

Vitamin D Levels of COVID-19 Positive Symptomatic Pediatric Cases

COVID-19 Pozitif Semptomatik Çocukların D Vitamini Düzeyleri

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Abstract

Introduction: Vitamin D is known as a vitamin but also it acts as a prohormone and has many functions. The aim of this study is to investigate the vitamin D levels in pediatric patients with COVID-19.

Materials and Methods: A retrospective study was performed in a tertiary education and research hospital in İstanbul, Turkey during the period of March to April 2020. Children diagnosed with symptomatic COVID-19 infection were included in the study. Demographic, clinical and laboratory findings were recorded from patient charts retrospectively. All patients investigated for vitamin D levels. Control group consists of healthy children admitted to pediatric outpatient units for routine check-up in the same season. Thirty children with COVID-19 and 82 healthy children included in this study were compared due to 25-OH vitamin D levels.

Results: The median age of COVID-19 positive patients was 11.8 (1.8-17.6) years and the median age of control group was 12.7 (1-16.4) years old. There were 15 (50%) females and 15 (50%) males in infected group and there were 39 (47.5%) females and 43 (52.5%) males control group. Age and gender did not differ among the groups. Median vitamin D level in COVID-19 positive group was 8.9 ng/ml (3-42 ng/ml) and 18.5 ng/ml (9-40.7 ng/ml) in control group. We detected significantly lower vitamin D values in COVID-19(+) group when compared with control group ($p<0.001$). CT was performed in 19 patients in COVID-19 positive group and viral pneumonia was detected in 12 (63%) of 19. pneumonia (+) group a 17.4-years-old female patient and a 13.1-years-old male patient had low phosphorus levels by age (2.2 and 2.4 mg/dl). Both of them needed high flow oxygen therapy. None of the other cases needed oxygen therapy.

Conclusions: This is the first study to date has measured vitamin D levels in children with COVID-19 in Turkey. We detected significantly lower vitamin D values in COVID-19(+) hospitalized children.

Keywords

COVID-19, vitamin D, hypophosphatemia

Anahtar kelimeler

COVID-19, D vitamini, hipofosfatemi

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Öz

Giriş: D vitamini bir vitamin olarak bilinmesine rağmen aynı zamanda bir prohormon görevi görür ve birçok işlevi vardır. Çalışmamızda COVID-19 enfeksiyonu tanısı ile izlenen pediyatrik hastalarda D vitamini düzeylerinin değerlendirilmesi amaçlandı.

Gereç ve Yöntem: Çalışmamız Mart-Nisan 2020 tarihlerinde İstanbul'da bir 3. basamak eğitim ve araştırma hastanesinde gerçekleştirildi. Semptomatik COVID-19 enfeksiyonu tanısı alan çocuklar çalışmaya dahil edildi. Demografik, klinik ve laboratuvar bulgular retrospektif olarak hasta dosyalarından kaydedildi. Tüm hastaların D vitamini seviyeleri değerlendirildi. Kontrol grubu aynı mevsimde pediyatri polikliniğine rutin kontrol için başvuran sağlıklı çocuklardan oluşturuldu. Otuz COVID (+) ve 82 sağlıklı çocuk 25-OH vitamin D düzeyleri açısından karşılaştırıldı.

Bulgular: COVID-19 pozitif hastaların ortanca yaşı 11,8 (1,8-17,6), kontrol grubunun ortanca yaşı 12,7 (1-16,4) idi. Enfekte grupta 15 (%50) kız, 15 (%50) erkek, kontrol grubunda 39 (%47,5) kız, 43 (%52,5) erkek vardı. Yaş ve cinsiyet gruplar arasında farklılık göstermiyordu. COVID-19 pozitif grupta medyan D vitamini seviyesi 8,9 ng/ml (3-42 ng / ml), kontrol grubunda 18,5 ng/ml (9-40,7 ng/ml) idi. COVID19 (+) grupta kontrol grubuna göre istatistiksel olarak anlamlı daha düşük D vitamini düzeyleri saptandı ($p<0.001$). COVID-19 pozitif grupta 19 hastaya BT yapıldı ve 19 hastanın 12'sinde (%63) viral pnömoni tespit edildi. Pnömoni (+) grupta 17,4 yaşında kız hasta ve 13,1 yaşında erkek hastada yaşa göre düşük fosfor seviyeleri (2,2 ve 2,4 mg/dl) bulundu. Her ikisinin de yüksek akımlı oksijen tedavisine ihtiyacı oldu, diğer vakaların hiçbiri oksijen tedavisine ihtiyaç duymadı.

