

LETTER TO THE EDITOR

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IS VITAMIN D ONE OF THE KEY ELEMENTS IN COVID-19 DAYS?

Dear Editor,

The epidemic that emerged in recent months and related to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) caused a global threat. When ineffective treatment methods and the lack of vaccines were considered, these issues caused a serious international concern (1). 80% of people who have had COVID-19 disease as a result of SARS-CoV-2 infection have mild illness or no symptoms (asymptomatic). In the rest of population, serious illness can occur. In addition to the clinical picture difference in COVID-19 disease, another striking feature is the variability in mortality rates between regions / countries. This difference in clinical table can be attributed to changes in age, comorbidity, race, diet, climate (air temperature / sun exposure), access to healthcare, reporting and surveillance of the population.

SARS-CoV-2, which initially shows its effect as immune suppression, continues its effect with excessive increase in immune system response and results in cytokine storm. Afterwards, with the development of acute respiratory distress syndrome (ARDS) and systemic inflammatory response syndrome (SIRS), the COVID-19 has far more severe consequences. On the other hand, the antiviral efficacy of vitamin D, which can also be thought as an immunomodulator and anti-inflammatory, has been shown in many studies of recent years (2, 3). Here, we will briefly examine the effects of vitamin D on the immune system as well as in the course and prognosis of COVID-19 disease under the light of recent literature data.

As mentioned in a recent published review (4), where many large studies have been addressed, vitamin D enhances cellular immunity by inducing some antimicrobial peptides, such as some antimicrobial peptides, defensins, e.g. cathelicidine (5-7). Cathelicidines have a direct antimicrobial effect against Gram-positive, Gram-negative bacteria, enveloped and non-enveloped viruses and fungi (8). These peptides kill pathogens by breaking their cell membranes. They can counteract the biological activities of their endotoxins and have many other significant functions like this (9). Vitamin D was shown to reduce influenza A virus replication in a mouse model (10). In another study, 1,25 (OH)₂ D₃ has been shown to reduce both in vitro and in vivo replication of rotavirus (11). In a clinical study, supplementation of 4000 IU / day vitamin D has also

been reported to reduce Dengue virus infection severity (12).

In addition, vitamin D increases cellular immunity by partially decreasing the cytokine storm caused by the innate immune system. The innate immune system produces both pro-inflammatory and anti-inflammatory cytokines in return to viral and bacterial infections, as seen in COVID-19 patients. Vitamin D can diminish the production of T helper 1 (Th1) cells such as IL-2, TNF- α , and interferons. Not only vitamin D supplementation decreases the expression of pro-inflammatory cytokines mentioned earlier but also enhances the expression of anti-inflammatory cytokines by monocytes / macrophages (13).

Vitamin D deficiency is thought to be a risk element for ARDS itself as well. In experiments on animals with ARDS, it has also been shown that virus transmission to the lungs could be reduced by modulating the activity of renin-angiotensin system and ACE-2 expression with vitamin D treatment (14).

Vitamin D deficiency poses an important health problem in all age groups (15). Quite a few foods contain vitamin D. Its main source is the non-enzymatic synthesis of ultraviolet-B (UVB) rays emitted from the sun. With increasing age, the production of vitamin D in the skin and serum 25 (OH) D₃ concentrations decrease considerably (16). This may be one of the key factors for COVID-19 disease because case death rates rise with age. The reason may be due to less time exposure to the sun and decreased vitamin D production as a result of low 7-dehydrocholesterol levels in the skin. Additionally, medication use also characteristically increases with age. Some pharmaceutical medications activate the pregnan-X receptor, reducing serum 25 (OH) D concentrations. These drugs consist of antiepileptics, antineoplastics, antibiotics, anti-inflammatory agents, antihypertensives, antiretrovirals, endocrine drugs, and some herbal medicines.

On the other hand, when we look at past pandemics in the world, a strong correlation was found between the case death rates and UVB exposure rates in the influenza epidemic of 1918-1919 (17). When the mortality rates in the United States (USA) were analyzed, the case mortality rate was approximately 6% in the northern states, whereas in the southern states it decreased to 3.5% (18). At this point, it comes to our mind that the change in mortality rates may be due to the difference of UVB exposure and vitamin D levels depending on the geographical locations in these regions. In accordance

with our opinion, we see that the frequency of vitamin D deficiency is known to be very high in European countries such as Italy, Spain and France (19), where the mortality rates due to COVID-19 disease are the highest.

When another study of 212 patients with proven SARS-CoV-2 infection was examined, serum 25 (OH) D level was the lowest in clinically severe cases, whereas it was highest in mild cases. Relation with serum 25 (OH) D levels was demonstrated to be statistically meaningful among clinical results. When all the results in the study are evaluated, the rise in serum 25 (OH) D levels in the COVID-19 patients suggests that it may improve clinical course or alleviate clinical outcomes even in severe cases. On the other hand, it may mean that the decline in serum 25 (OH) D levels in the body may worsen the clinical outcomes in patients (20). In another study involving twenty European countries, a negative correlation was found between serum 25 (OH) D levels and the total number of cases with COVID-19 disease and mortality rates due to this disease (21).

In the light of the literature knowledge above, we know that the antiviral and anti-inflammatory effectiveness of vitamin D is quite high. It comes to mind that vitamin D supplementation in the treatment may have a preventive effect on some negative consequences. Among the causes of this clinical diversity in the course and mortality rates of the COVID-19 cases, it is an important to remind that vitamin D deficiency can also be underlying comorbidity in the patients.

As a conclusion, in this period when we fought against the COVID-19 pandemic, which affected many countries around the world and caused thousands of people to die, no clear agent has been found in its treatment. In fact, an easily accessible agent such as vitamin D may be an important weapon in our hands. However, there is no clear evidence for high-dose or dose of vitamin D supplementation in patients with SARS-CoV-2 infection. Although there is a need for more research related to this subject, we think that supplementing vitamin D as a part of standard nutrition may be somewhat effective in providing clinical benefit.

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