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LETTER TO THE EDITOR

Reply to Jakovac and to Rocha et al.: Can vitamin D prevent or manage COVID-19 illness?

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TO THE EDITOR: The outstanding articles by Jakovac (4) and Rocha et al. (8) emphasize an association between vitamin D deficiency/insufficiency and enhanced coronavirus disease (COVID-19) severity, which is also presented in recent reports (1, 3), and led to unofficial recommendations for taking vitamin D supplements (https://doi.org/10.1016/S2213-8587(20)30183-2). Therefore, we want to further discuss this issue on different levels.

COVID-19 pandemic. As the COVID-19 pandemic accelerates, it is important to explore different therapeutic options that are effective, economical, and without significant side effects. The clinical spectrum of COVID-19 presentation is wide, ranging from asymptomatic infection to severe viral pneumonia associated with respiratory failure from acute respiratory distress syndrome (ARDS) and multi-organ failure. Older people, racial minorities, and patients with a variety of comorbidities are at higher risk of being vitamin D deficient. The same populations are affected disproportionally by severe symptoms and increased mortality from the COVID-19.

Cytokine storm and oxidative stress take the center stage at the COVID-19 pathophysiology. Around 5% of patients develop ARDS from a likely dysfunctional immune response, which results in a cascade of events leading to a "cytokine storm". The main proinflammatory elements in a cytokine storm are IL-1β, IL-6, TNFα, INFγ, and IL-17 (7). In severe cases, these inflammatory responses lead to the damage to the lung and other organs, culminating in the end-stage disease (7). The important master regulator of proinflammatory responses is NF-κB, while Th17 responses are downstream of retinoic acid receptor-related orphan (RORγ) (5). Oxidative stress can be another etiological factor in the development of ARDS. It can be triggered by viruses and it can activate toll-like receptors (TLR) with subsequent release of cytokines (6). Nuclear factor erythroid 2p45-related factor 2 (NRF-2) plays an important role in the induction of antioxidative responses (6). The oxidative stress induced by the viral infection or cytokine storm can act reciprocally in a vicious cycle to amplify the damage inflicted on the target organs. Therefore, placing the break on this vicious, self-amplifying cycle without toxic side effects and an impairment of the anti-viral host response, would represent a logical management of COVID-19 (Fig. 1).

Vitamin D solution. Active forms of vitamin D, including the classical calcitriol [1,25$(OH)_2$D3] (2), and novel CYP11A1-derived hydroxyderivatives can inhibit production of proinflammatory cytokines of a cytokine storm with a mechanism of action involving downregulation of NF-κB and inverse agonism on RORγ (10). They can also counteract the oxidative stress through activation of NRF-2 and p53-dependent pathways (10). Therefore, we suggest that vitamin D3-hydroxyderivatives are candidates for management of COVID-19, because while targeting both the cytokine storm and oxidative stress, they might also have antiviral effects (Fig. 1). However, their immediate clinical use has limitations, because it requires FDA approval for CYP11A1-derived hydroxyderivatives or for administration of calcitriol, 25-hydroxyvitamin D or 1α-hydroxyvitamin D for severe symptoms of COVID-19 (2). Vitamin D precursor, however, is readily available and can be consumed within reasonable doses without a need for such approval. According to the Endocrine Society, the upper daily limit for an average healthy adult individual is 10,000 IU/day. This oral dose could be applied preventively to reduce probability of moderate to severe COVID-19. However, such a dose may not be sufficient to stop cytokine↔oxidative storm in patients entering the hospital, which would require aggressive solutions. In the past, mega doses of vitamin D were used to treat different pathologies (2). In most recent studies, 200,000 IU, but not 50,000 IU, of orally delivered vitamin D3 was effective in significant attenuation of proinflammatory responses induced by solar radiation after 48 h of observation without any sign of toxicity (9). These findings suggest the use of high doses of vitamin D after admission to the hospital, since patients can be carefully monitored for any signs of adverse effects.

Considering the routes and forms of delivery, in the United States, only oral forms are available in the form of pills or liquid. Intravenous delivery at high doses is not available, and vitamin D3 form for intramuscular injections is marketed in Europe and India.

