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Original Research Article

Vitamin D deficiency as a risk factor for COVID-19 infection in children

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ABSTRACT

Background: Vitamin D deficiency is a major public health problem in all age groups. Through its immunomodulatory, anti-inflammatory and antioxidant effects it is shown to have a protective effect in COVID affected children. The objective of the study was to evaluate vitamin D deficiency as a risk factor for developing COVID-19 infection in children and to study the relationship between vitamin D deficiency and the clinical findings in COVID-19 positive children.
Methods: A retrospective study of all COVID positive children aged 1 month to 15 years admitted to COVID Paediatric ward of Rajarajeshwari Medical hospital from July 2020-November 2020. All COVID positive children confirmed with RTPCR of age group 1 month to 15 years will be included in the study the age at admission, clinical and laboratory data, and 25-hydroxycholecalciferol (25-OHD) levels will be recorded. Patients diagnosed with COVID 19 are divided into 2 groups those with deficient and insufficient vitamin D levels were determined as group 1 and patients with normal vitamin D levels as Group 2. Those with vitamin D Levels below 20ng/ml were determined as group 1 and those with >20 ng/ml as group 2. The various clinical outcomes and laboratory parameters were compared between the two groups.
Results: Patients with COVID 19 had significantly lower vitamin D levels 22.39±6.27 ($p \leq 0.0001$). Patients in group A that is vitamin D deficient and insufficient group had higher levels of ferritin ($p \leq 0.0001$).
No significant difference was found between other clinical and laboratory parameters between group 1 and group 2.
Conclusions: This is one of the first to evaluate vitamin D levels and its relationship with clinical findings in paediatric patients with covid-19. Although vitamin D does not play a role in the pathogenesis of COVID-19 we do believe its putative role in preventing and treating the disease The results suggest that vitamin D levels may be associated with the occurrence and management of the COVID-19 disease by modulating the immunological mechanism to the virus in paediatric population.

Keywords: COVID 19, Vitamin D deficiency, Children, Immunomodulatory effects, Risk factor, Retrospective study

INTRODUCTION

A new coronavirus (CoV) infection was reported to begin in late 2019 in Wuhan, Hubei, China, which the World Health Organization (WHO) called coronavirus disease 2019 (COVID-19) on February 11,2020.[1]

On March 11, 2020, COVID-19 infection was declared a pandemic by WHO due to the global logarithmic increase of cases.[2]

Chinese data reported that only 2% of the 44,672 cases with COVID-19 were children.[3]

In an Italian paper reported that only 1.2% of 22,512 confirmed cases of COVID-19 were children.

Although studies from Asia and America report that new corona virus disease in children may be less serious than adults.[4-5]

Vitamin D deficiency is a major public health problem in all age groups. More than one billion people all over the world are estimated to have vitamin D deficiency.

Although vitamin D is usually acknowledged for the maintenance of bone health and calcium–phosphorus metabolism, many other roles of this hormone have been recently discovered, such as stimulation of insulin production, effects on myocardial contractility, prevention of inflammatory bowel disease (IBD), and promotion of thyroid-stimulating hormone (TSH) secretion. Furthermore, the immunomodulatory role of vitamin D has been the subject of several studies.[3,8]

Vitamin D is a pluripotent hormone modulating the adaptive and innate immune response.[6]

Vitamin D induces cathelicidins and defensins that can reduce the viral replication rate.

In addition, it increases the concentrations of anti-inflammatory cytokines and decreases the concentration of proinflammatory cytokines that cause pneumonia and lung damage.[1]

In previous studies, vitamin D deficiency has been shown to increase respiratory infections risk including respiratory syncytial virus, tuberculosis and flu, and is a risk factor for acute respiratory distress syndrome (ARDS).[6]

The severe acute respiratory syndrome coronavirus 2 (SARS- CoV-2) virus among the COVID-19 patients, enters host cells by binding to receptors of angiotensin-converting enzyme 2 (ACE2) in the respiratory tract of infected patients.[7]

The primary targets of coronaviruses are Type-II pneumocytes and there is high expression of ACE2 receptors in these cells.[8]

