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Coronavirus disease 2019 and vitamin D

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Vitamin D deficiency is one of the most common vitamin deficiencies across different populations. It has primarily been implicated in the development of metabolic bone disease in adults and children. However, in recent years its role in immunomodulation has also emerged and has gained further importance since the occurrence of coronavirus disease 2019 (COVID-19). Here, we describe the most recent literature on vitamin D and its impact on immunomodulatory pathways. Furthermore, the current evidence on the impact of vitamin D deficiency on COVID-19 infection, severity, and prognosis is summarised. We also highlight the key research gaps in this field that need further research.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has had a major impact on the health systems across the world. After the initial massive outbreaks, there have only been occasional regional spurts in

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its occurrence. Nevertheless, the fear of another virulent and lethal mutant that could eventually develop has always existed. This is a greater concern in those who are more at risk of contracting the disease or those susceptible to severe illness. This fear has led to continued efforts by the scientific community build to improve our understanding the natural history of the virus and the ways through which its spread can be minimised. The same principles are also applicable to other viral illness and may be helpful in the management of future pandemics.

Vitamin D deficiency is one of the most common vitamin deficiencies across different populations. It has primarily been implicated in the development of metabolic bone disease in adults and children. However, in recent years its role in immunomodulation has also emerged and has gained increased importance since the occurrence of COVID-19.

In this manuscript, the authors describe the most recent literature on vitamin D and its impact on immunomodulatory pathways. Furthermore, the current evidence on the impact of vitamin D deficiency on COVID-19 infection, severity, and prognosis are summarised. Based on a detailed literature review, the authors also highlight the key research gaps in this field that need future research. This will enable a better understanding of the pathophysiological link between vitamin D and COVID-19.

Vitamin D deficiency in COVID-19 infection

Vitamin D deficiency is considered as one of the most common vitamin deficiencies in the world. A recently published study by Cui et al., who analysed the global prevalence of vitamin D Deficiency in over 7.9 million individuals from 81 countries, found that around 76.6% had vitamin D insufficiency (< 75 nmol/L). The key factors that were associated with a high prevalence of vitamin D deficiency were individuals living at a higher latitude and those analysed during winter/spring compared with the summer/autumn. Individuals residing in the Eastern Mediterranean region and lower to middle-income countries had a higher prevalence of vitamin D deficiency. Female sex was another important risk factor found to increase vulnerability to vitamin D deficiency [1]. While overall prevalence showed a slightly declining trend over the past two decades from 2001 to 2010–2011–2022, the current values remain considerably high and require attention from policy makers, health care professionals, and public at large.

Another study that used the NAHANES (National Health and Nutrition Examination Surveys) database to analyse vitamin D levels in 71,685 participants over the past two decades showed a slight increment in the proportion of those with sufficient vitamin D levels. However, the proportion of patients with severe vitamin D deficiency remained the same. The key factors that showed a strong association with vitamin D deficiency included age (20–29 years), sex (female), ethnicity (non-Hispanic, Black Americans), season (winter), sun-protective behaviours, lower body mass index (BMI), lower socioeconomic status, drinking, and lower milk consumption were predictors of severe vitamin D deficiency [2].

When interpreting global literature on vitamin D deficiency, it is also important to understand the different definitions used as this can have a major bearing on the prevalence data in different studies. It is also interesting to note that many tropical countries that have high levels of sunlight but also have large populations with vitamin D deficiency [3]. While ultraviolet-rich sunlight is important for the synthesis of vitamin D in the skin, there are several environmental factors that can impeded this process. Personal characteristics, such as staying indoors, covering up with clothing, use of sunscreen, or even poor air quality can nullify the effects of sunlight [4]. Furthermore, dietary consumption of vitamin D is often very poor due to limited availability in commonly consumed food items. This not only poses a risk factor in the causation of vitamin D deficiency but also poses challenges in initiating its treatment through natural methods. Therefore, food fortification and periodic supplementation are the only most effective methods in improving the vitamin D levels of a given population.

A systematic review and metanalysis that assessed the association of vitamin D deficiency and risk of COVID-19 development showed that lower vitamin D levels were associated with a higher risk of symptomatic COVID-19 infection across many countries in Asia, Europe, and the United states. Furthermore, lower mean 25-hydroxy vitamin D levels were found in those with a positive covid-19 infection compared with those without covid-19 infection [5]. In another meta-analysis, the odds of developing COVID-19 in individuals with vitamin D deficiency was found to be 1.46 (95%CI: 1.28–1.65; $P < 0.0001$). Moreover, individuals with vitamin D deficiency were found to be more susceptible to

hospitalization and intensive care unit admission, and had a higher mortality [6]. Similar findings were also replicated in other studies [7,8].

