Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Vitamin D and COVID-19

Severe coronavirus disease 2019 (COVID-19) is a consequence of an exuberant and dysregulated immune response to high viral loads of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Severe COVID-19 most commonly results in a clinical presentation and pathophysiology similar to acute respiratory distress syndrome (ARDS). Like ARDS, severe COVID-19 can have multisystemic effects related to the release of proinflammatory cytokines.

Vitamin D ingested orally or produced in the skin in response to ultraviolet light is metabolized to the active steroid hormone 1,25-dihydroxyvitamin D ($1,25[OH]_2D$). Receptors for this hormone are widely distributed in most human tissues. The primary action of $1,25(OH)_2D$ is to promote active absorption of calcium in the gut. However, vitamin D is also an important immune and inflammatory modulator, which could—theoretically—decrease the severity of COVID-19 infection by reducing the expression of genes involved in the inflammatory pathway. Experimental evidence supports the potentially beneficial effects of vitamin D in cytokine production, macrophage response, airway epithelial repair and permeability, the renin-angiotensin system, and risk of infection.[1] Vitamin D status is usually assessed by measuring the intermediate metabolite, 25-hydroxyvitamin D (25[OH]D), as it has a long half-life of approximately 3 weeks. People from racial groups with darker skin are at greater risk for severe COVID-19 and have lower serum 25(OH)D concentrations than Whites. In a meta-analysis of randomized controlled trials of vitamin D supplementation, daily or weekly—but not bolus doses of vitamin D—were associated with a reduced risk of respiratory infection, particularly among those with 25(OH)D values <10 ng/mL.[2] This contextual framework underpins the rationale for studying the therapeutic benefit of vitamin D in COVID-19.

In this issue of *Mayo Clinic Proceedings*, Angelidi et al report the relationship between vitamin D status and hospital outcomes in 144 patients with COVID-19 in New York and Boston early in the pandemic (February to May, 2020).[3] Using a retrospective cohort design, they found that patients with lower serum 25(OH)D values within 6 months before or during hospital admission for COVID-19 had increased mortality and need for invasive mechanical ventilation. Particular strengths of this study include the racial diversity represented and the consistency of the relationship of 25(OH)D concentrations with mortality and invasive mechanical ventilation across different multivariable models, adjusting for a variety of covariates that could affect illness severity or vitamin D status. The median 25(OH)D concentration was 28 ng/mL, and mortality in those with 25(OH)D values <30 ng/mL was 25%, compared with 9% in those with values ≥30 ng/mL. Similar results were obtained using a 25(OH)D threshold of 20 ng/mL in a sensitivity analysis. Approximately one-half of the patients had 25(OH)D measurements before infection and hospitalization for COVID-19. Importantly, there was no modification of the effect of vitamin D status on mortality and invasive mechanical ventilation by the timing of 25(OH)D measurement before or during hospitalization.

Although the work of Angelidi et al is encouraging, it is premature to conclude that vitamin D supplementation improves outcomes in COVID-19, and limitations of the current state of evidence need to be recognized. First, low vitamin D status could be a cause or consequence of more severe COVID-19. The observational retrospective study design prohibits us from determining causation, and patients with 25(OH)D measurement were not selected with a random sampling technique. Studies examining the relationship of serum 25(OH)D levels and

Mayo Clin Proc. ■ April 2021;96(4):838-840 ■ https://doi.org/10.1016/j.mayocp.2021.02.014
www.mayoclinicproceedings.org ■

hospital outcomes in COVID-19 have had mixed results,[4] and randomized controlled trials of vitamin D supplementation in COVID-19 are necessary to demonstrate benefit.[1]

Second, low serum 25(OH)D levels may be a marker of illness severity or inflammation and not an indicator of therapeutic benefit of supplemental vitamin D. Other investigators have observed an inverse relationship of 25(OH)D values with inflammatory and acute phase markers, both postoperatively and in COVID-19.[5] In addition, those who have chronic illnesses and are at greater risk of severe COVID-19 may have low vitamin D status resulting from their disease, inadequate dietary intake, or limited exposure to the sun.

