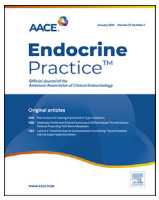
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Endocrine Practice 27 (2021) 1266–1268

Contents lists available at ScienceDirect

Endocrine Practice

journal homepage: www.endocrinepractice.org



Commentary

Vitamin D for COVID-19 on Trial: An Update on Prevention and Therapeutic Application

William B. Grant, PhD [1, *], Ronan Lordan, PhD [2, 3]

[1] Sunlight, Nutrition, and Health Research Center, San Francisco, California
[2] Institute for Translational Medicine and Therapeutics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania
[3] Department of Systems Pharmacology and Translational Therapeutics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

ARTICLE INFO

Article history:
Received 30 September 2021
Received in revised form
6 October 2021
Accepted 6 October 2021
Available online 11 October 2021

The results of a pilot, randomized, placebo-controlled, double-blind clinical trial of calcifediol calcifediol {25-hydroxyvitamin D3 [25(OH)D3]} treatment in 106 COVID-19 patients in Iran are presented in an article in this issue.[1] The primary significant effects of calcifediol treatment were an increase in lymphocyte percentage and a decrease in the ratio of neutrophils to lymphocytes in the patients. In addition, there were modest trends for hospitalization, intensive care unit duration, needing ventilator assistance, and mortality in the calcifediol group compared to the placebo group. This commentary reviews what is known about vitamin D in preventing and treating COVID-19, in order to put the article by Maghbooli et al[1] in perspective.

Calcifediol has an advantage over vitamin D_3 supplementation as it increases serum 25(OH)D concentrations more rapidly, in a matter of hours rather than days. This property is very important for treating COVID-19 because the two main effects of vitamin D regarding COVID-19 are reduced viability and replication of SARS-CoV-2 and reduced risk of a cytokine storm.[2] In fact, calcifediol treatment of COVID-19 patients in the COVIDIOL pilot randomized clinical trial in Spain found a significant reduction in progression to an intensive care unit (odds ratio [OR], 0.02; 95% CI, 0.003-0.25),[3] albeit with some controversy relating to trial design.[4] The primary difference between the two trials was that the first week's calcifediol dose in the Spanish study was 1.064 mg,[3] compared to 0.175 mg in the Iranian study.[1] Calcifediol increases the serum 25(OH)D concentration by a factor of approximately 3-fold than does vitamin D_3. Thus, the weekly dose in the Spanish study was approximately equivalent to 43 000 international units (IU) vitamin D_3, whereas the dose used in the Iranian study was considerably lower and approximately equivalent to 7000 IU vitamin D_3.

The first task for vitamin D in reducing the risk for COVID-19 is to reduce the viability and replication of SARS-CoV-2. This can be done through the induction of antimicrobial peptides, such as cathelicidin and defensins. Their mechanisms include direct binding to virions, binding to and modulating host cell surface receptors, blocking viral replication, and functioning as chemokines to enhance or curb adaptive immune responses.[5]

A retrospective observational analysis of SARS-CoV-2 positivity with respect to serum 25(OH)D concentration measurements in the United States reported that vitamin D is effective at reducing SARS-CoV-2 infection.[6] Those who achieved a serum concentration of 55 ng/mL had about half the SARS-CoV-2 positivity of those with a serum concentration of $\leq$20 ng/mL.

The second task of vitamin D is to reduce the risk of a cytokine storm, which is associated with COVID-19-induced acute respiratory distress syndrome and can lead to severe multiorgan damage. A review outlined the evidence for the possible pathophysiologic mechanism of the cytokine storm in elderly adults with COVID-19, based on the concept of "inflame-aging."[7] The mechanisms include: disrupted immunologic responses in adults with severe COVID-19, an increased concentration of angiotensin-converting enzyme 2 receptors, excess production of reactive oxygen species, decreased autophagy, increased accumulation of senescent cells, and immune senescence. In addition, there can be reduced serum 25(OH)D concentrations, reducing the body's ability to dampen the production of inflammatory cytokines and reduce the immunomodulatory effects that vitamin D may exert.

A number of studies have reported that the risk and severity of COVID-19 are inversely correlated with serum 25(OH)D concentrations. A study was reported involving 464 participants who tested positive for SARS-CoV-2 in two main hospitals in the United Arab Emirates and had blood drawn for serum 25(OH)D assays at

See related Original Article by Maghbooli et al in this issue (https://doi.org/10.1016/j.eprac.2021.09.016).

Abbreviations: IU, international unit; 25(OH)D, 25-hydroxyvitamin D.

