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Nutrition

Review

The possible benefits of vitamin D in COVID-19

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ABSTRACT

Molecular studies have demonstrated the importance of the exacerbated immune response to SARS-CoV-2 infection, called the cytokine storm, in more severe COVID-19. The pathophysiology is complex and involves several homeostatic factors; among them, a deficit of vitamin D draws attention because of its high frequency in the population. Some evidence suggests that people with low serum vitamin D levels have worse outcomes, often requiring intensive care. This review analyzed the studies available in the global literature addressing the benefits of vitamin D in COVID-19, relating serum levels to the severity of the disease, and indicating vitamin D as a possible prophylactic and therapy in infection.

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Introduction

The COVID-19 pandemic caused by SARS-CoV-2 infection has had a great impact on health systems, and the search for a cure has been a great challenge for science. First identified in a seafood market in Wuhan, China, and transmitted by airborne droplets, the infection spread quickly to all continents [1−3].

COVID-19 presents a broad clinical spectrum, ranging from absence of symptoms to acute respiratory distress syndrome (ARDS) [4]. The main symptoms observed are fever (88.5%), cough (68.6%), myalgia or fatigue (35.8%), expectoration (28.2%), and dyspnea (21.9%). Other symptoms include headache or dizziness (12.1%), diarrhea (4.8%), and nausea and vomiting (3.9%) [2]. Those who progress to ARDS need ventilatory support and other prolonged intensive care. Such respiratory complications can lead to systemic deterioration, which leads to worse outcomes for these people [5].

It is known that the presence of chronic comorbidities, such as diabetes mellitus, systemic arterial hypertension, obesity, and cardiovascular diseases, is associated with increased morbidity and mortality in COVID-19 [6]. Current evidence indicates that these diseases have in common a chronic inflammatory pattern with high levels of proinflammatory cytokines [7]. It has been observed that people with severe symptoms of COVID-19 have an uncontrolled production of proinflammatory cytokines, associated with a low serum level of vitamin D and other micronutrients, which suggests severity of disease [6].

Vitamin D makes up a group of molecules derived from 7-dehydrocholesterol (7-DHC), the most important of which are its active metabolite 25-dihydroxyvitamin D and its precursors ergocalciferol and cholecalciferol [8]. Ergocalciferol, or vitamin D_2, is the result of ultraviolet irradiation of ergosterol. Previtamin D_3, or cholecalciferol, originates from a photochemical cleavage of the skin precursor of vitamin D (7-dehydrocholesterol) when exposed to ultraviolet radiation [9,10].

Besides its classic regulatory function in osteomineral metabolism, especially calcium metabolism, vitamin D also actively participates in blood pressure control [11], the synthesis of interleukins, and autoimmunity modulation [12]. It has also proven to be essential in the molecular niche of innate immunity [13] and in regulation of cell multiplication and differentiation, having antioncogenic potential [14].

Recent studies indicate that 25-dihydroxyvitamin D not only negatively regulates the renin-angiotensin system but also has immunoregulatory properties, with the ability to suppress interferon-γ, tumor necrosis factor-α, and interleukin-6 (IL-6) and to stimulate antiinflammatory cytokines such as IL-10 and IL-12 [7,14]. In addition, there is evidence that vitamin D is effective in the prevention and treatment of influenza and other viral infections [15,16].

This study aimed to analyze the studies available in the global literature addressing the benefits of vitamin D in COVID-19, relating serum levels to the severity of the disease, and indicating vitamin D as possible a prophylactic and therapy in infection.

Materials and methods

This article is a narrative review of the literature for studies that have considered the benefits of vitamin D in COVID-19. We sought to evaluate studies on the prophylactic and therapeutic role of vitamin D in COVID-19. Two independent

reviewers read the titles and abstracts of the articles, and common conclusions were summarized. In cases of divergence, a third reviewer decided on the inclusion of the study.

