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IM - COMMENTARY

# Extraosseous effects of vitamin D: a role in the prevention and treatment of COVID-19?

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The article by Israel et al. recently published on Internal and Emergency Medicine [1] tries to shed light on the question whether vitamin D status could influence the risk of infecting from SARS-CoV-2 and of developing a severe disease. Authors retrospectively evaluated data from a large population cohort from Israel using a healthcare service registry [1].

First, Authors compared characteristics of 130,582 subjects testing positive for SARS-CoV-2 during the first pandemic wave (Mar–Oct 2020) with the whole CHS population (4,502,455 subjects) testing negative for the new coronavirus. Of these, 1,350,000 subjects had tested at least once during previous 10 years their serum vitamin D levels. Authors found that vitamin D levels were significantly lower among infected patients, particularly female. Moreover, besides lower vitamin D levels, those testing positive for SARS-CoV-2 showed a slightly higher BMI.

To eliminate confounders, a total of 41,757 patients testing positive for the new coronavirus were matched per age, gender, geographic region, and socioeconomic status with control subjects (ratio 1:10). Differences observed between cases and controls in terms of vitamin D levels, ethnic group, and BMI distributions in the matched cohort were similar to the unmatched population. Low vitamin D levels, particularly its severe deficiency (< 30 nmol/L), significantly predicted the risk of SARS-CoV-2 infection (OR = 1.442, 95% CI 1.392–1.494), the lower the levels, the higher the risk. Moreover, the risk of infection was significantly increased by comorbidities (e.g. chronic renal failure, congestive heart failure, diabetes, obesity). However, in multivariable models, the association between poor vitamin D status and infection persisted even after adjusting for BMI, ethnicity and comorbidities.

Finally, 2533 patients hospitalized for COVID-19 were compared (1:1 ratio) with patients who developed the infection but not required hospitalization, to test the association between vitamin D levels and disease severity. Again, low vitamin D levels significantly associated with the risk of hospitalization for severe disease (deficiency OR = 1.777, 95% CI 1.477–2.138; insufficiency OR = 1.256, 95% CI 1.057–1.492). Even this association persisted even after adjusting for BMI, ethnicity and comorbidities.

The paper by Israel and Colleagues represents one of the broadest observational study supporting the association between vitamin D deficiency and both the risks of infection and of severe COVID-19 [1].

This study comes with strengths and limitations. The significantly large population used as reference and the single geographic area represents the main strengths. On the contrary, the use of historical vitamin D levels (up to 10 years backwards) instead of those measured during acute infection represents a significant study limitation. Moreover, although vitamin D was independently associated with the outcomes, it is noteworthy to underline that even comorbidities associated with endpoints are typically characterized by vitamin D deficiency. In addition, information on eventual vitamin D supplementation is lacking. With this regard, authors considered the last available vitamin D value, arguing that subjects taking vitamin supplements would have been retested for plasmatic levels after treatment. Assuming this hypothesis

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as possibly true, it should also be said that vitamin D levels measured during "healthy state" are more reliable than those measured during infection, because serum vitamin D concentrations could be lowered by acute inflammatory states [2]. However, the main limitation of this study resides in its retrospective, observational, non-interventional design [1]. Nevertheless, observed results are in line with a recent meta-analysis of observational studies confirming the increased susceptibility to COVID-19 and severe COVID-19 among patients with vitamin D deficiency/insufficiency [3].

In the last decades, "nonclassical" effects of vitamin D, particularly its immunomodulating effects have been extensively studied [4]. The possible role of vitamin D in regulating both innate and adaptive immunity led to the design of several clinical trials exploring its effects in different fields, including metabolic [5], autoimmune [6, 7] and infectious [8] disorders. For what concerns its role against infections, vitamin D stimulates the production of antimicrobial peptides [9] with most of the knowledge coming from sepsis [10, 11]. It should be underlined that the COVID-19 syndrome has several similarities with sepsis, being defined by some authors a "viral sepsis" [9]. Specifically, the role of vitamin D against viruses helps in maintaining cellular barriers (e.g. tight and gap junctions), producing cathelicidins and defensins (natural immunity), balancing TH1/TH2 response (adaptive immunity) [12], and reducing pro-inflammatory cytokines and cytokine storm [13].

Vitamin D supplementation in COVID-19 patients has a rationale [1, 3, 14]; however, its optimal dosing, levels, form, and route of administration are still matter of debate [15]. It is conceivable that target levels could vary depending on indication (e.g. bone metabolism, prevention of infections, inhibition of autoimmune response, etc.). As per COVID-19, most of studies suggest a target of 30 ng/mL (75 nmol/L) [16]. However, despite the consensus on the use of 25-hydroxyvitamin D concentrations as a marker of vitamin D storages [15], there are still no indications to prefer cholecalciferol or its activated metabolites for treating vitamin D deficiency/insufficiency. Probably, the administration of calcifediol is able to raise vitamin D concentrations more rapidly (i.e. hours) than cholecalciferol (i.e. days) [17]. However, if this could translate in a clinical benefit has still to be demonstrated.

At present, interventional studies assessing the potential role of vitamin D supplementation for preventing infection and death from COVID-19 are few [18–20], and most of them still ongoing [21, 22]. A recent review and meta-analysis of randomized controlled trials on COVID-19 and vitamin D (Co-VIVID study) found 6 high-quality studies for a total of 551 COVID-19 patients included [23]. Despite the limited number of patients, the pooled effect of vitamin D administration resulted in a 40% relative risk reduction of overall COVID-19-related outcomes [RR = 0.60, (95% CI 0.40–0.92)] and a 56% relative risk reduction for RT-PCR positivity [RR = 0.46, (95% CI 0.24–0.89)] [23]. However, despite its possible global beneficial effect, analysed data did not find a significant association between vitamin D supplementation and an improvement of hard outcomes (e.g. admission to ICU and death). Authors conclude highlighting the need for future robust interventional trials [23].

As already evidenced from studies conducted in the field of critically ill septic patients, it is still unknown if reduced levels of vitamin D represent the causative mechanism for susceptibility to infections (e.g. sepsis, COVID-19), the effect of greater peripheral catabolism due to inflammation [2, 24], or the marker of a comorbid state (e.g. diabetes, obesity, frailty) [23].

As a matter of fact, those patients presenting with a poor vitamin D status are at higher risk for worse outcomes [1, 11, 14] and the immunomodulatory effects of vitamin D have a pathophysiological rationale [25]. While waiting for robust evidences supporting the administration of vitamin D in the acute phase of disease, available data favour vitamin D supplementation at a population basis, at least in those subjects showing deficiency/insufficiency, to enhance innate immune function against SARS-CoV-2 [12], under the shield of vaccines, independently from SARS-CoV-2 variants.

## Declarations

**Conflict of interest** The authors declare that they have no conflict of interest.

**Human and animal rights statement** This commentary is the original work of the named authors, who reviewed previously published information. No new human or animal studies were performed by the authors.

**Informed consent** For this type of study, no informed consent is required.

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