Vitamin D binding protein and its polymorphisms may explain the link between vitamin D deficiency and COVID-19

Marijn M. Speeckaert¹,² and Joris R. Delanghe³
¹Department of Nephrology, Ghent University Hospital, Ghent, Belgium
²Research Foundation-Flanders (FWO), Brussels, Belgium
³Department of Diagnostic Sciences, Ghent University, Ghent, Belgium

Keywords
COVID-19, outcome, polymorphism, vitamin D binding protein, vitamin D deficiency

With interest, we read the paper of Teama et al.¹ which investigated the association between vitamin D concentrations and the severity of coronavirus disease 2019 (COVID-19). More specifically, a high frequency of hypovitaminosis D in severe COVID-19 patients was observed, suggesting a potential association between vitamin D deficiency and a poor disease outcome. Despite the correlation between vitamin D deficiency and severe COVID-19, the potential protective role of vitamin D against severe COVID-19, based on its influence on both adaptive and innate immunity, remains unclear.² We would like to discuss the potential influence of vitamin D binding protein (DBP) and its polymorphisms on the reported results.

DBP is the major serum transporter and reservoir of all circulating vitamin D metabolites. In healthy subjects, ~85% of the vitamin D metabolites are bound with high affinity to DBP, whereas albumin binds ~15% with low affinity. This member of the albumin and alpha-fetoprotein gene family is characterized by a considerable polymorphism with three major alleles determined by the single nucleotide polymorphisms (SNPs) rs7041 and rs4588 [DBP1F (rs7041-T/rs4588-C), DBP1S (rs7041-G/rs4588-C), and DBP2...
and more than 120 variants. The DBP-phenotypes are associated with discriminatory differences in plasma concentrations of 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D and DBP, being highest in DBP1-1 subjects, intermediate in DBP2-1 individuals and lowest in the DBP2-2 group. The serum DBP concentration and the DBP genotype affect the bioavailable 25-hydroxyvitamin D concentration. Several additional SNPs affect the concentration of 25-hydroxyvitamin D, as demonstrated in a genome-wide meta-analysis. Among these SNPs, rs2282679 (located in the DBP gene) is a near-perfect proxy of rs4588. rs2282679-A is typically co-inherited with rs4588-C, whereas rs2282679-C is co-inherited with rs4588-A. rs2282679-A/A carriers have higher vitamin D levels than carriers of one such allele, who in turn have higher vitamin D concentrations than rs2282679-C/C subjects. Variants near genes involved in cholesterol synthesis [7-dehydrocholesterol reductase, NAD synthetase 1 (DHCR7/NADSYN1)] and hydroxylation [cytochrome P450, subfamily IIR (CYP2R1)] influence vitamin D status. More specifically, carriers of rs7944926 in DHCR7 and rs12794714 in CYP2R1 have an estimated reduction in the concentrations of 25-hydroxyvitamin D by 2–3 nmol/L per risk allele and these variants explain between 0.3% and 0.6% of the total variance in 25-hydroxyvitamin D concentrations.

Investigating the association between the DBP polymorphism and a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, Speeckaert et al. found a negative correlation between the country-specific DBP1 allele frequency and the prevalence and mortality of COVID-19, respectively. Besides, a significant positive correlation between the metabolism score (DBP rs2282679 + CYP24A1 s17216707) and COVID-19 disease severity has been reported. The DBP polymorphism rs2282679 could explain most of this interesting correlation. In another study, the GT genotype at the rs 7041 locus correlated positively with the prevalence and mortality rates, whereas a negative significant correlation was found between prevalence and mortality rates and the TT genotype. All these findings could be partly attributed to the protective effect of higher concentrations of vitamin D metabolites and DBP in these carriers of specific polymorphisms. Besides in the study of Teama et al., the median age was significantly higher in cases of severe COVID-19 than in the group of mild COVID-19. It should be mentioned that increasing age is not only associated with an elevated risk of vitamin D deficiency, but also with lower serum DBP concentrations.

A more severe course of COVID-19 is frequently accompanied by the presence of hypercoagulation, thromboembolic complications and acute respiratory distress syndrome (ARDS). Besides the already well-known potential protective immunomodulatory effects of vitamin D, DBP may play several roles in the course of COVID-19. Reduced serum DBP concentrations have been reported in patients with sepsis and ARDS. As a multifunctional protein, DBP is not only the major carrier of vitamin D metabolites, but acts also as an actin scavenger, a neutrophil chemotactic factor and a macrophage activator. The occurrence of thrombotic microangiopathy and ARDS will induce the release of globular actin (G-actin) by damaged cells into the extracellular space and the bloodstream, which may saturate the actin-scavenging proteins, gelsolin and DBP. The accumulation of G-actin will lead to polymerization and formation of actin filaments (F-actin),
contributing to pulmonic vessel obstruction, microthrombi, and endothelial dysfunction in COVID-19.

In conclusion, lower serum concentrations of DBP and vitamin D, as observed in DBP-2 and rs2282679-C carriers, may potentially make certain patients more prone to a more severe course of COVID-19.

Declaration of conflicting interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding
The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD
Marijn M. Speeckaert https://orcid.org/0000-0001-9183-4390

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Author Biographies

Marijn M. Speeckaert is a professor in Internal Medicine, Ghent University Hospital, Belgium. He published more than 160 papers and is team member of the nephrology research group of Ghent University.

Joris R. Delanghe is a professor in Clinical Chemistry, Ghent University, Belgium. He published more than 500 papers.