The link between vitamin D deficiency and COVID-19

One of the factors that has been invoked with regard to the risk and severity of COVID-19 is vitamin D deficiency. There is available evidence to support this hypothesis. vitamin D deficiency (serum 25-hydroxyvitamin D [25(OH) D] <50 nmol/L) is present in 30%–60% of the populations of western, southern, and eastern Europe and in up to 80% of populations in Middle-Eastern countries.[1] In India also, it is very high and the prevalence of vitamin D deficiency (25[OH] D <20 nmol/L) has ranged from 40% to 99%, with most of the studies reporting a prevalence of 80%–90%.[2] vitamin D deficiency is common globally, and serum 25(OH) D levels follow a well-known seasonal and geographical pattern.[3] Spain, located in temperate zones of the Northern Hemisphere, but with a higher prevalence of vitamin D deficiency, has reached very high rates of SARS-CoV-2 infection and lethality.[3,4]

Vitamin D is a steroid hormone involved in the modulation of the innate and acquired immune system and also in the production of antimicrobial peptides, such as cathelicidin and humanβ-defensin-2, as well as in the expression of genes involved in the intracellular destruction of pathogens.[5-7] Thrombotic complications are common in COVID-19 patients. Interestingly, vitamin D is also involved in the regulation of thrombotic pathways, and vitamin D deficiency is associated with an increase in thrombotic episodes.[8]

The known risk factors for low vitamin D status are old age and the underlying medical disorders such as hypertension, diabetes mellitus, cardiovascular disorders, and cancer. These are also poor prognostic factors for COVID-19.[9-13] Finally, the downregulation of ACE2 by SARS-CoV-2 leads to a dysregulation of the renin–angiotensin system, which contributes to the "cytokine storm" that precedes acute respiratory distress syndrome characteristic of the severe form of COVID-19. In this sense, vitamin D can inhibit pro-inflammatory cytokine production in human monocytes/macrophages.[14]

Therefore, there is a strong case for invoking a link between vitamin D deficiency and both susceptibility to COVID-19 infection and disease severity and death.

Hermandez *et al.* showed that vitamin D deficiency (serum 25[OH]D levels <20 ng/mL) was found in 82.2% of COVID-19 cases and 47.2% of population-based controls ($P < 0.0001$). Levels of 25(OH) D inversely correlated with serum ferritin ($P = 0.013$) and D-dimer levels ($P = 0.027$). vitamin D-deficient COVID-19 patients had a greater prevalence of hypertension and cardiovascular diseases, raised serum ferritin and troponin levels, as well as a longer length of hospital stay.[15]

Kaufman *et al.* matched the results of SARS-CoV-2 testing performed in a laboratory from mid-March through mid-June 2020, with 25(OH)D results from the preceding 12 months. They showed an association between lower SARS-CoV-2 positivity rates and higher circulating 25(OHD levels, which remained significant in a multivariable logistic model adjusting for all included demographic factors (adjusted odds ratio [OR], 0.984 per ng/mL increment; $P < 0.001$).[16] Davies *et al.* analyzed the global daily reports of fatalities and recoveries from 239 locations from January 22, 2020, to April 9, 2020, using a novel causal inference analysis and showed that vitamin D status plays a key role in COVID-19 outcomes.[17]

It appears prudent to supplement vitamin D screen and treat patients with vitamin D deficiency with the hope of reducing their risk of contracting COVID-19 and also reducing the severity. The key question is the effect of short-term vitamin D supplementation in improving outcomes. Rastogi *et al.* randomized asymptomatic or mildly symptomatic SARS-CoV-2 RNA-positive vitamin D-deficient (25[OH]D <20 ng/mL) Indian individuals to receive high dose (60,000 IU) of cholecalciferol for 7 days or placebo. Greater proportion of those who received cholecalciferol turned SARS-CoV-2 RNA negative with a significant decrease in fibrinogen.[18] A more dramatic short-term response to treatment was shown by Entrenas Castillo *et al.* who randomized 76 consecutive patients hospitalized with COVID-19 infection to calcifediol or no calcifediol. Of 50 patients treated with calcifediol, one required admission to the intensive care unit (ICU) (2%), whereas of 26 untreated patients, 13 required admission (50%) ($P < 0.001$). Of the patients treated with calcifediol, none died, and all were discharged, without complications. The 13 patients not treated with calcifediol, who were not admitted to the ICU, were discharged. Of the 13 patients admitted to the ICU, two died and the remaining 11 were discharged.[19]

The link between vitamin D and COVID-19 remains an important factor for further research with large well-controlled studies, particularly focusing on acute response to treatment early in the course of disease.

Conflicts of interest

There are no conflicts of interest.

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