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Exploring the Link Between COVID-19 and Vitamin D: A Concise Overview

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ABSTRACT

SARS-CoV-2, the virus that causes the COVID-19 pandemic, is a major global public health challenge with severe outcomes worldwide. A robust immune system plays a crucial role in limiting the spread of the virus and supporting recovery. While several nutrients are important for immune function, vitamin D is particularly important in bolstering immunity. This review aimed to investigate the interplay between viral infection, immune response, and vitamin D in determining the prognosis of COVID-19. It is believed that vitamin D possesses anti-inflammatory, immunomodulatory, antifibrotic, and antioxidant properties, potentially aiding in the fight against SARS-CoV-2 infection. Severe complications associated with SARS-CoV-2, including cytokine storms, acute respiratory distress syndrome, and disruption of the renin-angiotensin system, are influenced by various mechanisms. Vitamin D helps regulate these processes by inhibiting inflammatory cytokines, thereby reducing disease severity and risk of mortality. Vitamin D is recommended for both prevention and support of COVID-19 treatment, because it reduces the likelihood of viral infections such as the common cold, enhances cellular immunity, modulates adaptive immunity, and increases the expression of antioxidant-related genes. However, current evidence on the direct relationship between vitamin D levels, COVID-19 severity, and mortality remains insufficient. Therefore, further randomized controlled trials and large-scale cohort studies are needed to investigate this association.

Keywords: COVID-19, Vitamin D, SARS-CoV-2, Cytokine Storm

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Introduction

COVID-19, caused by the SARS-CoV-2 virus, was officially named by the World Health Organization (WHO) [1] and declared a global pandemic [2]. The virus has spread rapidly across the globe, impacting nearly every country. Despite the absence of a definitive treatment for COVID-19, preventive strategies have been developed to mitigate its spread and effects [3].

Coronaviruses are classified as RNA viruses and are divided into four subfamilies: alpha, gamma, beta, and delta [4]. Alpha and beta coronaviruses primarily affect mammals, while gamma and delta coronaviruses can infect both mammals and birds [5]. Human infections are typically caused by alpha and beta coronaviruses [6]. The viruses that infect the upper respiratory tract in humans, such as HCoV-229E, HCoV-NL63, HCoV-HKU1, and HCoV-OC43, generally lead to mild symptoms similar to a common cold and are transmitted through respiratory droplets. In contrast, more severe coronaviruses like SARS-CoV and MERS-CoV primarily target the lower respiratory system and can result in fatal respiratory distress [7].

The immune system plays an essential role in determining the severity of COVID-19 [8]. Balanced nutrition is key to maintaining a strong immune response, helping the body defend against infections [9]. Inadequate or poor nutrition weakens immunity, increasing the risk of illness. During the COVID-19 pandemic, it has been recommended that individuals maintain a balanced intake of macronutrients such as proteins, fats, and

carbohydrates, while also ensuring sufficient intake of micronutrients to support immune function [10, 11]. Vitamins and minerals, including vitamins A, C, D, and E, along with zinc, iron, and selenium, are particularly important for immune health [7]. Among these, vitamin D plays a crucial role in defending against viral respiratory infections by modulating both the innate and adaptive immune systems [12].

Vitamin D deficiency has a detrimental impact on key immune processes, such as lung function, cytokine regulation, preventing apoptosis in epithelial cells, and facilitating their repair. This disruption weakens the body's immune response. As a result, regions with limited sunlight exposure and lower vitamin D levels may experience higher COVID-19 mortality rates. In contrast, countries closer to the equator, where sunlight is more consistent, tend to report lower death rates from the virus. Additionally, a study found that 76% of COVID-19 patients were vitamin D deficient [13].

With the emergence of the pandemic, there has been an increasing focus on the role of vitamin D, known for its effects on upper respiratory tract infections. Researchers have suggested that vitamin D could help mitigate the severity of COVID-19 by modulating immune responses. The vitamin influences various genes that immune cells express, potentially reducing the severity of not just COVID-19 but also other respiratory infections [14].

This review aimed to investigate the interplay between viral infection, immune response, and vitamin D in determining the prognosis of COVID-19.

Results and Discussion

Immune Evasion and Cytokine Storm

Severe complications such as ARDS, cardiac issues, multi-organ failure, and even death in COVID-19 patients are often driven by cytokine storms. A cytokine storm is characterized by an excessive and unregulated release of cytokines, leading to widespread inflammation. SARS-CoV-2 contributes to this storm by interfering with the renin-angiotensin system, triggering acute lung damage and ARDS [15, 16]. The virus also evades immune detection by suppressing the innate immune response, inhibiting type I interferon (IFN) production, and preventing the recognition of pathogen-associated molecular patterns (PAMPs) by pattern recognition receptors (PRRs). Furthermore, it disrupts NF-κB activation, further impairing immune function [17].

