

Vitamin D and Covid-19 State of Evidence: Literature Review

Barkat A.^{a,1}, Hattoufi K.^a, Benkirane, H.^b, Elfahim M.^c, Aguenau H.^b

^a Université Mohamed V de Rabat

^b Université Ibn Tofail

^c CNRST

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Abstract

Following the occurrence of the global pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), some studies highlighted the possible importance of vitamin D against the disease. Several studies have supported the role of vitamin D in the regulation of the immune system. Vitamin D can suppress cytokine production simultaneously by stimulating the innate immune system, thus reducing viral load, and by decreasing the overactivation of the adaptive immune system to respond immediately to viral load. Vitamin D activity is mediated by its receptor (VDR), which acts as a transcription factor modulating the expression of genes triggering the response against viruses. Observational studies report an independent association between low serum concentrations of 25-hydroxyvitamin D and susceptibility of the respiratory tract to acute infections. Calcitriol (1,25-dihydroxyvitamin D₃) is acting on the ACE-2/Ang (1-7)/ MasR axis leading to improved expression of the angiotensin converting enzyme (ACE-2). ACE-2 is a receptor used by SARS-CoV-2 to infect host cells. Previous studies identified an association between high levels of ACE2 and improvement in the general health status of covid-19 cases. In addition, ACE-2 has been shown to protect against acute respiratory lesions. We conducted a review of the literature to clarify the protective role of vitamin D against SARS-CoV-2 infection through a review of the recently published studies.

Keywords: COVID-19; Vitamin D, Immune system; Respiratory system

1. Introduction

The novel Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) who was first reported in Wuhan, China, in December 2019, is defined by the World Health Organization as a global pandemic. This global health concern leading to a substantial need for patient hospitalization, treatment at intensive care units (ICUs), and invasive ventilation [1,2].

Immune systems, play a major role in the susceptibility and pathogenesis of viral diseases. The importance of vitamin D in the modulation of both innate and adaptive immune systems has been since many years. Moreover, several studies have previously found that there is evidence that vitamin D may help to prevent viral infections, such as SARS-CoV-19, through its role in immunity [3,4,5].

Vitamin D or 1,25-dihydroxyvitamin D or calcitriol is a fat-soluble vitamin that has long been known for its role in protecting bone tissue. It is also known to have significant effects on overall health [6,7], hence studies on vitamin D have increased exponentially in recent years.

In our country, although sunlight is important, hypovitaminosis D is estimated at 90% in women and 85% in men. For this reason, in order to reach an optimal concentration, which must be higher than 30ng/ml, it is necessary to systematically supplement at risk individuals [8,9,10,11].

¹ Corresponding author. *Email addresses:* (Bakrat, A.)

Vitamin D deficiency is caused by a range of risk factors, including age, aging skin, limited sun exposure and increased body mass index (BMI) [12,13].

The aim of this study is to clarify the protective role of vitamin D against SARS-CoV-2 infection through a review of the recently published studies.

2. Methods

We narratively reviewed the published literature. PubMed search was performed with the keywords: COVID-19 and Vitamin D. The selected language was English. Among the 437 publications identified, 8 were retained. The first selection was based on the article type and the second was based on title and abstracts (Figure 1).

