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Do vitamin D levels or supplementation play A role in COVID-19 outcomes?—a narrative review

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Background and Objective: Hypovitaminosis D has been proposed as a risk factor for increased susceptibility to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection and severe outcomes in coronavirus disease 2019 (COVID-19). Likewise, vitamin D supplementation has been proposed as an effective means for preventing and improving clinical outcomes in COVID-19. Nevertheless, available data are markedly inconsistent and contradictory. Considering the heterogeneity in the available clinical evidence, we planned to undertake a narrative review and provide a precise summary of the role of vitamin D in COVID-19.

Methods: PubMed/MEDLINE database was searched from inception till September 30, 2023 using appropriate MeSH terms. The initial search revealed 900 results. Thereafter, titles and abstracts were scanned and commentaries, letters, and editorials were excluded. Relevant observational studies and clinical trials/randomized controlled trials (RCTs) were full-text assessed and pertinent data were extracted for this narrative review.

Key Content and Findings: Data from observational and ecological studies suggest that hypovitaminosis D is associated with a higher risk of acquiring COVID-19. Similarly, evidence support a negative association between 25-hydroxyvitamin D levels and COVID-19 severity, nevertheless, causality remains to be established. With regard to vitamin D supplementation and COVID-19-related health outcomes, data from observational studies and RCTs are contradictory. Even in moderate-to-severe/severe COVID-19, vitamin D supplementation has not been shown to be beneficial. Besides, data suggest that vitamin D levels might alter COVID-19 vaccine efficacy and be associated with long COVID.

Conclusions: Vitamin D deficiency is linked to an increased risk of acquiring SARS-CoV-2 infection and poor COVID-19 prognosis, however, available evidence with regard to improved clinical outcomes with vitamin D supplementation is inconsistent.

Keywords: Vitamin D; coronavirus disease 2019 (COVID-19); hypovitaminosis D; cholecalciferol

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Introduction

Background

The outbreak of the novel coronavirus disease 2019 (COVID-19) at the dawn of 2020 was soon followed by its rapid spread worldwide (1). Hitherto, COVID-19 has claimed more than 6.9 million lives worldwide and has left a significant proportion of the population with post-COVID sequelae (2,3). The disease has been more severe in the elderly and those with pre-existing comorbidities (4,5).

Rationale and knowledge gap

Hypovitaminosis D has been proposed as a risk factor for increased susceptibility to COVID-19 (6,7). Ample clinical evidence derived from observational and ecological studies suggest that vitamin D deficiency increases the risk for severe disease and mortality with COVID-19 (8-10). Likewise, vitamin D supplementation has been proposed as an effective means for reducing the risk of COVID-19 infection and severity and thereby improve clinical outcomes (11-16). Nevertheless, available data are inconsistent and most of the randomized controlled trials (RCTs) suggest that vitamin D supplementation does not improve COVID-19-related health outcomes (17-22). Besides, available systematic reviews and meta-analyses also reveal conflicting results (23-29).

Objective

Considering the heterogeneity in the available clinical evidence, we planned to undertake a narrative review and provide a precise summary of the role of vitamin D in COVID-19. We present this article in accordance with the Narrative Review reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-23-113/rc).

Methods

PubMed/MEDLINE database was searched by RP from inception till September 30, 2023 using the following search strategy: "Vitamin D"[Mesh] AND "COVID-19"[Mesh]. The search was restricted to the English language only. The initial search revealed 900 results. Thereafter, titles and abstracts were scanned, and commentaries, letters, and editorials were excluded. Relevant observational studies and clinical trials/randomized controlled trials (RCTs) were full-text assessed, and pertinent data were extracted for this narrative review.

The search strategy has been summarized in *Table 1*.

Narrative review

25-hydroxyvitamin D [25(OH)D] levels and incidence of COVID-19

Ever since the inception of the pandemic, it had been hypothesized that higher latitude, nutritional risk of vitamin D deficiency and lack of fortification of food with vitamin D could increase the risk of COVID-19 infection and disease severity (30,31). Subsequently, multiple studies have been published to investigate the link between vitamin D levels and the risk of COVID-19. Notably, most of the studies are observational in nature.

In a retrospective cohort study conducted at an urban academic medical center in Chicago, the chances of testing positive for COVID-19 was associated with likely deficient vitamin D status [relative risk =1.77, 95% confidence interval (CI): 1.12–2.81, P=0.02] compared with likely sufficient vitamin D status (6). Similarly, in another retrospective observational analysis that included 191,779 subjects from 50 states of the United States of America, the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) positivity rate was 9.3%. The SARS-CoV-2 positivity rate was higher in the 39,190 patients with "deficient" vitamin D status [25(OH)D <20 ng/mL] (12.5%) than in the 27,870 patients with "adequate" vitamin D status (30–34 ng/mL) (8.1%) and the 12,321 patients with values ≥55 ng/mL (5.9%). The association between lower SARS-CoV-2 positivity rates and higher circulating 25(OH)D levels remained significant in a multivariable logistic regression model even after adjusting for multiple demographic factors [adjusted odds ratio (OR) 0.984 per ng/mL increment in 25(OH)D, 95% CI: 0.983–0.986, P<0.001] (32). In another observational study conducted by our group, the prevalence of vitamin D deficiency in non-severe COVID-19 patients admitted to a tertiary care hospital was 97% (7); it is noteworthy that a cross-sectional survey conducted in the same region and the same ethnic population from December 2016 to May 2018 had revealed a prevalence of hypovitaminosis D of 65.4% (33).

