Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Commentary. Eliminating vitamin D deficiency during the COVID-19 pandemic: A call to action

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Long known as critical for bone health, and increasingly recognized as important for cardiometabolic and other non-skeletal outcomes, vitamin D has most recently attracted interest for its possible protective role against COVID-19. If vitamin D is beneficial in this regard—and accumulating evidence suggests that it may be—then the high prevalence of vitamin D deficiency in the United States and globally, especially among nonwhite racial/ethnic groups, is cause for heightened concern and should be rectified expeditiously. This commentary serves as an urgent call to action, with the aim of improving public health during—and after—the COVID-19 pandemic.

Current clinical vitamin D guidelines, which focus on maintenance of bone health, classify serum 25-hydroxyvitamin D (25(OH)D) levels of 20-50, 12-20, and less than 12 ng/mL as indicative of vitamin D sufficiency, inadequacy, and deficiency, respectively (to convert from ng/mL to nmol/L, multiply by 2.5) [1]. By these criteria, nearly one quarter (23.3%) of the overall U.S. population has 25(OH)D levels in the insufficient or deficient range [2]. Race/ethnicity differentials are striking; in the U.S., more than one half (53.3%) of Blacks, more than one third (36.7%) of Asians, and nearly one third (32.2%) of Hispanics have 25(OH)D levels that place them at risk of vitamin D insufficiency or deficiency, compared with about 1 in 7 (13.9%) non-Hispanic whites. For vitamin D deficiency alone, the corresponding percentages are 17.5%, 7.6%, 5.9%, and 2.1%, respectively.

Multiple lines of evidence suggest that vitamin D status may be relevant to COVID-19 incidence and severity (Table 1).

Laboratory (cell-culture) investigations have documented vitamin D action in pathways relevant to immune function, as well as the expression of the vitamin D receptor in innate and adaptive immune system cells [3]. Vitamin D may reduce infection risk by lowering viral replication rates through the induction of antimicrobial peptides, including cathelicidin. Vitamin D also has immunomodulatory properties and can lower inflammation, which may help to avert the inflammatory response thought to be at least partly responsible for the respiratory complications seen in some COVID-19 patients [4]. Moreover, vitamin D is a key modulator of the renin-angiotensin system and may counteract the reduction in angiotensin-converting enzyme 2 (ACE2) activity, rise in angiotensin-converting enzyme (ACE) activity, increased production of angiotensin II, and pulmonary vasoconstriction that occur when inhaled severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) binds to ACE2 receptors on alveolar epithelial cells [5].

Ecologic studies show lower COVID-19 mortality in countries or regions with greater solar ultraviolet-B radiation (associated with increased cutaneous synthesis of vitamin D) or populations with higher mean 25(OH)D levels [4]. Moreover, within a given country or region, demographic groups known to be at elevated risk for vitamin D insufficiency—not only Black individuals, but also the elderly, nursing-home residents, and those with obesity, vascular comorbidities, or chronic kidney disease—are also those at higher risk of COVID-19 hospitalization and/or mortality.

Observational studies also suggest a beneficial role of vitamin D. Studies of individuals tested for SARS-CoV-2 show that 25(OH)D levels measured concurrently with or up to 1 year prior to viral testing are inversely associated with the likelihood of a positive test result [6]. In addition, a growing number of studies of patients with confirmed SARS-CoV-2 infection find that 25(OH)D levels correlate inversely with illness severity [6]. For example, among 212 COVID-19 patients at three South Asian hospitals, the risk of severe as opposed to mild illness was approximately eight times higher in those who were vitamin D deficient than in those who were vitamin D sufficient [7]. Among 780 COVID-19 patients in Indonesia, 25(OH)D levels below 20 ng/mL, as compared with levels of 30 ng/mL or greater, were predictive of a 10-fold increase in mortality risk after controlling for age, sex, and comorbidity status [8]. Moreover, low vitamin D status has been consistently associated with increased risk of upper and lower acute respiratory infections (ARI) in observational studies conducted during the pre-COVID era. For example, among a nationally representative sample of 14,108 U.S. adults

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Table 1
Lines of evidence that vitamin D deficiency is an important modifiable risk factor for COVID-19.

