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Mini-Review

Consensus and Controversial Aspects of Vitamin D and COVID-19

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Abstract

Objective: This work aims to review and discuss controversial topics in the field of vitamin D, SARS-CoV-2 infection, and COVID-19.

Methods: The International Conferences "Controversies in Vitamin D" are a series of workshops that started in 2017 featuring international experts and leaders in vitamin D research and clinical practice. The fifth annual conference was held in Stresa, Italy, September 15 to 18, 2021.

Evidence: Before the event, participants reviewed available studies on their assigned topic, drafted a related abstract, and presented their findings at the time of the conference. Relevant literature that became available since was also discussed within the panel and updated accordingly.

Consensus: Before the event, the drafted abstracts had been merged to prepare a preliminary document. After the conference presentations, in-depth discussions in open sessions led to consensus. The document was subsequently modified according to discussions and up-to-date literature inclusion.

Conclusions: There is quite consistent evidence for an association between low 25 OH vitamin D (25(OH)D) levels and poor COVID-19 outcomes, despite heterogeneous publications of variable quality. However, the low vitamin D status in COVID-19 patients might also reflect reverse causality. Vitamin D supplementation might have a positive role in COVID-19 prevention. The evidence supporting a beneficial effect of vitamin D treatment in decreasing the risk of COVID-19 complications is conflicting. Conclusive statements regarding the beneficial effect of vitamin D in this context await high-quality, randomized controlled trials.

Key Words: vitamin D, COVID-19, SARS-CoV-2, vitamin D supplementation, respiratory tract infections, inflammation

Abbreviations: 25(OH)D, 25 hydroxyvitamin D; ACE2, angiotensin-converting enzyme 2; ICU, intensive care unit; RCT, randomized controlled trial.

The COVID-19 pandemic has refocused attention on strategies to prevent acute respiratory infection. Although vaccination represents the mainstay for disease control, its effectiveness at a global level is compromised by factors including cost, availability, vaccine hesitancy, vaccine failure, and variants, as well as novel respiratory pathogens (1-3). Complementary, low-cost approaches to enhance immunity to a broad spectrum of respiratory pathogens could help in this latter instance. In this regard, vitamin D may play a major role. Indeed, most immune cells express the vitamin D receptor. Moreover, enzymes related to vitamin D metabolism are present in virtually all cells of the innate and adaptive immune systems. Vitamin D metabolites modulate immunopathological inflammation and induce the expression of genes encoding antimicrobial peptides (4-6). Notably, vitamin D metabolites have long been recognized to support diverse immune responses to respiratory viruses and bacteria. The vitamin D–inducible antimicrobial peptides cathelicidin LL-37 and human beta-defensin 2 bind the SARS-CoV-2 spike protein and inhibit binding to its cellular angiotensin-converting enzyme 2 (ACE2) receptor (7, 8). Observational studies have reported that higher 25 hydroxyvitamin D (25(OH)D) levels and vitamin D supplements are independently associated with reduced risk and severity of acute respiratory infections, including COVID-19 (9-11). However, other studies have reported null data (12) or even the opposite

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association (13). A meta-analysis of randomized controlled trials (RCTs) of vitamin D supplementation to prevent acute respiratory infections found a small but significant protective effect, strongest when modest daily doses of vitamin D (400-1000 IU) are given for up to 1 year (14). Results from phase 3 clinical trials on prophylactic vitamin D and COVID-19 are currently scarce and sometimes conflicting (15, 16), as are studies comparing the effectiveness of different doses for the prevention of acute respiratory infections of any cause in adults. There is also a lack of studies designed to evaluate the effectiveness of practical approaches to identifying and treating vitamin D deficiency in the general population to improve health outcomes.

The International Conferences "Controversies in Vitamin D" are a series of workshops that started in 2017 (17-24) in which international experts and leaders in vitamin D research and clinical practice review and discuss controversial topics. The fifth annual conference was held in Stresa, Italy, September 15 to 18, 2021. During this meeting, the following major aspects related to vitamin D were discussed: aging (24), gastrointestinal system, guidelines, and COVID-19. Before the event, participants reviewed available studies on their assigned topic and presented their findings at the time of the conference. In-depth discussion in open sessions led to consensus. A separate document was prepared for the 4 major topics of the conference.

