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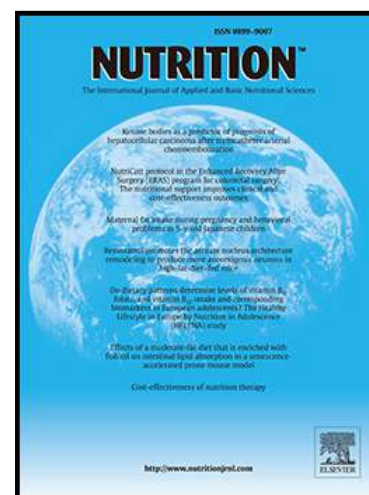
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Highlights

- Vitamin D deficiency may be related to the severity of COVID-19 infection;
- Adequate vitamin D concentration can prevent COVID-19 infection in the vulnerable population;
- Vitamin supplementation can improve the outcome in hospitalized patients and susceptible individuals.

Journal Pre-proof

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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 cytokine storm in more severe patients with COVID-19. The pathophysiology is complex and involves several homeostatic factors; among them, the deficit of vitamin D draws attention because of the high frequency in the population. Some evidence suggests that patients with low serum vitamin D levels have a worse outcome, often requiring intensive care. This review analysed the studies available in the global literature that address the benefits of vitamin D in COVID-19, relate its serum levels to the severity of the disease, and indicate it as possible prophylaxis and therapeutic in infection.

Keywords:

COVID-19; vitamin D; cytokine storm immunomodulation

1. Introduction

The pandemic caused by the SARS-CoV-2 infection, (COVID-19), has had a great impact on health systems and has been a great challenge for science in search of a cure. First identified in the seafood market of Wuhan-China and transmitted by airway 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%), diarrhoea (4.8%), and nausea and vomiting (3.9%) [2]. Patients who evolve to ARDS need ventilatory support and other prolonged intensive care. Such respiratory complications can lead to a systemic deterioration, which confers a worse outcome to these patients [5].

It is known that the presence of chronic comorbidities, such as diabetes mellitus, systemic arterial hypertension (SAH), obesity, and cardiovascular diseases are associated with increased morbidity and mortality in COVID-19 [6]. Current evidence states that these diseases have in common a chronic inflammatory pattern with high levels of pro-inflammatory cytokines [7]. It has been observed that patients with severe symptoms of COVID-19 have an uncontrolled production of

pro-inflammatory cytokines, associated with a low serum level of vitamin D and other micronutrients, which suggests the severity of disease [6].

Vitamin D makes up a group of molecules derived from 7-dehydrocholesterol (7-DHC), among which its active metabolite, 25-dihydroxyvitamin D (25(OH)D), and its precursors, ergocalciferol and cholecalciferol are the most important substances. Ergocalciferol or vitamin D₂ is the result of ultraviolet irradiation on ergosterol. Pre-vitamin D₃ or cholecalciferol originates from a photochemical cleavage suffered by the skin precursor of vitamin D (7-DHC), 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], in the synthesis of interleukins and autoimmunity modulation [12]. It also has proven to be essential in the molecular niche of innate immunity [13] and the regulation of cell multiplication and differentiation, being an antioncogenic potential [14].

Recent studies indicate that 25(OH)D not only negatively regulates the renin-angiotensin system, but also has immunoregulatory properties with the ability to suppress interferon-gamma (INF- γ), tumour necrosis factor-alpha (TNF- α) and IL-6, and to stimulate anti-inflammatory cytokines such as IL-10 and IL-12 [7,15]. In addition, there is evidence that vitamin D is effective in the prevention and treatment of influenza and other viral infections [16,17].

This study aimed to analyse the studies available in the global literature that address the benefits of vitamin D in COVID-19, relate its serum levels to the severity of the disease, and indicate it as possible prophylaxis and therapeutic in infection.

2. Materials and Methods

This paper is a narrative review of the literature for studies that have considered the benefits of vitamin D in patients with COVID-19.

