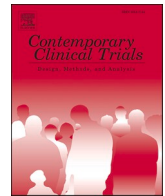




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## Response to the letter to the editor: “The link between Vitamin D and COVID-19”

Camposa et al. [1] propose that we consider using larger doses of vitamin D<sub>3</sub> supplementation in our randomized trial [2]. In the Vitamin D and COVID-19 (VIVID) trial, we are testing vitamin D<sub>3</sub> supplementation for prevention of moderate or severe COVID-19 illness requiring healthcare visits, as well as its role for post-exposure prophylaxis among those with a household member with the infection.

To clarify a few points about our design:

- We propose administering 10,000 IU per day for two days followed by 3200 IU per day for the remaining 4 weeks, in order to quickly raise levels among those whose levels are low to a replete level, without incurring the adverse events that can occur with high-dose bolus dosing) [3,4]. These doses are high enough to achieve and maintain serum 25(OH)D levels of at least 30 ng/ml (75 nmol/l) in most participants [5], but are below the upper intake limit set by the Institute of Medicine of 4000 IU/day for adults) [6]. We expect these doses will also help to attenuate the cytokine-mediated inflammatory response seen in more severe COVID-19 [2].
- In choosing the dose, we considered evidence from prior RCTs testing vitamin D in acute respiratory infections (ARIs). The few trials that used a large bolus dose did not show evidence of benefit. Among residents of assisted living facilities in London, giving 96,000 or 120,000 IU of vitamin D for 2 months followed by 400 IU/day did not influence risk of ARI in older adults and was associated with increased duration of upper respiratory tract infections [7]. Bolus dosing of vitamin D also did not influence the duration or severity of upper respiratory infections [8] or outcomes following community-acquired pneumonia [9]. Of note, our meta-analysis of vitamin D trials revealed no benefit of bolus dosing in preventing ARIs, but did show a protective effect of daily or weekly regimens. [10]. It has been postulated that high vitamin D concentrations after bolus dosing may dysregulate enzymes responsible for synthesis and degradation of the active vitamin D metabolite [11] and attenuate its ability to support protective immune responses.
- We also believe that our vitamin D dosing is appropriate for the question of post-exposure prophylaxis.
- We are measuring 25(OH)D levels at baseline and at 4 weeks in most participants, although a subset will have measurements at 1 or 2 weeks to assess the time course of the response to supplementation. The blood will be sampled by fingerprick, using a microsampling device. We are not specifically targeting a vitamin D deficient population because of ethical concerns about randomizing half to placebo among a deficient group. In fact, we have advocated that during the COVID-19 pandemic, it is particularly important to avoid vitamin D deficiency [12].
- Finally, an additional follow-up survey will be done at 8 weeks to assess persistence of symptoms; this will allow us to evaluate whether vitamin D supplementation hastens recovery from COVID-19 and reduces the risk of the post-acute sequelae of COVID-19 syndrome.

### Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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