Vitamin D Serum Concentrations and COVID-19

Subjects: Infectious Diseases

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Active vitamin D [1,25$(OH)_2D_3$—calcitriol] is a secosteroid hormone whose receptor is expressed on all cells of the immune system. Vitamin D has a global anti-inflammatory effect and its role in the management of a SARS-CoV-2 infection has been investigated since the beginning of the COVID-19 pandemic.

Keywords: vitamin D ; neuroendocrine immunology ; intracrinology ; COVID-19

1. Effects of Vitamin D on Susceptibility to COVID-19

In recent years, 25$(OH)D_3$ serum concentrations, especially below 25 nmol/L (10 ng/mL) have been identified as a risk factor for susceptibility to viral respiratory infections [1]. As a consequence, several studies have been performed to investigate the correlation between 25$(OH)D_3$ serum concentrations and the susceptibility to SARS-CoV-2 and a recent meta-analysis of fifty-four papers has shown that a 25$(OH)D_3$ deficiency (less than 30 ng/mL) was significantly associated with a SARS-CoV-2 infection (odds ratios between 1.49 and 1.83 depending on the levels of 25$(OH)D_3$ deficiency) [2]. Of note, an observational study of 379 United Kingdom (UK) healthcare workers has found a U-shaped relationship between 25$(OH)D_3$ serum concentrations and SARS-CoV-2 seropositivity: the susceptibility to COVID-19 increases with 25$(OH)D_3$ serum concentrations below 30 ng/mL (the lower the levels, the greater the risk), but, surprisingly, even with 25$(OH)D_3$ serum concentrations above 40 ng/mL (the higher the levels, the greater the risk) [3]. Therefore, 25$(OH)D_3$ serum concentrations of 40 ng/mL seem the optimal target in the general population [4]. However, to explain the increase in the infectious risk reported in the previous study, it is important to remember that reaching high 25$(OH)D_3$ serum concentrations too quickly is counterproductive, as they activate fibroblast growth factor-23 (FGF-23) and 24-hydroxylase signaling, which inactivates calcitriol [5][6].

2. Effects of Vitamin D on Severity of COVID-19

Several studies have investigated the correlation between 25$(OH)D_3$ serum concentrations and the severity of a SARS-CoV-2 infection (disease duration, pulmonary involvement, risk of need for intensive care units—ICUs—and overall mortality) [7]. 25$(OH)D_3$ significantly correlates with the length of hospitalization, the need for invasive cares, such as mechanical ventilation, the lung involvement and the mortality [8][9][10][11][12][13][14][15][16]. Although there is not a total agreement in the observational studies conducted so far [17][18], most of the meta-analyzes confirm the significant correlation between 25$(OH)D_3$ serum concentrations and the severity of COVID-19, even when caused by the more recent omicron subvariants of SARS-CoV-2 [19][20][21][22][23].

3. COVID-19 and Effects of Vitamin D Supplementation

In light of the previously reported evidence, firstly open-label and subsequently placebo-controlled RCTs evaluated the efficacy of a vitamin D supplementation in reducing the impact of COVID-19 [24]. Some authors were concerned that low 25$(OH)D_3$ serum concentrations found in COVID-19 patients could be interpreted more as a consequence of the systemic inflammation, rather than a predisposing factor for the development of the disease [25][26].

The evidence from open label and single-blinded RCTs was immediately encouraging. In fact, even in the presence of different prescriptive schemes (i.e., 0.266–0.532 mg of oral calcifediol three times for the first week of the disease and then weekly, 0.5 mcg of calcitriol per day for two weeks, 1000–2000 IU of cholecalciferol for 7–14 days, 5000 IU of cholecalciferol per day for two weeks, 10,000 IU of cholecalciferol per day for two weeks, 50,000 IU of cholecalciferol on the first and eighth day of hospitalization or 400,000 IU of oral cholecalciferol within 72 h after COVID-19 diagnosis), a vitamin D supplementation was associated with a reduction in inflammatory markers (IL-6), an improvement in the lung functions (arterial oxygen saturation/inspired fraction of oxygen ratio) and a reduction in hospitalization, access to ICUs

and the mortality rate of COVID-19 patients [27][28][29][30][31][32][33][34]. However, in a large open-label RCT regarding 6200 adults in the UK (CORONAVIT Study), 800 IU per day or 3200 IU per day of cholecalciferol for six months were not able to reduce the risk of acquiring SARS-CoV-2 in healthy volunteers, in comparison to a control group [35].