This paper summarizes expert deliberations on vitamin D and COVID-19–related inflammation and on vitamin D and incidence, severity, and treatment of COVID-19. Due to the fast-moving nature of the field, the expert panel critically evaluated additional literature published since. Further inclusion of papers occurred throughout the submission period.

COVID-19, a Multisystem Disease

COVID-19 was first recognized as a severe respiratory disease. SARS-CoV-2 has infected more than 630 million human beings and caused more than 6.6 million deaths (25). However, actual deaths might have been underestimated and be more than 18 million (26). Currently, SARS-CoV-2 is now recognized as having the potential to involve many other organ systems (27-29). This can be attributed to the ubiquity of the ACE2 receptor, to which the virus spike protein binds to enter cells. The pervasiveness of ACE2 receptors helps explain how this virus can invade so many organ systems and, even within an organ system, how the virus can infect different cell types. Vitamin D status has been implicated through various studies in the susceptibility and severity of SARS-CoV-2 infection, as well as innate and acquired immunity (5). It might be possible that low 25(OH)D levels could lead to a destructive, exuberant immune response, a major complication of COVID-19 (5). Interestingly, the systems that SARS-CoV-2 can affect are those in which vitamin D has been proposed to have a physiological role: the lungs, immune system, coagulation, cardiac function, gastrointestinal, skin, and endocrine systems (27-31). Moreover, an osteometabolic phenotype of the disease has been recently reported (32), including hypocalcemia (33), hypovitaminosis D (34), and vertebral fractures (35).

Vitamin D, Inflammation, and COVID

Inflammation is a complex and heterogeneous response to various acute and/or chronic stressors (36, 37). To consider "inflammation" as a single entity, as is often done in vitamin D research related to this topic, is an oversimplification. Nonetheless, several studies have evaluated the effect of vitamin D supplementation on autoimmune conditions (38) and associations between various acute and chronic inflammatory conditions and circulating levels of 25(OH)D (39-50), the widely accepted biomarker of vitamin D status (51). Current data generally support a conclusion that the acute inflammatory response may be associated with acute lowering of the circulating 25(OH)D concentration. A meta-analysis of 8 longitudinal studies suggested that there could be an abrupt approximately 20% to 40% decrease in circulating 25(OH)D following the onset of an inflammatory stimulus (52). Thus, current data seem to suggest that acute inflammation could also acutely lower circulating 25(OH)D concentration although the underlying mechanisms are still unclear. In fact, it has been suggested that the decline is a dilution effect due to the large amounts of intravenous fluids administered to very sick individuals (44), an observation not replicated by others (43). Alternatively, it has been postulated that this decline is due to a reduction in plasma proteins that bind 25(OH)D, namely vitamin D binding protein and/or albumin (40). Regardless of the possible underlying mechanism(s), acute reduction in circulating 25(OH)D could be hypothesized to occur in COVID-19 in the context of the acute inflammatory response induced by SARS-CoV-2 infection (reverse causality?) with possible functional consequences at the tissue/cellular level (53, 54). Since experimental evidence (55) and RCT data show that vitamin D attenuates inflammation (38, 56), and studies showed preexisting low 25(OH)D levels in patients developing COVID-19 (57), a possible bidirectional relationship between inflammation and low circulating 25(OH)D concentrations may be considered, leaving still open the issue of inflammation as a cause and/or effect of vitamin D status.

25 Hydroxyvitamin D Levels and Incidence of SARS-CoV-2 Infection

From the beginning of the pandemic, it was hypothesized that high latitude with consequent differences in sun exposure (58) as well nutritional risk of vitamin D deficiency (59) or lack of systematic food fortification with vitamin D (60) could influence the risk for SARS-CoV-2 infection and COVID-19 severity. Since then, many studies have been published to investigate a possible link between vitamin D and COVID-19. These were mostly cross-sectional observational studies, retrospective cohort studies, and, to a lesser extent, prospective cohorts or RCTs with different numbers of enrolled participants and differing vitamin D doses and supplementation/treatment approaches.

Emerging evidence suggests that vitamin D deficiency may be associated with an increased risk of COVID-19 (5, 20). Data from a recent meta-analysis also suggest a correlation with increased susceptibility to SARS-CoV-2 infection (61). Unfortunately, hypovitaminosis D is widespread, particularly in southern European countries (62), where COVID-19 has had a great effect. This is due, in part, to a reduction in sun exposure without compensatory measures, such as vitamin D food fortification or supplementation (63). Moreover, older individuals with comorbidities, such as diabetes and obesity, are at the greatest risk of adverse outcomes of COVID-19, and they are more likely to have low vitamin D status

(24, 64) Furthermore, some evidence suggests that vitamin D deficiency may be associated with hypocalcemia, a condition reported in up to 80% of symptomatic SARS-CoV-2-infected Italian patients seen in hospital emergency departments (65, 66).

