COVID-19 revolution: a new challenge for the internist

Hypovitaminosis D and COVID-19

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ABSTRACT

As the main title '*COVID-19 revolution: a new challenge for the internist*' states, the global coronavirus infection disease 2019 (COVID-19) pandemic represented a new challenge for the internists. This paper is part of a series of articles written during the difficult period of the ongoing global pandemic and published all together in this fourth issue of the *Italian Journal of Medicine*, with the aim of sharing the direct experiences of those who were the first to face this severe emergency, expressing each point of view in the management of COVID-19 in relation to other diseases. Each article is therefore the result of many efforts and a joint collaboration between many colleagues from the Departments of Internal Medicine or Emergency Medicine of several Italian hospitals, engaged in the front line during the pandemic. These preliminary studies therefore cover diagnostic tools available to health care personnel, epidemiological reflections, possible new therapeutic approaches, discharge and reintegration procedures to daily life, the involvement of the disease not only in the lung, aspects related to various comorbidities, such as: coagulopathies, vasculitis, vitamin D deficiency, gender differences, *etc*.. The goal is to offer a perspective, as broad as possible, of everything that has been done to initially face the pandemic in its first phase and provide the tools for an increasingly better approach, in the hope of not arriving unprepared to a possible second wave.

This paper in particular deals with hypovitaminosis D and COVID-19.

Since December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has spread globally, causing a respiratory illness called coronavirus infection disease 2019 (COVID-19), ranging from self-limiting flu-like symptoms to severe pneumonia, multi-organ failure, and death.[1] To date, no treatment, chemoprevention, and vaccine has been proven to be effective for the treatment and prevention of COVID-19.[2] By analogy with other respiratory tract infections,[3,4] the role of supplementation of vitamin D in the prophylaxis of SARS-CoV-2 pneumonia and the prevention of progression toward more severe form is interesting and challenging. Its role has also been investigated in autoimmune diseases[5] and other infectious diseases, such as HIV infection,[6] chronic viral hepatitis,[7] and sepsis.[8] In fact, vitamin D also has antimicrobic activities and immuno-modulatory properties.[9,10] Firstly, vitamin D helps to maintain tight junctions, gap junctions, and adherens junctions that are disrupted by virus.[11] Moreover, vitamin D enhances innate cellular immunity by induction of antimicrobial peptides, including cathelicidin and defensins, that play direct antimicrobial activities against microbes.[11] Vitamin D also seems to reduce the oxidative stress induced by viral infection.[11] Finally, it also enhances cellular immunity and down-regulates the T helper 17 cells response, preventing and reducing the cytokine storm induced by the innate immune system.[11]

Although all these mechanisms may be involved in the prevention of SARS-CoV-2 pneumonia and its complication, as cytokine storm syndrome, only low-quality studies have been published about the possible

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link between vitamin D deficiency and higher susceptibility to SARS-CoV-2 infection and its complications. In a retrospective study assessing 25-hydroxyvitamin D concentrations in plasma of Swiss patients, lower levels were found in SARS-CoV-2 infected patients compared to subjects without infection.[12] Ilie and colleagues found a negative correlation between mean levels of vitamin D in European Countries, the number of COVID-19 patients, and death for one million of inhabitants.[13] They also found severely low vitamin D levels in the aging population that are the most vulnerable subjects of SARS-CoV-2 infection.[13] Conversely, a recent retrospective study, collecting data from UK Biobank, does not support this potential link between vitamin D concentrations and risk of COVID-19 infection.[14] However, vitamin D levels considered in this study were obtained a decade ago and not during the current outbreak.

Kara and colleagues highlighted as SARS-CoV-2 has spread in subtropical and mid-latitude countries, where people commonly have vitamin D deficiency due to a low ultraviolet exposure.[15,16] For the same reason, according to the letter of Panarese and Shahini, the northerly latitude is associated with an increased mortality rate and hospitalization rate for COVID-19.[17] In line with these data, the study of Marik and colleagues showed as the case fatality rate of SARS-CoV-2 infected patients in the United States of America was directly associated with latitude.[18] However, other factors, such as racial makeup, population density, adherence to social distancing, the use of vitamin supplements, and access to quality medical care, may play an additional role in explaining these geographical variations. It has also been suggested that weather conditions of low temperature and relative humidity might allow the virus to survive longer outside the body than under warmer conditions.

A recent observational study of Parkinson's disease population showed a higher rate of vitamin D supplemented patients in the group of unaffected patients than in those with confirmed or probable SARS-CoV-2 infection.[19] Although the authors found a possible protective role of vitamin D supplementation in this population, this preliminary hypothesis should be tested by appropriate randomized controlled trials (RCT).

The quality and the design of published studies assessing the relationship between vitamin D level and susceptibility to SARS-CoV-2 infection do not allow to identify the prognostic role of vitamin D in this disease. The supplementation of vitamin D has a pathophysiological rationale in the prevention of SARS-CoV-2 infection and in the development of more severe forms, but additional studies are required to validate this hypothesis and translate this into clinical practice. An RCT is currently underway in Spain with the aim to investigate whether vitamin D supplementation in non-severe symptomatic COVID-19 patients induces significant improvements in health status and outcomes.[20] Finally, the greatest challenge is also represented by the correct identification of the optimal regimen of supplementation (dose, duration of treatment and timing).

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