VITAMIN D
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Native vitamin D and its relation with COVID-19

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INTRODUCTION

The first case of severe SARS-CoV-2 (Severe Acute Respiratory Syndrome-CoronaVirus-2) disease, later named COVID-19 (Corona Virus Disease-19) was reported in the city of Wuhan, China, in January 2020 [1]. Subsequently, the viral infection and disease spread rapidly to many geographical areas of the world. In March 2020, the disease was recognised as a pandemic by the World Health Organisation (WHO) [2]. By 23 March 2021, just under 125,000,000 confirmed cases had been recorded worldwide since the start of the pandemic, with 2,727,837 deaths [3]. As is known, in Italy and in a large part of the planet, also in relation to the infection containment measures adopted by different countries, the infection and the disease have been characterised by successive waves (Fig. 1). Patients with COVID-19 typically present with signs and symptoms of severe infectious respiratory disease, increased leukocytes and frequent lymphocytopenia [4]. Interstitial pneumonia of variable severity is also usually evident. A considerable proportion of individuals infected by SARS-CoV-2 may actually remain asymptomatic or develop very mild symptoms. Conversely, a not insignificant proportion of individuals develop such severe disease that they require hospitalisation. Approximately 20% of these individuals present with respiratory conditions requiring transfer to an Intensive Care Unit (ICU) [5]. Mortality among these patients can be very high, particularly those from older age groups with significant comorbidities [6].

VITAMIN D AND COVID-19: WHAT IS THEIR RELATIONSHIP?

To date, no real therapy has been identified for the treatment of SARSCoV-2 infection. Although several vaccines appear to be promising, the scientific community is looking very carefully at any drug that can slow viral replication and/or improve the course of the disease [7]. Activation of the vitamin D receptor (VDR) signalling pathway seems to generate positive effects in acute respiratory distress syndrome (ARDS) [8], inducing a mitigation of the so-called "cytokine storm", thus playing an important immunomodulatory and anti-inflammatory role [9]. The possible protective role of vitamin D supplementation is supported by many observational studies and meta-analyses of clinical trials studying the prevention of acute respiratory viral infections [10]. An insufficient vitamin D status has been proposed as a risk factor for virus-induced acute respiratory diseases [11,12]. However, a compromised vitamin D status is common in our nation and in many other countries as well [13]. This fact has drawn attention to a possible relationship between hypovitaminosis D, SARS-CoV-2 infection and COVID-19 [14,15]. Analysing data from 20 European countries, Ilie et al. [16] observed a negative correlation ($r = -0.44$, $p = 0.05$) between serum vitamin D (56.8 ± 10.6 nmol/L) and the number of cases of COVID-19 per million inhabitants. In the same study, COVID-19 mortality was higher in subjects with low levels of vitamin D. A dose-response relationship was shown in a cohort of > 190,000 patients in whom SARS-CoV-2 infection was correlated with serum vitamin D levels over the previous 12 months [17]. In this cohort, an inverse correlation was observed between vitamin D levels and SARS-CoV-2 positivity. Furthermore, the rate of virus positivity was significantly higher in the 39,190 patients with vitamin D < 20 ng/mL (12.5%, 95% CI: 12.2-12.8%), compared to the 27,870 patients with "adequate" serum levels (30-34 ng/mL) (8.1%, 95% CI: 7.8-8.4%) and subjects with serum levels > 55 ng/mL (5.9%, 95% CI: 5.5-6.4%). In a multivariate analysis, those with serum vitamin D < 20 ng/mL had a 54% higher positivity rate than those with normal levels.

The risk of contracting SARS-CoV-2 decreased progressively until levels of 55 ng/mL were reached. Numerous other studies have further confirmed the relationship between hypovitaminosis D, SARS-CoV-2 infection and COVID-19 mortality. In recent months, two

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Conflict of interest
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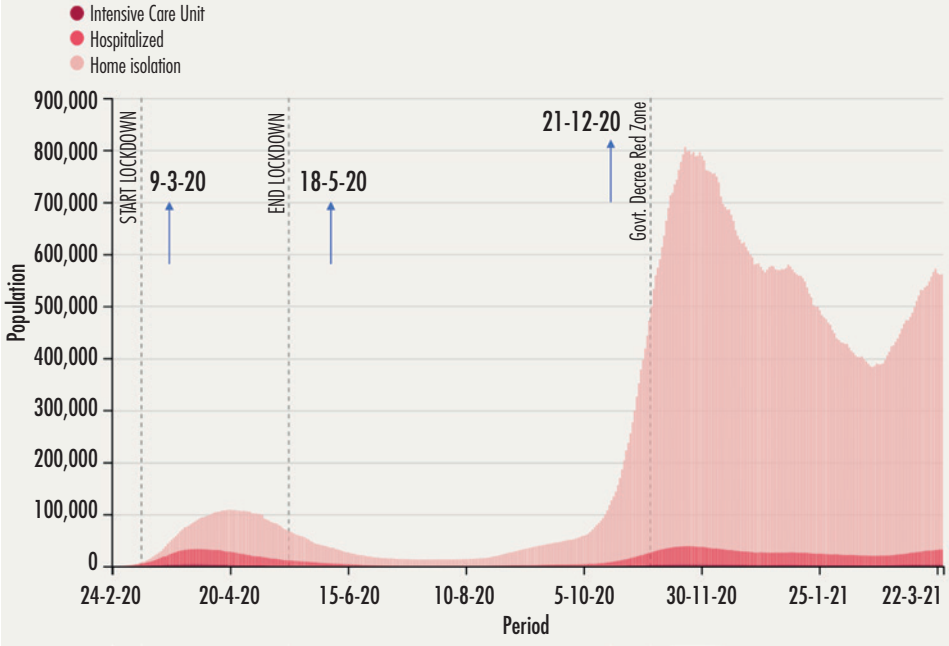


