

**MINI-REVIEW**

# Potential benefit of vitamin D supplementation in people with respiratory illnesses, during the COVID-19 pandemic

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Email: chettyvas@gmail.com**Funding information**

No funding was obtained for this work.

**Abstract**

This review describes the evidence for the potential benefit of vitamin D supplementation in people with respiratory diseases who may have a higher susceptibility to coronavirus disease 2019 (COVID-19) infection and its consequences. Clinical evidence indicates that vitamin D may reduce the risk of both upper and lower respiratory tract infections and offers benefit particularly in people with vitamin D deficiency. Some evidence exists for a higher incidence of active tuberculosis (TB) in patients who are deficient in vitamin D. An association between low levels of 25(OH)D (the active form of vitamin D) and COVID-19 severity of illness and mortality has also been reported. In addition, low 25(OH)D levels are associated with poor outcomes in acute respiratory distress syndrome (ARDS). The cytokine storm experienced in severe COVID-19 infections results from excessive release of pro-inflammatory cytokines. Due to its immunomodulatory effects, adequate vitamin D levels may cause a decrease in the pro-inflammatory cytokines and an increase in the anti-inflammatory cytokines during COVID-19 infections. Vitamin D deficiency was found in 82.2% of hospitalized COVID-19 cases and 47.2% of population-based controls ( $p < 0.0001$ ). The available evidence warrants an evaluation of vitamin D supplementation in susceptible populations with respiratory diseases, such as TB, and particularly in those who are deficient in vitamin D. This may mitigate against serious complications of COVID-19 infections or reduce the impact of ARDS in those who have been infected.

**INTRODUCTION**

The severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2; coronavirus disease 2019 [COVID-19]) pandemic has been the cause of 245 deaths per million people globally, with 1193 deaths per million in the United Kingdom and 1296 deaths per million in Italy as of January 9, 2021.<sup>1</sup> About 70% of those who test positive for the infection are either asymptomatic or experience

mild symptoms, whereas the remaining 30% experience high fever, cough, loss of taste and smell, and a severe respiratory syndrome that may require hospitalization in an intensive care unit. Because both tuberculosis (TB) and severe COVID-19 infections target the lungs, higher morbidity and mortality is feared especially in this susceptible group of people. This may be compounded in the winter months with the influenza season. A systematic review of COVID-19 in countries with a high HIV/TB burden,

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showed that TB was a risk factor for COVID-19 both in terms of severity and mortality, irrespective of HIV status.<sup>2</sup>

Measures which are affordable, safe, sustainable, and show some proven efficacy in reducing risk of the COVID-19 infections and severity can be highly beneficial in these circumstances. There is evidence that the immunomodulatory effects conferred by vitamin D reduces the incidence of respiratory tract infections and plays a protective role in the event of severe respiratory tract infections. This review considers the evidence for the possible role of vitamin D during COVID-19 with reference to the susceptible population group of those with respiratory illnesses, such as TB, as well as in the elderly. The potential for the use of vitamin D as an affordable intervention, which may be of benefit during this pandemic, is evaluated.

## PROTECTIVE EFFECT OF VITAMIN D IN RESPIRATORY TRACT INFECTIONS

Vitamin D is a fat-soluble vitamin belonging to a group of secosterols, which plays an important role in calcium homeostasis and bone metabolism, and it also has the capacity to modulate the innate and adaptive immune function. Several studies describing the beneficial effect of vitamin D on immunity particularly affecting infections of the upper respiratory tract have been reviewed.<sup>3–5</sup> Present data indicate that vitamin D deficiency increases the risk of acute airway infections. The deficiency may be due to lower dietary intake of vitamin D and/or reduced exposure to sun, which is essential in the biosynthesis of vitamin D. A meta-analysis of 16 randomized clinical trials (RCTs) reflect a significant risk reduction by vitamin D supplementation in acute respiratory tract infections (odds ratio [OR] = 0.65, 95% confidence interval [CI] 0.50–0.85), with daily administration being more effective than high-dose bolus administration.<sup>3</sup> Daily or weekly supplementation with vitamin D (D2 or D3) has been shown to offer protection from acute respiratory infections—particularly among individuals exhibiting vitamin D deficiency (where blood levels of the active form of vitamin D viz, 25 hydroxy vitamin D or 25(OH)D <20 ng/ml). A systematic review and meta-analysis by Charan et al. (2012)<sup>4</sup> of RCTs on the effect of vitamin D supplementation for the prevention of respiratory tract infections, such as influenza, pneumonia, and the common cold, concluded that vitamin D significantly reduces the respiratory tract infections and related events compared to placebo in adults (OR = 0.579 [0.417–0.812]  $Z = -3.185$ ,  $p = 0.001$ ). Meta-analysis of individual participant data from 10,933 patients in 25 RCTs showed an overall protective effect of vitamin D supplementation against acute respiratory tract

