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*Mini review*

# Does vitamin D level have effect on COVID-19 outcomes?

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**Abstract:** The severe acute respiratory syndrome coronavirus 2 (SARS-COV-2), a type of coronavirus that causes the condition known as coronavirus disease, was first reported in Wuhan, China in 2019. It commonly affects the respiratory system and is known to produce, in some cases, pneumonia like symptoms, and even death. However, 25 hydroxyvitamin D commonly known as vitamin D, is, when in its hormonal form, involved in many processes throughout the body, including bone health and immune function. Several studies have linked vitamin D to increased resistance to infection, but the link between vitamin D levels and COVID-19 infection, severity and mortality is yet to be fully ascertained. Several studies have linked vitamin D serum levels and deficiency to differing levels of COVID-19 outcome. This review seeks to investigate these claims made in these studies to help add to the body of knowledge and come to a greater understanding of the link between vitamin D and COVID-19 infection.

**Keywords:** COVID-19; vitamin D; infections; immunity; mortality

## 1. Introduction

### *1.1. The SARS-CoV-2 virus*

The severe acute respiratory syndrome coronavirus 2 (SARS-COV-2), a type of coronavirus that causes the condition known as coronavirus disease, was first reported in Wuhan, China in 2019 [1]. It commonly affects the respiratory system and is known to produce, in some cases, pneumonia-like symptoms, and even death. Symptoms can usually appear an average of five days after exposure and

can include dry cough, fever, fatigue, shortness of breath, body aches, headaches and even gastrointestinal symptoms [2–4]. This particular species is one of a few zoonotic coronaviruses to have emerged in the past decade that have posed some threat to humans, others being the severe acute respiratory syndrome (SARS-CoV) and the Middle East respiratory syndrome (MERS) [5]. The virus, after its first emergence in Wuhan was subsequently linked to viruses of similar sequence homology in bats. It was seen, through RNA sequencing, to share more than 95% similarity to the bat coronavirus and, only around 70% homology to SARS-CoV [6]. Person-to-person transmission of this virus is mediated via direct contact or through inhalation of water droplets expelled via coughing or sneezing.

The SARS-CoV-2 virus is a positive sense ssRNA (single stranded RNA) virus, just like the other members of the coronavirus family to which it belongs. They can range in size from 80–160 nm and are quite large at 8.4–12 kDa. Their genomes can range from 26 to 32 kb in length [7]. It is known to contain nucleocapsid, membrane, envelope spike proteins. Its spike protein is the structure that is critical for its entry into human cells via interaction with the ACE2 receptor in humans. This receptor is known to be highly expressed in oral mucosa, type II alveolar cells, kidney cells and cells of the gastrointestinal (GI) tract. This is what is thought to be responsible for the manifestation of COVID-19 as a respiratory virus, as well as what gives it the ability to affect the GI tract. The SARS-CoV-2 spike protein is comprised of two subunits, S1 and S2. The S1 subunit is further subdivided into three domains, A, B and C [8]. The B domain is primarily responsible for the interaction with the ACE2 protein and entry into the cell [9].

Central to the understanding of how COVID-19 infection leads to mortality is the understanding of the phenomenon known as a cytokine storm. In this occurrence, cytokine-mediated inflammatory response to infection may be initially delayed but subsequently become much more aggressive. In this response, several pro-inflammatory cytokines, such as TLF and IN-6, as well as pro-inflammatory chemokines like CCL2, CCL3 and CCL5, are seen in high concentrations [10]. This can then combine with a rush of neutrophils, macrophages and monocytes to the site to bring about this cytokine storm. This is what normally results in the greatest levels of severe COVID-19 symptoms [11].

The cytokine storm in the case of COVID-19 infection, as previously stated, mainly affects the upper and lower respiratory tract, though other cells and tissues can also be affected. The major cause of morbidity and mortality during SARS-CoV-2 infection is the severe and acute pro-inflammatory response known as acute respiratory distress syndrome. It occurs in the lungs and is brought about by initial rapid viral replication and simultaneous initial inhibition of the production of class I interferon expression in dendritic cells [12,13]. These interferon signalling molecules would normally facilitate the natural innate immune response of the clearing of infected cells by CD8 cells.

