

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 patients⁹. 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 deficiencies¹¹ – including hypovitaminosis D¹²⁻¹⁶ – 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 groups¹⁸. Extraskelatal 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 1 α -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 responses¹⁹. These studies involved Haemophi-

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 supplementation¹⁹.

Cross-sectional clinical studies found that lower serum vitamin D levels are significantly associated with respiratory tract infections²⁵⁻²⁷ and epidemic influenza²⁸. 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 vaccination²⁹. 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 studies²⁹.

Overall, clinical studies regarding the role of vitamin D in the immune response to vaccines against distinct infectious diseases yielded disparate findings¹⁹. However, the majority of these studies were observational and retrospective, had small sample sizes, and were not adequately powered¹⁹. 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 supplementation¹⁹. 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 deficiency³⁰⁻³² along with adverse outcomes of COVID-19³³.

Rayman and Calder outlined the importance of optimizing COVID-19 vaccine efficacy by ensuring nutritional adequacy¹². 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 administration¹². 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 system³⁴ 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 disorders³⁷. 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 flares³⁸. It is also worth reminding that hypovitaminosis D has been suggested as a risk factor for the development of several autoimmune disorders³⁹⁻⁴¹. 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 health⁴⁴. 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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ORCID

Tsvetelina Velikova: <https://orcid.org/0000-0002-0593-1272>. Andrea Fabbri: <https://orcid.org/0000-0003-2269-1554>. Marco Infante: <https://orcid.org/0000-0003-2032-8735>.

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T. Velikova¹, A. Fabbri², M. Infante^{2,3,4}

¹Department of Clinical Immunology, University Hospital Lozenetz, Sofia University St. Kliment Ohridski, Sofia, Bulgaria

²Division of Endocrinology, Metabolism and Diabetes, Department of Systems Medicine, CTO A. Alesini Hospital, Diabetes Research Institute Federation, University of Rome Tor Vergata, Rome, Italy

³UniCamillus, Saint Camillus International University of Health Sciences, Rome, Italy

⁴Network of Immunity in Infection, Malignancy and Autoimmunity (NIIMA), Universal Scientific Education and Research Network (USERN), Rome, Italy