Data from systematic reviews and meta-analyses also suggest an inverse association between vitamin D levels and the risk of acquiring COVID-19 (34-36). Notably, in a meta-analysis that included 76 studies pooling data from 1,976,099 patients, vitamin D deficiency/insufficiency was associated with an increased risk of developing COVID-19

Table 1 Table showing the search strategy adapted for the narrative review

Items	Specifications
Date of search	October 1, 2023
Database searched	PubMed/MEDLINE
Search terms used	"Vitamin D"[Mesh] AND "COVID-19"[Mesh]
Timeframe	Inception till September 30, 2023
Inclusion and exclusion criteria	Search was restricted to English language only; observational studies, clinical trials, randomized controlled trials, reviews, systematic reviews and meta-analyses were included; commentaries, letters, and editorials were excluded
Selection process	Only Rimesh Pal conducted the search

with an OR of 1.46 (95% CI: 1.28–1.65, P<0.0001). No significant publication bias was observed in the meta-analysis (36).

Although available data favors an association between low vitamin D levels and risk of acquiring COVID-19, prophylactic vitamin D supplementation has not been consistently shown to reduce the risk of contracting the disease. In a double-blinded parallel RCT, the SARS-CoV-2 infection risk was lower in the vitamin D-treated group than in the control group (37). However, in the phase 3 CORONAVIT RCT, 6,200 participants from the United Kingdom (UK) were recruited to evaluate the effectiveness of a test-and-treat approach to identify and treat vitamin D deficiency to prevent COVID-19 and other acute respiratory tract infections. The results suggested that vitamin D replacement did not reduce the risk of all-cause acute respiratory infections or COVID-19; nevertheless, the enrolled cohorts had a high baseline prevalence of vitamin D insufficiency (38). Likewise, in a quadruple blinded, randomized placebo-controlled trial conducted in Norway, 34,601 adults were randomized to receive 5 mL/day of cod liver oil (equivalent to 10 µg) or placebo for 6 months. Supplementation with cod liver oil did not reduce the incidence of SARS-CoV-2 infection, serious COVID-19, or other acute respiratory infections compared with placebo (39). Similarly, healthcare workers in the USA receiving 5,000 IU daily of cholecalciferol for nine months did not have a statistically significant difference in the incidence of COVID-19 influenza-like illness than those who did not receive the same (40). A meta-analysis of RCTs failed to demonstrate the role of vitamin D supplementation in preventing COVID-19 (28).

Thus, to summarize, based on the aforementioned evidence, it appears that hypovitaminosis D might be associated with a higher risk of acquiring COVID-19. On the contrary, data with regard to the efficacy of vitamin D supplementation on the reduction of risk of COVID-19 is conflicting.

25(OH)D levels and COVID-19-related health outcomes

Apart from increasing the risk of contracting COVID-19, low vitamin D levels have been linked to an increased risk of severe COVID-19, hospitalization and/or mortality. In a retrospective case-control study from North West England that included 80,670 individuals with test results for serum 25(OH)D between April 1, 2020 and January 29, 2021, 1,808 were admitted to the hospital with COVID-19. Although hypovitaminosis D was not associated with an increased risk of mortality, patients with a serum 25(OH)D <20 ng/mL were at a 2.3–2.4 times higher risk of requiring hospital admission for COVID-19 (41). Likewise, another retrospective observational study from Madrid, Spain found no correlation between vitamin D levels and COVID-19 mortality; nevertheless, vitamin D deficiency [25(OH)D <20 ng/mL] was correlated with an increased risk of hospital admission and the need for critical care (42). In another study that included 105 patients aged ≥65 years presenting with symptoms consistent with COVID-19, vitamin D deficiency (≤12 ng/mL) was associated with higher peak D-dimer levels and higher incidence of non-invasive ventilation support and high dependency unit admission. It is noteworthy that vitamin D status did not predict mortality (8).

Ilie *et al.* showed an inverse relationship between the mean levels of vitamin D in various European countries and the mortality caused by COVID-19 (43). Similarly, Marik *et al.* compared fatality rate for COVID-19 in Northern (>40° N latitude) *vs.* Southern states (6.0% *vs.* 3.5%,

P<0.001) in the US and found a higher mortality rate (44). In a retrospective study from Germany, low serum 25(OH)D levels among COVID-19 patients were associated with invasive mechanical ventilation and/or death (10). In yet another study, vitamin D deficiency was associated with more severe lung involvement, longer disease duration and risk of death, in elderly COVID-19 patients (45). Similarly, another study published from the United Arab Emirates (UAE) that had included 464 patients with COVID-19, serum 25(OH)D levels <12 ng/mL were significantly associated with higher risk of severe COVID-19 infection and mortality (46). Other studies have also shown an inverse association between vitamin D levels and COVID-19 disease severity (47-53).

However, not all studies have yielded consistent results; on the contrary, some studies have shown a lack of association between vitamin D levels and COVID-19 levels (54-57). A mendelian randomization study that had included 443,734 individuals, involving 401,460 participants from the UK Biobank, suggested no association between serum 25(OH)D levels and COVID-19 severity; unfortunately, the 25(OH)D levels were measured on samples obtained many years earlier (57).

Data from systematic reviews and meta-analysis are also conflicting. Few recently published meta-analyses have reported a significant association between low serum 25(OH)D level and an increased risk of mortality, ICU admission, and need for invasive or non-invasive ventilation (26,36,58). However, a systematic review and meta-analysis that included 31 peer-reviewed observational studies failed to show any statistically significant difference between serum 25(OH)D level <20 ng/mL and COVID-19-related health outcomes, notably, mortality, ICU admission, invasive mechanical or non-invasive ventilation requirement or SARS-CoV-2 positivity status (59).

