

Response to Singh and Singh

Philip C. Calder^{1,2}

¹School of Human Development and Health, Faculty of Medicine, University of Southampton, Southampton, United Kingdom

²NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust and University of Southampton, Southampton, United Kingdom

Email: pcc@soton.ac.uk

I thank Singh and Singh for their interest in my article [1]. However, they misinterpret the message of the article. They summarise that the article “emphasises the need for appropriate nutrition supplementation for the old, frail, obese, diabetic, and generally malnourished, who have been adversely impacted in COVID-19” and they urge caution about micronutrient supplementation in those who are infected. In fact, the summary of my article is that “attention should be focussed on addressing current nutritional inadequacies (frailty, obesity, general undernutrition, micronutrient insufficiency or deficiency) that are widespread in the population in order to better support the immune response ...for ensuring the population is better prepared for future pandemics” [1]. With regard to micronutrients, the summary of my article is that “multiple micronutrients play vital roles in supporting all aspects of the immune response and therefore their intake and status need to be considered in the context of susceptibility to SARS-CoV-2 infection and COVID-19 severity” [1]. Thus, the focus of my article is prevention of infectious disease by creating a nutritional environment that supports an appropriate immune response should the individual become infected; the context is not treatment of those already infected. Indeed, my article contains no recommendation to treat those already infected with micronutrients, although it does refer to some studies where vitamin D and zinc have been used as treatments in those with COVID-19. The proposal that several micronutrients are important in supporting the immune system is based upon studies in model systems, including of underlying mechanisms of action, and in humans, as summarised elsewhere [2,3,4]. Furthermore, this is consistent with the World Health Organisation’s statement in October 2020 that “Micronutrients are critical for a well-functioning immune system, which is of utmost importance during the COVID-19 pandemic. If a population has poor status for key micronutrients, such as vitamin A, zinc or vitamin D,

then they may be less well equipped to mount a proper immune response when exposed to viral or bacterial infections than if they had adequate micronutrient status” [5].

The main thrust of the argument of Singh and Singh is that supplementation with micronutrients in those already infected should be approached cautiously. I fully agree with this and with the proposal that the low status of some micronutrients in infected individuals reflects the acute phase response rather than low intakes *per se*. This is one reason why I avoided making any recommendation for, or against, supplementation in those with infectious disease. Nevertheless, some studies have reported that vitamin D [6-8] and zinc [9,10] both reduce severity of COVID-19 in hospitalised patients. What is clear is that more needs to be understood about the determinants and meaning of alterations in micronutrient status in those with infections. Thank you to Singh and Singh for drawing attention to this.

Conflicts of interest

PCC has research funding from Bayer Consumer Care and acts as an advisor/consultant to DSM, BASF AS, Cargill, Smartfish, Fresenius-Kabi, Bayer Consumer Care, GSK Consumer Healthcare, Danone/Nutricia, Nutrileads and Kemin.

References

1. Calder PC. Nutrition and immunity: lessons for COVID-19. *Nutr Diab*. 2021;11:19.
2. Gombart AF, Pierre A, Maggini S. A review of micronutrients and the immune system – working in harmony to reduce the risk of infection. *Nutrients*. 2020;12:236.
3. Calder PC. Nutrition, immunity and COVID-19. *BMJ Nutr Prev Health*. 2020;3:e000085.
4. Berger MM, Herter-Aeberli I, Zimmermann MB, Spieldenner J, Eggersdorfer M. Strengthening the immunity of the Swiss population with micronutrients: A narrative review and call for action. *Clin Nutr ESPEN*. 2021;43:39-48.
5. World Health Organisation. New electronic survey manual supports countries to combat micronutrient deficiencies. <https://www.who.int/news/item/15-10-2020-new-electronic-survey-manual-supports-countries-to-combat-micronutrient-deficiencies>. 2020 (accessed 14 December 2021).
6. Ling SF, Broad E, Murphy R, Pappachan JM, Pardesi-Newton S, Kong MF, et al. High-dose cholecalciferol booster therapy is associated with a reduced risk of mortality in

patients with COVID-19: A cross-sectional multi-centre observational study. *Nutrients*. 2020;12:3799.

7. Giannini S, Passeri G, Tripepi G, Sella S, Fusaro M, Arcidiacono G, et al. Effectiveness of in-hospital cholecalciferol use on clinical outcomes in comorbid COVID-19 Patients: A hypothesis-generating study. *Nutrients*. 2021;13:219.
8. Alcala-Diaz JF, Limia-Perez L, Gomez-Huelgas R, Martin-Escalante MD, Cortes-Rodriguez B, Zambrana-Garcia JL, et al. Calcifediol treatment and hospital mortality due to COVID-19: A cohort study. *Nutrients*. 2021;13:1760.
9. Carlucci PM, Ahuja T, Petrilli C, Rajagopalan H, Jones S, Rahimian J. Zinc sulfate in combination with a zinc ionophore may improve outcomes in hospitalized COVID-19 patients. *J Med Microbiol*. 2020;69:1228-1234.
10. Frontera JA, Rahimian JO, Yaghi S, Liu M, Lewis A, de Havenon A, et al. Treatment with zinc is associated with reduced in-hospital mortality among COVID-19 patients: a multi-center cohort study. *Res Sq*. 2020;rs.3.rs-94509. [Preprint]