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Vitamin D and COVID-19: Lessons from Spaceflight Analogs

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The biomedical community is racing to better understand the mechanism of action behind the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that is causing the coronavirus disease 2019 (COVID-19) pandemic. Having a better understanding of the mechanism and characteristics that make some individuals more susceptible than others to severe symptoms and preventing viral reactivation in people who have had a history of exposure to SARS-CoV-2 will help protect everyone. We postulate here that vitamin D status may be involved in the severity of the immune response to SARS-CoV-2 infection.

It is evident that the renin-angiotensin system (RAS) is involved in COVID-19 pathogenesis (1). Angiotensin-converting enzyme (ACE) converts angiotensin I to angiotensin II, a protein that mediates blood pressure and promotes inflammation, fibrosis, and oxidant responses through interaction with angiotensin II type I receptor (AT1) (2) (**Figure 1**). ACE2 converts angiotensin II to angiotensin-(1,7), and the interaction of angiotensin-(1,7) with the Mas receptor counter-regulates the inflammatory effects of angiotensin II (3). Membrane-bound ACE2 was identified as a receptor for SARS-CoV-1, the virus responsible for the 2003 SARS pandemic (4), and ACE2 is also the receptor for SARS-CoV-2 (1). SARS-CoV-2 penetrates epithelial cells by binding its transmembrane spike glycoprotein to membrane-bound ACE2. ACE2 receptors are found in lung (alveolar), heart, kidney, endothelium, and intestine (5), and ACE2 plays an important role in counterbalancing the negative proinflammatory downstream effects triggered by angiotensin II binding to AT1. Although SARS-CoV-2 must bind with ACE2 to penetrate cells, it also simultaneously downregulates ACE2, subsequently causing the receptors to lose function (6). ACE2 is critical for protecting against tissue damage, so loss of function of ACE2 can promote acute lung damage caused by angiotensin II (4, 7).

Preliminary data show that the mortality rate from COVID-19 is lower in countries proximal to the equator compared with more distal countries (8). A higher rate of infection and mortality exists among the elderly, and although all ethnic populations are affected, the death rate among African Americans is disproportionately higher than in other populations (9, 10). One possible explanation for these trends is vitamin D status.

Vitamin D is a unique nutrient in that it can be synthesized in the skin from 7-dehydrocholesterol after UV-B exposure from the sun. It is found naturally in relatively few foods. Vitamin D that is synthesized in the skin or is available from food and/or supplements is hydroxylated in the liver by the enzyme 25-hydroxylase to form 25-hydroxyvitamin D [25(OH)D]. 25(OH)D is converted to the biologically active form, 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], by the enzyme 1-α-hydroxylase (CYP27B1), mainly in the kidneys. 1,25$(OH)_2$D has many roles in the body, and vitamin D receptors are present in many types of tissue, but perhaps the most well-known function of vitamin D is its endocrine-related role in the homeostasis of calcium and other minerals. Some paracrine and autocrine mechanisms of action depend on vitamin D substrates, and some cells including B cells, T cells, and antigen-presenting cells can locally convert 25(OH)D to the 1,25$(OH)_2$D form (11) and upregulate >200 genes in tissues that have 1-α-hydroxylase activity (12).

It is estimated that ~1 billion people worldwide are vitamin D deficient [i.e., circulating 25(OH)D concentrations <20 ng/mL] and 50% of the population have insufficient vitamin D status (< 30 ng/mL) (13). Aging decreases the ability of the skin to synthesize vitamin D, and increased skin pigmentation reduces the efficacy of UV-B to stimulate synthesis of vitamin D (14, 15). It is well known that individuals living farther from the equator have lower vitamin D status (13, 16), and concentrations are lower in individuals with darker skin pigmentation (15). The prevalence of vitamin D deficiency is highest in the elderly (61%) (17), the obese (35% higher than in nonobese) (18), nursing home residents (50–60% of nursing home and hospitalized patients) (13), and those with higher melanin in their skin (40%) (19).

