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Letter to the Editor

The role of vitamin D as a potential adjuvant for COVID-19 vaccines

Dear Editor,

Since there are still no effective therapies and chemoprevention strategies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) associated with convincing success[1,2], we must focus on nationwide and global vaccination campaigns to curb the coronavirus disease 2019 (COVID-19) pandemic. Vitamin D deficiency has progressively emerged as an independent risk factor for adverse outcomes of COVID-19[3,4]. Given the anti-infective, anti-inflammatory and immunomodulatory properties of vitamin D (which have been reviewed elsewhere)[5,6], it is likely that a lower vitamin D status may favour the development or the exacerbation of the hyperinflammatory state (the so-called "cytokine storm") that has been associated with the most severe cases of COVID-19[7,8]. Preliminary intervention studies evaluating the efficacy of vitamin D supplementation in mitigating COVID-19 severity and mortality showed promising results[9,10]. For example, the GERIA-COVID quasi-experimental study demonstrated that bolus vitamin D supplementation was associated with less severe COVID-19 and better survival in hospitalized frail elderly patients[9]. Therefore, one can speculate that vitamin D administration may improve COVID-19 prognosis in older individuals and other frail populations at high risk for worse outcomes.

Since we rely on vaccination against SARS-CoV-2 to control and eventually end the COVID-19 pandemic, the scientific community is currently focused on factors able to determine an effective immune response against the virus after vaccination. In particular, concerns exist regarding factors able to decrease the immune response to COVID-19 vaccines, thereby preventing an adequate immunization against SARS-CoV-2. Subjects at higher risk for poor immune response to COVID-19 vaccines include frail elderly people, malnourished individuals and patients taking immunosuppressive drugs such as organ transplant recipients. Poor immune response in such populations may reduce the effectiveness of the current vaccination campaigns. Importantly, frail elderly people, malnourished individuals and organ transplant recipients often exhibit different vitamin and nutritional deficiencies[11] – including hypovitaminosis D[12-16] – which can be easily addressed.

An adequate host nutritional status is crucial to ensuring an effective immune response, and various vitamins (A, B6, B9, B12, C, D and E) and minerals (zinc, selenium, iron and copper) have been shown to promote the normal functioning of the immune system[12,17]. A healthy diet may thus be an essential determinant of the effective host defense against pathogens (bacteria, viruses, toxins, parasites and fungi). Vitamin D deficiency currently represents a global pandemic afflicting more than one billion individuals across all age groups[18]. Extraskeletal actions of vitamin D, including its anti-infective and immunomodulatory properties, have been increasingly recognized[5,6]. Indeed, it has been demonstrated that immune cells are local producers and target of vitamin D at the same time, as they express vitamin D-activating enzymes 25- and 1α-hydroxylase as well as vitamin D receptor (VDR)[5].

In light of the vitamin D's actions on the immune system, it would be interesting to examine the potential role of vitamin D as an adjuvant for COVID-19 vaccines. Previous studies demonstrated that mice vaccinated with inactivated vaccines co-administered with calcitriol (the biologically active form of vitamin D) exhibited production of antigen-specific mucosal immunity (IgA and IgG antibodies) along with enhanced systemic immune responses[19]. These studies involved Haemophi-

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lus influenzae type b oligosaccharide conjugated to diphtheria toxoid vaccine, inactivated polio vaccine, and hepatitis B surface antigen (HBsAg)[19-22]. Therefore, vitamin D deficiency may negatively influence the immune response to diverse COVID-19 vaccines.

We previously showed that 36-month high-dose vitamin D3 supplementation (in combination with the dipeptidyl peptidase-4 inhibitor sitagliptin) led to the normalization of IgG1 levels in a patient with pure sensory mononeuritis multiplex associated with selective IgG1 deficiency[23,24]. The exact mechanisms behind the association of vitamin D administration with enhanced mucosal immunity and antibody production have not been entirely defined. Mechanistic studies are needed in this direction to evaluate differences in gene expression and cytokine response after vitamin D supplementation[19].