The level of surfactant can be reduced due to dysfunction of Type-II pneumocytes, and this can lead to increased surface tension in COVID-19. It has been shown that surfactant synthesis in alveolar Type-II cells is stimulated by 1,25- dihydroxy vitamin D metabolites.[8]

Vitamin D is a secosteroid with a wide range of immunomodulatory, anti-inflammatory, antifibrotic and antioxidant effects. It is thought that inflammatory cytokine expression is inhibited by vitamin D and its deficiency is associated with overexpression of Th1 cytokines.[9]

Epidemiological studies have reported an association between vitamin D deficiency and acute lung injury and viral respiratory infections.[10]

A randomized trial from China reported the beneficial effects of vitamin D is appropriate for the prevention of seasonal influenza as proved by rapid relief from symptoms, fast reduce, in viral loads and disease recovery.[11]

Another randomized trial of daily high dose versus standard dose of vitamin D in Canadian children showed that the incidence of influenza infections in the high-dose group was reduced by 50%.[12]

The immune response against respiratory virus infections might be improved by a sufficient level of 25 (OH) D in serum.[13]

In the face of the COVID-19 pandemic, and in the lack of a vaccine or any effective antiviral treatment, supplementation of vitamin D hospital inpatients might be beneficial.

In this study, we aimed to determine the prevalence and clinical importance of vitamin D deficiency in children and adolescent patients who were hospitalized with the diagnosis of COVID-19.

METHODS

The study was conducted at the paediatric ward of the Department of paediatrics, Bangalore, Karnataka. The hospital is a tertiary health facility located in Bangalore, the capital of Karnataka, South India. The paediatric COVID ward is a 30 bedded unit which was designated to admit all mild to moderate COVID positive cases.

Study design and subjects

The study was a retrospective survey of children between the ages of 1 month and 15 years admitted to Raja Rajeshwari medical college and hospital between July 2020-November 2020. 50 patients who were diagnosed to have COVID-19 and hospitalized with real time reverse transcription polymerase chain reaction method (RTPCR)were included. Inclusion criteria for subjects were age 1 month to 15 years All COVID positive children with mild to moderate severity tested by RTPCR test were included. An informed written consent from the caregiver and assent from children above 7 years was taken. Neonates and infants less than 1 month of age were excluded from the study. All children tested COVID positive and discharged were called for follow up and their Vitamin D levels were checked after taking consent along with other demographic data of the patients collected from the respective case files.

Data collection

Subjects that satisfied the inclusion criteria were recruited into the study.

The age at admission, gender, address and socioeconomic status according to kupuswamy classification was determined. Clinical data of the child including symptoms like fever, dry cough,anosmia,loss of taste tiredness and lassitude were determined. Laboratory data included Ferritin levels and D-dimer levels and WBC counts done during the admission period was obtained from the retrospective case files.25-hydroxycholecalciferol (25-OHD) levels were recorded on follow up. Under all aseptic precautions venous blood was drawn and sent for 25-hydroxycholecalciferol (25-OHD). 25-hydroxycholecalciferol was examined by high performance liquid chromatography method.

Patients diagnosed with COVID 19 are divided into 2 groups those with deficient and insufficient vitamin D levels were determined as group 1 and patients with normal vitamin D levels as Group 2 and the various clinical outcomes and laboratory parameters were compared between the two groups

Vitamin D Levels of 25-OHD level less than 12 ng/ml are considered as vitamin D deficient those between 12 and 20 ng/ml are considered vitamin D insufficient those with greater than 20 ng/ml are considered to have a normal vitamin D.

Ethics statement

Ethical approval for the study was sought and obtained from the health research and ethics committee of Rajarajeshwari medical college and hospital.

Written informed consent was obtained from the parents and caregivers of the children and assent was sought from children of sufficient age.

The data obtained were treated with utmost confidentiality.

Statistical analysis

Microsoft Excel Statistical package for social sciences version 23.0 was used to analyze the data.

The data collected was analyzed using Descriptive statistics for summarizing data using Mean and Standard deviation and inferential statistics using unpaired t test and Z test.

