ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

The Relationship Between System Involvement and Vitamin D Level in Cases Diagnosed with Multisystem Inflammatory Syndrome in Children

Multisistemik Enflamatuvar Sendrom Tanılı Olgularda Sistem Tutulumlarının D Vitamini Düzeyi ile İlişkisi

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Abstract

Introduction: Vitamin D is a steroid prehormone that is produced in the skin as a result of exposure to UV-B, is fat-soluble and has immunomodulatory properties by affecting immune cells. In this study, it was aimed to evaluate the relationship between systemic involvement and 25-OH vitamin D level in patients with a diagnosis of MIS-C.

Materials and Methods: It is a descriptive research. It was conducted at AFSÜ, Health Application and Research Center between 01.10.2020-01.04.2022. Patients aged between 1 month and 18 years who were diagnosed with MIS-C and who applied to AFSU, Child Health and Diseases Clinic, and whose serum 25-OH vitamin D was in the electronic archive system, were included in this study. The collected data were analyzed with the Statistical Package for Social Sciences version 26.0. It was done with the S package program.Since vitamin D was not distributed normally, the Mann-Whitney U test was used when comparing between paired groups. The Kruskal Wallis test was used when comparing vitamin D levels between more than two groups.

Results: This retrospective study was conducted with 34 patients diagnosed MIS-C. The mean age of the cases was 7.03±3.9 years; 52.9% (n=18) were males and 47.1% (n=16) were females. Gastrointestinal system (58.8%; n=20), cardiac (64.7%; n=22) and neurological involvement (23.5%; n=8) were found. Mean 25-OH vitamin D were found to be 15.7 (IQR= 18) ng/mL in gastrointestinal system, 16.8 (IQR=17) ng/mL in cardiac, and 12 (IQR= 8) ng/mL in neurological system involvement. No statistically significant differences were found between systemic involvement of the cases and their 25-OH vitamin D (p values: 0.779, 0.957, 0.144, respectively). A negative correlation was found between 25-OH vitamin D of the cases and their age (r=-0.414; p=0.015). When the relationship between 25-OH vitamin D and fibrinogen in patients diagnosed with MIS-C was evaluated, a negative correlation was also found (r=-0.414; p=0.015).

Conclusion: As a result, mean 25-OH vitamin D levels in cases diagnosed with MIS-C were found to be at an insufficient level. It was suggested that prophylactic vitamin D should be administered in children. In addition, no significant difference was found between system involvement and vitamin D level.

Keywords
MIS-C, 25-OH vitamin D, COVID-19, SARS-CoV-2.

Anahtar kelimeler
MIS-C, 25-OH vitamin D, COVID-19, SARS-CoV-2

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Öz

Giriş: D vitamini, ultraviole B ışınlarına maruz kalma sonucu ciltte üretilen, yağda çözünen ve bağışıklık hücrelerini etkileyerek immünomodülatör özelliği olan steroid ön hormondur. Bu çalışmada Multisistemik inflamatuar sendrom (MIS-C) tanılı hastaların sistemik tutulumları ile 25-OH vitamin D düzeyi arasındaki ilişkinin değerlendirilmesi amaçlandı.

Gereç ve Yöntem: Tanımlayıcı bir araştırmadır. Afyonkarahisar Sağlık Bilimleri Üniversitesi, Sağlık Uygulama ve Araştırma Merkezi'nde 01.10.2020-01.04.2022 tarihleri arasında yürütüldü. Bu araştırmaya AFSÜ, Çocuk Sağlığı ve Hastalıkları Kliniği'ne başvuran MIS-C tanısı almış olan 1 ay-18 yaş arasındaki hastalardan serum 25-OH vitamin D düzeyi eletronik arşiv sisteminde olan hastalar dahil edildi. Toplanan veriler Statistical Package for Social Sciences versiyon 26.0 (SPSS IBM, Armonk, NY, Amerika Birleşik Devletleri) ile analiz edildi. S paket programı ile yapıldı. Kategorik değişkenler yüzde ve frekanslar ile sunuldu. Sürekli değişkenlerin normal dağılıma uygunluğu Shapiro Wilk testi ve görsel histogramlar ile kontrol edildi. Normal dağılan sürekli değişkenler ortalama±standart sapma olarak, normal dağılmayan sürekli değişkenler ise ortanca ve çeyrekler-arası aralık (IQR=interquartile range) olarak ifade edildi. D vitamini normal dağılmadığı için ikili gruplar arasında karşılaştırılırken Mann-Whitney U testi kullanıldı. İkiden fazla grup arasında D vitamini düzeyi karşılaştırılırken Kruskal Wallis testi kullanıldı. Anlamlılık düzeyi $p<0.05$ olarak kabul edildi. 25-OH vitamin D ile laboratuvar değerleri arasındaki korelasyon için Spearman korelasyon testi kullanıldı.