### *1.2. Vitamin D*

Additionally, 25 hydroxyvitamin D (25OHD), commonly known as vitamin D, is, when in its hormonal form, involved in many processes throughout the body. 25OHD is normally produced by the liver from parental vitamin D, which is itself produced by photolysis from 7-dehydrocholesterol in the presence of sunlight. The 25OHD is then converted in the kidneys to form the main hormonal form of vitamin D (1,25(OH)2D), catalyzed by the enzyme 25OHD-1α-hydroxylase (CYP27B1) [14]. This vitamin D produced in the kidneys is known to be involved in the mineral homeostasis of Ca and bone metabolism, and it acts through interaction with the vitamin D receptor (VDR). The VDR then acts as

a transcription factor targeting the VDR response element DNA motifs, which then most commonly activate the expression of genes associated with Ca and phosphorus uptake [15,16].

### 1.2.1. Vitamin D in immune function

In addition to the conventionally recognized role in mineral metabolism, vitamin D is also known to have a role in the regulation of the innate and adaptive immune system. Vitamin D has long been shown to be produced in elevated levels during infection with *Mycobacterium tuberculosis*, and that increased exposure to the hormonal form of vitamin D suppressed the proliferation of this pathogen in human monocytes [17,18]. It was only more recently that it was discovered that immune cells can be induced to express the enzyme responsible for conversion of 25OHD to hormonal vitamin D when said cells were introduced to *M. tuberculosis* immunogens, demonstrating that vitamin D appeared to have a role in their functioning in response to exposure to pathogens [19].

The VDR is also shown to be expressed in cells common to the innate immune system, such as macrophages and dendritic cells [20]. Vitamin D receptor is also expressed on T and B lymphocytes, cells central to adaptive immunity, while their expression increases as these cells increase proliferation.

Some cytokines are thought to have an effect on the expression of CYP27B1, the enzyme responsible for the conversion of 25OHD to 1, 25(OH)2D, implying that vitamin D may have a role in the immune response initiated by these cytokines [21].

One important role of vitamin D in the adaptive immune system is the regulation of several cells and molecules related to the adaptive immune response that can be involved in the so-called “cytokine storm” that is very often seen in COVID-19 patients. Vitamin D plays a role in reducing CD4+ T cells and cytokines, increasing regulatory T cells, the downregulation of T cell-driven IGg production and the downregulation of dendritic cell differentiation [22,23].

### 1.2.2. Vitamin D in respiratory infections

Vitamin D, as it has a strong role in immune function and regulation, would also then show efficacy in assisting the body in its fight against viral infection. In addition to the previously stated implications and involvement of vitamin D in the immune system, vitamin D is shown to help regulate the production of known immune system barriers to infection in the body, such as tight junctions, gap junctions and adherens junctions; these proteins play a role in selective cellular entry, cell-to-cell communication via the cytoplasm and contact between epithelial cells, respectively [24–26]. The active hormonal form of vitamin D activates the transcription of vitamin D-activated genes like cathelicidin (small, cationic antimicrobial peptides found in some animals, including humans) and the toll-like receptor coreceptor CD14 in human tracheobronchial epidermal cells. In humans, cathelicidin is shown to decrease the viral particles produced by epithelial cells of the respiratory syncytial virus in Hep-2 epithilial cells [27]. Double-stranded RNA viruses can initiate the expression of 1-alpha hydroxylase i.e., the enzyme responsible for production of active hormonal vitamin D. This vitamin D production can then lead to the initiation of the expression of vitamin D-induced genes that aid in the immune response [28].

Vitamin D, as previously mentioned, is involved in the regulation of T cells. Not only is vitamin D involved in the production of some T cells, but in their reduction of others as well. Vitamin D is known to reduce the production of T helper type 1 (Th1) [29] and induce the production of T helper

type 2 (Th2) cells [30]. Th1 cells are known to be involved in the pro-inflammatory response and produce pro-inflammatory cytokines such as interferon gamma and TNF beta, while Th2 cells are known to produce antiinflamatory signalling molecules such as IL-4, IL-5, IL 10 and IL-13 [31].

As previously stated, this gives evidence to support the fact that, in addition to contributing to the initial barrier, innate and adaptive immunity responses of the immune system toward viruses, vitamin D may also be involved in the reduction of the cytokine storm often seen in many respiratory infections.

