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ASSOCIATION OF VITAMIN D DEFICIENCY TO SEVERITY OF COVID-19 : A SYSTEMATIC REVIEW

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Abstract

As a pathogen invades, phagocytes quickly respond, but the adaptive immune response is more specific. Antigen-recognizing cytotoxic T cells control this immunological response. Cytotoxic T cells kill infection. These cells participate in humoral, antiparasitic, and antiviral immune responses. Balanced nutrition helps the immune system fight infections and neoplastic cells. Research describes how the immune system and defensive mechanisms defend the body from invaders, especially with optimal diet. Respiratory tract infections can worsen chronic diseases, increasing mortality. Vitamin D reduces respiratory infections, including pneumonia, through numerous mechanisms. UVB exposure converts 7-dehydrocholesterol into fat-soluble vitamin D. The liver converts it to 25(OH)D, which the kidneys or other organs convert to calcitriol 1, 25(OHD). Bones and teeth need vitamin D. Vitamin D aids bone metabolism, gastrointestinal calcium and phosphorus absorption, and the immune system, according to in vitro research. Most studies indicate COVID-19 severity with vitamin D levels below 12. Vitamin D pills benefit COVID-19 patients.

Keyword: *Calcitriol 1, 25(OHD); COVID-19; Inflammation; Vitamin D; Severity*

INTRODUCTION

The World Health Organization (WHO) has declared the 2019–20 coronavirus outbreak a Public Health Emergency of International Concern (PHEIC). Evidence of local disease transmission was found in multiple countries across all six WHO regions as of 7 March 2020.[1] COVID-19 infection is an ongoing pandemic characterized by high morbidity and mortality. There is an urgent need to identify clinical and biological predictors of severity and mortality associated with COVID-19 infection for the judicious use of limited resources.[2]

Food contains immune-boosting micronutrients. Fresh animal and plant meals provide vitamins A, D, E, C, B6, B12, and folate, as well as minerals like iron, zinc, and selenium, which can assist the body fight infection.[3] The innate immune response is mechanically rapid via phagocytes when a pathogen invades, but the adaptive immune response is more specific in identifying the invading pathogen. This immune response is primarily controlled and coordinated by antigen-recognizing T cells and are classified as cytotoxic T cells. Cytotoxic T cells kill infected cells. These cells are involved in antiviral and cellular immune responses as well as humoral and antiparasitic responses.[3,4]

A strong immune system ensures host defense against pathogens and neoplastic cells, and balanced nutrition augments the immune system to provide optimal defense against infectious agents. Study describe the important role of the immune system as well as the defense mechanisms involved in protecting the body from invading agents, especially in the presence of proper nutrition.[3] Chronic disorders can be exacerbated by respiratory tract infections, increasing the chance of death. Vitamin D may reduce the incidence of respiratory infections, including pneumonia, through multiple pathways.[5,6]
This article discusses the association of vitamin D deficiency to severity of COVID-19.

METHODS

For data collection, processing, and reporting, this study adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 project criteria. Based on these factors, the adopted regulations were formulated. The goal of this literature review is to look at the association of vitamin D deficiency to severity of COVID-19.

These are the primary issues raised by the current study. 1) To be considered for publication, articles must always be written in English and emphasize the link between vitamin D deficiency to severity of COVID-19. 2) Articles published after 2019 but before the period of this systematic review were considered for this evaluation. The anthology will not include editorials, submissions without a DOI, reviews of previously published articles, or entries that are substantially identical to those in the journal.

