An Epidemiological Investigation to evaluate the link between hypovitaminosis D and COVID-19

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Abstract

Background: The COVID-19 pandemic has become a global threat, with an inexplicable course of action and suboptimal response to the multitudes of therapies being tried. Vitamin D's pleiotropic effects (immunomodulatory, anti-inflammatory, and antiviral) have lately received considerable attention in the scientific community, and it has been shown to be helpful in the defense against viral respiratory infections. **Aim:** To find out the association between vitamin D and COVID-19. **Methods:** Overall, 360 (156 COVID-19 +ve and 204 COVID-19 −ve) subjects were investigated in this hospital-based case-control study. The study participants were taken from the COVID-19 wards and Flu clinic of a dedicated COVID hospital between August 1 and September 15, 2020. The demographics and clinical data including alcohol and smoking history along with serum vitamin D levels were recorded. Binary logistic regression analysis was performed to assess the association between age, gender, alcohol intake, smoking history, vitamin D status, and COVID-19. **Results:** There was no significant difference in the mean vitamin D levels between cases and controls. Bivariate analysis of predictors and COVID-19 revealed that predictors such as advanced age, BMI, alcohol intake, smoking habit, diabetes, hypertension, and vitamin D deficiency were significantly associated with COVID-19. **Conclusions:** This study showed that serum vitamin D status might be able to reduce the impact of COVID-19, although more studies are required to establish clear causality.

Keywords: Case-control study, COVID-19, prevention, treatment, vitamin D

Introduction

The rapid spread and brutal attack of SARS-CoV-2 has become a global threat worldwide. With the complete and utter lack of suitable targeted therapies, the immediate repurposing of existing drugs has remained the only avenue worth exploring. A host of reused drugs, such as favipiravir, tocilizumab, ivermectin, and remdesivir, have been tested in COVID-19; however, despite extensive and comprehensive efforts, effective treatment to this deadly disease remains elusive. The role of diet supplementation, probiotics, and nutraceuticals to boost immunity has therefore become an area of increasing focus. In this context, vitamin D, the sunlight hormone with a clear-cut mechanism of action and a demonstrated benefit against viral infections, has merged as the new kid on the block. We have traditionally known that vitamin D has a role to play in bone health and calcium–phosphate metabolism. However, recent research has focused on its pleiotropic (immunomodulatory, anti-inflammatory, and antiviral) effects, which may have a role in infectious diseases, autoimmune diseases, pulmonary fibrosis, cancer, diabetes, osteoarthritis, osteoporosis, Alzheimer's, dementia, myopia, macular degeneration, multiple sclerosis, depression, etc., There is no debate that vitamin D is required for optimal well-being

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and homeostasis, and deficiency lays one vulnerable to several problems related to the endocrine, cardiovascular, and nervous systems besides impacting immune systems within the body. Therefore, routine measurement of vitamin D should be recommended as a part of primary care to ensure optimal levels, although there is a lack of consensus regarding vitamin D testing.[1]

Vitamin D's distinct properties might be beneficial even in the case of SARS-CoV-2 infection. Currently, several mechanistic and anecdotal pieces of evidence corroborate the protection offered by an optimal vitamin D status against several inflammatory and infectious disorders and COVID-19 as well.

These protective mechanisms range from maintaining the integrity of the physical barrier through tight junctions, gap junctions, and adherens, to modulation of innate and adaptive immunity, benefitting in respiratory tract infections (RTIs). The expression of two anti-microbial peptides, cathelicidin (showing apoptosis and autophagy of infected cells in HIV-1, influenza, HCV, and rhinovirus) and β-defensin, is also enhanced by vitamin D. The recognition of viral dsRNA by toll-like receptors, possessing antimicrobial properties against pathogens, is modulated by human cathelicidin peptide LL37.[2] All these mechanisms may contribute toward the role of vitamin D in RTIs, COVID-19, and several other viral infections, as has also been witnessed in several studies.[2,3]

It is now certain that SARS-CoV-2 utilizes immune evasion mechanisms initially, followed by an overreaction and cytokine storm in some patients, resulting in massive production of interleukins, specifically IL-1, IL-2, and IL-6, resulting in acute respiratory distress syndrome (ARDS) and systemic inflammatory response syndrome (SIRS).[4,5] Therefore, tocilizumab (an IL antagonist), a repurposed but highly expensive drug, was used extensively in COVID-19. Vitamin D deficiency has also been shown to be associated with increased levels of IL-6 in patients with HIV.[6] It seems logical to suggest that there may be a role of vitamin D in SARS-CoV-2 infection, which also manifests with excessive IL-6 production.[7] Multiple studies have shown that low solar UVB levels, which are directly linked to vitamin D concentrations, might be one of the reasons why seasonal influenza infections rise over the winter months, another fact firmly linking hypovitaminosis D with RTIs and probably COVID-19.[8]