Bulgular: Bu retrospektif çalışma MIS-C tanılı 34 hasta ile yapıldı. Olguların yaş ortalaması 7.03±3.9, %52.9 (n=18)'u erkek, %47.1 (n=16)'i ise kız idi. Olgularda gastrointestinal sistem tutulum (%58.8;n=20), kardiyak tutulum (%64.7;n=22), nörolojik tutulum (%23.5;n=8) olduğu tespit edildi. Ortalama 25-OH vitamin D düzeyleri; gastrointestinal sistem tutulumu olanlarda 15.7 (IQR= 18) ng/mL, kardiyak tutulumu olanlarda 16.8 (IQR= 17) ng/mL, nörolojik sistem tutulumu olanlarda 12 (IQR= 8) ng/mL saptandı. Olguların sistem tutulumları ile 25-OH vitamin D düzeyleri arasında istatiksel olarak anlamlı fark saptanmadı.(p değerleri sırasıyla; (p= 0.779), (p= 0.957), (p=0.144).) Olguların 25-OH vitamin D düzeyleri ile yaş arasındaki ilişki değerlendirildiğinde negatif bir korelasyon saptandı. (r=-0.414; p=0.015) MIS-C tanılı olguların 25-OH vitamin D düzeyleri ile fibrinojen arasındaki ilişki değerlendirildiğinde negatif bir korelasyon saptandı. (r=-0.414; p=0.015)

Sonuç: Sonuç olarak MIS-C tanılı olgularda 25-OH vitamin D düzeyi ortalaması yetersizlik seviyesinde olduğu saptandı. Çocuklarda profilaktik D vitamini yapılması gerektiği düşünüldü. Sistem tutulumlarının D vitamini ile ilişkisi incelendiğinde anlamlı bir fark bulunmadı.

Introduction

The coronavirus disease first appeared in late 2019 and was declared as a pandemic in March 2020. During this period, many studies have been initiated to understand the disease and to find an effective and an appropriate treatment (1). Although children and adolescents are as susceptible to infection by Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) as adults, COVID-19 disease rarely causes serious illness among them. However, a proportion of children suffer from a life-threatening condition following 4-6 weeks of primary COVID-19 infection, so-called multisystemic inflammatory syndrome (MIS-C) (2). Multisystemic inflammatory syndrome was first described in the United Kingdom in April 2020. The Pediatric Intensive Care Association issued an alert describing a recognized increase in inflammation and evidence of SARS-CoV-2 infection among the critically ill patients admitted with hyperinflammatory shock. The United States Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) have issued case definitions for multisystemic inflammatory syndrome. The incidence of MIS-C in populations with COVID-19 infection is 5.1 in 1.000.000 (3). All of the definitive case criteria must be met for multisystemic inflammatory syndrome. Exact case criteria were identified by CDC, WHO.

1,25 dihydroxy vitamin D, also known as calcitriol, is the active form of vitamin D. When interacting with the vitamin D receptor gene (VDR) on the immune system (B cells, T cells, and antigen presenting cells) and in pulmonary epithelial cells, the calcitriol-VDR complex induces the transcriptional expression of antimicrobial peptides such as cathelicidins and defensins (4). Cathelicidins serve to disrupt bacterial cell membranes as well as enveloped viruses such as SARS-CoV-2, while defensins promote chemotaxis of inflammatory cells through increased capillary permeability. Although vitamin D promotes the expression of various inflammatory cytokines through T cell inactivation and interferon-γ activation, it simultaneously downregulates the proinflammatory markers as interleukin-6 and tumor necrosis factor-α. According to this study, it can be said that cases with 25-OH vitamin D deficiency have a high risk of developing more severe symptoms and/or worse prognosis of

COVID-19 (5). In this study, it was aimed to evaluate the relationship between systemic involvement of patients with multisystemic inflammatory syndrome (MIS-C) and their 25-OH vitamin D levels.

Among the patients who admitted to Afyonkarahisar Health Sciences University, who were aged between 1 month-18 years old and diagnosed with MIS-C and those who had a recorded serum 25-OH vitamin D level in the electronic archive system were included in the study. The MIS-C definition of the patients was made according to the clinical guidelines of the American Academy of Pediatrics, WHO and CDC (6). Patients under 1 month and over 18 years of age, patients whose serum 25-OH vitamin D level has not been studied, patients who did not fully meet the diagnostic criteria of MIS-C, patients with a chronic disease (asthma, diabetes, tuberculosis, juvenile idiopathic arthritis, chronic renal failure, hematological and oncological diseases), patients receiving immunosuppressive treatment or taking medications continuously and patients who have received vitamin D therapy in the last 3 months were excluded from the study.

Echocardiographic findings included cardiac function, coronary artery abnormalities, cardiac valve insufficiency, and pericardial effusion. Standard echocardiographic parameters such as left ventricular ejection fraction (LVEF) assessed by two methods (Simpson biplane and M-mode methods), spectral doppler mitral inflow peak velocities, early diastolic septal and lateral mitral ring peak velocities assessed by tissue doppler imaging (TDI), tricuspid circular plane systolic excursion (TAPSE) and lateral tricuspid circular peak velocity assessed by TDI (TAPSV) were included. Coronary arteries were evaluated according to the American Heart Association (AHA) Guidelines for Kawasaki disease (7). Abnormalities were classified using the Boston z-score system. When the coronary artery Z-score was between +2.0 and +2.5, it was defined as mild coronary dilatation. The treatments of patients diagnosed with MIS-C were arranged according to the criteria determined by the American Society of Rheumatology and Erciyes MIS-C guidelines (8-10).