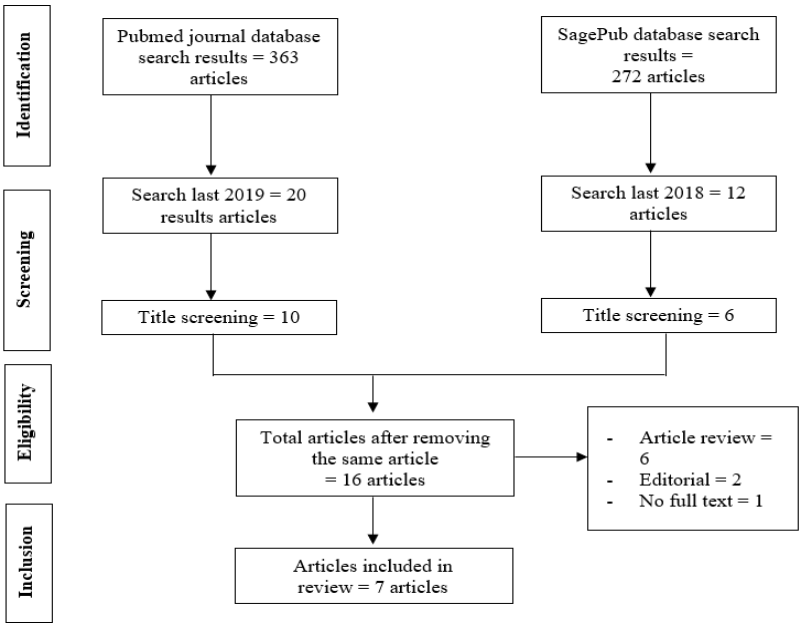

Figure 1. Article search flowchart

The search for studies to be included in the systematic review was carried out from March, 16th 2023 using the PubMed and SagePub databases by inputting the words: “Vitamin D deficiency” and “COVID-19 severity”. Where *("vitamin d deficiency"[MeSH Terms] OR "vitamin d deficiency"[All Fields]) AND ("covid 19"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] OR "covid 19 nucleic acid testing"[All Fields] OR "covid 19 nucleic acid testing"[MeSH Terms] OR "covid 19 serological testing"[All Fields] OR "covid 19 serological testing"[MeSH Terms] OR "covid 19 testing"[All Fields] OR "covid 19 testing"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication])) AND ("sever"[All Fields] OR "severe"[All Fields] OR "severed"[All Fields] OR "severely"[All Fields] OR "severer"[All*

Fields] OR "severes"[All Fields] OR "severing"[All Fields] OR "severities"[All Fields] OR "severity"[All Fields] OR "severs"[All Fields]) is used as search keywords.

The authors assessed each study's eligibility based on its abstract and title. Thus, the authors select historical literature as their primary source. After assessing multiple research with the same outcome, submissions in unpublished English are required. Only studies meeting the inclusion criteria were considered for inclusion in the systematic review. This restricts search results to only match the specified criteria. After then, the research will be assessed. The study analysis showed the names, authors, publication dates, location, study activities, and parameters. After placing search results in an EndNote file, duplicate articles were removed from the database. The relevance of each paper's title and abstract to this study was reviewed by two reviewers.

Each author individually read the research provided in the publication's title and abstract before deciding which papers to investigate in greater detail. Next, we will evaluate all of the papers that meet the review's inclusion criteria and should be considered for inclusion. When our research is complete, we will select relevant research articles for review. On the basis of this rule, reviewable manuscripts will be chosen. The approach for selecting items for additional scrutiny should be as streamlined as possible. Which past studies were done, and what about them authorized their inclusion, if appropriate, in the review?

RESULT

A study was carried out by AlSafar, et al (2021) with a total of 522 people, all of whom tested positive for SARS-CoV-2 at one of the most prominent hospitals in Abu Dhabi and Dubai. They demonstrated that levels of 25(OH)D lower than 12 ng/mL were considerably connected with an increased risk of severe COVID-19 infection as well as an increased risk of death. Age was the only other independent risk factor, but comorbidities and smoking did not contribute to the outcomes once adjustment was made for them. Age was the only other independent risk factor.[7]

D'Avolio, et al (2020)[8] has hypothesized that vitamin D may reduce the risk of infection; therefore, we examined the 25-hydroxyvitamin D (25(OH)D) concentrations in plasma taken from a cohort of Swiss patients. In they cohort, PCR-positive for SARS-CoV-2 was associated with considerably lower 25(OH)D levels ($p = 0.004$) compared to negative patients (24.6 ng/mL); this was also validated by stratifying patients based on age >70 years. On the basis of this first discovery, vitamin D supplementation may be an effective method for lowering the risk of infection.

