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Original Article *Özgün Araştırma*

THE RELATION BETWEEN SEVERITY OF COVID-19 DISEASE AND VITAMIN D LEVEL IN CHILDREN

Çocuklarda COVİD-19 Şiddeti ile D Vitamini Arasındaki İlişki

Tahir DALKIRAN[1] Sevcan İPEK[2]

[1] *Necip Fazıl City Hospital, Pediatric Intensive Care Unit, KAHRAMANMARAŞ, TÜRKİYE*
[2] *Mustafa Kemal University, Department of Pediatrics, HATAY, TÜRKİYE*

ABSTRACT

Objective: It is suggested that vitamin D regulates the immune response in infectious and autoimmune diseases. In our study, we aimed to compare vitamin D levels in pediatric patients with severity of COVID-19 disease and a healthy control group.

Material and Methods: Retrospectively, we compared the serum vitamin D levels in patients between 1 month and 18 years of age who were followed up with the diagnosis of COVID-19 in the pediatric intensive care unit (PICU) and pediatric ward of Necip Fazıl City Hospital with as a control group healthy children who outpatient between March 2020 and November 2020.

Results: Fifteen pediatric patients hospitalized in the COVID PICU and 25 pediatric patients hospitalized in the COVID pediatric service and 40 children in the healthy control group were included. Vitamin D level in PICU was found to be lower than inward median (min-max) was 11.69 (3-27) ng/mL vs 20.8 (6.3-36.8) ng/mL (p=0.005).

Conclusion: In our study, we showed that vitamin D deficiency may be a risk factor for having severe COVID-19 disease. Vitamin D supplementation can help the treatment of severe clinical disease COVID-19 by balancing the immune system and response to infection.

Keywords: *Child, COVID-19, pandemics, vitamin D*

ÖZ

Amaç: Koronavirüs hastalığı-2019 (COVİD-19) pandemisi küresel olarak büyük bir halk sağlığı sorunu oluşturmaktadır. D vitamininin enfeksiyöz ve otoimmün hastalıklarda bağışıklık yanıtını düzenlediği ileri sürülmektedir. Çalışmamızda COVİD-19 hastalığını hafif, orta ve ağır klinik tabloda geçiren çocuk hastalarda ve sağlıklı kontrol grubunda D vitamini düzeylerini karşılaştırmayı amaçladık.

Gereç ve Yöntemler: Retrospektif olarak Mart 2020 ve Kasım 2020 tarihleri arasında Necip Fazıl Şehir Hastanesi' nde Çocuk Yoğun Bakım Ünitesi' nde ve Çocuk Sağlığı ve Hastalıkları servisinde COVID-19 tanısı ile takip edilen 1 ay ile 18 yaş arası çocuk hastaların serum D vitamini düzeylerini ve kontrol grubu olarak ta poliklinik kontrolüne gelen sağlıklı çocukların serum D vitamini düzeylerini karşılaştırdık.

Bulgular: COVID Çocuk Yoğun Bakım Ünitesi' nde yatan 15 çocuk hasta ve COVID çocuk hastalıkları servisinde yatan 25 çocuk hasta çalışmaya dahil edildi. Sağlıklı kontrol grubunda 40 çocuk çalışmaya dahil edildi. Hasta grupları arasında cinsiyet ve yaş açısından fark yoktu (p>0,05). Çocuk yoğun bakım ünitesinde yatan hastaların 25-OH D vitamini düzeyi; çocuk hastalıkları servisinde yatan hastaların 25-OH D vitamini düzeyinden anlamlı olarak düşük bulundu (median (min-max) 11,69 (3-27) ng/mL ve 20,8 (6,3-36,8) ng/mL idi (p=0,005).

Sonuç: Çalışmamızda D vitamini eksikliğinin COVID-19 u ciddi olarak geçirme açısından bir risk faktörü olabileceğini gösterdik. D vitamini desteği, bağışıklık sistemini ve enfeksiyona cevabı dengeleyerek ağır klinik düzeyde geçirilen COVID-19 hastalığının tedavisinde yardımcı olabilir.

Anahtar Kelimeler: *Çocuk, COVİD-19, pandemi, vitamin D*

Correspondence / Yazışma Adresi: **Dr. Tahir DALKIRAN**
Necip Fazıl City Hospital, Pediatric Intensive Care Unit, KAHRAMANMARAŞ, TÜRKİYE
Phone / Tel: +905303904616 **E-mail** / E-posta: tahirdalkiran@hotmail.com
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INTRODUCTION

The epidemic, defined as coronavirus disease-19 (COVID-19) in Wuhan, China in December 2019, spread all over the world in a short time (1). The World Health Organization declared on March 11, 2020 that it considers this epidemic a global pandemic (2). It has been reported that the virus causes severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), accompanied by complications such as septic shock, and results in high mortality in patients with chronic diseases and elderly patients (3). Although it was stated that children were affected less than adults at the beginning of the pandemic, it was observed that children were also exposed to infection at least as severely as adults (4).