COVID-19 arrived in the northern hemisphere at the end of 2019 in winter, when levels of vitamin D are at rock bottom. The northern hemisphere suffered maximally in terms of cases and mortality. Ecological studies have reported that high latitudes (N+30°N) and winter season, risk factors for low Vitamin D, are associated with higher mortality rates in COVID-19 infections, a pattern that has also been very clearly established through ecological studies using case-fatality rate (CFR) data of previous non-COVID-19 epidemics.[9]

Immunodeficiency, respiratory illness, and old age with mild-to-severe vitamin D deficiency are all factors associated with a high risk of getting severe COVID-19 disease. Italy, having the worst CFR of COVID-19, has a higher proportion of older people, with almost 76% of women showing a deficiency of vitamin D.[9,10]

The two atypical symptoms, anosmia and ageusia, are present in patients with vitamin D deficiency and COVID-19. This may serve to strengthen the causal relationship between vitamin D and COVID-19, implying that COVID-19 infections may be associated with or lead to vitamin D deficiency.[11,12]

A study correlating the hormone-modulated expression of a SARS-CoV-2 receptor, angiotensin-converting enzyme (ACE2), and hypovitaminosis D was recently reported. Although vitamin D increases the expression of ACE2, which may assist the virus bind better, it also helps by dramatically preventing the pulmonary vasoconstrictor response observed in COVID-19 cases. It makes sense then to keep ACE2 levels elevated by any means, one of them being vitamin D.[13,14]

Vitamin D deficiency is associated with an increase in thrombotic episodes, which are also very common in COVID-19 patients. More than half of those with severe COVID-19 have been found to have elevated levels of D-dimer, a strong link between vitamin D deficiency and major complications (such as thrombosis) of COVID-19.[15]

Vitamin D deficiency is associated with obesity, increasing age, lack of proper sun (UV-B) exposure, dark skin, smoking, living with air pollution, and the presence of comorbid diseases such as infection, cancer, cardiovascular disease, chronic respiratory disease, osteoporosis, sarcopenia, and diabetes mellitus.[9] All of these risk factors have to an extent been associated with a greater incidence of COVID-19 infection.

All these factors strengthen the hypothesis that vitamin D may offer protection against COVID-19. Surprisingly, there are hardly any reports on the vitamin D status of SARS-CoV-2 positive patients, although a large number of well-established studies in the past have shown multiple characteristics by which it might be able to help in RTIs and possibly in the recent outbreak. In a scenario where uncertainty in treatment and prevention abounds, studies like this that offer evaluation of risk factors are vitally important. Therefore, this study was conducted to establish an association between vitamin D deficiency and COVID-19.

Materials and Methods

Aim
The study aimed to find the association between vitamin D level and COVID-19.

Study setting
The current study was carried out in tertiary care dedicated COVID hospital. RT-PCR-positive cases were taken from the

wards and Flu clinic of the hospital. RT-PCR-negative controls were taken from the Flu clinic. The duration of the study was 1.5 months (Aug 1, 2020 to Sep 15, 2020). Therefore, all SARS-CoV-2-positive cases and RT-PCR-negative controls were enrolled consecutively during the study period.

Study participants

RT-PCR-positive patients for COVID-19 were included as cases and negative patients were included as controls. Those patients taking vitamin D supplements or having taken them in the last 6 months were excluded from the study. Of the 170 RT-PCR positive cases and 250 RT-PCR negative controls screened, 16 participants among cases and 41 participants among controls, respectively, were excluded because they were taking vitamin D supplements. Figure 1 shows the selection of cases and controls for the study.

Data collection

Data were collected on a pre-validated case recording form. During the study duration, demographic data (age, sex, alcohol and smoking history, and comorbidities) of COVID-19 cases admitted in the wards and fulfilling the inclusion criteria were collected. Following the receipt of written informed consent, a sample for vitamin D estimation was sent along with other routine investigations immediately after admission. Vitamin D level was estimated using a chemiluminescence-based immunoassay analyzer.

From the Flu clinic during the study period, all patients who came to the Flu clinic for RT-PCR were informed about the study, and samples from those who were not taking vitamin D supplements and consented to participate in the study were submitted for vitamin D estimation. They were categorized into cases or controls based on the RT-PCR report collected the next day. Demographic data were collected on the case recording form on the day of enrolment.

