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

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Since the beginning of 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. 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.

The review authors found one trial of vitamin D conducted in participants with asymptomatic or mild COVID-19. The placebo-controlled trial was conducted in India in participants (n = 40) with serum levels of vitamin D ≤ 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. 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.
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’. 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.

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