The importance of vitamins in pediatric COVID-19 patients

Pediatrik COVID-19 hastalarında vitaminlerin önemi

Meyri Arzu Yoldaş[ID], **Halil İbrahim Atasoy**[ID]

ABSTRACT

Introduction: This study aims to determine the effects of vitamin D (25-OH D), vitamin B12, and folic acid levels on the development and severity of the disease in pediatric COVID-19 patients.

Methods: The files of 104 pediatric patients aged 0-17 years who applied to the pediatric service of our hospital with the suspicion of COVID-19 were reviewed retrospectively. Patients with positive PCR tests belong to the COVID-19 group (Group P), and patients with negative PCR tests were included in the control group (Group C). Patients diagnosed with COVID-19 were further divided into two groups: low vitamin D (Group I) and normal vitamin D (Group II).

Results: The levels of vitamin D (25-OH D) and B12 were statistically significantly lower in the COVID-19 patient group (p<0.05).

Discussion and Conclusion: We think that adequate vitamin B12 and vitamin D (25-OH) levels in children may be important in fighting against the COVID-19 infection.

Keywords: COVID-19, children, vitamin D, vitamin B12

ÖZ

Giriş ve Amaç: Bu çalışmanın amacı, pediatrik COVID-19 hastalarında vitamin D (25-OH D), vitamin B12 ve B9 (folik asit) düzeylerinin hastalığın gelişimi ve ciddiyeti üzerindeki etkilerini belirlemektir.

Yöntem ve Gereçler: Hastanemiz çocuk servisine COVID-19 şüphesiyle başvuran 0-17 yaş arası toplam 104 çocuk hastanın dosyaları retrospektif olarak incelendi. PCR testi pozitif olan hastalar COVID-19 grubuna (Grup P); PCR testi negatif olan hastalar kontrol grubuna dahil edildi (Grup C). COVID-19 tanısı konan hastalar ayrıca düşük D vitamini (Grup I) ve normal D vitamini (Grup II) olarak iki gruba ayrıldı.

Bulgular: Vitamin D (25-OH D) ve B12 düzeyleri COVID-19 hasta grubunda istatistiksel olarak anlamlı derecede düşük olarak saptandı (p<0.05).

Tartışma ve Sonuç: Çocuklarda yeterli B12 vitamini ve D vitamini düzeylerinin COVID-19 enfeksiyonu ile mücadelede önemli olabileceğini düşünüyoruz.

Anahtar kelimeler: COVID-19, çocuklar, D vitamini, B12 vitamini

Corresponding Author:
M. A. Yoldaş
ORCID: 0000-0003-0288-1529
Bolu Abant İzzet Baysal University,
Faculty of Medicine, Department of
Pediatrics, Bolu, Turkey
✉ m.arzuyoldas@gmail.com

H. İ. Atasoy
ORCID: 0000-0003-1685-0352
Bolu Abant İzzet Baysal University,
Faculty of Medicine, Department of
Pediatrics, Bolu, Turkey

INTRODUCTION

COVID-19 is a respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which affects the whole world. The most important factor in the severity of the disease has been accepted as a hyper inflammation mechanism caused by uncontrolled immune response (1). Increased patient mortality is reported to be due to pneumonia, acute respiratory distress syndrome (ARDS), and multiorgan failure that these patients develop (2). The proposed risk factors for the disease include age, obesity, diabetes mellitus, hypertension, chronic obstructive pulmonary disease, and ethnic origin (3). The international scientific community is currently investigating the disease caused by SARS-CoV-2 therapeutic agents used in the treatment and the effectiveness of these agents. However, a definitive treatment method with proven effectiveness has not been found yet (4).