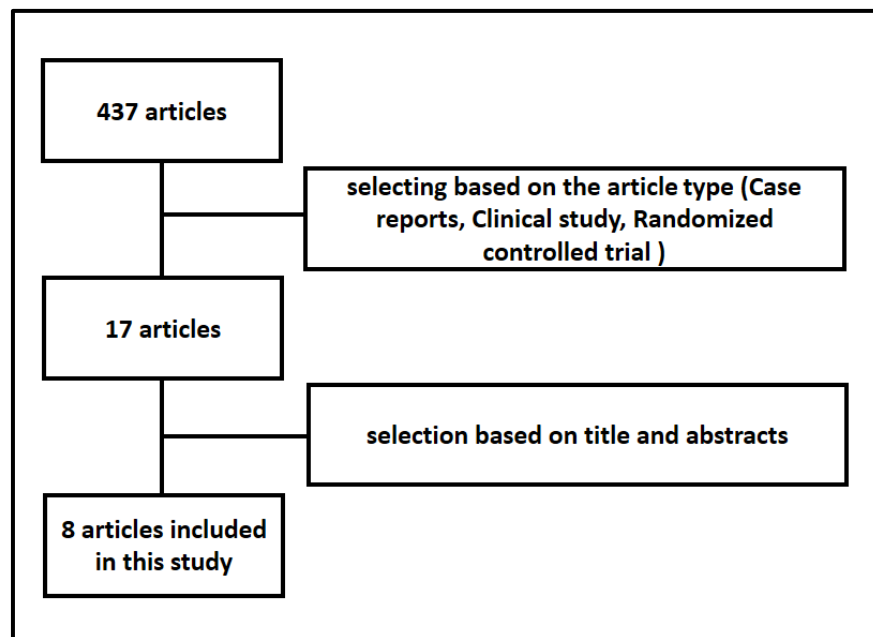


Figure 1: Flow chart showing article selected

3. Results

The results of the different studies were homogeneous concerning the protective role of vitamin D against COVID-19 infection. Castillo et al stated that calcifediol can significantly reduce the admission of covid-19 patients to intensive care units. The calcifediol appears to have the potential to reduce the severity of COVID-19 by improving clinical outcomes in hospitalized patients. According to Tan et al, a supplementation combining vitamin D / magnesium / vitamin B12 in COVID-19 positive cases was significantly associated with a reduction in clinical deterioration requiring oxygen therapy during hospitalization (17.6% vs 61.5%, $p = 0.006$).

In the same sense Vassiliou demonstrated that COVID-19 non-survivor's cases had lower ICU admission 25(OH)D levels compared to survivors.

The study protocol for a randomized controlled trial conducted by Annweiler et al aimed to compare the effect of a single oral dose of cholecalciferol versus a single oral standard dose in COVID-19 older adults. They initiated this study based on the hypothesis that vitamin D supplementation will improve the prognosis of COVID-19.

In order to analyze the vitamin D level in COVID-19 patients and its impact on the disease severity Jain et al have measured the vitamin d status in two groups infected with SARS-CoV-2; the first group was symptomatic and the second group was severely ill. The prevalence of hypovitaminosis D was higher in group B and the mean level of vitamin D was highly significant between both groups. These results are similar to those obtained in india by Padhi et al. which revealed a significant association of lower 25(OH)D with SARS-CoV-2 related deaths and susceptibility to infection. In additionally,

Karahan et Katkat, they found that mean serum 25(OH) vitamin D level was significantly lower in patients with severe-critical COVID-19 compared with moderate COVID-19 (10.1 ± 6.2 vs. 26.3 ± 8.4 ng/mL, respectively, $p < 0.001$). While according to Ling et al the high-dose cholecalciferol booster therapy, regardless of baseline serum 25(OH)D levels, appears to be associated with a reduced risk of mortality in acute in-patients admitted with COVID-19. Also, they report that the serum 25(OH)D levels were not associated with COVID-19 mortality.

Table 1: Studies including the role of vitamin D against COVID-19.

Author, reference	Design of study	Population	Methods and/or Aims	Results
Castillo et al. 2020 [14]	Parallel pilot randomized open label, double-masked clinical trial, Spain	76 COVID-19 patients were enrolled	50 patients was treated with calcifediol and 26 patients did not treated with calcifediol	Only one cases in the group who treated with calcifediol required admission to the Intensive Care Unit, while in the untreated group 13 patients required admission in the Intensive Care Unit (2% vs 50%; $p < 0.001$) Of the patients treated with calcifediol, none died, and all were Discharged. Of the patients untreated two cases died.
Vassiliou et al. 2020 [15]	Prospective observational study, Greece	30 COVID-19 patients were enrolled	25(OH)D was measured in serum of COVID-19 critically ill patients on ICU admission	COVID-19 patients who died in the ICU within 28 days appeared to have lower ICU admission 25(OH)D levels compared to survivors
Tan et al. 2020 [16]	Cohort observational study, Singapore	43 COVID-19 patients aged ≥ 50 years old were enrolled	17 patients were received vitamin D, magnesium, and vitamin B12 and 26 were a control group	Fewer treated patients than controls required initiation of oxygen therapy during hospitalization (17.6 % vs 61.5%, $P = 0.006$)
Annweiler et al. 2020 [17]	Open-label, multicenter, randomized controlled superiority trial, France	260 COVID-19 patients aged ≥ 65 years old were enrolled	Compare the effect of a single oral high dose of cholecalciferol (Two 200000IU drinking vials at once on the day of inclusion)versus a single oral standard dose of cholecalciferol (One 50000IU drinking vials at once on the day of inclusion)	Study protocol
Jain et al. 2020 [18]	Prospective observational study, India	154 COVID-19 patients aged between 30 and 60 years old were enrolled	Current Study included 91 asymptomatic COVID-19 patients (Group A) and 63 severely ill patients requiring Intensive Care Unit admission (Group B). Serum 25 (OH)D estimation was performed to compare both groups	The mean level of vitamin D was highly significant between both groups studied (27.89 ± 6.21 in Group A and 14.35 ± 5.79 in Group B ; $p < 0.001$)