Cross-sectional clinical studies found that lower serum vitamin D levels are significantly associated with respiratory tract infections[25-27] and epidemic influenza[28]. These findings suggest that low vitamin D levels may increase the risk of viral respiratory infections and prompted researchers to better investigate the role of vitamin D deficiency in these conditions in children, adolescents and adults, as well as the influence of vitamin D on immune response to influenza vaccine and other vaccines against infectious diseases. A systematic review and meta-analysis of nine studies involving 2367 patients evaluated the impact of vitamin D deficiency on seroprotection and seroconversion rates following influenza vaccination[29]. Although there was no significant association between vitamin D levels and the immunogenic response to influenza vaccination, authors documented the existence of interesting strain-specific differences. Of note, authors observed significantly lower seroprotection rates of influenza A virus subtype H3N2 and B strain in patients with vitamin D deficiency compared to patients with normal vitamin D levels. The cut-off level adopted to define vitamin D deficiency was 20 ng/mL in half of the enrolled studies, whereas 25 ng/mL was used in the other studies[29].

Overall, clinical studies regarding the role of vitamin D in the immune response to vaccines against distinct infectious diseases yielded disparate findings[19]. However, the majority of these studies were observational and retrospective, had small sample sizes, and were not adequately powered[19]. Vitamin D status is likely to differently influence the immune response based on the specific vaccine type (e.g. live attenuated viral or bacterial vaccines, inactivated viral vaccines, inactivated bacterial polysaccharide or conjugate vaccines, toxoid vaccines)[19]. The same concept may apply to the spectrum of different COVID-19 vaccines, namely: whole virus vaccines, viral vector-based vaccines, mRNA vaccines and protein subunit vaccines. Large prospective studies are, therefore, needed to clarify the impact of vitamin D supplementation on the immune response to different COVID-19 vaccines in subjects with hypovitaminosis D. These studies should aim to detect significant differences between vaccine responders and non-responders in terms of innate, humoral and cellular immune responses after vitamin D supplementation[19]. Well-designed studies should also take into account genetic, geographic and ethnic variations that may affect the individual response to vitamin D supplementation[30,31]. Moreover, these studies should primarily enroll selected populations such as the elderly and patients with obesity and/or chronic kidney disease, since these conditions are associated with an increased risk of vitamin D deficiency[30-32] along with adverse outcomes of COVID-19[33].

Rayman and Calder outlined the importance of optimizing COVID-19 vaccine efficacy by ensuring nutritional adequacy[12]. Since nutritional deficiency and malnutrition are common in the elderly, authors proposed that a nutritional supplement containing various minerals and vitamins important to immune function (including vitamin D) should be provided to all people aged over 70 years for a certain period of weeks before and after the COVID-19 vaccine administration[12]. Given the inexpensive cost of multivitamin and multimineral supplements, this intervention would probably be cost-effective and would represent a small investment to better ensure a robust vaccine response, particularly in older people, who frequently have a weakened immune system[34] as well as an inadequate immune response to several vaccines including the seasonal influenza vaccine[35,36].

There has been concern about the fact that COVID-19 vaccines may theoretically exacerbate autoimmune responses in patients with chronic autoimmune and inflammatory disorders[37]. Yet, this hypothesis has not been confirmed and patients with these conditions have been shown to develop excellent immune responses regardless of their immunosuppressive therapy, without

showing significant side effects or induction of disease flares[38]. It also worth reminding that hypovitaminosis D has been suggested as a risk factor for the development of several autoimmune disorders[39-41]. In addition, vitamin D supplementation led to promising beneficial effects in many of these conditions[39,40,42,43]. This provides an additional reason for investigating the role of vitamin D supplementation in patients with chronic autoimmune and inflammatory conditions receiving COVID-19 vaccines.

It is also important to remind that serum vitamin D levels that are generally adopted to define hypovitaminosis D (<30 ng/mL) are based on the vitamin D's effects on calcium homeostasis and bone health[44]. The same cut-off level cannot be translated to the effects of vitamin D on the immune system. Even though the exact threshold of serum vitamin D that is relevant to the vitamin D's anti-infective and immunomodulatory actions has not been clearly defined, emerging evidence suggests that circulating levels of 40-60 ng/mL would be optimal to achieve the overall health benefits of this vitamin (including its effects on the immune system)[5,45]. To date, there are no specific indications on how to administer vitamin D supplements as immunoadjuvants in subjects receiving different types of vaccines, including COVID-19 vaccines. In this regard, another aspect to be considered is the exact timing of vitamin D administration prior to vaccination (days to weeks), which should be aimed to rapidly increase circulating vitamin D levels up to ~40 ng/mL in vitamin D-deficient individuals. With regard to the vitamin D dose, a dietary and/or supplemental intake of vitamin D3 (cholecalciferol) of 4000-6000 IU/day is generally safe and effective in achieving and maintaining the aforementioned concentrations in adults[5,45].