infection among all participants (adjusted OR = 0.88, 95% CI 0.81–0.96,  $p$  for heterogeneity <0.001). The protective effects were strongest in those with profound vitamin D deficiency at baseline.<sup>6</sup> Cross-sectional data from 6789 participants in a nationwide British study compared the 25(OH)D levels and record of respiratory infections from the age of 45 years. The prevalence of respiratory infections had a strong seasonal pattern and were associated with lower 25(OH)D levels. Each 10 nmol/L increase in 25(OH)D was associated with a 7% lower risk of infection (95% CI 3–11%).<sup>5</sup> The possibility that vitamin D deficiency might also arise as a consequence of pulmonary inflammation warrants investigation. The studies reviewed used an oral vitamin D dose range of 300 IU to 4000 IU daily and parenteral bolus dose of 100,000 IU to 120,000 IU for respiratory infections. This evidence weighs in favor of vitamin D lowering the risk of respiratory tract infections and the protective effect appears to be more significant in people who are vitamin D deficient.

## EFFECT OF VITAMIN D IN COVID-19 MORTALITY

Serum 25(OH)D concentrations tend to decrease with age,<sup>7</sup> which may be of importance in COVID-19 because case-fatality rates increase with age. In the United Kingdom, 88% of the COVID-19-related deaths occurred in people who were 65 years and older, whereas in Italy, 95% of COVID-19-related deaths occurred in people over the age of 60 years.<sup>1</sup> The reasons for the reduced serum 25(OH)D include less time spent in the sun and reduced production of vitamin D as a result of lower levels of 7-dehydrocholesterol in the skin.<sup>7</sup> A negative correlation was observed between vitamin D levels and case mortality in Italy and Spain during the COVID-19 pandemic, especially in the elderly who have been the most affected. The mean 25(OH)D levels in older people were 26 nmol/L in Spain, 28 nmol/L in Italy, and 23 nmol/L in Swiss nursing homes.<sup>8</sup> Although reduced exposure to sun may result in reduced vitamin D levels in people in nursing homes, an important confounding factor to consider is the beneficial effects of outdoor activity and adequate airflow in reducing the spread of COVID-19.

Vitamin D deficiency was found in 82.2% of hospitalized COVID-19 cases versus 47.2% in population-based controls ( $p < 0.0001$ ).<sup>9</sup> Vitamin D deficient patients with COVID-19 had a longer length of hospital stay than those with serum 25(OH)D levels greater than or equal to 20 ng/ml. However, this study showed no correlative relationship between vitamin D deficiency and COVID-19 severity.<sup>9</sup>

Another study on 212 patients with laboratory confirmed COVID-19 infection, also correlates the low blood

concentration of 25(OH)D to clinical outcomes.<sup>10</sup> The cases were classified as mild without pneumonia, ordinary with pneumonia and other respiratory symptoms, severe with hypoxia and respiratory distress, and, finally, critical with respiratory failure requiring intensive case monitoring. With each SD increase in serum 25(OH)D, the odds of having a mild clinical outcome rather than a severe clinical outcome were increased ~ 7.94 times (OR = 0.126,  $p < 0.001$ ). The odds of having a mild rather than a critical outcome was increased ~ 19.61 times (OR = 0.051,  $p < 0.001$ ). All those with critical outcomes were deficient in vitamin D with 25(OH)D less than 50 nmol/L (i.e., 20 ng/ml).<sup>10</sup>

The mean levels of vitamin D for 20 European countries and its association with COVID-19 morbidity and mortality were studied. Negative correlations were observed between mean levels of vitamin D (average 56 nmol/L, SD 10.61) in each country and the number of COVID-19 cases/1 million (mean 295.95, SD 298.7, and mortality/1 million (mean 5.96, SD 15.13). Vitamin D levels were found to be severely low in the aging population especially in Spain, Italy, and Switzerland. This is also the most vulnerable group of the population in relation to COVID-19 with raised levels of morbidity and mortality.<sup>8</sup>