Type I interferons (IFNs) are essential for the body's initial defense against viral infections and for regulating adaptive immunity. The effectiveness of the innate immune response largely depends on the production of these interferons. However, certain viruses, including SARS-CoV-2, can evade this defense mechanism by inhibiting the production of type I IFNs and by disrupting receptors like retinoic acid-inducible gene-I (RIG-I)-like receptors. The immune system identifies viral RNA through a set of receptors known as pathogen-associated molecular pattern (PAMP) sensors, which include pattern recognition receptors (PRRs), cytoplasmic RNA sensors, and nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs). Among these, TLR-3, TLR-7, and TLR-8 are involved in the detection of PAMPs, while RIG-I and MDA5 are key cytoplasmic RNA sensors, and NLR proteins like NLRP1, NLRP3, NLRP7, and NLRC4 also play a role [18].

When immune cells detect viral RNA, they trigger inflammatory signaling pathways through PRRs, particularly TLR-3 and TLR-7. However, SARS-CoV-2 uniquely interferes with these pathways by inhibiting TRAF-3 and TRAF-6, molecules linked to TNF receptors. Although the virus activates TLR-3 and TLR-7, it simultaneously suppresses TRAF-3 and TRAF-6, leading to the inhibition of NF-kB and IRF-3/7, which diminishes the early inflammatory and antiviral responses triggered by type I IFN [17]. The recognition of viral RNA by PRRs activates transcription factors such as IRF-3 and IRF-7, leading to the production of type I IFNs. These IFNs, in turn, stimulate the expression of IFN-stimulated genes (ISGs) through the JAK-STAT signaling pathway [19]. A disruption in this pathway can worsen the severity of SARS-CoV-2 infections and impair the antiviral response [20].

As the infection progresses, cell death releases viral particles and intracellular components, which further activate the immune system. These particles are detected by PRRs on monocytes and macrophages, which then initiate pro-inflammatory signaling pathways involving NF-kB and IRF. This leads to the release of pro-inflammatory cytokines, including TNF-α, IL-1, IL-6, and chemokines such as CXCL10, CXCL9, CXCL8, CCL2, and CCL5 [21]. While some of these cytokines, like type I IFN and IL-7, are beneficial, others, such as IL-1β, IL-6, and TNF-α, can exacerbate the inflammatory response, especially during a cytokine storm, which contributes significantly to the pathophysiology of COVID-19. The overwhelming release of cytokines and chemokines attracts immune cells like neutrophils and monocytes to the lungs, leading to excessive infiltration and damage to

lung tissue [22]. Delayed type I IFN responses worsen the situation by encouraging the accumulation of inflammatory monocytes and macrophages, which further drives the cytokine storm, resulting in severe tissue damage, pneumonia, ARDS, and coagulation issues [23].

A connection exists between type B beta coronaviruses, which are responsible for severe diseases and even fatalities, and COVID-19 [4]. The body's ability to mount a protective response to infections is influenced by various factors, including genetics, epigenetics, and lifestyle. Vitamin D has been shown to reduce the risk of viral infections and to protect against conditions like pneumonia and lung damage through multiple mechanisms. These include enhancing anti-inflammatory cytokine levels and suppressing the production of pro-inflammatory cytokines. As such, vitamin D is considered a key factor in mitigating the severity of COVID-19 [22, 23].

The Role of Vitamin D in COVID-19

Vitamin D, which is primarily synthesized through ultraviolet-B (UVB) exposure, is present in very few foods. The vitamin D receptor (VDR) plays a crucial role in regulating immune function and exhibits anti-inflammatory properties. VDRs are found on most immune cells, including dendritic cells, macrophages, and activated T and B cells. Vitamin D impacts both innate and adaptive immunity, enhancing the antimicrobial activity of macrophages and monocytes. Additionally, vitamin D influences the expression of various genes, reducing the production of pro-inflammatory cytokines (such as IL-12 and IL-23) while promoting the production of anti-inflammatory molecules like IL-10 and TNF-alpha. Through its modulation of cytokine expression, vitamin D plays a significant role in T cell responses by either stimulating or inhibiting cytokines [24, 25].

Active vitamin D, along with its receptor (VDR) and the enzyme 1α-hydroxylase, is expressed by dendritic cells, macrophages, and activated T and B cells. This enables vitamin D to regulate immune responses, particularly by modulating cytokine expression and interacting with both adaptive and innate immune cells [25, 26]. The immunomodulatory effects of vitamin D lead to enhanced antimicrobial activity and a reduction in pro-inflammatory actions. By promoting the differentiation of monocytes into macrophages, vitamin D enhances phagocytosis, decreases the production of inflammatory cytokines, and increases the production of antimicrobial proteins. This helps mitigate inflammation, especially in the lungs. Studies suggest that vitamin D supplementation can reduce the incidence of viral respiratory infections, particularly in individuals with vitamin D deficiency [26].

Variations in vitamin D-related genes may influence the severity of COVID-19. Specifically, mutations in genes such as VDR, DBP, CYP27B1, and CYP24A1 have been shown to negatively affect vitamin D activity. Research has revealed a connection between polymorphisms in the VDR gene and the occurrence of respiratory infections. Toll-like receptors, specifically TLR2/1, have been observed to increase the expression of VDR and CYP27B1 in monocytes, while also promoting the production of antimicrobial peptides like cathelicidin and defensin 2. Additionally, immune cells such as dendritic cells, macrophages, and activated T and B cells are involved in expressing VDR and CYP27B1 [27].

