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Letter to the Editor

# Vitamin D binding protein: A key regulator of vitamin D deficiency among patients with pneumonia

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With interest, we read the paper of Sarhan et al. [1], which investigated the prevalence of vitamin D deficiency among pneumonia patients and the correlation between vitamin D levels and patients' outcomes. Vitamin D deficiency was associated with pneumonia severity, complications [e.g. acute respiratory distress syndrome (ARDS) and septicemia], and mortality rate. Following these findings, we would like to highlight the important role of vitamin D binding protein (DBP), which may affect clinical outcomes by influencing the plasma vitamin D concentration and by mechanisms other than its interaction with vitamin D.

DBP is an alpha-2-globulin with a molecular weight of 52–59 kDa with diverse physiologically important properties. One of the main functions of this plasma protein is binding, solubilization, and transport of vitamin D and its metabolites. The majority of 25-hydroxyvitamin D (88%) and 1,25-dihydroxyvitamin D (85%) in plasma is tightly bound to DBP (Ka = 5 × 10-8 M and Ka = 4 × 10-7 M, respectively) [2], whereas the remaining fraction (12–15%) forms a complex with albumin with a lower affinity [25-hydroxy vitamin D (Ka = 6 × 10-5 M) and 1,25-dihydroxyvitamin D (Ka = 5.4 × 10-4 M)] [3]. A much lower percentage (<1%) of circulating vitamin D exists in an unbound form. The free hormone hypothesis states that protein-bound hormones are inactive, while unbound hormones are free to exert biological activity [4]. In general, the total plasma 25-hydroxyvitamin D is measured in the clinical laboratory, which consists of the 3 forms of DBP-bound, albumin-bound, and free fraction. Bioavailable 25-hydroxyvitamin D (the free plus albumin-bound fractions) has been proposed as a better indicator of vitamin D activity, which can be calculated using several equations and a mathematical model, which incorporate 25-hydroxyvitamin D, DBP concentration, albumin level, and DBP binding affinity by phenotype to varying degrees [5]. DBP is characterized by three well-known alleles (DBP 1F, DBP 1S, and DBP 2), which are defined by the single-nucleotide polymorphisms (SNPs) rs7041 and rs4588, and more than 120 variants. The major 3 alleles lead to a simple classification of DBP phenotypes, namely DBP 1-1 (DBP 1F-1F, DBP 1F-1S, and DBP 1S-1S), DBP 2-1 (DBP 2-1F and DBP 2-1S), and DBP 2-2 (DBP 2-2). The DBP phenotype determines the plasma concentration of DBP, as well as of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D with the highest levels in DBP 1-1, intermediate levels in DBP 2-1, and lowest levels in patients with the DBP 2-2 phenotype [6].

In agreement with the findings of Sarhan et al. [1], a significant decrease in serum 25-dihydroxyvitamin D as well as of serum DBP has been reported in children under 3 years with pneumonia [7]. The interpretation of 25-hydroxyvitamin D measurement during critical care may be problematic due to variations of binding protein concentrations. Altered serum DBP and albumin levels in the setting of inflammation, fluid shifts, capillary leaks, and renal wasting are likely to have a strong influence on the bioavailable 25-hydroxyvitamin D pool [8]. Although total plasma 25-hydroxyvitamin D concentrations are lower in critically ill patients, calculated free 25-hydroxy vitamin D levels are comparable to those measured in the general population, which has also been demonstrated for other hormones (cortisol, thyroxine). The decreased plasma concentration of total 25-hydroxyvitamin D in pneumonia patients may be due to decreases in DBP and albumin, which act as negative acute-phase proteins [9].

In critically-ill trauma patients, an association has been found between low serum DBP concentrations and a higher risk of respiratory failure and sepsis development [10]. Although a lower amount of serum DBP has been measured in patients with sepsis [11], higher serum DBP concentrations were detected in survivors of sepsis at 30 days in comparison to nonsurvivors [8]. Besides the transport of vitamin D metabolites, which covers only 1–2% of the sterol binding, DBP is a scavenger of monomeric G-actin (globular) (Kd = 10-9 M), released from injured tissue, and prevents polymerization into F-actin (fibrillar). A large percentage of the circulating DBP pool (>50%) can be complexed with actin during tissue injury, which may play a protective role against the microembolization of end-organs. The binding of F-actin to with coagulation factor Va may trigger disseminated intravascular coagulation and multiple organ dysfunction syndrome [12]. Actin binding with DBP lowers the circulating DBP as well as the vitamin D metabolite concentrations, providing another mechanism to explain why vitamin D insufficiency is common in pneumonia patients with sepsis and why it is associated with an increased mortality rate [11]. On the other hand, it should be noted that prolonged exposure to DBP-actin complexes may induce endothelial cell injury and death, particularly in the lung microvasculature. The mechanism of endothelial cell death proceeds via both caspase-3 dependent and independent pathways [13]. Finally, as demonstrated in a mice model of immune complex alveolitis, DBP-actin complexes may be the active chemotactic

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cofactor by recruiting neutrophils to sites of inflammation [14].

In conclusion, we propose to take into account DBP when studying the role of vitamin D deficiency on the severity of pneumonia and its clinical outcomes.

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## Conflict of interest

The authors declare that they have no conflict of interest.

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