

A possible role of vitamin D in the treatment of COVID-19 disease

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ABSTRACT

Vitamin D has antimicrobial and immunomodulatory activities playing an essential role as an adjuvant treatment to reduce the incidence and severity of various conditions, including influenza and recurrent respiratory infections. Vitamin D insufficiency and deficiency are reported by many countries, especially in the elderly population, requiring intervention by vitamin D supplementation even before the onset of the COVID-19 pandemic. From the beginning of the pandemic, it was considered that vitamin D has a role in preventing and treating COVID-19. The few available studies show a perspective of vitamin D therapy in preventing and early treatment of SARS-CoV-2 infection.

Keywords: vitamin D, COVID-19, treatment

INTRODUCTION

An unprecedented threat is a COVID-19 pandemic. More than 1.7 million people died from SARS-CoV-2 infections by December 2020 (1). Therapeutic options are still limited, and intensive care units' capacity is often exceeded due to a large number of patients. The population's active vaccination campaign is an option, but the effectiveness will be visible over time.

Vitamin D has antimicrobial and immunomodulatory activities playing an essential role as an adjuvant treatment to reduce the incidence and severity of various conditions, including influenza and recurrent respiratory infections (2). A low level of vitamin D predisposes to an increased risk of developing respiratory infections (3). The antimicrobial action of vitamin D

depends on activating the innate and adaptive immune response, facilitating the infectious agent's elimination. At the molecular level, vitamin D promotes monocytes' differentiation into macrophages, improves chemotaxis, leukocyte recruitment, and antimicrobial activity of innate immune system cells (4). The immunomodulatory role of vitamin D is complex; in particular, it reduces immunoglobulin production, the T-helper 1 and T-helper 17 response, decreases the release of pro-inflammatory cytokines, and promotes the proliferation of regulatory T cells and the development of a T-helper response 2 (5,6).

Vitamin D insufficiency and deficiency are reported in many countries, especially in the elderly population, requiring intervention by vitamin D supplementation

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even before the onset of the COVID-19 pandemic (7). Large-scale supplementation of vitamin D, especially for the elderly and high-risk groups, seems to be necessary even in the absence of the COVID-19 pandemic, being recommended and practised in some countries (8).

Since the beginning of the SARS-CoV-2 pandemic, it was considered that vitamin D has a role in preventing and treating COVID-19 (9). Its broad-spectrum immunomodulatory action allows the hypothesis of the usefulness of vitamin D supplementation in COVID-19 to prevent progression to severe manifestations of the disease and to reduce the transmission of the infectious agent. However, few studies support this hypothesis, especially given the short time since the pandemic's onset. However, vitamin D should be considered an affordable, viable variant with reduced side effects in preventing or early treatment of SARS-CoV-2 infection (Figure 1).

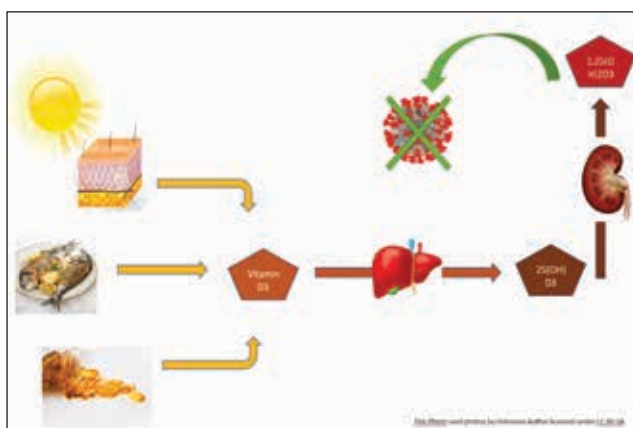


FIGURE 1. The mechanism of vitamin D

VITAMIN D SUPPLEMENTATION TO PREVENT SARS-COV-2 INFECTION

Merzon et al. conducted a study on 7,807 people between February 1 and April 30, 2020, following the COVID-19 positive ratio with the value of vitamin D, this ratio is 1.45 ($p < 0.001$); Low levels of vitamin D (< 30 ng/ml) were reported in 85% of the population tested (10).