Considering the heterogeneity in the results of the available meta-analyses, it is prudent to mention that many studies included in these meta-analyses suffer from certain limitations, notably, inappropriate selection of controls, presence of confounding covariates, marked variability of assays used to measure 25(OH)D levels, as well as cutoffs considered to define low vitamin D levels. Besides, severe hypoalbuminemia and the direct effect of acute illness could imply reverse causality resulting in low levels of 25(OH)D in COVID-19 patients with severe outcomes requiring hospital admission (60). The role of confounding factors in modifying the association between vitamin D status and COVID-19-related health outcomes has been eloquently depicted in the recently published systematic review and meta-analysis by Bignardi *et al.* The authors included 21 observational studies and observed that the overall mortality was significantly higher in patients who were vitamin D deficient as compared to those who were vitamin D sufficient [risk ratio (RR) =1.49, 95% CI: 1.15–1.83, P<0.001]. Subsequently, they performed a subgroup analysis including only studies adjusted for age and at least one more confounding factor (obesity, hypertension, diabetes, chronic kidney disease, or cardiovascular disease) that revealed no association between low vitamin D levels and death (RR =1.82, 95% CI: 0.61–3.04 for cutoff levels of <10 or <12 ng/mL and RR =1.56, 95% CI: 0.80–2.31 for cutoff levels of <20 or <25 ng/mL). In contrast, the analysis including studies not mentioning adjustment for confounders, showed an increased risk of death for low vitamin D levels (RR =1.72, 95% CI: 1.09–2.36 for cutoff levels of <10 or <12 ng/mL and RR =1.48, 95% CI: 1.23–1.72 for cutoff levels of <20 or <25 ng/mL) (61).

Thus, to conclude, the majority of the available literature, based only on observational studies, hints towards a negative association between 25(OH)D levels and COVID-19 severity, nevertheless, the data is conflicting and causality remains to be established.

Vitamin D supplementation and COVID-19-related health outcomes

With the inception of the pandemic, numerous retrospective, quasi-experimental and non-randomized interventional studies have been conducted exploring the effect of vitamin D supplementation on COVID-19-related health outcomes (11,12,14,15,54,62-71). However, hitherto, only 20 randomized clinical trials have been published looking into the effect of COVID-19 supplementation and hardcore clinical outcomes in COVID-19 patients, notably, disease severity, the requirement of hospital/ICU admission, oxygen requirement, need for non-invasive/invasive ventilation, and/or mortality (13,16-22,72-84). In addition, two randomized clinical trials have looked into the effect of vitamin D supplementation solely on the rate of SARS-CoV-2 RNA negativity (85,86).

The study designs and outcomes of all the relevant clinical trials have been summarized in *Table 2*. Of note, the majority of the clinical trials does not show any significant difference in clinical outcomes between the intervention (vitamin D supplementation) and control/placebo group (17-22,76,78-84). Only three randomized trials showed

Table 2 Table summarizing the hitherto available randomized controlled clinical trials looking into the effect of vitamin D supplementation on COVID-19-related health outcomes

