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Study of Vitamin D Levels in Patient Diagnosed with COVID-19 Infection

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ABSTRACT

Background: *In the pandemic of COVID-19 because an adequate immune response is crucial for overcoming this viral infection, it is important to identify the existing and known substances that strengthen immune system activity. On the other hand, India being a tropical country is blessed with sunlight in almost all of its territory and so it would be more interesting to have an estimate of vitamin D levels representative of the Indian population who suffered from COVID-19 infection.* ***Aim:*** *To study the levels of vitamin D in patients with COVID-19 infection.* ***Material and Methods:*** *This study is a cross-sectional study conducted for estimating the prevalence of vitamin D deficiency in patients diagnosed with COVID-19 infection. The present study was conducted at tertiary care COVID-19 hospital at Indian Institute of Medical Science and Research, Jalna, Maharashtra in collaboration with Hedgewar Multispeciality Hospital, Aurangabad, Maharashtra.* ***Result:*** *Among the 141 study subjects 86 were vitamin D insufficient, 38 were vitamin D deficient while the remaining 14 subjects were having normal vitamin D levels. When the prevalence rate was estimated from this data the prevalence of vitamin D insufficiency was reported to be 60.99% whereas the prevalence of vitamin D deficiency was found to be 29.07% in the COVID-19 population of this study.* ***Conclusion:*** *Vitamin D deficiency and insufficiency were prevalent in COVID-19 patients and so vitamin D supplementation may help in the prognosis of COVID-19 disease.*

Keywords: Vitamin D, COVID-19, Vitamin D deficiency, Prevalence

INTRODUCTION

The novel Coronavirus (COVID-19) has infected millions of people, and World Health Organization (WHO) has declared COVID-19 as a pandemic in March 2020 [1]. The clinical manifestations of this disease have a broad spectrum, including asymptomatic infection, mild upper respiratory tract infection, and severe pneumonia with respiratory failure, for which hospitalization with sub-intensive or intensive care is required [2]. The etiology of COVID-19 has not yet been fully elucidated. The main cause of death in COVID-19 patients is inflammation, especially in the lung which leads to Acute Respiratory Distress Syndrome (ARDS) [1]. Because an adequate immune response is crucial for overcoming this viral infection, it is important to identify the existing and known substances that strengthen immune system activity. Nutrition has been a determinant factor for the maintenance of homeostasis and the health of different organs and physiological systems of an organism, including immune function [3]. In the current scenario of the COVID-19 pandemic, the "nutritional status-immune response" dyad of an individual becomes even more significant because of the absence of a definitive treatment supported for COVID-19. While vitamin D is commonly known for its contribution to bone health and metabolism of calcium and phosphorus, it has also been known to have an important function in the immune system [4]. Vitamin D was found to have a critical role as an "immune-modulator" that modulates the body's immune response during infection [4]. Vitamin D modulates both the innate immune system and the adaptive immune system by increasing the cathelicidins and β-defensins levels in the body, and by reducing the secretion of immunoglobulin by plasma cells and the production of pro-inflammatory cytokines, respectively [5]. It has both antimicrobial and anti-inflammatory effects and is known to be effective in preventing various upper Respiratory Tract Infections (RTIs) [5]. It also has the potential to prevent or lessen the possibility of having complications from RTIs. Vitamin D can also hasten the healing process of affected areas, specifically lung tissues [5]. Vitamin D

deficiency has been associated with increased levels of inflammatory cytokines and increased risk of pneumonia and viral upper respiratory tract infections [6]. It is also an important risk factor for Acute Respiratory Distress Syndrome (ARDS), which is an important determinant of the severity of illness among COVID-19 patients [6]. Vitamin D deficiency is also associated with increased episodes of thrombosis, which is commonly observed among COVID-19 patients [6]. A low level of vitamin D is commonly observed among those in the older age group, obese, and smokers, and among patients with chronic diseases like hypertension, gastroenterological disease, and diabetes [7]. It is also among these groups that COVID-19 was observed to be more prevalent and have more severe complications. With the observation that the group of people with vitamin D deficiency are also the same group suffering from more complications and higher mortality from COVID-19, then vitamin D deficiency might be an important risk factor for COVID-19. On the other hand, India being a tropical country is blessed with sunlight in almost all of its territory and so it would be more interesting to have an estimate of vitamin D levels representative of the Indian population who suffered from COVID-19 infection.

Aim and Objective

- To study the levels of vitamin D in patients with COVID-19 infection
- To create awareness among Indian subjects about the importance of vitamin D in this pandemic of COVID-19

MATERIALS AND METHODS

Study Design

This study is a cross-sectional study conducted for estimating the prevalence of vitamin D deficiency in patients diagnosed with COVID-19 infection.

Study Duration

April 2021-July 2021.

