Irish Medical Journal
Established 1867

Issue: Ir Med J; Vol 113; No. 5; P83

Authors of Article **'Optimisation of Vitamin D Status for Enhanced Immuno-Protection against Covid-19'** by McCartney et al (Ir Med J; Vol 113; No. 4; P58) *comment on response letter* **'Vitamin D and Covid-19: A Note of Caution'** by Rabbitt et al (Ir Med J; Vol 113; No. 5; P92)

D.M. McCartney[1], D.G. Byrne[2,3]

1. School of Biological and Health Sciences, College of Sciences & Health, Technological University Dublin - City Campus, Kevin Street, Dublin D08 NF82, Ireland.
2. Department of Internal Medicine, St. James's Hospital, James's Street, Dublin 8, Ireland.
3. Dept. of Clinical Medicine, School of Medicine, Trinity College Dublin, Dublin 2, Ireland.

Dear Editor,

In response to Rabbitt & Slattery's mainly rhetorical commentary on our article, while the limitations of the observational data linking vitamin D and respiratory infection cited in our paper were clearly stated, their letter fails to acknowledge the significant body of evidence from supplementation trials which suggests biological plausibility in this regard.

For example, the findings of Martineau et al.[1] are mis-reported in the BMJ editorial by Bolland and Avenell[2] to which they refer. Those authors described a reduction in the proportion of participants experiencing an acute respiratory infection from 42% to 40% to be a 2% absolute risk reduction, rather than the correct 4.8% reduction (i.e. 2/42%), but they do at least acknowledge the topline 12% overall risk reduction observed across the 25 constituent randomised control trials incorporating data from 11,321 participants. In contrast, Rabbitt & Slattery fail to mention this 12% overall reduction in risk of acute respiratory tract infection (odds ratio 0.88), nor do they refer to the 70% reduction in risk amongst those with baseline serum 25(OH)D levels <25nmol/l after vitamin D supplementation also reported by Martineau et al. In the current context, we should think that a 12% reduction in overall risk of respiratory infection, and a 70% reduction in risk amongst those with serum 25(OH)D of <25nmol/l (i.e. >40% of Irish nursing home residents) would be most welcome. Rabbitt & Slattery also fail to highlight the findings from Rejnmark et al. (2017)[3], which examined pooled data from 7 meta-analyses incorporating 30 RCTs and concluded that "the overall findings suggest a beneficial effect of vitamin D on respiratory tract infections." Nor do they refer to the findings of the systematic review by Autier and colleagues (2017)[4] also cited in our paper, which similarly identified a possible protective effect of vitamin D supplementation against respiratory tract infection.

The supposed failure of other nutrient studies to demonstrate effects on immune function is not only irrelevant to the current discussion which relates specifically to vitamin D, but can also not be verified as Rabbit & Slattery have provided no reference to support it. The inclusion of vitamin D in this unreferenced conflation also ignores the interventional data highlighted above which were cited in our paper to support our suggestion for vitamin D supplementation. The authors' statement that all micronutrients can have toxic effects at high pharmacological doses is well recognised but also has very little relevance to the specific issue of vitamin D supplementation at the doses we have suggested, the safety of which is very well established[5,6]as the authors have acknowledged.

In the current situation, we are dealing with a novel virus where emerging observational data indicate significantly poorer outcomes in those who are vitamin D deficient[7,8]. There are also mechanistic pathology studies which suggest a causal role for vitamin D deficiency in mediating increased risk of acute respiratory infection[9] and poorer prognosis in ARDS patients[10].

Rabbitt & Slattery have posited that "to recommend urgent supplementation of a population as a strategy against Covid-19 is imprudent and not supported by any clear evidence." We would argue that given the established high population prevalence of deficiency, especially in the groups highlighted; the emerging associative data linking vitamin D deficiency to poorer clinical

outcome in Covid-19 patients; the established safety of vitamin D supplementation and the grave individual and societal consequences of Covid-19 infection, it is imprudent not to recommend supplementation. Our assertion in this regard would appear to be supported by the statutory guidance for vitamin D supplementation amongst the general public which has issued from UK public health authorities over recent days.

