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.

Contemporary Clinical Trials 105 (2021) 106418

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

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 D3 supplementation in our randomized trial [2]. In the VItamin D and COVID-19 (VIVID) trial, we are testing vitamin D_3 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.

References

[1] Camposa D, Silva Jr ED, Fulcoa UL, Oliveira JIN. The link between vitamin D and COVID 19. Letter to Editor, VIVID.
[2] R. Wang, V. DeGruttola, Q. Lei, K.H. Mayer, S. Redline, A. Hazra, S. Mora, W. C. Willett, D. Ganmaa, J.E. Manson, The vitamin D for COVID-19 (VIVID) trial: a pragmatic cluster-randomized design, Contemp. Clin. Trials. 100 (2021 Jan) 106176, https://doi.org/10.1016/j.cct.2020.106176. Epub 2020 Oct 10. PMID: 33045402; PMCID: PMC7547023.
[3] K.M. Sanders, A.L. Stuart, E.J. Williamson, J.A. Simpson, M.A. Kotowicz, D. Young, G.C. Nicholson, Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial, JAMA 303 (18) (2010 May 12) 1815–1822, https://doi.org/10.1001/jama.2010.594. Erratum in: JAMA. 2010 Jun 16;303(23): 2357. PMID: 20460620.
[4] L.A. Burt, E.O. Billington, M.S. Rose, D.A. Raymond, D.A. Hanley, S.K. Boyd, Effect of high-dose vitamin D supplementation on volumetric bone density and bone strength: a randomized clinical trial, JAMA. 322 (8) (2019) 736–745.
[5] R.P. Heaney, K.M. Davies, T.C. Chen, M.F. Holick, M.J. Barger-Lux, Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol, Am. J. Clin. Nutr. 77 (1) (2003 Jan) 204–210, https://doi.org/10.1093/ajcn/77.1.204. Erratum in: Am J Clin Nutr. 2003 Nov;78(5):1047. PMID: 12499343.
[6] Institute of Medicine, Dietary Reference Intakes for Calcium and Vitamin D, National Academies Press, Washington, D.C., 2010.
[7] A.R. Martineau, Y. Hanifa, K.D. Witt, N.C. Barnes, R.L. Hooper, M. Patel, N. Stevens, Z. Enayat, Z. Balayah, A. Syed, A. Knight, D.A. Jolliffe, C.L. Greiller, D. McLaughlin, T.R. Venton, M. Rowe, P.M. Timms, D. Clark, Z. Sadique, S. M. Eldridge, C.J. Griffiths, Double-blind randomised controlled trial of vitamin D3 supplementation for the prevention of acute respiratory infection in older adults and their carers (ViDiFlu), Thorax. 70 (10) (2015 Oct) 953–960, https://doi.org/10.1136/thoraxjnl-2015-206996. Epub 2015 Jun 10, 26063508.
[8] D.R. Murdoch, S. Slow, S.T. Chambers, L.C. Jennings, A.W. Stewart, P.C. Priest, C. M. Florkowski, J.H. Livesey, C.A. Camargo, R. Scragg, Effect of vitamin D3 supplementation on upper respiratory tract infections in healthy adults: the VIDARIS randomized controlled trial, JAMA. 308 (13) (2012 Oct 3) 1333–1339, https://doi.org/10.1001/jama.2012.12505. 23032549.
[9] S. Slow, M. Epton, M. Storer, R. Thiessen, S. Lim, J. Wong, P. Chin, P. Tovaranonte, J. Pearson, S.T. Chambers, D.R. Murdoch, VIDCAPS Group, Effect of adjunctive single high-dose vitamin D3 on outcome of community-acquired pneumonia in hospitalised adults: The VIDCAPS randomised controlled trial, Sci. Rep. 8 (1) (2018 Sep 14) 13829, https://doi.org/10.1038/s41598-018-32162-2. PMID: 30218062; PMCID: PMC6138743.
[10] A.R. Martineau, D.A. Jolliffe, R.L. Hooper, L. Greenberg, J.F. Aloia, P. Bergman, G. Dubnov-Raz, S. Esposito, D. Ganmaa, A.A. Ginde, E.C. Goodall, C.C. Grant, C. J. Griffiths, W. Janssens, I. Laaksi, S. Manaseki-Holland, D. Mauger, D.R. Murdoch,

https://doi.org/10.1016/j.cct.2021.106418
Received 22 April 2021; Accepted 26 April 2021
Available online 29 May 2021

R. Neale, J.R. Rees, S. Simpson Jr., I. Stelmach, G.T. Kumar, M. Urashima, C. A. Camargo Jr., Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data, BMJ. 356 (2017 Feb 15) i6583, https://doi.org/10.1136/bmj.i6583. PMID: 28202713; PMCID: PMC5310969.

[11] R. Vieth, How to optimize vitamin D supplementation to prevent cancer, based on cellular adaptation and hydroxylase enzymology, Anticancer Res. 29 (9) (2009 Sep) 3675–3684. 19667164.

[12] J.E. Manson, S.S. Bassuk, Eliminating vitamin D deficiency during the COVID-19 pandemic: A call to action, Metabolism 112 (2020;Jul 23) 154322, https://doi.org/10.1016/j.metabol.2020.154322.

Davaasambuu Ganmaa[a,b,*], Rui Wang[c,d], Walter C. Willett[b,e], JoAnn E. Manson[e,f]

[a] *Channing Division Network of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA*

[b] *Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA, USA*

[c] *Department of Population Medicine, Harvard Pilgrim Health Care Institute and Harvard Medical School, Boston, MA, USA*

[d] *Department of Biostatistics, Harvard T. H. Chan School of Public Health, Boston, MA, USA*

[e] *Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA*

[f] *Division of Preventive Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA*

[*] Corresponding author at: Channing Division Network of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA.

E-mail address: gdavaasa@hsph.harvard.edu (D. Ganmaa).