Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Endocrine Practice 27 (2021) 646–647

Contents lists available at ScienceDirect

Endocrine Practice

journal homepage: www.endocrinepractice.org

Letter to the Editor

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

In Response:

We would like to thank Speeckaert et al[1] for their interest in our study and for providing an insightful perspective on vitamin D binding protein (DBP) level or polymorphism as a possible explanation for the association between vitamin D status and coronavirus disease 2019 (COVID-19) outcomes. The authors mentioned their previous study, in which the DBP1 allele frequency, which affects DBP concentration, was associated with lower prevalence and mortality of COVID-19.[1] They further brought evidence to support their conclusion that DBP has an independent biological effect on actin scavenging, which is thought to be protective against the development and severity of acute respiratory distress syndrome. Therefore, DBP concentration or certain polymorphisms that affect the circulating concentration of DBP and thus total serum 25-hydroxyvitamin D level might be one of the unaddressed potential confounders in our analysis.

We agree with Speeckaert et al that DBP polymorphism or concentration along with multiple other unmeasured confounders such as physical activity, sunlight exposure, nutritional intake, and occult comorbidities could be a possible link for the association between vitamin D status and COVID-19 outcomes that we observed, which has been replicated in several studies.[2] Therefore, we performed additional statistical analysis to determine the E-value for each statistically significant outcome. The E-value indicates the minimum effect size on the odds ratio scale that an imaginary unmeasured confounder would have to have with both the exposure and outcome to null the observed association. As shown in the Table, it could be interpreted that the combination of any unaddressed confounders would need to have the association with both vitamin D status and outcomes with the odds ratio of at least 8.6 and 10.6 to null the observed association of vitamin D sufficiency with acute respiratory distress syndrome in patients aged >65 years old and with death in patients with body mass index <30 kg/m^2, respectively. It is therefore very unlikely for any combination of genetic, biochemical, and environmental factors that are left unaddressed in our study to have such strong associations with both vitamin D status and/or outcomes.

In fact, the topic of DBP and COVID-19 is as interesting as that of vitamin D because the causal associations for both factors are still unclarified. The results from clinical trials that gave different forms of vitamin D to hospitalized patients with COVID-19 are conflicting, suggesting that the immunomodulatory actions of vitamin D, if clinically significant, are likely to be long-term rather than short-term effects.[3] Therefore, the impact of correcting vitamin D deficiency or insufficiency over the short term may not be as strong as maintaining adequate serum 25-hydroxyvitamin D level over the long term.

Similar to vitamin D status, DBP polymorphisms have been shown to be associated with prevalence and mortality of COVID-19,[4,5] as well as presence of other chronic diseases.[6] The study by Speeckaert et al,[4] which expanded the previous finding by Batur et al,[5] showed a significant correlation between the prevalence of DBP gene polymorphism (rs7041) in each of the 55 countries and incidence and mortality of COVID-19. However, caution is needed while interpreting this observation, because using aggregated country data may be susceptible to ecological fallacy. In addition, there might be other conditions that link the presence of DBP polymorphism with COVID-19, such as comorbidities. In conclusion, we believe that the observed association between vitamin D sufficiency and COVID-19 outcomes in our study was sufficiently strong, especially for acute respiratory distress syndrome in patients aged ≥65 years old and death in patients with body mass index <30 kg/m^2. Nevertheless, the possible causal association of DBP, as suggested by Speeckaert et al, is a topic of interest. Further studies are warranted to investigate the association of COVID-19 with DBP polymorphism(s), DBP levels, as well as total and free 25-hydroxyvitamin D.

Disclosure

M.F.H. is a consultant for Quest Diagnostics, Inc, Biogena, Inc, and Ontometrics, Inc, and is on the speaker's bureau for Abbott, Inc. C.M.A. reports receiving personal fees from Nutrisystem, Zafgen, Sanofi-Aventis, Orexigen, EnteroMedics, GI Dynamics, Scientific Intake, Gelesis, Novo Nordisk, SetPoint Health, Xeno Biosciences, Rhythm Pharmaceuticals, Eisai, and Takeda outside of the funded work, reports receiving grant funding from Aspire Bariatrics, GI Dynamics, Orexigen, Takeda, the Vela Foundation, Gelesis, Energesis, Coherence Lab, and Novo Nordisk outside of the funded work, and reports past

DOI of original article: https://doi.org/10.1016/j.eprac.2021.03.011.

Abbreviations: COVID-19, coronavirus disease 2019; DBP, vitamin D binding protein.

https://doi.org/10.1016/j.eprac.2021.03.016

Table
Evalues for the outcomes that had statistically significant association with vitamin D sufficiency [25-hydroxyvitamin D ≥30 ng/mL] in the multivariate models.

Subgroup	Outcome	Adjusted odds ratio (95%CI)	E-value
Age ≥65 years old	Death	0.33 (0.12, 0.94)	2.9
	ARDS	0.22 (0.05, 0.96)	8.6
	Severe sepsis/septic shock	0.26 (0.08, 0.88)	3.3
BMI <30 kg/m^2	Death	0.18 (0.04, 0.84)	10.6

Abbreviations: ARDS: Acute Respiratory Distress Syndrome; BMI: Body Mass Index; E-value: the minimum effect size on the odds ratio scale that an unmeasured confounder would have to have with both the exposure and outcome to null the observed association.

equity interest in ScienceSmart, LLC. The remaining authors have no conflicts of interest.

Acknowledgment

N.C. received an institutional research training grant from the Ruth L. Kirchstein National Research Service Award program from the National Institutes of Health (2 T32 DK 7201-42). C.M.A. is supported by P30 DK046200.

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Available online 2 April 2021