* Address correspondence to Dr William B. Grant, Sunlight, Nutrition, and Health Research Center, P.O. Box 641603, San Francisco, CA 94164-1603.
E-mail address: wbgrant@infionline.net (W.B. Grant).

https://doi.org/10.1016/j.eprac.2021.10.001

the first hospital visit.[8] Only serum 25(OH)D concentrations <12 ng/mL were significantly associated with COVID-19 severity (adjusted OR, 1.76; 95% CI, 1.19-2.61; $P = .005$) and mortality (adjusted OR, 2.58; 95% CI, 1.01-6.62; $P = .048$). Moreover, an observational study was conducted in Boston involving 287 COVID-19 patients, 136 of whom were ≥65 years of age and had serum 25(OH)D concentrations measured within 1-year prior to testing positive for SARS-CoV-2.[9] The most important finding was that the risk of death was greatly reduced for those who had their serum 25(OH)D concentrations >30 ng/mL, and a body mass index of <30 kg/m^2 (adjusted OR, 0.18; 95% CI, 0.04-0.84). For those ≥65 years of age, the risk of death, acute respiratory distress syndrome, and severe sepsis/septic shock were significantly reduced. However, many adverse outcomes were not significantly reduced with serum 25(OH)D concentrations >30 ng/mL.

A meta-analysis of 43 observational studies, with a total of 612 601 patients published by January 31, 2021 found that among subjects with vitamin D deficiency (ie, having a serum 25(OH)D concentration <20 ng/mL), the risk for COVID-19 infection was higher compared to those with serum 25(OH)D concentrations >30 ng/mL (OR, 1.26; 95% CI, 1.19-1.34; $P < .01$). Vitamin D deficiency was also associated with increased severity and higher mortality than in nondeficient patients (OR, 2.6; 95% CI, 1.84-3.67; $P < .01$; and OR, 1.22; 95% CI, 1.04-1.43; $P < .01$, respectively].[10]

A therapeutic role for vitamin D amid the COVID-19 pandemic has also been suggested, and a few studies have reported the outcomes of treating COVID-19 patients with vitamin D_3. A recent study investigated the 3-month survival of hospitalized geriatric COVID-19 patients supplemented with vitamin D on a regular basis prior to or during the pandemic. Various bolus doses (ie, 50 000 IU per month; or 80 000 IU, 100 000 IU, or 200 000 IU every 2 to 3 months; or a daily supplementation of 800 IU) were administered.[11] The comparator group did not take vitamin D supplements. It was observed that 76% ($n = 51$) of the participants survived at three months in the intervention group, compared to 54% ($n = 15$) in the comparator group ($P = .03$). The fully-adjusted hazard ratio for 3-month mortality was 0.23 (95% CI, 0.09-0.58; $P = .002$) in the intervention group compared to the comparator group.

Another recent study from Turkey included 207 hospitalized patients with COVID-19 pneumonia.[12] Thirty-seven of the patients with low 25(OH)D concentrations were given a 300 000-IU vitamin D supplement. Those patients taking the supplement had a mean achieved serum 25(OH)D concentration of 51 ± 16 ng/mL, compared to 17 ± 6 ng/mL for those not taking the supplement. The only significant finding was that only 3% of those supplemented with vitamin D died, compared to 14% of those not supplemented ($P = .04$). Other factors that might affect mortality, such as the presence of a comorbidity or the biochemical parameters at admission, were not significantly different between the two groups.

Conflicting results have also been reported. A meta-analysis of 5 studies, including some of those discussed in this manuscript, reported no significant differences in major health outcomes in response to treatment of COVID-19 with vitamin D.[13] However, the one commonality among all these trials was that their dosing regimens, time of administration, and the main primary and secondary outcomes vary, among other differences. Therefore, future trials must consider these factors in their trial designs.

While it seems that sufficient vitamin D status does reduce the risk of susceptibility to SARS-CoV-2 infection and COVID-19, including severity, collectively, vitamin D does not seem to provide full protection. However, its role as an adjuvant in treating those with COVID-19 would likely be beneficial.[14] An extensive review of vitamin D and its potential benefit for the COVID-19 pandemic that appeared in *Endocrine Practice* earlier this year recommends maintaining serum 25(OH)D concentrations >30 ng/mL, preferably between 40 and 60 ng/mL.[15] To achieve these concentrations, an adult would require 4000 to 6000 IU per day of vitamin D. Those who would benefit the most include the elderly and those with existing chronic diseases.

