



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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



## Cochrane Corner

## Vitamin D supplementation for the treatment of COVID-19: Summary of a living Cochrane review



L. Susan Wieland

**Stroehlein JK, Wallqvist J, Iannizzi C, Mikolajewska A, Metzendorf MI, Benstoem C, Meybohm P, Becker M, Skoetz N, Stegemann M, Piechotta V. Vitamin D supplementation for the treatment of COVID-19: a living systematic review. *Cochrane Database of Systematic Reviews* 2021, Issue 5. Art. No.: CD015043. DOI: 10.1002/14651858. CD015043**

During the COVID-19 pandemic, several studies have observed an association between vitamin D deficiency, defined as blood levels of 25(OH)D below 20 ng/ml, and increased risk of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) positivity, severe COVID-19 disease (including ICU admission and both invasive and non-invasive ventilation), and COVID-19 mortality.<sup>1</sup> These observational studies are likely confounded by the presence of overlapping risk factors for vitamin D deficiency and risk factors for severe COVID-19 disease, such as age and certain underlying medical conditions. However, the observed associations have suggested that vitamin D supplementation, particularly in people with vitamin D deficiency, may have a role in preventing or treating COVID-19.<sup>2</sup>

Since the beginning of the COVID-19 pandemic, Cochrane has produced several systematic reviews on COVID-19, including special collections of evidence on infection control and prevention and on critical care. A Cochrane review on the effects of vitamin D in the treatment of COVID-19 has now been conducted in order to find, critically appraise, and summarize the most recent randomized trial evidence on vitamin D as a treatment for COVID-19.<sup>3</sup> This summary presents the results of that review.

The authors of the Cochrane review classified the randomized controlled trials on vitamin D into two groups based on the severity of participant COVID-19 disease, as defined by a clinical progression scale developed by the World Health Organization.<sup>4</sup> The first group was trials conducted in participants with a confirmed diagnosis of

COVID-19 (e.g., infection with SARS-CoV-2) and asymptomatic or mild disease. For this group, the outcomes of interest included all-cause mortality, development of moderate to severe COVID-19, admission to hospital, duration of hospitalization, quality of life, vitamin D serum levels, and adverse events. The second group was trials conducted in participants with a confirmed diagnosis of COVID-19 and hospitalized with moderate or severe disease. For this group, the outcomes of interest included all-cause mortality, clinical status, need for dialysis, quality of life, viral clearance, vitamin D serum levels, and adverse events. The authors also planned to carry out subgroup analyses by baseline participant vitamin D status and vitamin D dose, administration, and formulation.

The review authors found one trial of vitamin D conducted in participants with asymptomatic or mild COVID-19.<sup>5</sup> The placebo-controlled trial was conducted in India in participants (n = 40) with serum levels of vitamin D  $\leq$  20 ng/mL at baseline. The participants randomized to vitamin D received 60,000 IU of cholecalciferol daily for seven days followed by additional daily and then weekly supplementation, depending on the vitamin D serum levels achieved. The trialists reported that serum vitamin D levels increased in participants treated with vitamin D and not in participants treated with placebo. However, none of the other outcomes of interest for the review were reported. Based on the information from this single small trial, the review authors were unable to reach conclusions on the potential benefits or harms of vitamin D as a treatment for asymptomatic or mild COVID-19.

The review authors found two trials of vitamin D conducted in participants hospitalized with moderate or severe COVID-19.<sup>6,7</sup> One trial was an open-label trial conducted in Spain in participants (n = 76) with clinical acute respiratory infection confirmed by viral pneumonia on x-ray and a positive SARS-CoV-2 test. The trialists did not provide information on participant vitamin D status at baseline. The participants randomized to vitamin D received calcifediol 0.532 mg orally on day one, followed by 0.266 mg on days three and seven, and then 0.266 weekly until discharge or ICU admission. Study participants also received a combination of hydroxychloroquine and azithromycin, together with a broad-spectrum antibiotic if needed. The second trial was a multi-center placebo-controlled trial conducted in Brazil in participants (n = 240) with moderate to severe COVID-19 as defined by a positive SARS-CoV-2 test or compatible CT findings, together with a diagnosis of flu syndrome meeting criteria for hospitalization, a respiratory rate greater than 24 breaths/minute, blood oxygen levels less than 93%, or risk factors (e.g. diabetes) for COVID-19 complications. Some participants had low vitamin D status

