DOI: 10.4274/TP.2022.13008
Trends in Pediatrics 2022;3(4):149-55

Original Article

Serum Vitamin D and B12 Levels in School-aged Children and Adolescents with Frequent Primary Headache Attacks

Gül Demet Kaya Özçora[1], Elif Söbü[2], Mehmet Canpolat[3], Fatih Kardaş[4], Mustafa Kendirci[4], Hakan Gümüş[3], Hüseyin Per[3], Sefer Kumandaş[4]

[1]Hasan Kalyoncu University Faculty of Health Sciences, Department of Pediatric Neurology, İstanbul, Türkiye
[2]University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar City Hospital, Clinic of Pediatric Endocrinology, İstanbul, Türkiye
[3]Erciyes University Faculty of Medicine, Department of Pediatric Neurology, Kayseri, Türkiye
[4]Erciyes University Faculty of Medicine, Department of Pediatric Metabolism, Kayseri, Türkiye

Cite this article as: Kaya Özçora GD, Söbü E, Canpolat M, Kardaş F, Kendirci M, Gümüş H, Per H, Kumandaş S. The Effects of Serum Vitamin D and B12 Levels on the Frequency of Primary Headaches in School-aged Children and Adolescents. Trends in Pediatrics 2022;3(4):149-55

ABSTRACT

Objective: Headaches are among the most frequent disorders in children and adults. Recent evidence suggests that various neurological disorders, including headaches, epilepsy, and neurodegenerative disorders, are associated with deficiencies in vitamins D and B12. In this context, this study aims to compare serum vitamin D and B12 levels in pediatric patients with migraine or tension-type headaches with those of healthy children and to explore the relationship between the frequency of headache attacks and the deficiencies in the aforementioned vitamins.

Methods: The population of this retrospective study consisted of pediatric patients who presented with a headache lasting at least six months to the pediatric neurology outpatient clinics. The patients included in the study sample were categorized into two groups: Patients with migraines (n=54) and tension-type headaches (n=72). Additionally, 64 children without headaches were included in the control group. Detailed data on the features of headaches were obtained from the patients or their parents. Patients were categorized into three groups according to the frequency of the headaches as patients who had headache attacks a) once a week, b) twice or three times a week and c) ≥ four times a week. The patients were grouped into four grade levels based on their PedMIDAS scores. All participants included in the study were subjected to thyroid function tests, and vitamin D and vitamin B12 levels.

Results: There was no significant difference between the groups in serum vitamin B12 levels ($p>0.05$). However, the median vitamin D level was significantly higher in patients with migraine-type headaches ($p<0.001$). The rate of patients with vitamin D deficiency was significantly lower in the tension-type headache group than in the migraine group ($p=0.005$). There was no significant correlation between the Pediatric Migraine Disability Assessment (PedMIDAS) grades and vitamin B12 levels ($p>0.05$). However, the serum vitamin D levels of patients with a PedMIDAS grade between 1 and 3 were significantly higher in patients with migraine than in those with tension-type headaches ($p<0.05$). The serum vitamin D levels of migraine patients with a PedMIDAS grade of 4 were significantly lower than those of migraine patients with a PedMIDAS grade of 3 ($p=0.018$). The migraine patients with one and 2-3 attacks per week had significantly higher vitamin D levels than those patients with tension-type headaches ($p=0.031$ and $p<0.001$, respectively). Additionally, the vitamin D levels in migraine patients with ≥4 attacks per week were significantly lower than those of migraine patients with 2-3 attacks per week ($p=0.010$).

Conclusion: The patients with migraine and higher frequency of attacks had lower vitamin D levels.

Keywords: Vitamin D, children, migraine, tension-type headache, vitamin B12 deficiency

GD. Kaya Özçora: 0000-0003-3316-8654; E. Söbü: 0000-0002-2037-7046; M. Canpolat: 0000-0002-6877-2109; F. Kardaş: 0000-0002-2276-7611; M. Kendirci: 0000-0002-2100-3628; H. Gümüş: 0000-0001-5896-074X; H. Per: 0000-0001-9904-6479; S. Kumandaş: 0000-0003-0117-1218.

