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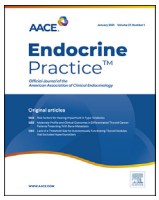
Endocrine Practice 27 (2021) 645

Contents lists available at ScienceDirect

Endocrine Practice

journal homepage: www.endocrinepractice.org



Letter to the Editor

Vitamin D Sufficiency and COVID-19: Is Vitamin D Binding Protein (and Its Polymorphism) the Missing Link?

To the Editor:

With interest, we read the paper of Charoenngam et al,[1] which revealed an independent association between vitamin D sufficiency and decreased risk of mortality from coronavirus disease 2019 (COVID-19) in elderly patients and patients without obesity. Besides the investigated comorbidities, we would like to highlight the potential influence of vitamin D binding protein (DBP) and its polymorphism on the reported results.

DBP, a serum 458-amino acid protein (molecular weight of 51.2 kDa), is the major vitamin D carrier, characterized by a considerable polymorphism with 3 common alleles (DBP1F, DBP1S, and DBP2). In healthy, White, premenopausal women, the median plasma concentrations of 25(OH)-vitamin D and $1,25(OH)_2$-vitamin D were determined by the DBP phenotypes: DBP1-1 was highest, DBP1-2 was intermediate, and DBP2-2 was lowest. Plasma DBP showed a similar concentration gradient among these phenotypes.[2] In a previous study of our group, the DBP1 allele frequency was associated with a lower prevalence and mortality due to a severe acute respiratory syndrome corona virus-2 infection.

Although a favorable prognosis is observed in most patients with COVID-19, severe acute respiratory syndrome corona virus-2 infection can lead to pneumonia, severe hypoxemia, and acute respiratory distress syndrome (ARDS). In patients with ARDS, vitamin D deficiency is ubiquitous, and significantly higher vitamin D levels have been found in survivors in comparison with nonsurvivors. A 30% reduction of DBP in patients with ARDS supports a role for either reduced production or increased losses as a partial explanation of vitamin D deficiency.[3]

Several potential hypotheses could explain these findings. First of all, as mentioned by Charoenngam et al,[1] vitamin D exerts some anti-inflammatory and immunomodulatory effects. However, apart from its specific sterol binding capacity (only 1%-2% of the total circulating DBP pool is vitamin D bound), DBP has several other important biological functions, such as actin scavenging, macrophage activation, fatty acid transport, and chemotaxis, which could play a role in the pathophysiology of COVID-19.[2] Increased serum F-actin concentrations have been detected in patients with ARDS, which may lead to the development of pulmonary vascular angiopathy, microembolisms, and multiple organ dysfunction syndrome. DBP and plasma gelsolin work in tandem in the actin scavenging system to clear extracellular actin released from dead or damaged cells for removal from the circulation. Actin essentially exists in 2 states inside a cell: monomeric globular actin, which can polymerize into filaments. DBP binds to globular actin monomers in a 1:1 molar complex with a high affinity (K_d of 10^{-9} M) for transport and eventual clearance primarily in the liver. A direct correlation has been demonstrated between low plasma DBP levels and poor overall survival. Although DBP-actin complexes generally have been considered as benign by-products, these complexes may also serve as an alarmin and possess a cytokinelike function. Based on current evidence, DBP likely plays a role in both the mediation and resolution of tissue injury via its actin-binding function.[2]

In conclusion, DBP and its polymorphism should be taken into account in future studies investigating the association between vitamin D and COVID-19.

Abbreviations: ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; DBP, vitamin D binding protein.

Disclosure

The authors have no multiplicity of interest to disclose.

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Marijn M. Speeckaert, MD, PhD
Department of Nephrology
Ghent University Hospital
Corneel Heymanslaan 10
Ghent 9000, Belgium

Research Foundation-Flanders (FWO)
Brussels, Belgium
E-mail address: marijn.speeckaert@ugent.be.

Reinhart Speeckaert, MD, PhD
Research Foundation-Flanders (FWO)
Brussels, Belgium

Department of Dermatology
Ghent University Hospital
Ghent, Belgium

Joris R. Delanghe, MD, PhD
Department of Diagnostic Sciences
Ghent University
Ghent, Belgium

Available online 2 April 2021

https://doi.org/10.1016/j.eprac.2021.03.011
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