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Letter to the Editor

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Letter to the Editor from Speeckaert et al: "Vitamin D Deficiency Is Associated With Higher Hospitalization Risk from COVID-19: a Retrospective Case-control Study"

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Abbreviations: ARDS, acute respiratory distress syndrome; DBP, vitamin D binding protein; Gc-globulin, group-specific component globulin.

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With interest, we read the paper of Jude et al (1), which investigated the role of vitamin D in the severity of COVID-19. In detail, vitamin D insufficiency or deficiency was associated with a 2.3 to 3.6 times higher risk of SARS-CoV-2 infection necessitating hospital admission. We would like to stress the potential influence of vitamin D binding protein (DBP) polymorphisms on the reported results.

Vitamin D and its metabolites are mainly bound to a specific transport protein, DBP, or group-specific component globulin (Gc-globulin), and in a minor fraction to albumin. More specifically, 88% of circulating 25(OH)-vitamin D_3 and 85% of 1,25$(OH)_2$-vitamin D_3 is bound to DBP, whereas 10% to 15% is bound to albumin. DBP is a polymorphic plasma protein, which is characterized by 3 major alleles (DBP1F [rs7041-T/rs4588-C], DBP1S [rs7041-G/rs4588-C], and DBP2 [rs7041-T/rs4588-A]) with the following phenotypes: DBP1-1 (DBP1F-1F, DBP1F-1S, and DBP1S-1S), DBP2-1 (DBP2-1F and DBP2-1S), and DBP2-2 (DBP2-2), and with more than 120 unique variants. The 3 common DBP phenotypes have an influence on the plasma vitamin D and DBP concentrations, being highest in DBP1-1 individuals, intermediate in DBP2-1 individuals, and lowest in the DBP2-2 group (2). In a genome-wide association study, the *DBP* locus was 1 of the 3 most associated loci with the 25(OH)-vitamin D_3 concentration. Mendelian randomization models have demonstrated that many phenotypes have (direct or indirect) causal effects on 25(OH)-vitamin D_3 concentration (3).

Focusing on the potential association between DBP polymorphisms and COVID-19, a correlation between the rs7041 polymorphism and COVID-19 prevalence and mortality has been suggested (4). We have demonstrated that a higher country-specific DBP1 allele frequency is linked to a lower prevalence and mortality due to a SARS-CoV-2 infection, which could be partly explained by the potential protective effects of vitamin D and DBP (5). As DBP2 carriers may be more predisposed to vitamin D insufficiency relative to individuals with DBP1 isoforms, the former group may have higher odds of severe SARS-CoV-2 infection necessitating hospital admission. Vitamin D deficiency appears to contribute to the development of acute respiratory

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distress syndrome (ARDS) (6), which is one of the common clinical manifestations of severe COVID-19. In addition, a 30% reduction in plasma DBP in patients with ARDS supports a role for either reduced production or increased losses. Actin released from damaged cells is removed from the circulation by the extracellular actin-scavenger system, consisting of gelsolin and DBP. Gelsolin forms 1:2 molar complexes with filamentous, polymeric (F-)actin and stimulates its depolymerization, whereas DBP binds globular, monomeric (G-)actin and inhibits filament formation. The DBP-actin complexes are removed from the circulation by the reticuloendothelial system, primarily in the liver (7). So, patients with lower serum DBP levels, especially the DBP2-allele carriers, may consequently be more prone to endothelial damage. This can play an early and central pathogenic role in the development of ARDS and thrombosis during COVID-19 (8).

In conclusion, we suggest taking DBP polymorphisms into account in the evaluation of vitamin D concentrations in COVID-19 patients.

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Additional Information

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Disclosures: The authors have nothing to disclose.

Data Availability: Some or all data sets generated during and/or analyzed during the present study are not publicly available but are available from the corresponding author on reasonable request.

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