In conclusion, successful mass immunization programs aimed to reach herd immunity are keys to controlling the present COVID-19 crisis. Future studies are warranted to ascertain whether vitamin D sufficiency can significantly improve seroconversion and seroprotection rates after full COVID-19 vaccination (including the first and/or the second vaccine dose, depending on the vaccine type). Also, substudy results of the CORONAVIT trial (ClinicalTrials.gov Identifier: NCT04579640) are awaited to hopefully help in clarifying these aspects[46,47].

Conflict of Interest

The Authors declare that they have no conflict of interest to disclose.

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References

1) Martinez MA. Lack of effectiveness of repurposed drugs for COVID-19 treatment. Front Immunol 2021; 12: 635371.
2) Infante M, Ricordi C, Alejandro R, Caprio M, Fabbri A. Hydroxychloroquine in the COVID-19 pandemic era: in pursuit of a rational use for prophylaxis of SARS-CoV-2 infection. Expert Rev Anti Infect Ther 2021; 19: 5-16.
3) Infante M, Buoso A, Pieri M, Lupisella S, Nuccetelli M, Bernardini S, Fabbri A, Iannetta M, Andreoni M, Colizzi V, Morello M. Low vitamin D status at admission as a risk factor for poor survival in hospitalized patients with COVID-19: an Italian retrospective study. J Am Coll Nutr 2021; 18: 1-16.
4) Angelidi AM, Belanger MJ, Lorinsky MK, Karamanis D, Chamorro-Pareja N, Ognibene J, Palaiodimos L, Mantzoros CS. Vitamin D status is associated with in-hospital mortality and mechanical ventilation: a cohort of COVID-19 hospitalized patients. Mayo Clin Proc 2021; 96: 875-886.
5) Fabbri A, Infante M, Ricordi C. Editorial - Vitamin D status: a key modulator of innate immunity and natural defense from acute viral respiratory infections. Eur Rev Med Pharmacol Sci 2020; 24: 4048-4052.