Sonuç: Çalışmamız, Türkiye'de çocuklarda COVID-19 enfeksiyonu ile yatırılarak tedavi edilen olguların D vitamini düzeylerinin araştırıldığı ilk çalışmadır. Yatırılarak tedavi edilen COVID-19 (+) çocuklarda daha düşük D vitamini değerleri tespit ettik.

Introduction

Coronaviruses are positive-stranded RNA viruses which causes 5-10% of all acute upper respiratory tract infections in adults (1). A novel coronavirus was described as the causative agent of viral pneumoniae in a cluster of patients in December, 2019 in China which is named SARS-CoV-2 infection by World Health Organization (WHO) (2). In a short period, the infection has spread all over the world and on 11, March, 2020, WHO declared the situation as a pandemic (3).

Children with SARS-CoV-2 infection usually show mild clinical course, however severe cases have been described (4,5). Risk factors for severe SARS-CoV-2 infection are described as follows; advanced age, chronic renal disease, obesity, smoking, malignancy, chronic lung disease, hypertension, cardiovascular disease and diabetes mellitus (6-8). Most of these risk factors are attributable to adult patient groups. Dong et al. (9). reported 731 COVID-19 laboratory-confirmed cases and 1412 (65.9%) suspected cases and they showed that; over 90% of all patients were asymptomatic, mild, or moderate cases and young children, especially infants, were vulnerable to COVID-19. Little is known about risk factors for children age group.

Vitamin D is known as a vitamin but also it acts as a prohormone and has many functions (10,11). There have been studies on the protective effects of vitamin D in community-acquired pneumonia, interstitial pneumonia, influenza A infections and the regulatory effects on IL-6 and monocyte activation in cytokine storm (12-15). 1,25(OH)₂D₃, the active hormonal form of vitamin D, increases expression of ACE2 which has protective activity on lung injury and reduces interstitial edema, hemorrhage, and the neutrophil count in the lung tissues of rats (16-18).

In COVID-19, cytokine storm is problematic and vitamin D may play a role in COVID-19 by reducing proinflammatory cytokines (19). Ilie et al. (20) observed in their study that there is a negative correlation between levels of mean vitamin D and number of cases of COVID-19 in some of European countries.

As far as we know, no study to date has studied vitamin D levels in children with COVID-19. Because of lack of data, we aimed to investigate the vitamin D levels in children patients with COVID-19.

Materials and Methods

This retrospective descriptive study was conducted in a tertiary education and training hospital in İstanbul, Turkey during the period of March to April 2020. The participants were identified through the pediatrics department's patient files archive (age, sex, laboratory results, CT findings, respiratory support). Thirty patients between 1-18 years age hospitalized with symptomatic SARS-CoV-2 infection included the study. In all patients, diagnosis of COVID-19 infection was confirmed by PCR studied from nasopharyngeal swab. Ethics committee approval was obtained for the study (number 2020/514/176/25). Criteria for inclusion were set as; PCR positivity, 25-OH vitamin D measurement performed during hospitalization, and age between 1-18 years. Vitamin D measurements were done with two-step competitive binding immunoenzymatic assay method. Patients under 1 year-old were not included in the study because they received vitamin D prophylaxis. Asymptomatic cases were excluded. None of the patients in the COVID-19 positive group had any underlying chronic disease or medication that could affect vitamin D levels.

Control group consists of healthy children from middle income families; admitted to pediatric

outpatient units for routine check-up in March-April 2020, with normal body mass index, no chronic diseases and no vitamin D replacement at the time of the examination. Cases using steroids or antiepileptic drugs that may affect vitamin D metabolism were not included in the control group.

Body mass index standard deviation scores of the patients were grouped as <-2 SD low body weight, $>+1$ SD overweight and $>+2$ SD obesity.