Furthermore, also placebo-controlled RCTs have been designed and conducted, providing conflicting data (the results are resumed in **Table 1**).

Table 1. Randomized double-blind, placebo controlled clinical trials regarding the biological and clinical effects of vitamin D supplementation in COVID-19 prevention and treatment.

Trials	Study Population	Patients' Cohorts' Characteristics	Recruitment Period	Time of Follow-Up	Supplementation Regimen	Effects of Vitamin D Supplementation
Treatment with 25-hydroxyvitamin D_3 (calcifediol) is associated with a reduction in the blood neutrophil-to-lymphocyte ratio marker of disease severity in hospitalized patients with COVID-19: a pilot multicenter, randomized, placebo-controlled, double-blinded clinical trial (Maghbooli Z et al., 2021, Ref. [36])	**106 COVID-19 adult hospitalized patients with 25(OH)D_3 serum concentrations < 30 ng/mL**	**53 patients on vitamin D_3 group 53 patients on placebo group**	**May 2020–October 2020**	**2 months**	**25 mcg of 25(OH)D_3 daily (equivalent to 3000–6000 IU of cholecalciferol) in addition to standard care**	**Increase in neutrophils to lymphocytes ratio**
Short term, high-dose vitamin D supplementation for COVID-19 disease: a randomized, placebo-controlled, study (SHADE study) (Rastogi A et al. 2022, Ref. [37])	**40 COVID-19 hospitalized patients with mild symptoms or asymptomatic**	**16 patients with 25(OH)D serum concentrations < 20 ng/mL received vitamin D_3 treatment 24 patients received placebo**	**2020**	**21 days**	**60,000 IU daily of cholecalciferol (oral nano-liquid droplets) for a week in addition to standard care. If 25(OH)D serum concentrations were < 50 ng/mL in the treatment group, supplementation was continued for another week**	**Faster healing Decrease in serum fibrinogen**
Positive effects of vitamin D supplementation in patients hospitalized for COVID-19: a randomized, double-blind, placebo-controlled trial (De Niet S et al., 2022, Ref. [38])	**50 COVID-19 hospitalized patients with 25(OH)D_3 serum concentrations < 20 ng/mL**	**26 patients received vitamin D_3 supplementation 24 patients received placebo**	**August 2020–August 2021**	**9 weeks**	**25,000 IU daily of cholecalciferol over four consecutive days followed by 25,000 IU weekly of cholecalciferol in addition to best available treatment**	**Decrease in length of hospital stay Decrease in duration of supplemental oxygen request Improve of clinical recovery, assessed by WHO scale**

