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METABOLISM IN TROPICAL MEDICINE (K SCHLOSSER-MONTES, SECTION EDITOR)

Vitamin D Status: Can It Affect the Risk of Infection and the Severity of COVID-19 Symptoms?

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Abstract

Purpose of Review In the midst of the COVID-19 pandemic, several academic studies have emerged that explore the importance of vitamin D in the development of the SARS-CoV2 infection. The basis of this interest comes from the established effect vitamin D status has on other acute respiratory infections, such as influenza. This article aims to determine the role and effect of vitamin D serum concentration in the prevalence and severity of COVID-19.

Recent Findings Several observational studies have demonstrated that suboptimal levels of vitamin D serum concentrations can significantly increase the risk of developing COVID-19 and lead to a more severe symptomatology. One study suggests, however, that supplementation of vitamin D could potentially increase the incidence of mortality in COVID-19 patients.

Summary Vitamin D status could have an influential role in the development and progression of SARS-CoV2 infection. Further studies are warranted to understand fully the veracity and the extent of this association.

Keywords COVID-19 · Vitamin D · SARS-CoV2 infection · Vitamin D deficiency · 25(OH)D3 · COVID-19 severity

Introduction

The spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), the causing agent of coronavirus disease 2019 (COVID-19), has had an unprecedented effect on the global economy, social structure, and health. As of January 21, 2021, there have been 95,612,831 confirmed cases and 2,066,176 deaths attributed to COVID-19. This data does not take into account the number of unreported cases and deaths caused by differing strategies in the diseases' testing and diagnosis [1, 2], suggesting that the impact of COVID-19 may be greater than the reports demonstrate.

One of the most alarming aspects of this disease is its high infection rate, leading researchers to investigate how the immune system responds to the SARS-CoV2 virus in order to develop effective preventive and treatment strategies. A key focus of study in this field has been vitamin D, as research has already determined that it plays a key role in the immune response. This situation increases the concern of the high prevalence of vitamin D deficiency within the global population [2, 3].

The possible connection between vitamin D deficiency and the development of COVID-19 has already garnered interest in the scientific community. Countries that have reported high rates of COVID-19 mortality, such as Spain and Italy, also suffer from a high prevalence of vitamin D deficiency. Although this association could also be attributed to the high percentage of elderly in their population, who are especially vulnerable to both infectious diseases and vitamin D deficiency [4]. On the other hand, it should be noted that vitamin D has been found to play an important role in the prevention of acute respiratory infections, proving to be effective in reducing the severity of some symptoms [5, 6]. Therefore, there are grounds to explore the possible impact this vitamin could have in the development of SARS-CoV2 infection. The purpose of this review is to determine the role vitamin D has on the pathophysiology of COVID-19 and how its status can affect the risk of infection and severity of COVID-19 symptoms.

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Vitamin D: the Basics

Vitamin D is a liposoluble vitamin that can be found in dietary sources as vitamin D2 (ergocalciferol) in plants and in animals as vitamin D3 (cholecalciferol) [7, 8]. However, the most significant source of vitamin D3 is dermal synthetization, a process that occurs when the skin is exposed to ultraviolet (UV) light. Both forms of vitamin D go through enzymatic hydroxylation to produce 1α,25-dihydroxyvitamin D3 (1,25(OH)2D3), the active form of vitamin D. The first hydroxylation occurs in the liver and results in the production of 25-hydroxyvitamin D3 (25(OH)D3), through the action of cytochrome P450 2R1 (CYP2R1) and cytochrome P450 27 (CYP27A1). Subsequently, in the kidney, 1,25(OH)2D3 is synthesized by the enzyme 1-α-hydroxylase (Fig. 1) [6, 8, 9]. This same enzyme is present in other tissues, such as monocytes, macrophages, and dendritic cells, which allows for vitamin D to be activated locally in a paracrine manner [9]. To evaluate vitamin D status, 25(OH)D3 serum concentrations are measured (Table 1).