Vitamin D serves as an important immune system regulator, promoting the production of antimicrobial peptides, including cathelicidin and defensins, which are essential in controlling inflammation caused by viral, bacterial, and fungal infections [28]. When human monocytes and macrophages are activated through TLRs, there is an increase in VDR expression as well as the expression of vitamin D-1-hydroxylase, which enhances the production of antimicrobial peptides like cathelicidin. These peptides are crucial for killing pathogens such as *Mycobacterium tuberculosis*. Similar mechanisms occur in lung epithelial cells, where vitamin D activation leads to the expression of antimicrobial peptides, including cathelicidin and defensin β2. Human defensin-2 activates the innate immune system by releasing antiviral cytokines and chemokines, which help recruit immune cells like monocytes, macrophages, NK cells, and T cells. Additionally, cathelicidin, in combination with antiviral proteins such as IFN-γ, IFN-β, and MxA, stimulates the production of molecules like PKR and RNase L [27-31].

LL-37, a product of cathelicidin cleavage, exhibits antimicrobial effects against a wide range of pathogens, including viruses, bacteria, parasites, and fungi. It also limits viral replication, including the replication of SARS-CoV-2 [30]. Moreover, defensins play a key role in reducing inflammation caused by viruses like SARS-CoV and influenza A [31]. Human α-defensin 5 has been shown to prevent SARS-CoV-2 from entering host cells by binding to the ACE2 receptor [32].

Vitamin D has an essential role in modulating immune responses, particularly by influencing T regulatory (Treg) cells. By regulating T cell responses, vitamin D helps prevent excessive cytokine production. It reduces the activity of Th1 cells, which are implicated in the development of ARDS, and diminishes the secretion of proinflammatory

cytokines like IFN-γ and TNF-α. Studies have demonstrated that vitamin D supplementation increases the presence of CD11c+ cells, reduces the production of cytokines such as TNF-α, IFN-γ, and IL-6, and regulates antioxidant genes like glutathione reductase. Additionally, vitamin D promotes the expression of antimicrobial peptides and genes involved in autophagy [33].

In COVID-19 patients, there is a notable reduction in peripheral CD4+ and CD8+ T cell counts, alongside an increased concentration of CCR6+ Th17 cells in CD4+ T cells [34]. Severe cases of COVID-19 also show abnormalities such as a decreased lymphocyte count, elevated leukocytes, a higher neutrophil-lymphocyte ratio, and lower levels of monocytes, eosinophils, and basophils [35]. These changes underscore the importance of both innate and adaptive immune responses in the pathophysiology of cytokine storms seen in severe COVID-19.

Vitamin D helps to regulate immune responses by modulating the activity of a wide range of immune cells. These include CD4+ and CD8+ T cells, neutrophils, B cells, macrophages, monocytes, and dendritic cells, with the help of their receptor, the vitamin D receptor (VDR). It reduces the differentiation of Th1 and Th17 cells by promoting VDR expression in CD4+ T cells and enhances Th2 cell differentiation. This balance between T cell subsets plays a significant role in preventing the cytokine storm [36].

The presence of SARS-CoV-2 amplifies inflammation by stimulating IL-6 production in CD14+ and CD16+ monocytes, which are derived from Th1 cells [37]. A range of cytokines, including TNF-α, IFN-γ, IL-2 from Th1 cells, and IL-13, IL-9, IL-5, and IL-10 from Th2 cells, are elevated in individuals with COVID-19. The overproduction of these proinflammatory cytokines, particularly from both Th1 and Th2 cells, contributes to the cytokine storm, immune dysfunction, and the development of conditions like pneumonia and ARDS [37, 38]. Vitamin D reduces the production of proinflammatory cytokines such as TNF-α, IFN-γ, IL-2, IL-1, IL-12, IL-17, IL-23, and IL-22 from Th1 and Th17 cells, while simultaneously enhancing Th2 responses by promoting IL-4 production. This shift in immune response helps control inflammation and regulate immune function [36, 39].

Macrophages exhibit distinct functional states depending on the immune response. M1 macrophages are activated in response to Th1 and Th2 responses and produce various proinflammatory cytokines, including TNF-α, IL-1β, IL-6, IL-8, IL-12, IL-18, and a variety of chemokines such as CXCL1, CXCL8, CXCL9, CXCL10, CXCL11, CXCL5, CXCL3, and CXCL13. These macrophages contribute to inflammation and immune responses. In contrast, M2 macrophages are associated with the resolution of inflammation and tissue repair. They generate anti-inflammatory cytokines such as TGF-β, IL-4, IL-10, and IL-13, which help control tissue damage through phagocytic activity.

Vitamin D, specifically its active form 1,25(OH)2D, has been shown to reduce the production of proinflammatory cytokines such as IL-6, IL-12p40, and IL-1β, as well as chemokines including CXCL9, CXCL10, and CXCL11, produced by M1 macrophages. Additionally, vitamin D can promote the shift from the M1 proinflammatory phenotype toward the M2 anti-inflammatory phenotype, supporting tissue repair and mitigating inflammation [40].

Vitamin D's influence extends to modulating the immune balance, which is crucial for counteracting the cytokine storm seen in severe COVID-19 cases. It may initially curb viral replication and later help alleviate hyperinflammation [36, 39-41]. Maintaining adequate levels of vitamin D is therefore critical for controlling the severity of viral infections like COVID-19.

