Vitamin D and COVID-19 – Let's Explore the Relationship!

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ABSTRACT

Introduction: Vitamin D plays a protective role against COVID-19. Patients with deficiency of vitamin D are more prone to severe SARS-CoV-2 infections. It is known to enhance human β -defensin 2 and antimicrobial peptide. Vitamin D can easily stabilise and manage immunological reactions against SARS-CoV-2. It can also suppress the cytokine storm by boosting the innate system.

Material and methods: RT-PCR confirmed COVID-19 positive subjects were divided into two groups, one comprising asymptomatic subjects (Group 1) and the other one ICU admitted patients (Group 2). In both groups, various comorbidities such as obesity, diabetes mellitus, hypertension, cardiovascular disease, respiratory disease, renal disease and malignancy were taken into consideration. Vitamin D estimation was performed along with serum levels of interleukin-6 (IL-6) and ferritin using automated immunoassays on Siemens Advia Centaur XP.

Results: On acknowledging the cut-off serum concentration level of vitamin D as < 30 ng/mL for establishing vitamin D deficiency the prevalence of vitamin D deficiency was 66.18% in Group 1 and 98.30% in Group 2. Diabetes mellitus, followed by hypertension was associated comorbidity in both groups. In total, 33 patients were found to be severely deficient (<10 ng/mL) in vitamin D, out of which 27 were critically ill and six asymptomatic. In both groups, diabetes mellitus, followed by hypertension were the highest comorbid associations. Fatality rate (discharge vs fatality) was 0% in Group 1 and 16.94% (10 patients died) in Group 2.

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Conclusion: To conclude, the present study addressed the significant relationship between vitamin D levels and clinical outcomes of COVID-19 patients. Vitamin D deficiency distinctly upswings the chance of disease severity as well as mortality after SARS-CoV-2 infection.

Keywords: COVID-19, vitamin D, deficiency.

INTRODUCTION

Almost a year since reporting of the first case of COVID-19 (coronavirus disease 2019) caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2) in Kerala, India, stands strong and hopeful with its vaccination programs. The main challenge for bringing the pandemic to an end lies in effective treatment and vaccinations but also providing effectual additional supplements. Several studies regarding the correlation of vitamin D [1,25-dihydroxyvitamin D, or 1,25 (OH)₂D] with the clinical severity of COVID-19 have been conducted (1).

Vitamin D is a lipid-soluble vitamin and is required for growth of bones and good health. The daily recommended doses can be fulfilled either by taking it in diet or the form of supplements. It also plays a major role in monitoring the immune system. Vitamin D plays a shielding role against enveloped viruses. Behind this antiviral action there are several postulations suggesting the possibility that vitamin D may increase human β -defensin 2 and antimicrobial peptide37 (2, 3). Vitamin D can easily stabilise and manage immunological reactions against SARS-CoV-2.

Several observational studies have shown that patients with vitamin D deficiency are more prone to severe SARS-CoV-2 infections (1, 4-8). It has been suggested that vitamin D had a safeguarding effect against COVID-19. Vitamin D regulates the immune system by interacting with its receptor on the immune cells. This in turn helps to stimulate the acquired and innate immunity whenever there is any exposure to antimicrobials. Some theories also suggest that vitamin D also accentuates the renin-angiotensin pathway and decreases angiotensin-converting enzyme-2 (ACE-2). Vitamin D has an immunomodulatory action. It also boosts the innate system and thus can suppress the cytokine storm (9).

Hence, the present study was carried out to explore the relationship between vitamin D and COVID-19. $\square$

MATERIAL AND METHODS

Study design and setting

The present research was designed as a prospective observational study that was conducted for five months (August 2020 to December 2020) in the Department of Biochemistry in collaboration with the Department of Microbiology, Subharti Medical College and associated Chhatrapati Shivaji Subharti Hospital, Meerut, India, a tertiary COVID-19 care center (Level 3).

Study group

All RT-PCR confirmed COVID-19 subjects admitted to the dedicated COVID-19 management center throughout the study were followed till the closure of case (i.e., either discharge or death).

We included in our study COVID-19 patients aged 20 to 60 years who were admitted in our hospital. Participants were distributed into two groups: Group 1, including RT-PCR confirmed COVID-19 patients who were asymptomatic at the time of admission and remained asymptomatic till discharge on the 14th day, and Group 2, including RT-PCR confirmed COVID-19 patients requiring ICU admission.

Patients with pregnancy, history of chronic obstructive pulmonary disease, chronic kidney disease and immunocompromised patients such as those with HIV infection or undergoing chemotherapy were excluded from the study.

