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Vitamin-D and COVID-19: do deficient risk a poorer outcome?

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For the **2017 meta-analysis on vitamin D supplementation and respiratory infections** see *BMJ* 2017; **356:** i6583

For the **cross-sectional analysis of COVID-19 mortality and vitamin D deficiency** see *Ir Med J* 2020; **113:** 81

For the **UK report on mortality and COVID-19 in ethnic minorities** see https://tinyurl.com/onscovid19bame

For **COVIDENCE UK** see https://www.qmul.ac.uk/covidence/

Despite difficulties in comparing data across nations, mortality from COVID-19 is clearly higher in some countries than in others. Many factors could have a role in this disparity, including differences in proportion of elderly people in a population, general health, accessibility and quality of healthcare, and socioeconomic status. One mostly overlooked factor that could influence outcome of COVID-19 is the relative vitamin D status of populations. Because people are advised to stay at home as much as possible, the government health agencies of Great Britain have recommended that people take vitamin D supplements through summer and autumn during this pandemic. Vitamin D supplementation could be especially important for older people as they are at high risk of poor outcome from COVID-19 and of vitamin D deficiency.

Vitamin D has a well-characterised role in calcium and phosphate balance, affecting bone growth and turnover. Low vitamin D status is also associated with other non-communicable diseases and with increased susceptibility to infectious disease; notably, upper respiratory tract infections. However, whether low vitamin D levels are a cause or consequence of disease has remained a point of heated debate. Intervention trials have rarely shown benefits of vitamin D supplementation as treatments or preventive measures. However, one important exception to this general trend is for upper respiratory tract infections: a 2017 meta-analysis of individual patient data from 11 321 participants in 25 randomised controlled trials showed that vitamin D supplementation protected against acute respiratory tract infections and that patients with very low (<25 nmol/L) serum 25-hydroxyvitamin D concentrations (a marker of vitamin D status) gained the most benefit.

A growing body of circumstantial evidence now also specifically links outcomes of COVID-19 and vitamin D status. SARS-CoV-2, the virus responsible for COVID-19, emerged and started its spread in the Northern hemisphere at the end of 2019 (winter), when levels of 25-hydroxyvitamin D are at their nadir. Also, nations in the northern hemisphere have borne much of the burden of cases and mortality. In a cross-sectional analysis across Europe, COVID-19 mortality was significantly associated with vitamin D status in different populations. The low mortality rates in Nordic countries are exceptions to the trend towards poorer outcomes in more northerly latitudes, but populations in these countries are relatively vitamin D sufficient owing to widespread fortification of foods. Italy and Spain are also exceptions, but prevalence of vitamin D deficiency in these populations is surprisingly common. Additionally, black and minority ethnic people—who are more likely to have vitamin D deficiency because they have darker skin—seem to be worse affected than white people by COVID-19. For example, data from the UK Office for National Statistics shows that black people in England and Wales are more than four times more likely to die from COVID-19 than are white people.

A role for vitamin D in the response to COVID-19 infection could be twofold. First, vitamin D supports production of antimicrobial peptides in the respiratory epithelium, thus making infection with the virus and development of COVID-19 symptoms less likely. Second, vitamin D might help to reduce the inflammatory response to infection with SARS-CoV-2. Deregulation of this response, especially of the renin–angiotensin system, is characteristic of COVID-19 and degree of overactivation is associated with poorer prognosis. Vitamin D is known to interact with a protein in this pathway—angiotensin-converting enzyme 2 (ACE2)—which is also exploited by SARS-CoV-2 as an entry receptor. While SARS-CoV-2 downregulates expression of *ACE2*, vitamin D promotes expression of this gene.

Rose Anne Kenny (Trinity College Dublin, University of Dublin, Ireland) led the cross-sectional study into mortality and vitamin D status and is the lead investigator of the Irish Longitudinal Study on Ageing (TILDA). She is adamant that the recommendations from all public health bodies should be for the population to take vitamin D supplements during this pandemic. "The circumstantial evidence is very strong", she proclaims regarding the potential effect on COVID-19 outcomes. Adding, "we don't have randomised controlled trial evidence, but how long do you want to wait in the context of such a crisis? We know vitamin D is important for musculoskeletal function, so people should be taking it anyway". Kenny recommends that, at the very least, vitamin D supplements are given to care home residents unless there is an extremely good reason not to do so.

Adrian Martineau (Institute of Population Health Sciences, Barts and The London, Queen Mary University of London, UK), lead author of the 2017 meta-analysis has joined with colleagues from universities around the UK to launch **C**OVIDENCE UK, a study to investigate how diet and lifestyle factors might influence transmission of SARS-CoV-2, severity of COVID-19 symptoms, speed of recovery, and any long-term effects. They aim to recruit at least 12 000 people and to obtain interim results by the summer. Despite his enthusiasm for the study, Martineau is pragmatic: "At best vitamin D deficiency will only be one of many factors involved in determining outcome of COVID-19, but it's a problem that could be corrected safely and cheaply; there is no downside to speak of, and good reason to think there might be a benefit".

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