Beyond immune modulation, vitamin D also interacts with the renin-angiotensin system (RAS) by increasing the expression of angiotensin-converting enzyme 2 (ACE2). This enzyme plays a key role in the entry of SARS-CoV-2 into host cells. ACE2 is highly expressed in respiratory epithelial cells, lung alveolar cells, heart, kidneys, blood vessels, and the gastrointestinal system [42]. When SARS-CoV-2 binds to ACE2, it reduces ACE2 levels and simultaneously increases ACE activity, leading to an overproduction of angiotensin II, which exacerbates inflammation and disease severity [43]. ACE2 counters the inflammatory effects of angiotensin II by converting it into angiotensin 1-7, which has anti-inflammatory properties [44]. ACE2 is crucial in protecting against acute respiratory distress syndrome (ARDS) and acute lung injury.

Research indicates that vitamin D can help regulate the renin-angiotensin system by enhancing ACE2 expression, reducing ACE activity, and decreasing the levels of angiotensin II. Additionally, vitamin D lowers renin expression, further inhibiting angiotensin II production [45]. Studies have shown that 1,25(OH)2D can prevent acute lung injury caused by lipopolysaccharides by modulating key components of the renin-angiotensin system, including ACE2.

However, measures like isolation and social distancing, which reduce COVID-19 transmission, also decrease sun exposure, leading to potential vitamin D deficiencies in the population. This raises the need for vitamin D

supplementation, especially in light of its possible role in reducing the severity of COVID-19. Despite promising findings, more research is required to definitively link vitamin D deficiency with COVID-19 infection and to evaluate whether vitamin D supplementation could mitigate the spread and impact of the virus [46, 47].

Research has indicated a link between vitamin D deficiency and higher COVID-19 mortality rates, particularly in Europe [14]. One study suggested that vitamin D supplementation, whether before or after a COVID-19 diagnosis, was associated with less severe symptoms and better survival rates, especially among frail elderly individuals [48]. A systematic review and meta-analysis found that while vitamin D deficiency was not directly linked to a higher likelihood of contracting COVID-19, those with severe cases were 64% more likely to be vitamin D deficient compared to those with mild symptoms. Deficiency in vitamin D has been connected to increased hospitalization rates and higher mortality from COVID-19, with a positive correlation between vitamin D levels and disease severity [49].

In a study by Annweiler *et al.* [50], vitamin D3 supplementation before or during COVID-19 infection was linked to less severe illness and improved survival rates among older and frail individuals. Another study examining individuals between the ages of 30-60 found that more than half of those with COVID-19 had vitamin D deficiency. These patients also had elevated inflammatory markers, and those with lower vitamin D levels experienced more severe COVID-19 symptoms, which contributed to a higher mortality rate. These findings suggest that mass vitamin D supplementation for at-risk populations may help mitigate COVID-19 severity [51].

Other research emphasized that while vitamin D deficiency was common among COVID-19 patients, it did not appear to be directly associated with disease outcomes [52]. A retrospective study also showed that cholecalciferol supplementation seemed to reduce the mortality risk in acute COVID-19 patients, regardless of their initial serum 25(OH)D levels [53]. Additionally, a study proposed that exposure to sunlight might offer some protective effects against COVID-19 mortality [54]. A study conducted in India also found that low levels of 25(OH) vitamin D were inversely related to both SARS-CoV-2 infection rates and mortality in the Indian population [55].

In a randomized, placebo-controlled trial examining high-dose vitamin D supplementation for COVID-19, patients who received 60,000 IU of cholecalciferol daily achieved 25(OH)D levels above 50 ng/mL in 75% of the participants by the 14th day. This high-dose treatment led to improved recovery and survival rates in 41.7% of the patients [56]. However, another study found no clear evidence that vitamin D supplementation provided protective effects against COVID-19, and it did not reduce the severity of the illness [57].

A study by Hastie et al. [58] initially identified a link between vitamin D levels and COVID-19 outcomes, but after adjusting for other variables, this relationship became insignificant. The researchers also highlighted that ethnicity could influence COVID-19 outcomes [58]. Similarly, research by Merzon *et al.* [59] found that people infected with COVID-19 had lower vitamin D levels compared to uninfected individuals. Lower vitamin D concentrations were associated with a higher risk of contracting the virus and requiring hospitalization [59].

Ilie et al. found an inverse relationship between vitamin D levels and the number of COVID-19 cases and deaths [60], whereas Pizzini *et al.* [52] did not find any significant associations between vitamin D levels and the severity of the disease. Raharusun *et al.* [61] reported that 98.9% of individuals with vitamin D deficiency and 87.8% of those with inadequate vitamin D levels died. The mortality risk for those with deficiency was 12.55 times higher than for those with sufficient levels, and for those with severe deficiency, the mortality rate was 19.12 times higher. This demonstrated a significant link between vitamin D levels and COVID-19 mortality [61].