Related to this, adults with adequate levels of vitamin D in the blood have a decreased risk of acute respiratory tract infection [32]. In addition to this, adequate levels of vitamin D in serum was inversely correlated with respiratory tract infections in children as well [33].

### *1.3. Factors affecting vitamin D production and their relationship to COVID-19 outcomes*

Understanding the role of vitamin D in the immune response and COVID-19 prognosis and progression is incomplete without understanding the underlying factors affecting vitamin D synthesis. There are several factors which will help or hinder vitamin D production in the body, and thus its role in immunity and the immune response. One of the most glaring factors affecting the production of vitamin D in the body would be skin tone and, by extension, ethnicity.

Exposure to sunlight is a very relevant factor to vitamin D production in the body, and greater exposure to sunlight is linked to higher levels of native vitamin D production, as is oral vitamin D supplementation [34]. Living at lower latitudes, along with adequate sun exposure and larger amounts of ambient sunshine, are associated with lower levels of vitamin D deficiency [35]. Low levels of summer time sun exposure is seen to produce vitamin D sufficiency in lighter-skinned people with minimal DNA damage, but it produces lower levels of vitamin D in those of darker skin [36].

Another factor affecting vitamin D sufficiency is the body mass index (BMI), with those of higher BMI likely having higher levels of vitamin D insufficiency [37]. Some studies have even suggested a graded relationship between vitamin D status and BMI and adiposity, with several theories put forward to explain this. Some theories as to why those with a higher BMI and adiposity have decreased levels of overall vitamin D levels include sequestration in adipose tissue, volumetric dilution and negative feedback mechanisms from increased circulating vitamin D. Other theories state that larger individuals may engage in less outdoor physical activity and may also have a greater tendency to cover their bodies from the sun, thus limiting their vitamin D production [38].

The BMI has interestingly been found to also be linked to more adverse outcomes during COVID-19 infection. Several studies have linked higher BMI and adipose tissue distribution to a greater rate of hospitalization, treatment in the intensive care unit (ICU), need for ventilation and assisted breathing and mortality [39,40].

Yet another factor affecting vitamin D production is skin pigmentation. At higher latitudes where solar insolation is naturally lower than at lower latitudes, darker-skinned people are more vulnerable to vitamin D deficiency. One study purported that African Americans had as high as a 15–20 times greater incidence of vitamin D deficiency as European Americans [41]. It is theorized that this lower level of vitamin D production is linked to the higher incidence of several diseases, including cancer, Alzheimer's, rickets and adverse pregnancy and birth outcomes [42].

Sex is also linked to vitamin D production and insufficiency. In one study, subjects of both sexes were stratified according to BMI and vitamin D level. Vitamin D deficiency was defined as a serum

vitamin D level of less than 20 ng/mL. It was shown that biological females had a lower average vitamin D level in all weight classes than biological males [43].

### *1.4. Vitamin D and COVID-19 infection*

Since the start of the SARS-COV-2 pandemic, many studies have been conducted to ascertain a link, if any, between COVID-19 infection, morbidity and mortality and vitamin D in the human body. One such study compared COVID-19 infection rates between vitamin D-deficient and -sufficient persons. It found that COVID-19 rates in the deficient group were 21.6% (95% CI, 14.0–29.2%) vs 12.2% (95% CI, 8.9–15.4%) in the sufficient group. The study concluded that deficiency in vitamin D can lead to a higher risk of being infected with COVID-19 [44]. Also, low plasma 25(OHD) levels were observed as an independent risk factor for COVID-19 infection and hospitalization, with a mean plasma vitamin D level being observed to be significantly lower among those who tested positive than those who tested negative for COVID-19 [19.00 ng/mL (95% CI 18.41–19.59) vs. 20.55 (95% CI 20.32–20.78) [45]. The analysis also established an association between low plasma 25OHD levels and a greater possibility of COVID-19 infection [crude odds ratio (OR) of 1.58 (95% CI 1.24–2.01, $p < 0.001$)], and of hospitalization due to the SARS-CoV-2 virus [crude OR of 2.09 (95% CI 1.01–4.30, $p < 0.05$)] [45]. Another study also demonstrated this, with vitamin D deficiency also being associated with hospitalization and/or disease severity among coronavirus patients [46].