Material and Methods

Data Collection Technique and Tools

Patients aged between 1 month and 18 years who were diagnosed with MIS-C and who were retrospectively admitted to Afyonkarahisar Health Sciences University, Child Health and Diseases Clinic, and whose serum 25-OH vitamin D level was in the electronic archive system were included in this study retrospectively. The data of the patients diagnosed with MIS-C were accessed from the hospital electronic archive system (Nucleus-HBYS). A separate data form was created for each patient; and their demographic characteristics, diagnoses, fever history and duration, age, gender, 25-OH vitamin D, inflammation markers (C-reactive protein level, ferritin, lactate dehydrogenase), platelet, albumin, amylase, lipase, GGT, total bilirubin, direct bilirubin, creatinine kinase, INR, troponin-T and CK-MB, presence and characteristics of gastrointestinal findings, presence of cardiac findings and characteristics, treatments of given, serum 25-OH vitamin D levels, echocardiographic findings, abdominal ultrasonography and computed tomography imaging findings were recorded. Ethics committee approval was taken from Afyon Health Sciences University Clinical Research Ethics Committee (date: 04.01.2022, approval number: 2022/4).

RT-PCR test

Combined nasopharyngeal and oropharyngeal swab samples were collected from children with suspected COVID-19 and they were sent to the medical microbiology laboratory. A rapid antibody test was used to detect SARS-CoV-2 immunoglobulin (Ig) M and G (Nadal COVID-19 IgM/IgG Rapid Test). , BioServUK Ltd., UK).

Evaluation of Serum Vitamin D Level

25-OH vitamin D level was measured by electrochemiluminescence immunoassay (ECLIA) method. Vitamin D levels of the patients were considered as adequate at >20 ng/ml, inadequate between 12-20 ng/ml and deficient at <12 ng/ml (11).

Statistical Analysis

Collected data were analyzed with the Statistical Package for Social Sciences version 26.0 (SPSS IBM, Armonk, NY, United States). S package program was used. Categorical variables were presented with percentages and frequencies. Normality assumption of continuous variables was carried out with the Shapiro Wilk test and visual histograms. Normally distributed continuous variables were expressed as mean±standard

deviation, and non-normally distributed continuous variables were expressed as median and interquartile range (IQR=interquartile range). Since vitamin D was not normally distributed, Mann-Whitney U test was used when comparing the two groups. The Kruskal Wallis test was used when comparing vitamin D levels between more than two groups. Significance level was accepted as $p<0.05$. Spearman correlation test was used to analyze the correlation between 25-OH vitamin D and laboratory values.

Results

This study was conducted with 34 patients diagnosed with MISC. 52.9% (n= 18) of the cases were males and 47.1% (n= 16) were females. Mean age of the cases was 7.03±3.9 years old. The clinical, radiological and echocardiographic characteristics of the patients were shown in Table 1, and their laboratory characteristics were shown in Table 2.

There was a history of contact with COVID-19 in 82.4% (n= 28) of the cases, and 11.8% (n= 4) had SARS-Co-V PCR positivity in the nasal swab, and 35.3% (n= 12) had positive SARS CoV IgG serology. When the clinical classification of the cases was made, 82% (n= 28) were evaluated as having mild, 8.8% (n= 3) as moderate and 8.8% (n=3) as severe MIS-C. When the systems, signs and symptoms of the cases were evaluated; mucocutaneous (73.5%; n=25), cardiac (64.7%; n=22), mesenteric lymphadenopathy (61.8%; n=21), gastrointestinal (58.8%; n=20), limb edema (32.4%; n=11) and neurological (23.3%; n=8) involvement were observed. Fever symptoms were also observed in all patients (100%; n=34). It was determined that the duration of fever was longer than 72 hours in 91.1% of patients with symptoms, and longer than 24 hours in 8.8%.

It was determined that all MIS-C cases were treated with human immunoglobulin, acetylsalicylic acid and proton pump inhibitor. It was observed that acetylsalicylic acid was given to 67.6% (n=23) at 5 mg/kg dose and to 32.4% (n= 11) at 50 mg/kg dose. Antibiotic treatments of the cases were given as cefuroxime axetil (73.5%; n= 25), vancomycin (73.5%; n= 25), metronidazole (64.7%; n= 22), meropenem (29.4%; n= 10), amikacin (17.6%; n= 6) and ampicillin-sulbactam (5.9%; n= 2). It was observed that methylprednisolone was administered at a dose of 2 mg/kg in 85.3% (n=29) and at a dose of 10mg/kg in 14.7% (n=5). 11.7% (n=4) of the cases also needed inotropes; and they received dopamine infusion (8.8%; n=3) and adrenaline infusion (2.9%; n=1) as inotropic treatment. It was observed that low molecular weight heparin (enoxaparin sodium) treatment was given to the cases (38%; n=13). It was also observed that fresh frozen plasma (70.6%; n= 24), albumin (38.2%; n= 13), vitamin K (17.6%; n= 6) were given to the cases. The treatment characteristics of patients diagnosed with MIS-C are shown in Table 3.

When the distribution of the cases with mucocutaneous involvement was evaluated, conjunctivitis (55.9%; n=19), strawberry tongue (52.9%; n=18) and rash (58.8%; n= 20) were found. Mean 25-OH vitamin D levels of the cases were found to be 15.3 (IQR= 11) ng/mL in those with mucocutaneous involvement and 20 (IQR= 20) ng/mL in those without mucocutaneous involvement.

