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

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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

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(rs7041-T/rs4588-A)] 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.[3] The serum DBP concentration and the DBP genotype affect the bioavailable 25-hydroxyvitamin D concentration.[4] 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.[5] 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.[6]

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.[7] 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.[8] 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.[9] 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.[10] Besides in the study of Teama et al.[1] 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.[11,12] 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.[3] 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.

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