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LETTER TO THE EDITOR

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Vitamin D axis status and the severity of COVID-19

Dear Editor,

We read with great interest the article recently published in *Journal of Medical Virology* by Demir et al.,[1] examining the relationship between serum vitamin D levels and the laboratory findings and clinical outcomes of COVID-19 positive patients. They found that COVID-19 positive individuals with sufficient vitamin D levels had significantly lower D-dimer and CRP levels, reduced frequencies of ground-glass opacities on chest scanning, and shorter hospital stays. However, we would like to add some points which may be taken into consideration.

Vitamin D works together with the vitamin D-binding protein (VDBP) and vitamin D receptor (VDR). VDBP is a highly polymorphic serum glycoprotein synthesized and secreted by the liver.[2] It is the major carrier of vitamin D and its metabolites, including 25-hydroxyvitamin D (circulating reservoir) and 1,25-dihydroxyvitamin D (active form). VDBP is essential for vitamin D metabolism, as it binds 85%–90% of total circulating vitamin D. The non-VDBP fraction (bioavailable vitamin D) consists primarily of albumin-bound (10%–15%), leaving the remainder in the free form (<1%).[2] Compared to the overall vitamin D status, serum 25-hydroxyvitamin D levels before the COVID-19 positivity, appear to have limited value to predict the severity in COVID-19. Through the altered pharmacokinetics, insufficient circulating vitamin D may result in a greater concentration of bioavailable or free vitamin D of which the roles are not yet completely defined during critical illness.[3] Also, the reduced VDBP biosynthesis mainly due to the disturbed liver function with the upregulation of proinflammatory cytokines may change its affinity for vitamin D, which can take a role in the clinical severity during the COVID-19 pandemic.

Active vitamin D leads to multiple biological responses by binding to intracellular nuclear receptors, the VDRs, which are found on immune and pulmonary epithelial cells.[4] VDR expression is very low in resting conditions but upon activation, possibly due to the inflammatory conditions, it is significantly upregulated. This upregulation allows the upregulated vitamin D responsive genes that promote differentiation and proliferation of immune system cells to produce more anti-inflammatory cytokines.[4,5] Possible idea is that COVID-19-related proinflammatory state might induce a VDR overexpression tending to be accompanied by an increased potency of circulating vitamin D on target cells.

Considering the above, it seems that vitamin D, VDBP, and VDR, as a whole share complex mechanisms underlying the COVID-19 severity. Large-scale longitudinal studies measuring all three may give the insight to evaluate the contributions of these proteins in the development of vitamin D deficiency-related poor clinical outcomes.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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