Table 1. Clinical, radiological and echocardiographic characteristics of the patients diagnosed with MIS-C

Symptom	**(n; %)**
Fever	34; 100
Duration of fever > 24 hours	3; 8.8
Duration of fever > 72 hours	31; 91.1
Rash	20; 58.8
Conjunctivitis	19; 55.9
Strawberry tongue	18; 52.9
Abdominal pain	27; 79.4
Diarrhea	9; 26.5
Vomiting	10; 29.4
Headache	8; 23.5
Change of consciousness	3; 8.8
Abdominal ultrasonographic findings	**(n; %)**
İleitis	16; 47.1
Free fluid in the abdomen	20; 58.8
Mesenteric lymphadenopathy	23; 67.6
Transient invagination	2; 5.9
Echocardiographic findings	**(n; %)**
Dilatation of coronary artery	19; 55.9
Pericardial effusion	11; 32.4
Valve anomaly	9; 26.5
Enlargement in left spaces	6; 17.6
Myocarditis	5; 14.7
Aneurysm	5; 14.7

MIS-C: Multisystem inflammatory syndrome in children

Table 2. Laboratory characteristics of MIS-C patients	
Laboratory parameter	**Mean ± SD; IQR, (lower-upper limits)**
Leukocyte (mcL)	13.081±6945; (12.053); (4000-10.000)
Lymphocyte (mcL)	1195±1500; (1680); (1.200-4000)
Thrombocyte (mEq/L)	241±132; (178.8); (160.000-370.000)
Sodium (mEq/L)	133.5±3.9; (132.5); (135-145)
Albumin (g/dL)	3.65±0.5; (3.6); (3.5-5.2)
LDH (U/L)	324±117.5; (115); (135-225)
Amilase (U/L)	43±168.4; (37); (28-100)
Lipase (U/L)	28.5±179.2; (39); (13-60)
AST (U/L)	72.1±139.1; (27); (5-41)
ALT (U/L)	55.3±95; (36); (5-40)
GGT (U/L)	18±54.1; (13); (5-60)
ALP (IU/mL)	148.5±67.3; (77); (35-130)
Total bilirubin (mg/dL)	0.57±0.8; (0.21); (0.3-1.2)
Direct bilirubin (mg/dL)	0.32±0.7; (0.13); (0-0.3)
Creatine kinase (U/L)	93.67±91.1; (61); (0-190)
Sedimentation (mm/saat)	56.7±24.6; (34); (1-15)
CRP (mg/L)	32.39±62.1; (13.5); (0-5)
Fibrinogen (mg/dL)	493.8±121.8; (166); (200-400)
INR	1.08±0.09; (0.14); (0.8-1.25)
D-dimer (ng/L)	4.41±2.28; (4.72); (0-0.5)
Troponin-T (ng/mL)	0.015±0.017; (0.007); (0-0.014)
CK-MB (pg/mL)	1.81±2.64; (1.14); (1.72-6.22)
Pro-BNP (pg/mL)	4313.3±7657; (2949); (0-125)
Vitamin D (ng/mL)	18.92±13.3; (14); (15-20)

MIS-C: Multisystem inflammatory syndrome in children, IQR: Inter quantile range, LDH: Lactate dehydrogenase, U/L: unit/ liter, LDH: Lactate dehydrogenase, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma glutamyl transferase, ALP: Alkaline phosphatase, CRP: C-reactive protein, INR: International normalized ratio, CK-MB: Creatine kinase-MB, Pro-BNP: pro-B-type natriuretic peptide

When the mean 25-OH vitamin D levels were compared in cases with and without mucocutaneous involvement, no statistically significant difference was found (p= 0.545) (Figure 1).

At least one cardiac pathology was detected in 67.6% (n= 23) of the cases with cardiac involvement in the echocardiographic assessment. Coronary artery dilatation (55.9%; n=19), pericardial effusion (32.4%; n= 11), valve anomaly (26.5%; n= 9), left cavities enlargement (17.6%; n=6), myocarditis (%) 14.7; n= 5) and aneurysm (14.7%; n= 5) were observed among the cases. Mean 25-OH vitamin D levels of the cases were found to be16.8 ng/mL (IQR=17) in cases with cardiac involvement, and 14.27 ng/mL (IQR= 11) in cases without cardiac involvement. When the mean 25-OH vitamin D levels were compared in cases with and without cardiac involvement, no statistically significant difference was found (p= 0.957) (Figure 2).

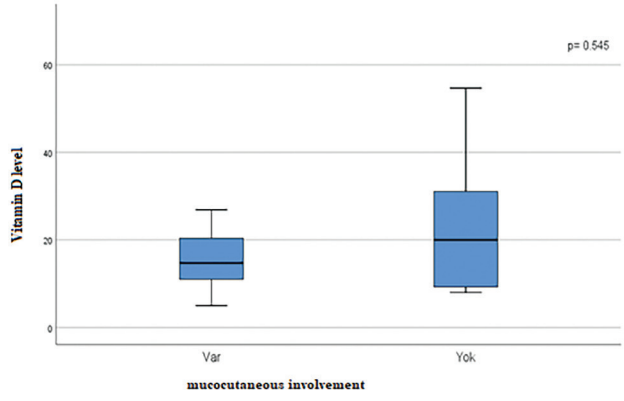

Figure 1. The comparison of mean 25-OH vitamin D levels based on the presence of mucocutaneous involvement

While mean 25-OH vitamin D level was 15.3 ng/mL (IQR= 23) in cases with mesenteric lymphadenopathy, it was 16.1 ng/mL (IQR=12) in cases without mesenteric lymphadenopathy. When mean 25-OH vitamin D levels were compared in cases with and without mesenteric lymphadenopathy, no statistically significant difference was found (p= 0.901) (Figure 3).