- Laboratory studies: Vitamin D is important for immune function, modulates the inflammatory response to infection, and regulates the renin-angiotensin system.
- Ecologic studies: Countries with lower average levels of 25(OH)D or lower solar ultraviolet-B radiation exposure have higher COVID-19 mortality.
- Demographic groups known to be at higher risk of vitamin D deficiency—Black individuals, the elderly, nursing-home residents, and those with obesity, vascular comorbidities, or chronic kidney disease—are also those at high risk of COVID-19 hospitalization and/or mortality.
- Observational studies of individuals tested for SARS-CoV-2[a]: Low 25(OH)D levels are associated with a greater likelihood of testing positive for the virus.
- Observational studies of COVID-19 patients: 25(OH)D levels correlate inversely with COVID-19 severity.
- Observational studies (pre-COVID era): Low vitamin D status is associated with increased risk of acute respiratory tract infections.
- Randomized clinical trials (pre-COVID era): Vitamin D supplementation decreases risk of respiratory tract infection, especially in those with low 25(OH)D levels.

[a] SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

aged 17 years and older, individuals with 25(OH)D levels below 30 ng/mL had a 58% higher odds of ARI compared with those with levels of 30 ng/mL or greater [9]. The inverse relationship between 25(OH)D and ARI risk was nearly linear over the range of <10 to 30 ng/mL.

Results of randomized trials of supplemental vitamin D are also encouraging. In a 2017 meta-analysis of 25 trials involving 11,321 participants, vitamin D led to a significant 12% reduction in risk of upper and lower ARI [10]. Among participants with baseline 25(OH)D levels of less than 10 ng/mL who received daily or weekly vitamin D, supplementation was associated with a 70% lower risk of ARI.

Considered as a whole, the accumulating evidence is becoming increasingly compelling. That said, it is not yet definitive. Ecologic and observational data are susceptible to confounding, reverse causation bias, and other threats to validity that preclude their use for establishing causality, and randomized trial data regarding other viral diseases may not generalize to COVID-19. Well-designed trials that overcome these limitations are needed to evaluate the efficacy of vitamin D supplementation for COVID-19 prevention and/or treatment. Several such trials are underway, including our own. Their eventual results should allow a definitive determination of whether, and at what dose, vitamin D reduces risk of developing COVID-19, improves clinical outcomes, and strengthens response to future vaccination. In the meantime, it is more important than ever to embrace commonsense measures that will, on a population-wide basis, reduce the risk for vitamin D insufficiency and deficiency.

With summer upon us, clinicians and public health authorities should encourage patients and the general public to spend time outdoors and be physically active, while adhering to evolving social distancing guidelines. The skin can synthesize enough vitamin D to avert deficiency with as little as 15 minutes per day of sun exposure, although this time varies according to latitude, season, time of day, cloud cover, clothing coverage, sunscreen use, and skin pigmentation (those with darker skin will need more time in the sun than those with lighter skin), and extended exposure increases skin cancer risk. Therefore, the message that diet is also important to achieve a healthy vitamin D level should be conveyed. Good dietary sources include fortified foods such as milk, yogurt, orange juice, and cereals; oily fish such as salmon, rainbow trout, canned tuna, and sardines; eggs; and sun-dried mushrooms. A helpful table listing the vitamin D content of these and other foods is available [11]. Patients and the general public should also be advised to read nutrition labels, which are required to list the vitamin D content. In this period of heightened "vitamin D awareness," clinicians and public health authorities in countries that lack food fortification policies should advocate for a timely implementation of such policies to reduce vitamin D deficiency.

For people who are unable to be outdoors and also have low dietary vitamin D intake, supplementation is prudent. The recommended dietary allowance of vitamin D from food plus supplements is 600 IU/day for adults up to age 70 years and 800 IU/day for those above age 70 [1], but during the current pandemic, a supplement containing 1000-2000 IU/day of vitamin D would be reasonable. However, routine use of doses above the safety limit of 4000 IU/day should be avoided to minimize risk of hypercalcemia and other adverse events.

Vitamin D is essential for health. Although additional research on its contribution to attenuating COVID-19 risk and severity is in progress, eliminating vitamin D deficiency will improve public health during the current pandemic and after the threat subsides.

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Author contributions

The authors contributed equally to the conceptualization and writing of the manuscript.

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