In Italy, Ferrari and Locatelli [62] found no significant difference in vitamin D levels between COVID-19-positive and COVID-19-negative individuals. On the contrary, Li *et al.* [63] suggested that vitamin D could reduce the number of COVID-19 cases and deaths, with the relationship influenced by sunlight exposure and geographical location. Furthermore, a study conducted on elderly COVID-19 patients indicated that vitamin D deficiency was associated with more severe lung damage, longer illness duration, and higher mortality rates [64]. These findings underscore the potential importance of maintaining adequate vitamin D levels to reduce the severity and risk of COVID-19.

Vitamin D Requirements

Vitamin D deficiency is defined as having a 25(OH)D level below 20 ng/mL, while levels between 21-29 ng/mL are considered insufficient. To promote good health, it's advised to maintain a 25(OH)D level above 30 ng/mL for individuals of all ages, including children, adults, the elderly, and pregnant or breastfeeding women. While levels under 30 ng/mL are considered risky, levels ranging from 50-125 ng/mL are generally regarded as safe. Research from a meta-analysis suggests that vitamin D supplementation might improve clinical outcomes,

especially in patients with moderate or severe COVID-19 who require hospitalization, reducing the need for ICU care and lowering mortality risk. Additionally, studies indicate that maintaining vitamin D levels above 30 ng/mL could lessen the severity of COVID-19 and lower the likelihood of death. In contrast, lower levels have been linked to higher rates of hospital infections. It's been recommended that optimal vitamin D levels be kept between 40-60 ng/mL. To raise serum 25(OH)D levels to this preferred range, an intake of 10,000 IU per day for the first month is advised, followed by a reduced dose of 5,000 IU per day for maintenance [65, 66].

Conclusion

During the COVID-19 pandemic, maintaining a strong immune system is crucial for reducing the risk and severity of the disease. The rationale behind using vitamin D stems from its immune-modulatory properties, which may help prevent COVID-19 infection or alleviate its severity. One of the main complications of COVID-19 is acute respiratory distress syndrome, triggered by mechanisms such as cytokine storms, disturbances in the renin-angiotensin system, and imbalances in ACE2 levels. Vitamin D is known to counteract the cytokine storm by decreasing pro-inflammatory cytokine production through both the innate and adaptive immune systems, while also reducing disease severity by increasing ACE2 concentrations. Consequently, maintaining adequate vitamin D levels is vital for preventing acute respiratory illnesses.

It is well-documented that vitamin D deficiency is prevalent in individuals with COVID-19, especially among the elderly. Therefore, assessing blood vitamin D levels should be an essential part of clinical practice. While individuals with low vitamin D levels can benefit from supplementation, those with adequate levels may not experience significant benefits from additional vitamin D intake. The recommended daily intake of vitamin D, as set by the FNB, is 600 IU for adults. Supplements typically contain 1000 IU of vitamin D, and the upper limit for daily intake is 4000 IU. Excessive vitamin D intake can lead to toxicity. Health authorities suggest that it is more effective to take smaller, consistent doses of vitamin D daily rather than a large dose at once [67].

Vitamin D supplementation may be beneficial for individuals with deficiencies or insufficiencies in the context of COVID-19. However, for those with normal vitamin D levels, there is no strong evidence supporting the use of supplementation to prevent or reduce the severity of the disease. In such cases, lifestyle changes should be prioritized to prevent deficiency and promote a balanced, healthy diet. Caution should also be exercised regarding high-dose vitamin D supplements, particularly those exceeding the recommended upper limits. More prospective studies are needed to determine whether administering high-dose vitamin D3 to elderly patients at the time of or before infection could improve outcomes or prevent COVID-19.

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References

1. Cascella M, Rajnik M, Aleem A, Dulebohn SC, Di Napoli R. Features, evaluation, and treatment of coronavirus (COVID-19). In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2021.
2. Cintoni M, Rinninella E, Annetta MG, Mele MC. Nutritional management in hospital setting during SARS-CoV-2 pandemic: A real-life experience. Eur J Clin Nutr. 2020;74(5):846-7. doi:10.1038/s41430-020-0625-4
3. Uversky VN, Elrashdy F, Aljadawi A, Ali SM, Khan RH, Redwan EM. Severe acute respiratory syndrome coronavirus 2 infection reaches the human nervous system: How? J Neuroscience Res. 2021;99(3):750-77. doi:10.1002/jnr.24752
4. Esakandari H, Nabi-Afjadi M, Fakkari-Afjadi J, Farahmandian N, Miresmaeili SM, Bahreini E. A comprehensive review of COVID-19 characteristics. Biol Proced Online. 2020;22(1):1-0. doi:10.1186/s12575-020-00128-2