It is suggested that vitamin D regulates the immune response in infectious and autoimmune diseases (5). It has powerful effects on the immune system. Calcitriol, the active form of vitamin D, regulates the production of antimicrobial peptides such as cathelicidin and defensin, which control the natural intestinal flora and support intestinal barriers. Again, the expression of antimicrobial peptides such as defensin and cathelicidin produced in immune system cells such as monocytes, neutrophils and NK cells increases in the presence of vitamin D (6). In addition, connexin-43 in epithelial barriers may protect the lungs against infection by increasing the expression of proteins involved in intercellular junctions such as tight junctions and E-cadherin (7). Studies have shown a relation between the severity of infectious respiratory tract-related diseases such as tonsillopharyngitis, bronchiolitis, pneumonia, and influenza and vitamin D deficiency (8). It is reported that the severity of the disease decreases in respiratory tract infections with the administration of vitamin D (9). In our retrospective study, we aimed to compare the vitamin D levels of pediatric patients with COVID-19 in need of intensive care with a milder clinical picture of pediatric patients with COVID-19 disease and a healthy control group. Thus, we aimed to show how vitamin D affects the course of COVID-19 disease in children. When we scanned the literature, we found that although there are many studies showing a relationship between serum vitamin D level and the clinical course of COVID-19 disease, serum vitamin D levels were not compared between patient groups with mild-severe clinical COVID-19 disease. Therefore, we think that we will contribute to the literature with our study.

MATERIALS AND METHODS

Between March 2020 and November 2020, the records of pediatric patients between 1 month and 18 years of age who were followed up with the diagnosis of COVID-19 in the pediatric intensive care unit and pediatric ward of Necip Fazıl City Hospital were retrospectively scanned. The control group was determined as healthy children aged between 1 month and 18 years who came to the outpatient clinic. Patients whose vitamin D levels were measured were randomly enrolled in the study. Patients with bone metabolism disorders were excluded from the study. Demographic characteristics and 25-OH vitamin D levels of the patients were recorded. 25 - OH Vitamin D level below 20 ng/mL (<50 nmol/L) Vitamin D deficiency, values between 21-29 ng / mL (52.5-72.5 nmol / L) insufficient vitamin D level, values above 30 ng / ml those above were accepted as normal vitamin D levels (10,11). Calcium, phosphorus, alkaline phosphatase and parathyroid hormone levels of the patients were measured. Reference ranges 8.8-10.8 mg/dl for calcium, 1-3 yr 3.8-6.5, 4-11 yr 3.7-5.6, 12-15 yr 2.9-5.4, 16-19 yr 2.7-4.7 mg/ dl for phosphorus, <18 y 33-345 U/L for alkaline phosphatase, 16 to 60 ng/mL for parathyroid hormone (12).

The clinical level of COVID-19 patients was classified as asymptomatic, mild, moderate, severe and severe according to the clinical, laboratory and chest radiography findings of the patients (13). Accordingly, cases with a positive COVID-19 RT-PCR test without clinical and radiological findings are asymptomatic; Patients with upper respiratory tract infection symptoms such as fever, fatigue, myalgia, cough, sore throat, runny nose and normal respiratory system examination are mild; Cases of pneumonia with complaints of fever and cough but without symptoms of dyspnea and hypoxemia or cases with COVID-19 findings on chest computed

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tomography scanning are moderate; severe fever and cough (arterial oxygen saturation <92%) in the early period developing shortness of breath and central cyanosis within one week; Cases with acute respiratory distress or respiratory failure, shock, encephalopathy, myocardial involvement, coagulation disorder and acute kidney injury were classified as critical cases.

Statistical analysis

SPSS version 20.0 statistical package program was used for data analysis. The conformity of the obtained data to normal distribution was examined by visual (histogram and probability graphics) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). In the display of the descriptive statistics of the study, mean ± standard deviation (SD) for continuous numerical variables, minimum-maximum values, number (n) and percentage (%) for categorical variables were used. Chi-square or Fisher test was used to compare categorical variables in comparison of groups. The statistic was evaluated parametrically by means of t-test and one-way ANOVA for normal distribution. The statistical significance limit value was accepted as $p<0.05$. The study was initiated after ethical consent was obtained.