An electronic search was done using Medline and Latin American and Caribbean Health Sciences Literature (LILACS) with the combinations of terms/descriptors "'vitamin D' AND 'COVID-19'" and "'vitamin D' AND 'SARS-CoV-2,'" without restrictions of language, between March and November 2020. Studies that did not directly refer to the benefits or consequences of vitamin D levels in COVID-19 were excluded from the analysis. Letters and editorials were also excluded.

Results

Figure 1 represents the flow and selection criteria of the articles analyzed. Most of the 19 articles were observational studies and previous reviews. To date, there is only one randomized clinical trial.

In the first analysis, the immunomodulatory role of vitamin D was correlated as a protective factor against SARS-CoV-2 infection; and individuals with low serum levels showed a higher probability of progressing to severe forms of the disease (an inversely proportional relationship). Other functions and consequences of vitamin D deficiency in COVID-19 have also been described in the literature. These results are summarized in Table 1.

Discussion

Observational evidence was found that vitamin D can be an important ally against COVID-19. The pilot randomized clinical trial indicates that low levels of vitamin D are associated with severity and mortality from infection.

We observe that mortality and lethality rates have been higher in countries at high latitudes both north and south. This is probably due to a lower incidence of ultraviolet B rays, especially in winter [33], and consequently a greater proportion of the elderly population with severe vitamin D deficiency compared to in countries close to the equator [34,35].

The immunologic function of vitamin D shown in a short time great value against bacterial and viral infections, especially in the respiratory tract, with a satisfactory level of evidence [36,37]. It has been shown to stimulate the production of cathelicidin and defensins which decrease cell death in HEp-2 human epithelial cells, and to modulate the immune response from type 1 to type 2 T-helper cells, suppressing interferon-γ and tumor necrosis factor-β and producing IL-4, IL-5, IL-10, and IL-13 [38]. In addition, vitamin D deficiency is an important factor in the direct contribution to the progression from acute infectious disease to ARDS [39]; COVID-19 is not different, with vitamin D deficiency showing an important relation to the severity of the clinical condition [23].

Those who progress to ARDS, and consequently need intensive care, have in common the cytokine storm, a phase of infection characterized by uncontrolled production of inflammatory cytokines [6,40]. Studies claim that vitamin D has an immunoregulatory potential at this stage, suppressing the production of interferon-γ, tumor necrosis factor-α, and IL-6 and other proinflammatory cytokines, as well as stimulating antiinflammatory factors [26,27].

