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.

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Reply to Vitamin D deficiency in COVID-19: mixing up cause and consequence

Dear Editor,

The SARS-Cov-2 tsunami has engulfed the global community into an accelerated search for preventive and therapeutic strategies to halt its devastating toll; immune modulation being the fulcrum of all. The effect of vitamin D role on innate and adaptive immunity is undisputable [1], yet its role in this viral illness is unclear [2]. While biologic plausibility supports an association between vitamin D status and COVD-19 infection, establishing causality remains elusive. It was not implied in our commentary [3]. COVID-19 patients often seek medical advice after the onset of symptoms, and past the trigger of its inflammatory cascade. We concur with Smolders et al., reverse causality is a consideration [4].

These authors show that the inoculation of 9 healthy volunteers with E.Coli-derived lipopolysaccharide, at a relatively high dose of 4 ng/kg over 4 h [5], resulted in a rise in inflammatory markers, and a concomitant drop in mean serum 25-hydroxyvitamin D (25OHD), by 2.6 ng/ml, 2–3 h later [4]. Several other small studies (N 19–90) examined changes in 25OHD in acute illnesses, using for the most part standardized assays. These included elective orthopedic [6,7], and cardiac surgery [8], acute pancreatitis [9], or shock and ICU admissions [10,11]. The drop in mean 25OHD of 1–12 ng/ml occurred during the first 48 h of admission [6–11]. The response was however quite variable, some studies registering no change or an increase [9,12]. Serum 25OHD level may return to baseline within 5–14 days [6,8,9], but this return was not linked to recovery from illness [12]. Both 25OHD and $1,25OH_2D$ decreased similarly by day 5 in one study, but while 25OHD returned to baseline, there was a subsequent *overshoot* in $1,25OH_2D$ level [8].

The reasons for decrements in 25OHD level in acute illness are not clear. The association of CRP and albumin, most frequently assessed predictors for a change in 25OHD during illness, were inconsistent [6–9]. The dilutional effects of fluids during illness [6], a drop in vitamin D binding protein (VDBP) [7], and a possible increase in 1-α hydroxylation of 25OHD [9], may all contribute. Free 25OHD may also be affected. In a study of 33 patients undergoing knee arthroplasty, levels of total and free 25OHD, and VDBP, decreased by 40% and 15%, respectively, starting day 1 post-operatively [6].

The collider effect challenges association studies, reverse causality is one of them [13]. The severity of COVID-19 infection affects the decision for hospitalization, and causal inferences in hospitalized patients might not be well-grounded [13]. A thorough assessment of the evidence available, with particular attention to matters relevant to 25OHD assays [14], reverse causality, and quality assessment, is crucial [15]. Such scrutiny provides the framework to provide guidance on vitamin D supplementation, given in a preventive or adjuvant-therapy mode, in the spectrum of COVID-19 illnesses. Well conducted observational studies will also provide the basis, when coupled with forthcoming evidence from vitamin D randomized controlled trials where vitamin D effect may be confounded by the standard use of steroids, to confirm or refute the putative role of vitamin D in Covid-19 illnesses.

Declaration of competing interest

None

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