Whilst clinical data from supplementation trials are required to definitively establish causal relationships between vitamin D deficiency and Covid-19 outcomes, the prevalence and depth of vitamin D deficiency in Ireland highlighted by our paper and others; the critical importance of vitamin D for optimal immune function[11], the already established relationships between low vitamin D status and poorer health outcomes (including mortality); and the growing observational evidence specifically linking low vitamin D status and risk of poorer outcome in Covid-19 patients commend this issue as one which requires urgent and decisive remedial action. Finally, the allusion to the current incumbent of 1600 Pennsylvania Avenue by the authors is wholly apt; hamartia such as the failure to listen to best available evidence, an inability to objectively assimilate and weigh such data, and an over-willingness to casually dismiss consequential information out of hand where it doesn't fit the preferred narrative, all have resonance here. However, in the spirit of collegial support, we are happy to recommend to our colleagues the following by Hanel and Carlberg[12] which takes an evolutionary view of vitamin D with a focus on the pharmacological.

Yours sincerely,

Dr D.M. McCartney, Dr D.G. Byrne

Corresponding Author:
Dr Daniel McCartney,
School of Biological and Health Sciences,
Technological University of Dublin - City Campus,
Kevin Street,
Dublin D08 NF82,
Ireland.
Email: Daniel.McCartney@TUDublin.ie

References:

1. Martineau AR, Jolliffe DA, Hooper RL, Greenberg L, Aloia JF, Bergman P, Dubnov-Raz G, Esposito S, Ganmaa D, Ginde AA, Goodall EC, Grant CC, Griffiths CJ, Janssens W, Laaksi I, Manaseki-Holland S, Mauger D, Murdoch DR, Neale R, Rees JR, Simpson S Jr, Stelmach I, Kumar GT, Urashima M, Camargo CA Jr. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. *BMJ*. 2017; 356:i6583. doi: 10.1136/bmj.i6583.
2. Bolland MJ, Avenell A. Do vitamin D supplements help prevent respiratory tract infections? *BMJ*. 2017 Feb 15;356:j456. doi: 10.1136/bmj.j456.
3. Rejnmark L, Bislev LS, Cashman KD, Eiríksdottir G, Gaksch M, Grübler M, Grimnes G, Gudnason V, Lips P, Pilz S, van Schoor NM, Kiely M, Jorde R. Non-skeletal health effects of vitamin D supplementation: A systematic review on findings from meta-analyses summarizing trial data. *PLoS One.* 2017; 12:e0180512. doi: 10.1371/journal.pone.0180512. eCollection 2017.
4. Autier P, Mullie P, Macacu A, Dragomir M, Boniol M, Coppens K, Pizot C, Boniol M. Effect of vitamin D supplementation on non-skeletal disorders: a systematic review of meta-analyses and randomised trials. *Lancet Diabetes Endocrinol.* 2017; 5:986-1004. doi: 10.1016/S2213-8587(17)30357-1.
5. European Food safety Authority (EFSA) Scientific Opinion on the Tolerable Upper Intake Level of vitamin D. *EFSA Journal* 2012;10(7):2813.
6. Institute of Medicine (2011) *Dietary Reference Intakes for Calcium and Vitamin D.* Washington DC: The National Academies Press, 2011.
7. Alipio, M. (2020). Vitamin D Supplementation Could Possibly Improve Clinical Outcomes of Patients Infected with Coronavirus-2019 (COVID-2019). Available at SSRN: https://ssrn.com/abstract=3571484 or http://dx.doi.org/10.2139/ssrn.3571484 https://ssrn.com/abstract=3571484 (Accessed: 24 April 2020).
8. Raharusuna P, Priambada S, Budiarti C, Agung E, Budi C. Patterns of COVID-19 Mortality and Vitamin D: An Indonesian Study. Available at SSRN: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3585561#.XqWfqZvYqW0.twitter.
9. Zdrenghea MT, Makrinioti H, Bagacean C, Bush A, Johnston SL, Stanciu LA. Vitamin D modulation of innate immune responses to respiratory viral infections. *Rev Med Virol.* 2017; 27(1). doi: 10.1002/rmv.1909

10. Xu J, Yang J, Chen J, Luo Q, Zhang Q, Zhang H. Vitamin D alleviates lipopolysaccharide‐induced acute lung injury via regulation of the renin‐angiotensin system. *Mol Med Rep.* 2017;16(5):7432-7438. doi: 10.3892/mmr.2017.7546. Epub 2017 Sep 20.
11. Calder PC, Carr AC, Gombart AF, Eggersdorfer M. Optimal Nutritional Status for a Well-Functioning Immune System Is an Important Factor to Protect against Viral Infections. *Nutrients* 2020; 12: 1181; doi:10.3390/nu12041181.
12. Hanel A, Carlberg C. Vitamin D and evolution: Pharmacologic implications. *Biochem Pharmacol.* 2020; 173:113595. doi: 10.1016/j.bcp.2019.07.024. Epub 2019 Aug 1.