



# Vitamin D for COVID-19: where are we now?

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Vitamin D has received much interest during the COVID-19 pandemic as a potential prophylactic or therapeutic agent — but do the available data support its use?

Early in the COVID-19 pandemic, a lack of vaccines and therapies prompted interest in a potential role for vitamin D in reducing risk or severity of disease. This was based on the recognized effects of vitamin D on host responses to other respiratory viruses, and evidence from randomized controlled trials (RCTs) showing the efficacy of vitamin D supplementation for the prevention of other acute respiratory infections. Since then, effective drugs and vaccines have been developed for COVID-19, with major effects on mortality. Numerous reports associating low vitamin D status with adverse outcomes in COVID-19 have also emerged, together with results of some RCTs. Here, we briefly review the accumulated evidence in this field.

Vitamin D belongs to a group of fat-soluble vitamins with vitamin D<sub>3</sub> being the major form in humans. The primary source is via cutaneous synthesis in response to sunlight, but it can also be ingested in the diet. The active vitamin D metabolite, 1,25-dihydroxyvitamin D (1,25(OH)<sub>2</sub>D), induces innate antiviral effector mechanisms and regulates inflammation in response to infection with rhinovirus, respiratory syncytial virus and influenza viruses (FIG. 1). The relevance of these actions for the host response to SARS-CoV-2 is supported by two lines of evidence. First, the vitamin D-inducible antimicrobial peptide cathelicidin LL-37 has been shown to inhibit SARS-CoV-2 attachment to host cells by blocking both the receptor-binding domain of the S1 subunit of the viral spike protein and the ligand-binding domain of the host-expressed viral entry receptor ACE2 (REF.<sup>1</sup>). Second, a study in transgenic mice expressing human ACE2 has shown that SARS-CoV-2 induces the expression of *CYP27B1*, which encodes the 1 $\alpha$ -hydroxylase enzyme that catalyses the conversion of the major circulating metabolite 25-hydroxyvitamin D (25(OH)D) to 1,25(OH)<sub>2</sub>D (REF.<sup>2</sup>). Prophylactic administration of high-dose vitamin D<sub>3</sub> increased the expression of *IFNB* and reduced inflammation in the lungs after SARS-CoV-2 infection, although this was not associated with a survival benefit<sup>2</sup>. The relevance of these findings for human disease is supported by the observation that CD4<sup>+</sup> T cells in the bronchoalveolar lavage fluid of patients with COVID-19 exhibit increased expression of vitamin D-repressible genes that encode pro-inflammatory cytokines<sup>3</sup>. However, a case

study of COVID-19 arising in a family lacking functioning vitamin D receptor reported a mild disease course and normal development of antigen-specific cellular and humoral immune responses to SARS-CoV-2 (REF.<sup>4</sup>). This suggests that vitamin D-mediated signalling may have a role in regulating SARS-CoV-2-induced inflammation, but it may not be a pre-requisite for averting severe outcomes or mounting adaptive immune responses to this pathogen.

Observational studies have associated low circulating 25(OH)D concentrations with increased severity of COVID-19 (REF.<sup>5</sup>). In cross-sectional and case-control studies, in which vitamin D status and clinical outcomes are assessed contemporaneously, such associations may be explained by reverse causality, as SARS-CoV-2 induces the expression of *CYP24A1* (REF.<sup>3</sup>), which results in 25(OH)D catabolism (FIG. 1). Prospective studies circumvent this problem by measuring vitamin D status before outcomes, but they are still potentially open to confounding by factors associated with both low circulating 25(OH)D concentrations and increased COVID-19 severity. Mendelian randomization studies are less open to the effects of reverse causation and confounding, and these have consistently reported no associations between genetically predicted 25(OH)D concentrations and COVID-19 susceptibility or severity<sup>6</sup>. Ultimately, however, RCTs are needed to determine whether vitamin D supplements may have a role in the treatment or prevention of COVID-19.