Address for Correspondence: Gül Demet Kaya Özçora
Hasan Kalyoncu University Faculty of Health Sciences, Department of Pediatric Neurology, İstanbul, Türkiye
E-mail: guldemetkaya@hotmail.com **ORCID-ID:** orcid.org/0000-0003-3316-8654
Received: 24.08.2022 **Accepted:** 22.11.2022

INTRODUCTION

Headaches are the most common neurological symptom among children and adolescents who seek medical consultations.[1-3] Headaches are also the leading cause of school absenteeism. Headache prevalence increases throughout childhood and peaks at approximately 11-13 years, regardless of gender. A student-based epidemiological study in Türkiye reported that the prevalence of recurrent headache attacks in adolescents aged 12 to 17 was 52.2%[4]. Most cases present with a benign course secondary to primary headache disorders such as tension-type headaches and migraine, whereas in some cases, headaches might also be associated with severe intracranial pathologies.[2,5,6] It has been reported in the literature that tension-type headaches and migraine are the two most common headache diagnoses, in decreasing order, among Turkish adolescents.[5] However, the exact pathophysiology and predisposing factors remain controversial, particularly for primary headache disorders.[2,7]

The proper diagnosis of a primary headache disorder and its management significantly impact school life, daily life productivity, and overall quality of life in the pediatric population. Prophylactic therapy and lifestyle changes may help reduce the frequency and severity of headache attacks in children with chronic headaches. In addition to using medications such as antiepileptics or antidepressants, treatment modalities based on dietary ingredients, including vitamins, minerals, herbs, or other botanicals, are used for treating primary headaches.[8] Given its potential role in the pathogenesis of various neurological diseases, the possible role of vitamin D in headache prophylaxis has been mentioned in the literature.[9-12] Vitamin B12 is another essential vitamin that plays a key role in the central nervous system. However, the number of studies on the potential role of vitamin B12 levels among different pediatric headache groups is limited.[13,14] Although vitamin D and B12 deficiency/insufficiency have been reported frequently in patients with migraine in recent studies, there is no consensus on prescribing these vitamins in routine clinical practice.

In this context, this study was conducted to compare the serum vitamin D and B12 levels in pediatric patients with migraine and tension-type headaches with those of healthy children and to determine the relationship between the frequency of headache attacks and serum vitamin D and B12 levels.

MATERIALS AND METHODS

Research Design

The protocol of this retrospective study was approved by the Erciyes University Clinical Research Ethics Committee (decision no: 2016/479, date no: 12.08.2016). The study was conducted in accordance with the principles set forth in the Declaration of Helsinki. Patients' legally authorized representatives provided informed consent for patient information to be published.

Population and Sample

The population of this retrospective cohort study consisted of pediatric patients (aged between 6 to 18 years) who presented with a headache lasting at least six months to the Pediatric Neurology Outpatient Clinics. Patients' data were obtained from their medical records available in the hospital medical record/database. The diagnoses of primary headaches, i.e., migraine and tension-type headache, were made based on the 3rd edition of the criteria of the International Classification of Headache Disorders[15]. Accordingly, patients diagnosed with a primary headache were included, whereas patients on vitamin D and B12 medication, patients with headaches secondary to diseases such as brain tumors, paranasal sinus diseases, infections, other systemic diseases, and vision problems, as well as patients with any neurological disorders other than headaches were excluded from the study to avoid any confounding effects.

The control group consisted of children randomly selected using a random sequence number generator from the children with age and gender characteristics that match those of the patient group who were admitted to the general pediatric outpatient clinic in the same period for routine examination and did not have a history of headaches and have not been receiving any vitamin supplementation.

The same pediatric neurologist performed all the patients' physical and neurological examinations. Detailed data on the features of headaches, such as the frequency of headaches, were obtained from the patients or their parents. Patients were categorized into three groups according to the frequency of the headaches as patients who had headache attacks a) once a week, b) twice or three times a week, and c) ≥ four times a week.

All patients underwent an ophthalmological examination. In cases where deemed necessary, patients also undergo brain magnetic resonance imaging and/or electroencephalogram examinations.

Questionnaire

The headache-related functional impairment of the children in school and at home was evaluated using the 6-item Pediatric Migraine Disability Assessment (PedMIDAS) tool for three months.[16] The total PedMIDAS scores were calculated using the method described by Hershey et al.[17] The total number of days the children were affected by the headache attacks during the last three months was determined.[16,18] The patients were grouped into four grade levels based on their PedMIDAS scores: Grade 1: No or slight impairment (scores 0-10), grade 2: Mild impairment (scores 11-30), grade 3: Moderate impairment (scores 31-50), and grade 4: Severe impairment (scores >50).

