# The Relationship Between Serum Vitamin D Levels and the Severity of Headache in Children with Migraine

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## ABSTRACT

***Objective:*** *Migraine is a primary episodic headache disorder accompanied by neurological, gastrointestinal, and autonomic changes. The aim of this study is to compare vitamin D levels with the severity of headache in patients with migraine.*
***Methods:*** *A total of 108 children diagnosed with migraine were evaluated. We measured vitamin D levels and 25-hydroxy vitamin D3 with the enzyme-linked immunosorbent assay (ELISA) method. Serum vitamin D was defined as <12 ng/ml insufficiency. Serum vitamin D was defined as deficiency in those with 12-30 ng/ml. Serum vitamin D was defined as normal in those with >30 ng/ml. The severity of the headache was assessed according to the Migraine Disability Assessment Score (MIDAS).*
***Results:*** *The mean serum 25-hydroxy vitamin D3 levels of migraine patients was 16.6±5.9 ng/ml. As the level of vitamin D decreased, so the severity of the headache increased, with a higher MIDAS grade ($p<0.05$). No relationship was determined between the MIDAS grade and levels of calcium, phosphorus, and alkaline phosphatase ($p>0.05$).*
***Conclusion:*** *The severity of headache is associated with reduced serum vitamin D levels in children with migraine.*

## INTRODUCTION

Migraine is a common disease characterized by progressive and recurrent headaches in children and adolescents. Its prevalence is about 7.7% [(1)]. Its characteristic features are (i) attacks last more than 4 hours and less than 3 days without medication, (ii) headache is one-sided and throbbing, (iii) patients experience discomfort from light and sound and attacks often accompanied by nausea or vomiting, (iv) pain is moderate or severe [(2-6)].

Vitamin D deficiency is a global public health problem. The incidence of vitamin D deficiency is estimated to be 30-80% in children and adults worldwide [(2,3,7)]. Vitamin D deficiency leads to many health problems including cardiovascular diseases, autoimmune diseases, infectious diseases, diabetes mellitus, osteoarthritis, inflammatory diseases, mental and skin disorders [(8-11)]. Additionally, vitamin D deficiency has been suggested to play an important role in pathogenesis of a number of neurological diseases particularly in migraine [(12,13)].

## MATERIAL and METHODS

In this prospective cross-sectional study, 108 children with recently physician-diagnosed migraine between the ages of 3 and 15 yr were recruited from a tertiary referral pediatric neurology center between December 2017 and December 2019. The demographic data, symptoms and findings at the time of

diagnosis, frequency and duration of the headache, and the diagnostic methods of cranial magnetic resonance imaging (MRI) and electroencephalography (EEG) were recorded.

The diagnosis of migrane was based on diagnostic criteria of the International Classification of Headache Disorders-III (ICHD-III) published by the International Headache Society (IHS) in 2013 [14]. The severity of the headache was determined according to the MIDAS scale as; 0-5: Grade I, 6-10: Grade II, 11-20: Grade III, and ≥21: Grade IV [15]. The participants were assigned to two groups as those with aura and those without aura.

Subjects with any previous neurological diseases (mental retardation, seizure, epilepsy, etc.), any systemic or autoimmune diseases, any drug use (steroids, immunosuppressants, vitamin D supplements, etc.), acute/chronic infection, or hospitalization within the previous four weeks were excluded from the study.

After eight hours of fasting, blood samples were taken from all subjects. The samples were processed immediately by centrifugation at 4000 rpm at room temperature. Laboratory tests including complete blood count, serum calcium, phosphorus, alkaline phosphatase, albumin, vitamin B12 as well as liver, thyroid, and kidney function tests and vitamin D [25-hydroxy vitamin D3, 25(OH)D3] were obtained and measured by routine methods. Study groups were assigned according to serum vitamin D levels as deficiency (<12 ng/ml), insufficiency (12-30 ng/ml), and sufficiency (>30 ng/ml).

The study was approved by the Ethics Committee. Informed consent was obtained from all parents.

