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Letter: does vitamin D have a potential role against COVID-19?

We read with interest the article by Tian *et al* reviewing the gastrointestinal aspects of COVID-19 and the letter published in connection with that by Panarese and Shahini.[1,2] The latter recommended vitamin D prophylaxis for prevention of COVID-19 particularly in cases of vitamin D deficiency.

In this context, several authorities believe that vitamin D will be beneficial, and clinical trials are currently underway.[3] There is a paucity of data to show the role of vitamin D on COVID-19. It is also vital to know the role of vitamin D on asymptomatic COVID-19 cases. The positive role of vitamin D in diabetes mellitus, and cardiovascular disease may be beneficial in controlling COVID-19.[4]

However, there is a paradoxical effect of vitamin D for preventing the severity of COVID-19. Since the world is currently facing a pandemic, discussion of this is also essential. When inhaled, the SARS-CoV-2 virus, attaches to angiotensin-converting enzyme 2 (ACE2) expressed on the surface of alveolar epithelial cells. Once the virus binds to ACE2, it reduces its activity and, in turn, promotes ACE1 activity forming more angiotensin II. It causes heightened pulmonary vasoconstriction and severity of COVID-19.[5,6]

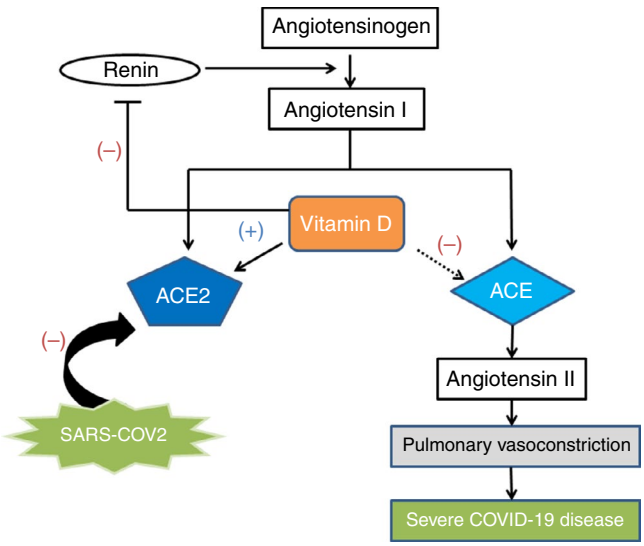

FIGURE 1 The role of vitamin D in COVID-19. SARS-CoV-2 binds to the ACE2 of alveolar cells and disturbs the ratio of ACE2/ACE activity. It increases ACE activity and, in turn, results in more angiotensin II formation causing pulmonary vasoconstriction to precipitate severe COVID19. Vitamin D induces ACE2 expression, which limits the formation of angiotensin II via ACE and reduces lung injury. Besides, vitamin D also acts on renin and inhibits its activity, which further contributes to the reduction in angiotensin II. Therefore, vitamin D supplementation may have a protective role against COVID-19. (Dotted line indicates indirect effect)

The vitamin D analogue calcitrol increases expression of ACE2 in the lungs in experimental animals in specific experimental conditions.[7] ACE2 thus expressed more as a consequence of vitamin D supplementation might reduce lung injury.[8] It can promote binding of the virus to the pulmonary epithelium. Also, vitamin D may suppress renin activity.[7] That in turn may generate less angiotensin II resulting in less pulmonary vasoconstriction (Figure 1). Although vitamin D induces the expression of ACE2, which indeed promotes the binding of the virus, it prevents pulmonary vasoconstriction response in COVID-19 cases. COVID-19 is not an isolated disease where vitamin D behaves in this manner. A similar mechanism is observed in influenza. The influenza virus H7N9 also produces a heightened angiotensin II response, and lung injury is prevented by the expression of ACE2 protein.[9] However, vitamin D supplementation prevents influenza-related illness.[10] Although the exact mechanism remains unclear, ACE2 over-expression could be a possibility. Based on the above observation, we conclude that vitamin D may reduce the severity of COVID-19 in a manner analogous to influenza.

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AUTHORSHIP

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LINKED CONTENT

This article is linked to Tian et al and Tian and Rong papers. To view these articles, visit https://doi.org/10.1111/apt.15731 and https://doi.org/10.1111/apt.15817.

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Letter: does vitamin D have a potential role against COVID-19? Authors' reply

EDITORS,

We thank Kumar et al for their comments on our review article and the letter connected with that by Panarese and Shahini.[1,2] We agree that there is a complicated effect of vitamin D in preventing the severity of COVID-19, while this mechanism is not exactly the same as that of influenza.

Vascular injuries have become a focus of attention in COVID-19, especially in its severity and mortality; major risk factors include hypertension, diabetes and age. ACE2 is widely expressed in arterial and venous endothelial cells and arterial smooth muscle cells.[3] This provides the possibility for the virus to attack and damage blood vessels followed by increased blood clotting and platelet aggregation, which will eventually lead to thrombus formation.

Accumulating evidence suggests that coagulopathy is an important pathological process in COVID-19. Extensive coagulopathy can explain phenomena like ischemic skin lesions, increased risk of stroke and hypoxaemia in some severely ill patients even without breathing problems.[4] Several studies have shown that vitamin D deficiency was related to endothelial dysfunction and pathological changes to the vascular system.[5] $1,25(OH)_2D$ has been reported to promote vascular endothelial repair by inducing vascular smooth muscle cells to produce vascular endothelial growth factor (VEGF).[6] Vitamin D receptor knockout mice have coagulation disorders with injury.[7] Therefore, we speculate that the possible role of vitamin D in SARS-CoV-2 infection is not only from its impact on innate and adaptive immune responses (as in influenza), but also from effects on the cardiovascular system.

A recent retrospective study showed that 11 of 13 ICU patients had vitamin D insufficiency, compared to four of seven non-ICU patients. The mean serum 25(OH)D levels were 19.2 ± 10.8 ng/mL in ICU patients and 29.8 ± 13.3 ng/mL in non-ICU patients.[8] Based on evidence from the current literature, we propose that patients with low vitamin D levels might be at increased risk of severe COVID-19, but no evidence supports that vitamin D has any benefit as COVID-19 treatment. We suggest that groups at high risk for vitamin D deficiency, including the elderly, pregnant women, those exposed to insufficient UV radiation, and medical staff performing shift work should, if infected with COVID-19, take an appropriate dose of vitamin D, which may reduce the possibility of aggravation.

However, the recommended dosage of vitamin D supplementation remains unclear. Guidelines for many countries recommend 600-4000 IU/d and consider that a 25(OH)D concentration of 20 ng/mL is sufficient. Grant et al[9] have argued that a concentration of 40-60 ng/mL might be beneficial to high-risk groups for virus infection and have suggested taking 5000 IU/d after an initial 10 000 IU/d to raise the concentration rapidly. Since the safety of high serum 25(OH)D levels is uncertain, a serum concentration of 20-30 ng/mL seems appropriate. The actual supplementary dose should be determined according to the baseline level of vitamin D, an individual's general condition and risk of COVID-19 infection.

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LINKED CONTENT

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