What is the Impact of Vitamin D Levels on COVID-19 Severity?: A Systematic Review

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Research Article

Keywords:

Posted Date: November 5th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-2219827/v1

Abstract

Keywords:

Vitamin D, Covid-19

BACKGROUND

COVID-19, a novel virus, was first discovered in 2019. It is a respiratory disease caused by SARS-CoV-2. It has been suspected that vitamin D levels play an important role in the immune response to respiratory illnesses causing the attenuation of infection. Considering this, vitamin D levels have also been found to have a similar effect on patients infected with COVID-19.

Declarations

Acknowledgements:

Acknowledgements: We thank Michael B. Roberts, PsyD Director of Institutional Research at PCOM for his helpful statistical advice and Kyla Geary, a Research Assistant III at the Philadelphia College of Osteopathic Medicine, for her editorial guidance.

Unsectioned Paragraphs

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METHODS

We measured mean, standard deviations, and 95% CI of many studies to determine if there is a consistent relationship between vitamin D levels and COVID-19. Independent sample t-test compared non-survivors vs. survivors of COVID-19 and vitamin D levels, and moderate vs. severe COVID-19 symptoms and vitamin D levels.

RESULTS

We evaluated the difference in vitamin D levels (serum 25(OH)D, nmol/L) among those who tested positive for COVID-19 to those who tested negative. The average median serum 25(OH)D, nmol/L for patients who tested positive was 27.08 nmol/L (± 0.58 SD, 95% CI: 1.88) and the average median of serum 25(OH)D, nmol/L for patients who tested negative was 48.67 nmol/L (± 13.66 SD, 95% CI: 2.17) this difference was near significant (p = .059). When looking at the relationship between vitamin D levels and severity of COVID-19 progression the result was not statistically significant, t(df) = 0.84, p = .216. When comparing the average values of vitamin D level among those who survived COVID-19 vs. those who did not the results were not statistically significant, $t(269) = 0.17$, $p = .438$.

CONCLUSIONS

There seems to be a correlation between vitamin D deficiency and likelihood of developing severe illness of COVID-19 when observing studies individually. However, when comparing studies on a larger scale it seems that the significant difference seems to fade.

Trial registration:

retrospectively registered

Abbreviations:

None

Declarations:

Availability of data and materials:

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Funding:

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Authors' contributions:

The authors confirm contribution to the paper as follows: study conception and design, data collection, analysis and interpretation of results, and draft manuscript preparation: L. Kersh. All authors reviewed the results and approved the final version of the manuscript.

1.0 Introduction

COVID-19 is a respiratory disease first observed in 2019 that is caused by the novel SARS-CoV-2 virus. As of December 2021, the World Health Organization (WHO) reports that the impact of COVID-19 continues worldwide as death tolls rise and many countries' essential health services are thoroughly disrupted (1). According to the WHO, globally there have been roughly 282 million COVID-19 cases, and about 5.4 million reported deaths (2) (with many unaccounted for); COVID-19 continues to be a major area of concern and a significant health crisis (1).

Once the virus becomes airborne via an infected individual sneezing or breathing, it can enter the body through either the mouth or nose. The viral spike protein initially attaches to the angiotensin-converting enzyme- 2 (ACE2) on nasal and bronchial epithelial cells. Once this interaction occurs, ACE2 is cleaved, and this allows for viral entry into the cells (3). The virus enters human nasal, bronchial, and pneumocyte epithelial cells and begins replicating. Once rapid replication occurs, there is a disruption of the epithelial-endothelial barrier, which can lead to dysregulation of the inflammatory response, and increased coagulation. Further progression of disease can lead to the disruption of the renin-angiotensin-aldosterone system leading to further tissue damage (3).

One of the many troubling side effects of contracting COVID-19 is that it can lead to an overdrive in the immune system, known as a cytokine storm. A cytokine storm occurs when the body ramps up its immune response, leading to hyperinflammation, which can cause damage to tissues and organs in the body if not properly treated (4).

A cytokine storm is initiated by the accumulation of many pro-inflammatory cytokines (such as TNF-alpha, INF-gamma, Interleukin (IL)-6, and IL-1beta) without enough anti-inflammatory cytokines (such as IL-10) to maintain a safe balance in the body. Vitamin D is found to decrease the production of pro-inflammatory cytokines, and increase the production of anti-inflammatory cytokines (5). In severe cases, when COVID-19 (SARS-CoV2) rapidly replicates in the lungs, it can lead to a strong immune response causing a cytokine storm and induced acute respiratory distress syndrome (ARDS). ARDS can cause death, which is why finding ways to prevent the induction of a cytokine storm in patients is crucial to lowering the chances of severe disease by COVID-19 (5).