Trials	Study Population	Patients' Cohorts' Characteristics	Recruitment Period	Time of Follow-Up	Supplementation Regimen	Effects of Vitamin D Supplementation
Efficacy and safety of vitamin D supplementation to prevent COVID-19 in frontline healthcare workers. A randomized clinical trial. (Villasis-Keever. et al., 2022, Ref. [39])	**321 SARS-CoV-2 free healthcare workers not receiving vitamin D supplementation**	**160 healthcare workers received vitamin D supplementation 161 healthcare workers received placebo**	**15 July 2020–30 December 2020**	**30 days**	**4000 IU daily of cholecalciferol capsules**	**Lower infection rate without serious adverse events**
Effect of a single high dose of vitamin D3 on hospital length of stay in patients with moderate to severe COVID-19: a randomized clinical trial (Murai IH et al., 2021, Ref. [40])	**240 COVID-19 adult hospitalized patients**	**120 patients received vitamin D supplementation 120 patients received placebo**	**2 June 2020–7 October 2020**	**Hospitalization period**	**200,000 IU of cholecalciferol in a single oral dose**	**No effects on in-hospital mortality, admission to intensive care unit or need for mechanical ventilation**
High-dose vitamin D versus placebo to prevent complications in COVID-19 patients; multicentre randomized controlled clinical trial (Mariani J et al. 2022, Ref. [41])	**218 COVID-19 adult hospitalized patients**	**115 patients received vitamin D_3 supplementation 103 patients received placebo**	**14 August 2020–22 June 2021**	**Hospitalization period**	**500,000 IU of oral cholecalciferol (5 capsules of 100,000 IU) in a single oral dose**	**No change in the respiratory Sepsis related Organ Failure Assessment (SOFA) score between baseline and the highest value recorded up to day 7 No difference for length of hospital stays, intensive care unit admissions and in-hospital mortality**
Prevention of COVID-19 and other acute respiratory infections with cod liver oil supplementation, a low dose vitamin D supplement: quadruple blinded, randomised placebo controlled trial (Brunvoll SH et al., 2017, Ref. [42])	**34,601 adults not receiving vitamin D supplementation**	**17,278 adults received cod liver oil 17,323 adults received placebo**	**10 November 2020–2 June 2021**	**6 months**	**400 IU daily of cholecalciferol**	**No decrease in the incidence of SARS-CoV-2 infection and serious COVID-19 (self-reported dyspnoea, admission to hospital, death)**

On the one hand, there were studies in favor of a vitamin D supplementation. Oral calcifediol, equivalent to 3000 to 6000 IU of cholecalciferol per day for two months, significantly decreased the peripheral neutrophil-to-lymphocyte ratio in COVID-19 patients, a functional parameter associated with a reduction in the access to ICUs and mortality [36]. Similarly, oral cholecalciferol (60,000 IU daily for a week) significantly accelerated the healing, decreasing the SARS-CoV-2 RNA in infected patients [37]. Moreover, 25,000 IU of cholecalciferol for four consecutive days, followed by 25,000 IU weekly for up to six weeks significantly improved the clinical conditions of COVID-19 patients reducing the request of an oxygen

supplementation and the length of their hospital stay [38]. At last, a supplementation of 4000 IU daily of cholecalciferol for 30 days significantly decreased the risk of suffering from a SARS-CoV-2 infection [39].

However, other placebo-controlled RCTs questioned the usefulness of a vitamin D supplementation. For example, a single high dose of 200,000 IU of cholecalciferol proved ineffective to reduce the rate of ICUs access or the global mortality of COVID-19 hospitalized patients [40]. A similar conclusion was obtained with a single supplementation of 500,000 IU of oral cholecalciferol [41]. Although these results were predictable, due to the negative effects of FGF-23 and 24-hydroxylase, activated by single high doses of vitamin D, another more recent study was disappointing [42]. A total of 17,278 adults were supplemented with 5 mL/day of cod liver oil (containing approximately 400 IU of cholecalciferol) for up to six months in Norway: no difference was found in COVID-19 incidence and disease course in comparison with a placebo group (17,323 adults) [42].

Taken together those studies suggest that a vitamin D supplementation is efficient in COVID-19 when administered for a medium or long term, whereas high and/or single doses were found not to be effective.

4. Effects of Vitamin D Supplementation in COVID-19 Vaccinations

The development of anti-COVID-19 vaccines has turned the fight against SARS-CoV-2 and its variants in a positive way [43]. It has been hypothesized that vitamin D may positively influence the efficacy of vaccines, considering that low vitamin D serum concentrations were associated with an insufficient humoral response after a COVID-19 vaccinations in patients suffering from solid tumors [44][45]. However, a sub analysis of the recent aforementioned open-label CORONAVIT study found no efficacy from a supplementation of 800 or 3200 IU of cholecalciferol daily for 6 months in improving the immunogenicity of anti-COVID-19 vaccines ChAdOx1 nCoV-19 and BNT162b2 [46].

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