Third, a randomized controlled trial evaluating vitamin D supplementation in critically ill patients (unrelated to COVID-19) found no benefit in patients with baseline 25(OH)D levels less than 20 ng/mL.[6] In this trial of a single-bolus dose of vitamin D 540,000 IU, the group that received vitamin D had no survival benefit, even among those with the most severe deficiency (25[OH]D <12 ng/mL). In fact, mortality was increased in the subgroups with infection or ARDS who received vitamin D. Of note, only 8% of subjects in this trial had ARDS at baseline, and the results may not be generalizable to those with COVID-19.

Fourth, as has been observed with studies of monoclonal antibodies for COVID-19, vitamin D status may have differing effects in prevention vs treatment of severe COVID-19. Vitamin D may have greater benefit before immune activation in severe illness, possibly accounting for the absence of benefit of vitamin D supplementation in critical illness. In a randomized controlled trial of vitamin D 60,000 IU per day for 7 days in 40 subjects with baseline 25(OH)D <20 ng/mL and mild or asymptomatic COVID-19, SARS-CoV-2 RNA levels became negative before day 21 in a greater proportion of those randomized to vitamin D (63% vs 21%).[7] An additional finding in this study was that fibrinogen levels, but not other inflammatory markers, decreased with vitamin D supplementation. In a retrospective observational analysis of 191,779 subjects tested for SARS-CoV-2 at a national reference laboratory, who also had 25(OH)D measured in the preceding 12 months, lower SARS-CoV-2 positivity rates were associated with greater 25(OH)D concentrations (odds ratio, 0.979 per 1 ng/mL increment; 95% confidence interval, 0.977 to 0.980).[8]

Besides vitamin D intake and exposure to sunlight, additional factors influence 25(OH)D values. Polymorphisms of genes related to vitamin D transport and metabolism are predictive of 25(OH)D concentrations.[9] Individual variability in the metabolic consequences of a low 25(OH)D concentration likely exists, given the multiple intermediary steps leading to the $1,25(OH)_2D$ effect on genetic expression. In patients with COVID-19 in Spain, investigators identified 2 susceptibility loci with genome-wide significance for severe COVID-19 with respiratory failure.[10] This raises the possibility that low 25(OH)D levels may be linked with genetic loci associated with an increased risk of severe disease in COVID-19.

Our knowledge of the role of vitamin D deficiency and supplementation in infection and inflammation is limited. It is unknown what degree of vitamin D deficiency is likely to have a detrimental effect on inflammatory and immune regulation. In vitamin D-deficiency rickets and osteomalacia, for example, 25(OH)D concentrations are nearly always below 12 ng/mL and often undetectable. It is important to recognize that serum 25(OH)D is a marker of vitamin D stores but not a functional measure of the action of $1,25(OH)_2D$ on vitamin D receptor-mediated gene expression. Better biochemical markers of the functional effects of vitamin D are needed.

Until more is known about the role of vitamin D in COVID-19, it is reasonable to provide vitamin D supplementation of 20 to 50 μg (800 to 2000 IU) daily to prevent vitamin D deficiency in persons at risk. No harm is associated with this dose range of vitamin D, and 800 IU daily maintains 25(OH)D concentrations above 20 ng/mL in the vast majority of healthy adults. High

doses of vitamin D, greater than 100 μg (4000 IU) daily, have no established role in the treatment or prevention of COVID-19, and excessive vitamin D can lead to hypercalcemia and nephrocalcinosis.

Tom D. Thacher, MD
Department of Family Medicine
Mayo Clinic
Rochester, MN

Potential Competing Interests: Dr Thacher is an Investigator in the Mayo Biobank study of vitamin D status and COVID-19.

Correspondence: Address to Tom D. Thacher, MD, Department of Family Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905 (Thacher.thomas@mayo.edu).

ORCID
Tom D. Thacher: https://orcid.org/0000-0002-7644-8173

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