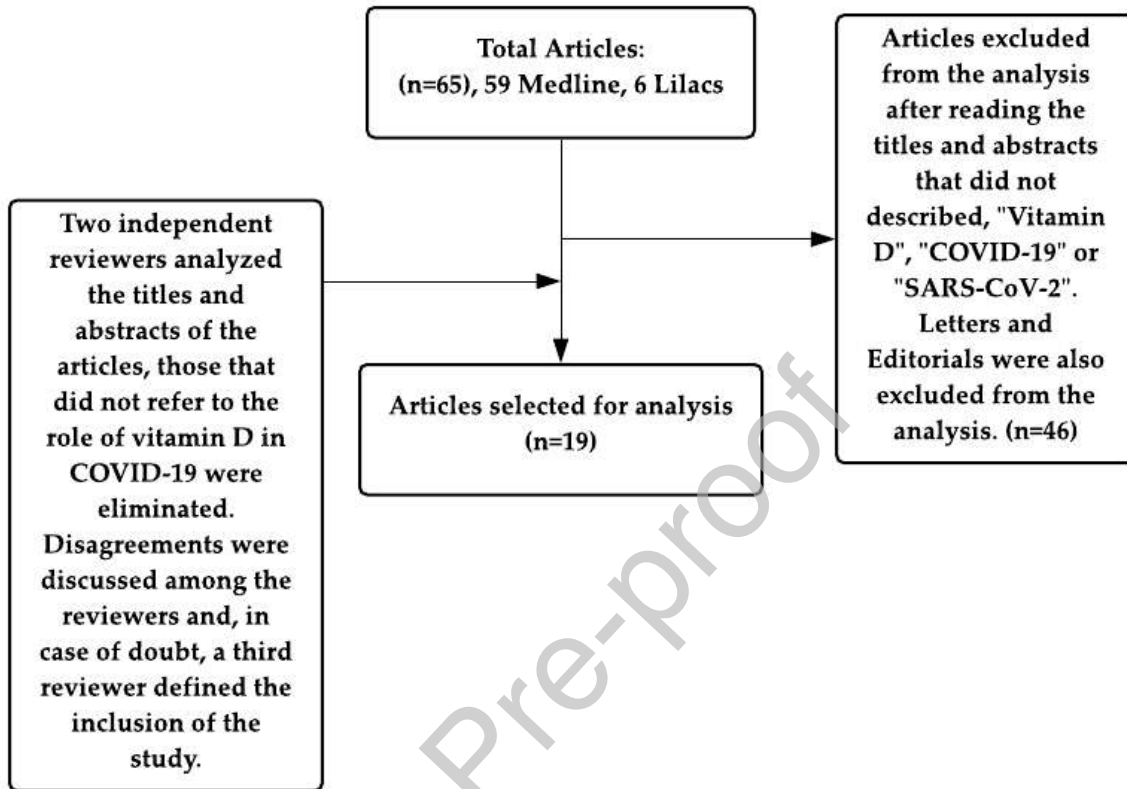
It was sought to evaluate studies on the prophylactic and therapeutic role of vitamin D in COVID-19. Two independent reviewers read the titles and abstracts of the articles, and the common conclusions were summarised. In case of divergences, a third reviewer defined the inclusion of the study in the results.

An electronic search was done using Medline and Lilacs with the combination of terms/descriptors: "vitamin D" AND "COVID-19" and "vitamin D" AND "SARS-CoV-2" without restrictions of language between March and November, 2020. Those studies that did not directly refer to the benefits and/or consequences of vitamin D levels in COVID-19 were excluded from the analysis. Letters and Editorials were also excluded.

3. Results

Figure 1 represents the flow and selection criteria of the analysed articles. Most of the 23 articles were composed of observational studies and previous reviews. To date, there is only one randomised clinical trial.

Figure 1: Selection flow of the analyzed studies



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

Table 1: Results of vitamin d role in COVID-19 in chronological order.