How could vitamin D deficiency or insufficiency possibly affect SARS-CoV-2 severity and mortality? The answer may be related to the paracrine and autocrine actions of vitamin D. All cells of the immune system express, or have the ability to express, vitamin D receptors, and all are sensitive to 1,25$(OH)_2$D (12). Vitamin D can influence the immune system in a number of ways, including inhibition of B-cell proliferation and differentiation as well as inhibition of T-cell proliferation (11). Vitamin D also facilitates an induction of T-regulatory cells, resulting in decreased production of

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Abbreviations used: ACE, angiotensin-converting enzyme; AT1, angiotensin II type I receptor; COVID-19, coronavirus disease 2019; EBV, Epstein-Barr virus; IOM, Institute of Medicine; RAS, renin-angiotensin system; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VZV, varicella-zoster virus; 1,25$(OH)_2$D, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D.

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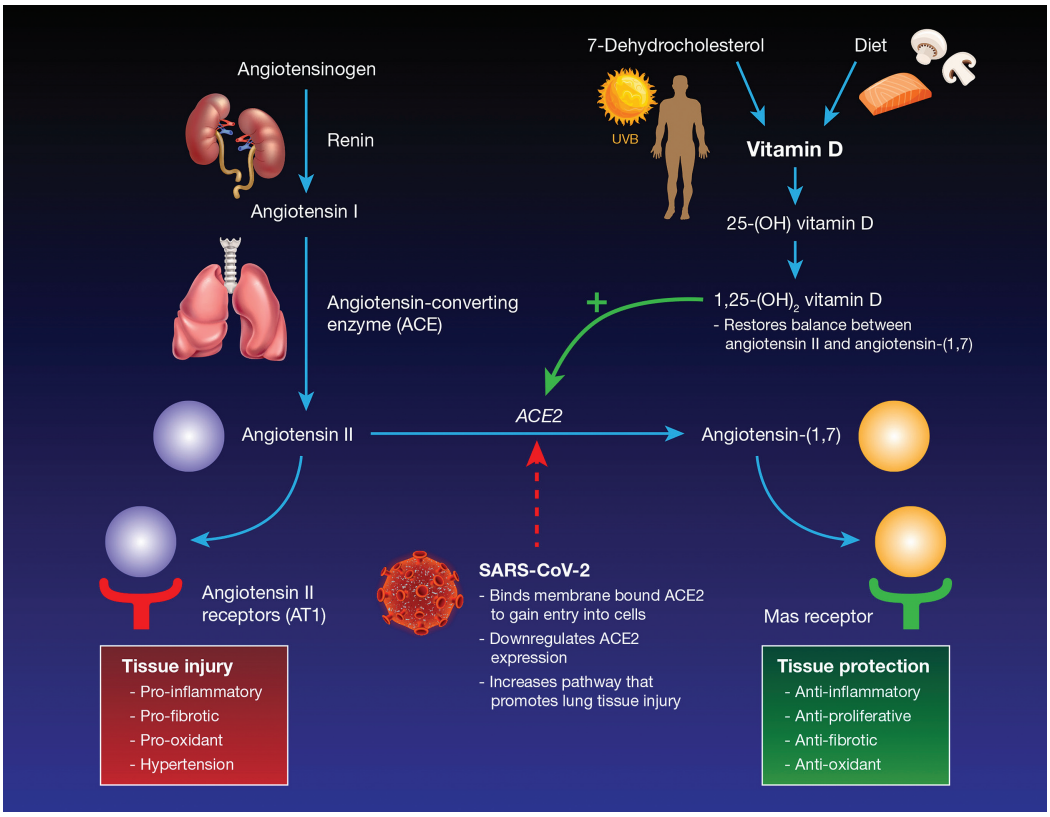

FIGURE 1 Vitamin D actions on the RAS. The figure summarizes how vitamin D can act on the RAS to promote tissue protection from SARS-CoV-2 infection. ACE2 is the primary entry point into cells, and SARS-CoV-2 downregulates expression, promoting tissue injury. Vitamin D is a negative endocrine RAS modulator and can increase expression and concentration of ACE2, having a potentially protective role against tissue injury. ACE2, angiotensin-converting enzyme 2; RAS, renin-angiotensin system; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

inflammatory cytokines and an increase in anti-inflammatory cytokine production (11). SARS-CoV-2 infection results in an aggressive inflammatory response (20), and it is possible that adequate vitamin D status may blunt the production of inflammatory cytokines during infection. Vitamin D is also a negative regulator of the RAS, and this regulation is independent of calcium metabolism (21). $1,25(OH)_2D$ can increase ACE2 expression and attenuate the angiotensin II–induced inflammatory response that includes generation of reactive oxygen species and vasoconstriction (22), which is the pathway that is stimulated during SARS-CoV-2 infection (7). $1,25(OH)_2D$ can alleviate lipopolysaccharide-induced acute lung injury through this mechanism (23).