Author (reference)	Study design, place of study	Study participants	Intervention	Baseline serum 25(OH)D level		Outcomes
				Vitamin D group (ng/mL)	Placebo/control/ comparator group (ng/mL)	
Entrenas Castillo *et al.* (13)	Parallel, pilot randomized, open label, double-masked clinical trial; Spain	76 consecutive patients hospitalized with COVID-19	Oral calcifediol, in soft capsules (0.532 mg) on the day of admission and continued with oral calcifediol (0.266 mg) on day 3 and 7, and then weekly until discharge or ICU admission	NR	NR	Decreased ICU admission (OR =0.03, 95% CI: 0.003–0.25) after adjustment for diabetes and hypertension
Sabico *et al.* (16)	Multicenter, randomized clinical trial; Saudi Arabia	69 patients hospitalized for mild to moderate COVID-19	5,000 *vs.* 1,000 IU (standard control) of cholecalciferol daily for 14 days	25.2±1.0	21.4±1.2	5,000 IU group had a significantly shorter time to recovery (days) than the 1,000 IU group in resolving cough, D-dimer, and ageusia
Murai *et al.* (17)	Double-blind, randomized, placebo-controlled trial; Brazil	240 hospitalized patients with COVID-19	Single, oral dose of 200,000 IU of cholecalciferol dissolved in a 10 mL peanut oil solution soon after admission *vs.* placebo	21.2±10.1	20.6±8.1	No difference in length of hospital stay, ICU admission, need for mechanical ventilation, and in-hospital mortality
Murai *et al.* (18)	Ancillary analysis of double-blind, randomized, placebo-controlled trial; Brazil	32 hospitalized patients with COVID-19 with severe hypovitaminosis D (<10 ng/mL at baseline)	Single, oral dose of 200,000 IU of cholecalciferol dissolved in a 10 mL peanut oil solution soon after admission *vs.* placebo	7.7±1.6	7.9±1.6	No significant difference in the median length of hospital stay between the cholecalciferol group *vs.* placebo
Maghbooli *et al.* (19)	Multicenter, randomized, double-blinded, placebo-controlled clinical trial; Iran	106 hospitalized, vitamin D-deficient COVID-19 patients	Calcifediol 25 µg/day for 60 days *vs.* placebo	19±8	18±8	Lower trend for hospitalization, ICU duration, need for ventilator assistance, and mortality in the calcifediol group compared with that in the placebo group, but differences were not statistically significant
Bychinin *et al.* (20)	Prospective, single-center, randomized, placebo-controlled pilot trial; Russia	110 adults aged ≥18 years admitted to ICU with serum 25(OH)D <30 ng/mL (106 included in final analysis)	Cholecalciferol 60,000 IU once per 7 days (days 8, 16, 24, 32), followed by daily maintenance doses of 5,000 IU *vs.* placebo	9.6	11.0	Mortality rate, need for mechanical ventilation, incidence of nosocomial infection did not significantly differ between the two groups
Cannata-Andía *et al.* (21)	Multicenter, international, randomized, open label, clinical trial; Spain, Argentina, Guatemala, Chile	543 patients (>18 years) requiring hospitalization for moderate-severe COVID-19	Single oral bolus of 100,000 IU of cholecalciferol *vs.* placebo	17.0	16.1	No significant difference in median length of hospitalization, admission to ICU and death rate; nevertheless, the highest serum 25(OH)D category at admission (>25 ng/mL) was associated with lower percentage of pulmonary involvement and better outcomes
Mariani *et al.* (22)	Multicenter, randomized, double-blind, sequential, placebo-controlled clinical trial; Argentina	218 adult patients hospitalized in general wards with mild-to-moderate COVID-19, and risk factors for disease progression	Single oral dose of 500,000 IU of cholecalciferol *vs.* placebo	32.5	30.5	No significant differences in change in respiratory SOFA score between baseline and highest value recorded up to day 7, median length of hospital stay, ICU admissions or in-hospital mortality
Sarhan *et al.* (72)	Prospective randomized controlled study; Egypt	116 adults ≥18 years hospitalized with COVID-19	Oral alfacalcidiol 1 µg/day *vs.* intramuscular cholecalciferol 200,000 IU	NR	NR	Significant difference in the length of hospital stay, need for high oxygen or non-invasive mechanical ventilator, need for a mechanical ventilator, clinical improvement, and occurrence of sepsis in favor of high-dose vitamin D
De Niet *et al.* (73)	Randomized, parallel, two-treatment, two-arm, double-blind and placebo-controlled pilot study; Belgium	50 hospitalized patients with COVID-19 (43 included in final analysis)	Cholecalciferol 25,000 IU per day over 4 consecutive days, followed by 25,000 IU per week up to 6 weeks or placebo	16.8±9.5	17.8±10.1	Length of hospital stay decreased significantly in the cholecalciferol group compared to the placebo group
Sánchez-Zuno *et al.* (74)	Randomized clinical trial; Mexico	42 outpatients with asymptomatic or mildly symptomatic COVID-19	10,000 IU of cholecalciferol daily for 10 days *vs.* placebo	20.2	23.4	At day 7 and day 14 after diagnosis of COVID-19, there were a significantly greater number of patients with more than three symptoms in the non-supplemented group compared to the supplemented group
Annweiler *et al.* (75)	Multicenter, randomized, controlled, open-label, superiority trial; France	254, ≥65-year-old patients admitted to hospital units or living in nursing homes adjacent to the investigator centers, with SARS-CoV-2 infection diagnosed within the preceding 3 days, and at least 1 COVID-19 worsening risk factor	Single oral dose of 400,000 IU (high-dose) *vs.* 50,000 IU (standard-dose) of cholecalciferol administered within 3 days after COVID-19 diagnosis	21.2	17.2	Reduced overall mortality on day 14, but not day 28, in high-dose group *vs.* standard-dose group
Elamir *et al.* (76)	Open label, randomized clinical trial; USA	50 consecutive hospitalized adult patients with COVID-19	Calcitriol 0.5 µg/day for 14 days *vs.* no treatment	NR	NR	Significant improvement in SaO_2/FiO_2 in the calcitriol group. However, no significant differences in length of hospital stay, need for ICU admission, mortality, and readmission
Torres *et al.* (77)	Multicenter, single blind, prospective, randomized clinical trial; Spain	85 patients hospitalized for ≥7 days from onset of COVID-19 symptoms, oxygen saturation <94% and 25(OH)D serum levels <30 ng/mL	Cholecalciferol 10,000 IU/day (high-dose) *vs.* 2,000 IU/day (moderate-dose) for 14 days	15.0±6.0	14.0±6.0	Significantly shorter duration of hospital stay in the high-dose compared to the moderate-dose group

Table 2 (*continued*)

Table 2 (*continued*)

