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Is Vitamin D Deficiency a Risk Factor for Covid 19 in Children?

Running Title: Vitamin D Deficiency in Covid 19

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Introduction

A new coronovirus (CoV) infection was reported to begin in late 2019 in Wuhan, Hubei, China, which the World Health Organization (WHO) called 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). Studies have reported that crude mortality rates worldwide due to the COVID-19 outbreak vary between 5.6% and 15.2%. The risk of death was found to be higher for elderly individuals and those with comorbid conditions such as hypertension and diabetes mellitus. In an article reviewing 46,248 cases, hypertension, diabetes mellitus, cardiovascular disease and respiratory morbidity were specified to be the most common comorbidities (3).

Otherwise COVID-19 is also occurenced in healthy children commonly, Chinese data reported that only 2 % of the 44 672 cases with COVID-19 were children (4). In an italian paper reported that only 1.2% of 22 512 confirmed cases of COVID-19 were children (5). Although studies from Asia and America report that new corona virus disease in children may be less serious than adults (6,7).

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. Vitamin D is a pluripotent hormone modulating the adaptive and innate immune response (8). The risk of infection by several mechanisms can be reduced by vitamin D. 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 pro-inflammatory 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 (RSV), tuberculosis and flu, and is a risk factor for acute respiratory distress syndrome (ARDS) (8).

The 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 (9). The primary targets of coronaviruses are type-II pneumocytes and there is high expression of ACE2 receptors in these cells. 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 (10). It has been shown that surfactant synthesis in alveolar type-II cells is stimulated by 1,25-dihydroxyvitamin D metabolites (11).

The vitamin D agonist calcitriol is thought to have protective effects against acute lung injury by modulating the expression of members of the renin-angiotensin system such as ACE 2 in lung tissue (12). This information suggests that vitamin D deficiency may have a potential role as a pathogenic factor in COVID-19. CD26 is a putative adhesion molecule for COVID-19 host cell invasion. Adjustment of vitamin D deficiency is thought to suppress CD26. Vitamin D may also reduce, interleukin-6 (IL-6) and interferon gamma (IFNγ) inflammatory reactions, both potent predictors of worse clinical outcome in severe COVID-19 (13).

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 (14).

Epidemiological studies have reported an association between vitamin D deficiency and acute lung injury and viral respiratory infections (15). 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 (16). 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% (17). The immune response against respiratory virus infections might be improved by a sufficient level of 25 (OH) D in serum (18).

In the face of the COVID-19 pandemic, and in the lack of a vaccine or any effective anti-viral 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.

Material and Methods

This study included 85 children between the ages of 1 month to 18 years in Dicle University Faculty of Medicine between March 2020 and May 2020.

40 patients who were diagnosed to have COVID-19 and hospitalized with the real-time reverse transcription polymerase chain reaction (RT-PCR) method were included. The control group was composed of 45 healthy children who were previously examined in Pediatric Endocrinology or Pediatric outpatient clinics and whose vitamin D level was checked. Cases with chronic diseases and co-morbidities, and those younger than 1 month and older than 18 were excluded from the patients group and control group.

The data of the cases included in the study were obtained from retrospective file records. The age of admission, clinical and laboratory data, and 25-hydroxycholecalciferol (25-OHD) and parathormone (PTH) levels were recorded. 25-hydroxycholecalciferaol level was examined in Shimatzu device by high performance liquid chromatography method. PTH level was examined by electro chemiluminescence method in Siemens Advia Centaur device. Those with 25-OHD level <12ng/ml were considered as vitamin D deficient, those between 12-20 ng/ml were considered vitamin D insufficient and those with >20 ng/ml were considered to have a normal vitamin D (19). Patients diagnosed with COVID-19 were divided into 2 groups. Those with vitamin D levels which are below 20 ng/ml were determined as Group 1 and those with ≥20 ng/ml as Group 2, and clinical and laboratory variables between the 2 groups were compared.

The severity of the disease was classified as asymptomatic, mild, moderate, severe, and critical according to the clinical characteristic, laboratory results, and chest radiography findings (20).