Obesity has been identified as one of the risk factors for mortality in COVID-19. Circulating vitamin D shows a negative correlation with body mass index.<sup>11</sup> In a systematic review and meta-analysis, the prevalence of vitamin D deficiency was 35% higher in patients with obesity compared with the eutrophic group (prevalence ratio = 1.35, 95% CI 1.21–1.50) and 24% higher than in the overweight group (prevalence ratio = 1.24, 95% CI 1.14–1.34).<sup>12</sup>

A randomized controlled clinical trial to compare the effect of a single oral high dose of cholecalciferol versus a single oral standard dose of vitamin D on COVID-19 mortality rate in older adults is currently being conducted (ClinicalTrials.govNCT04344041). This is the first and only prospective trial which will evaluate the beneficial effects of vitamin D supplementation and address the current knowledge gaps regarding appropriate dosing of vitamin D and the existence of possible threshold levels required for a beneficial effect.

## IMMUNOMODULATORY EFFECT OF VITAMIN D

Cathelicidin cAMP belongs to a group of proteolytically activated peptides. They have broad spectrum antimicrobial activity against bacteria, enveloped viruses, and fungi and are capable of triggering specific defense mechanisms in the host. Cathelicidins stimulate production of anti-inflammatory cytokines. Vitamin D has extensive

immunomodulatory effects and its effects within the lungs include increased secretion of the antimicrobial peptide cathelicidin, decreased chemokine production, inhibition of dendritic cell activation, and alteration of T-cell activation. Epidemiological studies suggest that vitamin D deficiency predisposes to viral respiratory tract infections and mycobacterial infections.<sup>13</sup>

A review by Aranow of *in vivo* and *in vitro* evidence of the vitamin D effects on the immune system indicates a decreased production of inflammatory cytokines (IL-17 and IL-21) with increased production of anti-inflammatory cytokines, such as IL-10. Vitamin D also inhibits monocyte production of inflammatory cytokines, such as IL-1, IL-6, IL-8, IL-12, and TNF $\alpha$  and additionally it dampens the dendritic cell differentiation and maturation.<sup>14</sup>

Low vitamin D levels have been shown to be associated with upper respiratory tract and enteric infections, pneumonia, otitis media, Clostridium infections, vaginosis, urinary tract infections, sepsis, influenza, Dengue fever, hepatitis B, hepatitis C, and HIV infections. The fight against some infections may be associated with suppression of proinflammatory cytokines (IL12, TNF- $\alpha$ , and interferon-gamma). Vitamin D causes a decrease in some cytokines while suppressing mononuclear cell and T lymphocyte cell proliferation. The relation of vitamin D with severity of Dengue fever has been investigated by altering the pro-inflammatory cytokine TNF- $\alpha$  and the anti-inflammatory cytokine IL-10 levels. Vitamin D prevents Dengue fever growth by causing changes through cytokines.<sup>15</sup> The ability of vitamin D to mitigate the disease course through immunomodulatory effects in Dengue fever virus infections may be of significance for its potential to do the same in COVID-19.

It is important to note that the beneficial effects of vitamin D supplementation have been observed mainly in deficient individuals prior to contracting COVID-19. However, patients with COVID-19 tend to present to hospital in the hyperinflammatory stage of the disease, so it might be too late for them to obtain any beneficial effects induced by vitamin D during the severe state of the disease.<sup>16</sup>

## VITAMIN D DEFICIENCY AND TB

During infections, the host defense against intracellular pathogens depends upon innate and adaptive antimicrobial effector pathways. Vitamin D enhances innate immunity against mycobacterial infection through the antimicrobial peptide, cathelicidin.<sup>11</sup> These researchers reported that ethnicity, skin pigmentation, season, disease state, latitude, and urbanization are critical factors to be

considered in vitamin D supplementation for prevention and treatment of TB.