5. Chang L, Yan Y, Wang L. Coronavirus disease 2019: Coronaviruses and blood safety. Transfus Med Rev. 2020;34(2):75-80. doi:10.1016/j.tmrv.2020.02.003
6. Hartenian E, Nandakumar D, Lari A, Ly M, Tucker JM, Glaunsinger BA. The molecular virology of coronaviruses. J Biol Chem. 2020;295(37):12910-34. doi:10.1074/jbc.REV120.013930
7. Gasmi A, Noor S, Tippairote T, Dadar M, Menzel A, Bjørklund G. Individual risk management strategy and potential therapeutic options for the COVID-19 pandemic. Clin Immunol. 2020;215:108409. doi:10.1016/j.clim.2020.108409
8. Calder PC. Nutrition, immunity and COVID-19. BMJ Nutr Prev Health. 2020;3(1):74-92. doi:10.1136/bmjnph-2020-000085
9. Zabetakis I, Lordan R, Norton C, Tsoupras A. COVID-19: The inflammation link and the role of nutrition in potential mitigation. Nutrients. 2020;12(5):1466. doi:10.3390/nu12051466
10. World Health Organization. Nutrition advice for adults during the COVID-19 outbreak. Available from: http://www.emro.who.int/nutrition/news/nutrition-advice-for-adults-during-the-COVID-19-outbreak.html (Accessed: May 10, 2022).
11. Barazzoni R, Bischoff SC, Breda J, Wickramasinghe K, Krznaric Z, Nitzan D, et al. ESPEN expert statements and practical guidance for the nutritional management of individuals with SARS-CoV-2 infection. Clin Nutr. 2020;39(6):1631-8. doi:10.1016/j.clnu.2020.03.022
12. Martens PJ, Gysemans C, Verstuyf A, Mathieu C. Vitamin D's effect on immune function. Nutrients. 2020;12(5):1248. doi:10.3390/nu12051248
13. Im JH, Je YS, Baek J, Chung MH, Kwon HY, Lee JS. Nutritional status of patients with COVID-19. Int J Infect Dis. 2020;100:390-3. doi:10.1016/j.ijid.2020.08.018
14. Ali N. Role of vitamin D in preventing of COVID-19 infection, progression, and severity. J Infect Public Health. 2020;13(10):1373-80. doi:10.1016/j.jiph.2020.06.021
15. Iddir M, Brito A, Dingeo G, Fernandez Del Campo SS, Samouda H, La Frano MR, et al. Strengthening the immune system and reducing inflammation and oxidative stress through diet and nutrition: Considerations during the COVID-19 Crisis. Nutrients. 2020;12(6):1562. doi:10.3390/nu12061562
16. Gao YL, Du Y, Zhang C, Cheng C, Yang HY, Jin YF, et al. Role of renin-angiotensin system in acute lung injury caused by viral infection. Infect Drug Resist. 2020;13:3715-25. doi:10.2147/IDR.S265718
17. Felsenstein S, Herbert JA, McNamara PS, Hedrich CM. COVID-19: Immunology and treatment options. Clin Immunol. 2020;215:108448. doi:10.1016/j.clim.2020.108448
18. Bahari Z, Jangravi Z, Ghoshooni H, Afarinesh MR, Meftahi GH. Pharmacological mechanism of immunomodulatory agents for the treatment of severe cases of COVID-19 infection. Inflamm Res. 2021;70:389-405. doi:10.1007/s00011-021-01445-2
19. Li G, Fan Y, Lai Y, Han T, Li Z, Zhou P, et al. Coronavirus infections and immune responses. J Med Virol. 2020;92(4):424-32. doi:10.1002/jmv.25685
20. Catanzaro M, Fagiani F, Racchi M, Corsini E, Govoni S, Lanni C. Immune response in COVID-19: Addressing a pharmacological challenge by targeting pathways triggered by SARS-CoV-2. Signal Transduct Target Ther. 2020;5(1):1-0. doi:10.1038/s41392-020-0191-1
21. Kircheis R, Haasbach E, Lueftenegger D, Heyken WT, Ocker M, Planz O. NF-κB pathway as a potential target for treatment of critical stage COVID-19 patients. Front Immunol. 2020;11:598444. doi:10.3389/fimmu.2020.598444
22. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the `Cytokine Storm' in COVID-19. J Infect. 2020;80(6):607-13. doi:10.1016/j.jinf.2020.03.037
23. Kempuraj D, Selvakumar GP, Ahmed ME, Raikwar SP, Thangavel R, Khan A, et al. COVID-19, mast cells, cytokine storm, psychological stress, and neuroinflammation. Neuroscientist. 2020;26(5-6):402-14. doi:10.1177/1073858420941476
24. Chang SW, Lee HC. Vitamin D and health - The missing vitamin in humans. Pediatr Neonatol. 2019;60(3):23744. doi:10.1016/j.pedneo.2019.04.007
25. Sassi F, Tamone C, D'Amelio P. Vitamin D: Nutrient, hormone, and immunomodulator. Nutrients. 2018;10(11):1656. doi:10.3390/nu10111656
26. Calder PC, Carr AC, Gombart AF, Eggersdorfer M. Optimal nutritional status for a well-functioning immune system is an important factor to protect against viral infections. Nutrients. 2020;12(4):1181. doi:10.3390/nu12041181