**Statistical Analysis**

For statistical analysis, Social Sciences Statistics Package for Windows (SPSS Inc., Chicago) 21 package program was used. Variables were expressed as mean±standard deviation, number (n), and percentage (%). Kolmogorov Smirnov test was used to determine the normal distribution of numerical variables. Student's t test or one-way analysis of variance (ANOVA) was used for the comparison of the parameters with normal distribution. Mann Whitney U-test or Kruskal Wallis test was used for the comparison of non-normally distributed parameters. Chi-square test was used for comparison of categorical variables. One-way ANOVA test was used to determine the arithmetic mean of a dependent variable between two independent groups and whether there was a significant difference. A P value of <0.05 was considered statistically significant.

## RESULTS

There were 108 patients in the study, consisting of 70 female and 38 male with an age of 11.72±3.21 years (range, 6-17 years). A family history of migraine was determined in 42 (38.9%) patients and there was a triggering factor for the pain in 86 (79.6%) patients. According to the history and neurological examination, cranial imaging was applied to 78 (63%) patients (CT to 11 patients, MRI to 67 patients) and the results of those were determined as normal. EEG was determined as normal in all patients. The frequency of headache was reported as every day in 15, 2-6 times per week in 37, once a week in 33, and 1-3 times in a month in 25 patients, respectively. According to the MIDAS grade evaluations, 31 (28.7%) patients were grouped as MIDAS grade 1, 41 (37.9%) were MIDAS grade 2, 21 (19.5%) were MIDAS grade 3, and 15 (13.9%) were MIDAS grade 4, respectively (Table 1).

The mean (±SD) level of vitamin D was 13.37±8.43 ng/ml (range, 1.34 ng/ml-35 ng/ml). The mean level of vitamin D in males was significantly higher than that of females (15.6±8.52 ng/ml vs. 12.1±8.18 ng/ml) (p=0.042). According to vitamin D status, sixty (55.6%) patients were vitamin D deficient, 38 (35.2%) were insufficient, and 10 (9.3%) were sufficient. There was a significant difference among patients with MIDAS Grade 1 and Grade 2 and those with MIDAS Grade 3 and Grade 4 in terms of vitamin D levels (p< 0.001). Also, 95.2% of the subjects with MIDAS Grade 3 and in all subjects with MIDAS Grade 4 were vitamin D deficient (Table 2). Migraine with aura was determined in 19 patients and migraine without aura in 89 patients. There was no difference between patients with aura and patients without aura in terms of the mean vitamin D levels (p=0.121) (Table 2). The rate of vitamin D deficiency in subjects with aura was 47.4% and 57.3% in subjects without

**Table 1. Comparison of vitamin D status among MIDAS grades**

| | MIDAS Grade 1 (n=31) n (%) | MIDAS Grade 2 (n=41) n (%) | MIDAS Grade 3 (n=21) n (%) | MIDAS Grade 4 (n=15) n (%) | p |
|---|---|---|---|---|---|
| Vitamin D deficiency (<12 ng/ml) | 11 (35.5) | 14 (34.1) | 20 (95.2) | 15 (100) | <0.0001 |
| Vitamin D Insufficiency(12-30 ng/ml) | 13 (41.9) | 24 (58.5) | 1 (4.8) | 0 | |
| Vitamin D Sufficiency (>30 ng/ml) | 7 (22.6) | 3 (7.3) | 0 | 0 | |

*Statistics: *Crosstabs-Chi-square. Statistically significant value: (p<0.05)*
***Abbreviations:*** *MIDAS: Migraine Disability Assesment Score*

**Table 2. Comparison of vitamin D levels among study groups**

| | Serum Vitamin D level Mean ± SD | P |
|---|---|---|
| MIDAS Grade 1 | 18.2±6.4 | 0.0001* |
| MIDAS Grade 2 | 16.0±5.7 | |
| MIDAS Grade 3 | 7.1±4.3 | |
| MIDAS Grade 4 | 4.9±1.4 | |
| Migraine with aura | 16.0±11.0 | 0.121** |
| Migraine without aura | 12.8±7.7 | |

