

Vitamin D levels and risk of COVID-19 infection: A systematic review

Ana C. Coelho-Oliveira,^{1,2*} Bruno B. Monteiro-Oliveira,^{1,2,3} Rebeca B. M. Cavalcante,¹ Daniel B. Santos,² Anelise Sonza,⁴ Danúbia C. de Sá-Caputo,^{2,3} Mario Bernardo-Filho²

Abstract

Objective: Consistent independent associations between low serum 25-hydroxyvitamin D concentrations and susceptibility to acute respiratory tract infections have suggested a possible involvement of vitamin D in reducing the risk of respiratory infections and proposing its replacement as a potential strategy for prevention or treatment in this context. However, the role of vitamin D supplementation in the infection by the novel coronavirus named SARS-CoV-2 is still under investigation and no clinical evidence has been reported to date. **Methods:** Electronic searches in Pubmed, Embase and Scopus databases were conducted and three cohort studies that analyzed the effects of interaction of vitamin D with COVID-19, published only in English, were included. Two reviewers, which independently examined titles and abstracts, identified records through database search and reference screening and irrelevant studies were excluded based in eligibility criteria. Relevant full texts were analyzed for eligibility, and all relevant studies were included in the systematic review. **Results:** Three cohort studies were included in this systematic review with a mean methodological quality low. Only one study demonstrated interaction of low vitamin D concentration in patients with a positive diagnosis for COVID-19. Randomized clinical trials and studies of good methodological quality are necessary to confirm the findings of this systematic review. **Conclusions:** This systematic review has not demonstrated consistent associations between low levels of vitamin D and susceptibility to COVID-19 infection. Further studies on vitamin D supplementation for the prevention of COVID-19 infection should be conducted.

Keywords: Vitamin D; COVID-19; Public health.

Resumo

Níveis de vitamina D e risco de infecção por COVID-19: Uma revisão sistemática

Objetivo: Associações independentes consistentes entre baixas concentrações séricas de 25-hidroxivitamina D e suscetibilidade a infecções agudas do trato respiratório sugeriram um possível envolvimento da vitamina D na redução do risco de infecções respiratórias e propuseram sua substituição como uma estratégia potencial para prevenção ou tratamento neste contexto. No entanto, o papel da suplementação de vitamina D na infecção pelo novo coronavírus denominado SARS-CoV-2 ainda está sob investigação e nenhuma evidência clínica foi relatada até o momento. **Métodos:** Foram realizadas buscas eletrônicas nas bases de dados Pubmed, Embase e Sco-

1. Programa de Pós-Graduação em Fisiopatologia Clínica e Experimental, Instituto de Biologia Roberto Alcântara Gomes. Universidade do Estado do Rio de Janeiro, Rio de Janeiro, RJ, Brazil.
2. Departamento de Biofísica e Biometria, Laboratório de Vibrações Mecânicas e Práticas Integrativas, Instituto de Biologia Roberto Alcântara Gomes. Universidade do Estado do Rio de Janeiro, Rio de Janeiro, Brazil.
3. Faculdade Bezerra de Araújo, Rio de Janeiro, RJ, Brazil.
4. Universidade do Estado de Santa Catarina, Florianópolis, SC, Brazil.

*Correspondence address:

UERJ, PPC, LAVIMP
Avenida Marechal Rondon, 381
Rio de Janeiro, RJ, Brasil
CEP: 20950-003
E-mail: anacarol_coelho@hotmail.com
ORCID <https://orcid.org/0000-0002-5491-6060>

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pus e incluídos três estudos de coorte que analisaram os efeitos da interação da vitamina D com o COVID-19, publicados apenas em inglês. Dois revisores, que examinaram de maneira independente títulos e resumos, identificaram registros por meio de pesquisa de banco de dados e triagem de referência e foram excluídos estudos irrelevantes com base em critérios de elegibilidade. Textos completos relevantes foram analisados para elegibilidade, e todos os estudos relevantes foram incluídos na revisão sistemática. Resultados: Três estudos de coorte foram incluídos nesta revisão sistemática com uma qualidade metodológica média baixa. Apenas um estudo demonstrou interação de baixa concentração de vitamina D em pacientes com diagnóstico positivo para COVID-19. Ensaio clínico randomizado e estudos de boa qualidade metodológica são necessários para confirmar os achados desta revisão sistemática. Conclusões: Esta revisão sistemática não demonstrou associações consistentes entre baixos níveis de vitamina D e suscetibilidade à infecção por COVID-19. Mais estudos sobre a suplementação de vitamina D para a prevenção da infecção por COVID-19 devem ser realizados.