Laboratory Tests

Blood samples were obtained from all subjects after overnight fasting. Patients' serum vitamin D and B12 levels were routinely measured in the pediatric outpatient clinic per the institutional policy. The collected blood samples were centrifuged at 4000 rpm

at room temperature. The serum vitamin D levels were evaluated by the two step competitive binding immunoenzymatic assay method. Vitamin D levels >30 ng/mL were considered normal, whereas vitamin D levels ≤30 ng/mL were considered deficient.[9]

The electrochemiluminescence immunoassay procedure was used to measure the serum vitamin B12 levels. Vitamin B12 levels <200 pg/mL were considered deficient, whereas vitamin B12 levels <160 pg/mL were considered severely deficient.[2]

Statistical Analysis

The descriptive statistics obtained from the collected research data were expressed as mean ± standard deviation values in the case of normally distributed continuous variables, as median and minimum - maximum values in the case of non-normally distributed continuous variables, and as numbers and percentage values in the case of categorical variables. The Shapiro-Wilk, Kolmogorov-Smirnov, and Anderson-Darling tests were used to analyze the normal distribution characteristics of the numerical variables.

The independent samples t-test and the Mann-Whitney U test were used to compare two independent groups in the case of normally and non-normally distributed numerical variables, respectively. Pearson's chi-squared and Fisher's exact tests were used to compare the differences between categorical variables in 2x2 tables, whereas the Fisher-Freeman-Halton test was used to compare the differences between categorical variables in the RxC tables.

The one-way analysis of variance (ANOVA) test and the Kruskal-Wallis test were used to compare more than two independent groups in the case of normally and non-normally distributed numerical variables, respectively. In analyses featuring parametric tests, the differences between the groups were evaluated with the Games-Howell test, provided that the data were heterogeneous according to their distribution. However, in analyses featuring non-parametric tests, the Dwass-Steel-Critchlow-Fligner test was used to evaluate the differences between the groups.

The Jamovi project 2.2.5.0 (Jamovi, version 2.2.5.0, 2022, retrieved from https://www.jamovi.org) and JASP 0.16.1 (Jeffreys' Amazing Statistics Program, version 0.16.1, 2022, retrieved from https://jasp-stats.org) software packages were used in the statistical analyses. Probability (p) statistics ≤0.05 were deemed to indicate statistical significance

RESULTS

The distribution of patients' demographic and clinical characteristics by the group is shown in Table 1. There were 72 patients (47 girls/25 boys) with tension-type headaches, 54 patients with migraine (37 girls/17 boys), and 64 healthy children (20 girls/34 boys). There was no statistically significant difference between the groups in age and gender (p>0.05).

The distribution of the frequency of attacks and PedMIDAS grades by the study groups is given in Table 2. Accordingly, there was no significant difference between the patients with tension-type headaches and migraine in the frequency of attacks and PedMIDAS grades (p=0.388 and p=0.551, respectively).

There was no significant difference between the groups in terms of serum B12 levels (p>0.05) (Table 3). The incidence of vitamin B12 deficiency was 19.4% among patients with tension-type headaches, 13.0% among patients with migraine, and 14.1% among healthy children. There were more patients with vitamin B12 deficiency in the tension-type headache group than in the migraine group and the healthy control group; however, the difference between the groups was insignificant (p=0.551). However, the groups significantly differed in serum vitamin D levels and the rate of patients with vitamin D deficiency (p<0.001 and p=0.005, respectively) (Table 3). Accordingly, the median vitamin D levels were significantly higher among patients with migraine (p<0.001). In parallel, the rate of patients with vitamin D deficiency was significantly higher among patients with tension-type headaches (p=0.005). Paired comparison of the patients with tension type-headache and migraine revealed similar results (Table 4).

There was no significant difference in the serum vitamin B12 levels between patients with different PedMIDAS grades for each group (p>0.05) (Table 5).