*This article is based on a Cochrane Review previously published in the Cochrane Database of Systematic Reviews 2021, Issue 5. Art. No.: CD015043. DOI: 10.1002/14651858. CD015043 (see [www.cochranelibrary.com](http://www.cochranelibrary.com) for information). Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and Cochrane Database of Systematic Reviews should be consulted for the most recent version of the review. The views expressed in this summary are those of the summary author(s) and in no way represent the Cochrane Library or Wiley. The Cochrane Complementary Medicine Field, which coordinates this column, is a group within Cochrane that is dedicated to facilitating the production and dissemination of Cochrane systematic reviews focused on complementary, alternative, and integrative medicine interventions. The Field is supported by the National Center for Complementary & Integrative Health of the National Institutes of Health under award number R24AT001293. For additional information on Cochrane and the Cochrane Complementary Medicine Field please contact L. Susan Wieland, PhD at [swieland@som.umaryland.com](mailto:swieland@som.umaryland.com).*

E-mail address: [swieland@som.umaryland.com](mailto:swieland@som.umaryland.com)

at baseline but others did not; the mean serum vitamin D level was approximately 21 ng/mL overall. The participants randomized to vitamin D received a single oral dose of 200,000 IU cholecalciferol. All participants also received standard care, including corticosteroid therapy for the majority of patients.

The review authors considered the two trials in hospitalized COVID-19 patients to be so different in vitamin D formulations and intervention strategies that they were not appropriate to combine statistically (meta-analysis), even in the presence of similar outcomes. For example, both trials reported information on all-cause mortality. One trial found that mortality was higher in participants in the control group while the other trial found that mortality was higher in participants in the vitamin D group. In both cases the confidence intervals were very wide and overall the findings were based on a total of only 313 participants and 17 deaths. Because of the inconsistency between studies, the limited amount of information, and some possible problems with conduct of one of the studies, the review authors concluded that the evidence on all-cause mortality was very uncertain. Data from one of the trials provided information for a subgroup analysis of all-cause mortality by participant vitamin D status at baseline, but the difference between deficient and non-deficient groups was inconclusive due to the limited amount of available information (a single study with 15 events). Other outcomes of interest for the review were also either unavailable from the studies or the quality and quantity of information was insufficient to make firm conclusions.

The overall findings from this review were that there is currently insufficient information to guide the use of vitamin D as a treatment for COVID-19, and that more information is urgently needed. The review authors identified more than 20 randomized controlled trials on vitamin D for COVID-19 that were either not yet published or were still in progress. The review authors have stated that they will conduct weekly searches for additional trial evidence and incorporate relevant evidence into the review on an ongoing basis, following the Cochrane guidance for what is called a 'living systematic review'.<sup>8</sup> The review will continue to be updated continuously, and a revised

version will be published as soon as the conclusions of the review are changed in a manner that may inform implications for research or clinical practice. Given the number of ongoing studies and the commitment of the review authors to continuously update the identification, appraisal and incorporation of this evidence, the hope is that an updated review may soon provide information allowing more insight into the effectiveness and safety of vitamin D for the treatment of COVID-19.

## References

1. Bassatne A, Basbous M, Chakhtoura M, El Zein O, Rahme M, El-Hajj Fuleihan G. The link between COVID-19 and Vitamin D (VIVID): a systematic review and meta-analysis. *Metabolism*. 2021;119: 154753.
2. Grant WB, Lahore H, McDonnell SL, Baggerly CA, French CB, Aliano JL, et al. Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. *Nutrients*. 2020;12(4).
3. Stroehlein JK, Wallqvist J, Iannizzi C, Mikolajewska A, Metzendorf MI, Benstoem C, et al. Vitamin D supplementation for the treatment of COVID-19: a living systematic review. *Cochrane Database Syst Rev*. 2021;5: CD015043.
4. WHO GotC Characterisation. Management of C-i. A minimal common outcome measure set for COVID-19 clinical research. *Lancet Infect Dis*. 2020;20(8):e192–e1e7.
5. Rastogi A, Bhansali A, Khare N, Suri V, Yaddanapudi N, Sachdeva N, et al. Short term, high-dose vitamin D supplementation for COVID-19 disease: a randomised, placebo-controlled, study (SHADE study). *Postgrad Med J*. 2020.
6. Entrenas Castillo M, Entrenas Costa LM, Vaquero Barrios JM, Alcalá Diaz JF, López Miranda J, Bouillon R, 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.
7. Murai IH, Fernandes AL, Sales LP, Pinto AJ, Goessler KF, Duran CSC, et al. Effect of a Single High Dose of Vitamin D3 on Hospital Length of Stay in Patients With Moderate to Severe COVID-19: A Randomized Clinical Trial. *JAMA*. 2021;325(11):1053–1060.
8. Guidance for the production and publication of Cochrane living systematic reviews: Cochrane Reviews in living mode. Available from <https://community.cochrane.org/review-production/production-resources/living-systematic-reviews> (accessed 4 June 2021).

**L. Susan Wieland, PhD** is a Director of the Cochrane Complementary Medicine Field and an Assistant Professor of Family & Community Medicine and Epidemiology at the University of Maryland School of Medicine in Baltimore, MD.