FIGURE 1.
Trend of the SARS-CoV-2 pandemic in Italy (source: https://lab24.ilsole24ore.com/ mod).

Italian studies have helped to strengthen the hypothesis of a relationship between hypovitaminosis D and COVID-19. A retrospective study of 137 patients, mean age 65 years, hospitalized for COVID-19, showed a 100% prevalence of hypovitaminosis D. Those who died, however, had significantly lower serum vitamin D levels than those who survived the disease (12 ng/mL *vs* 8 ng/mL, $p < 0.01$). In a multivariate logistic regression analysis, vitamin D levels showed an inverse correlation with in-hospital mortality (OR = 0.91; 95% CI: 0.85-0.98; $p < 0.01$) [18].

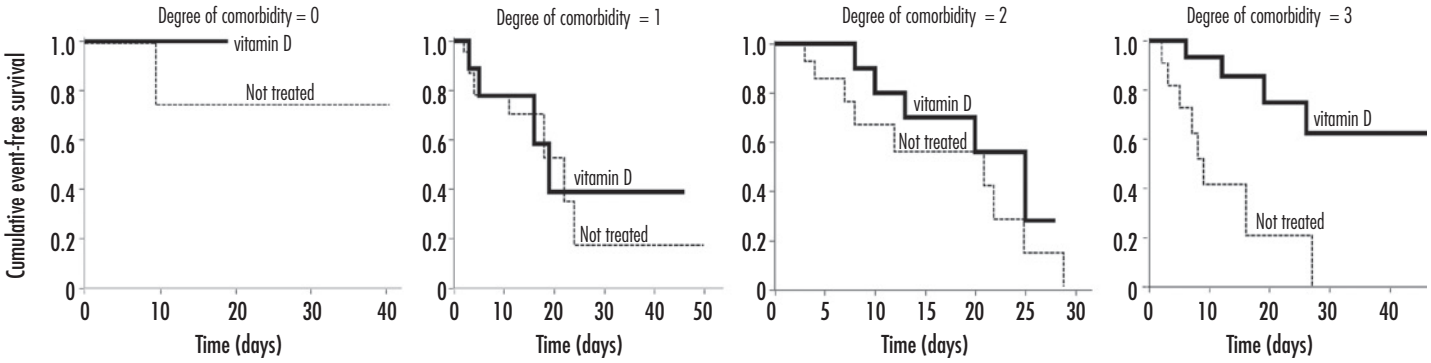
In a retrospective study, conducted at the University of Verona, in a cohort of 61 patients, mean age 69 years, admitted because of COVID-19, 72.1% were vitamin D-deficient (< 20 ng/mL) and 57.4% had serum levels of 25(OH)D < 15 ng/mL. Patients with respiratory failure (PaO2 < 60 mmHg) showed lower vitamin D levels compared to subjects with a normal blood oxygen level (13.3 ng/mL *vs* 20.4 ng/mL, respectively, p = 0,03). Hypovitaminosis D was associated with a three-fold increase in risk of hypoxaemia, increased CRP and the degree of dyspnoea [19].

VITAMIN D TREATMENT OF COVID-19

A truly different issue is whether there is a link between vitamin D administration and the clinical course of COVID-19. In other words, can cholecalciferol have a positive effect on the course of COVID-19?