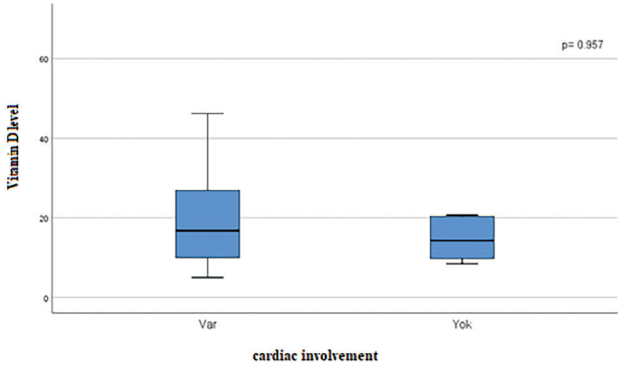

Figure 2. The comparison of mean 25-OH vitamin D levels based on the presence of cardiac involvement

Table 3. Treatment characteristics of patients diagnosed with MIS-C	
Treatment	**(n; %)**
Human immunoglobulin	34; 100
Methylprednisolone (2mg/kg)	29; 85.3
Methylprednisolone (20mg/kg)	5; 14.7
Acetylsalicylic acid (5mg/kg)	23; 67.6
Acetylsalicylic acid (50mg/kg)	11; 32.3
Albumin	13; 38.2
Fresh frozen plasma	24; 70.6
Vitamin K	6; 17.6
Dopamine infusion	3; 8.8
Adrenalin infusion	1; 2.9
Low molecular weight heparin (Enoxaparin sodium)	13; 38
Antıbıotherapy	(n; %)
Cefuroxime axetil	25; 73.5
Vancomycin	25; 73.5
Metronidazole	22; 64.7
Meropenem	10; 29.4
Amikacin	6; 17.6
Sulbactam- ampicillin	2; 5.9
MIS-C: Multisystem ınflammatory syndrome in children	

When the gastrointestinal system involvement of the cases was evaluated, abdominal pain (79.4%; n= 27), vomiting (29.4%; n= 10) and diarrhea (26.5%; n= 9) were detected. Mean 25-OH vitamin D level of the cases was found to be 15.7 ng/mL (IQR= 18) in the cases with gastrointestinal system involvement and 16.3 ng/mL (IQR= 11) in the cases without gastrointestinal involvement. When mean 25-OH vitamin D levels of cases with and without gastrointestinal system involvement were compared, no statistically significant difference was found (p= 0.779) (Figure 4).

While mean 25-OH vitamin D level was found as 14.1 ng/mL (IQR=13) in cases with extremity edema, it was 16.1 ng/mL (IQR=18) in cases without limb edema. When mean 25-OH vitamin D levels were compared in cases with and without extremity edema, no statistically significant difference was found (p= 0.912) (Figure 5).

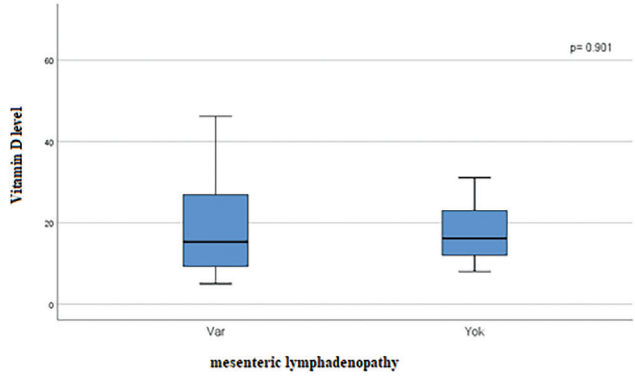

Figure 3. The comparison of mean 25-OH vitamin D levels based on the presence of mesenteric lymphadenopathy

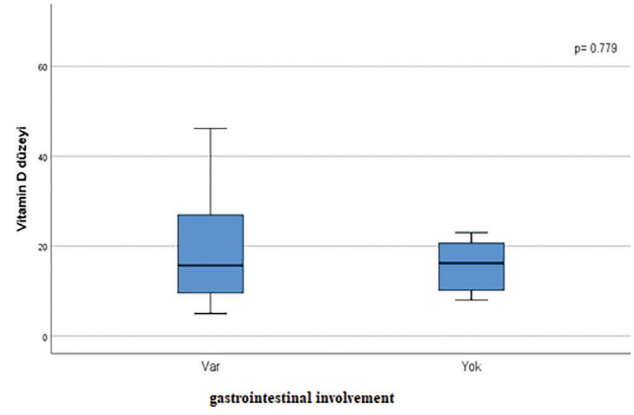

Figure 4. The comparison of mean 25-OH vitamin D levels based on the presence of gastrointestinal involvement

Headache (23.5%; n=8) and altered consciousness (8.8%; n= 3) were found in cases with neurological involvement. While mean 25-OH vitamin D levels were 12 ng/mL (IQR= 8) in cases with neurological involvement, it was 18.3 ng/mL (IQR= 18) in cases without neurological involvement. When mean 25-OH vitamin D levels were compared in cases with and without neurological involvement, no statistically significant difference was found (p=0.144) (Figure 6).