27. Teymoori-Rad M, Marashi SM. Vitamin D and COVID-19: From potential therapeutic effects to unanswered questions. Rev Med Virol. 2021;31(2):e2159. doi:10.1002/rmv.2159
28. Boulkrane MS, Ilina V, Melchakov R, Fedotova J, Drago F, Gozzo L, et al. COVID-19 disease and vitamin D: A Mini-Review. Front Pharmacol. 2020;11:604579. doi:10.3389/fphar.2020.604579
29. Kim J, Yang YL, Jang SH, Jang YS. Human β-defensin 2 plays a regulatory role in innate antiviral immunity and is capable of potentiating the induction of antigen-specific immunity. Virol J. 2018;15(1):1-12. doi:10.1186/s12985-018-1035-2
30. Crane-Godreau MA, Clem KJ, Payne P, Fiering S. Vitamin D deficiency and air pollution exacerbate COVID-19 through suppression of antiviral peptide LL37. Front Public Health. 2020;8:232. doi:10.3389/fpubh.2020.00232
31. Kerget B, Kerget F, Aksakal A, Aşkın S, Sağlam L, Akgün M. Evaluation of alpha defensin, IL-1 receptor antagonist, and IL-18 levels in COVID-19 patients with macrophage activation syndrome and acute respiratory distress syndrome. J Med Virol. 2021;93(4):2090-8. doi:10.1002/jmv.26589
32. Wang C, Wang S, Li D, Wei DQ, Zhao J, Wang J. Human intestinal defensin 5 inhibits SARS-CoV-2 invasion by cloaking ACE2. Gastroenterology. 2020;159(3):1145-7. doi:10.1053/j.gastro.2020.05.015
33. Bilezikian JP, Bikle D, Hewison M, Lazaretti-Castro M, Formenti AM, Gupta A, et al. Mechanisms in endocrinology: Vitamin D and COVID-19. Eur J Endocrinol. 2020;183(5):R133-47. doi:10.1530/EJE-20-0665
34. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020;8(4):420-2. doi:10.1016/S2213-2600(20)30076-X
35. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of immune response in patients with Coronavirus 2019 (COVID-19) in Wuhan, China. Clin Infect Dis. 2020;71(15):762-8. doi:10.1093/cid/ciaa248
36. Bishop EL, Ismailova A, Dimeloe S, Hewison M, White JH. Vitamin D, and immune regulation: Antibacterial, antiviral, anti-inflammatory. JBMR Plus. 2020;5(1):e10405. doi:10.1002/jbm4.10405
37. Wang J, Jiang M, Chen X, Montaner LJ. Cytokine storm and leukocyte changes in mild versus severe SARS-CoV-2 infection: Review of 3939 COVID-19 patients in China and emerging pathogenesis and therapy concepts. J Leukoc Biol. 2020;108(1):17-41. doi:10.1002/JLB.3COVR0520-272R
38. Weiskopf D, Schmitz KS, Raadsen MP, Grifoni A, Okba NM, Endeman H, et al. Phenotype and kinetics of SARS-CoV-2-specific T cells in COVID-19 patients with acute respiratory distress syndrome. Sci Immunol. 2020;5(48):eabd2071. doi:10.1126/sciimmunol.abd2071
39. Vyas N, Kurian SJ, Bagchi D, Manu MK, Saravu K, Unnikrishnan MK, et al. Vitamin D in prevention and treatment of COVID-19: Current perspective and future prospects. J Am Coll Nutr. 2021;40(7):632-45. doi:10.1080/07315724.2020.1806758
40. Atri C, Guerfali FZ, Laouini D. Role of human macrophage polarization in inflammation during infectious diseases. Int J Mol Sci. 2018;19(6):1801. doi:10.3390/ijms19061801
41. Mohan M, Cherian JJ, Sharma A. Exploring links between vitamin D deficiency and COVID-19. PLoS Pathogens. 2020;16(9):e1008874. doi:10.1371/journal.ppat.1008874
42. Malek Mahdavi A. A brief review of interplay between vitamin D and angiotensin-converting enzyme 2: Implications for a potential treatment for COVID-19. Rev Med Virol. 2020;30(5):e2119. doi:10.1002/rmv.2119
43. Kumar R, Rathi H, Haq A, Wimalawansa SJ, Sharma A. Putative roles of vitamin D in modulating immune response and immunopathology associated with COVID-19. Virus Res. 2021;292:198235. doi:10.1016/j.virusres.2020.198235
44. Alexandre J, Cracowski JL, Richard V, Bouhanick B. Drugs. COVID-19 working group of the French Society of Pharmacology, Therapeutics. Renin-angiotensin-aldosterone system and COVID-19 infection. Ann Endocrinol. 2020;81(2-3):63-7. doi:10.1016/j.ando.2020.04.005
45. Rhodes JM, Subramanian S, Laird E, Griffin G, Kenny RA. Perspective: Vitamin D deficiency and COVID-19 severity - plausibly linked by latitude, ethnicity, impacts on cytokines, ACE2, and thrombosis. J Intern Med. 2021;289(1):97-115. doi:10.1111/joim.13149
46. Alberca RW, Oliveira LM, Branco ACCC, Pereira NZ, Sato MN. Obesity as a risk factor for COVID-19: An overview. Crit Rev Food Sci Nutr. 2021;61(13):2262-76. doi:10.1080/10408398.2020.1775546

