

LETTER TO THE EDITOR

LETTER TO THE EDITOR

M.T. Aslan¹, İ.Ö. Aslan², Ö. Özdemir³, 1. *Istanbul University Istanbul Faculty of Medicine, Department of Pediatrics, Division of Neonatology, Istanbul, Turkey*; 2. *University of Health Sciences, Bakirkoy Dr. Sadi Konuk Training and Research Hospital, Department of Obstetrics and Gynecology, Istanbul, Turkey*; 3. *Sakarya University, Training and Research Hospital, Department of Pediatrics, Division of Allergy and Immunology, Sakarya, Turkey*. Corresponding author: *Öner Özdemir, Sakarya University, Training and Research Hospital, Department of Pediatrics, Division of Allergy and Immunology, Sakarya / Turkey, ozdemir_oner@hotmail.com*

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

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

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.

Acknowledgment: We would like to thank all our heroes actively working on this subject, both in the field and on the scientific platform, during these challenging days in the world, where the COVID-19 pandemic has been experienced.

References

1. Guo YR, Cao QD, Hong ZS, Tan YY, Chen SD, Jin HJ, Tan KS, Wang DY, Yan Y. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status. *Mil Med Res* 7: 11, 2020. doi:10.1186/s40779-020-00240-0
2. Teymouri-Rad M, Shokri F, Salimi V, Marashi SM. The interplay between vitamin D and viral infections. *Rev Med Virol* 29: e2032, 2019. doi:10.1002/rmv.2032
3. Hong M, Xiong T, Huang J, Wu Y, Lin L, Zhang Z, Huang L, Gao D, Wang H, Kang C, Gao Q, Yang X, Yang N, Hao L. Association of vitamin D supplementation with respiratory tract infection in infants. *Matern Child Nutr* 5: e12987, 2020. doi:10.1111/mcn.12987
4. Grant WB, Lahore H, McDonnell SL, Baggerly CA, French CB, Aliano JL et al. Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths. *Nutrients* 2020,12,988. doi:10.3390/nu12040988
5. Liu PT, Stenger S, Li H, Wenzel L, Tan BH, Krutzik SR, Ochoa MT, Schaubert J, Wu K, Meinkent C, et al. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. *Science* 2006, 311, 1770–1773.
6. Adams JS, Ren S, Liu, PT, Chun RF, Lagishetty V, Gombart, AF, Borregaard N, Modlin, RL, Hewison M. Vitamin d-directed rheostatic regulation of monocyte antibacterial responses. *J. Immunol.* 2009, 182, 4289–4295.
7. Laaksi, I. Vitamin D and respiratory infection in adults. *Proc. Nutr. Soc.* 2012, 71, 90–97.
8. Herr C, Shaykhiyev R, Bals R. The role of cathelicidin and defensins in pulmonary inflammatory diseases. *Expert Opin. Biol. Ther.* 2007, 7, 1449–1461.
9. Agier J, Efenberger M, Brzezinska-Blaszczyk E. Cathelicidin impact on inflammatory cells. *Cent. Eur. J. Immunol.* 2015, 40, 225–235.
10. Barlow PG, Svoboda P, Mackellar A, Nash AA, York IA, Pohl J, Davidson DJ, Donis RO. Antiviral activity and increased host defense against influenza infection elicited by the human cathelicidin LL-37. *PLoS ONE* 2011, 6, e25333.
11. Zhao Y, Ran Z, Jiang Q, Hu N, Yu B, Zhu L, Shen L, Zhang S, Chen L, Chen H, et al. Vitamin D Alleviates Rotavirus Infection through a Microm-155-5p Mediated Regulation of the TBK1/IRF3 Signaling Pathway In Vivo and In Vitro. *Int. J. Mol. Sci.* 2019, 20.
12. Martinez-Moreno J, Hernandez JC, Urcuqui-Inchima S. Effect of high doses of vitamin D supplementation on dengue virus replication, Toll-like receptor expression, and cytokine profiles on dendritic cells. *Mol. Cell. Biochem.* 2020, 464, 169–180
13. Cantorna MT, Snyder L, Lin YD, Yang L. Vitamin D and 1,25(OH)2D regulation of T cells. *Nutrients* 2015, 7, 3011–3021.
14. Xu J, Yang J, Chen J, Luo Q, Zhang Q, Zhang H. Vitamin D alleviates lipopolysaccharide-induced acute lung injury via regulation of the renin-angiotensin system. *Mol Med Rep* 16: 7432–7438, 2017. doi:10.3892/mmr.2017.7546
15. Palacios C, Gonzalez L. Is vitamin D deficiency a major global health problem? *J Steroid Biochem Mol Biol* 2014; 144:138-45.
16. McLaughlin J, Holick MF. Aging decreases the capacity of human skin to produce Vitamin D3. *J Clin Invest* 1985; 76:1536-38.
17. Grant WB, Giovannucci E. The possible roles of solar ultraviolet-B radiation and vitamin D in reducing case fatality rates from the 1918-1919 influenza pandemic in the United States. *Dermato-Endocrinology* 2009; 1:215-19.
18. Marik PE, Kory P, Varon J. Does vitamin D status impact mortality from SARS-CoV-2 infection?. *Medicine in Drug Discovery* (2020). doi:10.1016/j.medidd.2020.100041
19. Lips P, Cashman K, Lamberg-Allardt C et al (2019) Current vitamin D status in European and Middle East countries and strategies to prevent vitamin D deficiency: a position statement of the European Calcified Tissue Society. *Eur J Endocrinol* 180:23–54
20. Mark M. Alipio. Vitamin D supplementation could possibly improve clinical outcomes of patients infected with Coronavirus-2019 (COVID-2019). 09.04.2020. pre-print version. Electronic copy available at: <https://ssrn.com/abstract=3571484> (Date of access: 10.05.2020).
21. Ilie PC, Stefanescu S, Smith L. The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality. *Aging Clinical and Experimental Research.* 2020 May 6. doi:10.1007/s40520-020-01570-8