Role of vitamin D in immunomodulatory pathways

The key lethal aspect of the COVID-19 infection that caused a very high mortality in the initial outbreaks was the rapid development of the inflammatory response that led to an acute respiratory distress syndrome. This inflammatory response is secondary to the proinflammatory cytokine surge that may be regulated through underlying genetic influences, sex, age, comorbidities, and modifiable factors such as vitamin D deficiency [9].

The role of vitamin D in immunomodulation was initially described from earlier days when sunlight was used as part of therapy of cutaneous tuberculosis. More recent literature has found associations between vitamin D and immune mediated disorders, such as multiple sclerosis, type 1 diabetes mellitus, and infectious diseases [10].

The role of vitamin D has been implicated in the cytokine production during infection [11]. The expression of genes that encode cytokines and chemokines are regulated by 1,25 dihydroxy vitamin D and has been shown to impact transcription on interleukin 1 beta, which is often the first cytokine generated in response to infection. 1,25 dihydroxy vitamin D has also been shown to dose-dependently reduce the expression of proinflammatory cytokines, including interleukin 6, TNF-alpha, and interferon gamma in infected mononuclear cells [12]. While these inflammatory cytokines have been shown to reduce anti-inflammatory cytokines, some, such as interleukin 10 have been demonstrated to be upregulated. There is also evidence that active vitamin D in associated with other agents that also regulate the expression of interleukin 6 at baseline. Active vitamin D has also been shown to enhance the action of glucocorticoids in supressing interleukin 6 production [13,14].

It was also found that macrophages and other antigen presenting cells could actively metabolize inactive 25-hydroxyvitamin D to an active form 1,25-dihydroxyvitamin D with the help of 1-alpha hydroxylase. This was also the reason that some chronic inflammatory states exhibited mild hypercalcemia. Furthermore, it was noted that activated immune cells expressed the vitamin D receptor. This showed that 1,25 dihydroxy vitamin D was associated with a localized endogenous modulator of immune function. Subsequent studies have shown that vitamin D is responsible for activation of both the innate and adaptive arms of the immune system [15]. At an innate level, intra-cellular synthesis of dihydroxy vitamin D by macrophages and dendritic cells in turn activates the expression of proteins, like cathelicidin, which have a strong anti-microbial action. This potential action that enhances autophagy may be a protective during infections like *Mycobacterium tuberculosis* and some viral infections [11].

Moreover, local production of 1,25 dihydroxy vitamin D by both macrophages and dendritic cells also plays a critical role in mediating the T-cell response to vitamin D, which in turn causes suppression of inflammatory T helper cells (Th1 and Th17) and concomitant induction of immune tolerogenic T-regulatory responses [11].

These actions of vitamin D have gained prominence in recent months with the global COVID-19 health crisis [9,16]. These actions also highlight important new objectives for future studies on vitamin D and immune function [17].

Vitamin D as a risk factor for COVID-19

As described in the previous sections, strong physiologically plausible evidence is now available that links vitamin D deficiency and COVID-19. An observational study by De Smet et al. showed that low 25-hydroxy vitamin D level was associated with an increased severity of lung involvement as assessed by computed tomography in men with COVID-19 [18]. The occurrence of vitamin D deficiency increased from 55% in those with stage 1 radiological severity to 74% in those with stage 3 radiological severity. In other studies, the presence of vitamin D deficiency has been associated with increased rates of hospital admission and mortality, independently of other clinical risk factors [19–21].

More recently published metanalyses provided further evidence to support that low serum 25-hydroxy D levels are associated with an increased risk of mortality, admission to the intensive care unit, and use of invasive and non-invasive ventilation [22,23].

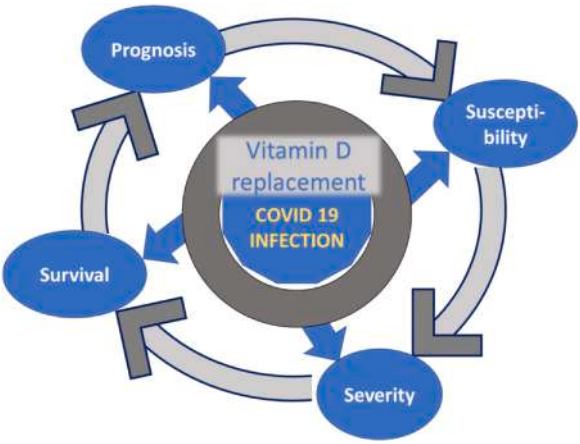

Fig. 1. The association between vitamin D and COVID-19 infection.