According to algorithms of 'Global Consensus Recommendations on Prevention and Management of Nutritional Rickets' classification of vitamin D status is defined as sufficiency >20 ng/ml, insufficiency 12-20 ng/ml, deficiency <12 ng/ml and we implemented oral Vitamin D 3000 IU <12 years and 6000 IU >12 years children who had low vitamin D levels (21).

Statistical Analyses

Statistical analyses were performed using the SPSS software version 21. The variables were investigated using visual (histogram, probability plots) and analytic methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to determine whether or not they are normally distributed. Descriptive analyses were presented using proportions, medians, minimum, and maximum values as appropriate. Chi square test was used to compare proportions. The Mann-Whitney U test was used to compare the non-normally distributed variables between two groups. A p-value of less than 0.05 was considered to show a statistically significant result.

Results

Thirty children with COVID-19 and 82 healthy children included in this study were compared due to 25-OH vitamin D levels.

The mean age of COVID-19 positive patients was 10.48 ± 4.75 (min-max: 1.8-17.6) years and the

mean age of control group was 10.43 ± 4.81 (min-max: 1-16.40) years old. There were 15(50%) females and 15(50%) males in infected group and there were 39(47.5%) females and 43(52.5%) males control group. Age, gender and the body mass indexes did not differ among the groups and were summarized in Table 1.

The most common presenting complaints were fever 46.6% (n=14), cough 26.6% (n=8), and dyspnea 13.3% (n=4). Two patients (2%) had sore throat and two patients (2%) had lack of taste and two patients (2%) had headache.

Median vitamin D level in COVID-19 positive group was 8.9 ng/ml (3-41.12 ng/ml) and 18.5 ng/ml (9-40.7 ng/ml) in control group. We detected significantly lower vitamin D values in COVID19(+) group when compared with control group ($p<0.000$).

Comparison of age, gender, vitamin D levels, body mass index of positive group and control group according to COVID-19 constant were summarized in Table 2.

CT was performed 19 patients in COVID-19 (+) group and viral pneumonia was detected in 12(63%) of 19. The median age of pneumonia (+) group was 12.8 years (8.4-17.6) and the median age of pneumonia (-) group was 8.2 years (1.8-16.5). The median age of the group with pneumonia was statistically significantly higher ($p=0.02$).

Vitamin D level of pneumonia (+) group was 8.4ng/ml (3-16.5) and was 9.8 (ng/ml (3-41) in pneumonia (-) group. In pneumonia (+) group vitamin D level was lower but there was not statistically difference ($p=0.49$). However in pneumonia (+) group a 17.4-years-old female patient and a 13.1-years-old male patient required respiratory support, vitamin D levels of these two patients were 3 ng/ml and 3,6 ng/ml. Although they had low phosphorus levels by

Table 1. Age, gender, vitamin D levels and body mass index characteristics of the groups

Variables	B	p	Odd ratio	95% CI for EXP β (B) Lower-Upper
Vitamin D	0.222	0.000	1.249	1.129- 1.38
BMI-SDS	0.021	0.936	1.021	0.616 -1.69
Gender	-0.139	0.784	0.870	0.322- 2.34
Age	0.084	0.161	1.088	0.967-1.22
COVID-19 (constant)	-2.971	0.019	0.051	

BMI-SDS: Body mass index standard deviation score

age(2.2 and 2.4 mg/dl) and no other cause was found that could lead to low phosphorus levels. Both of them needed high flow oxygen therapy. None of the other cases needed oxygen therapy.

Discussion

Some of studies reported the association between vitamin D level and viral infections. A study evaluating Indian children found that acute lower respiratory infection was significantly higher among children with vitamin-D deficiency in a six-month follow-up time (22). Banajeh investigated 79 cases between 2-59 months and found that vitamin D deficiency was associated with reduced circulating neutrophils and hypoxemia (23). Yao et al. reported two severe cases of H7N9 pneumoniae with Vitamin D insufficiency (24). In our study, we found 21(70%) children with vitamin D deficiency and 7 (23.3%) had insufficiency and vitamin D levels were lower than the control group. Two children who required respiratory support had the vitamin D level of 3 ng/ml and 3,6 ng/ml. In addition, these 2 patients had low phosphorus levels by age (2.2 and 2.4 mg/dl). Our small-scale study results suggest that vitamin-D deficiency is associated in children with COVID-19, however further studies are needed with more number of patients.