AUTHOR	TYPE OF STUDY/(N)	RESULTS
Grant WB, et al. [6]	Review	Previous studies show that vitamin D deficiency contributes to ARDS. In addition, RCTs demonstrated that vitamin D supplementation reduced the risk of influenza. The intake of vitamin D can help patients with chronic diseases because they have low levels of vitamin D, and consequently decrease the lethality by COVID-19.
McCartney DM, et al. [18]	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 PC, et al. [19]	Short communication	Through a statistical analysis it was observed a gross correlation between mean vitamin D levels (56.79 nmol/L) and mean number of cases of COVID-19/ 1M of inhabitants (1393.4) $r(20) = -0.4435$, and between mean vitamin D levels and number of deaths per COVID-19/ 1M of inhabitants (80.42), $r(20) = -0.4378$, is observed in some European countries.
Silberstein M. [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 M, et al. [20]	Review	25(OH)D increased the surfactant expression associated with B protein, a protein associated with pulmonary surfactant lipids, indicating the surface tension reducing the potential of vitamin D 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 its serum level between 40–60 ng/ml.
Zabetakis I, 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 patients 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 the prophylactic function of vitamin E against COVID-19. Zinc supplementation between 30–50 mg/d can be beneficial in SARS-CoV-2 infection, reducing its viral replication.
D'Avolio A, et al. [21]	Retrospective cohort (N = 107)	Patients aged >70 years with PCR- positive the mean value of 25(OH)D was 11.1 ng/mL while the negative was 24.6 ng/mL in Switzerland. Therefore, vitamin D supplementation can reduce the risk of infection in the elderly (>70 years).
Belančić A, et al. [22]	Review	The prevalence of vitamin d deficiency in obese individuals is between 40–80%. In summary, the alteration of vitamin D metabolism in obese patients may be responsible for the greater severity of COVID-19 in this population.
Iddir M, et al. [23]	Review	Macronutrients have been shown to have an important immunoregulatory role against infectious diseases in animal models. In addition, micronutrients have also been observed as important antioxidant agents, among which, vitamin D deficiency has been associated with covid-19 lethality, especially in high latitude countries.
Dhillon P, et al. [24]	Review	The study clarifies some controversies about the severity of COVID-19. The effect of ibuprofen on covid-19 is still controversial, therefore, it is prudent to use other analgesics to treat the symptoms. No evidence of the protective effect of nicotine was found; on the contrary, chronic exposure to nicotine can promote severe COVID-19. Ethnic black skin minorities living in the northern hemisphere are up to 4.3 times more susceptible to COVID-19, compared to white people because they have low serum levels of 25(OH)D.
Martín V., et al. [25]	Review	Vitamin D stimulates the regulatory T-cell to produce IL-10 at the same time as inhibiting the

		expression of CD80/86, CD40 and other pro-inflammatory lymphocytes. It was also observed that melatonin has an immunoregulatory potential on NF- κ B and MMP-3, attenuating inflammation and pulmonary fibrosis. The combined supplementation can prevent the unfavourable evolution of COVID-19.
Entreras M, et al. [26]	Pilot randomised clinical (N = 76)	Of the patients who were not treated with calcifediol (n = 26), 50% needed intensive care, while of the patients treated (n = 50) only one needed hospitalisation in ICU. The probability of ICU admission in patients treated with calcifediol versus untreated patients was (OR: 0.03 (95% CI: 0.003–0.25). Therefore, vitamin D supplementation may be associated with a better clinical outcome.
Xu Y, et al. [27]	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 its cytokines IFN- γ , TNF- α , IL-1, IL-2, IL12, IL-23, IL-17 and IL-21 can be extended to covid-19.
Cooper ID, et al. [28]	Review	Hyperglycemia stimulates the release of IL-6 and clotting factors, while hyperinsulinemia inhibits the fibrinolytic pathway and increases RAS, which can result in pulmonary embolism. In addition, hyperinsulinemia promotes renal excretion of magnesium disturbing vitamin D metabolism. In summary, patients diagnosed with covid-19 admitted with hyperglycemia and/or hyperglycemia should have their glucose monitored regularly and should be supplemented with vitamin D, magnesium and zinc in order to improve their outcomes.
Maghbooli Z, et al. [29]	Cross-sectional (N = 235)	Of the analysed sample, only 32.8% of the patients had adequate serum vitamin D concentration. Of the 206 patients >40 years of age, 20% had a blood concentration of 25(OH)D <30ng/mL, and only 9.7% who died had a concentration of 25(OH)D \geq 30 ng/mL. Mortality was very rare with concentrations \geq 40ng/mL. Therefore, vitamin D supplementation is recommended in the population, and especially in patients infected with COVID-19 in order to reduce mortality.