The bioavailability of vitamin D can be affected by a variety of factors. Its limited dietary sources, such as fatty fish (i.e., sardines, tuna, salmon), egg yolk, and organ meats, result in a higher dependency on dermal synthesis in order to meet daily requirements (Table 1) [8]. A significant amount of people do not meet the daily sunlight exposure needed in order to replenish the necessary vitamin D stores. Factors that contribute to the low UV

Table 1 Recommended dietary allowances and serum concentrations for vitamin D

Recommended dietary allowances (RDA)	
Age	**IU**
0–12 months	400
1–70 years*	600
*Including pregnancy and lactation	
> 70 years	800
Serum 25(OH)D3 concentrations	
Health status	**nmol/L**
Vitamin D deficiency	< 30
Vitamin D insufficiency	30 to < 50
(Inadequate for bone and overall health)	
Adequate for bone and overall health	≥ 50
Linked to potential adverse effects	> 125

Abbreviations: *IU*, international units; *25(OH)D3*, 25-hydroxyvitamin D3; *nmol/L*, nanomoles per liter. Adapted from: Chang and Lee [8] and Vitamin D - Health Professional Fact Sheet [Internet]. NIH Office of Dietary Supplements. U.S. Department of Health and Human Services. [cited 2021 Jan 7]. Available from: https://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/

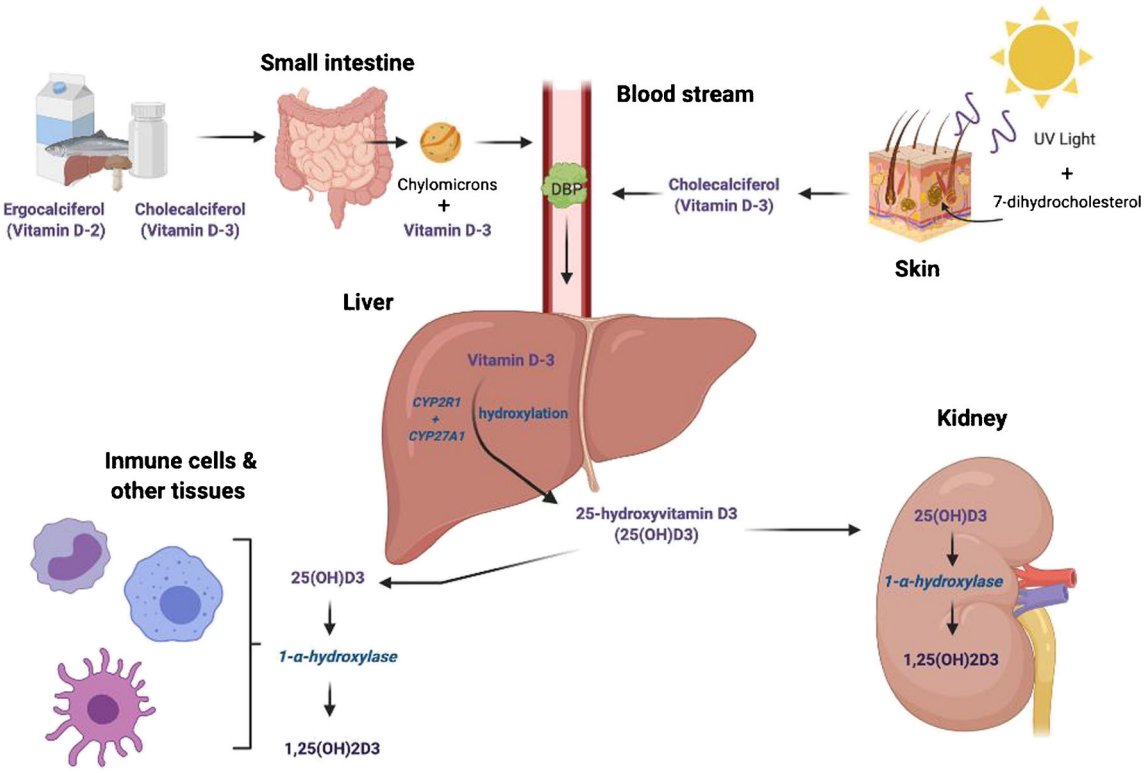

Fig. 1 Vitamin D can be obtained from UV exposure and dietary sources. Vitamin D3 is then hydrolyzed in the liver in order to create 25(OH)D3, the precursor to its active form. This final hydroxylation occurs primarily in the kidney, but can also take place in other tissues such as immune cells. Image created in Biorender.com. Abbreviations: DBP, vitamin D-binding protein; CYP2R1, cytochrome P450 2R1; CYP27A1, cytochrome P450 27; 25(OH)D3, 25-hydroxyvitamin D3; 1,25(OH)2D3, 1α,25-dihydroxyvitamin D3

exposure include dark skin pigmentation, use of sunscreen, climate, latitude, age, conservative clothing habits, and sun avoidant lifestyles [3, 7–10]. It is also important to note that those who present comorbidities, such as obesity, diabetes, and chronic renal disease, have a greater risk of presenting vitamin D and other nutritional deficiencies [8]. The combination of these factors contributes to the widespread prevalence of vitamin D deficiency [7].