Author (reference)	Study design, place of study	Study participants	Intervention	Baseline serum 25(OH)D level		Outcomes
				Vitamin D group (ng/mL)	Placebo/control/ comparator group (ng/mL)	
Karonova *et al.* (78)	Randomized single-center open-label study; Russia	129 patients (aged 18–75 years) hospitalized with COVID-19	Cholecalciferol at a dose of 50,000 IU on the 1st and the 8th day of hospitalization, with the total dose being 100,000 IU *vs.* no supplementation	17.8	15.4	Serum 25(OH)D level on the 9th day was negatively associated with the number of bed days (r=−0.23, P=0.006); no other clinical benefits in patients receiving an oral bolus of cholecalciferol was observed
Domazet Bugarin *et al.* (79)	Open label randomized clinical trial	152 patients with COVID-19 admitted for the first time to ICU along with a 25(OH)D level <50 nmol/L	10,000 IU of cholecalciferol daily administered orally or via gastric tube during ICU stay or for at least 14 days in case of ICU discharge before day 14 *vs.* no cholecalciferol supplementation	10.1	10.9	No statistically significant difference in number of days spent on respiratory support. No significant difference in overall 14-, 28-, and 60-day survival or number of days spent in ICU or hospital
Bishop *et al.* (80)	Double-blind randomized placebo-controlled phase 2 clinical trial; USA	171 symptomatic COVID-19 outpatients	Extended-release calcifediol (300 mcg on days 1–3 and 60 mcg on days 4–27) or placebo	37.7±12.1	37.1±15.6	Number of days to resolution for the five aggregated COVID-19 symptoms (three respiratory symptoms: trouble breathing, chest congestion, dry or hacking cough; two non-respiratory symptoms: body aches or pains, chills or shivering) was unchanged between intervention and placebo groups
Seely *et al.* (81)	Two-arm, parallel-group, double-blind, randomized placebo-controlled clinical trial; Canada	90 outpatient COVID-19 patients	Treatment arm received cholecalciferol 50,000 units orally once on day 1 of the study (capsule), vitamin K_2/cholecalciferol 120 µg/500 units orally two times per day for 21 days (liquid) and vitamin C/Zinc acetate 2 g/25 mg orally three times daily for 21 days (capsule); control arm received equivalent capsules of microcrystalline cellulose and equivalent liquid doses of medium chain triglyceride oil	NA	NA	EuroQol Visual Assessment Scale summed over 21 days was not statistically significant between the intervention and control groups
Jaun *et al.* (82)	Multicenter, randomized, placebo-controlled double-blind trial; Switzerland	78 hospitalized patients with COVID-19	Single high dose of cholecalciferol (140,000 IU) followed by treatment as usual (TAU) of daily cholecalciferol (800 IU) until discharge *vs.* placebo plus TAU	12.6±4.4	11.4±4.0	No significant difference between intervention group and control group in terms of length of hospital stay. Even in patients with severe vitamin D deficiency (<10 ng/mL), there was no difference in length of hospital stay between the two groups
Partap *et al.* (83)	Double-blind, randomly assigned 2×2 factorial placebo-controlled trial; India	181 hospitalized COVID-19 patients	Subjects randomly assigned to cholecalciferol (180,000 IU bolus, then 2,000 IU daily), zinc (40 mg daily), cholecalciferol and zinc, or placebo, for 8 weeks	18.2 (11.2–28.9)	21.5 (11.4–28.6)	Cholecalciferol supplementation did not improve time to resolution of fever, cough and shortness of breath. No significant difference in duration of individual symptoms, need for assisted ventilation, duration of hospital stay and all-cause mortality between subjects receiving and not receiving cholecalciferol
Soliman *et al.* (84)	Randomized placebo controlled clinical trial; Egypt	56 elderly type 2 diabetes adults with age >60 years having vitamin D deficiency [serum 25(OH)D <20 ng/mL] who were diagnosed with COVID-19	Cholecalciferol 200,000 IU intramuscular single dose *vs.* placebo	10.4±1.3	21.7±3.96	No significant difference in 6 weeks mortality between patients who received vitamin D and patients who received placebo
Rastogi *et al.* (85)	Randomized, placebo-controlled trial; India	40 asymptomatic or mildly symptomatic COVID-19 vitamin D deficient [25(OH)D <20 ng/mL] individuals with or without comorbidities	60,000 IU of cholecalciferol for 7 days *vs.* placebo	8.6	9.5	Significantly greater proportion of participants in the vitamin D group achieved SARS-CoV-2 negativity than the control group
Abroug *et al.* (86)	Randomized controlled clinical trial; Tunisia	117 patients aged >18 years who had confirmed RT-PCR and who remained positive on the 14th day	Oral 200,000 IU/1 mL of cholecalciferol *vs.* placebo (physiological saline 1 mL)	NA	NA	No significant difference in viral RNA conversion between intervention and placebo groups

25(OH)D, 25-hydroxyvitamin D; NR, not reported; ICU, intensive care unit; SaO_2/FiO_2, Ratio of peripheral arterial oxygen saturation to the inspired fraction of oxygen; SOFA, Sepsis-related Organ Failure Assessment.

improvement in clincial outcomes in the intervention arm as compared to the control/placebo group (13,73,74). Another open-label randomized controlled single-blind clinical trial conducted in the pediatric population (patient age being 1 month to 17 years) showed that vitamin D supplementation may decrease the risk of COVID-19 progression and death, however, the results failed to reach statistical significance (87). On the other hand, clinical trials comparing high-dose *vs.* low-dose vitamin D supplementation have consistently shown improved outcomes in the high-dose group (16,72,75,77); nevertheless, all these studies did not have a third placebo arm for comparison.

The observed differences in the outcomes of RCTs of vitamin D supplementation in COVID-19 may be attributed to variable study designs in terms of mode of administration, baseline vitamin D status, type and doses of vitamin D used and clinical outcomes observed. Of note, studies have been conducted with cholecalciferol, calcifediol or calcitriol and varying doses ranging from standard supplementation to mega doses (60). In addition, the interaction of vitamin D and corticosteroids has been implicated as a potential explanation for the divergent results reported in the literature with regard to the effects of vitamin D supplementation on COVID-19-related clinical outcomes (88). In this regard, dexamethasone treatment was observed to mitigate the adverse effects of hypovitaminosis D in hospitalized COVID-19 patients (89). Furthermore, the few available aforementioned clinical trials designed to examine the effect of vitamin D supplementation on COVID-19 outcomes are likely insufficiently powered to assure a balance of corticosteroid use between study arms (88).