Cases and controls were again divided into two groups based on their vitamin D level:

A) Non-deficient group - Vitamin D levels >10 ng/mL[16]
B) Deficient group - Vitamin D levels <10 ng/mL

Data processing and analysis

Categorical variables were presented as frequency (%) and continuous variables as means + SD. A Kruskal–Wallis H test with an exact *P* value for association was applied to compare continuous and categorical data, for example, age, sex, alcohol and smoking, and vitamin D deficiency between cases and controls. Bivariate, as well as binary logistic regression models, were applied to ascertain the relationship between age, BMI, smoking, alcohol intake, and COVID-19. Odds ratio (OR) and 95% CI were also reported to show the intensity and direction of the relationship. A *P* value of less than 0.05 was taken as statistically significant. IBM SPSS statistical software version 27.0 (IBM Corp. in Armonk, NY, USA) was used for the analysis of data.[17]

Results

Characteristics of the participants

A total number of 360 participants (156 COVID-19 cases and 204 non-COVID-19 controls) were included in the study. Their mean (SD) age was 35.63 (13.62) years, and almost 73% of them were male. Approximately 60% of the participants were within the normal range of BMI, 8.3% were underweight, 23% were overweight, and 8.6% were obese. Diabetes mellitus and hypertension were the most prevalent comorbidities among the participants (prevalence: 4.7% and 4.4%, respectively) [Table 1].

Vitamin D deficiency and risk of COVID-19

The mean (SD) of serum vitamin D level among the participants was 19.83 (9.94) ng/mL. However, the difference of neither the mean nor median of vitamin D concentrations between the cases and controls was statistically significant [Table 1 and Figure 2].

Binary logistic regression shows that the association between COVID-19 and vitamin D deficiency was statistically
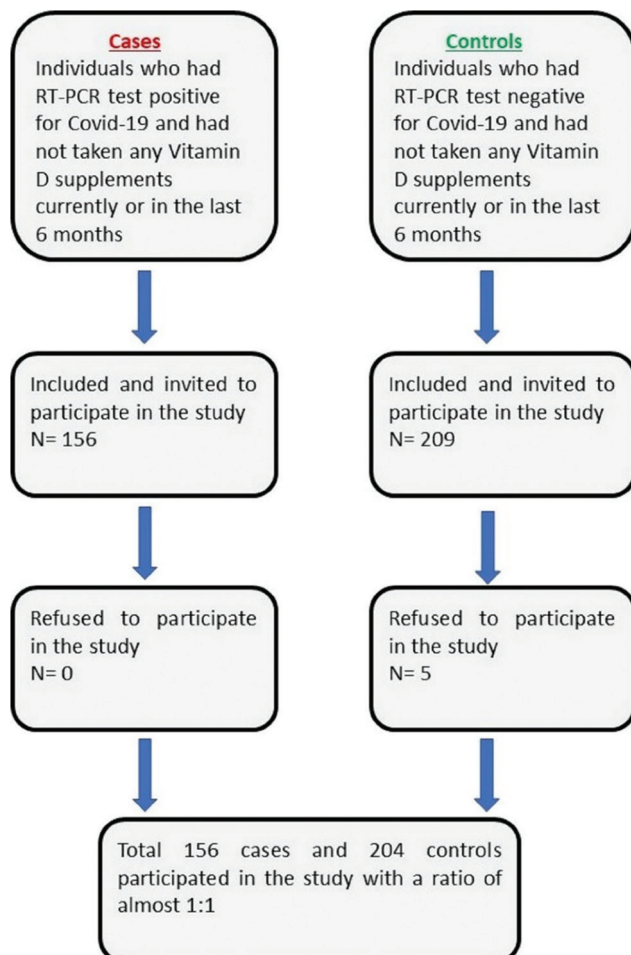