A study based on 40 996 25(OH)D determinations found no direct relationship between vitamin D status, putative ultraviolet dose, and SARS-CoV-2 infection risk (67). By contrast, in a systematic review and meta-analysis to assess the association between low vitamin D status and COVID-19, which included individuals older than 50 years within a wide range of ages from Asia, Europe, and the United States, vitamin D deficiency was associated with an increased risk of symptomatic SARS-CoV-2 infection. In addition, a lower mean 25(OH)D level was found in SARS-CoV-2–positive individuals compared to SARS-CoV-2–negative individuals. The authors concluded that, despite a significant publication bias, low vitamin D status might be associated with an increased risk of SARS-CoV-2 infection (68). Similar conclusions were achieved in other meta-analyses that included respectively 49 studies (for a total of 1 403 715 individuals) (61) and 76 studies for a total of 1 976 099 patients (69). In this latter recent meta-analysis, vitamin D deficiency/insufficiency increased the odds of developing COVID-19 (odds ratio [OR] 1.46; 95% CI, 1.28-1.65; $P < .0001$; $I^2 = 92\%$) (69). Interestingly, low vitamin D status was found to be associated with an increased risk of SARS-CoV-2 infection and an increased risk of hospitalization, intensive care unit (ICU) admission, and mortality. No relevant publication bias was suggested in this paper. In a large, retrospective study of a cohort of more than 190 000 US patients with SARS-CoV-2, testing results and matching 25(OH)D data obtained in the preceding 12 months found that the incidence rate of SARS-CoV-2 positivity was higher among those with vitamin D deficiency. This relationship persisted in a multivariable model across latitudes, races/ethnicities, sex, and age ranges (57).

Jolliffe et al (15) conducted an RCT to test for effects of prophylactic vitamin D supplementation on the risk and severity of COVID-19, the phase 3 pragmatic RCT CORONAVIT. This study enrolled 6200 patients 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 infections in UK adults during winter and spring, a period when vitamin D insufficiency is highly prevalent (70). Results showed that vitamin D replacement did not reduce the risk of all-cause acute respiratory infections or COVID-19, although the enrolled cohorts had a high baseline prevalence of vitamin D insufficiency (15). Another study, however, came to different conclusions. Villasis-Keever and colleagues (16) investigated the effects of vitamin D supplementation in the prevention of SARS-CoV-2 infection in highly exposed individuals in a double-blind, parallel RCT. The SARS-CoV-2 infection risk was lower in the vitamin D–treated group than in the control group. It was associated with an increase in serum levels of 25(OH)D, independently of vitamin D status (16). Therefore, based on the aforementioned results, it appears that low 25(OH)D levels either before or at time of testing may be associated with a higher risk of SARS-CoV-2 infection. On the other hand, conflicting evidence has been reported on the efficacy of vitamin D supplementation to reducing the risk of infection.

25 Hydroxyvitamin D Levels and COVID-19 Severity

A relationship between low vitamin D status and COVID-19 severity has been consistently reported. This is physiologically plausible as in vitro data suggest vitamin D is among the molecules that may attenuate the effects of COVID-19 through its effects on gene expression (71, 72). Unsurprisingly, there is intense interest in vitamin D and COVID-19; a PubMed search entering the key words "vitamin D" and "COVID-19" (accessed October 7, 2022) retrieved 1367 publications (> 200 in the last 6 months). Of these, 67 are systematic reviews, 65 are meta-analyses, and 13 are reports on RCTs exclusively examining the relationship of vitamin D to COVID-19–related outcomes. Many retrospective case-control studies, cohort studies, as well as meta-analyses of observational studies reveal inverse associations between serum 25(OH)D level and the risk of developing severe COVID-19, including an increased risk of mortality, ICU admission, length of ICU stay, and need for mechanical ventilation. A retrospective observational study found low 25(OH)D levels to be associated with severity of lung involvement as assessed by computed tomography in male patients with COVID-19. In fact, vitamin D deficiency rates increased from 55% in radiologic stage 1 to 74% in stage 3 pneumonia (73). Also, a negative effect of vitamin D deficiency, usually at hospital admission, on mortality besides other clinical end points of severe COVID-19 and independently of other clinical risk factors, has been consistently reported (74-76). Additionally, the combination of vitamin D deficiency and diabetes and/or obesity had worse outcomes (34). Several recently published meta-analyses also consistently reported a significant association between low serum 25(OH)D level and an increased risk of mortality, ICU admission, invasive, and noninvasive ventilation (69, 77, 78).