RESULTS

The study included 15 pediatric patients diagnosed with COVID-19 who were followed up in a severe clinical picture in the pediatric intensive care unit, 25 pediatric patients with a mild and moderate clinical picture followed in the COVID pediatric clinic, and 40 healthy children as the control group. The demographical and laboratory data of the patients are shown in table 1. There was no difference between the patient groups in terms of gender and age. When all these 3 groups were compared among themselves in terms of 25-OH vitamin D levels, there was a statistically significant difference between the groups ($p<0.001$). The 25-OH vitamin D level of the patients in the pediatric intensive care unit was found to be significantly lower than the patients in the pediatric ward ($p=0.005$).When control and pediatric patients were compared with each other, there was a statistically significant difference ($p=0.011$). There was no statistically significant difference in the calcium levels of the patients. ($p>0.05$). There was a statistically significant difference between the parathyroid hormone levels, phosphorus and alkaline phosphatase levels of the patients, respectively ($p= 0.04$, $p<0.001$, $p=0.001$). The parathyroid hormone levels of the patients in the intensive care unit were higher. Vitamin D supplementation was provided to patients with vitamin D deficiency and insufficiency in our study.

Table 1: 25-OH vitamin D level and demographical characteristics of the patients.

	Pediatric Intensive Care Unit n=15	Pediatric ward n=25	Control n=40	p*
Sex n(%) (male/female)	9/6	14/11	19/21	>0.05
Age (month) (median (min-max))	60 (4-192)	48 (3-192)	36 (3-204)	>0.05
25-OH D vitamin (ng/L) (median (min-max))	11.69 (3-27)	20.8 (6.3-36.8)	23.7 (16.8-54.1)	<0.001
Calcium mg/dL	10.05 (9.3-10.5)	9.9 (8.3-10.8)	10.1 (9.4-10.9)	>0.05
Fosfor mg/dL	4.35 (2.6-5.1)	3.9 (2.9-5.0)	4.6 (3.2-5.8)	<0.001
Alp U/L	252 (82-859)	78 (43-403)	89 (33-205)	0.001
Parathyroid hormone ng/L (median (min-max))	55 (26-132)	38 (17-78)	48 (28-112)	0.004

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DISCUSSION

In our study, serum vitamin D levels in pediatric patients requiring intensive care due to COVID-19 were found to be statistically significantly lower than those followed in the pediatric ward. In addition, vitamin D levels of patients requiring hospitalization were found to be lower than healthy control patients. In a study conducted by Ye et al. in adult patients with COVID-19, vitamin D levels were found to be lower in patients requiring intensive care, similar to our results (14). Yılmaz et al. and Alpcan et al. showed vitamin D level low in pediatric patients with COVID-19 (15,16). Respiratory viruses such as SARS-CoV-2 are associated with hypercytokinaemia (17). It is an infection initially characterized by cytokine storm causing acute respiratory distress syndrome and macrophage activation syndrome. Immune dysregulation develops after this initial phase, which is the major cause of sepsis-related deaths. The inflammatory response is exacerbated by epithelial and endothelial cell damage and increased viral replication (18). Vitamin D is a fat-soluble hormone that is synthesized mainly in the form of vitamin D3 by ultraviolet rays from sunlight on the skin and, to a lesser extent, directly from the diet as vitamin D2 (ergocalciferol) or D3 (cholecalciferol). The main sources of vitamin D are fatty fish, fish oils, egg yolks, cheese and vitamin D fortified foods. Recently, it has been reported to be involved in immune regulation, fetal development and pulmonary functions (7, 19). It induces the synthesis of antimicrobial peptides such as human beta defensin and cathelicidin from immune system cells such as neutrophils and macrophages, and epithelial cells of the intestinal and respiratory system (20,21). It can inhibit the production of proinflammatory cytokines (22). It can induce the generation of immunosuppressor regulatory T cells (Treg) and release of anti-inflammatory IL-10 from T cells (5,23). Vitamin D exerts an anti-inflammatory effect by reducing T cells so by indirectly reducing inflammatory cytokines and directly inhibiting IFN-γ (24). Vitamin D's immunomodulatory effect may be beneficial in viral infections ve SARS-CoV-2 infections. There is no consensus on the normal values of vitamin D in children and adults. Many studies have reported that the normal range of vitamin D should be 30-100 ng/mL (25). The immunomodulating effect of vitamin D can be achieved optimally within these ranges.

In the study, the parathyroid hormone levels of the in the intensive care unit were found to be higher. An increase in parathyroid hormone levels is an expected situation in vitamin D deficiency. (11). Although there was a statistically significant difference in phosphorus alkaline phosphatase levels, it was found within normal reference ranges.

The limitations of our study are the small number of patients and a retrospective study. Further prospective studies are needed to examine more patient numbers and biochemical parameters.

In our study, vitamin D was found to be lower in patients with severe COVID-19. This may indicate that vitamin D deficiency and insufficiency may have an important role in the prognosis of the disease. Therefore, treating vitamin D deficiency or taking it as a supplement even if vitamin D is not deficient can play a curative role in the disease.

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