In a study by Nayfeh et al. including 17 original articles with a total of 2756 individuals that were included in the analysis, vitamin D deficiency was associated with higher mortality (OR, 2.47; 95% CI, 1.5–4.1), higher rates of hospital admissions (OR, 2.18; 95% CI, 1.4–3.2), and longer hospital stay (0.52 days (0.25–0.80) compared with vitamin D-sufficient individuals. Furthermore, subgroup analyses based on different cut-offs for vitamin D deficiency, study geographic locations, and latitude also showed similar trends [22].

Similarly, another metanalysis by Pereira et al. that included 27 studies found that those with vitamin D deficiency had a more severe illness (OR, 1.6; 95% CI, 1.3–2.09). Furthermore vitamin D insufficiency increased the risk of hospitalisation (OR, 1.81; 95% CI, 1.4–2.2) and mortality (OR 1.82; 95% CI, 1.06–2.58) [23].

However, it should be noted that several studies that have been mentioned above are limited by certain caveats. These include inadequate selection of controls, presence of confounding covariates, lack of adjustment for other predictive markers, variability of assays to measure 25-hydroxy vitamin D, as well as the cut-off points used to define low levels. Moreover, low levels of 25-hydroxy vitamin D in COVID-19 patients with severe outcomes admitted to the hospital could be a reflection of reverse causality, and may either be related to severe hypoalbuminemia at hospital admission or, as mentioned earlier, to the effect of acute illness per se [24,25]. In conclusion, most published studies support a negative role of low vitamin D status in the severity of COVID-19 although it remains to be established whether low 25-hydroxy vitamin D is a consequence and a marker of illness severity or has a causal role in this clinical context. These conclusions are summarised in Fig. 1.

Common associations of low vitamin D that also predispose to COVID 19

In addition to the possibility of reverse causation, vitamin D deficiency is also associated with many comorbidities, like obesity, type 2 diabetes mellitus, and chronic obstructive pulmonary disease, that in turn have been associated with overall poor prognosis of COVID-19 disease. Multiple studies have cited the dual impact of COVID-19 and obesity [26]. There have been several modifiable and non-modifiable links that correlate with COVID-19 disease severity and the magnitude of obesity. Although obesity is associated with a poor prognosis of COVID 19, low vitamin D levels have also been frequently associated with obesity and metabolic syndrome [27,28]. Hence, obesity could be a confounding factor. More than just weight, even the presence of excessive fat in normal-weight patients has also been implicated with poor prognosis of COVID-19 [29].

Table 1
Impact of vitamin D therapy on COVID-19 outcomes across different regions in the world.

Region/country	Study population	Intervention	Outcome
North America Mexico	Multi centre, randomised double blind, placebo controlled RCT	To investigate the therapeutic efficacy of oral 25-hydroxy vitamin D3 in improving vitamin D status in vitamin D-deficient/vitamin D-insufficient patients infected with SARS-CoV-2 (COVID-19) virus.	The investigators observed an overall lower trend for hospitalization, intensive care unit duration, need for ventilator assistance, and mortality in the 25-hydroxy vitamin D3 group compared with that in the placebo group.
South America Argentina	Multicentre, randomized, double-blind, sequential, placebo-controlled clinical trial. The study was conducted in 17 s and third-level hospitals. Adult patients hospitalized in general wards with SARS-CoV-2 confirmed infection, mild-to-moderate COVID-19 and risk factors for disease progression.	Participants were randomized to a single oral dose of 500,000 IU of vitamin D3 or matching placebo. Randomization ratio was 1:1, with permuted blocks and stratified for study site, diabetes, and age (≤60 vs > 60 years). The primary outcome was change in the respiratory Sepsis-Related Organ Failure Assessment score between baseline and the highest value recorded up to day 7. Secondary outcomes included length of hospital stay, intensive care unit admission, and in-hospital mortality.	No statistically different outcomes were noticed in both the groups. Among hospitalized patients with mild-to-moderate COVID-19 and risk factors, a single, high oral dose of vitamin D3 as compared with placebo did not prevent respiratory worsening.
Europe Spain	A multicentre, single-blind, prospective, randomized clinical trial in patients with COVID-19 pneumonia and vitamin D deficiency	To test antiviral efficacy, tolerance and safety of 10,000 IU/day of cholecalciferol (vitamin D3) for 14 days was compared with 2000 IU/day.	Administration of high doses of vitamin D3 as an adjuvant to standard care treatment during hospitalization for COVID-19 improved the inflammatory environment and cytotoxic response against pseudotyped SARS-CoV-2 infected cells, shortened the hospital stay and, possibly improved prognosis.
Middle East Saudi Arabia	Multi-centre randomized clinical trial among patients with mild to moderate COVID-19 patients with suboptimal vitamin D status.	Studied the effects of 5000 IU versus 1000 IU daily oral vitamin D3 supplementation in the recovery of symptoms and other clinical parameters.	The analysis revealed 5000 IU group had a significantly shorter time to recovery (days) than the 1000 IU group in resolving cough, even after adjusting for age, sex, baseline BMI, and D-dimer.
Asia India	Randomized, placebo-controlled trial on symptomatic individuals or mildly symptomatic SARS-CoV-2 RNA-positive vitamin D-deficient [25(OH)D < 20 ng/ml] individuals.	Participants were randomised to receive daily 60,000 IU of cholecalciferol (oral nano-liquid droplets) for 7 days with therapeutic target 25(OH)D > 50 ng/ml (intervention group) or placebo (control group). 25(OH)D levels were assessed at day 7, and cholecalciferol supplementation was continued for those with 25(OH)D < 50 ng/ml in the intervention arm.	SARS-CoV-2 RNA and inflammatory markers fibrinogen, D-dimer, procalcitonin, C-reactive protein, and ferritin were measured periodically. Greater proportion of vitamin D-deficient individuals with SARS-CoV-2 infection turned SARS-CoV-2 RNA negative with a significant decrease in fibrinogen on high-dose cholecalciferol supplementation.

