Genetic polymorphisms, vitamin D binding protein and vitamin D deficiency in COVID-19

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Reply to M.M. Speeckaert and co-workers:

We thank M.M. Speeckaert and co-workers for their interest in our paper about vitamin D status and seroconversion for coronavirus disease 2019 (COVID-19) in UK healthcare workers [1]. We agree with the authors that vitamin D binding protein (DBP) is important in determining serum 25(OH)D3 levels. The majority of vitamin D in the circulation is bound to DBP, also known as gc-globulin, which has actin-binding and immunomodulatory functions independent of vitamin D carriage [2]. DBP levels may be particularly relevant to determining 25(OH)D3 levels in severely ill COVID-19 patients with acute respiratory distress syndrome (ARDS), as we have previously demonstrated that DBP is a negative acute phase protein with levels dropping by about a third in patients with ARDS [3]. This tends to lower circulating total vitamin D but releases free 25(OH)D that can be taken up by cells of the immune system and epithelial cells. The consequences of changes in serum 25(OH)D during illness are, therefore, complex and difficult to interpret [4]. Genome-wide association analyses have shown that single nucleotide polymorphisms (SNPs) in the gene for DBP (*GC*) are important contributors to the genetic component of circulating 25D concentrations, but this is still a relatively small proportion of overall serum 25D levels, and it is unclear how these SNPs impact DBP/25D homeostasis in the setting of disease.

In terms of the relevance of vitamin D levels to COVID-19 susceptibility and severity we disagree with the authors that no evidence supports a protective role for vitamin D supplementation in COVID-19 outcomes. There are many studies that support the importance of vitamin D deficiency on recent vitamin D measurements prior to COVID-19, as well as the results of studies that have measured 25(OH)D3 and looked at associations with COVID-19 severity, which are summarised in a recent review [4]. Most of these studies are of small patient numbers that fail to look at the full biological complexity of the vitamin D metabolome.

In terms of supplementation altering outcome, pre-COVID-19 the VITDALIZE trial was addressing whether high dose cholecalciferol therapy reduces mortality in critically ill patients with severe vitamin D deficiency (24(OH)D3 levels <30 nmol·L^{-1}) [5]. We are also encouraged by the results of the study using calcifediol (oral 25(OH)D3), which bypasses the need for liver metabolism of cholecalciferol in COVID-19 patients, that suggest a significant potential effect on outcome [6]. Clearly, larger studies are needed and we have proposed in the UK that calcifediol be added as an arm in the UK NHS COVID-19 RECOVERY trial.

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