The level of statistical significance was set at 5% which is $p<0.05$

Data entered was carefully checked to eliminate multiple or wrong entries and outliers.

RESULTS

Patients diagnosed with covid-19 were divided into two groups. Those who had deficient and insufficient vitamin D levels were determined as group 1 (n=26) and normal patients were determined as group 2 (n=24). The mean age ranges in group 1 and 2 were 6.115±3.12 and 12.04±2.42 in years The number of males was 15 in group 1 and females were 11. The number of males was 18 in group 2 and females were 6.

Table 1: Demographic characteristics of the study subjects (N=50).

Demographic characteristics	Frequency
Age in years	
Group 1	6.115±3.12
Group 2	12.04±2.42
Range	1-15 years
Gender	
Group 1	Males:15 Females:11
Group 2	Males:18 Females:6
Fever	
Group 1	19 (73%)
Group 2	16 (66%)
Dry cough	
Group 1	19 (73%)
Group 2	12(50%)
Loss of taste	
Group 1	0(0%)
Group 2	1(4.1%)
Anosmia	
Group 1	0(0%)
Group 2	1(4.1%)
Lassitude and fatigue	
Group 1	6(23%)
Group 2	2 (8.3%)
Vitamin D	
Group 1	22.39±6.27
Group 2	58.05±21.8
D-Dimer	
Group 1	3.61±5.07
Group 2	1.44±0.63
Ferritin	
Group 1	32.16±6.23
Group 2	21.3±5.72
WBC	
Group 1	7.15±3.55
Group 2	6.59±2.46

The demographic details of the study has been mentioned in table 1. Vitamin D was found to be both insufficient and deficient in significant number of COVID positive children than normal with a significant p value ($p<0.001$). There was significantly higher levels of ferritin in group 1 p value ($p<0.0001$) than in group 2. No significant difference was found between other clinical and laboratory

parameters between group 1 and group 2. Comparison of demographic clinical and laboratory characteristics between COVID-19 diagnosed children who had deficient and insufficient level of vitamin D and COVID-19 diagnosed children who had normal level of vitamin D is shown in table.

Table 2: Comparison of demographic clinical and laboratory characteristics between COVID-19 diagnosed children who had deficient and insufficient level of vitamin D and COVID-19 diagnosed children who had normal level of vitamin D.

Parameters	Group 1 (N=26)	Group 2 (N=24)	P value
Age (in years)	6.115±3.12	12.04±2.42	<0.0001
Gender	15-Males 11-Females	18-Males 6-Females	
Fever	19 (73%)	16 (66%)	0.62
Dry cough	19(73%)	12 (50%)	0.92
Loss of taste	0 (0%)	1 (4.1%)	0.29
Anosmia	0 (0%)	1 (4.1%)	0.29
Lassitude and fatigue	6 (23%)	2 (8.3%)	0.15
Vitamin D	22.39±6.27	58.05±21.8	<0.0001
D-dimer	3.61±5.07	1.44±0.63	0.0429
ferritin	32.16±6.23	21.3±5.72	<0.0001
WBC	7.15±3.55	6.59±2.46	0.523

DISCUSSION

Our study evaluated the vitamin D deficiency prevalence and the association between vitamin D deficiency and clinical and inflammatory markers in our patients hospitalized for COVID-19 infection.

We aimed to investigate whether children diagnosed with COVID-19 had vitamin D deficiency as well as the relationship between vitamin D deficiency and clinical outcomes.

Although there are no adequate studies on vitamin D levels and its effects in children with COVID-19, there are several studies evaluated the relationship between other respiratory pathogens and vitamin D.

