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Can vitamin D protect against covid-19?

Two new trials find no effect, but aren't the final word

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Vitamin D is an important regulator of calcium balance. In addition, it has important effects on the immune system, directly inducing antimicrobial peptides at mucosal surfaces and modulating the function of T cells.^{1,2} Observational studies from the pre-pandemic era found an association between low levels of vitamin D and an increased risk of respiratory tract infections.³ Results from randomised controlled trials were mixed, but two large meta-analyses found some evidence of a protective effect of vitamin D supplementation against respiratory tract infections, particularly in vitamin D deficient individuals.^{4,5} Could vitamin D help protect against covid-19?

At a mechanistic level, vitamin D boosts antiviral defences against other respiratory viruses, such as influenza A virus and rhinovirus.^{6,7} Data from observational studies suggest that low levels of 25-hydroxyvitamin D (25(OH)D) may be a risk factor for severe covid-19.⁸ However, this association could be due to reverse causality or confounding^{9,10}: both covid-19 and vitamin D deficiency are independently associated with obesity, old age (>65 years), and male sex, for example. Two linked new randomised studies add much needed evidence to this important question.

The first study (doi:10.1136/bmj-2022-071230) was conducted in the United Kingdom between May and October 2021.¹¹ Jolliffe and colleagues randomised 3100 participants to a vitamin D test and either 3200 IU/day or 800 IU/day of vitamin D₃ for six months if their blood 25-hydroxyvitamin D concentrations were <75 nmol/L. A further 3100 controls received no test and no supplementation. The authors found that neither of the vitamin D doses had any effect on incidence of covid-19. This trial had several strengths: a high prevalence (64.6%) of participants with inadequate 25-hydroxyvitamin D levels (<50 nmol/L), good adherence to the protocol, and a rigorous endpoint with polymerase chain reaction confirmed covid-19.

However, several important caveats need to be acknowledged. Firstly, vaccination against covid-19 was being rolled out during the study. At baseline, only 1.2% of participants had been vaccinated, although by the end of the study 89.1% (5523/6200) had received at least one dose. It is possible that vaccination masked any effect of vitamin D. Notably, in the unvaccinated group, covid-19 was less frequent among participants taking 3200 IU/day compared with the control group with no supplementation (0/68 (0.0%) v 9/191 (4.7%)), but the difference was not statistically significant. Secondly, the study drug was provided open label, so participants' awareness of taking an active drug could have influenced health

seeking behaviour and thereby the results. Finally, almost 50% of control participants took vitamin D supplements during the study period, which could have diluted any effects of vitamin D.

The other trial was conducted in Norway between November 2020 and June 2021, using cod liver oil as a surrogate for low dose (400 IU/day) vitamin D supplementation.¹² Brunvoll and colleagues (doi:10.1136/bmj-2022-071245) randomised 34 741 participants to either 5 mL cod liver oil or 5 mL placebo oil daily for six months. Again, the authors found no effect of cod liver oil on any outcome, including polymerase chain reaction confirmed covid-19.

A large sample size and masked placebo controlled design were this trial's key strengths. One limitation was that only 35% of participants were vaccinated during the study, although a stratified analysis found no effect in the unvaccinated group. In addition, participants were relatively young and healthy, and 86.3% had adequate vitamin D levels (>50 nmol/L) at baseline. Most participants were women (65%), most had normal body mass index (mean 26.1), and the mean age was 44.9 years. Finally, cod liver oil also contains a substantial amount of vitamin A, which is a potent immunomodulator.¹³ Excessive intake of vitamin A can cause adverse effects and may also interfere with vitamin D mediated effects on the immune system.¹⁴⁻¹⁶

Both research teams should be commended for having completed large and well designed clinical trials during the covid-19 pandemic with its unforeseen logistical challenges. However, the null findings of the studies should be interpreted in the context of a highly effective vaccine rolled out during both studies.

Vaccination is still the most effective way to protect people from covid-19, and vitamin D and cod liver oil supplementation should not be offered to healthy people with normal vitamin D levels. Importantly, these new trials remain compatible with the two large meta-analyses suggesting that vitamin D supplementation may be beneficial for vitamin D deficient individuals.^{4,5} A pragmatic approach for the clinician could be to focus on risk groups; those who could be tested before supplementation, including people with dark skin, or skin that is rarely exposed to the sun; pregnant women; and elderly people with chronic diseases. For those with inadequate vitamin D levels (<50 nmol/L), supplementation with 1000-2000 IU/day could be a safe, simple, and affordable way to restore vitamin D levels, improve bone health, and take advantage of any possible protective effect against respiratory tract infections.

The BMJ has judged that there are no disqualifying financial ties to commercial companies.

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