Descritores: Vitamina D; COVID-19; Saúde pública.

Resumen

Niveles de vitamina D y riesgo de infección por COVID-19: Una revisión sistemática

Objetivo: Las asociaciones independientes consistentes entre las concentraciones séricas bajas de 25-hidroxivitamina D y la susceptibilidad a las infecciones respiratorias agudas han sugerido una posible participación de la vitamina D en la reducción del riesgo de infecciones respiratorias y proponen su reemplazo como una estrategia potencial de prevención o tratamiento en este contexto. Sin embargo, el papel de la suplementación con vitamina D en la infección por el nuevo coronavirus llamado SARS-CoV-2 todavía está bajo investigación y hasta la fecha no se ha informado de evidencia clínica. **Métodos:** Se realizaron búsquedas electrónicas en las bases de datos Pubmed, Embase y Scopus y se incluyeron tres estudios de cohortes que analizaron los efectos de la interacción de la vitamina D con COVID-19, publicados solo en inglés. Dos revisores, que examinaron de forma indepen-

diente los títulos y los resúmenes, identificaron los registros mediante la búsqueda en la base de datos y la selección de referencias y se excluyeron los estudios irrelevantes según los criterios de elegibilidad. Se analizaron los textos completos pertinentes para determinar su elegibilidad y todos los estudios relevantes se incluyeron en la revisión sistemática. **Resultados:** En esta revisión sistemática se incluyeron tres estudios de cohortes con una calidad metodológica media baja. Solo un estudio demostró la interacción de una concentración baja de vitamina D en pacientes con un diagnóstico positivo de COVID-19. Se necesitan ensayos clínicos aleatorios y estudios de buena calidad metodológica para confirmar los hallazgos de esta revisión sistemática. **Conclusiones:** Esta revisión sistemática no ha demostrado asociaciones consistentes entre niveles bajos de vitamina D y susceptibilidad a la infección por COVID-19. Deben realizarse más estudios sobre la suplementación con vitamina D para la prevención de la infección por COVID-19.

Palabras clave: Vitamina D; COVID-19; Salud pública.

Introduction

The 2019 coronavirus disease global pandemic (COVID-19), caused by the SARS-CoV-2 coronavirus, has resulted in more than 6 million cases, has caused 376,000 deaths worldwide, and generally produces severe lower respiratory symptoms, according to the World Health Organization (WHO).¹ However, to this date, there is no specific treatment recommended to help alleviate the symptoms of patients affected with COVID-19 and SARS-CoV-2, and some non-pharmacological interventions during the hospitalization,² the confinement³ and post-COVID-19 infection have been suggested.⁴

COVID-19 is more prevalent among African-Americans,⁵ persons living in northern cities in the late winter,⁶ older adults,⁷ nursing home residents,⁸ health care workers,⁹ and populations at increased risk of vitamin D deficiency.

Since COVID-19 can manifest with different intensity of symptoms (from asymptomatic to severe symptoms), recently, some studies have reported consistent independent associations between low serum concentrations of 25-hydroxyvitamin D (the major circulating vitamin D metabolite) and susceptibility to acute respiratory tract infection,¹⁰ suggesting a possible involvement of vitamin D in reducing the risk of respiratory tract infections and proposing its replacement as a potential strategy for prevention or treatment,

especially in the context of influenza and COVID-19. However, the role of vitamin D supplementation in the context of virus infection is still under investigation, and no clinical evidence has been reported yet.