It has been reported that many have sought additional protection via the use of supplements and nutraceuticals to reduce the risk of SARS-CoV-2 and COVID-19. Minerals (selenium and zinc), vitamins (C and E), and ω-3 fatty acids saw increases in sales during the initial waves of the COVID-19 pandemic.[16] These supplements and nutraceuticals have been associated with improved immune support, reduced inflammation, and reduced risk of other viral infections. Consequently, these products are currently under investigation for their prophylactic effects against COVID-19.[16] It would be pertinent to maintain a healthy diet and lifestyle because of the links between nutritional status, immune function, and patient outcomes in order to maintain sufficient levels of key nutrients such as vitamin D.[16]

In terms of the therapeutic application of vitamin D, larger double-blind, randomized controlled trials are required. The study by Maghbooli et al[1] indicates that oral administration of calcifediol does ameliorate vitamin D insufficiency/deficiency, and can alter immune function. However, similar to previous trials investigating the therapeutic potential of calcifediol, this study only reported modest improvements in clinical outcomes. The advantage of using calcifediol over vitamin D_3 is that serum 25(OH)D concentrations are increased in a matter of a few hours rather than a few days. Since many who develop COVID-19 wait a few days before seeking medical treatment, and since the beneficial effects of vitamin D occur early in the COVID-19 trajectory, calcifediol should be preferred. Therefore, the quest continues to determine if vitamin D is of therapeutic value against COVID-19.

Disclosure

W.B.G.'s nonprofit organization, Sunlight, Nutrition and Health Research Center, receives funding from Bio-Tech Pharmacal, Inc. R.L. has no multiplicity of interest to disclose.

References

1. Maghbooli Z, Sahraian MA, Jamalimoghadamsiahkali S, et al. Treatment with 25-hydroxyvitamin D_3 (calcifediol) is associated with a reduction in the blood neutrophil-to-lymphocyte ratio marker of disease severity in hospitalized patients with COVID-19: a pilot multicenter, randomized, placebo-controlled, double-blinded clinical trial. *Endocr Pract*. 2021;27(12):1242–1251.
2. Grant WB, Lahore H, McDonnell SL, et al. Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. *Nutrients*. 2020;12(4):988.
3. Entrenas Castillo M, Entrenas Costa LM, Vaquero Barrios JM, et al. Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: a pilot randomized clinical study. *J Steroid Biochem Mol Biol*. 2020;203:105751.
4. Lordan R. Notable developments for vitamin D amid the COVID-19 pandemic, but caution warranted overall: a narrative review. *Nutrients*. 2021;13(3):740.
5. Ghosh SK, Weinberg A. Ramping up antimicrobial peptides against severe acute respiratory syndrome coronavirus-2. *Front Mol Biosci*. 2021;8:620806.
6. Kaufman HW, Niles JK, Kroll MH, Bi C, Holick MF. SARS-CoV-2 positivity rates associated with circulating 25-hydroxyvitamin D levels. *PLoS One*. 2020;15(9), e0239252.
7. Meftahi GH, Jangravi Z, Sahraei H, Bahari Z. The possible pathophysiology mechanism of cytokine storm in elderly adults with COVID-19 infection: the contribution of "inflame-aging". *Inflamm Res*. 2020;69(9):825–839.
8. AlSafar H, Grant WB, Hijazi R, et al. COVID-19 disease severity and death in relation to vitamin D status among SARS-CoV-2-positive UAE residents. *Nutrients*. 2021;13(5):1714.
9. Charoenngam N, Shirvani A, Reddy N, Vodopivec DM, Apovian CM, Holick MF. Association of vitamin D Status with hospital morbidity and mortality in adult hospitalized patients with COVID-19. *Endocr Pract*. 2021;27(4):271–278.

10. Petrelli F, Luciani A, Perego G, Dognini G, Colombelli PL, Ghidini A. Therapeutic and prognostic role of vitamin D for COVID-19 infection: a systematic review and meta-analysis of 43 observational studies. *J Steroid Biochem Mol Biol*. 2021;211:105883.
11. Annweiler C, Beaudenon M, Simon R, et al. Vitamin D supplementation prior to or during COVID-19 associated with better 3-month survival in geriatric patients: extension phase of the GERIA-COVID study. *J Steroid Biochem Mol Biol*. 2021;213:105958.
12. Yildiz M, Senel MU, Kavurgaci S, Ozturk FE, Ozturk A. The prognostic significance of vitamin D deficiency in patients with COVID-19 pneumonia. *Bratisl Lek Listy*. 2021;122(10):744–747.
13. Rawat D, Roy A, Maitra S, Shankar V, Khanna P, Baidya DK. Vitamin D supplementation and COVID-19 treatment: a systematic review and meta-analysis. *Diabetes Metab Syndr*. 2021;15(4):102189.
14. Bandeira L, Lazaratti-Castro M, Binkley N. Clinical aspects of SARS-CoV-2 infection and vitamin D. *Rev Endocr Metab Disord*. 2021:1–5.
15. Charoenngam N, Shirvani A, Holick MF. Vitamin D and its potential benefit for the COVID-19 pandemic. *Endocr Pract*. 2021;27(5):484–493.
16. Lordan R, Rando HM, Consortium C-R, Greene CS. Dietary supplements and nutraceuticals under investigation for COVID-19 prevention and treatment. *mSystems*. 2021;6(3). e00122-21.