WILEY

# Role of vitamin D in COVID-19 infections and deaths

Dear Editor,

As of August 31, 2020, there have been more than 25 million officially reported confirmed cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in the world (updated data available at https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6). Currently, the best strategies for mitigating the damage from COVID-19 involve policies to encourage social distancing, contact tracing, and the wearing of masks to reduce the spread of the coronavirus. There is no effective treatment for symptomatic patients, with various forms of supportive care being an active area of research. However, certain disparities in the case loads of different ethnicities and different populations are beginning to emerge. Although there are many other factors that are intertwined, one hypothesis at the present moment is that vitamin D supplementation might hold promise as a preventive or therapeutic agent for COVID-19 since the striking overlap between risk factors for severe COVID-19 and vitamin D deficiency, including obesity, older age, and Black or Asian ethnic origin.

Vitamin D is a fat-soluble vitamin that can regulate calcium and phosphorus metabolism, affecting bone growth and muscle health. It also plays significant role in the maintenance of immune homeostasis. Low vitamin D status is associated with many non-communicable diseases. A variety of studies have shown that $1,25\text{-}(OH)_2D$, the active vitamin D metabolite, is involved in the development of several immune-related diseases, such as psoriasis, type 1 diabetes, multiple sclerosis, rheumatoid arthritis, and so on.[1] Low levels of vitamin D is also associated with increased susceptibility to infectious disease. As a regulator of innate immunity, it could regulate the resistance to viruses, including induction of antimicrobial peptides and autophagy. Vitamin D can also be used as an adaptive immune regulatory factor. The active form $1,25(OH)_2D$ can inhibit inflammation reaction and inhibit inflammatory factor storms.[1] Vitamin D is related to the occurrence and development of many diseases. A recent meta-analysis has showed that vitamin D supplementation has a protective effect on acute respiratory infections.[2]

Recent research found that compared with non-infected people, patients with COVID-19 have lower vitamin D levels. It suggests that insufficient vitamin D levels in the body increase the risk of COVID-19 infection. However, another study found no association between vitamin D levels and COVID-19 test results. Researchers further found that COVID-19 mortality increases with northerly latitude after adjusting for age suggesting a link with ultraviolet and vitamin D. A study of 20 European nations found an association between the mean levels of vitamin D in various countries and the mortality caused by COVID-19. However, this cross-sectional study of the mean level for each country is limited. Also, the number of cases and COVID-19 mortality for each country is affected by the different measures taken by each country to prevent the spread of infection.[3–5] A recent retrospective cohort study of 489 patients found an association between low vitamin D status (a year before COVID-19 testing) and a positive COVID-19 test result. For patients with deficient vitamin D status, the relative risk of testing positive for COVID-19 was 1.77 times greater than patients with sufficient vitamin D status. Up to now, there is a lack of clinical trials and cohort studies in determining the preventing role of vitamin D in COVID-19 severity and mortality. However, several retrospective studies have shown that vitamin D levels are related to the clinical outcomes of COVID-19, such as increasing the appearance of severe respiratory dysfunction and the mortality risk. Low levels of vitamin D have also been reported in severe COVID-19 patients.[3] Some studies demonstrated the protective effects of combined vitamin D, Mg, and vitamin B12 against clinical deterioration of COVID-19. Therefore, supplementation with vitamin D may play a role in prevention of infection as well as improve the disease outcomes. A recent quasi-experimental study concluded that vitamin D3 supplementation taken during or just before COVID-19 was associated with less severe COVID-19 and better survival rate. However, it is important to note that some of the studies available online are not peer-reviewed, or authors of some preprints do not have verifiable medical or scientific credentials. The mechanism may be that SARS-CoV-2 virus binds to angiotensin converting enzyme 2 (ACE2) receptors as a functional receptor to enter host cells. Subsequent dysregulation of the renin-angiotensin system may lead to excess cytokine production resulting in prospective fatal acute respiratory disease syndrome. Down-regulation of ACE2 in lung tissue leads to increased alveolar permeability, causing severe lung injury and lung failure. Vitamin D can upregulate ACE2 receptors in lung microvascular endothelial cells, which can bind the virus to inactivate it.[3,4] On the other hand, vitamin D plays an important role in innate and adaptive immune responses. It has an important role in inhibiting the cytokine storm by downregulating of pro-inflammatory cytokines. It can also exert anti-viral activities and modulates inflammatory response to viral infection by stimulating cathelicidin release, modulation of toll-like receptor expression and natural killer (NK) cells function (Figure 1).

