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REPLY

Authors' reply: the biologic importance of the vitamin D binding protein polymorphism in pediatric COVID-19 patients

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What is Known?
- *Vitamin D has multiple roles in the immune system that can modulate the body reaction to an infection*
- *Vitamin D binding protein (DBP) is the key transport protein which, along with albumin, binds over 99% of the circulating vitamin D metabolites*

What is New?
- *Lower 25 OH vitamin D levels were associated with higher inflammation markers, suggesting an important role of vitamin D in the clinical course of COVID-19 in children and adolescents probably by regulating the systemic inflammatory response*
- *Further studies are warranted to investigate the possible causal association of DBP levels and polymorphism with vitamin D status (total and bioavailable vitamin D) in COVID-19 patients*

Keywords COVID-19, Vitamin D, Vitamin D binding protein

We would like to thank Speeckaert et al. for their interest in our study and for providing an insightful perspective on vitamin D binding protein (DBP) level or polymorphism as a possible explanation for the association between vitamin D status and COVID-19 outcomes.

The authors mentioned their previous study that the DBP1 allele frequency, which affects DBP concentration, was associated with lower prevalence and mortality due to SARS-COV-2 infection [1, 2]. Total 25(OH)D is defined by the DBP-bound fraction [approximately 85–90% of total 25(OH)D], the albumin-bound fraction [10–15% of total 25(OH)D], and the free circulating fraction [<1% of total 25(OH)D]. According to the free hormone hypothesis, vitamin D, which can enter the cell and have a biological effect, is in free form. It has been reported that DBP level and polymorphism affect the serum 25 OH vitamin D levels by changing the binding affinity to vitamin D, and also DBP may have an effect on 25 (OH) vitamin D related intracrine responses. Bioavailable vitamin D (not bound to DBP) is thought to be more biologically active in target tissues [3].

We agree with Speeckaert et al. that DBP polymorphism or concentration along could be a possible link for the

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Table 1 Correlations of 25 OH vitamin D with calcium, phosphorus, and parathormone

	r	*p* Value
Calcium (mg/dL)	0.330	0.001
Phosphorus (mg/dL)	0.431	<0.001
Parathormone (pg/mL)	−0.287	0.023

association between vitamin D status and COVID-19 outcomes. Although there are opinions that measuring the bioavailable vitamin D is more reliable to evaluate vitamin D activity and adequacy, serum 25 OH vitamin D level has been measured in most of the studies. As PTH increases in vitamin D deficiency, it is thought that PTH is a useful indicator of low vitamin D level [4, 5]. In our retrospective study, we evaluated the vitamin D status with 25 OH vitamin D. The vitamin D-deficient group had significantly lower calcium, phosphorus, and higher PTH levels. In addition, 25 OH vitamin D levels were positively correlated with calcium and phosphorus levels and negatively with the PTH levels demonstrating the reliability of 25 OH vitamin D levels to assess vitamin D bioactivity (deficiency) in our cohort (Table 1). There can be several reasons of the low 25 OH vitamin D level such as decreased intake, decreased biosynthesis due to lack of sun exposure, or as Speeckaert et al. stated DBP level or polymorphism.

In summary, our study shows the relationship between vitamin D deficiency and the clinical severity of COVID-19 and inflammatory markers. Further studies are warranted to investigate the possible causal association of DBP levels and polymorphism with vitamin D status (total and bioavailable vitamin D) in COVID-19 patients, as suggested by Speeckaert et al.

Author contribution EA, AA, and GA wrote the manuscript. EB, GA, KD, OA, AA, HNSD, and ME reviewed the manuscript.

Data availability The authors declare that (the/all other) data supporting the findings of this study are available within the article (and its supplementary information files).

Code availability Not applicable.

Declarations

Conflict of interests The authors declare no competing interests.

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