Vitamin D

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Vitamin D is critical for bone and mineral metabolism. Because the vitamin D receptor is present on immune cells such as B cells, T cells, and antigen-presenting cells, and because these cells can synthesize the active vitamin D metabolite, vitamin D also has the potential to modulate innate and adaptive immune responses.[1] It is postulated that these immunomodulatory effects of vitamin D could potentially protect against SARS-CoV-2 infection or decrease the severity of COVID-19.

Vitamin D deficiency (defined as a serum concentration of 25-hydroxyvitamin D ≤20 ng/mL) is common in the United States, particularly among people who identified as Hispanic or non-Hispanic Black.[2] These groups are overrepresented among cases of COVID-19 in the United States.[3] Vitamin D deficiency is also more common in older patients and patients with obesity and hypertension; these factors have been associated with worse outcomes in patients with COVID-19.[4] High levels of vitamin D may cause hypercalcemia and nephrocalcinosis.[5]

Recommendation

- There is insufficient evidence for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of vitamin D for the prevention or treatment of COVID-19.

Rationale

The results from several cohort studies, clinical trials, and meta-analyses on the use of vitamin D for the prevention or treatment of COVID-19 have been published in peer-reviewed journals or have been made available as manuscripts ahead of peer review. However, most of these studies had significant limitations, such as small sample sizes or a lack of randomization and/or blinding. In addition, these studies used varying doses and formulations of vitamin D, enrolled participants with a range of COVID-19 severities, included different concomitant medications, and measured different study outcomes. All these factors make it difficult to compare results across studies. The studies summarized below are those that have had the greatest impact on the Panel's recommendations.

Although multiple observational cohort studies suggest that people with low vitamin D levels are at increased risk of SARS-CoV-2 infection and worse clinical outcomes after infection (e.g., higher mortality), clear evidence that vitamin D supplementation provides protection against infection or improves outcomes in patients with COVID-19 is still lacking.[6,7]

Clinical Data on Vitamin D for Prevention

In a double-blind trial conducted at 4 hospitals in Mexico, frontline health care workers were randomized to receive vitamin D_3 4,000 IU or placebo for 30 days.[8] Participants were enrolled before COVID-19 vaccines became available. Over one-third of the enrolled participants dropped out before study completion. Of the 192 participants who completed follow-up, 6.4% of participants in the vitamin D_3 arm and 24.5% in the placebo arm acquired SARS-CoV-2 infection (relative risk 0.22; 95% CI, 0.08–0.59). At baseline, approximately 67% of participants had vitamin D deficiency, but this was not found to be an independent predictor of acquiring SARS-CoV-2 infection. The frequency of SARS-CoV-2 infection was very high in the placebo group, and it is unclear how these results translate to the use of vitamin D in vaccinated health care workers.

Clinical Data on Vitamin D for Treatment

In a double-blind trial conducted from June to October 2020 at 2 sites in Brazil, 240 hospitalized patients with moderate to severe COVID-19 were randomized to receive a single dose of vitamin D_3 200,000 IU or placebo.[9] Patients were considered to have moderate to severe COVID-19 if they had a positive polymerase chain reaction (PCR) result for SARS-CoV-2 or compatible computed tomography scan findings and a respiratory rate >24 breaths/min or oxygen saturation <93% on room air. The primary outcome was length of hospital stay. The study found no significant difference in the median length of stay between the vitamin D_3 arm (7.0 days; IQR 4.0–10.0 days) and the placebo arm (7.0 days; IQR 5.0–13.0 days; log-rank $P = 0.59$). No significant differences were observed between the arms in the proportion of patients who were admitted to the intensive care unit (ICU), the need for mechanical ventilation, or mortality. There were no significant safety concerns.

A randomized, double-blind, placebo-controlled study conducted in Argentina included 218 adult patients with COVID-19 who had been admitted to the hospital during the preceding 24 hours and who had oxygen saturation ≥90% on room air and a risk factor for disease progression.[10] Patients were randomized to receive a single oral dose of vitamin D_3 500,000 IU or placebo. The primary outcome was the change in the respiratory sepsis-related organ failure assessment (rSOFA) score between baseline and the highest value recorded up to Day 7. There was no significant difference between the arms for this outcome, with a median change of 0 in both arms ($P = 0.925$). There were also no significant differences between the arms in the median length of hospital stay, the number of patients admitted to the ICU, or in-hospital mortality.