Certainly, the latest study [20] did not provide any encouraging results. Regardless, although the cohort was large in terms of the number of subjects considered (240), their average age was rather low (around 56 years); the vitamin D (cholecalciferol) therapy, 200,000 IU, was administered more than 10 days after the onset of symptoms. The principal outcome, which was the duration of hospitalisation, did not differ between the active treatment and the placebo subjects. Nonetheless, hospitalis-ation was only seven days, which indicates that the subjects selected did not present with an exceptionally severe development of the disease. Among the secondary outcomes, neither mortality nor the need for transfer to the ICU differed between the groups. Still, once again, overall mortality of these patients was, whole, low (around 6%), as was the need for transfer to the ICU, which affected around 18% of patients. These results were also entirely similar among those subjects included in the study who showed baseline serum vitamin D levels at < 20 ng/mL, who were however in the minority. In contrast, a double-blind with the controlled trial [21] provided much more encouraging results. Subjects with SARS-CoV-2 infection and vitamin D deficiency (< 20 ng/mL, mean level circa 9 ng/mL), received more than 400,000 IU over about 7 days. Patients treated with native vitamin D, compared to those on placebo, showed earlier virus negativity and a significant drop in fibrinogen, one of the potential markers of disease severity. A retrospective British study of elderly hospitalised patients (mean age 74 years) also showed that a high dose of cholecalciferol (> 200,000 IU) was able to decrease mortality in patients hospitalised for COVID-19 [22].Annweiler et al. [23], in a prospective study of very elderly (88 ± 5 years) and very frail subjects, the researchers divided the 77 patients in the study into three groups: Group 1: hospitalised COVID-19 patients who, over the previous year, had received cholecalciferol at doses between 50,000 IU per month or up to 100,0000 IU every 2-3 months; Group 2: hospitalised COVID-19 patients who had not received stable supplementation with native vitamin D, but who did receive 80,000 IU of cholecalciferol once admitted; Group 3: hospitalised COVID-19 patients who had never received vitamin D, nor did they receive it during their hospital stay. The primary outcome was mortality during hospitalisation. The secondary outcome was the Ordinal Scale for Clinical Improvement Score for COVID-19 in Acute Phase (OSCI). Given the patients' morbidity and frailty, a long series of covariates were used as confounding factors for the outcome of the analyses. Of the patients in Group 1, 93% survived to 14 days, compared to 81% in Group 2 and 68% in Group 3 ($p < 0.05$). Taking Group 3 (untreated) as a reference, the HR for 14-day mortality, largely corrected for possible confounding factors, was 0.07 ($p < 0.05$), for Group 1 (treated the year before hospitalisation with cholecalciferol) and 0.37 (p ns) for Group 2, treated only during hospitalisation Group 1 was also associated with a better OSCI than Group 3 ($p < 0.05$). The authors concluded that cholecalciferol therapy among the frail and elderly had a positive effect in inducing less severe COVID-19 and in increasing survival.

Similar results were obtained from a retrospective study we conducted on 91 patients of advanced age (74 years), hospitalised for COVID-19, with significant comorbidities and very low baseline vitamin D levels (36 mmol/L, interquartile range 16-60) [24].



Degree of comorbidity	Analysis of the effect of change* (OR, 95% CI and p value)	Analysis of the adjusted effect of change** (OR, 95% CI and p value)
0	1.81 (0.45-7.27)	1.76 (0.44-7.06)
1	0.82 (0.35-1.93)	0.78 (0.32-1.90)
2	0.37 (0.19-0.72)	0.35 (0.17-0.73)
≥ 3	0.17 (0.06-0.46)	0.16 (0.05-0.46)
P as the effect of change in the degree of comorbidity	**0.02**	**0.02**

* Adjusted for the main effect of vitamin D treatment and the degree of comorbidity. ** Adjusted for the main effect of vitamin D treatment, the degree of comorbidity and the propensity score 2. OR: odds ratio; CI: confidence interval. P-value < 0,05 in bold.

FIGURE 2.
Kaplan-Meier curves showing the effect of modification by the degree of comorbidity on the efficacy of cholecalciferol on the combined endpoint "death/transfer to ICU" (from Giannini et al., 2021, mod.) [24].

In 36 subjects (39.6%) cholecalciferol was administered orally at a dose of 400,000 IU, split over two consecutive days upon admission. The remaining 55 patients (60.4%) were not treated with vitamin D. The aim of the study was to evaluate whether the proportion of patients who were transferred to the ICU and/or who died could be influenced by vitamin D intake. During a follow-up period of approximately 14 days, 27 (29.7%) patients were transferred to the ICU and 22 (24.2%) died.
Overall, 43 patients (47.3%) faced either "Death or transfer to the ICU". A statistical analysis revealed that the "weighting" of the comorbidities (represented by a history of cardiovascular diseases, COPD, chronic kidney impairment, neoplastic diseases not in remission, diabetes mellitus, haematological diseases and endocrine diseases) significantly and broadly modified, the protective effect of vitamin D on the study objective, such that the greater the number of comorbidities present, the more marked was the benefit induced by the vitamin D. Specifically, the risk of facing either "death/transfer to the ICU" was reduced by about 80% compared with subjects who did not take vitamin D (OR = 0.18, 95% CI: 0.04-0.83, $p < 0.05$, after correction for multiple confounding factors). The Kaplan-Meier analysis fully confirmed this result (Fig. 2).
In conclusion, in elderly, highly comorbid patients with COVID-19, cholecalciferol significantly reduced mortality and disease severity.

CONCLUSIONS

Considering the volume and the significance of the findings accumulated to date, several controlled, randomised, double-blind trials (RCTs) are currently underway to confirm the importance of the use of vitamin D in patients with COVID-19. At the present time, at least three large RCTs [25-27] are in advanced stages and at least two of these [25,26] appear to suggest highly robust outcomes. Therefore, it is categorically possible that in a reasonably short time the role of vitamin D, and of cholecalciferol in particular, may be confirmed as a possible medicine to help fight against the pandemic brought about by SARS-CoV-2, which has been afflicting almost all the inhabitants of our planet for quite some time now, with consequences that continue to be all too often fatal.

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