Considering 25-OH vitamin D levels of the cases, they were found to be <12 ng/mL in 38.2% (n= 13), 12-20 ng/mL in 23.6% (n=8) and >20 ng/mL in 38.2% (n= 13). Figure 7 shows the distribution of cases based on their 25-OH vitamin D levels.

Correlation analysis was performed between 25-OH vitamin D levels and age, CRP, lymphocyte count, fibrinogen, D-dimer, albumin, sodium and leukocyte counts. Vitamin D levels were found to have a statistically significant, moderately strong negative correlation with age and fibrinogen (Figures 8 and 9).

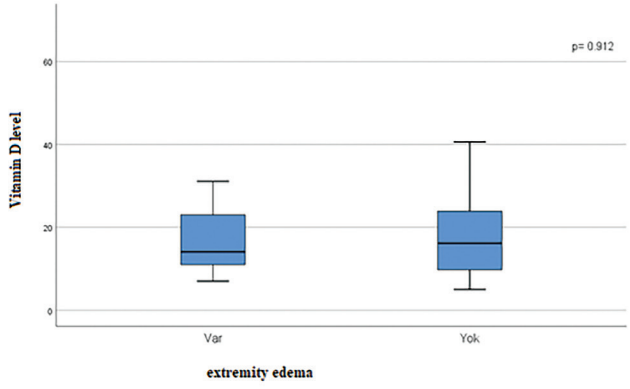

Figure 5. The comparison of mean 25-OH vitamin D levels based on the presence of extremity edema

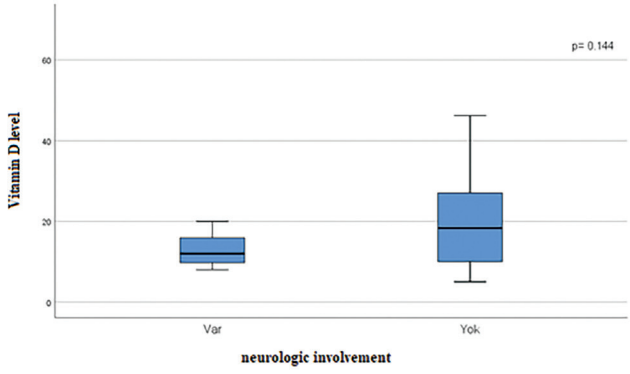

Figure 6. The comparison of mean 25-OH vitamin D levels based on the presence of neurological involvement

Table 4 shows the correlation between vitamin D and other parameters.

In our study, 3 patients received treatment in the pediatric intensive care unit and those all patients were covered well.

Discussion

In this study, we aimed to evaluate the relationship between system involvement rates and 25-OH

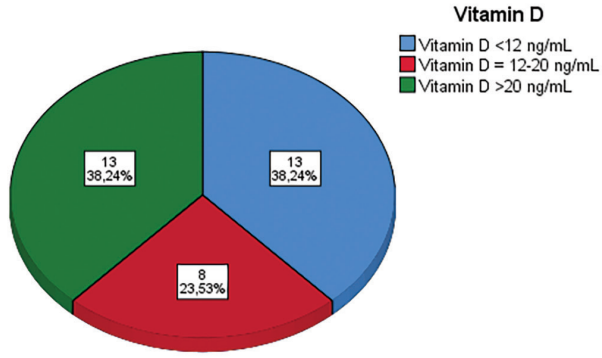

Figure 7. The distribution of 25-OH vitamin D levels of the cases

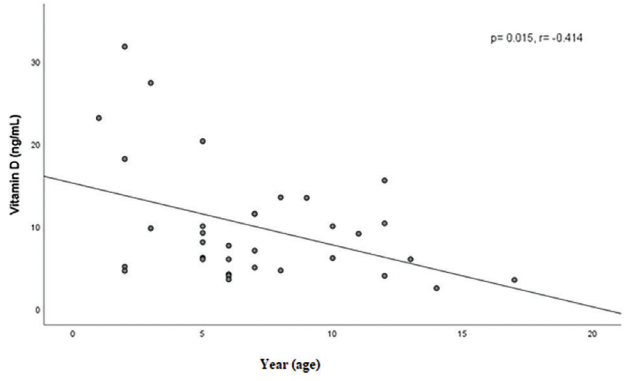

Figure 8. The correlation between 25-OH vitamin D level and age

Table 4. The correlations of 25-OH vitamin D levels with age and several parameters

Parameters	p and r values
25-OH vitamin D- Age	**0.015; -0.414**
25-OH vitamin D- CRP	0.680; 0.073
25-OH vitamin D - Lymphocyte	0.513; 0.116
25-OH vitamin D -Fibrinogen	**0.004; -0.482**
25-OH vitamin D -D-Dimer	0.983; -0.004
25-OH vitamin D -Albumin	0.662; 0.078
25-OH vitamin D -Sodium	0.817; 0.041
25-OH vitamin D -Leukocyte	0.621; -0.088

