Reassessing the Association of Vitamin D Level With SARS-CoV-2 Seropositivity

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The COVID-19 pandemic began a little more than 1 year ago, but the worldwide human and economic toll has prompted the rapid search for therapeutic agents to mitigate the morbidity and mortality associated with SARS-CoV-2 infection. Several therapeutic agents have been found to be effective for the management of this disease, and several vaccines are being deployed worldwide with great efficacy.1

In the effort to find new treatments, factors associated with the risk of disease progression have been evaluated to determine whether they can potentially identify available, off-the-shelf products as therapeutic agents. Consequently, there have been a large number of studies evaluating the association of low levels of vitamin D with SARS-CoV-2 infection to determine whether vitamin D supplementation may have a role in the prevention or mitigation of this disease.2 In a systematic review and meta-analysis of 31 peer-reviewed observational studies,2 very uncertain evidence was found for a cause-effect relationship of vitamin D status with various COVID-19–related health outcomes. Limitations of these studies included variability in the definition of vitamin D deficiency, the timing of blood drawing in relation to the diagnosis of COVID-19, and the small size of most of the studies. Importantly, only 14 studies adjusted for potential confounders of low vitamin D, such as age, body mass index (BMI), and comorbidities. The very uncertain evidence found in these observational studies did not deter the development of clinical trials to evaluate the effect of vitamin D prophylactically to prevent COVID-19 infection and therapeutically to mitigate the morbidity and mortality associated with SARS-CoV-2.3

The study by Li et al4 adopts this different approach. This was a multivariable cohort study of 18,148 individuals working for a US-based business with sites in all 50 states who elected to be tested for SARS-CoV-2 as part of an employer-sponsored health screening program conducted between August and November 2020 (pandemic period) and who had participated in the prior year’s screening program conducted between September 2019 and January 2020 (prepandemic period). Li and coauthors4 placed special emphasis on adjusting for potential confounders of the association between vitamin D level and SARS-CoV-2 infection, such as sex, age, race/ethnicity, US geographical region, BMI, blood pressure, smoking status, and education. Vitamin D levels were measured within the last year and analyzed in the same laboratory. As seen in other unadjusted analyses, whether vitamin D levels were measured in 2019 or 2020, and whether low vitamin D levels were defined as less than 20 ng/mL or less than 30 ng/mL, SARS-CoV-2 seropositivity was significantly associated with low levels of vitamin D, with odds ratios ranging from 1.28 (95% CI, 1.10-1.48; P = .001) to 1.47 (95% CI, 1.28-1.70; P < .001). However, in multivariable models adjusting for age, race/ethnicity, sex, education, BMI, blood pressure, smoking status, and geographical location, SARS-CoV-2 seropositivity was not associated with having a low vitamin D level at either designated level or when measured before or during the pandemic, with odds ratios ranging from 0.93 (95% CI, 0.79-1.09; P = .36) to 1.09 (95% CI, 0.93-1.27; P = .29). SARS-CoV-2 seropositivity was associated with obesity, not having a college degree, and Asian, Black, Hispanic, American Indian or Alaska Native, and Native Hawaiian or other Pacific Islander race/ethnicity, and was inversely associated with high blood pressure, current smoking, and living in the Northeastern and Western US. This study4 clearly demonstrated that a well-designed, appropriately sized observational study can provide more definitive evidence that multiple smaller poorly designed studies.

What is the message? Most of us who treat patients or conduct laboratory-based research have not also been trained to perform the sophisticated biostatistical analyses required to appropriately...
analyze relationship data from large databases. However, it is incumbent on us all to recognize when and what analyses are needed before funding and initiating large clinical trials on speculative or insufficient information. One study⁵ that evaluated how emerging data translated into clinical practice found that with the urgency to intervene in the clinical course of disease and in the absence of alternative therapies, the strength of the underlying evidence for a specific therapy played only a minor role in the adoption of that therapy. Resources to fund clinical trials are limited, but even more so are the participants' time, efforts, and, indeed, lives and well-being, which are the most important resources to consider when conducting clinical trials to develop effective therapeutics for COVID-19 and other diseases with few therapeutic options.

Insufficiently supported basic information has been used at great expense to support large clinical trials of putative therapeutic agents. A large (4716 participants) randomized clinical trial⁶ of hydroxychloroquine was conducted in hospitalized patients with COVID-19 on the basis of (relatively weak) in vitro SARS-CoV-2 antiviral activity and observational studies reporting reductions in viral loads and mixed clinical results from its use. The study was stopped early following a recommendation from an independent data monitoring committee that there would be no reasonable possibility for hydroxychloroquine to show any meaningful mortality benefit (the primary outcome). Conducting studies such as this one, where the rationale for the implementation of the trial may be considered to be based on inadequate data, diverts the use of funds, wastes researchers’ time and efforts, and, most importantly, potentially puts participants at undue risk when these resources could be devoted to the pursuit of better therapies.

Science mandates that we continually challenge what we know when faced with new evidence, or, said better (perhaps apocryphally), by Mark Twain, “It ain’t what you don’t know that gets you into trouble, it’s what you know for sure that just ain’t so.”⁷ Randomized clinical trials are still the reference standard by which new therapeutics are determined to be effective. Well-done observational studies are among the means by which we can determine which therapies are worth bringing to clinical trials.⁸
