Análise de ensaios clínicos e ensaios controlados sobre a inter-relação entre vitamina D e COVID-19.

Analysis of clinical trials and controlled trials on the interrelationship between vitamin D and COVID-19.

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Cristóvão Marcondes de Castro Rodrigues
Maxillofacial Surgeon at the Hospital de Clínicas of the Federal University of Uberlândia and Graduating of Department of Medicine, University of Taubaté. Taubaté, São Paulo, Brazil. Av. Tiradentes, 500 - Jardim das Nações, Taubaté - SP, 12030-180
E-mail: cristovao-marcondes@hotmail.com

Jessika Mata do Nascimento
Graduating of Faculty of Dentistry, Federal University of Uberlândia
E-mail: jessik_matt@hotmail.com

RESUMO
A pandemia mundial de coronavírus de 2019 (SARS-COVID-19) representou o mais substancial e sério problema de saúde pública do século até hoje, e as opções terapêuticas ainda estão em fase de estudo e otimização. Por se tratar de uma doença que afeta as vias aéreas em escala global, o presente estudo buscou esclarecer a correlação entre a doença e os níveis de vitamina D. Verificou-se que os níveis de vitamina D têm relação direta com a gravidade da doença. SARS-COVID-19, onde níveis mais baixos de vitamina D, foram desfavoráveis em relação ao prognóstico dos pacientes.

Palavras-chave: COVID-19, colecalciferol, Gravidade da doença, Envolvimento pulmonar

ABSTRACT
The 2019 worldwide coronavirus pandemic (SARS-COVID-19) represented the most substantial and serious public health problem of the century to date, and therapeutic options are still in the study and optimization phase. As it is a disease affecting the airways on a global scale, the present study sought to clarify the correlation between the disease and vitamin D levels. It was found that vitamin D levels have a direct relationship with the severity of the disease. SARS-COVID-19, where lower levels of vitamin D, were prognostically unfavorable in relation to the patients' outcome.

Key Words: COVID-19, cholecalciferol, Disease severity, Pulmonary involvement

1 INTRODUCTION
Coronavirus disease (COVID-19), caused by the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has represented a major threat to human health\textsuperscript{1}. 

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As diagnoses and deaths continue to have extreme fluctuations across the world, COVID-19 is now widely recognized as a global pandemic. Until the present closing of this work, the pandemic has already left more than 5 million deaths worldwide and has surpassed 260 million cases worldwide.

Patients with COVID-19 have clinical clusters of manifestations of severe respiratory disease, including fever, non-productive cough, dyspnea, myalgia, fatigue, abnormal WBC counts, and radiographic evidence of pneumonia, which are similar to the symptoms of SARS-CoV and Respiratory Syndrome Middle East coronavirus (MERS-CoV) previous infections.

With the lack of effective therapy, chemoprevention, and vaccination still proving to be questioned, especially in the context of the different mutations that the disease has been suffering, the focus on the immediate reuse of existing drugs is still seen as a potential solution allied to vaccination in mass that has been happening since 2020.

A recent unbiased genomic screening of SARS-CoV-2 targets in human cells has identified vitamin D among the three highest-scoring molecules that manifest patterns of potential infection mitigation through its effects on gene expression. Epidemiological and clinical studies have shown that vitamin D, acting as an important immunomodulator, can reduce the incidence of respiratory tract infections in adults and children.

2 MATERIALS AND METHODS

The present study was carried out by searching the following electronic database: PubMed and Scielo, whose descriptors used were: sars-covid-19, cholecalciferol, immunomodulation, lung disease and disease severity. Data collection was performed at different times. First all references were exported to the Mendeley Deskyop 1.13.3 software (Mendeley Ltd. London, England) in order to track possible duplicate records. Studies classified as clinical trials and controlled and randomized trials only were included. There was a language restriction, only articles in English were selected and regarding the period of publication, only articles published in the last 3 years were selected.

3 RESULTS AND DISCUSSION

Despite being part of a revisional methodology, the purpose of this article is to expose, in a simple and direct way, the most recent results found correlating to vitamin D and sars-covid disease 19, given that due to the rapid and temporal conditions that gave
rise to the enactment of this disease, the applicability of another more in-depth method requires further longitudinal studies that have been impossible to conclude until now. The flowchart presented (Table -1) demonstrates the selection scheme. Where after realizing the applicability of the inclusion and exclusion criteria adopted for this review, we arrived at a total of sixteen articles that allowed us to carry out an assessment on the subject. Vitamin D deficiency could be a potential aggravating factor for the clinical course of the pandemic. Several lines of evidence suggest that vitamin D deficiency, especially in the elderly, may be a negative factor affecting the clinical course of the pandemic\textsuperscript{4,9}.

