

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

Faniyi, Aduragbemi A; Lugg, Sebastian T; Faustini, Sian E; Webster, Craig; Duffy, Joanne E; Hewison, Martin; Shields, Adrian; Nightingale, Peter; Richter, Alex G; Thickett, David R

DOI:

[10.1183/13993003.00653-2021](https://doi.org/10.1183/13993003.00653-2021)

License:

Creative Commons: Attribution-NonCommercial (CC BY-NC)

### Document Version

Publisher's PDF, also known as Version of record

### Citation for published version (Harvard):

Faniyi, AA, Lugg, ST, Faustini, SE, Webster, C, Duffy, JE, Hewison, M, Shields, A, Nightingale, P, Richter, AG & Thickett, DR 2021, 'Genetic polymorphisms, vitamin D binding protein and vitamin D deficiency in COVID-19', *The European respiratory journal*, vol. 57, no. 5, 2100653. <https://doi.org/10.1183/13993003.00653-2021>

[Link to publication on Research at Birmingham portal](#)

### General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

### Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact [UBIRA@lists.bham.ac.uk](mailto:UBIRA@lists.bham.ac.uk) providing details and we will remove access to the work immediately and investigate.



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

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  $<30 \text{ nmol}\cdot\text{L}^{-1}$ ) [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.



@ERSpublications

**This work outlines the potential importance of vitamin D binding protein and vitamin D in immune function and COVID-19 infection** <https://bit.ly/3byTaO5>

**Cite this article as:** Faniyi AA, Lugg ST, Faustini SE, *et al.* Genetic polymorphisms, vitamin D binding protein and vitamin D deficiency in COVID-19. *Eur Respir J* 2021; 57: 2100653 [<https://doi.org/10.1183/13993003.00653-2021>].

Aduragbemi A. Faniyi<sup>1,5</sup>, Sebastian T. Lugg<sup>1,5</sup>, Sian E. Faustini<sup>2</sup>, Craig Webster<sup>3</sup>, Joanne E. Duffy<sup>3</sup>, Martin Hewison<sup>4</sup>, Adrian Shields<sup>2,3</sup>, Peter Nightingale<sup>3</sup>, Alex G. Richter<sup>2,3,6</sup> and David R. Thickett<sup>1,3,6</sup>  
<sup>1</sup>Birmingham Acute Care Research Group, Institute of Inflammation and Ageing, University of Birmingham, Birmingham, UK. <sup>2</sup>Clinical Immunology Service, Institute of Immunology and Immunotherapy, University of Birmingham, Birmingham, UK. <sup>3</sup>University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK. <sup>4</sup>Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, UK. <sup>5</sup>Joint first authors. <sup>6</sup>Joint last authors.

Correspondence: David R. Thickett, Institute of Inflammation and Ageing, University of Birmingham, Birmingham, B15 2TH, UK. E-mail: [d.thickett@bham.ac.uk](mailto:d.thickett@bham.ac.uk)

Received: 3 March 2021 | Accepted: 4 March 2021

Conflict of interest: A.A. Faniyi has nothing to disclose. S.T. Lugg has nothing to disclose. S.E. Faustini has nothing to disclose. C. Webster has nothing to disclose. J.E. Duffy has nothing to disclose. M. Hewison reports personal fees for lectures from Thornton Ross, outside the submitted work. A. Shields has nothing to disclose. P. Nightingale has nothing to disclose. A.G. Richter has nothing to disclose. D.R. Thickett reports personal fees for lectures from Thornton Ross, outside the submitted work.

## References

- 1 Faniyi AA, Lugg ST, Faustini SE, *et al.* Vitamin D status and seroconversion for COVID-19 in UK healthcare workers. *Eur Respir J* 2021; 57: 2004234.
- 2 Chishimba L, Thickett DR, Stockley RA, *et al.* The vitamin D axis in the lung: a key role for vitamin D-binding protein. *Thorax* 2010; 65: 456–462.
- 3 Dancer RC, Parekh D, Lax S, *et al.* Vitamin D deficiency contributes directly to the acute respiratory distress syndrome (ARDS). *Thorax* 2015; 70: 617–624.
- 4 Griffin G, Hewison M, Hopkin J, *et al.* Preventing vitamin D deficiency during the COVID-19 pandemic: UK definitions of vitamin D sufficiency and recommended supplement dose are set too low. *Clin Med (Lond)* 2021; 21: e48–e51.
- 5 Amrein K, Parekh D, Westphal S, *et al.* Effect of high-dose vitamin D3 on 28-day mortality in adult critically ill patients with severe vitamin D deficiency: a study protocol of a multicentre, placebo-controlled double-blind phase III RCT (the VITDALIZE study). *BMJ Open* 2019; 9: e031083.
- 6 Entrenas Castillo M, Entrenas Costa LM, Vaquero Barrios JM, *et al.* Effect of calcifediol treatment and best available therapy *versus* best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: a pilot randomized clinical study. *J Steroid Biochem Mol Biol* 2020; 203: 105751.

Copyright ©The authors 2021.

This version is distributed under the terms of the Creative Commons Attribution Non-Commercial Licence 4.0. For commercial reproduction rights and permissions contact [permissions@ersnet.org](mailto:permissions@ersnet.org)