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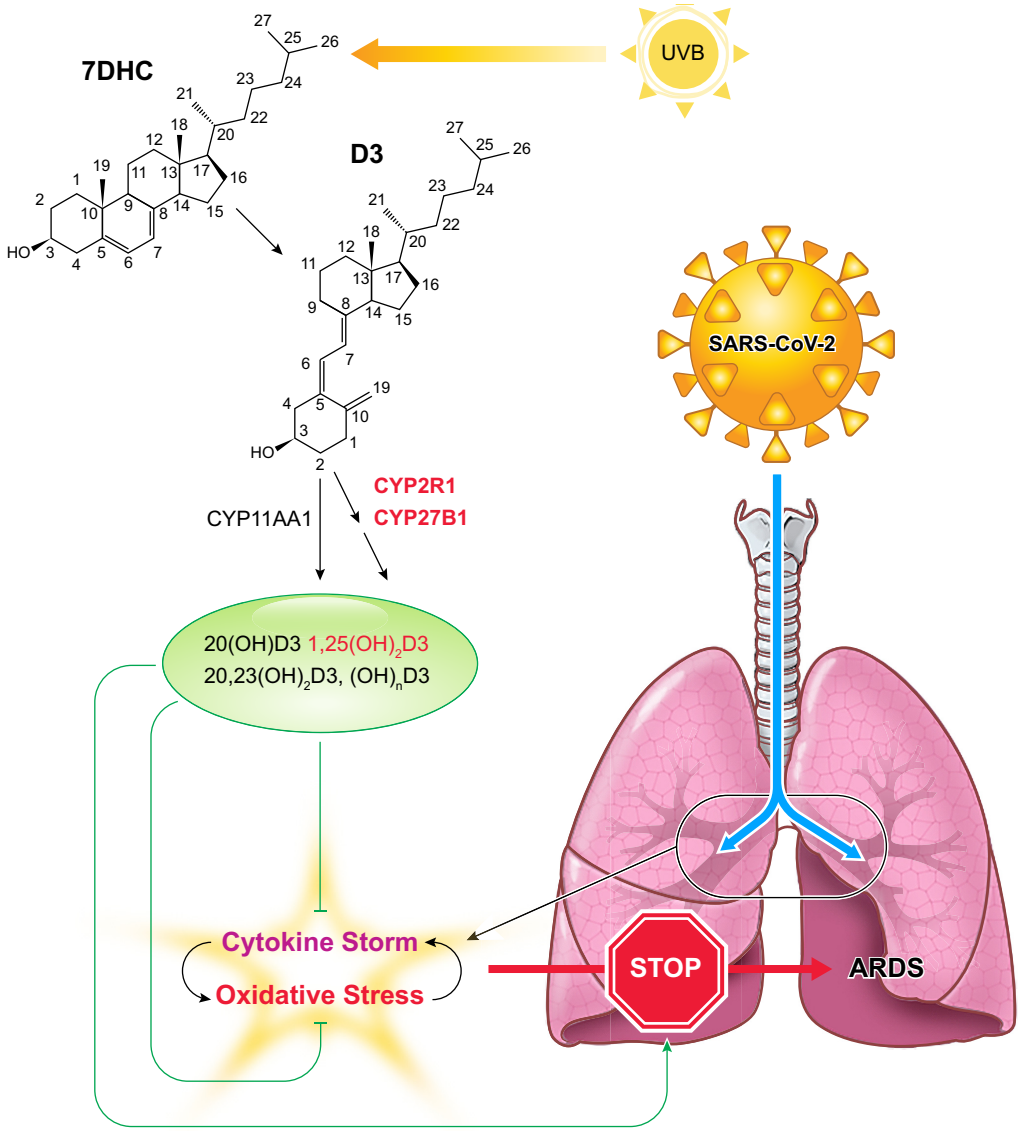

Fig. 1. Active forms of vitamin D3 by counteracting cytokine storm and oxidative stress will attenuate acute respiratory distress syndrome (ARDS) secondary to coronavirus disease. Arabic numbers, positions of hydroxyl groups on vitamin D3; *n*, number of hydroxyl groups; CYP11A1, CYP2R1, and CYP27B1, enzymes hydroxylating vitamin D3 with CYP2R1 hydroxylating at C25 and CYP 27B1 hydroxylating 25(OH)D3 at C1α to generate $1,25(OH)_2D3$ (calcitriol); SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

We agree with Jakovac (4) and Rocha et al. (8) that this calls for measurement of a 25(OH)D level in all COVID-19 patients. Patients who are vitamin D deficient or insufficient, i.e., 25(OH)D $<$ 30 ng/mL could be treated with an appropriate amount of vitamin D as soon as it is feasible to do so. In summary, we believe that different forms and routes of delivery of vitamin D at proper and clinically monitored doses might help in prevention or management of moderate to severe COVID-19.

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DISCLOSURES

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AUTHOR CONTRIBUTIONS

A.T.S. and T.-K.K. prepared figures; A.T.S., R.M.S., P.A.G., M.F.H., A.M.J., and C.R. drafted manuscript; A.T.S., R.M.S., P.A.G., M.F.H., A.M.J., and C.R. edited and revised manuscript; A.T.S., R.M.S., P.A.G., T.-K.K., M.F.H., A.M.J., and C.R. approved final version of manuscript.

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