The Role of Vitamin D Beyond the Skeleton

Vitamin D is most commonly known for playing an essential role in skeletal growth and bone mineral metabolism. The notoriety of this function has remained relevant in the scientific field ever since its discovery in 1922, when it was concluded that an ingredient in cod liver oil could cure rickets [8]. Further research into its function had led to the discovery of both its genomic and non-genomic actions. The vitamin D receptor (VDR) promotes the expression of numerous target genes by activating or inhibiting gene transcription, while the membrane VDR (MVDR) can exert non-genomic rapid actions [5, 11, 12].

Approximately 30 years ago, the discovery of VDR on a variety of different cells outside of the skeletal system has opened the possibility that vitamin D could also exert non-skeletal functions [5, 6, 12]. Many of these tissues also possess the enzyme 1-α-hydroxylase that enables vitamin D3 to be activated on site (Fig. 1) [8, 9]. In the immune system, for instance, the VDR is expressed in macrophages, monocytes, neutrophils, dendritic cells, and T and B lymphocytes, which indicate that vitamin D could play a critical role in the innate and adaptive immune response [3, 9, 12–14].

Recent studies have found that vitamin D has opposing effects on the innate and adaptive immune response [3]. In the innate immunity, it takes part in regulating the response of macrophages and monocytes to pathogenic organisms or tissue damage by facilitating chemotaxis, autophagy, phagocytation, and phagolysosomal fusion [5, 6, 12]. Vitamin D also promotes the production of defensin β2 and cathelicidin antimicrobial peptide (CAMP), to enhance antimicrobial activity, acting as first-line defense against fungi, bacteria, and enveloped viruses, such as corona viruses [3, 6]. Dendritic cell function is affected by vitamin D as it inhibits its differentiation and maturation, suppressing the ability to present antigens to T cells. In contrast, vitamin D has a suppressing effect on adaptive immunity [5, 6]. Vitamin D downregulates the immune response mediated by T helper 1 cells, inhibiting the production of proinflammatory cytokines (such as interferon-γ, IL-6, IL-2, and TNF-α) [6]. It can also regulate the production of B lymphocytes resulting in decreased secretion of immunoglobulins [5]. In short, vitamin D is critical to immune function as it balances both the innate and adaptive immune responses.

Vitamin D in the Development of Acute Respiratory Tract Infections

Acute respiratory tract infections (ARTI) are some of the most pervasive infections in the world. They are especially common during the winter months in temperate areas and can develop throughout the year in tropical regions. ARTI can be categorized as upper respiratory tract infections (URTI) or lower respiratory tract infections (LRTI) depending on the affected area [10]. The common cold and influenza are among the most prevalent URTI, with influenza affecting around 20 to 50% of the global population during epidemic periods, while LRTI, such as pneumonia, are less common but tend to be more severe and have higher rates of mortality, especially in children and the elderly [15].

Vitamin D status can impact the development and severity of ARTI [7, 8]. A recent meta-analysis of 25 randomized controlled trials (RCT) evaluated the effect of vitamin D3 supplementation on the risk of ARTI in 11,321 participants from 15 different countries. Among its main findings, they determined that the supplementation of vitamin D3 significantly decreases the risk of developing URTI from 42 to 39% (OR = 0.88; 95% CI: 0.81, 0.96; $p < 0.001$) [16]. Those who received daily or weekly doses of vitamin D3 supplementation had an even lower risk of infection (OR = 0.81; 95% CI: 0.72, 0.91; $p < 0.001$) [16]. This supplementation regime was especially effective in participants that presented low levels of serum 25(OH)D3 concentrations (< 25 nmol/L) at baseline period when compared to those with normal serum levels (≥ 25 nmol/L) (OR = 0.75; 95% CI: 0.60, 0.95; $p = 0.0006$) [16]. Indicating that serum 25(OH)D3 status influences the effectiveness of vitamin D3 supplementation.