The majority of the data from meta-analyses suggest significant benefits of vitamin D supplementation in terms of COVID-19 severity and mortality, however, hitherto, most of the meta-analyses have included both RCTs and observational studies. A meta-analysis conducted by our group in the early days of the pandemic that had pooled 13 studies (10 observational studies, 3 RCTs) showed that vitamin D use in COVID-19 was significantly associated with reduced ICU admission/mortality (OR =0.41, 95% CI: 0.20–0.81, P=0.01). On subgroup analysis, only vitamin D supplementation post-COVID-19 diagnosis was found to be associated with improved clinical outcomes and not in those who had received vitamin D before COVID-19 diagnosis (27). Another meta-analysis that had included 13 studies (6 RCTs, 7 non-randomized intervention studies) also showed that vitamin D supplementation was significantly associated with a reduced risk of ICU admission (RR =0.35, 95% CI: 0.20–0.62) and mortality (RR =0.46, 95% CI: 0.30–0.70) (90). In yet another meta-analysis that included only six RCTs, vitamin D supplementation was shown to reduce COVID-19 severity but had no effect on disease mortality (91). Shah *et al.* conducted a meta-analysis of seven systematic reviews, the majority of whom had included both RCTs and observational/non-randomized interventional studies. Pooled analysis showed that vitamin D supplementation reduces the risk of mortality, need for intensive care and mechanical ventilation (92).

A Cochrane living systematic review that had included three RCTs concluded that the evidence for the effectiveness of vitamin D supplementation for the treatment of COVID-19 was very uncertain (93). A systematic review and meta-analysis that had included only randomized clinical trials (n=9) reported no significant difference in length of hospital stay (mean difference =–1.05 days, 95% CI: –2.63 to 0.54, P=0.19) or mortality (RR =0.93, 95% CI: 0.57–1.52, P=0.78) compared to control. Based solely on systematic review, the authors concluded that high-dose vitamin D supplementation might have potential benefits in reducing hospital stays and ICU admission in COVID-19 patients compared to low-dose vitamin D, however, a formal meta-analysis was not conducted considering the limitation in the number of the studies (94). Likewise, another systematic review and meta-analysis including only RCTs showed that vitamin D supplementation significantly reduced ICU admission (RR =0.59, 95% CI: 0.41–0.84, P=0.003) compared to control; however, vitamin D supplementation had no significant effects on the need for ventilation, oxygen therapy or length of hospital stay or mortality. Besides, compared to control, vitamin D supplementation did not result in any significant change in biochemical parameters, notably, interleukin-6 (IL-6), C-reactive protein, lactate dehydrogenase, calcium, creatinine, d-dimer, neutrophil count, lymphocyte count, platelet count, or leucocytes (29). Finally, a recently published meta-analysis of only RCTs showed that vitamin D supplementation could significantly reduce the rates of ICU admission (RR =0.63, 95% CI: 0.44–0.89) and mechanical ventilation (RR =0.58, 95% CI: 0.39–0.84), but had no statistically significant effect on mortality (28).

To summarize, most of the available evidence from clinical trials suggest that vitamin D supplementation does not improve clinical outcomes in patients with COVID-19 as compared to no supplementation. However, the available data, as narrated, is heterogeneous and further research is

required in this field. Accordingly, the American Society for Bone and Mineral Research (ASBMR), American Association of Clinical Endocrinologists (AACE), Endocrine Society, European Calcified Tissue Society (ECTS), National Osteoporosis Foundation (NOF), and International Osteoporosis Foundation (IOF) in their joint guidance recommend that most adults 19 years and older obtain between 400–1,000 IU of vitamin D daily from food and/or with supplements as recommended by Institute of Medicine (IOM) guidelines (95,96). The joint guidance clearly states that the current data do not provide any evidence that vitamin D supplementation help prevent or treat COVID-19 infection (96).

Effects of vitamin D supplementation in patients with severe COVID-19

Most of the aforementioned RCTs that have evaluated the effects of vitamin D supplementation on COVID-19-related health outcomes have included hospitalized patients; in some of these studies, the severity of COVID-19 has not been clearly mentioned. Few studies have specifically included COVID-19 patients with moderate-to-severe or severe disease (17,18,20,21,72,77,79). Most of these studies did not show any beneficial effect of vitamin D supplementation on COVID-19-related health outcomes (17,18,20,21,79). Only two studies that have compared high-dose vitamin D *vs.* low-dose/moderate-dose vitamin D have shown improved clinical outcomes in the high-dose group (72,77); however, as mentioned above, these two studies did not include a placebo arm.

Vitamin D supplementation and COVID-19 vaccine efficacy

Vitamin D deficiency has been reported to be associated with the impaired development of antigen-specific responses following vaccination. In this context, few recent studies have shown that adequate vitamin D status may improve the immune response to SARS-CoV-2 messenger RNA vaccines (97,98). In a retrospective study, 119 consecutive healthcare-workers without a previous history of acute COVID-19 or presence of anti-SARS-CoV-2 immunoglobulins were immunized with two doses of Comirnaty-vaccine from January to February 2021. Serum 25(OH)D levels were measured at time of first-immunization. Immune response was evaluated at time 0 (T0), before the first-dose; T1, time of second-dose (21 days after T0); T2, T3, T4 at 1, 5 and 9 months after T1, respectively. Vitamin D deficiency, defined as 25(OH)D <20 ng/mL was observed in 29 subjects (24.8%). In those with vitamin D deficiency, the authors reported a non-significant trend towards lower antibody-titers at T3, and significantly lower titers at T4 as compared to those without hypovitaminosis D. A positive correlation between 25(OH)D levels and antibody-titers at T4 (P=0.043) was found. In multiple linear-regression analysis, 25(OH)D deficiency and older-age emerged as negative independent factors associated with antibody titer at T4 (P=0.026, P=0.004; respectively) (99). On the contrary, a recently published study found no significant association between 25(OH)D status and SARS-CoV-2 antibody response after COVID-19 vaccination in nursing home residents and staffs (100).

