

Could Vitamin D Play a Role in Preventing and Treating COVID-19?

Since the first cases were reported late last year, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), or COVID-19, has infected over 42 million people and resulted in over 1 million deaths worldwide¹. This single virus has given rise to previously unimaginable and wide-reaching economic and social change. COVID-19 positive cases range from clinically asymptomatic to those who progress to severe respiratory failure, multi-organ dysfunction and death². Once inside the host's cells, this virus is capable of inducing the release of unprecedented levels of pro-inflammatory cytokines³, leading to the so-called cytokine storm, which is thought to be responsible for respiratory and organ distress in severe cases of COVID-19². Research on the pathophysiology, treatment and prevention of COVID-19 continues to intensify. In the midst of this, it has been hypothesized that vitamin D ameliorates the cytokine storm⁴, and therefore could play protective and therapeutic roles in tackling the COVID-19 pandemic. Some have even proposed that a large dose of vitamin D should be part of our strategy to overcome this virus⁵.

Far from simply being a vitamin that is important for bone health, we now recognize that vitamin D is a key player in immune function⁶ and viral infections are more effectively controlled when vitamin D status is optimal³. Some data indicates that vitamin D status is associated with acute respiratory tract infections. For instance, death from respiratory disease was highest among vitamin D deficient participants in a community-based cohort study (n=9,548; 15-year follow-up period) in Germany⁷. Moreover, suboptimal vitamin D status is not solely a public health issue in temperate countries. It is in fact a global problem that prevails in sub-tropical and tropical countries which receive ample sunshine⁸. There are a limited number of dietary sources of vitamin D, and solar UVB-induced skin synthesis of vitamin D is reduced by biological factors (e.g. aging, more melanin in the skin i.e. darker skin type), behavioral factors (e.g. sun screen use, sun avoidance, extensive clothing), geographical factors (e.g. >35° N/S latitude) and environmental factors (e.g. air pollutants)⁸. Consequently, there has been growing interest in vitamin D status in relation to COVID-19 infection. Several studies have been published this year, in a quest to confirm or disprove the hypothesis that vitamin D is implicated in reducing an individual's susceptibility to this virus and lessening the severity of infection⁹⁻¹⁴.

A secondary data analysis, which represented 20 European countries, showed that higher vitamin D status correlated with a lower number of COVID-19 cases, but vitamin D status was not significantly correlated with COVID-19-related deaths⁹. Adults who had been diagnosed as vitamin D deficient up to 1 year prior to COVID-19 testing were more likely to test positive (relative risk = 1.77; 95% CI: 1.12-2.81; $p = 0.02$) based on the findings of a small ($n=489$) retrospective cohort study conducted in the USA¹⁰. In support of this, a much larger retrospective analysis ($n=191,779$) in the USA found that a higher plasma vitamin D concentration, measured within the past 12 months, was associated with a lower rate of COVID-19 positivity (adjusted odds ratio = 0.984; 95% CI: 0.983–0.986; $p<0.001$)¹¹.

On the contrary, both a retrospective analysis and a prospective study concluded that vitamin D status was not associated with COVID-19 infection^{12,13}. The first of these utilized COVID-19 test data from Public Health England for $n=1,474$ adults, together with data on their plasma vitamin D concentration, socio-economic status and health status which were obtained from the UK Biobank¹². After adjustment for confounding factors, vitamin D was not associated with COVID-19 infection (odds ratio = 1.00; 95% CI: 0.998-1.01; $p=0.208$), although it should be noted that the data for vitamin D and the covariates dated from 2006-2010. Second, the prospective study involved 109 adult inpatients and outpatients from several care centers in Austria¹³. Suboptimal vitamin D concentration at the time of receiving a positive COVID-19 result and 8 weeks after receiving the positive outcome were not associated with the symptoms or complications of the viral infection.

Most of the aforementioned observational studies used retrospectively-collected data for the exposure variable (plasma vitamin D concentration). Furthermore, all analytical observational studies are limited by unknown or unmeasured confounding factors that can easily influence the exposure and outcome variables of interest. Whether or not changes in one variable affect changes in another variable is best studied using experimental designs.

Published experimental studies of the effect of vitamin D on COVID-19 outcomes are scarce. So far, one randomized hospital-based trial in Spain has shown promising results¹⁴. Of the 50 patients who received standard care plus oral vitamin D in the form of calcifediol (0.532 mg: at the time of admission to hospital (day 0), day 3, day 7, and once weekly up to leaving hospital) and 26 patients who were given standard care alone, 1 (2%) from the former group and 13 (50%) from the latter group required intensive care. After adjustment for hypertension and type 2 diabetes mellitus, the odds ratio for admission to the intensive

care unit (ICU) in the supplementation group versus the no supplementation group was 0.03 (95% CI: 0.003-0.25), showing that the vitamin D supplemented patients were significantly less likely to be admitted to ICU. There were no deaths in the group treated with vitamin D in addition to standard care, in contrast with two deaths in the group who only received standard care. The lack of statistical adjustment for body mass index (another predictor of COVID-19 outcome) was one limitation of this study. Nevertheless, its findings justify carrying out further experimental trials of the effect of vitamin D supplementation on disease outcome in individuals with COVID-19. At the time of writing, a total of 44 recently registered experimental studies of vitamin D in COVID-19 infection were listed on the NIH Clinical Trials Database, 18 of which are now actively recruiting participants¹⁵. The settings for these trials are in North America, South America, Europe, Asia and Australia¹⁶. The findings of these and other trials will provide us with much needed data as the search continues for the most effective prevention and treatment protocols.

Although vitamin D *could* plausibly facilitate the prevention and treatment of COVID-19, to date, there is insufficient evidence to confirm this theory. It is worth noting that vitamin D sufficient individuals may be generally healthier due to overall healthier diets and lifestyles. It is also likely that other nutrients are equally as important as vitamin D in regulating immune response, as others have suggested^{17,18}. Therefore, at the current time, it would be unwise to promote the use of vitamin D supplements as a magic bullet for the prevention of this virus. Likewise, we should be cautious about administering large doses of vitamin D as an adjunct treatment for COVID-19 in the absence of data from more clinical trials. That being said, it is advisable for individuals, both young and old, to aim for a vitamin D status that meets the proposed sufficiency level (plasma vitamin D ≥ 30 ng/dl or ≥ 75 nmol/l)⁸, in order to promote good general health. This should be achieved primarily by consuming a healthy varied diet that includes sources of vitamin D, such as oily fish, meats, egg yolk, mushrooms that have been exposed to UVB radiation or are sun-dried, and vitamin D fortified dietary items, in addition to getting some exposure to sunlight whilst adhering to safe-exposure guidelines. Additionally, some countries in temperate regions recommend the use of low-dose supplemental vitamin D at specific life stages or during seasons in which the level of UVB radiation is low. At present, we must improve food security in order to guarantee that populations have access to affordable nutritious food, whilst further research is being conducted. We must not lose sight of the importance of a healthy lifestyle, which

includes consumption of a varied diet in line with a country's national guidelines. Meeting our recommended nutrient intakes and other lifestyle recommendations collectively strengthens our infection-control armory. This should be our current prevention advice, in conjunction with encouraging compliance with measures that aim to prevent the transmission of COVID-19.

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