In 2011, the Institute of Medicine (IOM) committee reviewed dietary requirements for vitamin D (24) and acknowledged that nonskeletal effects of vitamin D may exist, but they determined that there was not enough evidence at the time to define an RDA based on these factors that went beyond optimizing skeletal health (25). A comprehensive review of the effects of vitamin D supplementation on influenza concluded that vitamin D has some protective effect in reducing the risk of influenza, but more large clinical trials are necessary to confirm this observation (26). A recent review from Grant and colleagues (27) summarizes protective effects of vitamin D against other enveloped viral infections, including dengue, hepatitis B and C, HIV-1, H9N2 influenza, rotavirus, and respiratory syncytial virus. Additionally, a systematic review and meta-analysis by Martineau et al. documented that vitamin D supplementation reduced the risk of acute respiratory infections (28).

There is some evidence that individuals can test positive despite earlier recovery from SARS-CoV-2 infection (29). It is possible that the virus may persist in the body due to slower viral clearance in some individuals (30, 31). Some viruses, such as Epstein-Barr virus (EBV), varicella-zoster virus (VZV), and herpes-simplex-virus-1 (HSV-1), are known to persist in the body and can reactivate in response to certain stressors. Several case studies show evidence of VZV reactivation with SARS-CoV-2 infection (32, 33). We and others have documented factors that contribute to viral reactivation in astronauts during spaceflight and in spaceflight analog studies, such as those with crews wintering over in Antarctica. The advantage of these models is that viral reactivation can be studied in otherwise healthy individuals who are exposed to environmental and psychological stressors that result in latent viral reactivation (34–38). Some of the factors that influence viral reactivation in spaceflight and spaceflight analogs include cardiorespiratory fitness level and skeletal muscle endurance (39), stress (40), and stress combined with vitamin D status (41). Astronauts with greater cardiorespiratory fitness had a 29% less risk of latent virus reactivation, and crewmembers with greater preflight upper body muscular endurance were ~40% less likely to shed latent viruses during long-duration spaceflights, especially EBV and VZV (39). In a vitamin D supplementation study, subjects wintering over in Antarctica with lower vitamin D status and higher serum cortisol shed more EBV in their saliva than did subjects with higher vitamin D concentrations (41). Also of note in that study, the change in serum 25(OH)D response after either a daily 2000-IU or weekly 10,000-IU supplement of vitamin D depended on both BMI and baseline

25(OH)D concentration. In this, and other (42) studies, subjects with a higher BMI had less of a serum 25(OH)D response to supplementation, possibly because of decreased bioavailability of vitamin D in adipose tissue. Additionally, subjects with lower baseline concentrations of vitamin D had a greater elevation of serum 25(OH)D after supplementation. The association between vitamin D and viral reactivation was only present when serum cortisol concentrations were high. These data suggest that higher vitamin D status, along with physical fitness, may help protect against reactivation of latent viruses in high-stress environments, and the amount of vitamin D required to increase serum 25(OH)D depends on BMI and baseline status.

As others have mentioned, it is unlikely that one silver bullet will end the COVID-19 pandemic; however, evidence-based recommendations can be made that may reduce the risk of a severe response to SARS-CoV-2 infection or viral reactivation. Simpson and Katsanis (43) have reported the benefits of exercising during the COVID-19 pandemic that was based on the evidence they found in their spaceflight research. We recommend that people maintain optimal vitamin D status to support immune function and lower their risk of viral reactivation, a recommendation that also comes from our National Aeronautics and Space Administration (NASA)–funded research. We are not advocating for ultra-high doses of vitamin D supplementation because of possible side effects, but rather a level of supplementation that will prevent vitamin D deficiency and maintain serum concentrations >30 ng/mL. We determined from our Antarctic research that doses of 1000–2000 IU/d, which are within IOM guidelines (24), are likely sufficient. Modifiable measures such as these may have the potential to safely and easily offer some protection and reduce risk.

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