There is interest in a possible relationship between vitamin D deficiency and development of COVID-19 because of prior studies linking vitamin D deficiency with other respiratory syndromes. In a meta-analysis looking at the effects of vitamin D supplementation and its effect on acute respiratory syndrome, Martineau et al. found that there was a significant reduction in the number of patients who experienced respiratory tract infections. More importantly, this meta-analysis also looked at the effects of Vitamin D supplementation on acute respiratory infections, and found that there was a statistically significant difference between treated and untreated; and those who were given the supplementation had a reduced incidence of acute respiratory tract infections (6). Their results showed that daily and weekly Vitamin D supplementation with multiple additional doses provided significant protection against acute respiratory tract infection. A single bolus of Vitamin D supplementation was not enough to provide a protective effect, however (6).

Calcitriol is the active form of vitamin D in the body. While its primary role is to take part in calcium regulation, it also can decrease pro-cytokines through the vitamin D receptor (VDR). Also, calcitriol signals through this pathway to increase cathelicidin, an antimicrobial peptide in the body, that has antiviral properties against enveloped respiratory viruses. Telcian et al. found in their study that treating cells with RV and cathelicidin decreased the production of virions released, further supporting the notion that cathelicidin has antimicrobial properties (7) Telcian et al. also found that calcitriol treatment of infected human primary bronchial epithelial cells (HPBECs) resulted in downregulated production of pro-inflammatory cytokines such as IL-6 and IL-8 (7).

Additionally, all immune cells express the VDR, which means that calcitriol can potentially influence these cells. Vitamin D, in the form of calcitriol, can increase the production of macrophage cells, and inhibit the maturation of APC cells, reducing the production of IL-12,TNF-alpha, and Th1 cells in the body (8). It is hypothesized that these mechanisms allow vitamin D to attenuate the effects of COVID-19, in particular by attenuating the cytokine storm that may be initiated by this disease (7).

In a study looking at vitamin D deficiency and COVID-19 patient outcome, Radujkovic et al. found that patients deficient in vitamin D had significantly higher IL-6 levels possibly leading to a cytokine storm and therefore severe disease presentation (9). This may point to an underlying relationship between low levels of vitamin D and increased severity in COVID-19 patients.

In this systematic review, we assessed studies that probed at vitamin D deficiencies in both positive and negative COVID-19 cases. We compared vitamin D levels to see if there was a noticeable difference between the two groups; sufficient Vitamin D being serum 25(OH) D levels > 30ng/ml, insufficient serum 25(OH) D levels ranging from 21–29 ng/ml, and deficient serum 25(OH) D levels as < 20ng/ml (10). Finally, through the review of several studies, we investigated whether more severe cases (measured via days in hospital and survival rates) of COVID-19 were correlated with low vitamin D levels.

2.0 Materials and Methods

We used Pubmed to find research articles examining the relationship between Vitamin D and COVID-19. We were able to narrow our search by looking for articles that focused on the difference between vitamin D levels in positive and negative COVID-19 patients. We also explored articles that measured the difference in severity progression of COVID-19 in relation to their vitamin D levels. From this collection of 19 articles in April of 2021, we were able to further eliminate articles based on what they observed in their study. We eliminated studies that did not look at any of the following: Comparing median Serum 25(OH)D (nmol/L, or ng/ml) level control vs. median Serum 25(OH)D (nmol/L, or ng/ml) level + COVID-19, Hospital stay (days) vs. mean Serum 25(OH)D (nmol/L, or ng/ml) levels, median or mean Serum 25(OH)D (nmol/L, or ng/ml) levels in comparison between those who survived vs. non-survivors, and Severity in COVID-19 symptoms and Serum 25(OH)D (nmol/L, or ng/ml) levels. We eliminated studies that were systematic reviews or meta-analyses. We included retrospective cohort studies, cross-sectional studies, prospective cohort studies, case control studies, observational cohort studies, and one clinical study. A second search for studies was conducted in June 2021. Articles were found via PubMed and Clinical Key. Each article was reviewed for the same objectives and with the same criteria as in April, 2021. Following the search, in both April and June, 133 articles were found that related to our objectives and criteria, and a total of 19 articles were used for data collection.