There is an increasing interest in anti-inflammatory and immunomodulatory treatments in COVID-19 patients. Recent studies have shown that vitamin D induces the cellular immune system, stimulating the production of antimicrobial peptides such as cathelicidin, IL-37, and defensins, and leading to a decrease in the risk of developing an infection. In addition, it modulates immunity by increasing the production of proinflammatory cytokines such as TNF-α and IFNγ and inhibiting cytokine storms that are effective on mortality from COVID-19 infection (5). There is a remarkable relationship between low serum levels of vitamin D and community-acquired pneumonia and poor prognosis in critically ill patients (6). It was observed in a study that the prevalence of influenza A and acute respiratory tract infections decreased with vitamin D supplementation in children (7). In addition, the fact that serum vitamin D (25-OH D) concentrations decrease with age may be important for COVID-19 patients because mortality rates have been reported to increase with age (8). Vitamin B12 (cobalamin) increases proinflammatory cytokine levels, improves respiratory system functions, protects endothelial integrity, prevents hypercoagulation, and might decrease hospitalization (9). Vitamin B12 is essential for the fast synthesis of DNA, erythrocyte synthesis, nervous system health, myelin synthesis, and cellular growth. Low vitamin B12 increases methylmalonic acid and homocysteine, causing increased inflammation and oxidative stress (10). Vitamin B9 (folic acid) is an essential vitamin for DNA synthesis, protein synthesis, and immune system functions. Vitamin B9 and its derivatives, tetrahydrofolic acid and 5-methyl tetrahydrofolic acid, have strong and stable binding affinities to SARS-CoV-2. Therefore, it was thought that folic acid might be evaluated as a therapeutic approach to treating COVID-19 (11). This study aims to determine the effects of vitamins D and B on the development and severity of the disease in pediatric COVID-19 patients.

MATERIALS AND METHODS

Study Design and Population
The study protocol was approved by the local human studies committee (2020/481) and was conducted following the Declaration of Helsinki. The files of 104 children aged 0-17 years hospitalized in the pediatric service of our hospital between May 2019 and October 2020 with the suspicion of COVID-19 were retrospectively scanned. Patients with a positive PCR test were assigned to the COVID-19 group (Group P), and patients with negative PCR tests were included in the control group (Group C). Patients diagnosed with COVID-19 were further divided into two groups: low vitamin D (25-OH D) levels (Group I) and normal vitamin D level (Group II). Vitamin D, B12, and folic acid concentrations of all patients were measured by the chemiluminescence immunoassay method using the Abbott Architect 2000–SR (Germany) autoanalyzer. In the Endocrine Society consensus report, 25-OH D level is defined as <12ng/ml, vitamin D insufficiency, vitamin D deficiency as 12-20 ng/ml, and normal vitamin D >20 ng/ml level. (12). Following the reference values of the laboratory in our hospital, 200-900 pg/ml vitamin B12 levels were accepted as normal values.

The cutoff points used for serum folic acid were <3 ng/ml for deficiency, 3–6 ng/ml for low levels, and >6 ng/ml for normal (13). Vitamin levels were compared between both groups. In the COVID-19 group, serum vitamin D levels were compared with the most common disease symptoms (fever, cough) and hospitalization. Patients with chronic diseases, neuromotor growth retardation, heart disease, kidney disease, and immunodeficiency were excluded from the study. Demographic data of children such as age, gender, weight, and height were collected from the registration system, and body mass index (BMI) was calculated using the Quetelet equation [kg / √(body surface area in m² body surface area]).

Statistical Analysis

Data obtained in this study were evaluated by SPSS version 22.0 (SPSS IBM Inc., Chicago, IL, USA). The normality of the variables was tested through the Kolmogorov-Smirnov method. The variables were compared between the groups by the Independent Student t-test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. Continuous variables are expressed as mean ± standard deviation. The association between the parameters was examined with Pearson's correlation analysis. P values <0.05 were considered statistically significant.