Beyond the studies evaluating association between Vitamin D deficiency and infections, some of studies investigate the effect of Vitamin D supplementation on infections. Arihiro et al. showed that the incidence of upper respiratory infection was significantly lower in the vitamin D group, however the incidence of influenza did not differ (10). On the other hand, Urashima et al. reported that vitamin D (3) supplementation during the winter may reduce the incidence of influenza A, especially in schoolchildren (25). Similarly Camargo et al. showed that Vitamin D supplementation significantly reduced the risk of acute respiratory infections in Mongolian children with vitamin D deficiency (26). In our study, we measured the Vitamin D level in children with COVID-19 and we implemented oral Vitamin D 3000 IU<12 years and 6000 IU>12 years children who had Vitamin D deficiency. Children with vitamin D deficiency treated according to the 'Global Consensus Recommendations on Prevention and Management of Nutritional Rickets' (21).

To the date, various studies investigated vitamin D levels of healthy children in Turkey. In a study performed in Turkey, Ozhan et al. (27) found vitamin D deficiency of 39.3% in a large study group aged between 0-18 years and Akman et al. (28) found vitamin D deficiency of %8 and insufficiency of 25.5%

Table 2. Comparison of age, gender, vitamin D levels, body mass index of positive group and control group according to COVID-19 constant

	COVID-19 (+)	COVID (-)	p
Age (years)			
Mean ± SD	10.48±4.75	10.43±4.81	0.91
Min-max	(1.8-17.6)	(1-16.40)	
Gender n(%)			
Female	15 (50)	39 (47.5)	0.49
Male	15 (50)	43 (52.5)	
D vitamin (ng/ml)			
Median (IQR)	8.9 (7.26-12.80)	18.52 (14.31-24.03)	0.000
Min-max	(3-41.12)	(9-40.7)	
BMI			
Median (IQR)	0.25 (-0.31 - 1.20)	0.39 (-0.43-0.90)	0.679
Min-max	(-1.65 - 2.84)	(-1.96- 1.88)	
BMI group n (%)			
Normal	21 (70)	63 (76.8)	0.061
Overweight	7 (26.9)	19 (23.2)	
Obese	2 (6.7)	0 (0)	

BMI: Body Mass index, BMI-SDS: Body mass index standard deviation score

in healthy children aged 1-16. In our study, vitamin D deficiency in the COVID-19 (+) group was found in 21/30 cases (70%), and insufficiency in 7/30 (23.3%) of cases. Two cases (6.6%) had vitamin D levels in normal range.

In the review of Silva and Furlanetto, they suggest that the 25(OH)D measured during acute-phase response should be evaluated with attention as if it decreases during acute-phase (29). If vitamin D acts as a negative acute-phase reactant, supplementation of vitamin D is not going to benefit, but we think further studies are needed to strengthen this opinion. Because of vulnerable children patient group in our study, we gave supplementation of vitamin D to children who showed decreased level of vitamin D. Ebadi and Montano-Loza suggest in their article that level of vitamin D should be measured in patients with COVID-19 and they recommend vitamin D supplementation of 50,000 IU twice a week at the diagnosis (100,000 IU total) to patients whom have decreased Vitamin D levels (below 20 ng/ml) [28]. Because of lack data about vitamin D supplementation in children with COVID-19 we implemented oral Vitamin D 3000 IU <12 years and 6000 IU >12 years according to algorithms of 'Global Consensus Recommendations on Prevention and Management of Nutritional Rickets'(30).

Conclusion

In our study 28 (93.3%) of 30 COVID(+) children had vitamin D replacement due to deficiency or insufficiency. All the children in our study cured and showed good clinical improvement. But it is difficult to say that this favorable clinical response is contributed to Vitamin D supplementation because they also had supportive and medical therapy.

Ethics

Ethics Committee Approval: This article does not contain any studies with human participants or animals performed by any of the authors. This study was approved by the local medical ethical committee, and all data was processed anonymously, according to the privacy legislation.

Conflict of Interest: The authors declare that they have no conflict of interest.

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