Vitamin D and COVID-19: Can it be protective?

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The global pandemic is raging with >26 million confirmed cases in the United States and >441,000 deaths in the United States alone as of February 2021 (1). Survival is not without risk, as approximately one-third of all hospitalized patients have significant heart, lung, or brain sequalae of infection resulting in substantial disability 6 mo after infection (2). Although vaccines are now being rolled out, it will still take at least another 9 mo or so to get the pandemic under some semblance of control. In addition, therapeutics for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) seem to be lagging behindvaccine development (3). Is there any simple, safe remedy that might mitigate the effects of SARS-CoV-2 in the meantime?

Vitamin D has been shown to have a wide variety of immune-regulatory effects on both the innate and adaptive arms of immune functioning and almost all immune cells. One simple way to think about vitamin D is that it functions as a rheostat for the immune system, regulating the ability to turn on and off the host inflammatory response to an invading organism in a quick and coordinated fashion.

In this issue of *Am J Clin Nutr*, Ma et al. (4) present observational data on 8297 subjects in the UK Biobank who had coronavirus disease 2019 (COVID-19) test results and vitamin D measured between March and June 2020 as well as covariates and a genetically predicted vitamin D concentration. What did they find? Neither the vitamin D concentrations (crude or adjusted) nor the genetically predicted vitamin D concentrations were related to risk of COVID-19 infection. However, habitual use of vitamin D supplements, when controlling for multiple other health, nutrition, and lifestyle correlates, was associated with a substantial and significant 34% (OR: 0.66; 95% CI: 0.45, 0.97) lower risk of COVID-19 infection. How do we explain these results?

Several important features of vitamin D epidemiology, genetics, and biochemistry are critical to interpret these results. First, the concept of a normal serum concentration of vitamin D is controversial. For bone health, which is controlled endocrinologically, a serum concentration of 20 ng/mL (50 nmol/L) is sufficient, and serum concentrations exactly reflect physiologic function. But, for immune function, which is paracrine and autocrine controlled, based on tissue concentrations not serum concentrations, a serum concentration of 30 ng/mL (75 nmol/L) is the minimum for immune sufficiency and a serum concentration of 40–60 ng/mL (>100 nmol/L) seems more functionally appropriate (5, 6). Note that all immune cells have the full biochemical machinery to process vitamin D to its active form, 1,25(OH)vitamin D, and serum concentrations are only a proxy for what really matters for immune function—namely, tissue concentrations. The kinetics of serum and tissue concentrations of vitamin D and their relation to immune function deserve further investigation.

Based on this immune definition of sufficiency, vitamin D deficiency is the most common vitamin deficiency in the world, with two-thirds to 100% of the world's population being deficient (7). It is impossible to tell from the Ma et al. study how many subjects met this immune-based definition of immune sufficiency, but likely very few, since their highest category of vitamin D concentrations was >50 nmol/L. Based on these, and other, data, observational studies of the immune effects of vitamin D, such as that of Ma et al., will often be underpowered because they frequently have so few subjects in the >30 ng/mL (>75 nmol/L) category.

A novel feature of the Ma et al. study is a genetic risk score for vitamin D based on 6 single nucleotide polymorphisms (SNPs). The important comment here is that polygenic risk scores are a new approach to complex trait genetics; unfortunately, using only 6 SNPs is likely to severely underpower this technology. It would be worth repeating this exercise with whole-genome sequencing or at least a full genome-wide SNP panel.

Another limitation of the study acknowledged by the authors is the possibility of selection bias, in that one cannot rule out that those subjects reporting supplement use were healthier than those not reporting such use. However, Ma et al.'s results are very reminiscent of what we observed with vitamin D and asthma where the use of vitamin D supplements (not serum concentrations) by pregnant mothers was associated with a 50% reduction in asthma risk in their offspring in 2 observational studies (8, 9). We replicated almost exactly this magnitude of protective effect with vitamin D concentrations in a meta-analysis of 2 randomized controlled trials, when initial concentration of vitamin D at trial entry was controlled for (10), thus validating the concept that supplement use may be a proxy for tissue sufficiency that is more sensitive than serum concentrations. In addition, the current study measured the use of vitamin D supplements a median of 10 y before the outcome variable of

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COVID-19 infection; these analyses assumed consistent use of these supplements over time.

Whether supplementation with vitamin D will prevent infection or improve outcomes with SARS-CoV-2 is an open question currently under study in >50 clinical trials (11). There is randomized controlled trial evidence that increased concentrations of vitamin D can lead to decreased occurrence and severity of respiratory infection (12) and, by analogy, it makes sense that this might also be true for SARS-CoV-2. It is unfortunate that Ma et al. did not look at these secondary outcomes, which would have strengthened the argument for vitamin D in this clinical scenario.

We are in the middle of the worst health crisis in a century. In the absence of clinical trial data to support the use of vitamin D what should one do? It is heartening to know that trials are ongoing and that results are expected soon. Based on what I note above about tissue concentrations, it would be very important to not use bolus dosing in these planned trials (13). The goal should be to stabilize tissue concentrations at >30 ng/mL (>75 nmol/L) and not have widely varying tissue and serum concentrations. The immune system needs to see a stable concentration to maximize immune function (13). As with the results of the recently completed vaccine trials, the global community needs these results with warp speed!

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