The serum vitamin D levels of patients with PedMIDAS grades 1 to 3 were significantly higher in patients with migraine than in those with tension-type headaches (p<0.05) (Table 5). The serum vitamin D levels of migraine patients with a PedMIDAS grade of

Table 1. Demographic and clinical characteristics of the study groups

	Patients with tension-type headache (n=72)	Patients with migraine (n=54)	Control (n=64)	p-value
Age (year)[§]	13.5 (6.0-18.0)	13.5 (8.0-18.0)	13.8 (7.8-17.6)	0.969**
Sex[‡]				
Male	36 (50.0)	22 (40.7)	34 (53.1)	0.384*
Female	36 (50.0)	32 (59.3)	30 (46.9)	

[‡]n (%), [§]median (minimum-maximum)
*Pearson chi-square test, **Kruskal-Wallis H test

Table 2. Clinical characteristics of the patients with tension-type headache and migraine

	Patients with tension-type headache (n=72)	Patients with migraine (n=54)	p-value
Frequency of attacks‡			
1 per week	24 (33.3)	24 (44.4)	0.388*
2-3 per week	27 (37.5)	19 (35.2)	
≥4 per week	21 (29.2)	11 (20.4)	
PedMIDAS grades‡			
Grade 1	24 (33.3)	24 (44.4)	0.551*
Grade 2	14 (19.4)	11 (20.4)	
Grade 3	13 (18.1)	8 (14.8)	
Grade 4	21 (29.2)	11 (20.4)	

‡n (%), §Median (minimum-maximum)
*Pearson chi-square test.
**Kruskal-Wallis H test.
PedMIDAS: Pediatric Migraine Disability Assessment

4 were significantly lower than those of migraine patients with a PedMIDAS grade of 3 (p=0.018).

There was no significant difference between migraine patients with other PedMIDAS grades in terms of vitamin D levels (p=0.663).

There was no significant correlation between vitamin B12 levels and the frequency of attacks between the study groups (p>0.05) (Table 6). However, the migraine patients with one and 2-3 attacks per week had significantly higher vitamin D levels than those patients with tension-type headaches (p=0.031 and p<0.001, respectively). Additionally, the vitamin D levels in migraine patients with ≥4 attacks per week were significantly lower than those of migraine patients with 2-3 attacks per week (p=0.010).

DISCUSSION

Vitamin B12 and D play critical regulatory functions in brain development, cell differentiation, and apoptosis. In this context, this study explored the relationship, if any, between B12 and D vitamin levels and the frequency of migraine and tension-type headaches in the pediatric population. Although clinical neurological manifestations of low levels of vitamins in children

Table 3. Comparison of the laboratory parameters among study groups

	Patients with tension-type headache (n=72)	Patients with migraine (n=54)	Control (n=64)	p-value
Vitamin B12 (pg/mL)§	271.0 (92.0-679.0)	324.9 (94.0-682.5)	299.5 (63.0-714.0)	0.202*
≥200 pg/mL‡	58 (80.6)	47 (87.0)	55 (85.9)	0.551**
<200 pg/mL‡	14 (19.4)	7 (13.0)	9 (14.1)	
Vitamin D (pg/mL)§	13.0 (3.5-50.0)	20.8 (5.0-53.0)	15.9 (7.7-41.1)	**<0.001*** **
≥30 pg/mL‡	2 (2.8)[a]	11 (20.8)[b]	7 (10.9)[a,b]	**0.005****
<30 pg/mL‡	70 (97.2)[a]	42 (79.2)[b]	57 (89.1)[a,b]	

‡n (%), §Median (minimum-maximum)
[a,b]Different letters in the same row shows a significant difference.
*Mann-Whitney U test, **Pearson chi-square test, Fisher's exact test, or Fisher Freeman Halton test, ***Kruskal Wallis-H test.
Pairwise comparisons with Dwass-Steel-Critchlow-Fligner test.

Table 4. Comparison of the laboratory parameters between patients with tension-type headache and with migraine

	Patients with tension-type headache (n=72)	Patients with migraine (n=54)	p-value
Vitamin B12 (pg/mL)§	271.0 (92.0-679.0)	324.9 (94.0-682.5)	0.085*
≥200 pg/mL‡	58 (80.6)	47 (87.0)	0.469**
<200 pg/mL‡	14 (19.4)	7 (13.0)	
Vitamin D (pg/mL)§	13.0 (3.5-50.0)	20.8 (5.0-53.0)	<0.001*
≥30 pg/mL‡	2 (2.8)	11 (20.8)	0.003**
<30 pg/mL‡	70 (97.2)	42 (79.2)	

‡n (%), §Median (minimum-maximum)
*Mann-Whitney U test, **Pearson chi-square or Fisher's exact test

with primary headaches have been described in several case studies, the underlying mechanism of the frequency of headache attacks is not yet fully understood.[19] The results of this study, contrary to Ayanoğlu et al.[6], did not reveal any significant difference between the study groups in serum vitamin B12 levels. However, there was a significant difference between the groups in serum vitamin D levels. Accordingly, there was a significant correlation between low levels vitamin D in pediatric patients with migraine and a higher frequency of attacks. Additionally, there were significant relationships between the vitamin D levels, the PedMIDAS grades, and headache frequency.