Table 1. The litelature include in this study

Author	Origin	Method	Sample	Conclusion
Alsafar, 2021[7]	United Arab Emirates	Cross sectional study	522 participants who tested positive for SARS-CoV-2	Levels 25(OH)D lower than 12 ng/mL were substantially related with an increased risk of severe COVID-19 infection as well as an increased risk of death. Age was the only other independent risk factor, although comorbidities and smoking did not contribute to the outcomes once adjustment was made for them.
D'Avolio, 2020[8]	Switzerland	Cohort prospective study	27 patients PCR+ for SARS-CoV-2; 80 patients PCR– 1377 controls with 25(OH)D measured	In this group of patients, those who tested positive for SARS-CoV-2 by PCR had significantly lower 25(OH)D levels ($p = 0.004$) than those who tested negative (24.6 ng/mL). This was confirmed by grouping patients by age >70 years.
Panagiotou, 2020[9]	United Kingdom	Cohort prospective study	134 participants who tested positive for SARS-CoV-2	It is likely that graded supplementation with vitamin D was responsible for the lack of connection between death and baseline 25(OH)D.
Carpagnano, 2021[10]	Italy	Retrospective, observational study	42 patients with acute respiratory failure due to COVID-19	Eighty-one percent of patients had vitamin D deficiency. The population was divided into four categories based on vitamin D levels: no hypovitaminosis D, insufficiency, moderate deficiency, and severe deficiency. No variations were detected between demographic and clinical variables. An examination of survival revealed that after 10 days of hospitalization, individuals with severe vitamin D insufficiency had a 50% mortality risk, whereas those with vitamin D levels 10 ng/mL had a 5% mortality risk ($p = 0.019$).
Murai, 2021[11]	Brazil	Randomized Clinical Trial	240 randomized patients	When individuals hospitalized with COVID-19 were given either a placebo or a single high dosage of vitamin D3, there was no significant difference in the amount of time they spent in the hospital between the two. According to these data, the use of a high dose of vitamin D3 as a therapy for moderate to severe COVID-19 is not warranted.
Sabico, 2021[12]	Saudi Arabia	Randomized Clinical Trial	69 reverse transcriptase polymerase chain reaction (RT-PCR) SARS-CoV-2 positive adults	In individuals with suboptimal vitamin D status with mild to moderate COVID-19 symptoms, a daily oral supplementation of 5000 IU vitamin D3 for two weeks lowers the duration to recovery for cough and gustatory sensory loss. Even for a brief duration, it is advised that COVID-19 patients with inadequate vitamin D status receive 5000 IU of vitamin D3 as an adjuvant therapy.
Saponaro, 2022[13]	Italy	Cross sectional	Ninety-three consecutive patients with COVID-19-related pneumonia	Given the correlation between 25OHD levels and inflammatory marker concentrations, it seems reasonable to conclude that the vitamin D status of these patients should be taken into consideration in the treatment plan. There is still a need for further investigation into whether or not vitamin D levels are a marker of a poor prognosis or a possible risk factor that can be mitigated by supplementing.

Carpagnano, et al (2021)[10] conducted a study. They study population was divided into four vitamin D groups: no hypovitaminosis D, insufficiency, moderate deficiency, and severe deficiency. Demographic and clinical differences were absent. After 10 days in the hospital, severe vitamin D deficient patients had a 50% death rate, while those with vitamin D < 10 ng/mL had 5% ($p = 0.019$). In RICU-treated COVID-19 patients with acute respiratory failure, hypovitaminosis

D was common. Severe vitamin D insufficiency increased mortality. Adjunctive medication may improve illness outcomes in people with severe vitamin D insufficiency.

Murai, et al (2021)[11] showed the difference between the vitamin D3 group and the placebo group was not statistically significant in terms of in-hospital mortality (7.6% vs 5.1%; difference = 2.5% [95% CI = -4.1-9.2%]; P = 0.43), admission to the intensive care unit (16.0% vs 21.2%; difference = -5.2% [95% CI = -15.1-4.7%]; P = 0.30), or the need for mechanical ventilation (7.6% vs 25-hydroxyvitamin D levels rose considerably following a single dose of vitamin D3 compared to placebo (44.4 ng/mL vs. 19.8 ng/mL; difference, 24.1 ng/mL [95% CI = 19.5-28.7]; P = 0.001). One incident of vomiting was the only adverse event linked with the treatments.

Other study showed only the 5000 IU group experienced a significant rise in serum 25(OH)D levels after 2 weeks of vitamin D administration (adjusted p = 0.003). Within-group comparisons revealed a substantial decrease in BMI and IL-6 levels over time in both groups (p-values <0.05), but between-group comparisons were not clinically significant. Even after correcting for age, sex, baseline BMI, and D-dimer, Kaplan-Meier survival analysis revealed that the 5000 IU group had a significantly quicker time to recovery (days) than the 1000 IU group in clearing cough (6.2 ± 0.8 versus 9.1 ± 0.8; p = 0.039), and ageusia (11.4 ± 1.0 versus 16.9 ± 1.7; p = 0.035).