However, previous systematic reviews have shown that vitamin D has no significant effect in the treatment of acute respiratory tract infections [41], and in a randomized clinical trial it was found not to improve insulin sensitivity in people with obesity, nor to reduce the risk of type 2 diabetes [42]. These results may be a consequence of glutathione deficiency, observed in animal models fed a high-fat diet and in people with chronic diseases, including diabetes and immunologic diseases, implying oxidative stress and vitamin D metabolism. It has been noted that L-cysteine supplementation improved serum glutathione levels which may be an adjuvant therapeutic strategy [43−46]. Therefore, combined
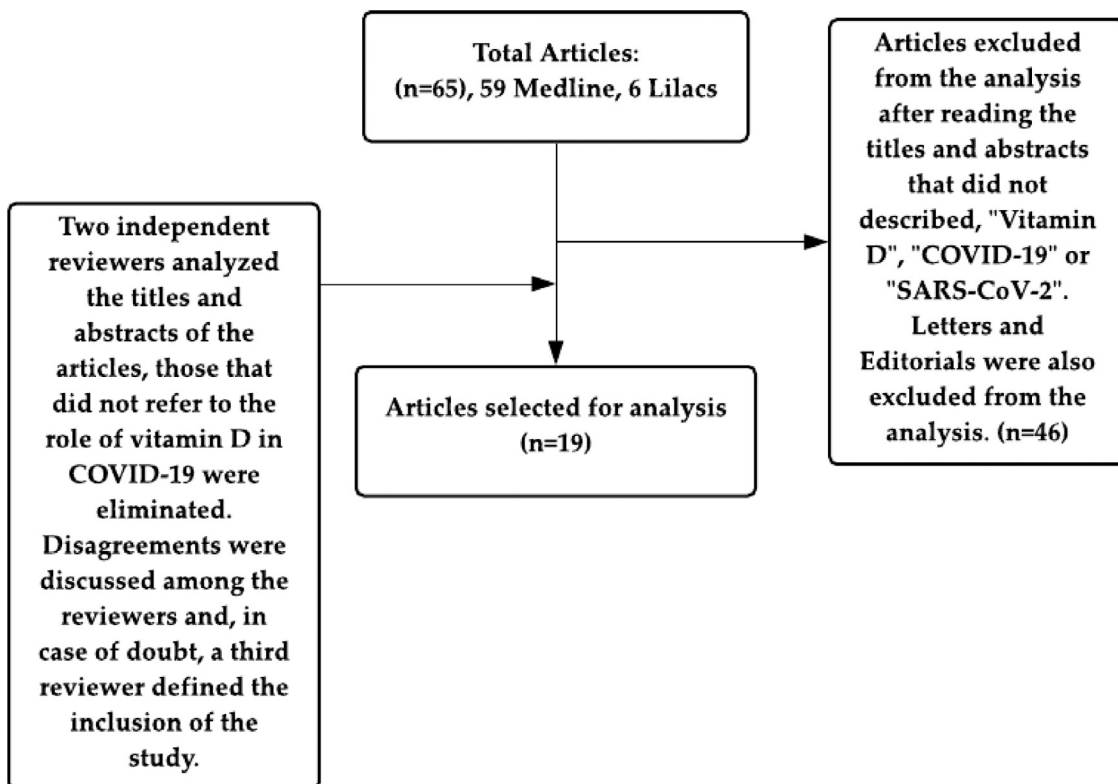

Fig. 1. Selection flow of the studies analyzed.

Table 1
Results of studies analyzed (in chronological order)

