



Vitamin D₃ Administration to Patients with Confirmed COVID-19

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Dear Editor-in-Chief

In the last month of 2019, a newly identified illness termed coronavirus disease 2019 (COVID-19) spread rapidly through the world. A new coronavirus, the cause of the disease, was identified as the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). This virus uses a monocarboxypeptidase named angiotensin-converting enzyme 2 (ACE2) as a functional receptor, expressed by epithelial cells of the lung, intestine, kidney, and blood vessels, to facilitate viral entry into target cells (1). Downmodulation and therefore loss of ACE2 expression in the tissues, especially lungs, due to the infection with SARS-CoV-2 (binding through spike protein of virus) results in severe acute respiratory failure (2). During infection with this virus, the following downmodulation/loss of alveolar ACE2 reduces angiotensin II metabolism which led to an increase in the concentration of this peptide in the relevant place and finally increases alveolar permeability and accelerates lung damage.

If we focus on ACE2 protein, as the recipient and also the important facilitator the virus entry into the host cell, to prevent tissue damage, especially to the alveolar; it seems likely to be useful to use the following two methods: by increasing the mass of ACE2 in the relevant tissue through a) administration of soluble recombinant human ACE2 protein and, b) endogenous routes. In the

first approach a shorter soluble form of ACE2 connected with the virus, outside the cell membrane without being attached to the host cell, and finally prevents the virus from entering the cell and multiplying inside it (3). The process of preparation, purification, as well as immunological studies of the soluble ACE2 on humans in the future also has limitations that are not addressed in this paper. In the second form, vitamin D₃ can increase the expression of ACE2 mRNA & protein in some tissues such as pulmonary microvascular endothelial cells (4-6). In this case, increasing the number of ACE2s attached to the cells can act as a double-edged sword; on the one hand, it can increase the number of receptors for the virus to enter the cell in patients with COVID-19 and on the other hand the excessive ACE2 may competitively bind with the virus and neutralize it on the one hand and it saves cellular activity of ACE2 on the other hand which protect the lung from damage (1).

Of course, the role of vitamin D₃ in these patients is not limited to this issue but also due to significant effects such as modulation of the activity of the innate and adaptive immune system (7) as well as reducing the cytokine storm induced by innate immune system (8), it can play a protective role against lung tissue damage in this disease. The ability in stimulation of neutrophils,



macrophages, and natural killer (NK) cells of the respiratory tract, as well as epithelial cells, by this vitamin to produce antimicrobial peptides (AMPs), including defensins and cathelicidins (7), it is also another topic that can attract researchers' attention to prevent the development of common secondary non-viral infections, which usually occur in such viral diseases of the respiratory tract.

Further research, especially the examination of the animal models, regarding the administration of vitamin D₃ in cases with confirmed COVID-19 as a potential therapy for acute lung injury is required.

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Conflict of interest

The authors declare that there is no conflict of interest.

References

1. Zhang H, Penninger JM, Li Y et al (2020). Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. *Intensive Care Med*, 46:586-90.
2. Kuba K, Imai Y, Rao S, et al (2005). A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat Med*, 11:875-9.
3. Battle D, Wysocki J, Satchell K (2020). Soluble angiotensin-converting enzyme 2: a potential approach for coronavirus infection therapy? *Clin Sci (Lond)*, 134:543-5.
4. Lin M, Gao P, Zhao T, et al (2016). Calcitriol regulates angiotensin-converting enzyme and angiotensin converting-enzyme 2 in diabetic kidney disease. *Mol Biol Rep*, 43:397-406.
5. Cui C, Xu P, Li G, et al (2019). Vitamin D receptor activation regulates microglia polarization and oxidative stress in spontaneously hypertensive rats and angiotensin II-exposed microglial cells: Role of renin-angiotensin system. *Redox Biol*, 26:101295.
6. Xu J, Yang J, Chen J, et al (2017). Vitamin D alleviates lipopolysaccharide-induced acute lung injury via regulation of the renin-angiotensin system. *Mol Med Rep*, 16:7432-8.
7. Bryson KJ, Nash AA, Norval M (2014). Does vitamin D protect against respiratory viral infections? *Epidemiol Infect*, 142:1789-801.
8. Grant WB, Lahore H, McDonnell SL, et al (2020). Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths. *Nutrients*, 12(4): E988.