The importance of serum vitamin D status in ARTIs is further evidenced in Pham et al. This systematic review of 24 meta-analysis demonstrated that those with lower serum 25(OH)D3 concentrations (< 37.5 nmol/L) presented a significantly greater the risk of developing ARTIs when compared to those with higher serum concentrations (pOR = 1.83; 95% CI: 1.42, 2.37; I^2:78.8%; $p < 0.001$) [15]. The duration of ARTI was also found to be inversely associated with vitamin D serum levels (95% CI: 1.65, 3.66; I^2: 66.7%; $p = 0.093$), which suggests vitamin D could affect the severity and mortality rate of ARTI [15]. These findings concur with the conclusion of the previous studies, further highlighting the influence vitamin D status has on ARTI.

Similar findings have been reported in LRTIs. A recent meta-analysis of 8 observational studies analyzed the relationship between serum 25(OH)D3 status and the prevalence of community-acquired pneumonia (CAP). A significant

association was found between vitamin D deficiency (< 50 nmol/L) and CAP (OR = 1.64; 95% CI: 1.00, 2.67; I^2: 89%; p = 0.05) [17]. The severity of vitamin D was especially important as it was observed to be inversely proportional to CAP prevalence. Those with severe serum 25(OH)D3 deficiency (< 25 nmol/L) had a greater risk of developing CAP (OR = 6.65, 95% CI: 2.58, 17.15; I^2: 90%; $p < 0.00001$), while those with higher vitamin D concentrations (50–75 nmol/L) presented no significant risk (OR = 1.37; 95% CI: 0.81, 2.32; I^2: 88%; p = 0.25) [17].

The impact that vitamin D status has on ARTIs can be attributed to its role in the immune system's physiology. During infections, vitamin D is involved in four main aspects of the immune response: maintaining physical barrier integrity, chemotaxis, phagocytosis, and production of antimicrobial proteins [13, 18]. It should be noted that although there is strong evidence that indicates that vitamin D status can affect the development of ARTI, the studies presented exhibit some limitations in their study design that can influence the validity of the results. Despite possible weakness in the publications, all studies concluded that vitamin D status plays an important role in preventing and reducing the severity of ARTIs [7, 15–17].

What Role Does Vitamin D Play in COVID-19?

Pathophysiology of COVID-19

Coronaviruses are large single-stranded enveloped RNA viruses. SARS-CoV2, a β-coronavirus, has a diameter of 60–140 nm and characteristic spikes, giving the appearance of a solar corona, therefore its name [2, 9, 20]. These viruses can adapt and infect new hosts through genetic recombination and variation, which explains SARS-CoV2's higher rate of infection and unique tissue tropism compared to other coronaviruses [2, 20].

SARS-CoV2 is made out of four main structural proteins: spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins. The M, E, and N proteins participate in the viral particle assembly and release, while the S protein participates in host attachment and viral and cellular membrane fusion, allowing host cell penetration. Due to its function, the S protein has garnered special attention. It is composed of two functional subunits: the S1 subunit, responsible for binding to the host cell receptor, and the S2 subunit that participates in the fusion of viral and host cell membranes [19, 21, 22].

During the early stages of infection, SARS-CoV2 targets epithelial cells through the binding of the S protein and angiotensin-converting enzyme 2 (ACE2) receptor. It is through this receptor that SARS-CoV2 starts the host cell invasion. Following the receptor binding, the S protein suffers protease cleavage, activating both of its subunits. This process is mediated by the type 2 transmembrane serine protease (TMPRSS2), allowing the structural protein changes that enable the virus to penetrate the host cell. Both ACE2 and TMPRSS2 are expressed in host target cells, such as alveolar epithelial type II cells [2, 19, 21]. Once inside the host cell, the viral content is released and the viral RNA undergoes transcription and translation to synthesize new viral particles that will be released to invade other adjacent host cells [19, 21].

To combat infection, the host utilizes the local innate immunity, including epithelial cells, alveolar macrophages, and dendritic cells, as an initial line of defense against SARS-CoV2 infection. These cells initiate the release of cytokines and immune-cell recruitment in order to fight against the virus. It has been suggested that the immune cells themselves can be infected by the virus due to their expression of ACE2 receptors. Direct infection of macrophages and dendritic cells results in a greater proinflammatory response [19, 22]. The adaptive immune response is activated when macrophages and dendritic cells present the viral antigen to T cells. The activation of T cells then results in their differentiation and the production of virus-specific immunoglobulins needed to kill the infected cells. The synergy of innate and adaptive immunity should result in the clearance of SARS-CoV2 from the lungs, as evidenced by almost 80% of COVID-19 patients recovering during the first 2 weeks of infection [19, 21, 22].

