 is significant when it comes to protection against acute respiratory distress syndrome along with acute lung injury. The line of literature shows that vitamin D boosts the release of ACE2, decreases the release of ACE, and accordingly decreases the levels of angiotensin II. Additionally, vitamin D lowers renin expression and thus prevents the formation of angiotensin II [45]. In a completed study, $1,25(OH)_2$ D was observed to prevent acute lung injury caused by lipopolysaccharide by modulating the expression of renin-angiotensin system members (including ACE2). Isolation policies to decrease COVID-19 prevalence also reduce exposure to the sun and can carry the potential to increase the need for vitamin D supplements [46]. However, there exists insufficient information to talk about the effect of vitamin D deficiency connecting it to COVID-19 infection and to speculate about whether vitamin D therapy can assist in reducing the spread as well as the burden that COVID-19 owns [47].

The studies on the link between Vitamin D and COVID-19

An association is found between vitamin D shortage in the population and higher COVID-19 mortality rates in Europe [14]. In one study, it was found that bolus vitamin D supplementation in regular fashion the year ago COVID-19 diagnosis or after COVID-19 diagnosis was ascribed to relatively less serious effects of COVID-19 and better survival rates in frail elderly [48]. Another systematic review and meta-analysis detected that vitamin D shortage was not connected to a higher risk of infection from COVID-19, but serious cases of COVID-19 were 64.0% more vitamin D insufficient than mild cases. Vitamin D deficiency has been observed to increase hospitalization and mortality from COVID-19, and a correlation of positive sort between vitamin D shortage and disease severity [49]. Annweiler *et al*. found that bolus vitamin D3 supplementation during/just before COVID-19 was ascribed to less serious COVID-19 and better rates of survival among frail and elderly individuals [50]. In another study, when individuals with COVID-19 belonging to in 30-60 years age group were classified according to vitamin D shortage, the deficiency was spotted in more than half of these individuals. The serum inflammatory marker level was higher in COVID-19

patients with vitamin D deficiency, and the vitamin D level was substantially lower in serious COVID-19 patients. Due to the response of high inflammatory sort, the results have been linked to a high mortality rate in the related individuals. Vitamin D supplement administration of mass sort to the population who are at risk of COVID-19 is recommended [51]. In another piece of research, it was italicized that vitamin D shortage was common among patients diagnosed with COVID-19, but it was not associated with disease outcomes [52]. In another retrospective study, cholecalciferol treatment appeared to be linked to a decreased mortality risk in acute inpatients with COVID-19, independent of baseline serum 25(OH)D levels in a participant with COVID-19 who received cholecalciferol supplementation [53]. Another study suggested that exposure to sunlight may possess an impact of protective sort against COVID-19 mortality [54]. Further, in a study carried out in India, it was articulated that low 25(OH) vitamin D had an inverse relationship between SARS-CoV-2 infection and mortality rates in the Indian population [55]. In a study that is randomized and constitutes a placebo-controlled trial of short-term and high-dose vitamin D supplementation for COVID-19 illness, 60,000 IU of cholecalciferol supplementation daily increased to 25(OH)D > 50 ng/mL in 75% of the individuals by the 14th day and therapeutic as well as high-dose cholecalciferol supplementation was proved effective in recovery and survival in 41.7% of patients [56]. In another study, it was stated that there was no evidence of vitamin D protection against COVID-19 and that the supplementation did not have any mitigating effect on COVID-19 [57]. Hastie *et al*. [58] figured out an important link between vitamin D levels and COVID-19 in univariate analysis, while no important association was observed after adjusting for potential confounders. Also, a meaningful correlation was found between ethnicity differences and COVID-19 in univariate analysis. Merzon *et al*. [59] have found that individuals with COVID-19 have relatively lower levels of vitamin D than individuals who are not infected with the virus. Univariate and multivariate analyses indicate that lower levels of vitamin D were found to be linked to an elevated risk of COVID-19 infection as well as to hospitalization. Ilie *et al*. [60] found a correlation of negative sort between the levels of vitamin D and the number of COVID-19 cases as well as deaths. Pizzini *et al*. [52] did not discover any significant links between the levels of vitamin D and disease severity groups. Raharusun *et al*. [61] unveiled that 98.9% of individuals with vitamin D shortage and 87.8% of individuals with vitamin D shortage died. Whereas the rates of mortality belonging to the patients with vitamin D deficiency was 12.55 times higher than those holding normal levels of vitamin D, the mortality rate of patients with vitamin D deficiency was 19.12 times higher. A significant correlation was observed between the levels of vitamin D and COVID-19 mortality. Ferrari and Locatelli [62] in Italy unearthed no important correlations between the mean levels of vitamin D in COVID-19-positive patients and COVID-19-negative individuals. In their research, Li *et al*. [63] pointed out that vitamin D held positive impacts on lessening the number of COVID-19 deaths and cases, depending on sunlight and latitude. In a study conducted on elderly individuals with COVID-19, vitamin D shortage was spotted to be linked to serious lung involvement, longer disease duration as well as higher mortality [64]. These findings suggest that vitamin D supplementation carries the potential to bear a positive impact on the seriousness that pertains to COVID-19 and the risk of infection, which is of paramount importance.