A randomized, open-label study conducted in France compared the effect of a high dose of vitamin D_3 (400,000 IU) to the standard dose of vitamin D_3 (50,000 IU) on mortality in 254 patients who were either hospitalized or living in nursing facilities near the study hospital sites.[11] Patients were aged ≥65 years, had been diagnosed with SARS-CoV-2 infection within the preceding 3 days, and had at least 1 risk factor for disease progression (i.e., aged ≥75 years, hypoxemia). Mortality was significantly different between the arms at 14 days, with 7 deaths (6%) among patients in the high-dose arm and 14 deaths (11%) among patients in the standard-dose arm (adjusted HR 0.33; 95% CI, 0.12–0.86; $P = 0.02$). However, mortality was not significantly different between the arms at 28 days (adjusted HR 0.70; 95% CI, 0.36–1.36; $P = 0.29$).

In an open-label pilot study, 50 hospitalized adults in New York with PCR-confirmed SARS-CoV-2 infection were randomized to receive calcitriol 0.5 µg daily for 14 days or no treatment.[12] Calcitriol is the active metabolite of cholecalciferol or vitamin D_3 and is more commonly used to treat parathyroid disease. The study evaluated the change in oxygen saturation between patient admission and discharge. Additional outcomes were the length of hospital stay; mortality; and the need for endotracheal intubation, ICU admission, or hospital readmission within 30 days. Oxygen saturation was calculated using the ratio of peripheral oxygen saturation (measured by pulse oximetry) to fraction of inspired oxygen (SpO_2/FiO_2) as a surrogate for the ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2). Between admission and discharge, the patients who received no treatment had an average increase of 13.2 (SD 127.7) in the ratio, and those who received calcitriol had an increase of 91.04 (SD 119.08; $P = 0.0305$), implying an improvement in oxygenation.[12] There were no differences between the arms in the length of hospital stay, mortality, or the need for ICU admission or hospital readmission.

References

1. Aranow C. Vitamin D and the immune system. *J Investig Med*. 2011;59(6):881-886. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21527855.

2. Liu X, Baylin A, Levy PD. Vitamin D deficiency and insufficiency among US adults: prevalence, predictors and clinical implications. *Br J Nutr*. 2018;119(8):928-936. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29644951.
3. Forrest KY, Stuhldreher WL. Prevalence and correlates of vitamin D deficiency in US adults. *Nutr Res*. 2011;31(1):48-54. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21310306.
4. Centers for Disease Control and Prevention. People with certain medical conditions. 2023. Available at: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Accessed November 20, 2023.
5. Committee to Review Dietary Reference Intakes for Vitamin D and Calcium, Food and Nutrition Board. *Dietary Reference Intakes for Calcium and Vitamin D*. National Academies Press; 2011. Available at: https://pubmed.ncbi.nlm.nih.gov/21796828.
6. Chiodini I, Gatti D, Soranna D, et al. Vitamin D status and SARS-CoV-2 infection and COVID-19 clinical outcomes. *Front Public Health*. 2021;9:736665. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35004568.
7. Chen J, Mei K, Xie L, et al. Low vitamin D levels do not aggravate COVID-19 risk or death, and vitamin D supplementation does not improve outcomes in hospitalized patients with COVID-19: a meta-analysis and GRADE assessment of cohort studies and RCTs. *Nutr J*. 2021;20(1):89. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34719404.
8. Villasis-Keever MA, López-Alarcón MG, Miranda-Novales G, et al. Efficacy and safety of vitamin D supplementation to prevent COVID-19 in frontline healthcare workers. A randomized clinical trial. *Arch Med Res*. 2022;53(4):423-430. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35487792.
9. Murai IH, Fernandes AL, Sales LP, et al. Effect of a single high dose of vitamin D_3 on hospital length of stay in patients with moderate to severe COVID-19: a randomized clinical trial. *JAMA*. 2021;325(11):1053-1060. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33595634.
10. Mariani J, Antonietti L, Tajer C, et al. High-dose vitamin D versus placebo to prevent complications in COVID-19 patients: multicentre randomized controlled clinical trial. *PLoS One*. 2022;17(5):e0267918. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35622854.
11. Annweiler C, Beaudenon M, Gautier J, et al. High-dose versus standard-dose vitamin D supplementation in older adults with COVID-19 (COVIT-TRIAL): a multicenter, open-label, randomized controlled superiority trial. *PLoS Med*. 2022;19(5):e1003999. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35639792.
12. Elamir YM, Amir H, Lim S, et al. A randomized pilot study using calcitriol in hospitalized COVID-19 patients. *Bone*. 2022;154:116175. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34508882.