

Is Vitamin D Associated with The Presence, Type and Severity of Migraine?

D Vitamini Migren Varlığı, Tipi ve Şiddeti ile İlişkili Midir?

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Öz

Amaç: Migren dünya genelinde yaygın olarak görülen nörovasküler bir hastalıktır. Yapılan birkaç çalışmada D vitamin düzeyleri ile baş ağrısı şiddeti, tipleri arasında ilişki saptanmıştır. Biz de bu çalışmada birincil olarak migren hastaları ile sağlıklı kontroller arasında D Vitamin düzeyleri arasında fark olup olmadığını, ikincil olarak migren tipleri ve şiddeti ile D vitamini düzeyi arasında ilişki olup olmadığını araştırdık.

Hastalar ve Yöntem: Bu vaka-kontrol çalışması Ocak 2021 - Temmuz 2022 tarihleri arasında Necmettin Erbakan Üniversitesi Meram Tıp Fakültesi Nöroloji Bölümünde gerçekleştirildi. Çalışmamıza 18 yaş üstü migren tanısı almış 204 hasta ve baş ağrısı olmayan 204 sağlıklı gönüllü dâhil edildi. Migren tanısı uluslararası baş ağrısı derneği 3 (ICHD-3) kriterlerine göre nöroloji uzmanı tarafından koyuldu.

Bulgular: Migren grubunda ortalama D vitamin düzeyi 15.30±9.93 ng/dl, kontrol grubunda 14.62±7.93 ng/dl idi. Her iki grup arasında istatistiksel açıdan anlamlı fark saptanmadı (p=0.976). Vitamin D eksikliği ve yetersizliği açısından da migren hastaları ile kontrol grubu arasında fark saptanmadı (p=0.365).

Sonuç: Çalışmamızın sonuçlarına göre migren hastaları ile normal popülasyon D vitamini düzeyleri arasında fark bulamadık. Migren alt tipleri arasında da D vitamini düzeyleri arasında istatistiksel bir fark yoktu. Ayrıca migren şiddeti ve migren atak sıklığı ile D vitamini düzeyleri arasında da ilişki saptanmadı. Çalışmamızın sonuçlarına göre D vitamini eksikliği prevalansının yüksekliği hem migren hastalarında hem de sağlıklı popülasyonda ortak sorun olarak gözükmekte olup bu konuda yapılacak geniş örnek sayılı randomize klinik çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Baş ağrısı, migren, vitamin D

Abstract

Aim: Migraine is a neurovascular disease that is common worldwide. In a few studies, a relationship was found between vitamin D levels and headache severity and types. In this study, we primarily investigated whether there was a difference in vitamin D levels between migraine patients and healthy controls, and secondarily, whether there was a relationship between types and severity of migraine and vitamin D levels.

Patients and Methods: This case-control study was carried out between January 2021 - July 2022 at Necmettin Erbakan University Meram Faculty of Medicine, Department of Neurology. 204 patients over the age of 18 who were diagnosed with migraine and 204 healthy volunteers without headache were included in our study. The diagnosis of migraine was made by a neurologist according to the International Headache Society 3 (ICHD-3) criteria.

Results: The mean vitamin D level was 15.30±9.93 ng/dl in the migraine group and 14.62±7.93 ng/dl in the control group. There was no statistically significant difference between the two groups (p=0.976). There was no difference between migraine patients and the control group in terms of vitamin D deficiency and insufficiency (p=0.365).

Conclusion: According to the results of our study, we did not find any difference in vitamin D levels between migraine patients and the normal population. There was no statistical difference in vitamin D levels among migraine subtypes. In addition, no relationship was found between severity and frequency of migraine attacks and vitamin D levels. According to the results of our study, the high prevalence of vitamin D deficiency appears to be a common problem in both migraine patients and the healthy population, and randomized clinical studies with large sample numbers are needed on this subject.

Keywords: Headache, migraine, vitamin D

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INTRODUCTION

Migraine is a common neurovascular disorder that affects 12-15% of the general population. Individuals with migraine experience various issues such as absenteeism and decreased productivity and this puts a heavy burden on the society (1).