The requirement of Vitamin D

While a 25(OH)D level below 20 ng/mL in individuals is considered deficiency, between 21-29 ng/mL is defined as inadequate, it is recommended to keep it above 30 ng/mL for health in children, adults, the elderly, pregnant and lactating women. Although serum 25(OH)D levels below 30 ng/mL are risky, values between 50-125 ng/mL are reported to be reliable. In a systematic meta-analysis, it was shown that the supplementation may be linked to developed outcomes of clinical sort regarding intensive care unit occupancy or the risk of death, particularly in individuals with moderate or severe COVID-19 requiring hospitalization. In another study, it was found that keeping the serum 25(OH)D level above 30 ng/mL could lessen the severity of COVID-19 and the risk of death. However, it was stated serum levels of vitamin D that are below 30 ng/mL will increase hospital infections and that levels of serum vitamin D should be between 40-60 ng/mL. To increase serum 25(OH)D levels to the range of 40-60 ng/mL, which is the preferred range, 10,000 IU/day intake for the first month is reasonable, and it is stated that it can be continued with a dose of 5,000 IU/day after the first month [65, 66].

CONCLUSION

In the COVID-19 epidemic, it is very important to keep the immune system strong in lessening the risk and severity that the disease holds. The logic behind using vitamin D is largely based on the immune modulator impacts that may protect against COVID-19 infection or reduce the severity that pertains to the disease. The main complication of COVID-19 infection is acute respiratory distress syndrome mediated by various mechanisms such as cytokine storm, renin-angiotensin system disorder, and imbalance in ACE2 levels. Vitamin D is known to prevent cytokine storm by reducing the proinflammatory

cytokine production through innate as well as adaptive immune systems and decreases disease severity by increasing ACE2 concentrations. Thereupon, adequate levels of vitamin D are very significant for the prevention of acute respiratory diseases. It is known that there is a high prevalence of vitamin D shortage in individuals with COVID-19, particularly in the elderly group. A thorough evaluation of blood vitamin D levels is recommended in clinical practice.

While individuals with low blood concentrations of vitamin D take vitamin D supplements, it may not be useful for individuals with normal blood concentrations to take vitamin D supplements. The reference intake level for vitamin D is stated by the FNB as 600 IU for adults. Vitamin D supplements taken as dietary supplements usually contain 1000 IU of vitamin D. The upper limit of vitamin D amount received for adults is 4000 IU, and a high intake of vitamin D as a dietary supplement can have toxic effects. According to the recommendation of health authorities, it is stated that it is more effective to take smaller amounts of vitamin D daily than to take high amounts of vitamin D at once [67]. Vitamin D supplementation may be evaluated as an option for individuals with vitamin D shortage and inadequacy if they have COVID-19. However, there is no supplementary support for the prevention, prophylaxis, or reduction of the seriousness of the disease among the groups with normal blood vitamin D levels. Instead, lifestyle strategies should be determined to avoid vitamin D shortage and maintain a healthy, balanced diet. In addition, to very high dosages of vitamin D, extreme care should be taken against doses above the upper limit. In particular, further prospective research is required to be able to approve if supplementing elderly patients with bolus vitamin D_3 at or just before the infection can ameliorate or avert COVID-19.

Acknowledgments: None

Conflict of interest: None

Financial support: None

Ethics statement: None

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