Reference	Type of study	Results
Grant et al. [15]	Review	Previous studies show that vitamin D deficiency contributes to ARDS. In addition, RCTs have demonstrated that vitamin D supplementation reduced the risk of influenza. Intake of vitamin D can help people with chronic diseases because they have low levels of vitamin D, and consequently decrease the lethality of COVID-19.
McCartney and Byrne [17]	Review	Molecular studies have demonstrated that one of the virulence factors of SARS-CoV-2 is related to the binding of the virus to the DPP-4/CD26 receptor, whose expression is drastically reduced after the correction of vitamin D levels. In addition to attenuating IFN-γ and IL-6, both predictors of worse prognosis.
Ilie et al. [18]	Short communication	Through a statistical analysis, a gross correlation was observed in some European countries between mean vitamin D level (56.79 nmol/L) and mean cases of COVID-19/million inhabitants (1393.4), $r(20) = -0.4435$, and between mean vitamin D level and number of COVID-19 deaths/million inhabitants (80.42), $r(20) = -0.4378$.
Silberstein [5]	Review	The immunosuppressant tocilizumab may be a therapeutic option against COVID-19. However, vitamin D, as well as tocilizumab, can modulate IL-6 by attenuating the severity of COVID-19 and can be an important alternative.
Ebadi and Montano-Loza [19]	Review	25(OH)D increased the surfactant expression associated with B protein, a protein associated with pulmonary surfactant lipids, indicating the potential of vitamin D to reduce surface tension in COVID-19. Because of the high prevalence of vitamin D deficiency and its relation to the severity of the infection, it is suggested to maintain a serum level between 40 and 60 ng/mL.
Zabetakis et al. [6]	Review	This review discussed nutritional aspects that seek to mitigate the cytokine storm. There were no indications that vitamin C is effective in COVID-19; however, its supplementation can reduce the symptoms and duration of a cold. RCTs with 11 000 participants showed a protective effect of vitamin D against respiratory infections. Serum concentration above 40–60 ng/mL may have benefits in COVID-19. There is still no evidence to show a prophylactic function of vitamin E against COVID-19. Zinc supplementation between 30 and 50 mg/d can be beneficial in SARS-CoV-2 infection, reducing viral replication.
D'Avolio et al. [20]	Retrospective cohort ($n = 107$)	Participants ages > 70 y in Switzerland: mean 25(OH)D of 11.1 ng/mL with positive PCR vs. 24.6 ng/mL with negative PCR. Therefore, vitamin D supplementation can reduce the risk of infection in older people.
Belančić et al. [21]	Review	The prevalence of vitamin D deficiency in obese individuals is between 40% and 80%. In summary, the alteration of vitamin D metabolism in people who are obese may be responsible for the greater severity of COVID-19 in this population.
Iddir et al. [22]	Review	Macronutrients have been shown to have an important immunoregulatory role against infectious diseases in animal models. In addition, micronutrients have been observed as important antioxidant agents; among them, vitamin D deficiency has been associated with COVID-19 lethality, especially in high-latitude countries.
Dhillon et al. [23]	Review	The study clarifies some controversies about the severity of COVID-19. The effect of ibuprofen on COVID-19 is still controversial, and therefore it is prudent to use other analgesics to treat the symptoms. No evidence for a protective effect of nicotine was found; on the contrary, chronic exposure to nicotine can promote severe COVID-19. People with dark skin living in the Northern Hemisphere are up to 4.3 times more susceptible to COVID-19 than white people, because they have low serum levels of 25(OH)D.
Martín et al. [24]	Review	Vitamin D stimulates regulatory T cells to produce IL-10 at the same time as inhibiting the expression of CD80/86, CD40, and other proinflammatory lymphocytes. It was also observed that melatonin has an immunoregulatory potential on NF-κB and MMP-3, attenuating inflammation and pulmonary fibrosis. The combined supplementation can prevent the unfavorable evolution of COVID-19.
Castillo et al. [25]	Pilot RCT ($n = 76$)	Of the participants who were not treated with calcifediol ($n = 26$), 50% needed intensive care, whereas of those who were treated with calcifediol ($n = 50$), only one needed hospitalization in the ICU. The odds ratio of ICU admission in people treated with calcifediol vs. untreated was 0.03 (95% CI, 0.003–0.25). Therefore, vitamin D supplementation may be associated with better clinical outcomes.
Xu et al. [26]	Review	Vitamin D presents innumerable antiviral mechanisms, including either innate or adaptive immunity. Its capacity to suppress the proliferation of Th1 and Th17 cells and regulate cytokines IFN-γ, TNF-α, IL-1, IL-2, IL12, IL-23, IL-17, and IL-21 can be extended to COVID-19.
Cooper et al. [27]	Review	Hyperglycemia stimulates the release of IL-6 and clotting factors, whereas hyperinsulinemia inhibits the fibrinolytic pathway and stimulates the RAS, which can result in pulmonary embolism. In addition, hyperinsulinemia promotes renal excretion of magnesium, disturbing vitamin D metabolism. In summary, patients admitted with COVID-19 and hyperglycemia or hyperinsulinemia should have their glucose monitored regularly and should be supplemented with vitamin D, magnesium, and zinc to improve outcomes.
Maghbooli et al. [28]	Cross-sectional ($n = 235$)	Only 32.8% of the analyzed sample had adequate serum vitamin D concentration. Of the 206 participants age > 40 y, 20% had a 25(OH)D blood concentration < 30 ng/mL, and only 9.7% of those who died had a 25(OH)D blood concentration $\geq$ 30 ng/mL. Mortality was very rare with concentrations $\geq$ 40 ng/mL. Therefore, vitamin D supplementation is recommended in the population, and especially in those infected with COVID-19, to reduce mortality.
Kara et al. [29]	Review	Recent data have shown that vitamin D deficiency is quite common in Europe, with 13% of Europeans having a severe disability (<30 nmol/L). Therefore, low levels of vitamin D can be related to COVID-19 mortality in subtropical and midlatitude countries, and its supplementation can minimize this public health problem.
Kaufman et al. [30]	Retrospective observational ($n = 191 779$)	In a total of 191 779 participants, it was noted that those with 25(OH)D values < 20 ng/mL had a SARS-CoV-2 positivity rate of 12.5% (95% CI, 12.2%–12.8%), compared to 8.1% (95% CI, 7.8%–8.4%) in those with 30–34 ng/mL and 5.9% (95% CI, 5.5%–6.4%) in those with $\geq$ 55 ng/mL. The inversely proportional correlation between vitamin D level and SARS-CoV-2 positivity rate was significant in a multivariable logistic model with adjusted demographic variables (adjusted OR = 0.984 per ng/mL increment; 95% CI, 0.983–0.986).
Annweiler et al. [31]	Quasi-experimental study ($n = 96$)	Study conducted in a group of 66 frail older residents of a nursing home: "intervention group," supplemented with vitamin D$_3$ bolus during or just before infection ($n = 57$; mean $\pm$ SD age = 87.7 $\pm$ 9.3 y; 79% women, 21% men) and "comparator group" ($n = 9$; age = 87.4 $\pm$ 7.2 y; 67% women, 33% men). A survival rate of 82.5 % was observed in the intervention group and only 44.4 % in the control group (HR = 0.11; 95% CI, 0.03–0.48). Kaplan–Meier survival analysis described a higher survival in the intervention group (log-rank $P = 0.002$), and vitamin D supplementation demonstrated an inverse correlation of OSCI score and COVID-19 ($\beta = -3.84$; 95% CI, −6.07 to −1.62).