Saponaro, et al (2021)[13] showed sixty-five percent of patients presented hypovitaminosis D (25OHD ≤20 ng/ml) and showed significantly higher IL-6 [20.8 (10.9-45.6) vs. 12.9 (8.7-21.1) pg/ml, p = 0.02], CRP [10.7 (4.2-19.2) vs. 5.9 (1.6-8.1) mg/dl, p = 0.003], TNF-α [8.9 (6.0-14.8) vs. 4.4 (1.5-10.6) pg/ml, p = 0.01], D-dimer [0.53 (0.25-0.72) vs. 0.22 (0.17-0.35) mg/l, p = 0.002], and IL-10 [3.7 (1.8-6.9) vs. 2.3 (0.5-5.8) pg/ml, p = 0.03]. A significant inverse correlation was found between 25OHD and all these markers, even adjusted for age and sex. Hypovitaminosis D was prevalent in patients with severe ARDS, compared with the other groups (75% vs. 68% vs. 55%, p < 0.001), and 25OHD levels were lower in non-survivor patients.

DISCUSSION

Vitamin D is a fat-soluble vitamin that is produced from 7-dehydrocholesterol as a result of the action of UVB radiation. It is then converted to 25(OH)D in the liver, and then to the active form (calcitriol 1, 25(OH)D) in the kidneys or other organs. Vitamin D is essential for maintaining healthy bones and teeth. In vitro research has shown that vitamin D, in addition to playing a function in bone metabolism and helping the body better absorb calcium and phosphorus through the gastrointestinal tract, also plays an important part in the body's immune system.[14,15]

Vitamin D deficiency and insufficiency are conditions that affect people all over the world, including both adults and children. Its relationship to metabolic, autoimmune, and infectious comorbidities has been the subject of a significant amount of research.[16] This article shows that serum 25(OH)D levels are associated with the severity of COVID-19 infection. The protective effect of vitamin D supplementation against viral respiratory infections has been well established, and similar results are starting to emerge for COVID-19.[13,17,18]

The processes that underlie vitamin D's ability to lower the risk of microbial infections were investigated. It does this via inducing antimicrobial peptides, like cathelicidins, IL-37, and defensins, which are then secreted into the bloodstream to boost innate cellular immunity. In addition to this, it suppresses the cytokine storm by lowering the production of inflammatory cytokines including IFN and TNF. Ultimately, it regulates the adaptive immune response by inhibiting the Th1 response and encouraging the production of cytokines by Th2 cells.[18]

The relationship between hypovitaminosis D, airway inflammation, and an increased risk of respiratory infections began before the age of COVID-19, when a vast number of research assessed the usefulness of vitamin D supplementation as an additional treatment for patients with respiratory disorders. There were no differences between the vitamin D and placebo in terms of median time to first exacerbation, exacerbation rate, FEV1, hospitalization, quality of life, or death. A post hoc examination of individuals with severe vitamin D insufficiency (10 ng/mL) revealed a significant reduction in the exacerbation rate in the vitamin D group.[19,20]

Several studies have demonstrated that vitamin D stimulates immune cells to generate AMPs, which include cathelicidins and defensins. AMPs have a broad spectrum of activity, including antibacterial and antiviral properties, and are capable of inactivating the influenza virus. The antiviral actions of AMPs are a result of cathelicidin's degradation of envelope proteins, among other effects. Cathelicidins are a separate class of mammalian innate immune proteins. LL-37 is the predominant type of cathelicidin found in humans. LL-37 inhibits viral entrance into the cell in a manner comparable to that of other antimicrobial peptides.[21,22]

Low 25-hydroxyvitamin D levels are linked to poor COVID-19 prognoses. Patients with COVID-19 who were older and more vulnerable and who had taken vitamin D3 boluses prior to infection fared better in terms of their ability to survive the infection and had a milder sickness overall. Study showed a single dose of vitamin D3 containing 200,000 IU did not produce any clinically relevant effects on hospitalized patients with moderate to severe COVID-19, which raises questions about the efficacy of the treatment as a whole.[10] Other study showed vitamin D3 containing 500,000 IU can give recorey earlier.[12]

Grant et al. recommend that people who are at risk of contracting influenza or COVID-19 take 10,000 international units (IU) of vitamin D3 per day as a preventative measure against infection. It is possible to administer modest doses or levels of vitamin D to pregnant women who are participating in a quarantine system and who are having restricted exposure to sunshine; nonetheless, it is still vital for these women to take vitamin D supplements in addition to eating nutritious meals.[23]

CONCLUSION

According to the majority of studies, vitamin D levels that are lower than 12 are an accurate indicator of the COVID-19 severity. Vitamin D supplements are therefore regarded as being beneficial for COVID-19 sufferers as a result.

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