Migraine is considered a complex neurological disorder involving interacting environmental and hereditary factors. Migraine prophylaxis supplements are used to prevent and/or alleviate headache attacks by improving mitochondrial function and energy production in neurological systems. This mechanism might be responsible for the pathogenesis of migraine[20]. The literature on vitamin D levels and headaches in children is sparse and contradictory. In one of these studies exploring the potential risk factors for primary headaches in children, Al Momani et al.[3] found that abnormal vitamin D levels were significantly associated with primary headaches. Similarly, the tension-type headache and migraine groups included in this study significantly differed in vitamin D levels. Yang et al.[21] reported a potential correlation between vitamin D deficiency and headaches. However, Kjaergaard et al.[22] reported a possible link between vitamin D levels and tension-type headaches but could not propose a correlation between vitamin D levels and migraine. There are several definitions of vitamin D deficiency. Vitamin D deficiency is most commonly characterized by plasma vitamin D levels of <10 ng/mL. However, the threshold level for vitamin D insufficiency is still a matter of debate[23]. The discrepancies in the literature on vitamin D levels and headaches in children may, in part, be attributed to the use of said different criteria for defining vitamin D deficiency. Furthermore, the migraine patients with higher PedMIDAS grades (grade 4) and frequent headache attacks (≥4 per week) in this study had significantly lower vitamin D levels. In line with the findings of this study, Kılıç and Kılıç[24] reported a negative correlation between the frequency of migraine attacks and serum vitamin D levels and determined that patients with pain are commonly advised to take vitamin D supplements, considering that vitamin D may reduce the frequency of migraine attacks. Similarly, Gungör et al.[9] reported that as the vitamin D levels decreased, the severity of the headache significantly increased, resulting in higher MIDAS grades.

Vitamin D reportedly exhibits an anti-inflammatory effect through the prevention of neuroinflammation that produces migraine and tension-type headaches.[11,25] Vitamin D balances T helper and regulatory T-cells to inhibit prostaglandin E_2 synthesis by reducing nitric oxide production.[26] Additionally, vitamin D is responsible for the upregulation of growth factor beta-1 and interleukin-4 and suppresses tumor necrosis factor-α[27]. The anti-inflammatory effect of vitamin D has also been explained by the inverse relationship between the C-reactive protein and vitamin D levels.[28] Hence,

Table 5. Comparison of vitamin B12 and D levels based on the PedMIDAS grades

	Patients with tension-type headache (n=72)	Patients with migraine (n=54)	p-value
Vitamin B12 (pg/mL)†			
PedMIDAS grades			
Grade 1	304.0±123.9	314.7±97.6	0.741*
Grade 2	300.1±128.1	376.4±166.6	0.225*
Grade 3	286.4±141.5	325.4±106.9	0.483*
Grade 4	304.1±122.7	289.6±130.1	0.763*
p**	0.979	0.395	
Vitamin D (pg/mL)§			
PedMIDAS grades			
Grade 1	16.5 (4.0-28.0)	20.8 (5.0-53.0)	**0.031*****
Grade 2	11.0 (6.0-25.0)	25.3 (10.0-43.0)	**0.007*****
Grade 3	12.0 (7.0-34.0)	27.3 (18.0-53.0)	**0.003*****
Grade 4	13.0 (3.5-50.0)	11.0 (7.0-49.5)	0.606***
p****	0.663	**0.018**	

†Mean ± standard deviation, §Median (minimum-maximum)
*Independent Samples t-test, **One-way ANOVA test, ***Mann-Whitney U test, ****Kruskal-Wallis H test.
Pairwise comparisons with Dwass-Steel-Critchlow-Fligner test.
PedMIDAS: Pediatric Migraine Disability Assessment

Table 6. Comparison of vitamin B12 and D levels based on the frequency of headache attacks