Although vitamin D deficiency is common in a large part of the general population, disparities in socioeconomic standards, housing conditions, socialization habits and risk perception, people living in higher latitudes, and especially ethnic conditions, have potential implications for the risk of COVID-19 exposure and transmission, presenting higher rates among people with darker skin or reduced exposure to ultraviolet (UV) radiation from the sun.^{11,12}

Authors describe vitamin D hormone as having important functions - including immunomodulant, anti-inflammatory and anti-infective roles.¹³ It acts via monocyte and cell-mediated immunity stimulation, suppression of lymphocyte proliferation, antibody production and cytokine synthesis.¹⁰ Human lung cells are able to intracellularly convert the inactive 25(OH)D to its active form 1,25(OH)D, which reduces proinflammatory cytokines and increases peptides (e.g. the innate antimicrobial peptide cathelicidin). Cathelicidin has direct antiviral activity against enveloped respiratory viruses such as hepatitis B, influenza, respiratory syncytial virus and possibly the COVID-19 as well.¹⁰ Nevertheless, evidence of whether vitamin D deficiency is associated with COVID-19 infection is lacking and/or could help

establish vitamin D as an evidence-based approach to decrease the burden and potentially the spread of COVID-19. Considering this rationale, the aim of this systematic review is to assess the effects of the association of vitamin D and COVID-19.

Methods

The review was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines¹⁴ and the methods were prespecified in a protocol that was registered under number CRD42020196135 in the PROSPERO International Prospective Register of Systematic Reviews (PROSPERO).¹⁵

Search Strategy: It was conducted an electronic search in Pubmed, Embase and Scopus databases in June 22th 2020, using the following search string (“*covid 19*” OR “*covid-19*” OR “*coronavirus*” OR “*SARS-Cov-2*”) AND (“*vitamin D*”). The keywords used in the search were defined based on the PICO strategy, focusing on patients with COVID-19 (Participants) and its relationship with vitamin D (Intervention) without restrictions regarding comparisons (Comparison). All reported outcomes (Outcomes) were allowed if considered relevant to the studied population.¹⁶

Eligibility Criteria

Inclusion criteria: To be included in this review, the works must be full articles, meet the search criteria and investigate effects of vitamin D on COVID-19 patients, independent of the year of the publication. A flowchart (Figure 1), based in the PRISMA analysis was done to show the steps in the selection of the full papers analyzed in this review.¹⁴

Exclusion criteria: Exclusion criteria allowed the elimination of unnecessary publications. Papers were excluded if: (i) published in a language other than English; (ii) with findings not related to COVID-19 and vitamin D; (iii) being replies, editorials, letters, abstracts, reviews, commentary’s or short communications; and (iv) being conducted with animal, or with combined treatments.

Level of evidence of the selected papers: The level of evidence of each selected publication was individually assessed by using the National Health and Medical Research Council hierarchy of evidence.¹⁷ The level of evidence was defined as follows: (i) I, the systematic review of level II studies; (ii) II, the randomized clinical trial (RCT); (iii) III-1, the pseudo-randomized controlled trial (alternate allocation, as a crossover study or some

other similar method); (iv) III-2, the comparative study with concurrent controls (non-randomized experimental trial, cohort study, case control study, interrupted time series with a control group); (v) III-3, the comparative study without concurrent control (historical control, two or more single arm study, interrupted time series without a parallel control group; and (vi) IV, the case series with either post-test or pretest/post-test outcomes.

Study Selection and Data Extraction: All references were exported to a data management software (EndNote X9), and duplicates were removed. The review was conducted following four steps. Records were identified through database search and reference screening (Identification), and two reviewers independently examined titles and abstracts and irrelevant studies were excluded based in eligibility criteria (Screening). Relevant full texts were analyzed for eligibility (Eligibility), and all relevant works were included in the systematic review. The disagreement was resolved by a third reviewer. The same researchers were responsible for the data extraction from the included studies. Data regarding study information (author and year), study design, objectives, and outcomes were extracted.

Results

A total of 277 studies were identified through a database search and, after the removal of 138 duplicates, 139 studies were identified. During the screening process, 127 publications were excluded for not being related to the research question and the full text of 11 articles was reviewed in detail. After careful analysis, 8 studies were excluded (5 review articles, 2 commentaries and 1 vitamin D and other treatment). Finally, three publications were included in the systematic review. The selection process is summarized in Figure 1.