The mean and standard deviations of the vitamin D levels in patients who tested positive and negative for COVID-19 were analyzed. We used Practical Meta-Analysis Effect Size Calculator developed by David B. Wilson, Ph.D., George Mason University (https://www.campbellcollaboration.org/escalc/html/EffectSizeCalculator-OR2.php) when looking at COVID-19 status and vitamin D (N = 50–80 nmol/L) deficient levels. In this systematic review, we measured mean, standard error and P-value for three studies looking at vitamin D levels in positive vs. negative COVID-19 patients. We calculated the means, standard deviations, and 95% confidence interval (CI). We also used a t-test calculator for two independent means (https://www.socscistatistics.com/tests/studentttest/default.aspx) to determine if there is a difference in vitamin D levels between moderate vs. severe COVID-19 symptoms and a difference in vitamin D levels between survivors and non-survivors of COVID-19. Finally, we qualitatively observed seven studies that observed vitamin D levels and length of stay in the hospital (days).

3.0 Results

Three studies carried out by Baktash et al. (11), D'Avolio et al. (12), and Luo et al. (13) were analyzed to compare the difference in vitamin D (25(OH)D, nmol/L) levels among those who tested positive for COVID-19 (n = 432) to those who tested negative (n = 675). The mean and standard deviations of the vitamin D levels in patients who tested positive and negative for COVID-19 were analyzed. We used the previously discussed meta-analysis effect size calculator when examining COVID-19 status and vitamin D (Normal = 50–80 nmol/L) deficient levels (14). In this descriptive review, we measured mean, standard deviations, and 95% CI, and t-values of 19 studies to determine if there is a consistent relationship between vitamin D levels and COVID-19.

It was found that the average median serum 25(OH)D for patients who tested positive was 27.08 nmol/L (10.83 ng/mL) (± 0.58 SD, 95% CI: 1.88) and 48.67 nmol/L (19.47 ng/mL)(± 13.66 SD, 95% CI: 2.17) for patients who tested negative. The mean vitamin D levels, the standard error, and p-value were calculated via Excel; this difference was near significant (p = .059) as seen in Fig. 1.

When looking at the effects of vitamin D on inflammation levels, Radujkovic et al. found that IL-6 levels were significantly higher in vitamin D deficient patients, than in patients with normal levels of vitamin D (9). It was also found that patients with vitamin D levels above 75 nmol/L had significantly lower levels of C-Reactive Protein (CRP), an indicator of inflammation, compared to those with vitamin D levels below 75 nmol/L. However, other studies found no significant difference in the CRP levels associated with vitamin D levels. Lastly, in patients with vitamin D levels < 30 nmol/L survival probability of COVID-19 decreased significantly, compared to those whose vitamin D levels were > 30 nmol/L.

C-reactive protein (CRP) levels studied in patients with 0–10 ng/mL (0–25 nmol/L), 10–20 ng/mL (25–50 nmol/L), 20–30 ng/mL (50–75 nmol/mL), and > 30 ng/mL (> 75 nmol/L), Demir et al. (10) found that patients with vitamin D levels above 30 ng/ mL had significantly lower levels of CRP, an indicator of inflammation, than those with vitamin D levels below 30 ng/mL. However, CRP levels showed no significant difference associated with vitamin D levels < 12 ng/mL as compared to vitamin D levels > 12 ng/mL in a study by Bakhtash et al. (11). Lastly, in a study comparing severity of COVID-19 and vitamin D levels, their inpatient subgroup (presentation of severe disease) had median vitamin D levels < 12 ng/mL, as compared to the outpatient subgroup (presentation of less severe disease) whose vitamin D levels were > 12 ng/mL. This was found to be statistically significant (p value = 0.004) (9) .

The most consistent measurement among various studies, for severity of disease progression in patients who tested positive for COVID-19 with varying vitamin D levels, was days spent in the hospital. The Demir et al. Study (15) found that those with vitamin D levels greater than 30 ng/mL (75 nmol/L) spent significantly less time in the hospital than those with vitamin D levels less than 10 ng/mL (25 nmol/L) (***p < .001) as seen in Fig. 2. Other studies found a similar outcome. When looking at the number of days spent in the hospital in a study by X. Lou et al., they discovered that the median number of the days spent in the hospital were fewer in those whose serum vitamin D levels were higher. However, it is important to note that these differences were not statistically significant, with a P-value of 0.38 (13). Osman et al. found that there was no significant difference between the hospital days in those with vitamin D levels in those with serum vitamin D levels > 50 mg/ml vs those that were < 50 ng/ml (16). Similarly, Maghbooli et al., found that there was no notable difference between hospital stay days in patients whose vitamin D serum levels were > 30 mg/ml vs. <30 ng/ml (17). On the contrary, two studies by Vassiliou et al. and Orchard et al. demonstrated in their data that those with higher levels of vitamin D levels stayed in the hospital longer than those whose vitamin D levels were lower. Vassiliou et al. compared patients with vitamin D levels > or = to 15 ng/ml to those with vitamin D serum levels < 15 ng/ml (18). Orchard et al. on the other hand, compared patients' days in the hospital with vitamin D levels > 50 ng/ml vs. those with vitamin D levels < 50 ng/ml (19). Additionally, Szeto, B. et al found that patients with vitamin D levels > 20 ng/ml stayed in the hospital on average longer than those who had vitamin D levels < 20 ng/ml (20).