	Patients with tension-type headache (n=72)	Patients with migraine (n=54)	p-value
Vitamin B12 (pg/mL)†			
Frequency of attack			
1 per week	314.5 (95-624)	339 (94-475)	0.529*
2-3 per week	265 (92-590)	320 (165-682.5)	0.069*
≥4 per week	258 (171-679)	320 (100-519)	0.736*
p**	0.744	0.852	
Vitamin D (pg/mL)§			
Frequency of attack			
1 per week	16.5 (4-28)	20.8 (5-53)	**0.031***
2-3 per week	12 (6-34)	26.6 (10-53)	**<0.001***
≥4 per week	13 (3.5-50)	11 (7-49.5)	0.606*
p**	0.497	**0.010**	

†Mean ± standard deviation. §Median (minimum-maximum)
*Mann-Whitney U test, **Kruskal-Wallis H test.
Pairwise comparisons with Dwass-Steel-Critchlow-Fligner test

the increase in the frequency of headache attacks in pediatric migraineurs included in this study is explained by the low serum vitamin D levels.

Patients with pain are advised to take vitamin D supplements since vitamin D may reduce the number of headache attacks in some patients, particularly patients with migraine. This positive effect of vitamin D is even more pronounced if the patients are vitamin D deficient. As a matter of fact, in a study conducted with 53 pediatric migraine patients, Cayir et al.[29] reported that vitamin D therapy and anti-migraine prophylactic treatment reduced the number of migraine attacks. In comparison, this study examined the effect of vitamin D levels on the number of childhood primary headache attacks. Studies on the effects of vitamin D deficiency and/or insufficiency among pediatric patients with tension-type headaches are limited. In a case series by Prakash and Shah[30] conducted with eight adult patients with chronic tension-type headaches and vitamin D deficiency, vitamin D and calcium supplementation was found to be beneficial in all patients, and thus, they speculated on the possible mechanisms for headaches in relation to vitamin D deficiency. Nevertheless, the effect of vitamin D and B12 supplements on the course of tension-type headaches in the pediatric population is needs to be determined. To the best of this study's authors' knowledge, this is the first study that assessed the relationship between vitamin D levels and the number of attacks comparatively between migraine and tension-type headaches in the pediatric population.

The lack of detailed clinical data, i.e., the severity of the headache and medication used, might be considered a limitation of this study.

CONCLUSION

The study findings revealed a significant relationship between migraine attacks and vitamin D levels in pediatric patients. Therefore, vitamin D supplementation may help prevent headache attacks in this patient population, particularly in migraine patients with a higher frequency of headaches. Additionally, no significant correlation was found between vitamin B12 levels and the total number of days the tension-type headache patients were affected by the headache attacks. The findings of this study support and contribute to the explanation of different mechanisms between migraine and tension-type headaches, the most common headache types seen in children. Randomized clinical trials with larger samples will be required to corroborate the findings of this study.

Ethics

Ethics Committee Approval: The protocol of this retrospective study was approved by the Erciyes University Clinical Research Ethics Committee (decision no: 2016/479, date no: 12.08.2016).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: G.D.K.Ö., M.C., S.K., Design: G.D.K.Ö., E.S., Data Collection or Processing: G.D.K.Ö., M.C., F.K., M.K., H.G., H.P., S.K., Analysis or Interpretation: G.D.K.Ö., Literature Search: G.D.K.Ö., Writing: G.D.K.Ö., E.S.

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

Funding: The authors received no financial support for the research, authorship, and/or publication of this article.