6) Caprio M, Infante M, Calanchini M, Mammi C, Fabbri A. Vitamin D: not just the bone. Evidence for beneficial pleiotropic extraskeletal effects. Eat Weight Disord 2017; 22: 27-41.
7) Mangalmurti N, Hunter CA. Cytokine Storms: understanding COVID-19. Immunity 2020; 53: 19-25.
8) Pinheiro MM, Fabbri A, Infante M. Cytokine storm modulation in COVID-19: a proposed role for vitamin D and DPP-4 inhibitor combination therapy (VIDPP-4i). Immunotherapy 2021; 13: 753-765.
9) Annweiler G, Corvaisier M, Gautier J, Dubée V, Legrand E, Sacco G, Annweiler C. Vitamin D supplementation associated to better survival in hospitalized frail elderly COVID-19 patients: the GERIA-COVID Quasi-Experimental Study. Nutrients 2020; 12: 3377.
10) Entrenas Castillo M, Entrenas Costa LM, Vaquero Barrios JM, Alcalá Díaz JF, López Miranda J, Bouillon R, Quesada Gomez JM. "Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: A pilot randomized clinical study". J Steroid Biochem Mol Biol 2020; 203: 105751.
11) Vural Z, Avery A, Kalogiros DI, Coneyworth LJ, Welham SJM. Trace mineral intake and deficiencies in older adults living in the community and institutions: a systematic review. Nutrients 2020; 12: 1072.
12) Rayman MP, Calder PC. Optimising COVID-19 vaccine efficacy by ensuring nutritional adequacy. Br J Nutr 2021 Jan 28:1-2. doi: 10.1017/S0007114521000386. Epub ahead of print.
13) Infante M, Ricordi C, Padilla N, Alvarez A, Linetsky E, Lanzoni G, Mattina A, Bertuzzi F, Fabbri A, Baidal D, Alejandro R. The role of Vitamin D and Omega-3 PUFAs in islet transplantation. Nutrients 2019; 11: 2937.
14) Stein EM, Shane E. Vitamin D in organ transplantation. Osteoporos Int 2011; 22: 2107-2118.
15) Meehan M, Penckofer S. The role of Vitamin D in the aging adult. J Aging Gerontol 2014; 2: 60-71.
16) Merker M, Amsler A, Pereira R, Bolliger R, Tribolet P, Braun N, Hoess C, Pavlicek V, Bilz S, Sigrist S, Brändle M, Henzen C, Thomann R, Rutishauser J, Aujesky D, Rodondi N, Donzé J, Stanga Z, Mueller B, Schuetz P. Vitamin D deficiency is highly prevalent in malnourished inpatients and associated with higher mortality: a prospective cohort study. Medicine (Baltimore) 2019; 98: e18113.
17) Gombart AF, Pierre A, Maggini S. A Review of Micronutrients and the Immune System-Working in Harmony to Reduce the Risk of Infection. Nutrients 2020; 12: 236.
18) Holick MF. The vitamin D deficiency pandemic: Approaches for diagnosis, treatment and prevention. Rev Endocr Metab Disord 2017; 18: 153-165.
19) Sadarangani SP, Whitaker JA, Poland GA. "Let there be light": the role of vitamin D in the immune response to vaccines. Expert Rev Vaccines 2015; 14: 1427-1440.
20) Enioutina EY, Visic D, McGee ZA, Daynes RA. The induction of systemic and mucosal immune responses following the subcutaneous immunization of mature adult mice: characterization of the antibodies in mucosal secretions of animals immunized with antigen formulations containing a vitamin D3 adjuvant. Vaccine 1999; 17: 3050-3064.
21) Ivanov AP, Dragunsky EM, Chumakov KM. 1,25-dihydroxyvitamin d3 enhances systemic and mucosal immune responses to inactivated poliovirus vaccine in mice. J Infect Dis 2006; 193: 598-600.
22) Daynes RA, Enioutina EY, Butler S, Mu HH, McGee ZA, Araneo B A. Induction of common mucosal immunity by hormonally immunomodulated peripheral immunization. Infect Immun 1996; 64: 1100-1109.
23) Maia Pinheiro M, Moura Maia Pinheiro F, Pires Amaral Resende LL, Nogueira Diniz S, Fabbri A, Infante M. Improvement of pure sensory mononeuritis multiplex and IgG1 deficiency with sitagliptin plus Vitamin D3. Eur Rev Med Pharmacol Sci 2020; 24: 8151-8159.
24) Maia Pinheiro M, Maia Pinheiro FM, Amaral Resende LLP, Diniz SN, Fabbri A, Infante M. 36-month follow-up of a pure sensory mononeuritis multiplex and IgG1 deficiency improved after treatment with sitagliptin and Vitamin D3. Eur Rev Med Pharmacol Sci 2021; 25: 1768-1769.
25) Laaksi I, Ruohola JP, Tuohimaa P, Auvinen A, Haataja R, Pihlajamäki H, Ylikomi T. An association of serum vitamin D concentrations < 40 nmol/L with acute respiratory tract infection in young Finnish men. Am J Clin Nutr 2007; 86: 714-717.
26) Ginde AA, Mansbach JM, Camargo CA Jr. Association between serum 25-hydroxyvitamin D level and upper respiratory tract infection in the Third National Health and Nutrition Examination Survey. Arch Intern Med 2009; 169: 384-390.
27) Cannell JJ, Vieth R, Willett W, Zasloff M, Hathcock JN, White JH, Tanumihardjo SA, Larson-Meyer DE, Bischoff-Ferrari HA, Lamberg-Allardt CJ, Lappe JM, Norman AW, Zittermann A, Whiting SJ, Grant WB, Hollis BW, Giovannucci E. Cod liver oil, vitamin A toxicity, frequent respiratory infections, and the vitamin D deficiency epidemic. Ann Otol Rhinol Laryngol 2008; 117: 864-870.
28) Cannell JJ, Vieth R, Umhau JC, Holick MF, Grant WB, Madronich S, Garland CF, Giovannucci E. Epidemic influenza and vitamin D. Epidemiol Infect 2006; 134: 1129-1140.
29) Lee MD, Lin CH, Lei WT, Chang HY, Lee HC, Yeung CY, Chiu NC, Chi H, Liu JM, Hsu RJ, Cheng YJ, Yeh TL, Lin CY. Does Vitamin D Deficiency Affect the Immunogenic Responses to Influenza Vaccination? A Systematic Review and Meta-Analysis. Nutrients 2018; 10: 409.

