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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The COVID-19 era recalls the importance of ensuring sufficient vitamin D status in the general population

Cédric Annweiler

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Title „The COVID-19 era recalls the importance of ensuring sufficient vitamin D status in the general population“

Response to Ghanbari-Afra & Azizi-Fini's Commentary on „Vitamin D and survival in COVID-19 patients: A quasi-experimental study“

Cédric Annweiler, MD, PhD [a,b,c,d,e]

a: Department of Geriatric Medicine and Memory Clinic, Research Center on Autonomy and Longevity, University Hospital, Angers, France; b: School of Medicine, Health Faculty, University of Angers, Angers, France; c: UNIV ANGERS, UPRES EA 4638, University of Angers, Angers, France; d: Gérontopôle Autonomie Longévité des Pays de la Loire, France; e: Robarts Research Institute, Department of Medical Biophysics, Schulich School of Medicine and Dentistry, the University of Western Ontario, London, ON, Canada

Corresponding author: Cédric Annweiler, MD, PhD, Department of Geriatric Medicine, Angers University Hospital, F-49933 Angers, France; E-mail: Cedric.Annweiler@chu-angers.fr; Phone: ++33 2 41 35 47 25; Fax: ++33 2 41 35 48 94

The possibility of a beneficial role of vitamin D supplementation in COVID-19 has been the matter of extensive discussion since the start of the pandemic based on previous meta-analyzes of randomized clinical trials (RCT) reporting protective effect on respiratory tract infections [1]. One year ago, at the end of the first wave of the COVID-19 pandemic, we published a quasi-experimental study reporting that vitamin D supplementation in nursing-home residents during or just before COVID-19 was associated with less severe COVID-19 symptoms and better survival [2]. In their Commentary, Ghanbari-Afra & Azizi-Fini [3] asked for more methodological details and expanded interpretation of our results.

Our study was "quasi-experimental", i.e. a retrospective observational follow-up of two groups of residents exposed to two different vitamin D regimens [4]: here the first group (called "Intervention") had received a bolus vitamin D supplement in the month preceding the diagnosis of COVID-19 or during the first week of the disease, and the second group ("Comparator") had received a bolus vitamin D supplement at an earlier date. The common points for all 66 study participants were to be residents within the same nursing-home in France, to have been infected with SARS-CoV-2 during the study period, and to have been followed (whether in nursing-home or in hospital) until 15 May 2020 or until death as appropriate (mean follow-up time, 36±17days) [2]. As this was an observational study on previously-acquired data sets, neither written informed consent nor sample size calculation were required for this specific analysis [4]. In contrast, the participants' selection and characteristics were described in detail in the published manuscript, as well as the collection from structured medical files of the nursing-home of all relevant clinical and biological information by the physician in charge. The retrospective data collection explains why some variables of interest, such as the 25-hydroxyvitamin D concentration at the time of COVID-19 diagnosis, were missing. Thus our quasi-experimental study did not reach, by definition, the

evidence level of a RCT but contributed to better understanding the link of vitamin D with COVID-19.

The study was to our knowledge the first one to examine the association between vitamin D supplements and COVID-19 outcomes. It was subsequently replicated with similar results in larger and different populations by members of our team and others [5-7]. Importantly, finding that recent vitamin D supplementation was associated with reduced mortality in older COVID-19 patients was consistent with the sparse observational data available at that time, as described in our published manuscript [4]. However, due to the observational design of our study and the lack of dedicated interventional literature at that time, we did our best to avoid speculation about the possible benefits of vitamin D supplementation in COVID-19. Several recent examples in the COVID-19 era have highlighted the importance of remaining cautious in the interpretation of study results and their implications in clinical routine [8]. However some interventions have been published in the meantime. In the SHADE study (India), which randomly assigned 40 middle-aged adults with COVID-19 and vitamin D deficiency to 50,000IU vitamin D3 per day for 7days or placebo, the proportion of negative conversion of SARS-COV-2 by 21days was higher with vitamin D than with placebo (63% vs. 21%, P=0.018) [9]. In a RCT conducted in Spain, which randomly assigned 76 middle-aged adults hospitalized for COVID-19 to standard care and oral calcifediol (0.532mg at baseline followed by 0.266mg at day3 and day7) or standard care alone, the proportion of individuals who needed ICU treatment was lower with calcifediol than in the control group (2% vs. 50%, P<0.001) [10]. Finally, a RCT conducted in Brazil, which randomly assigned 240 middle-aged participants hospitalized for moderate-to-severe COVID-19 to 200,000IU vitamin D3 supplementation or placebo administered 10.3days after symptoms onset on average, did not find any effect of the supplementation on the length of hospital stay [11]. Thus, taken together, observational and interventional studies

published so far support that normal-to-high vitamin D status at the time of infection may be beneficial during COVID-19. As of July 2021, it now seems reasonable to advise ensuring that everyone is vitamin D sufficient throughout the year. This requires circulating 25-hydroxyvitamin D concentrations ranging between 20-60 ng/mL in healthy adults, and between 30-60 ng/mL in those with chronic diseases [12]. At least 1200 IU/day of vitamin D are safe and necessary for this purpose [13]. In fact this attitude respects the recommendation (prior to COVID-19) to maintain a sufficient vitamin D status in the general population [14].

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CONFLICT OF INTEREST STATEMENT

C. Annweiler occasionally serves as a consultant for Mylan Laboratories Inc. The author declare he does not have any financial conflicts of interest with this manuscript.

SPONSOR'S ROLE

None.

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