Three sub-studies nested within the CORONAVIT RCT investigated the effects of offering vitamin D supplements at a dose of 800 or 3,200 IU/day *vs.* no offer on the risk of acute respiratory infections in UK adults with circulating 25(OH)D concentrations <75 nmol/L. It was observed that vitamin D supplementation did not influence the risk of breakthrough SARS-CoV-2 infection in vaccinated participants. Neither did it influence IgGAM anti-spike titers, neutralizing antibody titers, or interferon-gamma (IFN-γ) concentrations in the supernatants of S-peptide-stimulated whole blood (101). In another recently published study, volunteers being vaccinated with either Pfizer-BioNTech or Sinovac vaccines were randomized to receive either cholecalciferol (3,200 IU per day for 2 months) or no treatment. They were followed up twice at an interval of 28 days. There was no significant difference in immunoglobulin M levels between the two groups. However, the serum immunoglobulin G values were significantly higher in the vitamin D group as compared to control group at the 2nd and 3rd follow-up visits. Besides, in the vitamin D group, a positive and moderately strong correlation between serum immunoglobulin G and 25(OH) D levels was observed at the final visit (102).

Pathophysiological mechanisms implicated in the association between vitamin D and COVID-19

Multiple mechanisms have been hypothesized to explain the possible association between vitamin D and COVID-19 outcomes (27). First, vitamin D promotes the induction of cathelicidin (LL-37) and defensins. Cathelicidin (LL-37) impedes viral infection at multiple steps and is effective against both enveloped and non-enveloped

viruses (103). In addition, higher levels of LL-37 in serum correspond to lower expression of interleukin-17 (IL-17). In turn, IL-17 is involved in the pathophysiology of COVID-19, including the risk of thrombosis and acute respiratory distress syndrome (ARDS). Thus, COVID-19 severity and acute complications could partly be explained by the up regulation of IL-17 in the setting of hypovitaminosis D (27).

Second, vitamin D promotes up regulation of anti-inflammatory cytokines such as IL-10, and down regulation of proinflammatory cytokines such as IL-1, IL-6 and tumor-necrosis factor-alpha. Thus, a shift from a proinflammatory to an anti-inflammatory milieu can reduce risk of the cytokine storm in COVID-19 (104).

Third, modulation of the renin–angiotensin–aldosterone system (RAAS) and angiotensin-converting enzyme 2 (ACE2) has been proposed. Vitamin D induces the physiological ACE2/Ang [1–7] axis activity, thereby increasing the expression and concentration of ACE2 and Ang [1–7]. ACE2/Ang [1–7] system plays an important anti-inflammatory and antioxidant role in protecting the lung against ARDS; indeed, ACE2 has been protective against lethal avian influenza A H5N1 infection (105-107). Thus, up regulation of the ACE2/Ang [1–7] system could potentially protect against acute lung injury and ARDS (27,108).

In addition, certain alternative hydroxyderivatives of vitamin D have been proposed to exert anti-SARS-CoV-2 effects. Apart from the classical canonical pathway wherein vitamin D is activated through hydroxylation at C25 to produce 25(OH)D and then to its active moiety $1,25(OH)_2D$ following hydroxylation at C1 (109), certain alternative non-canonical pathways of vitamin D activation have been newly discovered. Metabolism of vitamin D by cytochrome P450scc (CYP11A1) generates novel D3-hydroxyderivatives, notably, 20-hydroxyvitamin D_3 [$20(OH)D_3$], $22(OH)D_3$, $20,23(OH)_2D_3$, $20,22(OH)_2D_3$, $1,20(OH)_2D_3$,$1,20,23(OH)_3D_3$, and $17,20,23(OH)_3$D3. The predominant metabolite in human serum is $20(OH)D_3$ with a relative concentration ~20 times lower than $25(OH)D_3$ (110). Besides, isomerization of previtamin D3 by ultraviolet B radiation generates tachysterol$_3$ (T_3) and lumisterol$_3$ (L_3). CYP11A1 and CYP27A1 hydroxylate T_3 producing 20*S*-hydroxytachysterol$_3$ [$20S(OH)T_3$] and $25(OH)T_3$, respectively (111). In addition, novel hydroxyderivatives of L_3 as a result of action of CYP11A1 have also been described. Like $20(OH)D_3$, $20S(OH)T_3$, $25(OH)T_3$ and hydroxyderivatives of L_3 are biologically active.

In the context of COVID-19, it has been hypothesized that CYP11A1-derived vitamin D and lumisterol hydroxymetabolites exert anti-inflammatory and antioxidant effects, possibly blunting the cytokine storm induced by SARS-CoV-2. In addition, the non-receptor mediated actions of vitamin D and related lumisterol hydroxymetabolites possibly include interactions with the active sites of SARS-CoV-2 transcription machinery enzymes (M^{pro}; main protease and RdRp; RNA dependent RNA polymerase). Furthermore, these metabolites might interfere with the binding of SARS-CoV-2 receptor binding domain region of the spike protein with ACE2 by interacting with ACE2 and cellular serine protease (TMPRSS2). These interactions might result in the conformational and dynamical motion changes in TMPRSS2 that might affect the priming of the SARS-CoV-2 spike proteins (112,113).