30) Mazahery H, von Hurst PR. Factors Affecting 25-Hydroxyvitamin D Concentration in Response to Vitamin D Supplementation. Nutrients 2015; 7: 5111-5142.

31) Infante M, Ricordi C, Baidal DA, Alejandro R, Lanzoni G, Sears B, Caprio M, Fabbri A. VITAL study: an incomplete picture? Eur Rev Med Pharmacol Sci 2019; 23: 3142-3147.

32) Obi Y, Hamano T, Isaka Y. Prevalence and prognostic implications of vitamin D deficiency in chronic kidney disease. Dis Markers 2015; 2015: 868961.

33) Noor FM, Islam MM. Prevalence and Associated Risk Factors of Mortality Among COVID-19 Patients: A Meta-Analysis. J Community Health 2020; 45: 1270-1282.

34) Pawelec G, Larbi A, Derhovanessian E. Senescence of the human immune system. J Comp Pathol 2010; 142 Suppl 1: S39-S44.

35) Pera A, Campos C, López N, Hassouneh F, Alonso C, Tarazona R, Solana R. Immunosenescence: Implications for response to infection and vaccination in older people. Maturitas 2015; 82: 50-55.

36) Goodwin K, Viboud C, Simonsen L. Antibody response to influenza vaccination in the elderly: a quantitative review. Vaccine 2006; 24: 1159-1169.

37) Velikova T, Georgiev T. SARS-CoV-2 vaccines and autoimmune diseases amidst the COVID-19 crisis. Rheumatol Int 2021; 41: 509-518.

38) Geisen UM, Berner DK, Tran F, Sümbül M, Vullriede L, Ciripoi M, Reid HM, Schaffarzyk A, Longardt AC, Franzenburg J, Hoff P, Schirmer JH, Zeuner R, Friedrichs A, Steinbach A, Knies C, Markewitz RD, Morrison PJ, Gerdes S, Schreiber S, Hoyer BF. Immunogenicity and safety of anti-SARS-CoV-2 mRNA vaccines in patients with chronic inflammatory conditions and immunosuppressive therapy in a monocentric cohort. Ann Rheum Dis 2021: annrheumdis-2021-220272.

39) Dankers W, Colin EM, van Hamburg JP, Lubberts E. Vitamin D in Autoimmunity: Molecular Mechanisms and Therapeutic Potential. Front Immunol 2017; 7: 697.

40) Infante M, Ricordi C, Sanchez J, Clare-Salzler MJ, Padilla N, Fuenmayor V, Chavez C, Alvarez A, Baidal D, Alejandro R, Caprio M, Fabbri A. Influence of Vitamin D on Islet Autoimmunity and Beta-Cell Function in Type 1 Diabetes. Nutrients 2019; 11: 2185.

41) Ricordi C, Clare-Salzler M, Infante M, Baggerly C, Aliano J, McDonnell S, Chritton S. Vitamin D and Omega 3 field study on progression of type 1 diabetes. CellR4 Repair Replace Regen Reprogram 2019; 7: e2737.

42) Pinheiro MM, Pinheiro FMM, Diniz SN, Fabbri A, Infante M. Combination of vitamin D and dipeptidyl peptidase-4 inhibitors (VIDPP-4i) as an immunomodulation therapy for autoimmune diabetes. Int Immunopharmacol 2021; 95: 107518.

43) Yang CY, Leung PS, Adamopoulos IE, Gershwin ME. The implication of vitamin D and autoimmunity: a comprehensive review. Clin Rev Allergy Immunol 2013; 45: 217-26.

44) Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, Weaver CM; Endocrine Society. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2011; 96: 1911-1930.

45) Charoenngam N, Holick MF. Immunologic effects of Vitamin D on human health and disease. Nutrients 2020; 12: 2097.

46) Gibson-Moore H. Vitamin D: what's new a year on from the COVID-19 outbreak? Nutr Bull 2021; 46: 195-205.

47) Proteomics & Metabolomics. (2021) Talking vitamin D and COVID-19 with Professor Adrian Martineau. Available from: https://www.technologynetworks.com/proteomics/articles/talking-vitamin-d-and-covid-19-with-professor-adrian-martineau-344615 [Accessed 26th July 2021].

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