(continued)

Table 1 (Continued)

Reference	Type of study	Results
Annweiler et al. [32]	Quasi-experimental study (n = 77)	A total of 77 patients from a geriatric unit were allocated into three groups: group 1 was supplemented with vitamin D in the previous year; group 2 was supplemented with vitamin D after COVID-19 infection; and group 3 (control group) received no vitamin D. Respective survival rates were 93.1% (n = 29), 81.2% (n = 16; P = 0.33) and 68.7% (n = 32; P = 0.02). With adjustment for 14-d mortality (and taking group 3 as the reference, HR =1), group 1 HR = 0.07 (P = 0.017), and group 2 HR = 0.37 (P = 0.28). Longer survival time was observed for group 1 than group 3 (log-rank P = 0.015). Group 2 (P = 0.40) had a lower risk of OSCI score 5 than group 3 (OR = 0.08, P = 0.03).

25(OH)D = 25-hydroxyvitamin D; ARDS = acute respiratory distress syndrome; CD = cluster of differentiation; CI = confidence interval; DPP-4 = dipeptidyl-peptidase 4; HR = hazard ratio; ICU = intensive care unit; IFN-γ = interferon-γ; IL = interleukin; MMP-3 = matrix metalloproteinase-3; NF-κB = nuclear factor κB; OR = odds ratio; OSCI = ordinal scale for clinical improvement; PCR = polymerase chain reaction; RAS = renin-angiotensin system; RCT = randomized controlled trial; TNF-α = tumor necrosis factor-α.

supplementation of vitamin D and ʟ-cysteine may be a significant therapeutic strategy to reduce oxidative stress and treat vitamin D deficiency and its systemic complications [47−50].

Conclusions

The immunomodulatory role of vitamin D in the natural history of viral and bacterial respiratory infections is relevant. These benefits should be extended to COVID-19, as people with vitamin D deficiency have exhibited worse clinical outcomes. To our knowledge, there is still no robust evidence of the prophylactic and therapeutic role of vitamin D in COVID-19, and more clinical trials are needed to prove its efficacy against infection. Considering that its pharmacologic safety profile is well known, it is prudent to keep its mean serum concentration > 30 ng/mL in people with COVID-19 and the susceptible population.

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