<table>
<thead>
<tr>
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<th>Results</th>
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Given that both COVID-19 and vitamin D deficiency are global pandemics and the significant and consistent associations between low vitamin D levels and many extraskeletal pathological conditions, including respiratory diseases\textsuperscript{10,11}, clinical trials are therefore guaranteed to provide robust evidence of vitamin D status, optimization through supplementation can be preventive and/or therapeutic against coronavirus epidemics\textsuperscript{12}. 


Observational studies have shown that higher levels of 25-hydroxyvitamin D are associated with better clinical outcomes in respiratory diseases. Positive associations between low levels of 25-hydroxyvitamin D and poor prognosis among patients with COVID-19 were also observed\(^1\).

In the lung, several types of alveolar cells express the ACE2 receptor. These cells play an important role in the production of surfactant, capable of regulating alveolar surface tension. SARS-CoV-2 can infect alveolar cells by binding ACE2 and suppressing the production of surfactant\(^13\). Loss of alveolar cells results in lung damage and respiratory failure due to loss of pulmonary surfactant. This damage can be avoided by vitamin D, as in vitro and in vivo studies have shown that 1,25(OH)\(_2\)-D induces the proliferation of type II pneumocytes and the synthesis of surfactant in the lungs\(^14,15\).

It has been proposed that activation of the vitamin D receptor (VDR) signaling pathway can generate beneficial effects in Acute Respiratory Distress Syndrome (ARDS)\(^9\), decreasing the cytokine/chemokine storm, regulating the renin-angiotensin system, modulating the activity of neutrophils and maintaining the integrity of the pulmonary epithelial barrier, stimulating epithelial repair and decreasing the increase in coagulability\(^5,9,10,11\).

Immune dysregulation in COVID-19 is marked by increased inflammatory biomarkers such as interleukin 6, lactate dehydrogenase and ferritin. Vitamin D is a potential immunomodulator and its adjuvant role in the treatment of COVID-19 is established as Lakkireddy et al. (2021)\(^11\) presented in their study.

In randomized clinical trial studies, administration of a high dose of calcifediol or 25-hydroxyvitamin D3, a major vitamin D metabolite, significantly reduced the need for intensive care unit treatment of patients requiring hospitalization due to COVID-19\(^14,15,16\).

In the studies by Sabico et al. (2021)\(^12\) it was observed that 5,000 IU of oral vitamin D3 taken daily for two weeks can substantially reduce recovery days from cough and ageusia, and this was clinically significant compared to those who took the standard dose for the control of vitamin D deficiency. Importantly, the circulating 25(OH)D levels of almost all participants at baseline were in the range of insufficiency or mild deficiency, and that 5000 IU vitamin D3 given for two weeks is safe and tolerable.

In the multicenter observational study by Alcala-Diaz et al (2021)\(^14\), patients hospitalized with COVID-19 and treated with calcifediol had lower in-hospital mortality during the first 30 days compared to those patients not supplemented.
In the study led by Carpagnano et al (2020)\(^1\), patients with severe vitamin D deficiency had a significantly higher risk of mortality. Severe vitamin D deficiency may be a marker of poor prognosis in these patients, suggesting that adjuvant treatment may improve disease outcomes.

Even with the limitations listed by Annweiler\(^{16}\), such as: limited number of patients and controlling important characteristics that could modify the association of vitamin D and clinical evolution, it was found that vitamin D3 supplementation before or during COVID-19 was associated with better survival after 3 months in older adults with COVID-19. Vitamin D supplementation may represent an effective, affordable, and well-tolerated adjuvant treatment for COVID-19.

The only study in this compilation, which showed no correlation between vitamin D activity and the improvement of patients hospitalized with SARS-CoV-2, was Murai (2021)\(^{13}\), who concluded through his clinical trial that patients hospitalized with COVID-19, a single high dose of vitamin D\(_3\), compared with placebo, did not significantly reduce the length of hospital stay. However, the study itself raises limitations such as: the relatively small sample size in this trial may have had inadequate power, patients had several coexisting diseases and were subjected to a different medication regimen, and patients received a dose of vitamin D\(_3\) after a relatively long time from onset of symptoms to randomisation.

As this is a more limited study and goes against the results found by most of the works carried out, it is possible to consider it as a counterpoint, but in a limited way.

**4 FINAL CONSIDERATIONS**

In a direct analysis of the results of the studies carried out, even in a short period of time, they showed that there is a direct relationship between serum levels of vitamin D and the evolution of the disease COVID-19. Which leads us to infer that the dosage and supplementation of vitamin D, can collaborate in an adjuvant way in a more favorable prognosis for the patients, of course that there are also multifactorial conditions such as obesity, hypertension, diabetes and immunosuppressive diseases that directly interfere in the individual's response against pulmonary infection, which should be considered, but vitamin D supplementation may be a more favorable way of evolution for patients during the hospital stay.
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