Ling et al. 2020 [19]	Retrospective cross-Sectional multi-centre observational study, Britain	986 COVID-19 patients were enrolled	Determine whether COVID-19 mortality was affected by serum 25-hydroxyvitamin D (25(OH)D) levels, or cholecalciferol therapy, and to elucidate any other predictors of COVID-19 mortality.	Regardless of the serum level of 25(OH)D at baseline, treatment with cholecalciferol appears to protect against mortality
Padhi et al. 2020 [20]	Observational study, India	Indian population	Determined the correlation between vitamin D and COVID-19 disease in the Indian population	Inverse correlation was observed between the mean level of 25(OH)D and SARS-CoV-2 infection rate ($r = -0.43$, $p = 0.02$) and mortality rate ($r = -0.42$, $p = 0.02$).
Karahan et Katkat, 2021 [21]	retrospective observational study, Turkey	149 COVID-19 patients were enrolled	Investigate the role of serum 25(OH) vitamin D level on COVID severity and related mortality	Mean serum 25(OH) vitamin D level was significantly lower in patients with severe-critical COVID-19 compared to that of patients with moderate COVID-19 (10.1 ± 6.2 vs. 26.3 ± 8.4 ng/mL, respectively, $p < 0.001$) Serum 25(OH) vitamin D was independently associated with mortality in COVID-19 patients.

4. Discussion

The recent global outbreak of COVID-19 has imposed devastating impacts worldwide, especially among at-risk individuals [22]. Studies have supported the importance of vitamin D in the regulation of the immune system. [5]. Vitamin D can suppress cytokine production by simultaneously stimulating the innate immune system and decreasing the overactivation of the adaptive immune system to respond immediately to viral load [23].

Vitamin D activity is mediated by its receptor (VDR), which acts as a transcription factor modulating the expression of genes that trigger the response against viruses. Previous observational studies show independent associations between low serum 25-hydroxyvitamin D levels and susceptibility of the respiratory tract to acute infections [24].

Calcitriol (1,25-dihydroxyvitamin D₃) is acting on the ACE-2/Ang (1-7)/ MasR axis leading to improved expression of the angiotensin converting enzyme (ACE-2). ACE-2 is a receptor used by SARS-CoV-2 to infect host cells. Previous studies identified an association between high levels of ACE2 and improvement in the general health status of covid-19 cases. In additional, ACE-2 has been shown to protect against acute respiratory lesions [25,26].

Mounting evidence indicates that vitamin D is strongly linked to pathogen elimination through increased expression of cathelicidin [27]. In additional, vitamin D can increase the production of regulatory T-lymphocytes through the adaptive immune response. Randomized controlled trials among healthy adults have consistently shown that a significant reduction in respiratory tract infections has been confirmed in people taking daily vitamin D supplementation, compared to controls [28].

A meta-analysis report of nine studies conducted by Laplana et al. confirmed that vitamin D can inhibit enveloped viruses [29]. British researchers have shown that the highest rates of infection and mortality have been found in populations with low vitamin D levels [30].

In some countries such as Spain and Italy where vitamin D deficiency, although, its receives adequate sunlight throughout the year, COVID-19 infections and deaths associated with the disease was very prevalent. While, in Norway and Sweden, where vitamin D supplementation and vitamin D-fortified foods are more current, mortality and infection rates were lower. The low population

mortality due to COVID-19 in southern countries (35° north latitude) supports the hypothesis that vitamin D is a significant determinant of disease severity [31].

5. Conclusion

As stated by the international literature data, it is necessary to prescribe vitamin D supplementation systematically for people at risk of hypovitaminosis (such as children, adolescents, women of childbearing age, pregnant women, the elderly, etc...). Thus, it is essential to support the immune system of people at risk of contracting respiratory viral infections by prescribing vitamin D supplementation.

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