Study Site

The present study was conducted at tertiary care COVID-19 hospital at Indian Institute of Medical Science and Research, Jalna, Maharashtra in collaboration with Hedgewar Multispeciality Hospital, Aurangabad, Maharashtra.

Inclusion Criteria for Study Subjects

Those who tested positive for SARS-CoV-2 by RT-PCR test from COVID-19 OPD and COVID ward were included in the study with their due consent.

Exclusion Criteria for Study Subjects

Those who were taking vitamin D supplements or having taken them in the last 6 months were excluded.

Study Subjects

In this study blood samples were taken from 141 patients who were diagnosed with COVID-19 by RT-PCR test and were admitted in the wards and ICCU of IIMSR as well as that of Hedgewar hospital. The study subjects were categorized into three groups "Mild, Moderate and Severe" based on the severity of their respective COVID-19 disease by the criteria laid down in guidelines of the Ministry of Health and Family Welfare, India [8]. These guidelines are tabularized as below (Table 1).

Table 1 COVID-19 severity categories according to clinical presentation and SpO^2

COVID-19 Severity	Clinical Presentation	SpO^2 on room air
Mild Case	Fever and Cough with no Dyspnoea and Hypoxia	95%-100%
Moderate Case	Fever and Cough with Dyspnoea and Hypoxia; RR >24/min	90%-94%
Severe Case	Pneumonia clinical signs along with severe respiratory distress evident by RR >30/min	<90%

Method of Sample Analysis

Blood samples were collected from patients by venipuncture into plain bulbs. Vitamin D estimations were done in the central clinical laboratory of Hedgewar hospital on Beckman Coulter Access 2 immunoassay analyzer which used the principle of chemiluminescence for vitamin D estimation.

25-hydroxy vitamin D was estimated instead of 1-25-dihydroxy vitamin D.

25-hydroxy vitamin D was preferred despite being an inactive precursor as it is present in higher concentration and major storage form in the blood with longer half-life and thus is very feasible to be estimated at a much lower cost when compared to its active form 1-25-dihydroxy vitamin D.

We took the reference from endocrine society clinical practice guidelines according to which vitamin D deficiency was labeled as levels below 20 ng/ml and vitamin D levels between 20 ng/ml-30 ng/ml were labeled as vitamin D insufficient while levels more than 30 ng/ml was considered as state of vitamin D sufficiency [9].

Method of Statistical Analysis

All the data were entered into Microsoft excel 365 versions and analysed using SPSS (Statistical Package for Social Science). The classification of vitamin D deficiency and clinical severity was defined. To find out the association, the chi-square test was applied and a p-value less than 0.05 was considered statistically significant. To understand the Vitamin D status among the different groups, deficiency, and insufficiency were calculated separately and compared. Further stratification of data was carried out in mean and standard deviation to get the overall picture of the respective group. Data of clinical severity were compared to check the association between clinical severity and vitamin D levels.

Ethical Consideration

All the patients were informed about the purpose of the study and written/digital consent was taken to participate in the study. The study protocol was approved by the institutional ethical committee of both i.e Indian Institute of Medical Science and Research as well as of Hedgewar hospital.

RESULTS

Among the 141 COVID-19 subjects, enrolled in this study and in accordance with guidelines of the Ministry of Health and Family Welfare, India, 102 (72.34%) were classified under the mild category, 27 (19.14%) were classified under the moderate category while the severe category comprised of remaining 12 (8.5%) COVID-19 subjects (Table 2).

Table 2 COVID-19 severity category and vitamin D status

COVID-19 Severity Category	Vit. D Deficiency (<20 ng/mL)	Vit. D Insuficiency (<20 ng/mL-30 ng/mL)	Vit. D Normal (>30 ng/mL)	p-value
Mild (102)	25	64	13	>0.05
Moderate (27)	12	14	1	>0.05
Severe (12)	4	8	-	>0.05
Total (141)	41	86	14	-
Prevalence	29.07%	60.99%	-	-

DISCUSSION

This study reported a 60.99% prevalence of vitamin D insufficiency as well as a 29.07% prevalence of vitamin D deficiency in the sample size. Similar findings were reported by Singh, et al. in their research study [6]. Another study claimed that the risk factors for vitamin D deficiency overlap strikingly with severe COVID-19 disease [10]. Consistent with the present study results, a recent study showed that nearly 75% of hospitalized and 85% of ICU care patients symptomatic for COVID-19 patients suffered from vitamin D insufficiency [11]. A recent study that assessed inflammatory response and lung involvement found that vitamin D deficiency was associated with altered inflammatory response and higher lung involvement [12]. Several have recently been performed in different populations to decipher the possible role of vitamin D in SARS-CoV-2 infection. In another study, a retrospective analysis of 3,48,598 UK bio-

bank participants showed a higher chance of SARS-CoV-2 in subjects with lower levels of 25(OH)D [13]. In addition to its significant role in calcium homeostasis and the maintenance of bone health, vitamin D had played an important role in the body's immune function [14]. The study reported that vitamin D acted as a powerful immune-modulator, for which the authors gave the following justification:

