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LETTER TO THE EDITOR

A key role for vitamin D binding protein in COVID-19?

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With interest, we read the paper of Abrishami et al. [1], which investigated the possible association of vitamin D status with lung involvement and outcome in patients with coronavirus disease 2019 (COVID-19). Higher 25-hydroxyvitamin D concentrations were associated with significantly less extent of total lung involvement, whereas a link was found between vitamin D deficiency and a significantly increased risk of mortality. We would like to highlight the importance of the polymorphic vitamin D binding protein (DBP), the major carrier of vitamin D, which plays probably an underestimated role in the pathogenesis of COVID-19.

DBP is a serum α_2-globulin with a molecular weight of 52–59 kDa. Under normal physiological conditions, nearly all (85–90%) circulating vitamin D compounds are tightly bound to DBP, which has a great influence on the vitamin D pharmacokinetic. Only 10–15% of the circulating vitamin D is associated with albumin, whereas < 1% of circulating vitamin D is present in its free form. The latter two form the bioavailable fraction of vitamin D [2]. Apart from its specific sterol binding capacity, DBP exerts several other important biological functions such as macrophage activation, enhancement of the leukocyte chemotactic activity of activated complement peptides, actin scavenging, and fatty acid transport. DBP is also characterized by a considerable polymorphism with three well-known alleles [DBP 1F (fast), DBP 1S (slow), and DBP 2], which are determined by two single-nucleotide polymorphisms (SNPs), *rs7041* and *rs4588*. The DBP 1F-proteins have a faster migration rate than those encoded by DBP 1S. The DBP phenotype determines the median plasma concentration of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D, being highest in DBP 1–1, intermediate in DBP 1–2, and lowest in DBP 2–2 [3]. The blood DBP concentration shows a similar pattern [4], and a positive correlation has been observed between serum 1,25-dihydroxyvitamin D and DBP concentrations in healthy women [5].

Although the exact pathophysiology of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection is not completely clear, different clinical stages of the disease have been identified, in which DBP can play a role. The early pathogenesis of COVID-19 pneumonia is characterized by a widespread endothelialitis affecting multiple organ systems. More specifically, viral inclusion bodies are detected within endothelial cells with apoptosis, inflammatory cell infiltration, and microvascular thrombosis. This is often accompanied by systemic inflammation with elevated concentrations of C-reactive protein, cytokines, and fibrinogen [6]. SARS-CoV can induce apoptosis and actin reorganization in mammalian cells under stressed conditions. During cell death and lung tissue injury, the release of globular actin (G-actin) in the extracellular compartment results in polymerization into filamentous actin (F-actin). An increased amount of F-actin is directly responsible for the aggregation of platelets in vitro and may lead to clogging of microvessels, reducing the flow of blood and generation of thrombus in the blood vessels. DBP and gelsolin are members of the extracellular actin scavenger system, which cleave actin and inhibit repolymerisation. However, elevated concentrations and/or prolonged exposure to DBP-actin complexes may induce endothelial cell injury and death, particularly in the lung microvasculature [7].

During a later phase of COVID-19, a disproportionate immune response may lead to cytokine storm syndrome, resulting in damage to the lung parenchyma, pneumonitis, acute respiratory distress syndrome (ARDS), viral septic shock, and death [6]. A 30% reduction in plasma DBP

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concentration, which is accompanied by lower circulating levels of 1,25-dihydroxyvitamin D, has been measured in patients with ARDS. This may be explained by either reduced production or increased losses of DBP or may be determined by the DBP phenotype [8]. DBP has also been detected in the bronchoalveolar lavage fluid of ARDS patients. DBP-release at sites of endothelial injury exerts a chemotactic effect on complement derived C5a and C5a des Arg. This leads to the attraction, aggregation, and activation of monocytes and neutrophils, generating an oxidative burst [2]. The competition of vitamin D metabolites for the same binding site on DBP may inhibit this chemotaxis, which may influence the course and outcome of COVID-19. DBP has also been identified as a good prognostic marker in septic patients. Lower serum DBP levels were associated with a higher risk of in-hospital mortality [9]. Therefore, we suggest exploring the value of DBP as a prognostic biomarker in patients with a SARS-CoV-2 infection [2, 9].

Finally, we have recently demonstrated the importance of the DBP polymorphism in COVID-19. More in detail, the frequency of the DBP 1 allele (a mixture of DBP 1F and DBP 1S) in 55 countries was compared with the prevalence and mortality data of COVID-19. The DBP 1 allele frequency was associated with a lower prevalence and mortality [10]. This could be partly explained by the potential protective effects of vitamin D, as higher concentrations of vitamin D metabolites are measured in patients with the DBP 1–1 phenotype [3].

In conclusion, future studies should explore the relationship between vitamin D, DBP, and COVID-19.

Compliance with ethical standards

Conflict of interest statement On behalf of all authors, the corresponding author states that there is no conflict of interest.

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