In the lungs, the inflammatory cell infiltration promotes the development of pulmonary edema and diffuse thickening of the alveolar-capillary wall, compromising oxygen diffusion [2]. The persistent injury results in the loss of alveolar epithelial type I and II cells, which leads to alveolar damage and ultimately acute respiratory distress syndrome (ARDS) [21]. With increasing viral replication, the epithelial-endothelial pulmonary barrier becomes compromised, facilitating viral invasion to other tissues [2].

When the infection becomes severe, the high viral load and exaggerated immune response impairs endothelial function, resulting in vasodilation, platelet aggregation and fibrinolysis. Consequently, the activation of coagulation and high consumption of clotting factors lead to the formation of microthrombi, contributing to the high incidence of thrombotic complications reported in severe COVID-19 patients [2, 19]. The virus can also infect other vital organs that have a high cellular expression of ACE2, such as the liver and kidney. Therefore, the final stages of the disease can turn fatal as viral sepsis develops and leads to multiorgan failure [2, 23]. A summary of the pathophysiology of SARS-CoV2 infection can be found in Fig. 2.

Can Vitamin D Influence the Development of COVID-19?

The established effect of vitamin D in preventing and reducing the severity of ARTIs, such as influenza, has led researchers to

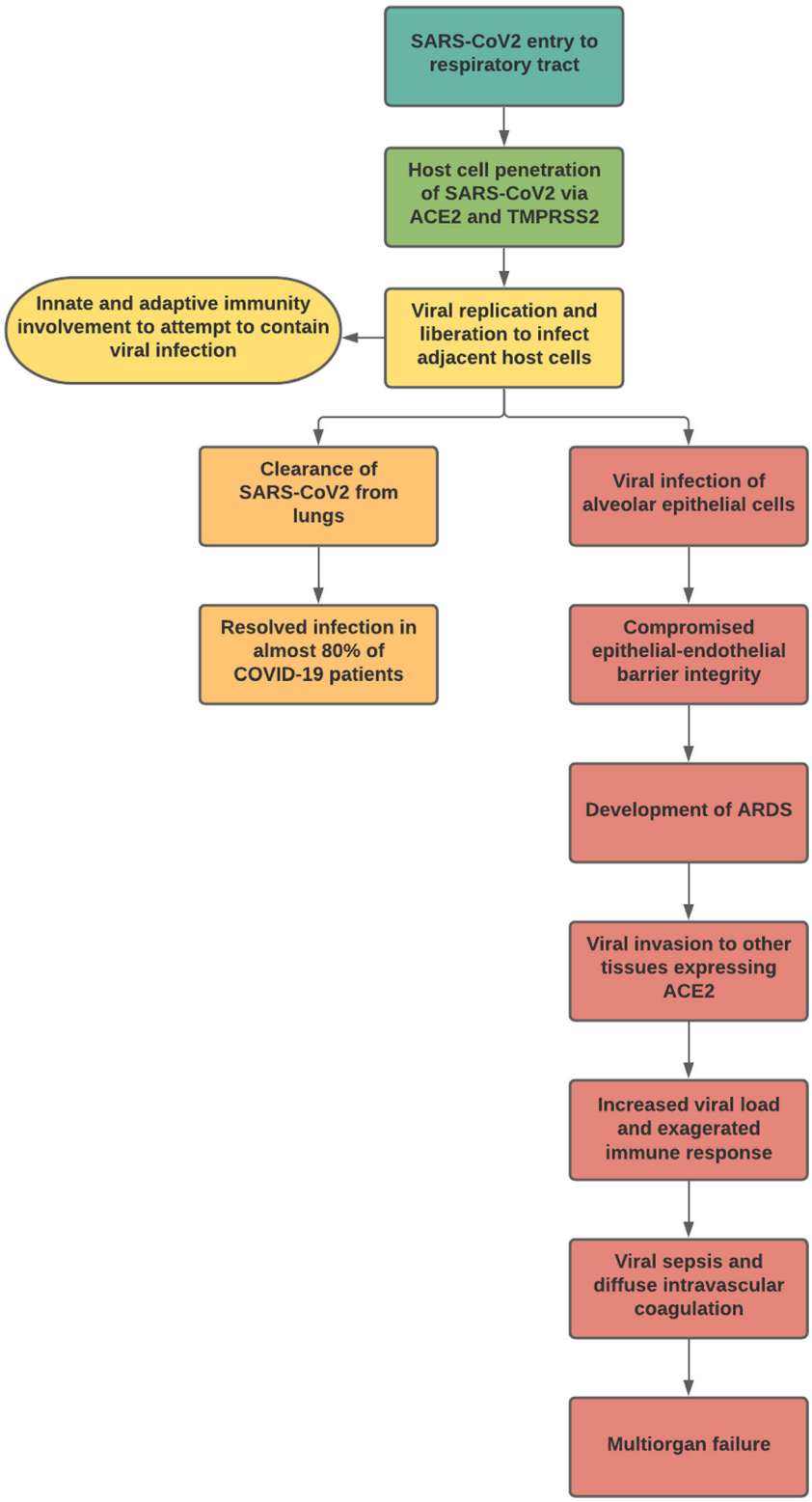

Fig. 2 Flowchart of the pathophysiologic progression of COVID-19. Abbreviations: SARS-CoV2, severe acute respiratory syndrome coronavirus 2; ACE2, angiotensin-converting enzyme 2; TMPRSS2, type 2 transmembrane serine protease; COVID-19, coronavirus disease 2019; ARDS, acute respiratory distress syndrome

hypothesize that the vitamin could also exert a similar effect on the SARS-CoV2 infection [3, 24, 25]. Research has focused on evaluating the potential effect of 25(OH)D3 status and vitamin D3 supplementation on the risk of infection and development of COVID-19. Special attention has been given to the specific role that vitamin D plays in preventing the development of the severe manifestations of COVID-19, such as ARDS [24].

The novelty of the virus has limited COVID-19 research to mainly observational studies. One of the largest studies done