When comparing moderate vs. severe COVID-19 symptomatic patients (as seen in table 1), we were able to compare four studies, D. De Smet et al., S. Ahmed et al., k Ye et al., and X lou et al. We utilized a calculator to calculate the mean of the medians (https://www.calculator.net/standard-deviation-calculator.html) and the standard deviation with a 95% confidence interval level when looking at the relationship between vitamin D levels and severity of COVID-19 progression. With a total number of 537 patients, the mean of the median vitamin D levels of 364 patients, across all three studies, who were categorized to have moderate COVID-19 symptoms, was 45.025 nmol/L ± 10.531 as compared to 173 patients with severe COVID-19 symptoms having a mean of the median vitamin D levels of 38.075nmol/L ± 9.241 (13) (21) (22) (23). An independent samples t-test was computed to compare the average values of these two groups using a t-test calculator for two independent means (https://www.socscistatistics.com/tests/studentttest/default.aspx). The result was not statistically significant, t(df) = 0.84, p = .216, indicating no differences between the moderate and severe symptom groups concerning level of vitamin D.

We looked at three studies, X lou et al., De Smet et al., and Ahmed et al., that measured vitamin D levels in survivors vs. non-survivors of COVID-19. To compare these data, we utilized a calculator to calculate the mean of the medians (https://www.calculator.net/standard-deviation-calculator.html) and the standard deviation with a 95% confidence interval level to get an average vitamin D level among those who survived COVID-19 vs. those who did not. With a total of 271 patients, 35 who died, and 236 who survived, the mean vitamin D level of COVID-19 survivors was 15.43 ng/ml with a SD of ± 4.932, and the mean vitamin D levels of those who were non-survivors of COVID-19 was 14.60 ng/ml with a SD of ± 6.311 (21) (22) (13). When comparing the average values of these two groups, an independent samples t-test was computed to compare the average values of these two groups using a t-test calculator for two independent means. (https://www.socscistatistics.com/tests/studentttest/default.aspx). The results was not statistically significant, $t(269) = 0.17$, $p = .438$, indicating no differences between the survivor and non-survivor groups concerning vitamin D levels.

4.0 Discussion

While it seems, when observing individual studies, that there is a substantial relationship between COVID-19 positivity, symptom progression and vitamin D levels, it cannot be concluded from the studies included in this review that there is any statistical significance. When looking at the data and comparing studies to one another on a larger scale, these individual significant findings seem to wane. The primary reasons seem to lie in the lack of uniformity in parameters and statistical analysis of the vitamin D levels and deficiency, as well as COVID-19 positivity rates and severity (see Table 1).

Studies by Baktash et al., D'Avolio et al., and Luo et al. were analyzed to compare the difference in vitamin D (25(OH)D, nmol/L) levels among those who tested positive for COVID-19 (n = 432) to those who tested negative (n = 675) and there was a near significance, when comparing the means. However, if more studies were able to be compared, this finding might change.

When looking at the effects of CRP levels (measurement of inflammation) among three studies: Radujkovic et al., Demir et al., and Bakhtash et al. the data from these studies are conflicting. Baktash looked at CRP levels in the context of comparing vitamin D levels < 12 ng/mL as compared to vitamin D levels > 12 ng/mL, and found no significance (11). However, when reporting the median instead of the mean, the Demir study found that vitamin D levels < 12 ng/mL, as compared to the outpatient subgroup (presentation of less severe disease) whose vitamin D levels were > 12 ng/mL were significantly different (15). The difference in reporting mean vs. median made it difficult to compare and conclude that Vitamin D has a meaningful effect on CRP levels. When Radujkovic et al. reports that vitamin D levels above 75 nmol/L had significantly lower levels of C-Reactive Protein (CRP), it cannot be compared to those that measured effects of vitamin D levels at much lower levels. More studies of measuring CRP levels at vitamin D levels above 75nmol/L have to be considered before making a definite statement one way or the other, as other studies with various vitamin D levels and measurements produce differing results.

Severity of COVID-19 based on days spent in hospital is inconclusive. Two studies by Demir et al. and Lou et al. report that increased vitamin D levels are correlated with fewer days in the hospital. However, two studies by Osman et al. and Maghbooli et al. report that there is no difference in hospital stay between those with higher vs. lower vitamin D levels. Finally, three studies, Vassiliou et al., Orchard et al., and Szeto et al. report the opposite, that those with higher vitamin D levels, were associated with more days in hospital.