Kara M, et al. [30]	Review	Recent data has 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 mortality by COVID-19 in subtropical and mid-latitude countries, and its supplementation can minimise this public health problem.
Kaufman H, el al. [31]	Retrospective observational (N = 191,779)	In a total of 191,779 patients, it was noted that patients with 25(OH)D values < 20 ng/mL (12.5%, 95% C.I. 12.2-12.8%), rate of positivity for SARS-CoV-2, compared to those with 30-34 ng/mL (8.1%, 95% C.I. 7.8-8.4%) and those with \geq 55 ng/mL (5.9%, 95% C.I. 5.5-6.4%). The inversely proportional correlation between vitamin D levels and SARS-CoV-2 positivity rates was significant in a multivariable logistic model with adjusted demographic variables (adjusted OR: 0.984 per ng/mL increment, 95% C.I. 0.983–0.986).
Annweiler C, et al. [32]	Quasi-experimental study (N = 96)	Study conducted in a group of 66 frail elderly, residents of a nursing home. "Intervention Group" - supplemented with vitamin D3 bolus during or just before infection - (n = 57; mean \pm SD, 87.7 \pm 9.3 years; 79 % women) and "Comparator Group" (n = 9; mean, 87.4 \pm 7.2 years; 67 % women). 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 - OSCI score to COVID-19 - (β =-3.84 [95 %CI:-6.07;-1.62]).

Annweiler G, et al. [33]	Quasi-experimental study (N =77)	A total of 77 patients from a geriatric unit were allocated into 3 groups. Group 1: supplemented with vitamin D in the previous year; Group 2: supplemented with vitamin D after COVID-19 infection; Group 3 (control group): received no vitamin D. Survival rates were: (n = 29), 93.1%; 81.2% (n = 16) (p = 0.33); 68.7% (n = 32) (p = 0.02) respectively. Group 3 (control): (HR) = 1; With adjustment for 14-day mortality Group 1: HR = 0.07 (p = 0.017); Group 2 HR = 0.37 (p = 0.28). Longer survival time was observed for Group 1 compared to Group 3 (log-rank p = 0.015). Group 2 (p = 0.40) had a lower risk of OSCI score 5 compared to Group 3 (OR = 0.08, p = 0.03).
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IFN- γ = i gamma; IL = interleukin; 25(OH)D = 25-hydroxyvitamin D; RAS = renin-angiotensin system; ACE-2 = angiotensin-converting enzyme 2; CRP = C-reactive protein; RCTs = randomized controlled trials; PTH = parathyroid hormone; TNF- α = tumour necrosis factor α ; NF- κ B = nuclear factor-kappa beta; MMP-3 = metalloproteinases-3; OR = Odds Ratio; HR = Hazard Ratio.

4. Discussion

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

It is observed that mortality and lethality rates by COVID-19 have been higher in countries of low and high latitudes. This is probably due to a lower incidence of UVB rays, especially in winter [34] and consequently, a large proportion of the elderly population with severe vitamin D deficiency compared to the countries closest to the equator [35,36].

The vitamin D immunological function found in a short time has shown great value against bacterial and viral infections, especially in the respiratory tract, with a satisfactory level of evidence [37,38], stimulating the production of cathelicidin and defensins which decrease cell death in HEP-2 human epithelial cells, and modulate the immune response from Th1 to Th2, suppressing IFN- γ and TNF- β and producing IL-4, IL-5, IL-10, and IL-13 [39]. In addition, its deficiency is an important factor in the direct contribution to the progression of the patient with the acute infectious disease for ARDS [40], at COVID-19 is not being different, in which its deficiency is showing an important inverse relation to the severity of the clinical condition [24].

Patients who progress to ARDS, and consequently need intensive care, have in common the cytokine storm, a phase of infection characterised by uncontrolled production of inflammatory cytokines [6,41]. Studies claim that vitamin D has an immunoregulatory potential at this stage, suppressing the production of INF- γ , TNF- α and IL-6 and other pro-inflammatory cytokines, besides stimulating anti-inflammatory factors [27,29].

However, previous systematic reviews have shown that vitamin D has no significant effect in the treatment of Acute Respiratory Tract Infections [42], as well as Randomized Clinical Trial (RCT) found not to improve insulin sensitivity in patients with obesity not reducing the risk of type 2 diabetes [43]. These results may be a consequence of Glutathione (GSH) deficiency, observed in animal models fed a high fat diet, and in patients with chronic diseases, including diabetes and immunological diseases, implying oxidative stress and vitamin D metabolism. It was noted that L-cysteine supplementation improved serum GSH levels which may be an adjuvant therapeutic strategy [44-47]. Therefore, combined supplementation of vitamin D and L-cysteine may be a significant therapeutic strategy to reduce oxidative stress and treat vitamin D deficiency and its systemic complications [48-51].

5. 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 patients with its deficiency have presented worse clinical outcome. There is still no robust evidence on 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 pharmacological safety profile is well known, it is prudent to keep its mean serum concentration >30 ng/mL in patients on COVID-19 and the susceptible population.

Declaration of Competing Interest

None

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