However, it should be noted that several studies included in the aforementioned meta-analyses suffer from some limitations, such as inadequate selection of controls, confounding by other covariates, lack of adjustment for other predictive markers, the wide variability of assays to measure 25(OH)D levels, as well as cutoffs used to define low levels (79). Moreover, low levels of 25(OH)D in COVID-19 patients with severe outcomes admitted to the hospital could be a reflection of reverse causality, and can be either related to severe hypoalbuminemia at hospital admission (40, 80) or, as mentioned earlier, to the effect of acute illness per se (81).

At odds with most published evidence, a mendelian randomization study of 443 734 individuals, including 401 460 from the UK Biobank, suggested no association between serum 25(OH)D levels and disease severity; unfortunately, 25(OH)D was measured on samples obtained many years before (82). In conclusion, most published studies support a negative role of low vitamin D status in the severity of COVID-19 although, due to previously reported consideration whether low 25(OH)D is a consequence and a marker of illness severity or has a causal role in this clinical context, this remains to be established.

Vitamin D Treatment of COVID-19

To date, 14 reports of clinical trials addressing the effect of vitamin D supplementation in the treatment of COVID-19 have been published (83-96), The country, design, sample size, intervention, and outcomes of these studies are

Table 1. Randomized controlled studies addressing vitamin D treatment of COVID-19

Type of study	Author/Country	Sample size	Intervention	Outcomes	Refs
Open-label RCT	Entrenas Castillo/Spain	76 consecutive patients hospitalized with COVID-19	Calcifediol 0.532 mg d 1, 0.266 d 3 and 7, and then weekly until discharge or ICU admission	Decreased odds ratio in ICU admission of 0.03 after adjustment for diabetes and hypertension	(83)
RCT	Caballero-García/Spain	30 patients	2000 IU of D3 for 6 wk vs placebo	Vitamin D supplementation produced decreases in indicators of muscle damage	(87)
RCT	Maghboobi/Iran	106 hospitalized, vitamin D–deficient patients infected with SARS-CoV-2	Calcifediol 25 μg/d for 60 d vs placebo	Lower trend for hospitalization, ICU duration, need for ventilator assistance, and mortality in 25(OH)D3 group compared with placebo group, but differences not statistically significant. Treatment with oral calcifediol associated with significant increase in lymphocyte percentage and decrease in neutrophil-to-lymphocyte ratio in patients	(88)
RCT	Murai/Brazil	240 hospitalized patients with COVID-19	Single oral dose of 200 000 IU of D3 vs placebo	No difference in length of hospital stays, admissions to ICU, need for mechanical ventilation, and mortality	(84)
RCT double-blind, placebo-controlled	De Niet/Belgium	50 hospitalized patients with COVID-19	D3 (25 000 IU per d over 4 consecutive d, followed by 25 000 IU per week up to 6 wk) or placebo	Length of hospital stay decreased significantly Vitamin D significantly reduced duration of supplemental oxygen among patients who needed it and significantly improved clinical recovery of patients, as assessed by WHO scale	(95)
RCT	Sabico/Saudi Arabia	69 patients hospitalized for mild to moderate COVID-19	5000 vs 1000 IU of D3 for 14 d	Decrease in duration of symptom recovery from 9.1 to 6.2 d and recovery of taste from 16.9 to 14 d	(91)
RCT	Sánchez Zuno/Mexico	42 outpatients	10 000 IU of D3 for 10 days vs placebo	Intervention arm also had lesser rates of seropositivity and RT-PCR positivity rates on 7th and 14th d, respectively, and fewer symptom severities on 7th and 14th d of follow-up	(85)
Open-label RCT	Annweiler/France	254, ≥ 65-year-old patients admitted to hospitals (or living in close-by nursing homes), with SARS-CoV-2 infection of < 3 d, and at least 1 COVID-19 worsening risk factor	Single oral dose of 400 000 IU vs 50 000 IU of D3 administered within 72 h after COVID-19 diagnosis	Reduced overall mortality on d 14, but not d 28, in high-dose group vs standard-dose group	(93)
RCT	Cannata-Andía/Spain, Argentina, Guatemala, and Chile	543 patients requiring hospitalization for moderate-severe COVID-19	Single oral bolus of 100 000 IU of D3 vs placebo	Median hospitalization length, ICU admission, and death rate did not differ. In cohort analyses, highest serum calcidiol category at admission (> 25 ng/mL) associated with lower % of pulmonary involvement and better outcomes	(90)
Open-label RCT	Elamir/Israel	50 consecutive hospitalized adult patients with COVID-19	Calcitriol 0.5 μg/d for 14 d vs placebo	No significant difference in oxygen requirements, length of hospital stay, need for ICU admission, mortality, and readmission. Calcitriol arm showed significant reduction in oxygen requirements in patients hospitalized with COVID-19	(89)
RCT	Mariani/Argentina	218 adult patients hospitalized in general wards with SARS-CoV-2 confirmed infection, mild-to-moderate COVID-19, and risk factors for disease progression	Single oral dose of 500 000 IU of D3 vs placebo	No significant group differences in change in respiratory Sepsis-related Organ Failure Assessment score between baseline and highest value recorded up to d 7, median	(94)