Table 1 shows the characteristics of the participants, the aims of the studies, the outcomes of the selected articles and the level of evidence of the selected papers. The levels of evidence¹⁷ for all studies included in the current review were considered LE III -2.

Several outcomes have been assessed in the matter of whether (i) vitamin D reduces the risk of infection, (ii) vitamin D deficiency is associated with COVID-19 infection and (iii) there is a correlation between vitamin D and COVID -19 in black and South Asian people.

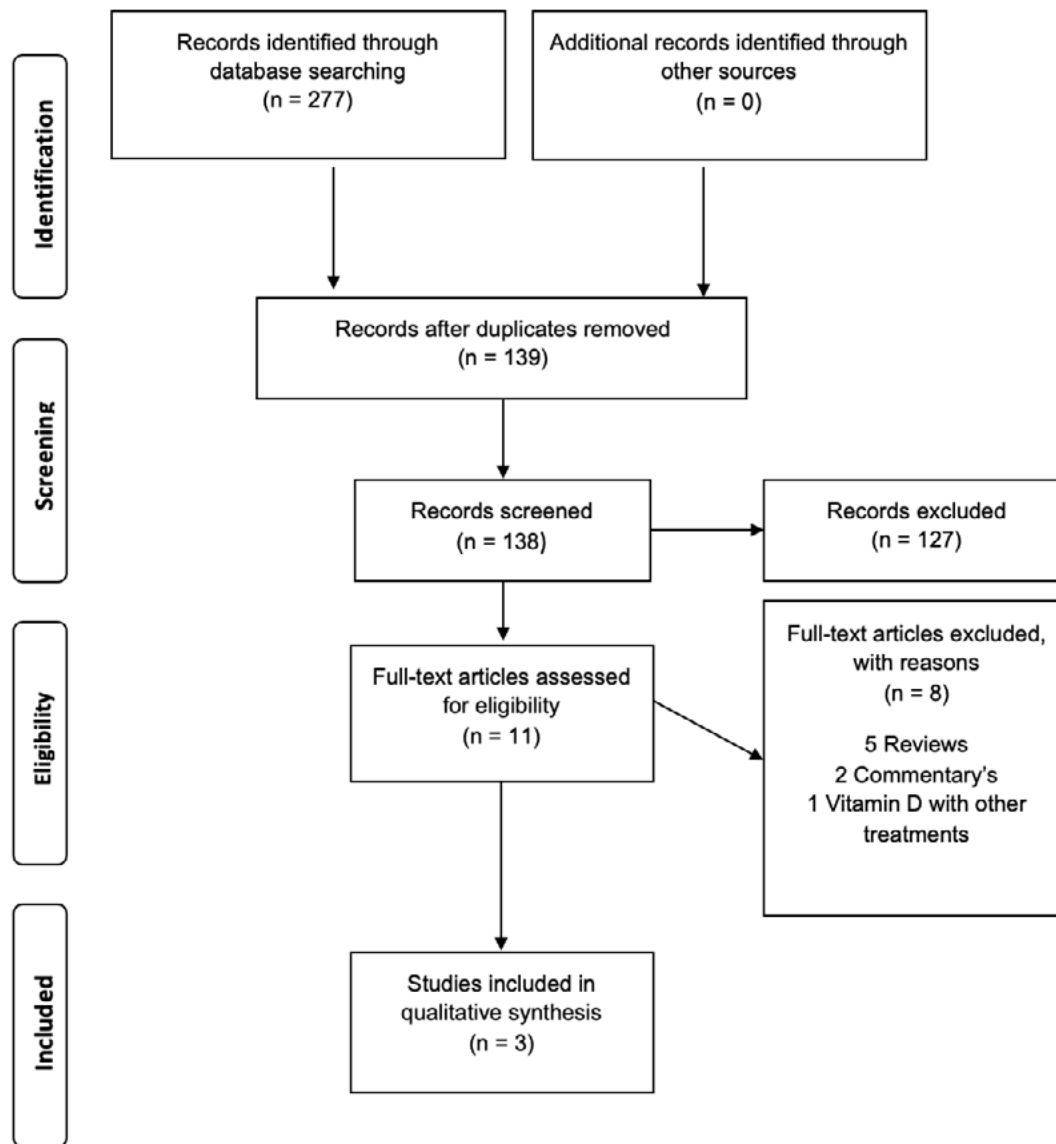


Figure 1. PRISMA flow diagram of the literature selection process

Regarding the main findings based on the results, vitamin D was lower in patients positive for SARS-CoV-2 PCR compared to negative patients.¹⁸