Several studies have demonstrated that higher levels of vitamin D are associated with better prognosis and outcome in infectious diseases.[34]

Indeed, vitamin D has been extensively studied as a putative preventive and therapeutic agent for acute respiratory tract infections (ARTIs) in both adults and children, especially in developing and low-income countries, owing to its safety and low cost. As a matter of fact, pneumonia is the leading cause of death in children in the world.[35]

A great number of studies have hypothesized a positive correlation between vitamin D defciency and the risk of developing ARTIs.[36]

In some clinical studies, vitamin D has been shown to protect children from lung infection. Children with vitamin D deficiency or insufficiency are more susceptible to respiratoryinfection.[14]

A meta-analysis and systematic review of 25 randomized controlled trials by Martineau et al showed that vitamin D generally protects against acute respiratory infection.[15]

In an important study covering 1582 people by Li et al with the aim of determining the relationship between 25(OH)D in children and pulmonary infection, the community-acquired pneumonia group displayed a lower value than the control group, and there were also significant differences between the pneumonia group and pneumonia-derived sepsis group ($p<0.001$), and there was association between lower serum 25(OH)D level and more serious symptoms.[16]

Daneshkhah et al observed that high C-reactive protein (CRP) was inversely correlated with 25(OH)D, and they thought vitamin D to have a possible role in reduction of complications caused by abnormal inflammation and cytokine storm given the CRP as a marker for cytokine storm and considering its association with vitamin D deficiency.[17]

According to the emerging relationship between vitamin D status and alleged Covid-19 infection, vitamin D supplementation has already been proposed elsewhere. Although we do not assume that vitamin D plays a role in the pathogenesis of COVID-19, we do believe that its putative role in preventing or even treating the disease urgently needs to be further addressed.[18]

At the moment of writing, an interventional randomized clinical trial has been proposed at the University of Granada, with enrolment of 200 participants, proposing vitamin D supplementations (a single dose of 25,000 UI of vitamin D) in preventing and treating mild forms of suspected COVID-19.[19]

In a recent paper, it is assumed that vitamin D prophylaxis (without overdosing) could reduce, especially in patients with hypovitaminosis D, the severity of illness caused by SARS–CoV-2.[20]

The importance of treating the hypovitaminosis D along with an early nutritional supplementation has been highlighted for the potential preventing role of malnutrition sequelae in these patients.[21]

Vitamin D proved to interact both with the innate immune system, by activating Toll-like receptors (TLRs) or increasing the levels of cathelicidins and β-defensins, and adaptive immune system, by reducing immunoglobulin

secretion by plasma cells and pro-infammatory cytokines production, thus modulating T cells function. Promising results have been extensively described as regards the supplementation of vitamin D in respiratory tract infections, autoimmune diseases and even pulmonary fibrosis.[22]

On the basis of the possible direct and indirect effect of vitamin D on immune system and cytokines production, we speculate a possible influence of this vitamin on the immunologic response to the virus and/or a modulating effect on the drugs being administered, namely hydroxychloroquine and anti-IL 6 and anti-IL 1 agents.[22]

In a study conducted by Alipio et al observed that vitamin D level was low or insufficient in 74.1% of patients diagnosed with COVID-19 and also found a statistically significant difference between serum 25(OH)D level and clinical outcomes ($p<0.001$).[23,30]

In another study of Lau et al regarding the relationship between vitamin D deficiency and the severity of COVID-19 disease in adult age group, low levels of vitamin D were found in 75% of the cases and 84.6% of the patients in intensive care unit.[24]

In a study conducted on adults, Raharusa et al found deficient or insufficient levels of vitamin D in 47.3% of 780 patients diagnosed with COVID-19. Vitamin D was insufficient in 27.3% of them and deficient in 20% of them. They observed mortality in 49.1% of vitamin D insufficient cases, 46.7% of deficient ones and 4.1% of normal ones, and found statistically significant results between vitamin D level and mortality ($p<0.001$). However, the comorbid factors concomitant with the majority of those with deficient and insufficient vitamin D levels in their studies make it difficult to evaluate the relationship between mortality and vitamin D alone.[25]

The pathology of COVID-19 involves a complex interaction between the virüs and the body immune system. COVID-19 is provoke, the release of proinflammatory cytokines. Vitamin D has been found to modulate macrophages' response, preventing them from releasing too many inflammatory cytokines and chemokines.[26]

Recently children have been presenting with a systemic inflammatory response, sharing features with other paediatric inflammatory conditions, such as, Kawasaki disease, toxic shock syndrome, and macrophage activation syndrome. In a study reported an important serious vitamin D deficiency in children with Kawasaki disease as compared to healthy controls, and low levels of vitamin D appears to correlate to the risk in developing cardiovascular lesions.[26]