RESULTS

In the study, 50 children were evaluated in the COVID-19 patient group and 54 children in the control group. No statistically significant difference was found between the groups in terms of the demographic data (Table 1). The vitamins D, B12, and B9 were within the normal range in both groups. However, in the intergroup comparison, there was no significant difference in vitamin B9 levels, whereas the levels of vitamin D and B12 were statistically significantly lower in the COVID-19 patient group (p<0.05) (Table 2). Fever, cough, and hospitalization were compared with vitamin D levels in the COVID-19 groups (Groups I and II). No statistically significant difference was found between both groups (Table 3). Appropriate vitamin therapy was initiated for all patients with vitamin deficiency. It was determined that only one patient needed intensive care follow-up, and all patients were discharged with recovery.

DISCUSSION

The literature has not clearly shown the prognostic value of these vitamins in the COVID-19 infection. However, numerous studies have shown a positive correlation between vitamin D deficiency and acute respiratory tract infections (14). In a study investigating clinical outcomes of 212

Table 1. Demographic and anthropometric characteristics of the groups.

	Group P Mean (±SD)	Group C Mean (±SD)	P
Age (year)	7.98 (±5.89)	6.57 (±4.63)	0.181
Weight (kg)	30.18 (±19.39)	27.27 (±17.24)	0.423
Height (cm)	119.24 (±38.04)	115.94 (±29.23)	0.623
Body mass index (kg/m²)	18.13 (±2.68)	18.43 (±5.57)	0.732

Table 2. Comparison of vitamin levels between the groups.

	Group P Mean (±SD)	Group C Mean (±SD)	P
Vit 25(OH)D (ng/ml)	21.56 (±10.47)	28.94 (±12.07)	**0,010**
Vit B12 (pg/ml)	314.48(±125.48)	405.89 (±148.91)	**0,010**
Vit B9 (ng/ml)	8.87 (±4.37)	10.10 (±3.68)	0,140

Table 3. Effect of Vit-D level on clinical manifestations.

	Group I Mean (±SD)	Group II Mean (±SD)	P
Fever (day)	2.20 (±1.85)	1.85 (±1.98)	**0.526**
Cough (day)	1.55 (±2.58)	1.47 (±2.04)	**0.909**
Hospitalization (day)	5.41 (±3.13)	4.23 (±1.81)	0.110

patients with SARS-CoV-2 infection, vitamin D level was correlated with disease severity. It was reported that vitamin D level could be a predictor marker (5). It has been thought that serum vitamin D levels between 20 ng/mL and 50 ng/mL create a sufficient level for an immunomodulator impact (15). In a study by Zdrenghea MT et al.[16], vitamin D supplementation used in different age groups was observed to decrease proinflammatory cytokines in the lungs through the modulation of T lymphocyte activity and macrophages. Therefore, it has been pointed out that 25-OH D prophylaxis (without overdose) can decrease the severity of the disease caused by SARS – CoV-2, especially in those with 25-OH D deficiency (17). In an animal study, 25-OH D levels were decreased in the calves infected by coronavirus (18). In a recent meta-analysis, 25-OH D level was statistically significantly lower in COVID-19 patients with a poor diagnosis than those with a good prognosis (19). In another study by D'Avolio et al.[20], 25-OH vitamin D concentrations were shown to be statistically significantly lower in patients with PCR (+) for SARS-CoV-2 compared to those with PCR (-). Supporting other studies, vitamin D levels in our study were statistically significantly lower in the hospitalized COVID-19 patients than in the control group.