A cross-sectional study of 196 HIV-uninfected and 174 HIV-infected people was conducted in Cape Town, South Africa, over an 8-year period, to determine whether vitamin D deficiency was associated with susceptibility to TB. Vitamin D deficiency (25[OH]D <50 nmol/L), was present in 232 (62.7%) of the 370 participants and was associated with TB in both HIV-uninfected and HIV-infected people (OR = 5.2, 95% CI 2.8–9.7,  $p < 0.001$ ) and the association was stronger in HIV-infected people. Vitamin D status varied according to season. The mean serum 25(OH)D was highest in January through March, after the summer months with longer hours of sunshine and lowest in July through September following the winter months (56.8 vs. 30.7 nmol/L,  $p < 0.001$ ). Peak vitamin D status in January through March directly preceded a trough in new TB notifications in April through June.<sup>17</sup> This seasonal correlation suggests that vitamin D supplementation will be especially beneficial during the winter months when exposure to sun and hence vitamin D biosynthesis is reduced. However, the lower incidence of TB following summer months could also be influenced by greater outdoor activity and exposure to improved airflow during this time.

A systematic review and meta-analysis were conducted to explore the association between low vitamin D status and the risk of active TB. Results showed that patients with TB had lower serum levels of vitamin D than healthy controls matched on sex, age, ethnicity, diet, and geographical location. Low serum vitamin D levels were associated with higher risk of active TB.<sup>18</sup> The reasons for the low serum vitamin D were not investigated in this study.

Interestingly, some anti-retroviral medicines (ARVs) and TB medications can lower the circulating 25(OH)D levels. Protease inhibitors and non-nucleoside reverse transcriptase inhibitors, classes of ARVs may enhance vitamin D metabolism via modulation of the cytochrome P-450 system and vitamin D hydroxylation.<sup>15</sup> Specific ARVs, including efavirenz and zidovudine, have been associated with lower serum vitamin D levels. Rifampicin 600 mg and INH 300 mg daily for 14 days decreased circulating levels of 25(OH)D and 1 $\alpha$ , 25(OH)D by 34% ( $p < 0.01$ ) and 23% ( $p < 0.05$ ), respectively, in 8 healthy subjects.<sup>16</sup> Drugs used in the treatment of TB and HIV, such as rifampicin and efavirenz, reduce the circulating 25(OH)D levels also due to the induction of enzymes of the cytochrome P450 system, which increase metabolism of 25(OH)D.<sup>19,20</sup>

The added susceptibility to influenza of those infected by TB is also important to consider during COVID-19 pandemics. A prospective South African study of hospitalized patients from 2010 to 2016 reported TB co-infection was associated with increased mortality in individuals

with influenza, and influenza coinfection was associated with increased mortality in individuals with TB. Among influenza-positive patients, laboratory-confirmed TB was associated with an increased risk of death (OR = 4.5, 95% CI 1.5–13.3).<sup>17</sup> In addition, among TB-positive patients, age ( $\geq 65$  years) was also independently associated with death compared with 15–24 years (OR = 3.6, 95% CI 1.2–11.0). This outcome can point to a possibly high risk presented by COVID-19 virus infection in people who have TB. However, in a systematic review, the association between increased prevalence of influenza co-infection in people hospitalized for TB was not conclusive.<sup>21</sup>

The above evidence indicates that vitamin D enhances immunity against TB and its deficiency is associated with an increased incidence of TB, which appears to have a seasonal variation co-incidental with decreases in 25(OH)D levels. TB medication and some ARVs also decrease 25(OH)D levels. Large prospective controlled clinical studies examining the association between vitamin D and TB, in which possible confounders are accounted for, are warranted.

## IMMUNOMODULATORY EFFECT OF VITAMIN D IN THE CYTOKINE STORM

A subgroup of patients with severe COVID-19 infections might experience a cytokine storm syndrome (CSS).<sup>22</sup> The CSS refers to the excessive and uncontrolled release of pro-inflammatory cytokines, which activate a severe inflammatory response. Throughout its activation, the inflammatory response must be regulated to prevent a damaging systemic inflammation, the “cytokine storm.” Several cytokines with anti-inflammatory properties are responsible for this regulation of the inflammatory response, such as IL-10 and transforming growth factor. Each cytokine acts on a different part of the inflammatory response. Without the ability to resolve the inflammation, the collateral damage to surrounding cells has the potential to be catastrophic, resulting in sepsis and even death. However, if it is controlled correctly, inflammation can be resolved.<sup>23</sup> As described in the previous section, adequate levels of vitamin D may assist with increased production of the much-needed anti-inflammatory cytokines during this crisis.