to date evaluated the correlation between 25(OH)D3 status and SARS-CoV2 positivity rates. This retrospective observational study included 191,779 patients from all 50 US states with diverse ethnic backgrounds during the period of March to June 2020. An inverse correlation was found between serum vitamin D status and COVID-19 positivity rates, which is exemplified by comparing the COVID-19 positivity rates between those with adequate levels of circulating 25(OH)D3 (75–85 nmol/L) (mean infection rate (MIR) = 8.1%; 95% CI: 7.8–8.4%) and those with vitamin D deficiency (< 50 nmol/L) (MIR = 12.5%; 95% CI: 12.2–12.8%) (difference 35%; $p < 0.001$). Once vitamin D circulating levels are above 137.5 nmol/L, the risk of infection plateaued [26••].

Vitamin D has also been associated with disease severity in COVID-19 patients. Radujkovic et al. studied the impact of vitamin D status on the severity of COVID-19 symptoms in 185 patients. In this cohort study, half of the patients included were outpatients while the other half were inpatients. The median vitamin D status of the cohort was inadequate (41.5 nmol/L) and 64% of patients had vitamin D insufficiency (< 50 nmol/L). Inpatients, in particular, had significantly lower median levels of vitamin D than outpatients ($p < 0.001$). The patients were followed up for a median of 66 days. At the end of the study, those who presented vitamin D deficiency at admissions had a greater risk of requiring invasive mechanical ventilation (IMV) (HR = 6.12; $p < 0.001$) and a higher mortality rate (HR = 14.73; $p < 0.001$). Vitamin D insufficiency also increased the risk of IMV (HR = 5.75; $p = 0.004$), and mortality (HR = 11.27; $p = 0.02$). This study suggests that vitamin D status could play an important role in the prognosis of COVID-19 patients [27].

Similar findings were reported in a continuous prospective observational study that analyzed how vitamin D levels affected the severity of COVID-19 in 154 patients. The patients were evaluated during a 6-week hospitalization period and separated into two groups: group A ($n = 91$) were asymptomatic reverse transcription-polymerase chain reaction (RT-PCR)–confirmed COVID-19 patients, while group B ($n = 63$) were RT-PCR-confirmed COVID-19 patients that presented severe symptoms at the time of admissions. The serum levels of 25(OH)D3 were significantly lower in those in group B (average 35.88 nmol/L) compared with those in group A (average 69.5 nmol/L) ($p = 0.0001$). Of those that presented severe vitamin D deficiency (< 25 nmol/L), 10 were asymptomatic and 52 were in critical condition (only two critical patients had normal levels of serum 25(OH)D3). Vitamin D deficiency was also found to be associated with higher levels of inflammatory markers such as IL-6 ($p = 0.03$), which lead to a greater risk of mortality [28].