OH: Hydroxyl, CRP: C-reactive protein

vitamin D levels in patients with multisystemic inflammatory syndrome. Mean age of 34 cases evaluated in our study was 7.03±3.9 years old. Radia et al. (12) identified 783 separate MIS-C cases in 35 documented articles about MIS-C cases, which they evaluated among 1726 articles, and reported the mean age of the cases as 8.6 years old (IQR, 7-10 years) (12). The mean age of patients with MIS-C was reported as 8.9 years old (IQR: 0.3-14.6) among 18 cases by Darren et al. (13), as 6.4±4 years old among 122 cases by Munshi et al. (14), as 8.8 years old (IQR: 5.6-12.3) among 51 cases by Ekemen Keles et al. (10), and as 6.9 years among 23 cases by Hadžić-Kečalović et al. (15). Our study is similar to the relevant studies in the literature.

Patients included in study, 52.9% (n= 18) were males and 47.1% (n= 16) were females. Radia et al. (12) evaluated 1726 articles and described 783 separate MIS-C cases in 35 documented articles on MIS-C cases, and found that 55% (n = 435) of the cases were males and 45% (n=348) were females (12). Male and female ratios were reported as 55% (n=10) and 45% (n=8) among 18 patients in the study by Darren et al. (13), as 64.7% (n=74) and 39.3% (n=48) among 122 patients in the study by Munshi et al. (14), as 64.7% (n=33) and 35.3% (n=18) among 51 patients in the study by Ekemen Keles et al. (10), as 56.6% (n=13) and 43.4% (n=10) among 23 cases in the study by Hadžić-Kečalović et al. (15), and Torpoco Rivera et al. (16) reported 45% as males and 58% as African American origin among 31 cases diagnosed with MIS-C. Morover reported, 67% (n=14) and 33% (n=7) among 21 patients in the study by Petrovic et al. (17) Our study is similar to the studies in the literature.

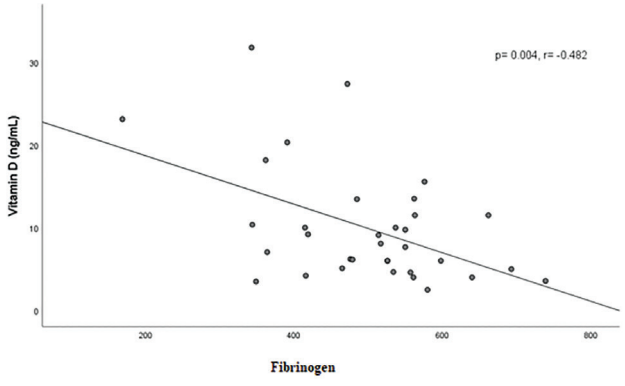

Figure 9. The correlation between 25-OH vitamin D level and fibrinogen

When mean values of laboratory findings were evaluated for the diagnosis of MIS-C in our study, platelet, albumin, amylase, lipase, GGT, total bilirubin, direct bilirubin, creatinine kinase, INR, troponin-T and CK-MB levels were evaluated as within the normal range. The studies in the literature have reported common laboratory abnormalities such as lymphocytopenia, neutrophilia, anemia, thrombocytopenia, elevated CRP, sedimentation, D-dimer, fibrinogen, ferritin, PCT, IL-6, troponin T, NT-pro-BNP and lactate in patients diagnosed with MIS-C (18-20). The results of our study is not sımılar to other studıes.

25-OH vitamin D below 12 ng/ml is vitamin D deficiency and causes serious health problems. As shown in the study by Topal et al. (21), 65% of children between the ages of 1-18 years old in Turkey have vitamin D deficiency. In our study, mean vitamin D level of 34 MIS-C patients was found as 13.2 ng/mL, and it was found to be below 12 ng/mL among 38.2% (n= 13). The results of our study were similar to the study by Topal et al (21).

Oscanoa et al. (22) reported in a meta-analysis including 23 studies (n= 2692) evaluating the effect of 25-OH vitamin D concentrations in COVID-19 patients that vitamin D deficiency appeared to be associated with increased severity and mortality. However, these studies did not show causality.

Mercola et al. (23) have provided evidence that 25-OH vitamin D levels are inversely related to the incidence or severity of COVID-19 in 14 studies.

In the study by Mohan et al. (24), it has been reported that vitamin D, an immunomodulatory hormone with proven efficacy against various upper respiratory tract infections, can stop hyperinflammatory responses and accelerate the healing process of affected areas, especially lung tissue. Since there is currently no curative drug for COVID-19, it was thought that the potential of vitamin D to change the course of disease severity should be investigated.

Rhodes et al. (25) compared the mortality rate of COVID-19 in relation to the latitude of various nations to establish a precise relationship between vitamin D levels and COVID-19. After comparison by age, they found a 4.4% increase in mortality for each degree of latitude north of 28°. This finding suggests that indirect vitamin D from UV light may play a role in protection against COVID-19.