(*continued*)

Table 1. Continued

Type of study	Author/Country	Sample size	Intervention	Outcomes	Refs
				length of hospital stay, ICU admissions, in-hospital mortality, and serious adverse events	
RCT	Rastogi/India	40 SARS-CoV-2 RNA-positive individuals	60 000 IU of D3 for 7 d vs placebo	Greater proportion of vitamin D–deficient individuals with SARS-CoV-2 infection turned SARS-CoV-2 RNA negative with significant decrease in fibrinogen on high-dose cholecalciferol supplementation	(86)
RCT	Torres/Spain	85 patients hospitalized for ≥ 7 d from onset of COVID-19 symptoms	10 000 IU/d of D3 vs 2000IU/d for 14 d	Increase in IL-10, higher levels of CD4+ T cells, 4-fold increase in cytotoxic response against SARS-CoV-2–infected cells, higher levels of IFNγ, and significantly shorter length of hospital stay in participants who developed ARDS (8.0 vs 29.2 d) in 10 000 IU/d vs 2000 IU/d group	(92)
Randomized, open-label, single-center study	Karonova/Russia	129 patients hospitalized with COVID-19	Group I (n = 56) received 50 000 IU bolus of D3 on 1st and 8th d of hospitalization. Patients from group II (n = 54) did not receive supplementation.	Serum 25(OH)D level on 9th day negatively associated with number of hospitalization days. In group I, neutrophil and lymphocyte counts were significantly higher ($P = 0.04$; $P = .02$), while C-reactive protein level was significantly lower on 9th d of hospitalization	(96)

Abbreviations: ARDS, acute respiratory distress syndrome; D3, vitamin D3; ICU, intensive care unit; IFN, interferon; IL, interleukin; IU, international unit; RCT, randomized controlled trial; RT-PCR, real-time polymerase chain reaction; WHO, World Health Organization.

summarized in Table 1. Many longitudinal, retrospective, and "quasi-experimental" (97, 98) studies have been conducted so far on vitamin D supplementation in COVID-19, and all the initial meta-analyses included predominantly observational studies, performed in the first months after the beginning of the pandemic with heterogeneous study designs leading to contradictory and likely not very reliable results (99-104).

Two years into the pandemic, RCTs on vitamin D administration in COVID-19 patients became available. Therefore, the most recent meta-analyses published (105, 106) were able to include data from 6 RCTs. They showed significant benefits of vitamin D supplementation in terms of COVID-19 severity and lower rates of ICU admission and mortality. In particular, Hosseini et al (106) showed that vitamin D supplementation was significantly associated with a reduced risk (relative risk [RR]) of ICU admission (RR = 0.35; 95% CI, 0.20-0.62) and mortality (RR = 0.46; 95% CI, 0.30-0.70). Moreover, in February 2022, a meta-analysis of systematic reviews was published (107) confirming that vitamin D supplementation may effectively reduce the COVID-19 clinical burden, with a reduction in mortality of roughly 50% in the odds ratio (OR) and similar results in ICU admission and need for ventilation. However, some caution should be used in the interpretation of this latter analysis because of the magnitude of the benefit of vitamin D supplementation (so far not yet achieved in any RCT) and for the observational nature of many of the studies that were the substrate for the systematic reviews (discussed earlier).