REFERENCES

1. Blume HK. Childhood Headache: A Brief Review. Pediatr Ann. 2017;46:155-65.
2. Calik M, Aktas MS, Cecen E, et al. The association between serum vitamin B12 deficiency and tension-type headache in Turkish children. Neurol Sci. 2018;39:1009-14.
3. Al Momani M, Almomani BA, Masri AT. The clinical characteristics of primary headache and associated factors in children: A retrospective descriptive study. Ann Med Surg (Lond). 2021;65:102374.
4. Karli N, Akiş N, Zarifoğlu M, et al. Headache prevalence in adolescents aged 12 to 17: a student-based epidemiological study in Bursa. Headache. 2006;46:649-55.
5. Ozge A, Termine C, Antonaci F, et al. Overview of diagnosis and management of paediatric headache. Part I: diagnosis. J Headache Pain. 2011;12:13-23.
6. Ayanoğlu M, Tuhan H, Kömürlüoğlu A, Tosun A. Is there a relation between vitamin B_{12} levels and headaches in children and adolescents?. İzmir Dr. Behçet Uz Çocuk Hast. Dergisi. 2021;11:73-9.
7. Togha M, Razeghi Jahromi S, et al. Serum Vitamin B12 and Methylmalonic Acid Status in Migraineurs: A Case-Control Study. Headache. 2019;59:1492-1503.
8. Orr SL. The Evidence for the Role of Nutraceuticals in the Management of Pediatric Migraine: a Review. Curr Pain Headache Rep. 2018;22:37.
9. Gungör, O, Gungör Ş, Acipayam C. The relationship between serum vitamin D levels and pain severity in children with migraine. TP. 2020;1:22-6.
10. Donmez A, Orun E, Sonmez FM. Vitamin D status in children with headache: A case-control study. Clin Nutr ESPEN. 2018;23:222-7.
11. Nowaczewska M, Wicinski M, Osinski S, Kazmierczak H. The Role of Vitamin D in Primary Headache-from Potential Mechanism to Treatment. Nutrients. 2020;12:243.
12. Ghorbani Z, Togha M, Rafiee P, et al. Vitamin D in migraine headache: a comprehensive review on literature. Neurol Sci. 2019;40:2459-77.
13. Aydin H, Bucak IH, Geyik M. Vitamin B12 and folic acid levels in pediatric migraine patients. Acta Neurol Belg. 2021;121:1741-44.
14. Serin HM, Arslan EA. Neurological symptoms of vitamin B12 deficiency: analysis of pediatric patients. Acta Clin Croat. 2019;58:295-302.
15. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018;38:1-211.
16. Sobe H, Richter M, Berner R, et al. Functional improvement in children and adolescents with primary headache after an interdisciplinary multimodal therapy program: the DreKiP study. J Headache Pain. 2022;23:109.
17. Hershey AD, Powers SW, Vockell AL, et al. Development of a patient-based grading scale for PedMIDAS. Cephalalgia. 2004;24:844-9.
18. Albers L, Straube A, Landgraf MN, et al. Migraine and tension-type headache in adolescents at grammar school in Germany - burden of disease and health care utilization. J Headache Pain. 2015;16:534.
19. Nelson KB, Richardson AK, He J, et al. Headache and biomarkers predictive of vascular disease in a representative sample of US children. Arch Pediatr Adolesc Med. 2010;164:358-62.

20. Domitrz I, Cegielska J. Magnesium as an Important Factor in the Pathogenesis and Treatment of Migraine-From Theory to Practice. Nutrients. 2022;14:1089.
21. Yang Y, Zhang HL, Wu J. Is headache related with vitamin D insufficiency? J Headache Pain. 2010;11:369.
22. Kjaergaard M, Eggen AE, Mathiesen EB, Jorde R. Association between headache and serum 25-hydroxyvitamin D: the Tromsø Study: Tromsø 6. Headache. 2012;52:1499-505.
23. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011;96:1911-30.
24. Kılıç B, Kılıç M. Evaluation of Vitamin D Levels and Response to Therapy of Childhood Migraine. Medicina (Kaunas). 2019;55:321.
25. Ghorbani Z, Togha M, Rafiee P, et al. Vitamin D in migraine headache: a comprehensive review on literature. Neurol Sci. 2019;40:2459-77.
26. Liu X, Nelson A, Wang X, et al. Vitamin D modulates prostaglandin E2 synthesis and degradation in human lung fibroblasts. Am J Respir Cell Mol Biol. 2014;50:40-50.
27. Garcion E, Wion-Barbot N, Montero-Menei CN, Berger F, Wion D. New clues about vitamin D functions in the nervous system. Trends Endocrinol Metab. 2002;13:100-5.
28. Mottaghi T, Askari G, Khorvash F, Maracy MR. Effect of Vitamin D supplementation on symptoms and C-reactive protein in migraine patients. J Res Med Sci. 2015;20:477-82.
29. Cayir A, Turan MI, Tan H. Effect of vitamin D therapy in addition to amitriptyline on migraine attacks in pediatric patients. Braz J Med Biol Res. 2014;47:349-54.
30. Prakash S, Shah ND. Chronic tension-type headache with vitamin D deficiency: casual or causal association? Headache. 2009;49:1214-22.