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NARRATIVE REVIEW

Associations between hypovitaminosis D and COVID-19: a narrative review

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Abstract
In the search for factors affecting incidence and lethality of the current COVID-19 pandemic, recent association studies explored the possible role of vitamin D deficiency. Altogether, these studies, in most cases based on cross-sectional analyses, could not yet provide a convincing demonstration of a cause–effect relationship. In this editorial, the authors describe the scientific evidence underlying a possible role of vitamin D in the prevention and development of the pandemic, considering its immunomodulatory role and antiviral effects. They conclude that further studies are needed to (1) better explore possible associations between vitamin D deficiency and COVID-19 morbidity and lethality, and (2) assess if compensating such deficiency could avoid or mitigate the worst manifestations of COVID-19. They highlight the need for public health campaigns to promote consumption of vitamin D-rich foods and proper sunlight exposition or, when this is not possible, controlled pharmaceutical supplementation, especially in countries with high prevalence of hypovitaminosis D.

Keywords COVID-19 · Vitamin D deficiency · Immune system · Viral infections

Introduction

In a previous issue of Aging Clinical and Experimental Research, Ilie and colleagues report a correlation across 20 European countries between vitamin D levels and COVID-19 incidence and death rates [1]. In view of the study limitations and of the observed borderline significance, the association should be considered suggestive and not demonstrative of a possible role of vitamin D deficiency in the current pandemic. Indeed, the authors state themselves that this is a potential crude association and call for more research. However, this work adds to a growing body of circumstantial evidence linking COVID-19 and vitamin D status, as nicely summarized by Fiona Mitchell in a recent editorial [2]. Association studies fall into two main categories: (1) comparing variation of estimated or historical vitamin D levels and COVID-19 incidence or death rates across countries; the analysis can be worldwide or within continents or also between hemispheres, considering latitude and associated seasonal state as indirect indicators of vitamin D status; (2) retrospective case–control studies comparing individual vitamin D levels (actual or estimated) with COVID-19 incidence, either for the general population or for specific minorities. Among the many association studies, to date only one has evaluated actual vitamin D levels in hospitalized patients either positive or negative for COVID-19 during the pandemic period [3]. In this work, D'Avolio and colleagues found a markedly lower 25(OH)D level in COVID-19 patients versus other hospitalized patients in Bellinzona, Switzerland. A limitation of this study is the missing adjustment for possible confounding factors. In another interesting work, still at the level of preprint, Meltzer and colleagues estimated vitamin D deficiency likeliness based on prior (up to 1 year) 25(OH)D measurements for 499 patients tested for COVID-19, and found that those who were COVID-19 positive had a significantly greater chance of being likely vitamin D deficient [4]. In a third work, vitamin D levels were estimated based on historical measurements from a UK biobank study, between 2006 and 2010 [5]. The work aimed at assessing whether higher incidence of COVID-19 in non-white minorities in UK could be associated with vitamin D deficiency. After correction for confounding factors, no significant association was found. Clearly in this case,

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the major limitation is the time distance between 25(OH)D measurements and COVID-19 status assessment.

After considering all association studies currently available, we conclude that the causal link between vitamin D levels and COVID-19 cannot be assumed at present. Indeed, we would like to point out that, even in the presence of strong and significant associations, a causal role of hypovitaminosis D in facilitating COVID-19 spread and lethality would still be far from confirmed, for three main reasons. First, low levels of 25(OH)D could be a consequence of COVID-19. Clarifying this ambiguity would require a prospective, large-scale baseline measurement of vitamin D followed by a second measurement upon COVID-19 positivization. Second, it would remain unclear whether compensating vitamin D deficiency could help preventing COVID-19 onset or avoiding its worsening. Third, and most important, association studies only generate solid hypotheses when these are corroborated by strong previously related biological and clinical evidence. We, therefore, summarize here what in our view are the most relevant findings in terms of biological and clinical soundness of a link between COVID-19 and vitamin D deficiency.

There is consolidated evidence on the immunomodulatory role of vitamin D, on its antiviral properties and on a possible role in mitigating pneumonia and hyperinflammation. Various reviews [6, 7] examined the relationship between vitamin D and the immune system, highlighting a protective role for many infective diseases, underlying the association between hypovitaminosis D and many respiratory, enteric and urinary tract infections, vaginosis, sepsis, flu-syndrome, dengue, and hepatitis. These properties of vitamin D have been attributed to its ability to modulate gene expression by activating the vitamin D receptor in many target cells, including immune cells, and by promoting the expression of antimicrobic peptides such as cathelicidins and beta-defensins, also endowed with antiviral and immunomodulatory activities [8]. As highlighted in a recent review [9], vitamin D has been reported to support innate immunity, keep the integrity of the tight junctions and the pulmonary barrier, provide immunoregulatory activity and modulate the renin–angiotensin system, all factors of potential relevance to acute pneumonia and hyperinflammation observed in patients with COVID-19.

There is clinical and preclinical evidence on a possible protective role of vitamin D supplementation. In patients with inflammatory bowel diseases [10], typically leading to defective vitamin D absorption, vitamin D3 administration (500 U/die) reduced two-third the incidence of respiratory infections in patients with 25(OH)D levels below 20 ng/ml. In the same cohort, a concentration of 25(OH)D higher than 38 ng/ml was associated with 50% reduction of respiratory infection risk. A metanalysis involving 25 randomized interventional studies and more than 11,000 patients [11] showed that vitamin D supplementation reduces two-third the incidence of acute respiratory infections in patients with 25(OH)D levels lower than 16 ng/ml. There is also preclinical evidence of a protective effect of vitamin D on lung damage. In rats, administration of calcitriol, the active form of vitamin D, was effective in reducing acute pulmonary damage induced by lipopolysaccharides, likely by modulating the renin–angiotensin system (RAS) [12]. Similarly, in mice, knock out of the vitamin D receptor increased the severity of lipopolysaccharide-induced acute lung injury [13] and chronic vitamin D deficiency was found to destruct lung structures, to impair lung development, and to promote lung fibrosis by activating the RAS [14]. Conversely, its administration to lung fibroblasts counteracted TGF-beta-induced lung fibrosis [15]. All this—and more—preclinical evidence points to RAS as a key node of vitamin D protective actions in the lung. It should be noted that the SARS-CoV-2 virus uses ACE2, a component of the RAS, as its receptor [16].

Conclusions and recommendations

We believe that further studies are needed to (1) better explore possible associations between vitamin D deficiency and COVID-19 morbidity and lethality, and (2) assess if compensating such deficiency could avoid or mitigate the worst manifestations of COVID-19. It is our opinion that the governments of all countries, especially where, as in Italy, there is a high prevalence of vitamin D insufficiency or deficiency [17], have to promote public health campaigns to increase consumption of foods rich in vitamin D and to promote adequate sunlight exposition or, when this is not possible, properly controlled pharmaceutical supplementation. Along this line, recently, the British Dietetic Association [18] and the Scottish Government [19] published some recommendations to ensure, particularly in this critical period, normal levels of vitamin D in the general population.

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Compliance with ethical standards

Conflict of interest Giancarlo Isaia and Enzo Medico declare that this study is compliant with the ethical standards.

Ethics approval This is a review and no ethical approval was required for this work.

Informed consent Not applicable.

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