Differences in the outcomes of RCTs of vitamin D treatment in COVID-19 may be due to variable study design in terms of mode of administration and type and doses of vitamin D. In fact, due to its half-life, a single but high dose of cholecalciferol (84) may be less effective than repeated lower doses (86).

Observational studies and RCTs have been conducted with cholecalciferol (84, 86), calcifediol (83, 108), or calcitriol (89) and with doses varying from standard supplementation (87) to very high dose (93), but head-to-head comparisons for type of vitamin D are lacking and for high vs standard dose are very few (93). This aspect may be clinically relevant since very high vitamin D doses, particularly of the more active forms, may induce side effects (19). Therefore, the issue of considering vitamin D in the context of COVID-19 as a nutritional supplementation or as an acute therapeutic for severe COVID-19 is still open although it has been hypothesized that vitamin D should be used as a drug more than as a supplement for treating acute respiratory diseases or other infectious diseases (108).

Another confounding factor that may be taken into account when interpreting data of vitamin D administration in COVID-19 patients is that dexamethasone is commonly used in the treatment of severe COVID-19 (109), and that glucocorticoids may impair vitamin D synthesis and action (110) thus possibly interfering with the effect of vitamin D treatment in such patients (111).

In conclusion, data from interventional studies suggest that vitamin D administration could positively affect outcome for COVID-19 patients. However, since available data are still heterogeneous regarding study design, enrolled population, intervention strategies, and have also sometimes yielded conflicting results, research in this setting should focus on producing novel, robust data rather than pooling ones with low-grade evidence. In addition, bearing this in mind,

narrative reviews can potentially encompass a larger body of evidence than would be achieved by adhering to inclusion based on a rigid trial design.

Vitamin D, COVID-19 Prevention, and Vaccination

Several studies were recently published including an RCT in health care workers at high risk of exposure to SARS-CoV-2 infection suggesting that supplementation with vitamin D is able to effectively prevent COVID-19 (16, 112, 113). Based on these observations, the Glucocorticoid-Induced Osteoporosis Skeletal Endocrinology Group expert panel recently suggested that it is reasonable to strive for adequate levels of 25(OH)D in populations at high risk both of hypovitaminosis D and COVID-19 (114), especially in males, since vitamin D status could have a primary role in prevention. In fact, males are not only at risk of more severe disease but also have traditionally less-monitored vitamin D levels than females (115) and, as previously reported, have progressively lower 25(OH)D levels across stages of increased computed tomography–based severity of COVID-19 pneumonia (73).

These considerations are also important in the setting of vaccinations. In fact, several recent studies have shown that adequate vitamin D status may improve the immune response to messenger RNA vaccines either after the first (116), second (117), or third dose (118). Accordingly, the Pfizer vaccine's label cites a possible positive role of concomitant immunomodulation (119). Moreover, vitamin D supplementation has been shown to augment antigen-specific immunity, especially in older individuals without optimal vitamin D status (120). In this perspective, vitamin D might be useful, specifically where hypovitaminosis D is prevalent. However, a substudy nested within the CORONAVIT RCT did not demonstrate significant improvement in the response to SARS-CoV-2 vaccination in adults with relatively low basal vitamin D status with fixed doses of vitamin D (800 or 3200 IU/d) (121). Finally, the possible role of adequate 25(OH)D levels (and vitamin D supplementation) in improving the host response to COVID-19 vaccination could represent an opportunity to tackle the widespread prevalence of vitamin D deficiency (114).

Conclusion

There is consistent evidence for the association between low 25(OH)D levels and poor COVID-19 outcomes. However, it stems in part from observational studies that are limited by confounding factors such as comorbidities and body mass index, known risk factors for low 25(OH)D levels and poor COVID-19 outcomes. Moreover, low 25(OH)D levels may also reflect reverse causality (122). Evidence supporting the beneficial effect of vitamin D administration as (co)treatment of COVID-19 is also accumulating but needs to be corroborated by robust RCTs as well as the possible beneficial effect of vitamin D in COVID-19 prevention.

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A.G. and J.P.B. reviewed conception and design and manuscript drafting; and all authors performed collection and interpretation of data from the literature, manuscript editing, and approval to submit.

Disclosures

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during the present study.

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