In conclusion, we aimed to draw attention to the fact that lower 25- OH D levels detected in COVID-19 patients may have increased the risk of hospitalization. In addition, we found that low or normal 25-OH D levels did not affect the duration of symptoms and hospitalization. We thought that the small number of patients included in our study and the milder course of the COVID-19 disease in children may have caused this result. SARS-CoV-2 may interfere with vitamin B12 and vitamin metabolism, impairing intestinal microbial proliferation. In a study, vitamin B12 supplementation, vitamin D, and magnesium given to COVID-19 patients decreased the severity of the symptoms. The supplements significantly decrease the need for oxygen and intensive care (21). Recent studies emphasized that vitamin B12 supplements have the potential to reduce organ damage and symptoms associated with COVID-19 disease (22). In a study by Fimognari et al.[23], lower vitamin B9 and vitamin B12 levels were reported in patients with the chronic obstructive pulmonary disease. Similarly, vitamin B12 levels in our study were statistically significantly lower in COVID-19 patients. Folic acid is part of the vitamin B complex and is a water-soluble vitamin. It is known to prevent megaloblastic anemia, neural tube congenital disabilities, cardiovascular diseases, dementia, cognitive function alterations, osteoporosis, and various cancer types (24). Recently, significantly lower serum folic acid levels were reported in patients with severe COVID-19 infection (25). In the present study, no statistically significant difference was found between the folic acid levels of both groups. We think that more comprehensive studies should support the results of our study since it was retrospective and conducted with a small number of patients. In this study, the levels of vitamins B12 and 25-OH D were lower in COVID-19 patients. Therefore, we think that adequate vitamin B12 and D levels in children can help fight against the COVID-19 infection.

REFERENCES

1. Park SH. An Impaired Inflammatory and Innate Immune Response in COVID-19. Mol Cells. 2021;44(6):384-391.
https://doi.org/10.14348/molcells.2021.0068
2. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China [published correction appears in Lancet. 2020 Jan 30;:]. Lancet. 2020;395(10223):497-506.
https://doi.org/10.1016/S0140-6736(20)30183-5.

3. Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China [published correction appears in JAMA Intern Med. 2020 Jul 1;180(7):1031]. JAMA Intern Med. 2020;180(7):934-943.
https://doi.org/10.1001/jamainternmed.2020.0994

4. Abd El-Aziz TM, Stockand JD. Recent progress and challenges in drug development against COVID-19 coronavirus (SARS-CoV-2) - an update on the status. Infect Genet Evol. 2020;83:104327.
https://doi.org/10.1016/j.meegid.2020.104327

5. Grant WB, Lahore H, McDonnell SL, et al. Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths. Nutrients. 2020;12(4):988. Published 2020 Apr 2.
https://doi.org/10.3390/nu12040988

6. Mamani M, Muceli N, Ghasemi Basir HR, Vasheghani M, Poorolajal J. Association between serum concentration of 25-hydroxyvitamin D and community-acquired pneumonia: a case- control study. Int J Gen Med. 2017;10:423-429. Published 2017 Nov 13.
https://doi.org/10.2147/IJGM.S149049.

7. Urashima M, Segawa T, Okazaki M, Kurihara M, Wada Y, Ida H. Randomized trial of vitamin D supplementation to prevent seasonal influenza A in schoolchildren. Am J Clin Nutr. 2010;91(5):1255-1260.
https://doi.org/10.3945/ajcn.2009.29094.

8. Vásárhelyi B, Sátori A, Olajos F, Szabó A, Beko G. Alacsony D-vitamin-szint a Semmelweis Egyetem betegei körében: a központi laboratóriumban egy év alatt meghatározott D-vitamin-szintek retrospektív értékelése [Low vitamin D levels among patients at Semmelweis University: retrospective analysis during a one-year period]. Orv Hetil. 2011;152(32):1272-1277.
https://doi.org/10.1556/OH.2011.29187

9. Sahin E, Orhan C, Uckun FM, Sahin K. Clinical Impact Potential of Supplemental Nutrients as Adjuncts of Therapy in High-Risk COVID-19 for Obese Patients. Front Nutr. 2020;7:580504. Published 2020 Oct 22.
https://doi.org/10.3389/fnut.2020.580504

10. Mikkelsen K, Stojanovska L, Prakash M, Apostolopoulos V. The effects of vitamin B on the immune/cytokine network and their involvement in depression. Maturitas. 2017;96:58-71.
https://doi.org/10.1016/j.maturitas.2016.11.012

11. Kumar V, Kancharla S, Jena MK. In silico virtual screening-based study of nutraceuticals predicts the therapeutic potentials of folic acid and its derivatives against COVID-19 [published online ahead of print, 2021 Jan 28]. VirusdiseASE. 2021;1-9.
https://doi.org/10.1007/s13337- 020-00643-6