Respiratory failure from acute respiratory distress syndrome (ARDS) is the leading cause of mortality in COVID-19 infections.<sup>22</sup> A cohort of patients with confirmed ARDS ( $n = 52$ ) and patients undergoing esophagectomy ( $n = 57$ ) and therefore at risk of ARDS, were assessed for vitamin D as a risk factor in ARDS. All patients with confirmed ARDS were vitamin D deficient (25[OH]D <50 nmol/L). In the at-risk group, patients who required

postoperative ventilation with ARDS had significantly lower pre-operative plasma 25(OH)D levels than those not requiring ventilation. The odds of ARDS in patients with 25(OH)D less than 20 nmol/L was 3.5-fold that of patients with 25(OH)D greater than or equal to 20 nmol/L (OR = 3.5, 95% CI 1.06–11.6,  $p = 0.040$ ). Vitamin D deficiency (<50 nmol/L) is common in people who develop ARDS and relates to the adverse outcome.<sup>24</sup>

The renin-angiotensin system (RAS) is a central regulator of renal and cardiovascular functions. Over-activation of the RAS leads to renal and cardiovascular disorders and to a cytokine storm. Vitamin D is a negative regulator of RAS. Long-term vitamin D deficiency (hypovitaminosis D) can lead to overactivation of RAS.<sup>25</sup>

The above discussion indicates that vitamin D appears to increase the levels of anti-inflammatory cytokines, dampens the pro-inflammatory cytokines, and the relationship between deficient vitamin D levels and ARDS has been reported. This together with its downregulation of the RAS may point to a role for vitamin D in attenuating a cytokine storm in the COVID-19 infection. Clinical studies to explore the association between vitamin D status and the probability of a cytokine storm in patients with COVID-19 would be useful.

## OPTIMAL VITAMIN D LEVELS

The 25(OH)D levels of greater than 20 ng/ml are considered to be sufficient for much of the general population and is based largely on vitamin D's requirements for bone and mineral homeostasis. The optimal 25(OH)D serum level regarding other aspects of human health is still under debate. For immune-mediated diseases, experts suggest that serum 25(OH)D levels higher than 20 ng/ml may be needed. Current evidence suggests that serum 25(OH)D of greater than or equal to 30 ng/ml may have significant benefits during infections.<sup>11</sup>

## DISCUSSION AND CONCLUSION

People who have respiratory illnesses, such as TB, could be at higher risk of developing serious health complications because of infection from COVID-19. The pathology of COVID-19 involves a complex interaction between the virus and the body's immune system, with vitamin D being one of the potential factors influencing this interaction.<sup>8</sup> The evidence in this review indicates that vitamin D is an immunomodulator in the innate and adaptive immune systems. Vitamin D deficiency is associated with increased respiratory tract infections compared with individuals with adequate levels. Adequate 25(OH)D ( $\geq 20$  ng/

ml or  $\geq 50$  nmol/L) can have the benefit of reduced probability of respiratory viral infections of influenza, TB infection rates, and may lower the likelihood of infection by COVID-19. As an immunomodulator, there is emerging evidence of a balance being achieved by vitamin D between the inflammatory cytokines (e.g., IL-6) and the anti-inflammatory cytokines (e.g., IL-10) during cell-mediated immunity. Additionally, due to its role as a negative regulator of the RAS, vitamin D may mitigate the severity of the COVID-19 infection. Although there are several risk factors associated with the outcomes of a COVID-19 infection, an adequate vitamin D status prior to the infection may contribute toward preventing or limiting a "cytokine storm," which occurs in some patients who are seriously ill from COVID-19, and thereby lower the case fatality rates. Interventional studies of vitamin D in those at risk of developing the severe form of COVID-19 are desirable.

Vitamin D is affordable, safe at recommended doses, and the evidence suggests that it provides a potential benefit especially in the elderly, in susceptible people living with TB, and people with other respiratory illnesses who are also vitamin D deficient. Daily or weekly supplementation has been shown to be more effective than high-dose bolus administration. In resource scarce countries, which are likely to have delays in access to the vaccines that have become available, even a modest benefit may justify evaluating the use of vitamin D as a supplement to ensure adequate levels of 25(OH)D in people with respiratory conditions and in the elderly during the COVID-19 pandemic.

## CONFLICT OF INTERESTS

V.V.C. is an employee of GSK Consumer Health, South Africa. All other authors declared no competing interests for this work.

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**How to cite this article:** Chetty VV, Chetty M. Potential benefit of vitamin D supplementation in people with respiratory illnesses, during the COVID-19 pandemic. *Clin Transl Sci*. 2021;14:2111-2116. doi:[10.1111/cts.13044](https://doi.org/10.1111/cts.13044)