A study conducted by Ilie et al found that average vitamin D levels in each country and the COVID-19 cases were negatively correlated with the number of deaths caused by COVID-19. Since there were no patients in our study who died, there was no evaluation of the relationship between vitamin D levels and mortality. In addition, there were no significant differences in length of stay in COVID 19 diagnosed children who had deficient and insufficient level of vitamin D (Group 1) and COVID 19 diagnosed children who had normal level of vitamin (Group 2).[27]

Just recently it has been directly hypothesized that vitamin D supplementation could be used as a therapeutic combination in COVID-19, based on the epidemiology of the disease, and on the decreased vitamin D status observed in calves infected with bovine coronavirus.[28-29]

The role of vitamin D as possible adjuvant to antibiotics treatment of acute childhood pneumonia has already been undetermined in a previous Cochrane review.[30]

A more recent study also showed how high-dose vs standard-dose wintertime vitamin D supplementation did not reduce viral upper respiratory tract infections in young healthy children.[31]

Nonetheless, the ineffectiveness of vitamin D in the younger might be due both to the lower prevalence of vitamin D deficiency, when compared with the elderly, and to a putative threshold effect of vitamin D in preventing Arti. It has been, indeed, demonstrated that the negative correlation between levels of vitamin D and respiratory tract infections, should be attributed to its active form (1,25-OH2-vit D); therefore, restoring the levels of inactive vitamin D might not be sufficient in some patients, like those affected by chronic kidney or liver disease.[32]

Interestingly, it has also been demonstrated that vitamin D supplementation in patients with ventilator-associated pneumonia (VAP) can significantly reduce IL-6, that can be considered a prognostic marker, and the mortality rate in patients treated with vitamin D was significantly lower than that of the placebo group. The authors concluded suggesting the administration of vitamin D at a high intramuscular dose (300.000 UI) as an adjunct to the standard treatment of VAP patients.[33]

In a stude done by Yılmaz et al patients with COVID-19 had significantly lower vitamin D levels 13.14 µg/L (4.19–69.28) than did the controls.[34] 81 (3.8–77.42) µg/L ($p<0.001$). Patients with COVID-19 also had significantly lower serum phosphorus (4.09±0.73 versus 5.06±0.93 versus (U/L) ($p<0.001$)) values compared with the controls. The symptom of fever was significantly higher in COVID-19 patients who had deficient and insufficient vitamin D levels than in patients who had sufficient vitamin D levels ($p=0.038$). There was a negative correlation found between fever symptom and vitamin D level ($r=-0.358$, $p=0.023$).[36]

While it is supposed that serum levels of vitamin D between 20 ng/mL and 50 ng/mL should be adequate to

provide an immunomodulatory effect, there has been great uncertainty on the vitamin D supplementation regimen to adopt.[39]

A recent systematic review studied the role of vitamin D as an adjunctive therapy to antibiotics in acute childhood pneumonia. It included seven RCTs conducted in low-income countries that involved 1529 children. Nonetheless, owing to the different supplementation regimens adopted for each study and the lack of reporting on the etiology of pneumonia, only low- to very low-quality evidence was made available.[40]

Our study has several limitations. It is possible the data may be incomplete or incorrect due to the retrospective study design. Some of the clinical parameters could not be assessed in all age groups example- anosmia and loss of taste. The number of patients in our study group may be small but despite all these limitations it may provide insight into future studies on whether there is a real relationship between Vitamin D deficiency and COVID 19.

CONCLUSION

In conclusion, our study is one of the first to evaluate vitamin D levels and its relationship with clinical findings in paediatric patients diagnosed with COVID-19. Vitamin-D levels were found to be significantly lower in COVID positive children. Although vitamin D does not play a role in the pathogenesis of COVID-19 we do believe its putative role in preventing and treating the disease. Since there were no reported cases of death in our study, the relationship with vitamin D deficiency and mortality could not be evaluated. However More studies are needed in children for evaluation of the association between vitamin D with clinical and laboratory findings of the disease and its effect on mortality.

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