Asymptomatic: Cases with a positive RT-PCR test without any clinical and radiological findings

Mild: Cases with upper respiratory tract infection symptoms such as fever, fatigue, myalgia, cough, sore throat, nasal flow with normal espiratory system examination

Moderate: Cases with pneumonia with complaints of fever and cough but without the symptoms of dyspnea and hypoxemia or cases with findings of COVID-19 on chest CT scan without any symptoms

Severe: Cases with fever and cough in the early period who develop dyspnea and central cyanosis within a week (arterial oxygen saturation of <92%)

Critical: Cases who develop acute respiratory distress or respiratory failure rapidly, and who tend to develop shock, encephalopathy, myocardial affection, coagulation dysfunction, and acute kidney injury.

The study was conducted based on the rules of Declaration of Helsinki and approved by the Institutional Ethics Committee of Dicle University, Faculty of Medicine.

Statistical Analysis

Data analyses were examined by using Statistical Package for Social Sciences (SPSS), Version 20.0 for Windows (SPSS Inc., Chicago, IL, USA). The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Simirnov test) whether or not they were normally distributed. Normally distributed variables were presented using means and standard deviations, and non-normaly distributed variables using median and range (maximum and minimum). Comparisions of the groups were performed using the Student t (normally distributed variables) and Mann-Whitney U (non normally distributed variables). The chi-square test was used to analyze of categorical variables. P values <0.05 were considered statistically significant.

Results

The mean age and age ranges of the groups were as follows: COVID-19 patients, 101.76 ± 27.91 months (range, 3 months-18 years) and the healthy control subjects, 75.68 ± 27.34 months (range, 1 month-18 years).

47.5% (n=19) of the patients and 60% (n=27) of the control group were male. No difference was found between the groups in terms of age and gender distribution (p = 0.061, p=0.248, respectively). The median levels of vitamin D level were 13.14 μg/L (4.19-69.28) in the group of patients with COVID-19 and 34.81 μg/L (3.8-77.42) in the control group. The COVID-19 patient group and the healthy control group were compared, there were statistically significantly lower serum phosphorus level ($p<0.001$) and vitamin D level ($p<0.001$) in the COVID-19 diagnosed patient group. Table 1 summarizes the comparison of demographic and laboratory characteristics between COVID-19 patient group and healty control subject group.

Patients diagnosed with COVID-19 were divided into 2 groups. Those who had deficient and insufficient vitamin D levels were determined as Group 1 (n: 29, 72.5%) and normal patients were determined as Group 2 (n: 11, 27.5%). 18 children in the COVID-19 patient group had vitamin D deficient and 11 children had vitamin D insufficient values. Eight children in the healthy group had vitamin D deficient and 3 children had vitamin D insufficient values.

The clinical and laboratory parameters of Group 1 and Group 2 are compared, at admission, the symptom of fever (34.5%) was significantly higher in Group 1 than in Group 2 (0%) (p = 0.038). There were significantly lower levels of vitamin D ($p<0.001$) and serum phosphorus ($p=0.013$) in group 1 than those in group 2. No significant difference was found between other clinical and laboratory parameters between the groups. Comparison of demographic, clinical and laboratory characteristics between 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) is shown in Table 2.

The distribution of disease severity according to vitamin D levels was not found significantly different (Table 3).

There was a negative correlation found between fever symptom and vitamin D level ($p = 0.023$, Table 4). However, no significant correlations were found between other clinical parameters and vitamin D level (data were not shown).

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. To the best of our knowledge, we have not found any study on vitamin D levels in pediatric patients diagnosed with COVID-19 in our literature review of resources in English. We aim 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. 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 respiratory infection (21). 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 (22). In an important study covering 1582 people by Li et al. with 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 (23).

Daneshkhah et al. observed that high 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 (24). Some previous studies found negative correlation between 25(OH) D vitamin level and pneumonia severity, CRP level, increased risk of sepsis, ARDS risk and increased production of proinflammatory cytokines such as IL-6 (25-29).