A study conducted in Serbia also found that DHCR7/NADSYN rs12785878 and CYP2R1 rs10741657 variants of known vitamin D metabolism genes were linked to severe COVID-19 in adults ($p = 0.03$, $p = 0.017$, respectively) [47]. In addition, survival analysis in research conducted in Italy revealed that, after 10 days of patients being hospitalized, severely vitamin D-deficient patients had a 50% chance of mortality, while patients with vitamin D levels of more than or equal to 10 ng/mL had a 5% risk of mortality ($p = 0.019$) [48]. A case control study among COVID-19 patients in Italy on vitamin D supplements showed low mortality and severity, as opposed to unsupplemented patients, many of whom showed an increased risk of chronic obstructive pulmonary diseases [49]. Even though all of the above mentioned data suggested that there was a relationship between COVID-19 and vitamin D status, a study done in the USA found no relationship between COVID-19 infection and vitamin D levels [50]. At least one other study found that, even though there was an association between COVID-19 and vitamin D level, a control trial was needed to draw a conclusion [23].

Some studies also looked at risk factors such as comorbidities, age [46], obesity and metabolic syndrome [48–50], and they all came out as risk factors for infection, severity and mortality. Skin color, race, standard of living and high levels of troponin, creatinine and melanin were each discussed as an independent predictor of COVID-19 severity and mortality [23,45,46,48,49].

In addition to this, more recent studies have been conducted in which the effect of the pre-infection level of vitamin D has been linked to COVID-19 severity. In this study, participants were classified by their vitamin D level prior to COVID-19 infection (deficient, insufficient, adequate and high normal). They were then categorized according to the severity of their COVID-19 infection using multivariate regression analysis. The results showed that illness classified as critical or severe was more commonly associated with those of lower vitamin D status (84.7%) than with those of a mild or moderate disease (34.3%). Patients with a vitamin D deficiency were up to 14 times more likely to have a more severe illness than patients without it [51].

Furthermore, recent studies in the UK have also suggested that vitamin D insufficiency is correlated with a worse prognosis for SARS-CoV-2 patients [52,53]. Further, in a study conducted by scholars from the UK which compared mean serum levels of vitamin D to COVID-19 deaths per million population in 20 European countries, it was found that there was a significant inverse relationship between mean blood serum levels and COVID-19 cases per million. In spite of this, however, no significant correlation was found between mean serum vitamin D levels and deaths per million population [54]. Similar studies done in a cohort of 412 patients in South Asia also found statistically significant differences between the serum vitamin D levels of patients who experienced mild, ordinary, severe and critical cases of SARS-CoV-2 [55]. In a study of 62 patients in a tertiary teaching hospital in Singapore, it was discovered that those treated with vitamin D showed a reduced need for additional oxygen, while patients treated with vitamins D (1000 mg), B12 (500 mg) and magnesium (150 mg) showed significantly more favorable outcomes than those not treated with this regimen [56]. Conversely, a study done in the UK using Biobank data found no significant correlation between COVID-19 cases and vitamin D levels [52], though subsequent studies using the same Biobank data did find a correlation between ethnicity and vitamin D levels, where those of Black and Asian ancestry had lower levels of vitamin D, as with those who had a higher BMI. It was found that Black and Asian persons who also had a high BMI were found to be at higher risk of testing positive for COVID-19, though the regression model did not predict COVID-19 positive status when taking BMI and ethnicity into consideration [57].

In addition to Black and Asian patients, studies done using European cohorts have also yielded similar results. For example, one study involving a cohort of 30 Greek patients admitted to an ICU showed that all admitted patients were either vitamin D deficient or insufficient. The cohort was then divided into those who had vitamin D levels that were either higher or lower than the median of the group at 15.2 ng/mL. Of those who died within the first 28 days in the ICU, all of them were classified as having lower vitamin D levels than those who survived. The lower vitamin D group was also seen to have a higher mortality rate than those with higher vitamin D levels overall [58].

## 2. Conclusions

Since the beginning of the SARS-COV-2 pandemic, the possible link between vitamin D consumption and serum levels in the body has been discussed. Both established knowledge about the role of vitamin D in the immune system and viral defense as well as new data linking vitamin D levels with COVID-19 infection, morbidity and mortality have served to strengthen this suspicion and can lead to a definitive establishment of a link between the two. Until then, more confirmatory studies should be done in order to contribute to possible prevention and treatment of this disease.

## Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

## Conflict of interest

The authors declare no conflict of interest.

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