Hastie et al. conducted a study in the United Kingdom on a group of 349,598 people between March 16, 2020 and April 14, 2020; they reported an inversely proportional association between vitamin D levels and the risk of COVID-19 infection, this association did not persist after covariate adjustment (11). It is important to note that this study used vitamin D levels measured between 2006 and 2010 and maybe weak indicators of vitamin D levels in 2020.

In the United States, a dose-response relationship was followed in a cohort of $> 190,000$ patients, a proportional inverse relationship was observed between

circulating levels of 25(OH)D and SARS-CoV-2 positivity, with a positive rate of 54%, higher in those who had a circulating level of 25(OH)D < 20 ng/ml compared to those who had a blood level of 30-34 ng/ml in the multivariable analysis (12).

Another case-control study in 201 hospitalized patients and 201 appropriate controls reported the inverse association between vitamin D levels and COVID-19 infection (13).

TABLE 1. Recommended doses of vitamin D (2,3,14)

Supplementation	Dose
Vitamin D	400–1200 IU daily for 6–12 months In patients with vitamin D deficiency or insufficiency, consider higher doses

Prevention of COVID-19 may be suggested in using the supplement in Table 1, individualized given the patient's risk factor and initial 25-OHD levels. The beneficial effect of high-dose administration of vitamin D for a short period of time in respiratory infections could not be highlighted (3).

VITAMIN D SUPPLEMENTATION TO PREVENT THE SEVERITY AND / OR MORTALITY OF COVID-19

Castillo et al. conducted a randomized study of 76 hospitalized patients with COVID-19 with radiologically confirmed acute respiratory infection who received standard therapy, including a combination of hydroxychloroquine and azithromycin. On the day of admission, eligible patients received 25-hydroxyvitamin D 3 at random, 0.532 mg = 21,280 IU. These selected patients received oral calcifediol (0.266 mg = 10.640 IU) on days 3 and 7, then weekly until discharge or hospitalization in the intensive care unit. Only 1 in 50 patients treated with calcifediol versus 13 in 26 who did not receive calcifediol treatment required intensive care admission (15).

In Germany, a cohort study of 185 patients showed an 80% decrease in the risk of invasive mechanical lethargy or death and a 90% decrease in mortality in patients with sufficient vitamin D levels than patients with vitamin D deficiency (16).

In a cohort study on 30 patients, Vassiliou et al. had observed an increase in mortality in patients with low vitamin D levels (17). In France, the risk of severe disease progression and death within 14 days of hospitalization was over 90% lower among patients who were regularly supplemented with vitamin D in the previous year compared to patients without a supplement of vitamin D (18).

In the United Kingdom, a study was reported in 986 hospitalized participants with COVID-19 and vitamin D

therapy; in the primary cohort of 444 patients, cholecalciferol booster therapy was associated with a strongly reduced risk of mortality COVID-19; this finding was replicated in a validation cohort of 541 patients (19).

Rastogi et al. supplemented with high doses of cholecalciferol (60,000 IU daily for at least seven days) in asymptomatic or vitamin D deficient RNA-positive SARS-CoV-2 patients, SARS-CoV-2 viral clearance improved, and levels increased other inflammatory markers (20).

In Brazil, a multicenter, double-blind, randomized, placebo-controlled study of 240 hospitalized patients with severe COVID-19 showed that a single dose of 200,000 IU of vitamin D3 was also safe and effective in increasing the level of 25-hydroxyvitamin D but did not

significantly reduce the duration of hospitalization or any other clinically relevant outcomes compared to placebo (21).

CONCLUSIONS

Given the potential immunomodulatory effects of vitamin D supplementation, it may help prevent respiratory infections and complications. The few available studies show a perspective of vitamin D therapy in preventing and early treatment of SARS-CoV-2 infection. Several ongoing studies and other future studies will help determine the effects of vitamin D supplementation on COVID-19 and determine the ideal dose.

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