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Association of Vitamin D Status and COVID-19-Related Hospitalization and Mortality

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With interest, we read the paper of Seal et al.,[1] which investigated the association of vitamin D status and COVID-19-related hospitalization and mortality. 25-Hydroxyvitamin D [25(OH)D] concentrations were connected in an inverse dose-response relationship to COVID-19-related hospitalization and mortality in a heterogeneous population of veteran patients. Although various confounders were considered, we want to emphasize the significance of vitamin D–binding protein (DBP) and its polymorphism on the obtained results.

Normally, 25(OH)D circulates mainly bound to DBP (approximately 85%) and albumin (15%), while only 0.03% exists in free form. DBP is the main transporter of vitamin D metabolites, and an extensive DBP polymorphism with a distinct allele distribution in various geographic areas has been identified.[2] The genetic polymorphisms *rs7041* and *rs4588* in exon 11 of the *DBP* gene identify the three major DBP alleles: DBP1F [*rs7041*-T (ASP), *rs4588*-C (Thr)], DBP1S [*rs7041*-G (ASP), *rs4588*-C (Thr)], and DBP2 [*rs7041*-T (ASP), *rs4588*-A (Lys)].[2,3] *rs2282679* is an *rs4588* proxy, and *rs2282679*-A is generally coinherited with *rs4588*-C, whereas *rs2282679*-C is usually coinherited with *rs4588*-A.[4] The concentrations of free and total 25(OH)D, as well as DBP, increase with the following phenotypes: DBP2-2<DBP2-1<DBP1-1.[2] *rs2282679*-C/C allele carriers have lower vitamin D and DBP levels than *rs2282679*-C/C allele carriers, who, in turn, have lower vitamin D and DBP levels than *rs2282679*-A/A people.[4] A genome-wide meta-analysis, however, revealed that, in addition to *rs4588*, *rs7041*, and *rs2282679*, the following SNPs had an effect on the 25(OH)D concentration: *rs6013897* (at CYP24A1), *rs10741657* (at CYP2R1), and *rs12785878* (near DHCR7).[3]

The relationship between the DBP polymorphism and COVID-19 has been studied before. We observed that DBP1 carriers are less likely to contract COVID-19 and die from it, which might be explained in part by vitamin D's supposed protective properties.[3] The metabolism score (*DBP*, *CYP24A1*) has been found to be significantly linked to COVID-19 severity, which may be due to the SNP *rs2282679*. A GWAS meta-analysis of COVID-19 host genetics that compared hospitalized and non-hospitalized patients found a significant link between DBP *rs2282679* and COVID-19 illness severity.[5] Furthermore, DBP has immunologic properties, as well as other biological functions, such as macrophage activation, chemotaxis, and actin scavenging,[2] which may contribute to the pathogenesis of COVID-19.

The current data show that the DBP polymorphism may have an impact on the connection between vitamin D and COVID-19-related hospitalization and death. However, the DBP haplotype effects may be less important in veterans than the effect of multiple chronic conditions.

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Marijn M. Speeckaert, MD, PhD[1,2]
Joris R. Delanghe, MD, PhD[3]

[1]Department of Nephrology, Ghent University Hospital,
Corneel Heymanslaan, 10 9000Ghent, Belgium
[2]Research Foundation-Flanders (FWO),
Brussels, Belgium
[3]Department of Diagnostic Sciences, Ghent University,
Ghent, Belgium

Corresponding Author: *Marijn M. Speeckaert, MD, PhD; Department of Nephrology, Ghent University Hospital, Corneel Heymanslaan, 10 9000Ghent, Belgium (e-mail: Marijn.Speeckaert@ugent.be).*

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