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OPINION REVIEW

- 1 Heart failure in COVID-19 patients: Critical care experience
John KJ, Mishra AK, Ramasamy C, George AA, Selvaraj V, Lal A

REVIEW

- 20 COVID-19: A pluralistic and integrated approach for efficient management of the pandemic
Bouare N, Minta DK, Dabo A, Gerard C
- 40 Animal models for SARS-CoV-2 and SARS-CoV-1 pathogenesis, transmission and therapeutic evaluation
Saravanan UB, Namachivayam M, Jeewon R, Huang JD, Durairajan SSK

MINIREVIEWS

- 57 Chronic hepatitis B: New potential therapeutic drugs target
Leowattana W, Leowattana T

ORIGINAL ARTICLE**Observational Study**

- 73 Rethinking hospital psychiatry in Italy in light of COVID-19 experience
Piccinelli MP, Bortolaso P, Wilkinson GD

LETTER TO THE EDITOR

- 82 Repurposing the antioxidant and anti-inflammatory agent N-acetyl cysteine for treating COVID-19
Finsterer J, Scorza FA, Scorza CA, Fiorini AC
- 85 Role of vitamin D deficiency and comorbidities in COVID-19
Alberca GGF, Alberca RW

ABOUT COVER

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Role of vitamin D deficiency and comorbidities in COVID-19

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Abstract

Recent manuscripts described the incidence of vitamin D hypovitaminosis in coronavirus disease 2019 (COVID-19) patients. Vitamin D deficiency is also common in patients with comorbidities that are associated with a poor COVID-19 prognosis. In this letter, we review the literature regarding the association of comorbidities, vitamin D deficiency, and COVID-19.

Key Words: COVID-19; SARS-CoV-2; Comorbidities; Vitamin D

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Core Tip: Vitamin D deficiency is a worldwide problem, and investigations on the benefits of regulating vitamin D levels and the immune response should be performed. Nevertheless, the association between low levels of vitamin D and coronavirus disease 2019 (COVID-19) needs to be further explored, especially investigations on the immune response to COVID-19 and COVID-19 vaccines in patients with and without comorbidities.

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TO THE EDITOR

We read with great interest the article entitled "Association between population vitamin D status and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) related serious-critical illness and deaths: An ecological integrative approach" recently published by Papadimitriou *et al*[1] in the *World Journal of Virology*[1]. This manuscript raised important questions and the authors performed an extensive analysis on vitamin D levels and COVID-19 incidence and severity in Europe, and the potential benefits of vitamin D supplementation to enhance the immune response to the SARS-CoV-2[1]. In the light of these results, we humbly want to state a few points for consideration.

Severe coronavirus disease 2019 (COVID-19) patients present a systemic inflammatory response with a coagulation disorder, possibly evolving to death[2]. Several comorbidities have been identified as risk factors for poor disease prognosis, such as old age[3], co-infections[4], obesity and diabetes mellitus[5], severe asthma, alcohol drinking[6], chronic obstructive pulmonary disease[7], chronic liver disease[8], and cancer[9].

Vitamin D deficiency is associated with poor response to respiratory infections[10], and few reports have identified vitamin D deficiency in moderate and severe COVID-19 patients with conflicting results[1,11,12].

Vitamin D receptor is expressed in many immune cells, including monocytes, macrophages, dendritic cells, neutrophils, and lymphocytes[13-15]. Vitamin D increases the antimicrobial activity of monocytes and macrophages[16] and has anti-inflammatory effects due to the induction of T regulatory cells and reduction in the T helper-17 immune response and pro-inflammatory cytokine production[15].

Papadimitriou *et al*[1] performed an important investigation on the association of vitamin D deficiency and COVID-19[1]. Vitamin D levels can be influenced by many factors such as sun exposure, genetics, supplementation, and comorbidities[17-20].

Vitamin D hypovitaminosis is associated with several comorbidities that are also related to poor COVID-19 prognoses such as old age[21], co-infections[18], obesity[22], diabetes mellitus[23], alcohol drinking, and smoking[24-26], uncontrolled asthma, but not controlled asthma, chronic obstructive pulmonary disease[25-28], cancer[29], and solid organ transplant recipient patients[30].

Besides comorbidities, vitamin D hypovitaminosis is associated with poor glycemic control[23], which is also associated with poor COVID-19 outcomes in diabetic and non-diabetic patients[31]. Cancer patients present low circulating levels of vitamin D[29] and experimental models have identified that vitamin D can modulate the disease development by regulating cell cycle and inflammatory response[32].

Vitamin D deficiency is a worldwide problem[33,34], and vitamin D supplementation has the potential to enhance the immune response to microorganisms[1]. Vitamin D supplementation has been investigated for the treatment and prevention of severe COVID-19, indicating a potential reduction in COVID-19 severity[35].

A recent investigation found that prophylactic vitamin D supplementation in elderlies improved the SARS-CoV-2 immune response[36], and another investigation identified that the treatment with vitamin D reduces COVID-19 severity[37]. Nevertheless, another report found no additional benefit in vitamin D supplementation during COVID-19[38].

Low vitamin D levels also modulate the Renin-Angiotensin-System, which could increase the susceptibility to COVID-19[39], since SARS-CoV-2 uses the angiotensin-converting enzyme 2 and Transmembrane Protease Serine 2 (TMPRSS2) to invade the host's cells[40]. In addition, the lack of vitamin D is a risk factor for the development of autoimmune and neuropsychiatric disorders[41].

Lakkireddy *et al*[42] identified that increasing the serum levels of vitamin D to 80-100 ng/mL significantly reduced inflammatory biomarkers such as interleukin-6, C-reactive protein, and neutrophil-to-lymphocyte ratio during COVID-19, without side effects[42].

In addition, Papadimitriou *et al*[1] recommendation for vitamin D supplementation should also be considered in a broader context[1], outside the COVID-19 pandemic situation, due to the high incidence of vitamin D hypovitaminosis worldwide, the vast associations with other diseases, and the proposed doses do not require medical supervision[1].

COVID-19 vaccination is ongoing worldwide[43-45], since vitamin D can modulate the immune response to vaccines[46,47], investigations on the vaccines should consider evaluating vitamin D levels and the effects of supplementation on the immune response to vaccines.

In summary, vitamin D hypovitaminosis is associated with comorbidities that are known to affect COVID-19 severity and outcome. Further investigations should focus on patients with low vitamin D levels with and without comorbidities and supplementation trials to investigate the effects of vitamin D on the immune response to COVID-19 and COVID-19 vaccines.

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