In a study conducted by Alipio M. 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) (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 (31). 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 (32).

In our study, 72.5% of our cases were vitamin D deficient or insufficient, and 2 patients in need of treatment in the intensive care unit had the vitamin D level of below 10 ng/ml, and had comorbid diseases, but there were no reported cases of mortality. In our study, the distribution of disease severity according to vitamin D levels was not found significantly different ($p = 0.097$). Yet, although the virulence mechanisms related to COVID-19 are not fully characterized, the fact that clinical severity and mortality rate of the disease generally progress better in children compared to adults suggests that the SARS-CoV-2 S protein binds to the angiotensin-converting enzyme (ACE) 2 and that children may be protected against SARS-CoV-2 because this enzyme is less mature at a younger age (33). 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) were compared at admission, Group 1 had significantly higher fever symptom (34.5%, 10) than Group 2 (0%) ($p = 0.038$). A negative correlation was found between vitamin D level and fever symptom ($p = 0.023$), but there was no significant finding in terms of CRP level and clinical severity. We suggest that the relationship between fever and vitamin D may be related to the inflammatory process and cytokine release caused by the virus in the body. Patients with COVID 19 were reported to have increased plasma concentrations of proinflammatory cytokines, including interleukin (IL)-6, IL-10, granulocyte-colony stimulating factor (G-CSF), macrophage inflammatory protein, and tumor necrosis factor (TNF)-α (34). Vitamin D may also reduce, interleukin-6 (IL-6) and interferon gamma (IFNγ) inflammatory reactions, both potent predictors of worse clinical outcome in severe COVID-19 (13). Cytokines are proteins manufactured throughout the body, primarily, by macrophages and T cells to coordinate the immune reactions, within the body, control inflammatory and may induce fever.

The pathology of COVID-19 involves a complex interaction between the virüs and the body immune system. COVID-19 is provoke, the release of pro-inflammatory cytokines. Vitamin D has been found to modulate macrophages' response, preventing them from releasing too many inflammatory cytokines and chemokines. 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 (35).

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 (36). 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 childrens who had deficient and insufficient level of vitamin D (group 1) and COVID 19 diagnosed childrens who had normal level of vitamin (group 2).

To our knowledge, there is no published data regarding using vitamin D in treatment of COVID-19 and the difference it made to outcomes. In our view, randomised controlled trials of vitamin D supplementation for the prevention and treatment of COVID-19 are needed to test for causality.

This study has several limitations. First, it is possible the data may be incomplete or incorrect due to the retrospective study design. Second, during this time some of the clinical parameters may not be able to be assessed in all of the age group eg anosmia

and loss of taste. In addition, 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.

In conclusion, our study is the first to evaluate vitamin D levels and its relationship with clinical findings in pediatric patients diagnosed with COVID-19. There are significantly lower levels of vitamin D in children with COVID-19 than those in the control group. In spite of we don't assume that vitamin D plays a role in the physiopathology of COVID-19 whether there is really an association between vitamin D deficiency and COVID-19 needs to be further addressed. Deficient/insufficient Vitamin D levels are associated with fever. Since there were no reported cases of death in our study, the relationship with vitamin D deficiency and mortality could not be evaluated. 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.

Conflict of Interest

None

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Authors' Contributions and Acknowledgements

KY and VS wrote the manuscript. All authors read and approved the final manuscript.

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Table 1. Comparison of demographic and laboratory characteristics between COVID 19 patient group and healty control subject group

Parameters	**COVID 19 patients (n=40)**	**Healthy Controls (n=45)**	**P**
Age (month)	101.76±27.91	75.68±27.34	0.061

Gender (M/F)	19/21	27/18	0.248
Serum calcium (mg/dL), ref:(8.8-10.6)	9.55±0.61	9.83±0.53	**0.028**
Serum phosphorus (U/L), ref:(2.5-4.5)	4.09±0.73	5.06±0.93	**<0.001**
Alkaline phosphotase (mg/dL), ref:(74-390)	205.80±67.38	197.69±64.71	0.625
Vitamin D levels (µg/L)	13.14 (4.19-69.28)	34.81 (3.8-77.42)	**<0.001**
Parathyroid hormone levels (pg/mL), ref:(14-72)	51.04±14.01	44.90±13.83	0.242

ref: references

Table 2: Comparison of demographic, clinical and laboratory characteristics between COVID 19 diagnosed childrens who had deficient and insufficient level of vitamin D (group 1) and covid 19 diagnosed childrens who had normal level of vitamin (group 2).