12. Munns CF, Shaw N, Kiely M, et al. Global Consensus Recommendations on Prevention and Management of Nutritional Rickets. J Clin Endocrinol Metab. 2016;101(2):394-415.
https://doi.org/10.1210/jc.2015-2175

13. García-Casal MN, Osorio C, Landaeta M, et al. High prevalence of folic acid and vitamin B12 deficiencies in infants, children, adolescents and pregnant women in Venezuela. Eur J Clin Nutr. 2005;59(9):1064-1070.
https://doi.org/10.1038/sj.ejcn.1602212

14. Zhou YF, Luo BA, Qin LL. The association between vitamin D deficiency and community- acquired pneumonia: A meta-analysis of observational studies. Medicine (Baltimore). 2019;98(38):e17252.
https://doi.org/10.1097/MD.0000000000017252

15. Esposito S, Lelii M. Vitamin D and respiratory tract infections in childhood. BMC Infect Dis. 2015;15:487. Published 2015 Oct 28.
https://doi.org/10.1186/s12879-015-1196-1

16. Zdrenghea MT, Makrinioti H, Bagacean C, Bush A, Johnston SL, Stanciu LA. Vitamin D modulation of innate immune responses to respiratory viral infections. Rev Med Virol. 2017;27(1):10.1002/rmv.1909.
https://doi.org/10.1002/rmv.1909

17. Panarese A, Shahini E. Letter: Covid-19, and vitamin D. Aliment Pharmacol Ther. 2020;51(10):993-995.
https://doi.org/10.1111/apt.15752

18. Nonnecke BJ, McGill JL, Ridpath JF, Sacco RE, Lippolis JD, Reinhardt TA. Acute phase response elicited by experimental bovine diarrhea virus (BVDV) infection is associated with decreased vitamin D and E status of vitamin-replete preruminant calves. J Dairy Sci. 2014;97(9):5566-5579.
https://doi.org/10.3168/jds.2014-8293

19. Munshi R, Hussein MH, Toraih EA, et al. Vitamin D insufficiency as a potential culprit in critical COVID-19 patients. J Med Virol. 2021;93(2):733-740.
https://doi.org/10.1002/jmv.26360

20. D'Avolio A, Avataneo V, Manca A, et al. 25-Hydroxyvitamin D Concentrations Are Lower in Patients with Positive PCR for SARS-CoV-2. Nutrients. 2020;12(5):1359. Published 2020 May 9.
https://doi.org/10.3390/nu12051359

21. Tan CW, Ho LP, Kalimuddin S, et al. Cohort study to evaluate the effect of vitamin D, magnesium, and vitamin B12 in combination on progression to severe outcomes in older patients with coronavirus (COVID-19). Nutrition. 2020;79-80:111017.
https://doi.org/10.1016/j.nut.2020.111017

22. BourBour F, Mirzaei Dahka S, Gholamalizadeh M, et al. Nutrients in prevention, treatment, and management of viral infections; special focus on Coronavirus [published online ahead of print, 2020 Jul 9]. Arch Physiol Biochem. 2020;1-10.
https://doi.org/10.1080/13813455.2020.1791188

23. Fimognari FL, Loffredo L, Di Simone S, et al. Hyperhomocysteinaemia and poor vitamin B status in chronic obstructive pulmonary disease. Nutr Metab Cardiovasc Dis. 2009;19(9):654-659. https://doi.org/10.1016/j.numecd.2008.12.006

24. Kishimoto K, Kobayashi R, Sano H, et al. Impact of folate therapy on combined immunodeficiency secondary to hereditary folate malabsorption. Clin Immunol. 2014;153(1):17-22. https://doi.org/10.1016/j.clim.2014.03.014

25. Itelman E, Wasserstrum Y, Segev A, et al. Clinical Characterization of 162 COVID-19 patients in Israel: Preliminary Report from a Large Tertiary Center. Isr Med Assoc J. 2020;22(5):271-274.