When comparing the vitamin D levels of non-survivors vs. survivors of COVID-19, on average they differed slightly; survivors on average had a higher vitamin D level than those who passed, however, it was not significant. Additionally, when comparing the average median vitamin D levels of moderate vs. severe

COVID-19 disease presentation, this data proved the difference to be insignificant. Therefore, we need more data and studies that use the same measurements and statistical methods to observe the relationship more clearly.

5.0 Conclusion

COVID-19 has had a horrendous effect on the world, mostly from the threat of death, initial lack of data, and possible long term effects of the disease. Finding ways to lessen the progression of the disease is paramount, and vitamin D is a readily available supplement that could make a great impact if proven that it could statistically prevent or lessen the severity of COVID-19.

In this systematic review, we assessed studies that probed at vitamin D deficiencies in both positive and negative COVID-19 cases, and investigated whether more severe cases of COVID-19 were correlated with low vitamin D levels. While we found in many studies that vitamin D deficiency demonstrated a significant difference in those that were positive vs. negative for COVID-19, as well as a significant difference in the days spent in the hospitals after contracting COVID-19, when comparing studies on a larger scale it seems that the significant difference seems to fade. In this review we found that the difference between vitamin D levels and positivity rates for COVID-19 were nearly significant in collective comparison. We compared days in the hospital and vitamin D levels, the data was inconsistent. While survivors vs. non-survivors had on average higher vitamin D levels, it is not determined that these were significant findings.

Due to the lack of consistent measurements and statistical analysis in the published literature, it was difficult to gather a large number of studies. For some studies, authors used the mean as a way to compare groups, while others used median to do so. Some studies focused on a younger population, while others focused on an older one, this led to many difficulties with comparison on a large scale. Lastly, studies varied in their vitamin D cut-off levels, making it harder to compare vitamin D efficacy levels.

From this review it is clear that vitamin D does play a role in the immune response in COVID-19 and that taking a vitamin D supplement may be warranted if one is deficient in vitamin D. Gathering more studies that have uniform parameters to observe the relationship between COVID-19 and vitamin D would be beneficial, because further research and more data would help to decipher if there is a consistent relationship, and beneficial effects of preventing severe COVID-19 disease progression.

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Table 1. Definition of COVID-19 Severity by Study

Figure 1. Comparison between COVID-19 positive (n = 432) vs. COVID-19 negative (n = 675) patients with respect to their serum vitamin D (25(OH)D) (nmol/L) levels. It was found that the average median serum 25(OH)D for patients who tested positive was 27.08 nmol/L (10.83 ng/mL) (± 0.58 SD, 95% CI: 1.88) and the average median of serum 25(OH)D, nmol/L for patients who tested negative was 48.67 nmol/L (19.47 ng/mL)(± 13.66 SD, 95% CI: 2.17). This difference was near significant (P-value = 0.059).

Figure 2. Demir et al. study looking at days spent in the hospital for patients who tested positive for COVID-19 with varying vitamin D levels. Those with vitamin D levels greater than 30 ng/mL (75 nmol/L) spent significantly less time in the hospital than those with vitamin D levels less than 10 ng/mL (25 nmol/L) (***p < .001).

Unsectioned Tables

Study	Definition
X. Lou et al.	Mild: symptoms with no signs of pneumonia on imaging; Moderate: fever, respiratory symptoms with radiological evidence of pneumonia; Severe: respiratory distress, respiratory rate ≥ 30 breaths/min, hypoxemia, oxygen saturation (SpO2) ≤ 93% (at rest), or lung infiltrates of > 50% within 24–48 h; Critical: respiratory failure requiring mechanical ventilation, shock, or multiple organ dysfunction requiring intensive care unit monitoring and treatment.
Jain A et al.	Severe: requiring admission to ICU
Karahan S et al.	Mild: mild clinical symptoms and normal lung on radiologic imaging. Moderate: fever and pulmonary symptoms along with pneumonia on radiologic imaging. Severe:respiratory distress (≥ 30 breaths/min); oxygen saturation ≤ 93% at rest; or PaO2/FiO2 ≤ 300 mmHg or chest imaging shows obvious lesion progression > 50% within 24–48 hours Critical: respiratory failure and need for mechanical ventilation, shock, or other organ failures that requires ICU care.
Pizzini et al.	Mild: patients in outward treatment; Moderate: patients in inward treatment; Severe: for patients requiring oxygen supplementation.