Vitamin D for COVID-19: a case to answer?

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Interest in a potential role for vitamin D in the prevention or treatment of acute respiratory infections dates back to the 1930s, when cod liver oil was investigated as a means to reduce industrial absenteeism due to the common cold. Meta-analyses of randomised controlled trials conducted from 2007–20 reveal protective effects of vitamin D against acute respiratory infections, albeit these effects were of modest size and with substantial heterogeneity.[1] The striking overlap between risk factors for severe COVID-19 and vitamin D deficiency, including obesity, older age, and Black or Asian ethnic origin, has led some researchers to hypothesise that vitamin D supplementation could hold promise as a preventive or therapeutic agent for COVID-19.

From a mechanistic angle, there are good reasons to postulate that vitamin D favourably modulates host responses to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), both in the early viraemic and later hyperinflammatory phases of COVID-19. Vitamin D metabolites have long been known to support innate antiviral effector mechanisms, including induction of antimicrobial peptides and autophagy. Laboratory data relating to effects of vitamin D on host responses to SARS-CoV-2 specifically are scarce, but one study that screened four compound libraries for antiviral activity has reported an inhibitory effect of the active vitamin D metabolite 1,25-dihydroxyvitamin D (the steroid hormone and biologically active vitamin D metabolite) in human nasal epithelial cells infected with SARS-CoV-2.[2] Vitamin D has also been shown to regulate immunopathological inflammatory responses in the context of other respiratory infections. The finding that these effects were mediated via regulation of the renin-angiotensin system (RAS) in an animal model[3] has particular relevance in the context of severe COVID-19, where overactivation of RAS associates with poor prognosis.

Epidemiological studies investigating links between circulating levels of 25-hydroxyvitamin D (25[OH]D; the biomarker of vitamin D status) and incidence and severity of COVID-19 are currently limited in number. Two ecological studies have reported inverse correlations between national estimates of vitamin D status and COVID-19 incidence and mortality in European countries.[4,5] Lower circulating 25(OH)D concentrations have also been reported to associate with susceptibility to SARS-CoV-2 infection[6] and COVID-19 severity.[7] Recently, we have shown that airway diseases are associated with dysregulated vitamin D metabolism,[8] raising the possibility that vitamin D deficiency might arise as a consequence of pulmonary inflammation. Prospective studies can provide insights into the potential for reverse causality, but results from those published to date are conflicting: one retrospective longitudinal study from Israel reported independent associations between low pre-pandemic 25(OH)D levels and subsequent incidence and severity of COVID-19,[9] but an analogous study in the UK showed no such associations.[10] Both of these studies are potentially limited by the use of historic 25(OH)D measurements, which might not reflect concentrations at the time of exposure to SARS-CoV-2. They are also open to residual and unmeasured confounding. Mendelian randomisation studies offer one approach to overcome these problems, but they need to be very large to detect small or moderate effects which might still be of clinical significance. In our view, well powered randomised controlled trials of vitamin D supplementation for the prevention and treatment of COVID-19 are now needed to test for causality.

A number of hospital-based treatment trials have been registered to date, but it may prove challenging to detect a signal for vitamin D supplementation in severe COVID-19 for two reasons. First, patients tend to present to hospital in the hyperinflammatory stage of the disease, so it might be too late for them to benefit from any antiviral effects induced by vitamin D supplementation. Second, it could be hard to show the effect of a micronutrient over and above dexamethasone, which has potent anti-inflammatory actions and now represents the standard of care in severe disease. Prevention of SARS-CoV-2 infection also represents an ambitious target, given the highly infectious nature of the pathogen. Perhaps the best hope for showing a clinical benefit lies in a population-based trial investigating prophylactic vitamin D supplementation as a means of attenuating the severity of incident COVID-19, to the extent that it is either asymptomatic or does not result in hospitalisation. The design of such a trial should be informed by findings of meta-analyses

of randomised controlled trials of vitamin D to prevent other acute respiratory infections, which suggest that the intervention would work best when given in daily doses of 400–1000 IU to individuals with lower baseline vitamin D status.[1]

Pending results of such trials, it would seem uncontroversial to enthusiastically promote efforts to achieve reference nutrient intakes of vitamin D, which range from 400 IU/day in the UK to 600–800 IU/day in the USA. These are predicated on benefits of vitamin D for bone and muscle health, but there is a chance that their implementation might also reduce the impact of COVID-19 in populations where vitamin D deficiency is prevalent; there is nothing to lose from their implementation, and potentially much to gain.

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The link between type 2 diabetes and dementia: from biomarkers to treatment

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Type 2 diabetes has been consistently associated with an increased risk of dementia, including Alzheimer's disease and vascular dementia; mild cognitive impairment, which is a condition preceding dementia; and cognitive decline, which is the progressive clinical hallmark of dementia.[1] Establishing whether type 2 diabetes is specifically associated with the biological features of Alzheimer's disease or other causes of dementia, and ascertaining whether the mechanisms that link type 2 diabetes to dementia can suggest new approaches to dementia treatment, have been fraught areas of research. The link between type 2 diabetes and cognitive dysfunction is largely consistent, and a large body of studies on animals and humans points toward biological mechanisms of type 2 diabetes that could be potentially actionable. Given this evidence, and in light of the accelerating rates of type 2 diabetes worldwide, establishing the effect of type 2 diabetes on the brain and neurodegenerative diseases is a puzzle that is important to solve.

A joint Series by *The Lancet Neurology* and *The Lancet Diabetes & Endocrinology*, consisting of four Reviews, addresses the issues related to diabetes and brain health. The two Reviews published by *The Lancet Neurology*, and discussed in this Comment, focused on the link between diabetes and dementia, from newly developed biomarkers to treatment approaches.[2,3]

In the first paper of the Series, published by *The Lancet Neurology*, Geert Jan Biessels and colleagues[2] extended the discussion about ongoing developments in research into fluid-based and brain-imaging biomarkers, to how these biomarkers can be used to further our knowledge of the pathophysiology of type 2 diabetes. Both older and newly developed biomarkers