Figure 1: Flowchart for the selection of cases and controls

Table 1: Characteristics of the case and controls				
Characteristics	Total (*n*=360)	Cases (*n*=156)	Controls (*n*=204)	*P*
Age (Category) (years)				
≤40	268 (74.4)	89 (57.1)	179 (87.7)	
41-60	69 (19.2)	45 (28.8)	24 (11.8)	
>60	23 (6.4)	22 (14.1)	1 (0.5)	
Sex				
Male	263 (73.1)	118 (75.6)	145 (71.1)	0.33
Female	97 (26.9)	38 (24.4)	59 (28.9)	
BMI, Mean (SD) (kg/m²)	23.55 (4.53)	24.44 (4.79)	22.87 (4.20)	
BMI (Category) (kg/m²)				
Underweight (<18.5)	30 (8.3)	12 (7.7)	18 (8.8)	<0.05
Normal (18.5-24.9)	216 (60.0)	78 (50.0)	138 (67.6)	
Overweight (25.0-29.9)	83 (23.1)	47 (30.1)	36 (17.6)	
Obese (≥30)	31 (8.6)	19 (12.2)	12 (5.9)	
Alcohol intake				
Yes	53 (14.7)	37 (23.7)	16 (7.8)	<0.05
No	307 (85.3)	119 (76.3)	188 (92.2)	
Smoking				
Yes	53 (14.7)	39 (25.0)	14 (6.9)	<0.05
No	307 (85.3)	117 (75.0)	190 (93.1)	
Comorbidities				
Diabetes mellitus	17 (4.7)	17 (10.9)	0 (0.0)	<0.05
Hypertension	16 (4.4)	16 (10.3)	0 (0.0)	<0.05
Chronic kidney disease	4 (1.1)	4 (2.6)	0 (0.0)	<0.05
Hypothyroidism	6 (1.7)	6 (3.8)	0 (0.0)	<0.05
Coronary artery diseases	4 (1.1)	4 (2.6)	0 (0.0)	<0.05
COPD or Asthma	1 (0.3)	1 (0.6)	0 (0.0)	0.43
Serum Vit-D, Mean (SD) (ng/ml)	19.83 (9.94)	20.04 (11.68)	19.66 (8.40)	0.71
Vitamin D deficiency (<10 ng/ml)				
Yes	37 (10.3)	25 (16.0)	12 (5.9)	<0.05
No	323 (89.7)	131 (84.0)	192 (94.1)	

significant (COR: 3.05, 95% CI: 1.48–6.29, Nagelkerke R²: 0.03), and it remained significant after adjustment of the model for age, BMI, and lifestyle-related factors such as alcohol taking and smoking in multiple logistic regression [Table 2].

Discussion

To the best of our knowledge, this is the first case-control study of its kind assessing the possible association between COVID-19 and serum vitamin D levels in India. The results of the current study showed that vitamin D deficiency (<10) was associated with greater odds of having COVID-19, significantly on both unadjusted and adjusted models of logistic regression. Advanced age, smoking, and alcohol intake were all associated with a higher risk of COVID-19 in the current investigation, which is consistent with numerous recent studies.[18–20] The data presented here clearly demonstrate the hypothesis that vitamin D status may be an important consideration when planning COVID-19 management strategies. In light of several recent studies that have reported the role of vitamin D in cancers, reproductive health, neurodegenerative disease, inflammatory bowel disease, etc., it would serve well for primary care physicians to consider the vitamin D global deficiency a real problem and practice aggressive testing and supplementation in individuals
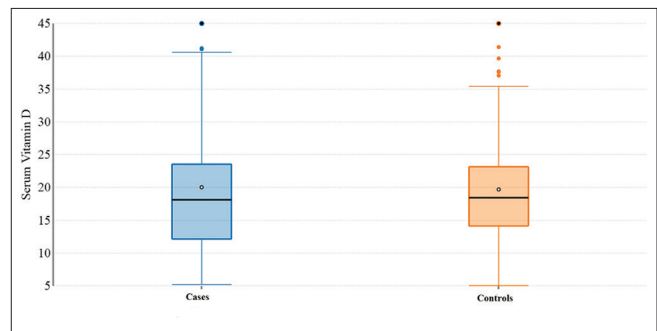

Figure 2: Box plot for the serum vitamin D level of the cases and controls

who seem to be at risk of hypovitaminosis D and thereafter ensure adequate supplementation in the correct dose and for the appropriate duration.[19–21]

In the context of RTIs, the relationship between vitamin D and respiratory infections has been one of the most promising areas of research. The role of vitamin D in RTIs and COVID-19 was investigated in various studies and significant associations were found.[18] Several RCTs and meta-analyses have been done over the last 10–20 years to establish this relationship.[21-25] Although

Table 2: Bivariate and multiple logistic regression between vitamin D deficiency and risk of COVID-19				
Characteristics	COR	AOR[a]	AOR[b]	AOR[c]
Vitamin D deficiency (<10 ng/mL) (Yes vs. No)	3.05 (1.48-6.29)*	2.85 (1.31-6.17)*	2.61 (1.18-5.72)*	2.51 (1.10-5.71)*
Nagelkerke R^2	0.03	0.21	0.23	0.27

*$P<0.05$; [a]Adjusted for age; [b]Adjusted for age and BMI; [c]Adjusted for age, BMI, alcohol taking and smoking. AOR: Adjusted OR

much of this information has not been translated into clinical practice guidelines, there is an emerging body of evidence to support cautious implementation in RTIs and even in COVID-19. A recent review stated the following: "Although contradictory data exist, available evidence indicates that supplementation with multiple micronutrients with immune-supporting roles may modulate immune function and reduce the risk of infection. Micronutrients with the strongest evidence for immune support are Vitamin C and D and zinc."[3,26,27]