Migraine attacks are featured as moderate-to-severe, throbbing, unilateral headaches with nausea, vomiting, phonophobia, and photophobia. The attacks duration usually lasts from a few hours to 2-3 days (2). Approximately 25% of the migraine patients experience an aura, (temporary disturbance in visual, sensory, language or motor functions) before the migraine attacks (3). Migraine is divided into 2 main types according to the frequency of headache. Chronic migraine has more than 15 headache days in a month and episodic migraine has less than 15 headache days in a month (2).

The pathogenesis of migraine is not clear due to various factors. In this context, specific factors such as cytokines (interleukin 1 beta (IL-1B), IL-6 and tumor necrosis factor α (TNF α)), immune cells (mast cells), genes and environmental characteristics play a crucial role. Several treatment options have been developed to target them. (4-5). In addition, various dietary supplements such as magnesium have been suggested to be effective in the prophylactic treatment of migraine. Also one of these is vitamin D (6).

In addition to the beneficial effects of vitamin D on calcium and bone metabolism, in epidemiological and clinical studies; low vitamin D levels have been associated with Alzheimer's, depression, psychosis, autism, autoimmune and endocrine disorders, and cancer (7). Several studies have found that a relationship between vitamin D levels and musculoskeletal pain, headache and chronic pain (8-9). There are also studies in the literature examining the relationship between vitamin D deficiency and migraine. However, this relationship has not been fully demonstrated in all these studies.

In this study, we aimed primarily to show whether there is a difference in vitamin D levels between migraine patients and healthy controls, and secondly, whether there is a relationship between migraine types and migraine severity and vitamin D levels.

PATIENTS AND METHOD

This case-control study was carried out between January 2021 and July 2022 at Necmettin Erbakan University Meram Faculty of Medicine, Department of Neurology. The Necmettin Erbakan University

Meram Medical Faculty Ethics Committee approved the study protocol on March 3, 2023, with the number of 2023/4214.

The study was conducted 204 migraine patients over the age of 18 as study group and 204 age- and gender-matched healthy volunteers as the control group. Migraine diagnosis was settled by a neurologist according to the International Headache Society 3 criteria. Healthy volunteers (who were admitted to the hospital for other reasons) without headache were included as the control group. In both groups; patients with known vitamin D disorders, those using vitamin D in the last 3 months, drugs that affect vitamin D metabolism, those with chronic kidney and liver disease, cancer patients and pregnant women were excluded.

After the diagnosis of migraine was made, the severity of migraine was determined by the Visual Analog Scale (VAS) score and the disability by the Migraine Disability Assessment Score (MIDAS) score. The MIDAS questionnaire validated in Turkish was applied for the MIDAS score. The MIDAS scores between 0-5 were classified as 1st degree, those between 6-10 as 2nd degree, those between 11-20 as 3rd degree and those who were 21 and above were classified as 4th degree (10). According to VAS, according to the point where the patients marked the severity of the pain on the 100 ml VAS line, 0-4 ml pain was evaluated as no pain, 5-44 ml mild pain, 45-74 ml moderate pain, 75-100 ml severe pain (11). Patients were grouped as migraine with or without aura according to whether they had aura or not, chronic migraine for 15 days or more a month headache, episodic migraine for 14 days or less. From the patient's anamnesis, the frequency of migraine attacks, the number of days spent with headache in a month, whether it was episodic or chronic, with or without aura were recorded.

Venous blood was collected from all participants during the first visit, and 25 Hydroxy vitamin D levels were measured were made with the enzyme-linked immunosorbent assay (ELISA, Fortress Diagnostics Limited, United Kingdom) method. Vitamin D measurements were also made in the control group in the same month. Vitamin D level <20 is considered as vitamin D deficiency, 21-29 vitamin D insufficiency, 30 and above were considered as normal (12).

Statistical analysis

Statistical analyzes were performed using the Statistical Package for Social Sciences 21.0 program. Continuous variables were given as mean

± standard deviation if the distribution was normal. Normal distribution was checked by the Kolmogorov-Smirnov test. In the comparison of independent group differences, the test of significance of the difference between two means (Independent samples t-test) was used when continuous variables conforming to normal distribution; Mann-Whitney U test was used to compare independent group differences when continuous variables not conforming to normal distribution. Chi-square test was used to compare categorical variables between independent groups. The comparison of migraine severity, disability scores and vitamin D levels was done with Kruskal-Wallis test. ANOVA test was used for the relationship between different subcategories of vitamin D and migraine characteristics. The correlation between vitamin D levels and migraine clinical features, Pearson or Spearman tests were used according to the distribution characteristics of the data. A p value of <0.05 for the differences was considered statistically significant.