Although some clinical findings indicate that vitamin D may reduce the infection rates and mortality of COVID-19, the evidence for vitamin D prevention and treatment of COVID-19 is still insufficient.
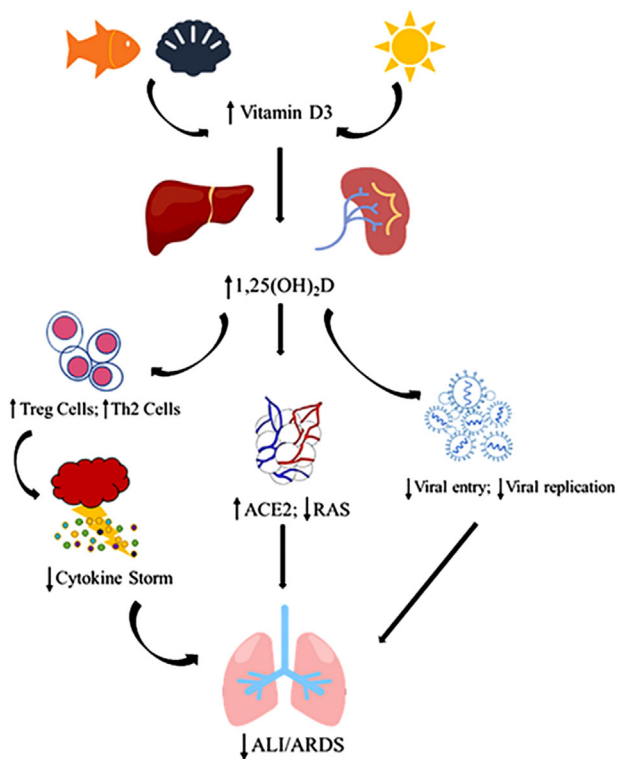
FIGURE 1 Vitamin D and anti-COVID19 mechanisms. Vitamin D is produced endogenously with the effect of ultraviolet radiation on the skin or available from exogenous food sources or dietary supplements. Vitamin D is converted to 25(OH)D in the liver and then to 1,25(OH)$_2$D in the kidneys. Vitamin D mediates the immune system responses through enhanced Treg cell and Th2 cell function. Inhibiting the cytokine storm that is thought to be a key pathogenic mechanism in defending against ALI/ARDS. Other mechanisms include modulating the pulmonary RAS and reducing viral entry and replication Abbreviations: ACE2, angiotensin converting enzyme 2; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease-19; RAS, renin-angiotensin system

There are some ongoing clinical trials to explore whether vitamin D will affect the clinical outcome of COVID-19, and whether vitamin D levels are related to SARS-CoV-2 infection. Pending results of such trials, people who are at higher risk of vitamin D deficiency including elderly, smokers, patients with chronic diseases, and excess uptake by adipose tissue in obesity should consider taking vitamin D supplements to maintain the circulating 25(OH)D. Although it is still debatable what level of serum 25(OH)D is optimal, guidelines for many countries consider 20 ng/mL (50 nmol/L) adequate. Public Health England updated its advice on vitamin D supplementation in April that everyone should consider taking a daily 10 μg vitamin D supplement. Even if vitamin D supplementation can be shown to provide a benefit in reducing cases or mortalities at the epidemiological level, it is unlikely that vitamin D alone can be a treatment or prevention for COVID-19 infection. Until then, the only certainty is that vitamin D supplementation for individuals deficient in vitamin D is known to be safe, cost-effective, and is of benefit for general immune system function and bone health.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

Xing Wang[1]
Yu Zhang[1,2]
Fang Fang[1] (iD)

[1] West China Hospital, Sichuan University, Chengdu, China
[2] Affiliated Hospital & Clinical Medical College of Chengdu University, Chengdu, China

Correspondence
Fang Fang, West China Hospital, Sichuan University, No. 37, Guo Xue Xiang, Chengdu, Sichuan 610041, China.
Email: fangfang01@scu.edu.cn

ORCID
Fang Fang (iD) https://orcid.org/0000-0002-8711-1920

REFERENCES
1. Charoenngam N, Holick MF. Immunologic effects of vitamin D on human health and disease. *Nutrients.* 2020;12(7):2097.
2. Martineau AR, Jolliffe DA, Hooper RL, et al. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. *BMJ.* 2017;356:i6583.
3. Ali N. Role of vitamin D in preventing of COVID-19 infection, progression and severity. *J Infect Public Health.* 2020;S1876-341(20):30531.
4. Grant WB, Lahore H, McDonnell SL, et al. Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. *Nutrients.* 2020;12(4):988.
5. Meltzer DO, Best TJ, Zhang H, Vokes T, Arora V, Solway J. Association of vitamin D deficiency and treatment with COVID-19 incidence. *medRxiv.* 2020. https://doi.org/10.1101/2020.05.08.20095893.