The institute adopts the following criteria for ICU admission of COVID-19 patients: a) clinical signs of pneumonia (fever, cough, breathlessness) plus one of the following: respiratory rate >30 breaths/min, severe respiratory distress, or SpO₂ <90% on room air; and b) signs of multi-organ involvement, including altered sensorium, decreased urine output, heart rate >120/min, with cold extremities or low blood pressure (BP) (systolic BP <90 mm Hg and/or diastolic BP <60 mm Hg).

Sample collection and transport

Venous blood samples were collected in a plain vial under all aseptic conditions by trained nur-

sing staff and then transported to the Central Laboratory immediately for processing.

Evaluation

Vitamin D estimation was performed along with serum levels of interleukin-6 (IL-6) and ferritin using automated immunoassays on Siemens Advia Centaur XP. On the basis of recommended guidelines serum 25(OH) vitamin D level of <20 ng/mL has been defined as vitamin D deficiency (10). All investigations were carried out as per the relevant guidelines and regulations.

Ethics

Approval from the Institutional Ethics Committee was obtained before conducting the study. Informed consent was taken from all subjects to confirm their willingness to participate voluntarily.

Statistical analysis

SPSS software version 19.0 (IBM, SPSS statistics) was used for statistical analysis. Chi-square test was performed for data analysis. The p values below 0.005 were considered to be significant. $\square$

RESULTS

During the defined period, a total of 792 COVID-19 positive patients were admitted

to our COVID level-3 hospital. After applying inclusion criteria, 402 patients were enrolled in the current study, out of which 343 were asymptomatic (Group 1) and 59 had highly severe symptoms which required ICU admission (Group 2). The mean age of ICU patients was higher (49.51 ± 8.35) than that of asymptomatic individuals (45.12 ± 16.29). The predominance of male gender was noted among ICU patients (male to female ratio 38:21) (Table 1). Various comorbid conditions were taken in both the groups (Table 2).

In the present study, vitamin D levels were found to be deficient in 11.96% of patients, insufficient in 54.22% of subjects and sufficient in 33.82% of patients in Group 1 (Table 1 and Figure 1) versus 62.71%, 35.59% and 1.70%, respectively for patients in Group 2 (Table 3, Figure 2). The mean concentration of total 25(OH) vitamin D was lower 11.49 ± 6.28 in the critical care group (Group 2) as compared to 33.66 ± 10.40 in the asymptomatic group (Group 1). Statistically, the difference was found to be highly significant (Table 1).

On acknowledging vitamin D deficiency as <30 ng/mL the prevalence was 66.18% in Group 1 and 98.30% in Group 2 (Table 2). A total of 33 patients were found to be severely defi-

Parameter	Group 1 (n = 343)	Group 2 (n = 59)	p value
Male to female ratio	202:141	38:21	-
Age (years)	45.12 ± 16.29	49.51 ± 8.35	0.04
25(OH) vitamin D (ng/mL)	33.66 ± 10.40	11.49 ± 6.28	< 0.0001*
Serum ferritin (ng/mL)	299 ± 18	674 ± 27	< 0.0001*
Serum IL-6 (pg/mL)	11.9 ± 8.1	37.5 ± 7.7	< 0.0001*

*P value – statistically significant

TABLE 1. Distribution of demographic parameters and levels of vitamin D, serum ferritin and IL-6 in Groups 1 and 2.

Comorbidities	Group 1 (n = 343)	Group 2 (n = 59)
Obesity	12.83%	30.51%
Diabetes	27.11%	49.15%
Hypertension	23.03%	44.07%
Cardiovascular disease	17.78%	25.42%
Respiratory disease	10.50%	18.64%
Renal disease	2.62%	5.08%
Malignancy	0.58%	1.69%

TABLE 2. Comorbidities of subjects in Group 1 (asymptomatic COVID-19 patients) and Group 2 (critically ill COVID-19 patients)

	Vitamin D levels		
	< 20 ng/mL (deficiency) n = 78	20–29 ng/mL (insufficiency) n = 207	> 30 ng/mL (sufficiency) n = 117
Group 1 (n = 343)	41	186	116
Group 2 (n = 59)	37	21	1
Serum ferritin (ng/mL)	593 ± 39	379 ± 22	148 ± 16
Serum IL-6 (pg/mL)	45.8 ± 9.1	27.1 ± 5.7	7.5 ± 6.8

TABLE 3. Relationship between inflammatory markers and vitamin D levels as a continuous variable

FIGURE 1. Prevalence of vitamin D deficiency in Group 1 (n=343)

FIGURE 2. Prevalence of vitamin D deficiency in Group 2 (n=59)

	Vitamin D levels		p value
	< 20 ng/mL (n = 78)	> 20 ng/mL (n = 207)	
Group 1 (n = 343)	41	302	-
Group 2 (n = 59)	37	22	-
Serum ferritin (ng/mL)	593 ± 39	283 ± 18	< 0.0001 *
Serum IL-6 (pg/mL)	45.8 ± 9.1	19.6 ± 7.4	< 0.0001 *

TABLE 4. Relationship between inflammatory markers and vitamin D concentrations (cut-off 20 ng/mL)

*P value – statistically significant

cient (<10 ng/mL) in vitamin D, out of which 27 were critically ill and six asymptomatic (Table 3).