In Wuhan, China, a cross-sectional study was conducted with 335 COVID-19 patients and 560 controls from before the SARS-CoV2 pandemic. The aim of the study was to measure the impact of vitamin D deficiency on the prevalence and severity of the SARS-CoV2 infection. Patients with COVID-19 were found to have a higher prevalence of vitamin D deficiency (< 30 nmol/L) than the 2018–2019 control groups (65.1% vs. 40.7%; $p < 0.0001$), even after adjusting for sex, BMI, and presence of comorbidities ($p = 0.014$). Additionally, vitamin D concentrations were found to be inversely correlated with disease severity; 82.4% of patients with severe COVID-19 presented vitamin D deficiency compared to 60.2% of non-severe COVID-19 patients ($p = 0.0004$). Age, sex, and presence of comorbidities also played a significant role in the severity of COVID-19 symptoms. The results of this study are of particular interest as it was conducted in the site of origin of the SARS-CoV2 pandemic [29••].

In contrast, Cereda et al. found that elevated levels of vitamin D could potentially increase the severity of the SARS-CoV2 infection. In this study, done in the outbreak area of Lombardy, Italy, 324 COVID-19 inpatients and outpatients were observed in order to determine how vitamin D supplementation affected disease outcome. 11.7% of the participants supplemented with vitamin D3, with an average intake of > 54,000 IU/month (> 1800 IU/day). The mean serum 25(OH)D3 levels in the supplemented participants was 80 nmol/L, which was significantly higher than the levels presented by the non-supplemented (28.25 nmol/L) ($p < 0.001$). Although vitamin D supplementation did appear to increase the risk of in-hospital mortality in COVID-19 patients, this association was not statistically significant. Supplementation was also not associated with a greater risk of hospitalization. Further studies are required to be able to fully understand the effect of vitamin D supplementation in the severity of SARS-CoV2 infection [30••].

The severe and abrupt impact of the pandemic in the past months has made it impossible for anything other than observational studies to be conducted on COVID-19 patients. The lack of high-quality RCT that explore the impact of vitamin D on the SARS-CoV2 infection makes it difficult to determine with certainty the causal relationship between vitamin D status and the prevalence and severity of COVID-19. Additionally, several limitations exist within the methodology of the aforementioned studies, such as, a small study population and a lack of clear standardization in determining deficiency levels, optimal dose of supplementation, and diagnostic criteria for COVID-19. Several studies also demonstrated heterogeneity in the study population, possibly as a consequence of the current state of emergency. These factors indicate that the studies conducted during the pandemic period could contain a bias due to the nature of the current health crisis.

The exact role of vitamin D in the pathophysiology of COVID-19 still remains unclear. However, evidence has demonstrated that vitamin D increases the expression of ACE2 and therefore participates in the regulatory pathway of renin-angiotensin-system (RAS) [3, 31]. Animal studies have shown an inverse relationship between vitamin D status and

plasma renin activity and angiotensin II concentrations, which result in increased circulating fluid volume and blood pressure, as a consequence of higher sodium reabsorption. This can contribute to the lung damage and cardiovascular injury that is commonly seen in COVID-19 patients [3, 32]. Contrary to this, recent evidence has indicated that the increased ACE2 expression induced by vitamin D can facilitate SARS-CoV2 host cell invasion. Higher concentrations of this receptor can also promote a greater proinflammatory response which can aggravate organ damage in these patients [30••]. More clinical trials are warranted to establish the role of vitamin D in SARS-CoV2 infection.

Conclusions

Vitamin D has garnered attention in the last decades due to its importance in human health and its widespread deficiency in the global population. Recently, with the COVID-19 pandemic, vitamin D has come to the forefront of discussions for its potential impact on the prevalence and severity of SARS-CoV2 infection, as it has shown to be effective in modulating the immune response of other ARTIs. Currently, several observational studies indicate that vitamin D could, in fact, play an influential role in the SARS-CoV2 inflection; however, further studies are required in order to comprehend fully the relationship between vitamin D status and the development of COVID-19.

Declarations

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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