Like obesity, even diabetes has shown to be a poor risk factor for development of severe COVID-19 disease [30–33]. Hyperglycaemia could be both a cause and effect of COVID 19 infection. Lower vitamin D levels have also been a shown to predispose to the development of insulin resistance and type 2 diabetes [34]. Thus, the ill effects of low vitamin D levels could also act via its effect on hyperglycaemia.

In a recent study by Filippo et al., the association of blood glucose, obesity, and vitamin D in predicting the severity of COVID-19 was published [35]. The mean 25-hydroxy vitamin D level in this study was 16.3 ng/ml and vitamin D deficiency was found in 68.2% of individuals. Multiple regression analysis showed that individuals with hypovitaminosis D along with either diabetes mellitus or overweight status were more frequently associated with severe CVODI-19 infection and worse inflammatory response (C-reactive protein, interleukin 6, and neutrophil/lymphocyte ratio) and respiratory parameters (PaO_2/FiO_2) to compered with those without diabetes and obesity.

The role of vitamin D in the prevention and treatment of COVID-19

Several randomised clinical trials have been done on this subject across different regions of the world. These have been summarised in Table 1 [36–40]. Overall, many recent studies have provided evidence in support of using vitamin D in patients with COVID-19; however, there are some differences reported in these studies. These differences could be attributed to the study design, mode of administration, type, and dose of vitamin D. These studies have been done using cholecalciferol, calcifediol, or calcitriol at varying doses. Therefore, the issue of considering vitamin D in the context of COVID-19 as a nutritional supplementation or an acute therapeutic for severe COVID-19 is still open, although it has been hypothesized that vitamin D should be used as a drug more than as a supplement for treating acute respiratory diseases or other infectious diseases. Another important fact that should be kept in mind while interpreting these studies is that many patients with acute COVID-19 are treated with glucocorticoids, which interfere with the activation and action of vitamin D [41].

Conclusion

To conclude, this review summarises the available literature highlighting the role of vitamin D and COVID-19 from bench to bedside. Several aspects, from epidemiological data to the pathophysiological connects, have been covered. From a therapeutic aspect, data from interventional studies suggest that vitamin D administration could have a positive impact on COVID-19 outcomes. However, since available data are still heterogeneous regarding study design, enrolled population, and intervention strategies, and have also yielded conflicting results, research in this setting should focus on producing novel, robust data rather than pooling data with low-grade evidence.

Practice points

- Vitamin D deficiency is common in patients with COVID-19.
- Several in vitro and in vivo studies have demonstrated a role of vitamin D in modulating T-cell-mediated and humoral-mediated immunity.
- A significant association has been demonstrated between vitamin D deficiency and severity of COVID-19 illness.
- Although an association between COVID-19 and vitamin D has been found in many studies, the exact causation has been difficult to demonstrate based on several confounders.
- Replacement of vitamin D has been associated with better outcomes in some randomised clinical trials, and larger studies that are adequately powered to demonstrate this effect on a larger sample size are needed.

Research agenda

- Does replacement of vitamin D in deficient individuals mitigate the severity of COVID-19?
- What preparations and dosage is required to obtain beneficial effects of vitamin D for a speedy recovery from COVID-19?
- Does this protective effect of vitamin D extend to other viral infections?
- Is there any interference on the beneficial effects of vitamin D supplementation by co-administration of glucocorticoids?

Declaration of Competing Interest

Both authors declare no conflict of interest or funding disclosures for this manuscript.

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