The works used populations of three countries, UK, USA, and Switzerland. The studied population ranged from 107 to 348,598 individuals with an average age ranging from 45.7 to 73 years and the concentration of

vitamin D ranged from 22 to 32.7 ng/mL. One work¹⁸ evaluated two groups: 27 individuals SARS-CoV2 positive (54,2% males) with median age of 73 years and median vitamin D of 22 ng/mL and 80 individuals SARS-Cov2 negative (48.8% males) with median age of 73 years and median vitamin D of 24.6 ng/mL; one work¹⁹ evaluated 4,314 individuals with median age

Table 1. Description of the selected studies

Study	Demograph	Type of study	Objective	Results	Level of Evidence
D'Avolio et al, 2020	<p>Total 107 patients in 2 groups.</p> <p>male = 54.2%; median age = 73 years 25(OH)D = 22.0 ng/mL.</p> <p>27 SARS-CoV-2 PCR-positive</p> <p>male = 70.4%; Median age = 74 years 25(OH)D = 11.1 ng/mL</p> <p>80 SARS-CoV-2 PCR-negative</p> <p>male = 48.8%; median age = 73 years median 25(OH)D = 24.6 ng/mL</p> <p>Switzerland</p>	Cohort retrospective study	The involvement of vitamin D in reducing the risk of infections.	<p>Statistically significant ($p = 0.004$) lower 25(OH)D levels (11.1 ng/mL) in patients positive for the SARS-CoV-2 PCR compared with the negative patients (24.6 ng/mL) was observed.</p> <p>When stratifying the 2020 patients by age (0–70 years and >70 years) and PCR positivity, and considering only patients with age >70 years ($n = 43$ vs. $n = 18$), the vitamin D concentrations are significantly different ($p = 0.037$), with median values of 23.1 ng/mL in PCR-negative patients vs. 9.3 ng/mL in PCR-positive patients.</p>	III - 2
D'Meltzer et al, 2020	<p>Total 4,314 patients. male = 35%, females (65%); median age = 45.7 years</p> <p>SARS-CoV-2 positive and deficiency Vitamin D</p> <p>32 of 178 (18%)</p> <p>SARS-CoV-2 positive and non-deficient patients</p> <p>40 of 321(11%)</p> <p>USA</p>	Cohort retrospective study	Deficiency analysis and vitamin D treatment are associated with a positive test for COVID-19.	The Vitamin D dose was not significantly associated with testing positive for COVID-19.	III - 2
Hastie et al, 2020	<p>Total 348,598 SARS-CoV-2 positive</p> <p>Male 265 (59.02%) Female 184 (40.98%) Mean Age 49 25(OH)D = 28.7 ng/mL</p> <p>SARS-CoV-2 negative</p> <p>Male 168,391 (48.37) Female 179,758 (51.63) Mean Age 49 25(OH)D = 32.7 ng/mL</p> <p>UK</p>	Cohort Prospective study	The objective of the study was to assess whether there is an association between (25 (OH) D) and the risk of COVID-19 and explaining the higher incidence of COVID-19 in black and South Asian people	<p>Did not find a potential between vitamin D concentrations and risk of COVID-19 infection, nor that vitamin D concentration can explain ethnic differences</p> <p>Contagion of COVID-19.</p>	III - 2

Legends: 25(OH)D: Vitamin D; UK: United Kindon; USA: United States of America.

of 45.7 years and a greater number of females (65%) than males (35%); and one work²⁰ evaluated 348,598 individuals in two groups: 449 individuals SARS-CoV2 positive (59.02% males) with median age of 49 years and median vitamin D of 28.7 ng/mL, and 348,149 individuals SARS-Cov2 negative (48.37% males) with median age of 49 years and median vitamin D of 32.7 ng/mL.