- The authors had reported that vitamin D receptors were found in all immune cells
- Vitamin D was associated with the differentiation of T and lymphocytes as well as with the maturation of monocytes and macrophages
- Vitamin D was also found to optimize the anti-inflammatory functions by alteration in the levels of IL-10 and cytokines
- Lastly vitamin D was found to play role in phagocytosis by inducing the secretion of the lysosomal enzymes like acid phosphatase [15]

In one of the studies, it was reported that this immune-modulating function of vitamin D was considered to be complex during viral infections and appeared to vary according to the nature of the pathogen and the type of immune function affected in the disease [16]. In the same context, another study reported that Vitamin D was found to play an immune-regulatory role *via* suppression of the adaptive immune responses in respiratory epithelial cells during viral infections [17]. This is manifested predominantly *via* dampening T cell proliferation and the resultant shift from T helper type 1 (Th1) cells to T helper type 2 (Th2) [18]. Apart from the role of immune-modulation, the Vitamin D Receptor (VDR) was also found in pulmonary epithelial cells as reported in a study done by Klotman ME, et al. The author further reported that when activated, VDR was found to stimulate the expression of defensins, cathelicidins, and peptides with antiviral activity [19]. In the same context of vitamin D's role in immune-modulation, it was speculated in one of the studies that, during vitamin D deficiency, the impaired antiviral immune response in COVID-19 patients may have been due to the reduction in LL37 levels, an antimicrobial peptide derived from cathelicidin [20]. Some authors have also postulated that vitamin D may down-regulate Angiotensin-Converting Enzyme-2 (ACE-2) receptors and thus can have protective effects in COVID-19 [21]. Now concerning the Indian context of vitamin D deficiency, it was surprising to come across a study that has estimated the prevalence of vitamin D deficiency in India [22]. This study has reported that although India because of its closeness to the equator had been receiving a large amount of sunlight throughout the year, most of the Indian population (50%-90%) was found to be deficient in vitamin D [22]. The author of this study further justified their finding by attributing such vitamin D deficiency in urban India to avoidance of sunlight and dietary deficiency [22]. They also further reported that the considerably similar status of vitamin D deficiency in rural India despite considerable exposure to sunlight may have been possibly attributed to various factors including the presence of phytates and phosphates in the Indian diet [22].

The correlation between vitamin D deficiency and COVID-19 disease was addressed in a retrospective, a multicentric study which had suggested that whilst the COVID-19 patients who were deficient in vitamin D generally had poor outcomes, those with high levels of vitamin D fared better outcomes [23]. Consistent with this study a review was published by Rhodes, et al. in which they had concluded that there was substantial ecological evidence to correlate vitamin D deficiency with the severity of COVID-19 infection [24]. In a study done by Jain et al., they had speculated that African Americans with vitamin D deficiencies as well as those with poorer COVID-19 outcomes may stand to benefit from vitamin D supplementation [25]. Similar conclusions were made by Merzon and colleagues in an Israeli population [26]. In another study, the authors concluded that vitamin D deficiency played an independent causal role in COVID-19 severity and that preventive or therapeutic supplementation in populations at risk can be useful to prevent poor disease outcomes [27]. Similarly Martineau AR, et al. had reported that vitamin D supplementation is taken daily or weekly, had been found to reduce ARI (Acute Respiratory Infection) by 32% to 60% [28]. Thus based on the findings in the present study in concordance with the above-mentioned studies it can be suggested that vitamin D supplementation may help in preventing the incidence of COVID-19 disease as well as may decrease the severity of COVID-19 disease although a web of confounders makes it difficult to label vitamin D supplementation as a conclusive preventive or therapeutic approach in COVID-19 pandemic.

CONCLUSION

The prevalence of Vitamin D Insufficiency and Deficiency in the present study was 60.99% and 29.07% respectively.

As vitamin D had been reported to be an immune-modulator bio-molecule in many studies its deficiency may lead to a decrease in immune function which may be attributed to increased susceptibility of such vitamin D deficient individuals to COVID-19 infection. But it needs the support of other research study designs such as cohort studies for proving such temporal association between COVID-19 and vitamin D deficiency. Given that vitamin D supplementation as per the above-mentioned reference studies had shown benefits in certain viral respiratory infections, the roles of vitamin D in COVID-19 warrant further exploration. The role of vitamin D in the management of COVID-19 needs strong Randomised Control Trial evidence.

DECLARATIONS

Conflicts of Interest

The authors declared no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

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