

The link between vitamin D and COVID-19: distinguishing facts from fiction

Vitamin D is produced in the skin under the influence of UVB light from the sun or obtained via the diet by eating fatty fish, enriched dairy products or supplements. Vitamin D is known to support a healthy bone, and severe deficiency may lead to osteomalacia or rickets, which still occur in poor areas of the world. In addition, vitamin D supports key functions in many organs, including the brain, muscle and the immune systems [1]. In fact, the vitamin D receptor (VDR) is expressed in most cell types and may activate somewhere between 200 and 500 genes, many related to the immune system. Thus, the role of vitamin D in human immunity has been studied intensely during the past 20 years [2]. For example, it has been hypothesized that vitamin D supplementation may prevent acute respiratory infections (ARIs), which is based on the fact that these infections are much more common during the winter, which coincides with lower vitamin D levels in the population [3]. Moreover, experimental evidence showed that vitamin D can activate antimicrobial peptides, which are secreted at mucosal surfaces and have the capacity to kill bacteria and viruses [2]. These observations spurred several randomized controlled trials (RCTs) testing the hypothesis. The results from these trials were not conclusive, with some showing beneficial effects and some not [4, 5]. However, a large individual patient data meta-analysis compiled individual data for almost 11 000 patients from 25 RCTs [6]. A general preventive effect of vitamin D supplementation against ARI was observed. The effect was greater in those with vitamin D deficiency ($<25 \text{ nmol L}^{-1}$) and if the supplement was given daily or weekly but not if given as large bolus doses.

A recent narrative review explains the rationale for further studies of vitamin D and COVID-19

Given previous data supporting that vitamin D could prevent ARI, it was natural to ask the question of whether vitamin D could prevent COVID-19. This was addressed in a narrative

review by Rhodes et al, published in JIM [7]. The authors first present a clear link between vitamin D levels and COVID-19 by comparing the mortality of COVID-19 in relation to the latitude of different countries. They observed a 4.4% increase in mortality for each degree latitude north of 28° , a link that remained after adjustment for age. This observation suggests that UV light, and thus indirectly vitamin D, may be involved in the protection against COVID-19. However, it should be noted that UV light also has a number of vitamin D-independent effects on immunity, such as suppression of T-cell activation in the skin, which may explain this observation [8]. In addition, the link between UV exposure and COVID-19 mortality on a nation-wide level is complex and may be severely hampered by inherent bias.

Further, they point out the fact that factors associated with death from COVID-19 (old age, ethnicity, male sex, obesity, diabetes, hypertension) overlap with risk for vitamin D deficiency. Although this is striking and something that deserves further studies, it may be fully explained by the 'healthy user effect', that is, that healthier people simply spend more time outdoor and eat healthier, compared to less healthy individuals, thereby explaining this overlap.

Rhodes et al also refer to the fact that vitamin D deficiency is a general risk factor for ARI and that supplementation may prevent ARI. This is clearly shown in associative studies but also in some interventional randomized and placebo-controlled trials as well as in one large individual patient data meta-analysis [6]. Notably, some recent associative data on the link between vitamin D and COVID-19 is presented in this narrative review. One questionnaire-based study of Italian patients ($n = 1486$) with Parkinson's disease reported that those taking vitamin D supplements were less likely to have COVID-19 [9]. Another small Italian study ($n = 107$) reported that serum levels of vitamin D were lower in patients who were PCR-positive for

SARS-CoV-2 [10]. A third study from the United States is mentioned ($n = 4314$) where low vitamin D levels increased the risk to test positive for COVID-19 [11]. However, this study is published at a preprint server and therefore not properly peer-reviewed, which is a common problem in these pandemic days where quick publication is of paramount importance. There are also studies – also published as preprint publications – that failed to find a link between low vitamin D levels and increased risk of COVID-19 infections (medRxiv 2020.04.29.20084277; medRxiv 2020.06.01.20118943). Importantly, there are no data from interventional trials showing that vitamin D supplementation may prevent COVID-19, although such trials are underway.

Finally, Rhodes et al present arguments that vitamin D increases the ratio of ACE2 to ACE, which potentially may protect against Covid-19. Again, this is an interesting hypothesis but only shown in experimental settings so far and thus lacking clinical validation.

What are the implications for the vitamin D research field?

To conclude, there is a strong rationale to study whether vitamin D may prevent COVID-19, given previous publications in the field. Future studies should involve experimental models to assess whether vitamin D can impair viral replication, block proinflammatory cytokines or have other effects related to SARS-CoV-2 pathogenesis. Here, it is crucial to select the best model system where vitamin D-responsive host factors are active. For example, the virus grows well in VeroE6 cells, but these cells are of primate origin and may not represent the best model. The virus is significantly more difficult to grow in human cells, but it is possible [12]. Further, large epidemiological studies can be employed to assess whether vitamin D levels correlate with the risk to get infected by the virus and also whether vitamin D levels are associated with the severity of disease. Importantly, blood levels should not be too old, but rather obtained within a 6-month period prior to disease onset to give a meaningful estimate of the impact of disease by vitamin D levels. Finally, and most important, is to perform randomized and placebo-controlled trials to test the hypothesis whether vitamin D can prevent COVID-19. Special consideration should be given to the inclusion criteria, where only those deficient in vitamin D should be included, to maximize the potential

effect. Also, a daily dosing schedule may be superior to weekly or monthly dosing, as judged by previous data [6, 13].

How should the clinician deal with this information about vitamin D and COVID-19?

It is not easy to fully understand the complex mechanistic underpinnings of vitamin D-mediated effects on immunity and translate this into the clinical practice. A simple rule of thumb could be the following: 1. Vitamin D is safe. Recently, results from a large meta-analysis failed to find any evidence that vitamin D caused adverse events in previously healthy people [6]. Doses up to 10 000 IU per day are safe, although well above what is needed. In fact, only 1000–2000 IU may be needed to obtain optimal effects on bone and immunity. Nevertheless, special attention should be paid in patients with certain rare diseases, such as tuberculosis and sarcoidosis, where ectopic activation of vitamin D may lead to hypercalcemia. 2. 1000–2000 IU per day is enough to keep the immune system healthy. No mega-doses are needed and may only lead to increased risk for adverse events. Small and daily doses are enough to boost immunity. 3. If possible, test your patients for 25OHD levels in serum and provide only supplements to those below 50 nmol L^{-1} . This will protect the bone and be enough to enhance respiratory immunity against ARI. By adopting this limit, you will only supplement individuals that need extra vitamin D, avoid unnecessary costs and follow available guidelines for bone health. 4. Be aware that the beneficial effect is small and may take some time (months) to develop. However, given the common problem with ARI and especially now in the corona epidemic, a small vitamin D supplement may be beneficial, and definitely not harmful. Risk groups (dark skin, the elderly, patients with chronic diseases and obese patients, to mention a few) should have first priority for supplementation.

Finally, the field of vitamin D and COVID-19 is very active and several trials are underway. Thus, new data will come, which may change these conclusions. However, in the meantime the conclusions above can be followed and we have massive data to say that vitamin D at low doses (1000–2000 IU per day) is safe and not harmful, which is in line with the historical proverb: *primum non nocere* (first, do no harm) – but potentially we may prevent a number of ARIs and perhaps also COVID-19.

Conflict of interest

No conflicts of interest to declare.

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