Discussion

The main goal of this systematic review was to assess the effects of the association of vitamin D and COVID-19. After analyzing the included studies and considering their limitations, it was clear that studies with better quality are lacking, indicating a promising field of study. The methodological quality and level of evidence of the included studies in this review were low, mainly regarding the lack of experimental studies with interventions on this context. So far, only observational studies have been carried out.

The results of the works included in this review are not sufficient to establish the association between the vitamin D concentration and the predisposition to COVID-19 infection, but this correlation may be possible. Two retrospective studies found this association. D'Avolio et al.¹⁸ found that individuals with a positive diagnosis of SARS-CoV-2 had lower plasma concentrations of 25-hydroxyvitamin D, compared to individuals with a negative diagnosis. Meltzer et al.¹⁹ observed that vitamin D deficiency that is not sufficiently treated is associated with COVID-19 risk. In the other hand, Hastie et al.,²⁰ in a prospective study, did not find this association.

Few reviews consider the mechanisms through which vitamin D reduces the risk of viral infections.^{21,22} It is believed that vitamin D, being a fat-soluble vitamin, is activated in the lung and acts in the modulation of the renin-angiotensin system, decreasing the release of the ECA2 enzyme, which is a gateway to COVID-19 in the lung.²³ Additionally, Martineau et al.²⁴ concluded in a meta-analysis that vitamin D supplementation was safe and protective against acute respiratory tract infections. However, although there are studies suggesting that this supplementation may also be effective for COVID-19, only one article included in this review suggests vitamin D as a protective factor for this virus.

According to the literature, vitamin D deficiency is highly prevalent around the world, as around 7% of

the world population has severe deficiency and about 40% live with modest deficiency.²⁵ Individuals from colder regions, higher latitudes, and the elderly, who experience little exposure to sunlight, are also more vulnerable to vitamin D deficiency and consequently to more respiratory symptoms,¹² as well as COVID-19.

Most vitamin D results from production in the skin following exposure to ultraviolet (UV) radiation from the sun; therefore, UV radiation is the main source of vitamin D, providing around 80% of its production. Individuals with dark skin have, on average, lower concentrations of blood vitamin D because the melanin in dark skin does not absorb as much UV radiation.²⁶ These findings corroborate with two studies in this review that suggest an association between deficiency of vitamin D and the development of COVID-19.

A recent population-based study utilizing data from a large health maintenance organization in Israel that evaluated associations of plasma 25(OH)D status with the likelihood of coronavirus disease infection and hospitalization concluded that low plasma 25(OH)D level appears to be an independent risk factor for COVID-19 infection and hospitalization, after adjusting for age, gender, socioeconomic status (SES) and chronic, mental and physical disorders.²⁷ The discrepancy between the results of Hastie et al.²⁰ and the findings of the Israeli population study can be explained by a smaller sample size, by the elderly population and by the inability to control various confounding factors in the first study, like SES and chronic medical conditions.

A review article on the plausible mechanisms that link vitamin D deficiency to increased susceptibility to severe COVID-19 infection in patients with diabetes found sufficient evidence of a shared pathophysiological and mechanistic link between diabetes and COVID-19 infection most evident in presence of vitamin D levels below 10 ng/mL, pointing out that health care providers need to ensure adequate level of vitamin D in such situation.²⁸

The present systematic review has some limitations and therefore the results should be interpreted with caution. It was not possible to assess the risk of bias, due to the design of the studies included in the review. Only cohort studies were included, the searches were performed only in three databases and in the English language.

The strength of this work is related to the identification of acceptable, relatively safe and inexpensive intervention (i.e., vitamin D) able to

determine improvements and reducing COVID-19 infection rate.

Conclusion

Vitamin D deficiency and insufficiency is a worldwide issue and adequate levels of this fat-soluble vitamin are required for the proper functioning of the body's defense system. This systematic review has not demonstrated widely consistent associations between low levels of vitamin D and susceptibility to COVID-19. Further placebo-controlled randomized clinical trials on vitamin D supplementation for the prevention of this infection should be conducted in populations with a high prevalence of vitamin D deficiency, addressing the impact of the replacement regimen and aiming to detect effects in different subgroups. Studies will

require careful consideration to adapt this treatment to the specific needs of each patient.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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