Keeping in mind the potential beneficial role of novel CYP11A1-derived hydroxyderivates of vitamin D, questions have been raised regarding the effectiveness of orally administered cholecalciferol in COVID-19. Cholecalciferol administered orally during the passage through the liver is hydroxylated to $25(OH)D_3$, which is not recognized by CYP11A. This likely results in 30 times lower concentration of $20(OH)D_3$ in serum in comparison with $25(OH)D_3$. CYP11A1, on the other hand is predominantly expressed in the adrenals, gonads and placenta in addition to its noticeable expression in the brain, gastrointestinal tract, immune systems, and skin (114). Thus, it has been hypothesized that vitamin D, administered parenterally (intramuscular) might result in higher concentration of 20(OH)D and possibly exert greater anti-SARS-CoV-2 activity (115). Nevertheless, hitherto, majority of the RCTs with vitamin D in the context of COVID-19 have used oral rather than parenteral vitamin D.

Despite the well-established role of vitamin D as a regulator of the immune system, firm conclusions cannot be drawn about a putative beneficial role of vitamin D in COVID-19. Patients with severe COVID-19 display a deficient vitamin D response and an enrichment of vitamin-D-repressed genes including pro-inflammatory cytokines. A lack of vitamin D-mediated regulation of pro-inflammatory cytokines might augment the cytokine storm observed in certain subgroups of patients with severe COVID-19. These discoveries suggest that hypovitaminosis D is unlikely to be a driving factor for the development of a severe COVID-19 (116).

Role of vitamin D in long COVID

Like post-acute viral syndromes described in survivors of other virulent coronavirus epidemics, there are ever-increasing reports of persistent and long-term effects on human health after acute COVID-19. Accordingly, the term long COVID has been coined which is defined as the continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least 2 months with no other explanation. The common symptoms of long COVID can include fatigue, shortness of breath and cognitive dysfunction (117). Whether vitamin D is associated with long COVID has not been explored in details.

In a case-control study, 120 COVID-19 survivors were compared with an equal number of age- and sex-matched healthy controls at least 3 months after recovery. Although the serum calcium levels did not differ between the 2 groups, healthy controls had significantly higher 25(OH)D levels (40.32±11.76 ng/mL) than COVID-19 survivors (23.22±8.45 ng/mL) (118). In a recently reported retrospective study, the authors compared 50 patients each with and without long COVID-19 matched for age, sex, comorbidities and previous COVID-19 severity. It was observed that subjects with long COVID had significantly lower vitamin D levels than those without (20.1 *vs.* 23.2 ng/mL, P=0.03). On multiple regression analyses, lower 25(OH)D levels at follow-up were the only variable significantly associated with long COVID in the cohort (OR =1.09, 95% CI: 1.01–1.16, P=0.008) (119).

Risk factors associated with long COVID-19 include elevated including D-dimer, interleukin-6 (IL-6), C-reactive protein, procalcitonin, and neutrophils count (120,121). A study conducted in western Mexico involving 22 vitamin D supplemented COVID-19 outpatients [mean 25(OH) D =22.4 ng/mL] and 20 non-supplemented patients [mean 25(OH)D =23.4 ng/mL] found that d-dimer concentrations were not significantly different (74). A study from Saudi Arabia also reported no significant effect on d-dimer concentrations with vitamin D supplementation of 69 COVID-19 patients (16). Additionally, a high-dose vitamin D supplementation study conducted in Turkey involving 95 hospitalized COVID-19 patients found that increasing mean 25(OH)D concentration from 23 to 35 ng/mL had no significant effect on ferritin or d-dimer concentrations (68). Thus, the aforementioned studies indirectly suggests that vitamin D supplementation has not been shown to reduce biomarkers that have been linked to the subsequent development of long COVID (121).

The role of vitamin D supplementation in the prevention or management of long COVID is hitherto unknown. A pilot double-blind clinical trial explored the effects of cholecalciferol supplementation at a dose of 2,000 IU/day for 6 weeks *vs.* placebo on muscle status in old patients recovering from COVID-19 infection. Vitamin D supplementation led to a significant reduction in creatine kinase compared to placebo. Physical status, as assessed by 6-minute walk test and handgrip strength and lung fucntion as assessed by spirometry did not change significantly with vitamin D supplementation (122). In a post hoc exploratory analysis from a multicenter, double-blind, placebo-controlled, randomized clinical trial, the authors investigated the effects of a single dose of 200,000 IU of cholecalciferol in hospitalized patients with moderate-to-severe COVID-19. Discharged patients were followed for up to 1 year and evaluated by telephone interviews at 6 and 12 months. No significant differences between groups were observed for fever, cough, fatigue, myalgia, joint pain, runny nose, nasal congestion, sore throat, hypertension, diabetes, cardiovascular disease, rheumatic disease, asthma, chronic obstructive pulmonary, chronic kidney disease, quality of life, and new or persistent symptoms up to 1-year of follow-up (123). Thus, vitamin D possibly does not have any palliative role in post-COVID-19 survivors.

Thus, although the role of vitamin D supplementation in the prevention of long COVID remains controversial, vitamin D deficiency and insufficiency has been reported to be very high in post-COVID-19 survivors (124). Thus, in the absence of further available evidence, it is suggested that 25(OH)D levels may be estimated in post-COVID-19 patients, and vitamin D may be supplemented accordingly (3).

Conclusions

Available data, primarily based on observational and retrospective studies, suggest an association between hypovitaminosis D and increased risk of acquiring SARS-CoV-2 infection and poor COVID-19 outcomes. Nevertheless, RCTs have failed to consistently demonstrate that vitamin D supplementation either reduces the incidence of COVID-19 or improves COVID-19-related clinical outcomes, even in subjects with severe vitamin D deficiency. Hence, based on the available evidence, routine vitamin D supplementation to prevent or treat COVID-19 should not be encouraged. Vitamin D supplementation should be

continued as per the standard Institute of Medicine (IOM) guidelines.

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