*Statistics: *One Way ANOVA, Posthoc=Scheffe Alpha Test, **Student t test, values are given in mean (standard deviation). Statistically significant value: (p<0.05)*
***Abbreviations:*** *MIDAS: Migraine Disability Assessment Score*

**Table 3. Comparison of vitamin D status in patients with or without aura**

| | Migraine with aura n (%) | Migraine without aura n (%) | p |
|---|---|---|---|
| Vitamin D deficiency (<12 ng/ml) | 9 (47.4) | 51 (57.3) | 0.148 |
| Vitamin D Insufficiency (12-30 ng/ml) | 6 (31.6) | 32 (36) | |
| Vitamin D Sufficiency (>30 ng/ml) | 4 (21.1) | 6 (6.7) | |

*Statistics: Crosstabs-Chi-square. Statistically significant value p<0.05*

aura (Table 3). There was no correlation between the scores of MIDAS and serum levels of calcium, phosphorus, and alkaline phosphatase (p=0.574, p=0.148, p=0.893, respectively).

## DISCUSSION

In present study, we found a significant negative relation between the serum levels of vitamin D and severity of migraine. The role of vitamin D in bone mineralization diseases is well defined, also low vitamin D levels may be related to non-specific pain and non-inflammatory skeletal myopathy [16-19]. Many studies reported that low vitamin D levels may be associated with headache [20-22]. In a cross-sectional study of 11.614 subjects, Kjærgaard et al. demonstrated a significantly low level of serum 25(OH)D3 in non-migraine headaches [23]. In another cross-sectional study, lower levels of serum 25(OH)D3 were measured in patients with musculoskeletal pain, fatigue, and headache [24,25]. Prakash et al. found that chronic tension headaches improved with vitamin D and calcium supplements in patients with vitamin D deficiency and osteomalacia [20].

Several studies reported vitamin D deficiency or insufficiency in migraine subjects, while many other studies showed normal levels of vitamin D [8,26]. In a study, authors found a higher serum vitamin D level (50-100 ng/mL) was associated with a lower odds ratio of migraine headaches than those with low serum vitamin D levels (<20 ng/mL) [27]. In another study, it has been reported that serum levels of both vitamin D and vitamin D receptors were lower in subjects with migraine than that of controls [8]. In addition, some studies reported no correlations between the levels of serum vitamin D and some parameters of headache such as aura, severity, and duration [28].

In a few studies, the authors found an increase in migraine attacks in the autumn and winter months and a decrease in vitamin D levels in the same period. The incidence of both migraine and vitamin D deficiency has been reported to increase at higher altitudes far from the equator [29-31]. The prevalence of childhood migraine in Turkey, height above sea level increases the frequency is higher than 2 times [32,33]. The patients in the current study lived in a region of the lowest altitude in Turkey. Prakash et al. showed that there is a relationship between altitude and headache [34]. A similar study found an association between vitamin D deficiency and headache [26].

In a study by Stewart et al, the relationship between severity and characteristics of headache and the MIDAS grade was examined [15]. The MIDAS grades of patients aged <25 years were found to be significantly higher and the MIDAS scale was reported to be reliable. In the current study, it was determined that as the vitamin D level decreased, so there was a significant increase in the severity of the headache. Bıçakçı et al studied university students with migraine and determined severity of MIDAS grade 1 in 49%, MIDAS grade 2 in 19.3%, MIDAS grade 3 in 29.1% and MIDAS grade 4 in 9.7%. In the same study, the rate of migraine without aura was determined as 6%. The low rates were attributed to denial of headaches by university students [35]. In the current study, these rates were higher. On the contrary, when MIDAS grades were evaluated, there was no statistically significant difference between those with migraine with aura and those with migraine without aura.

## CONCLUSION

In the present study we showed that the severity of headache is associated with reduced serum vitamin D levels in children with migraine. The strongest connection reported to date is between serum vitamin D levels and migraine headaches; but our results need to be confirmed by large-scale population based studies.

**Ethics Committee Approval:** Approval was obtained from Kahramanmaras Sutcu Imam University Faculty of Medicine Clinical Research Ethics Committee (22/11/2017/198).

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