A recent study that retrospectively studied the vitamin D plasma concentrations in a cohort of patients from Switzerland found significantly lower vitamin D levels ($P = 0.004$) in COVID-19 (median value: 11.1 ng/mL) patients compared with negative patients (24.6 ng/mL), which was also confirmed by stratifying patients according to age >70 years. It also suggested that vitamin D deficiency is more strongly associated with COVID-19 than with other respiratory diseases.[28] Another study with a single sample of 20 patients hospitalized with COVID-19 and with available vitamin D levels suggests that vitamin D insufficiency in COVID-19 patients is quite prevalent.[29]

In the manuscript titled "Possible preventive and therapeutic role of Vitamin D in the management of the COVID-19 pandemic," the authors advise correction of hypovitaminosis D through supplementation toward the prevention and treatment of COVID-19, in association with other essential preventive measures.[30] A recent retrospective cohort study from Chicago with 4314 patients tested for COVID-19, all of whom had vitamin D levels done in the previous year, demonstrated that vitamin D deficiency, if not sufficiently treated, may increase the COVID-19 risk. Therefore, the authors strongly recommended that vitamin D deficiency must be closely followed up and treated.[31]

Another study from Italy found that vitamin D supplements had been taken by 12.4% of cases versus 22.9% of those unaffected (age adjustment OR: 0.56 for vitamin D supplements), reducing the odds of COVID-19.[32] Several recent studies evaluating the role of vitamin D on the frequency and severity of COVID-19 as well the dreaded inflammatory markers serve to further consolidate and authenticate our findings. Higher vitamin D levels were associated with a lower risk of SARS-CoV-2 infection in a recent study checking the associations between predicted vitamin D status, vitamin D intake, and risk of SARS-CoV-2 infection and coronavirus disease 2019 severity.[33] Much of the data in this study, as well as data from other research and epidemiological investigations, seem circumstantial and associative. This is because vitamin D represents a very dynamic molecule that affects and is affected

by multiple pathways. This makes obtaining conclusive results a slightly difficult task. However, these associations remain very suggestive, and to our advantage, we do have a wealth of evidence in the form of a rigorous scientific mechanism that may work well to establish a further correlation between vitamin D and COVID-19. In several countries, routine 25-hydroxyvitamin D (25O HD) testing is regarded as unnecessary.[34] A point to be debated considering that vitamin D analysis is burdened by methods that lack standardization and deficiencies may remain undetected, with detrimental effects on the health and well-being of individuals.[1]

Limitations

To our knowledge, no case-control study has yet been carried out to explore the relationship between severe vitamin D deficiency and COVID-19 in India. There is an ongoing debate as to whether vitamin D deficiency causes inflammation or is a consequence of inflammation and critical illnesses such as COVID-19. In that context, the findings of any research, like the present one, which takes vitamin D along with disease, must be interpreted with care.

Conclusion

In the present study, logistic regression analysis revealed that the odds of having COVID-19 were significantly higher in vitamin-D-deficient (<10 ng/mL) subjects in comparison with non-deficient subjects (>10 ng/mL) in both unadjusted and adjusted models. These findings can then help to conclude aggressive measurement of serum vitamin D and establishment of a near-normal vitamin D status through supplementation.

Key message: In primary care, the level of vitamin D should be measured among COVID-19 patients. If found deficient, supplements should be given as there are no side effects.

Ethics approval and consent to participate

This study was performed in line with the principles of the Declaration of Helsinki and approved by the IRC and IEC, AIIMS Patna, vide Approval N0.-AIIMS/Pat/IEC/IRC/2020/501. The participants were enrolled in the study after obtaining written informed consent.

Consent to participate

Informed consent was obtained from all the study participants.

Consent for publication

The approval for publication was given by the review committee of the Institute.

Availability of data and materials

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

Code availability: IBM SPSS version 27.0

Authors Contributions: All authors contributed to design, data analysis, manuscript preparation, and read the final, submitted version.

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List of Abbreviations

Severe acute respiratory syndrome 2 - SARS-CoV-2
Respiratory Tract Infections - RTI
Acute Respiratory Distress Syndrome - ARDS
Systemic inflammatory response syndrome - SIRS
Case fatality rates - CFR
Angiotensin Converting Enzyme 2 - ACE2
Memory regulatory T cells - mtregs

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Conflicts of interest

There are no conflicts of interest.

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