47. Former CDC. Tom Frieden: Coronavirus infection risk may be reduced by Vitamin D. Fox News. 2020.
48. Annweiler G, Corvaisier M, Gautier J, Dubée V, Legrand E, Sacco G, et al. Vitamin D supplementation associated to better survival in hospitalized frail elderly COVID-19 patients: The GERIA-COVID quasi-experimental study. Nutrients. 2020;12(11):3377. doi:10.3390/nu12113377
49. Pereira M, Dantas Damascena A, Galvão Azevedo LM, de Almeida Oliveira T, da Mota Santana J. Vitamin D deficiency aggravates COVID-19: Systematic review and meta-analysis. Crit Rev Food Sci Nutr. 2022;62(5):1308-16. doi:10.1080/10408398.2020.1841090
50. Annweiler C, Hanotte B, Grandin de l'Eprevier C, Sabatier JM, Lafaie L, et al. Vitamin D and survival in COVID-19 patients: A quasi-experimental study. J Steroid Biochem Mol Biol. 2020;204:105771. doi:10.1016/j.jsbmb.2020.105771
51. Jain A, Chaurasia R, Sengar NS, Singh M, Mahor S, Narain S. Analysis of vitamin D level among asymptomatic and critically ill COVID-19 patients and its correlation with inflammatory markers. Sci Rep. 2020;10(1):20191. doi:10.1038/s41598-020-77093-z
52. Pizzini A, Aichner M, Sahanic S, Böhm A, Egger A, Hoermann G, et al. Impact of Vitamin D deficiency on COVID-19 prospective analysis from the COVILD registry. Nutrients. 2020;12(9):2775. doi:10.3390/nu12092775
53. Ling SF, Broad E, Murphy R, Pappachan JM, Pardesi-Newton S, Kong MF, et al. High-dose cholecalciferol booster therapy is associated with a reduced risk of mortality in patients with COVID-19: A cross-sectional multi-center observational study. Nutrients. 2020;12(12):3799. doi:10.3390/nu12123799
54. Lansiaux É, Pébaÿ PP, Picard JL, Forget J. Covid-19 and Vit-D: Disease mortality negatively correlates with sunlight exposure. Spat Spatio-Temporal Epidemiol. 2020;35:100362. doi:10.1016/j.sste.2020.100362
55. Padhi S, Suvankar S, Panda VK, Pati A, Panda AK. Lower levels of vitamin D are associated with SARS-CoV-2 infection and mortality in the Indian population: An observational study. Int Immunopharmacol. 2020;88:107001. doi:10.1016/j.intimp.2020.107001
56. Rastogi A, Bhansali A, Khare N, Suri V, Yaddanapudi N, Sachdeva N, et al. Short term, high-dose vitamin D supplementation for COVID-19 disease: A randomized, placebo-controlled, study (SHADE study). Postgrad Med J. 2022;98(1156):87-90. doi:10.1136/postgradmedj-2020-139065
57. Amin HA, Drenos F. No evidence that vitamin D is able to prevent or affect the severity of COVID-19 in individuals with European ancestry: A Mendelian randomization study of open data. BMJ Nutr Prev Health. 2021;4(1):42-8. doi:10.1136/bmjnph-2020-000151
58. Hastie CE, Mackay DF, Ho F, Celis-Morales CA, Katikireddi SV, Niedzwiedz CL, et al. Vitamin D concentrations and COVID-19 infection in UK Biobank. Diabetes Metab Syndr Clin Res Rev. 2020;14(4):561-5. doi:10.1016/j.dsx.2020.04.050
59. Merzon E, Tworowski D, Gorohovski A, Vinker S, Golan Cohen A, Green I, et al. Low plasma 25(OH) vitamin D level is associated with increased risk of COVID-19 infection: An Israeli population-based study. FEBS J. 2020;287(17):3693-702. doi:10.1111/febs.15495
60. Ilie PC, Stefanescu S, Smith L. The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality. Aging Clin Exp Res. 2020;32(7):1195-8. doi:10.1007/s40520-020-01570-8
61. Raharusun P, Priambada S, Budiarti C, Agung E, Budi C. Patterns of COVID-19 mortality and vitamin D: an Indonesian study. SSRN Electron J. 2020;7:1-2. doi:10.2139/ssrn.3585561
62. Ferrari D, Locatelli M. No significant association between vitamin D and COVID-19: A retrospective study from a northern Italian hospital. Int J Vitam Nutr Res. 2021;91(3-4):200-3. doi:10.1024/0300-9831/a000687
63. Li Y, Li Q, Zhang N, Liu Z. Sunlight and vitamin D in the prevention of coronavirus disease (COVID-19) infection and mortality in the United States. 2020. doi:10.21203/rs.3.rs-32499/v1
64. Sulli A, Gotelli E, Casabella A, Paolino S, Pizzorni C, Alessandri E, et al. Vitamin D and lung outcomes in elderly COVID-19 patients. Nutrients. 2021;13(3):717. doi:10.3390/nu13030717
65. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: An endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2011;96(7):1911-30. doi:10.1210/jc.2011-0385
66. Maghbooli Z, Sahraian MA, Ebrahimi M, Pazoki M, Kafan S, Tabriz HM, et al. Vitamin D sufficiency, a serum 25-hydroxyvitamin D at least 30 ng/mL reduced risk for adverse clinical outcomes in patients with COVID-19 infection. PloS One. 2020;15(9):e0239799. doi:10.1371/journal.pone.0239799

67. Vitamin D. Fact Sheet for Health Professionals. National Institutes of Health. 2022 (NIH). Available from: https://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/