Pereira et al. (26) selected 27 articles on COVID-19 and vitamin D out of 1542 articles, and vitamin D deficiency was not found to be associated with the risk of getting infected with COVID-19 (OR = 1.35; 95% CI = 0.80-1.88). However, vitamin D deficiency was observed in severe cases of COVID-19 more than mild cases at a rate of 64% (OR = 1.64; 95% CI = 1.30-2.09). Vitamin D deficiency was found to increase hospitalization (OR = 1.81, 95% CI = 1.41-2.21) and death rate due to COVID-19 (OR = 1.82, 95% CI = 1.06-2.58). It has been observed that there is a positive relationship between vitamin D deficiency and the severity of the disease.

Vitamin D modulates both innate and adaptive immunity and can also potentially prevent or reduce the complications associated with SARS-CoV-2 infection by increasing the concentrations of anti-inflammatory cytokines (IL-10) and Th2 cytokines as IL-4 and IL-5 (27).

25-OH vitamin D levels of our cases diagnosed with MIS-C were found to be below 12 ng/mL in 38.2% (n=13), between 12-20 ng/mL in 38.2% (n=13), and above 20 ng/mL in 23.6% (n=8), and its mean level was found as 13.6 ng/mL. In the study by Torpoco Rivera et al. (16) including 31 patients with MIS-C, 25-OH vitamin D levels were found to be 7.2±0.42 ng/ml in 10 (32.3%) patients with severe MIS-C, and severe vitamin D deficiency was found. They also reported severe disease in 90% of the patients with vitamin D deficiency (n=9) (p<0.001) (16). Although this study resembles the study by Torpoco Rivera et al. (16), future prospective studies at the basic science and clinical levels should be continued to better describe this relationship.

In the study conducted by Petrovic et al. (17) where they evaluated the relationship between 25-OH vitamin D levels and the clinical severity of MIS-C in 21 patients, it was found that vitamin D level was low in 95% (n=20), and severe vitamin D deficiency was found in 70% (n=14). Mean 25-OH vitamin D level was found to be 14.1 ng/mL. Hadžić-Kečalović et al. (15) conducted a study with 23 patients diagnosed with MIS-C, and they found mean 25-OH vitamin D level to be 17.8 ng/mL (IQR: 38.40-72.2). Ekemen Keles et al. (10) also reported a 25-OH vitamin D level of 14.6 ng/mL among 51 patients with MIS-C. Vitamin D deficiency was found at an insufficient level in 74.5% (n=38) of 51 patients and at a sufficient level in 25.5% (n=13) patients. In the study by Darren et al. (13) including 18 patients diagnosed with MIS-C, mean 25-OH vitamin D level was found to be 12 ng/mL in 78% (n=14) of the patients (13). Our study was found to be compatible with the literature.

When the relationship between 25-OH vitamin D levels and age of patients diagnosed with MIS-C was evaluated, a negative correlation was found (r=-0.414; p=0.015). In the study by Bayramoğlu et al. (28) with 103 COVID-19 positive pediatric patients, age and 25-OH vitamin D level were found to be negatively correlated (r = -0.496; p = <0.001) (28). Hadžić-Kečalović et al. (15) did not find any statistically significant correlation between the ages of the patients and their 25-OH vitamin D levels in their study including 23 patients with a diagnosis of MIS-C (r=0.11, P=0.26; 95%). Although our study resembled the study by Bayramoğlu et al. (28), more studies are needed to understand the correlation between 25-OH vitamin D level and age.

When the relationship between 25-OH vitamin D level and fibrinogen in cases diagnosed with MIS-C was evaluated, a negative correlation was found (r=-0.414; p=0.015). In the study by Heidari et al. (29) conducted on 144 COVID-19 positive adult patients, a negative correlation was reported between fibrinogen and 25-OH vitamin D levels (r=-0.52; p=<0.001) (29). Our study is very similar to the study carried out by Heidari et al. (29).

In their literature review Feketea et al. (30) concluded that vitamin D might not only be a biomarker but also a nutritional support product, and it might potentially have a positive effect on the clinical picture of MIS-C through correction of serum 25-OH vitamin D insufficiency with supplementation in very severe MIS-C cases (30).

This study is valuable because there are few publications regarding the relationship between MIS-C and vitamin D. In addition, it is also valuable in terms of the classification of laboratory, ultrasonographic findings, cardiac involvement, neurological involvement and gastrointestinal involvement rates in MIS-C patients.

It was determined that mean of 25-OH vitamin D level in cases diagnosed with MIS-C was at an insufficient level. It is thought that prophylactic vitamin D supplementation should be given according

to the age in children and should be recommended by healthcare professionals.

Study Limitations

Our study was limited to only 34 patients who admitted to the Department of Pediatric Health and Diseases in Health Practice and Research Center of Afyonkarahisar Health Sciences University. More cases are needed in terms of the relationship between MIS-C and vitamin D. In our study, were not found to be statistically significant because the number of cases was limited to 34, the mean vitamin D levels were far below the normal values and fewer patients receiving treatment in intensive care.

Conclusion

In cases diagnosed with MIS-C, the average 25-OH vitamin D level was found to be at the insufficiency level. It is thought that prophylactic vitamin D supplementation should be given to children according to age and recommended by healthcare professionals.

Ethics

Ethics Committee Approval: Ethics committee approval was taken from Afyon Health Sciences University Clinical Research Ethics Committee (date: 04.01.2022, approval number: 2022/4).

Footnotes

Conflict of Interest: No conflict of interest was declared by the authors.

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