



Future nutrient-dense diets rich in vitamin D: a new insight toward the reduction of adverse impacts of viral infections similar to COVID-19

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Dear Editor,

Today, the world is facing an unprecedented challenge of the pandemic of coronavirus disease 2019 (COVID-19). This viral infection has led to more than 18.58 million confirmed cases with over 700,000 deaths worldwide (<https://www.worldometers.info/coronavirus/>) [1]. The global economy, healthcare systems, and human life are negatively influenced by the COVID-19 outbreak. Although most countries are gradually moving to strike an equilibrium between people's safety planning and the revival of market economy status, policymakers must make efforts to protect poor and vulnerable individuals' availability to nutritional, high-quality foods with an acceptable calorific profile. Therefore, the design and supply of food supplements to COVID-19 patients and other presumed noninfected patients might be considered an intelligent approach for improving the state of public health, especially in low-income and middle-income countries.

Currently, the use of some micronutrients particularly vitamins has resulted in a reduction in the COVID-19 severity [2, 3]. Vitamin D is introduced as one of the important micronutrients in improving the health of patients with COVID-19 due to immunomodulatory functions [3, 4]. But, there is still an ambiguity in the recommended dosage of vitamin D for patients with COVID-19. In many countries, the recommended supplementation of vitamin D and sufficient 25-hydroxyvitamin D (25 (OH)D) levels are considered

600–4000 IU/d and 20 ng/mL, respectively. A serum concentration of 20–30 ng/mL would be suitable because the safety of high 25(OH)D levels is undetermined. Assessing the appropriated dose is dependent on some parameters such as the baseline level of vitamin D, patient's general conditions, and the severity rate of COVID-19 infection. Taking 5000–10,000 IU/d of vitamin D3 for several weeks has been recommended to elevate 25(OH)D levels by 40–60 ng/mL for a quick decrease in the infection risk of COVID-19. Results also pointed out that patients with COVID-19 should receive higher doses of vitamin D3 [5]. However, Panarese and Shahini [4] reported that the use of vitamin D supplements without overdosing would be a nutritional strategy for the severe reduction of COVID-2019. Alipio [6] has recently found that the increase of serum 25(OH)D level up to an optimal level could considerably improve clinical outcomes in 212 Philippine cases with this respiratory illness. Earlier, it was evidenced that the regular intake of vitamin D2/D3 (~2000 IU/d) by people with vitamin D deficiency could remarkably prevent the acute infection of the respiratory tract [7].

There is a high prevalence rate of vitamin D deficiency of up to one billion in the globe. Under the limited sunlight exposure, the commonly recommended daily intake (RDI) of vitamin D is insufficient. Low vitamin D status during this pandemic may be intensified owing to the decreased sun exposure with self-isolation and indoor living, arising a necessity to take vitamin D supplements [8]. Besides, since the epidemic of respiratory viral diseases occurs in cold seasons, the oral administration of this vitamin is necessary because of the low direct exposure to sunlight. For example, McCartney and Byrne [9] reported a low serum vitamin D level (< 50 nmol/L) in an annual checkup among old adults aged 50–64 (35.7%) and 65–84 (44.0%) years, whereas the corresponding deficiency values in winter increased by 55.4 and 48.1%, respectively. The severely low serum levels of vitamin D were also reported in the aging

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inhabitants in other European countries, such as Spain, Italy, and Switzerland [10]. Raharusun et al. [11] reported that most death cases were old-aged males with a serum level of vitamin D below normal.

At first, it was imagined that countries in the Southern Hemisphere had relatively low mortality from COVID-19 [5, 12]. However, it was argued that the SARS-CoV-2 transmits later to the Southern Hemisphere [12]. But, researchers had a common view that this fat-soluble vitamin is able to protect humans against the COVID-19 infection and to reduce the mortality rate by preventing the cytokine storm and following acute respiratory distress syndrome [5]. Therefore, there was a strong association between the mortality rate and vitamin D deficiency in patients with COVID-19. Under this condition, the target-organ damage with the short-term, severe deficiency of vitamin D may occur as a result of increased hypertension and detrimental effects on the blood pressure regulation of renin-angiotensin system (RAS) [13]. Accordingly, the vitamin D fortification of foods and supplements for older people with high vulnerability to COVID-19 can highly enhance the synthesis of the biologically active form of this vitamin (1,25-dihydroxyvitamin D [1,25(OH)₂D]) in the blood and reduce the adverse clinical outcomes with COVID-19. Increasing the uptake of vitamin D can downregulate the release of pro-inflammatory cytokines and chemokines caused by COVID-19 [4].

The angiotensin-converting enzyme II (ACE2) is the major receptor of COVID-19 for entrance into the host cells. The high expression of ACE2 in the lungs can be accompanied by better COVID-19 outcomes like strong protection against acute lung injury [10]. Vitamin D as a strong negative endocrine regulator can significantly suppress the RAS and downregulate the ACE2 expression both in vitro and in vivo through the canonical vitamin D receptor pathway [14]. On the other hand, the expression of ACE2 is affected by two key factors of gender and aging. The ACE2 expression evaluation in a rodent model showed that there was a lower content of ACE2 in older rats than younger ones. Also, higher ACE2 expression was recorded in the old male group compared with the old female group (78% vs. 67%) [15]. These results were comparable with findings obtained by Raharusun et al. [11]. Therefore, the absorption of vitamin D in the body may facilitate the ACE2 expression in the lungs.

To sum up, the use of vitamin D as a possible adjuvant therapy or in the formulation of fortified foods may regulate the ACE2 expression with a reduction in the generation of inflammatory cytokines. Compared with the direct addition/mixing method, micro-/nanoencapsulation of vitamin D into a polymer matrix and then the incorporation into food matrixes can notably improve its delivery rate through the enhanced physicochemical stability, water solubility, and bioavailability. It is recommended that the foods enriched with essential micronutrients such as vitamin D are mainly consumed by

malnourished people with COVID-19 as the European Society for Clinical Nutrition and Metabolism (ESPEN) recommended that these people should daily intake the average dietary level of micronutrients to optimize the general anti-infection response. In the future, this novel technology thus can lead to the production of vitamin D–fortified foods with an extended shelf life and diminished nutritional and organoleptic quality losses.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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Abbreviations COVID-19, Coronavirus disease 2019; 25(OH)D, 25-Hydroxyvitamin D; RDI, Recommended daily intake; ACE2, Angiotensin-converting enzyme II; RAS, Renin-angiotensin system

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