Inflammatory markers, including mean serum levels of IL-6 and ferritin, were 45.8 ± 9.1 and 593 ± 39 , respectively in patients with vitamin D levels < 20 ng/mL, and 19.6 ± 7.4 and 283 ± 18 , respectively in those with vitamin D levels >20 ng/mL, and the difference was found to be statistically significant (Table 4).

Fatality rate (discharge vs fatality) was 0% in Group 1 and 16.94% (10 patients died) in Group 2. Among the 10 patients who died, vitamin D levels were lower than 20 ng/mL in nine subjects and <10 ng/mL in seven of those nine patients. Hence, the authors observed that vita-

min D deficiency correlated with clinical severity in COVID-19 patients. ■

DISCUSSION

The authors present the first study in this geographical area aiming to assess the association between vitamin D deficiency and clinical severity of COVID-19.

It has been studied that vitamin D boosted the innate immunity, and thus it was presumed to decrease the transmission of COVID-19 (11). There are sufficient studies showing that various comorbidities are associated with low plasma levels of vitamin D, which in turn increases the risk of severe SARS-CoV-2 infection (12, 13).

In the current study, authors have found that on acknowledging serum concentration levels of 25(OH) vitamin D <30 ng/mL, the prevalence of severe COVID-19 requiring ICU admission was very high (98.30%), which subsequently increased the fatality rate. However, when dividing the two study groups into vitamin D deficiency (<20 ng/mL), insufficiency (20-29 ng/mL) and sufficiency (>30 ng/mL), we found the following prevalence: 11.96% for vitamin D deficiency, 54.22% for insufficiency and 33.82% for sufficiency in Group 1 (Table 1) versus 62.71%, 35.59% and 1.70%, respectively in Group 2 (Table 3).

Fatality rate was 0% among asymptomatic individuals included in Group 1 but reached 16.94% (10 patients died) among critically ill patients of Group 2. In nine of the 10 patients who died, vitamin D level was lower than 20 ng/mL and in seven of them it was <10 ng/mL. On comparing the fatality rate, it was found to be 21% (19 out of 90 patients died) among patients with vitamin D deficiency and 3.1% (two out of 64 patients died) among those with normal vitamin D level, which explains a sturdy relationship between fatality and vitamin D deficiency. Similar findings were reported by Anshul Jain *et al* (14), who firmly propounded that vitamin D deficiency increased clinical severity in COVID-19 cases and accentuated the risk of mortality.

Alipio *et al* stated that there was an inverse relationship between vitamin D levels and severity of COVID-19. They suggested that an increase in serum 25(OH)D level in the body could improve the clinical outcomes of COVID-19 patients, while its decrease could worsen them (15).

A study performed by Maghbooli Z *et al* has revealed that 25(OH)D levels of at least 30 ng/mL were associated with a significant decrease in the severity of COVID-19 (9).

Inflammatory markers such as serum ferritin and IL-6 were significantly elevated in critically ill patients. Higher levels of vitamin D correlate with lower levels of IL-6, which are a major target for controlling cytokine storm in COVID-19 (1).

Thus, there is a wide range of evidence to conclude that vitamin D supplements should be safely given to those with vitamin D deficiency (<20 ng/mL) or insufficiency (20–30 ng/mL). During the current pandemic, patients with sufficient vitamin D serum levels (>30 ng/mL) are better equipped to fight the disease (16).

Study strength

The strength of the present study consists in the large sample size collected in a short duration.

Study limitations

Vitamin D deficiency may be a consequence associated with a range of chronic health conditions or behavioural factors that plausibly increase the risk for COVID-19. □

CONCLUSION

The study concluded that a significant relationship was observed between vitamin D levels and clinical severity of patients with COVID-19. Severity of clinical disease and mortality in COVID-19 upturns in case of vitamin D deficiency. Vitamin D deficient patients have an enormous inflammatory response, which is accountable for the increase in morbidity and mortality. The authors believe that vitamin D supplementation will play a cardinal role in defying against COVID-19. □

Conflicts of interest: none declared.

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