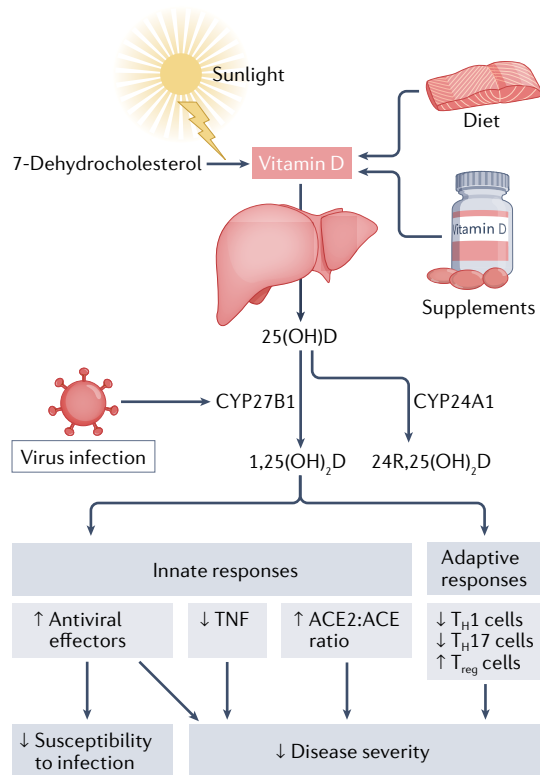
So far, 11 RCTs investigating the therapeutic effects of vitamin D in COVID-19 have reported. They are diverse with respect to study design (5 are placebo-controlled, 6 are open-label or single-blind), sample size (ranging from 30 to 543 participants), the nature of the intervention (8 investigate vitamin D<sub>3</sub>, 2 investigate 25(OH)D<sub>3</sub> and 1 investigates 1,25(OH)<sub>2</sub>D<sub>3</sub>) and primary outcomes (mortality, duration of hospital stay, intensive care requirement, resolution of symptoms and viral clearance). Their findings are also heterogeneous: seven trials report null results, whereas four report favourable effects of the intervention on a primary or co-primary outcome. The most striking positive result comes from an open-label RCT of oral 25(OH)D<sub>3</sub> administration conducted in 76 adults hospitalized with COVID-19 in Spain: this trial reported that just 2% of participants randomized to intervention were

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**Fig. 1 | Vitamin D in viral infection.** Vitamin D from cutaneous synthesis or oral intake is converted in the liver to 25-hydroxyvitamin D (25(OH)D), the major circulating vitamin D metabolite. In pulmonary epithelium and in leukocytes, respiratory viruses induce the expression of the 25(OH)D hydroxylase CYP27B1, which converts 25(OH)D to the active vitamin D metabolite 1,25-dihydroxyvitamin D (1,25(OH)<sub>2</sub>D). This supports antiviral effector mechanisms and regulates inflammation by reducing TNF expression, increasing the ACE2:ACE ratio, inhibiting the development of T<sub>H</sub>1 and T<sub>H</sub>17 cells, and promoting the development of T<sub>reg</sub> cells. These anti-inflammatory actions may reduce disease severity associated with cytokine storms. CYP24A1 can catabolize 25(OH)D to the relatively inactive metabolite 24R,25-dihydroxyvitamin D (24R,25(OH)<sub>2</sub>D).

admitted to intensive care, as compared with 50% of those randomized to control<sup>7</sup>. However, this study is at high risk of bias, owing to imbalance in baseline characteristics and its open-label design, as knowledge of allocation could have influenced physicians' decision to admit participants to intensive care. Moreover, background therapy (azithromycin and hydroxychloroquine) was unconventional, compromising the generalizability of results to patients receiving current standards of care. Other well-conducted RCTs (such as REF.<sup>8</sup>) have not demonstrated sustained or consistent benefits of vitamin D on mortality, intensive care requirement or duration of hospital stay.

Two RCTs investigating prophylactic vitamin D have also reported contrasting results. A phase 2 placebo-controlled RCT in 321 healthcare workers in Mexico, conducted before roll-out of SARS-CoV-2 vaccination, reported a strong protective effect of daily oral administration of 4,000 IU vitamin D<sub>3</sub> for one month against incident SARS-CoV-2 infection<sup>9</sup>. This finding surprised many, given that the duration of the intervention

(1 month) was insufficient for participants in the intervention arm to experience a large increase in circulating 25(OH)D concentrations. By contrast, an open-label phase 3 RCT in the UK involving 6,200 adults and conducted during the SARS-CoV-2 vaccine roll-out showed no effect of implementing a test-and-treat approach to the correction of sub-optimal vitamin D status via daily oral administration of either 800 or 3,200 IU vitamin D<sub>3</sub> over 6 months<sup>10</sup>. The interpretation of this result is complicated by the pragmatic nature of this trial, which allowed for the consumption of vitamin D supplements among participants randomized to its control arm; however, a sensitivity analysis excluding data from control arm participants who took off-trial supplements also yielded a null finding. Results from placebo-controlled phase 3 trials of prophylactic vitamin D and cod liver oil (ClinicalTrials.gov: [NCT04609423](https://clinicaltrials.gov/ct2/show/study/NCT04609423), [NCT04483635](https://clinicaltrials.gov/ct2/show/study/NCT04483635) and [NCT04536298](https://clinicaltrials.gov/ct2/show/study/NCT04536298)) are pending, and these should clarify whether prophylactic administration of vitamin D supplements can influence the risk or severity of COVID-19. However, the lack of a consistent protective signal from RCTs reporting so far is reflected by the absence of any recommendation relating to prophylactic or therapeutic use of vitamin D for COVID-19 in guidelines from national or international bodies.

If vitamin D does have favourable immunomodulatory effects in COVID-19, then demonstrating a meaningful clinical benefit of supplementation over existing standards of care is likely to become increasingly challenging, as ever more effective pharmacological therapies and vaccines emerge.

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#### Competing interests

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