Parameters	**Group 1 (n=29)**	**Group 2 (n=11)**	**P**

Age (month)	94.96±38.30	104.56±31.97	0.677
Gender (M/F)	11/18	8/3	**0.049**
Fever >38 °C (n,%)	10 (34.5%)	0 (0%)	**0.038**
Dry cough (n,%)	9 (31%)	1 (9.1%)	0.233
Loss of taste (n,%)	0 (0%)	1 (9.1%)	0.275
Headache (n,%)	6 (20.7%)	3 (27.3%)	0.686
Diarrhea (n,%)	1 (3.4%)	1 (9.1%)	0.479
Sore throat (n,%)	3 (10.3%)	0 (0%)	0.548
Anosmia (n,%)	2 (6.9%)	1 (9.1%)	0.814
Lassitude and fatigue (n,%)	7 (24.1%)	3 (27.3%)	0.838
Vitamin D (µg/L)	10.83(4.19-1 7.69)	24.01 (21.50-69.28)	**<0.001**

PTH (pg/mL)	46.80 (16.46-120.70)	42.10(24.80-78.50)	0.380
Serum calcium(mg/dL)	9.46±0.62	9.80±0.50	0.084
Serum phosphorus(mg/dL)	3.92±0.68	4.55±0.67	**0.013**
Alkaline phosphotase(U/L)	193.24±54.60	238.91±40.60	0.096
CRP (mg/dL), ref:(0.0-0.05)	0.1 (0.02-16.00)	0.07 (0.02-1.08)	0.202
Procalcitonin(ng/mL),ref:(0.0-0.12)	0.001 (0.00-4.80)	0.001 (0.00-0.21)	0.884
D-dimer(mg/dL), ref:(0.08-0.583)	0.31 (0.08-55.10)	0.25 (0.15-1.47)	0.449
Fibrinogen(mg/dL), ref:(170-420)	232.19±67.69	218.52±50.68	0.604
Ferritine	40.20 (3.10-795)	29.20 (4.50-78)	0.112
WBC (10^3/uL)	7.54±2.61	7.60±2.82	0.944
Neutrophil count (10^3/uL)	3.49±1.48	3.29±1.01	0.727
Lymphocyte count (10^3/uL)	3.14±1.26	3.45±1.13	0.700

Body temperatures, °C	36.97±0.66	36.70±0.39	0.203
Respiratory rate	25.72±7.27	21.34±3.41	0.969
Length of hospital stay (in days)	5(1-14)	5(1-7)	0.260
Chest CT findings (n,%)	7 (33.3%)	3 (37.5%)	0.833
PA chest X-ray findings(n,%)	16, (57.1%)	5, 45.5%	0.510

Ref: references, **WBC**: White blood cell, **PTH**: Parathyroid hormone**, CRP:** C-reactive protein, **PA**: posteroanterior, **CT**: computerized tomography

Table 3: The distribution of disease severity according to vitamin D level.

	Asymptomatic	Mild	Moderate	Severe	p
Normal level of vitamin D (n, %)	5 (45.5%)	4 (36.4%)	2 (18.2%)	0 (0%)	0.097
Low level of vitamin D (n, %)	3 (10.3%)	17 (58.6%)	7 (24.1%)	2 (6.9%)	

Table 4. Correlation analysis between Vitamin D levels and laboratory parameters

	r	p
Serum		
Calcium(mg/dL)	0.365	0.021
Phosphorus(mg/dL)	0.364	0.020
Fever	-0.358	0.023