RESULTS

Demographic features

204 migraine patients and 204 healthy volunteers as control groups were included in our study. The number of men and women was equal in both groups (F:176 M:28). There was no statistically significant difference between the two groups in terms of age and gender (p=0.131, p=1.00, respectively). The mean age was 41.73±11.95 years in migraine patients and

43.59±14.86 years in the control group. 155 (76%) of migraine patients had migraine without aura and 49 (24%) had migraine with aura. 120 (58.8%) patients had episodic, 84 (41.2%) patients had chronic migraine.

Serum vitamin D levels

The mean vitamin d level was 15.30±9.93 ng/dl in the migraine group and 14.62±7.93 ng/dl in the control group. There was no statistically significant difference between the two groups (p=0.976). In terms of vitamin d deficiency and insufficiency, no difference was found between migraine patients and the control group (p=0.365)(Table 1).

The mean number of migraine attacks was 6.02±3.37, and the mean number of days spent with headache was 13.03±6.81 days. There was no correlation between the number of migraine attacks, the number of days with headache and vitamin D levels (p=0.505, p=0.835, respectively). There was no difference in the number of attacks in the group with vitamin deficiency, insufficiency or sufficient vitamin D (p=0.467).

The mean vitamin D level was 14.31±8.98 ng/dl in migraine with aura, and 15.61±10.22 ng/dl in migraine patients without aura. There was no statistically significant difference between the two groups (p=0.443). In the aura group, vitamin D deficiency was found in 37 (75.5%) patients, vitamin D insufficiency in 9 (18.4%) patients, and adequate vitamin D in 3 (6.1%) patients. There was no difference between the migraine with aura and migraine without aura groups

Table 1. Comparison of demographic characteristics and vitamin D levels of migraine patients and control group

	Migraine Group (204)	Control Group (204)	p Value
Age(year)	41.73±11.95	43.59±14.86	0.131
Gender(male/female)	28/176	28/176	1.00
Vitamin D levels (ng/mL)	15.30±9.93	14.62±7.93	0.976
Vitamin D levels (ng/mL)			0.365
≥30	14	8	
21-29	39	36	
≤20	151	160	

Table 2. Comparison of migraine characteristics and vitamin D levels

	Episodic Migraine (n=120)	Chronic Migraine (n=84)	p Value	Migraine with aura (n=155)	Migraine without aura (n=49)	p Value
Vitamin D levels (ng/mL)	14.93±9.69	15.82±10.30	0.609	14.31±8.98	15.61±10.22	0.443
Vitamin D levels (ng/mL)			0.072			0.956
≥30	11(%9.2)	3 (%3.6)		11(7,1)	3 (%6.1)	
21-29	27(%22.5)	12(%14.3)		30(19,4)	9 (%18.4)	
≤20	82 (%68.3)	69(%82.1)		114(73,5)	37 (%75.5)	

Table 3. Comparison of migraine severity and vitamin d levels

	Vitamin D level (ng/mL)	p Value
VAS *		0.121
mild	9,35±4,73	
moderate	15,28±8,21	
severe	15,37±10,26	
MIDAS*		0.023
1(0-5 day/month)	15,68±8,20	
2(6-10 day/month)	14,87± 10,07	
3(11-21 day/month)	15,57±10,88	
4 (>21 day/month)	15,28±9,27	

*VAS:Visual Analog Scale MIDAS:Migraine Disability Assessment Score

in terms of vitamin D deficiency or insufficiency ($p=0.956$).

The mean vitamin D level was 15.82 ± 10.30 ng/dl in the chronic migraine group, and 14.93 ± 9.69 ng/dl in the episodic migraine group. There was no statistically significant difference between the two groups ($p=0.609$). 82 (68.3%) patients with episodic migraine had vitamin D deficiency, 27 (22.5%) patients had vitamin D insufficiency, 11 (9.2%) patients had sufficient vitamin D. Vitamin D deficiency was found in 69 (82.1%) patients with chronic migraine, 12 (14.3%) patients had vitamin d insufficiency and 3 (3.6%) patients had sufficient levels of vitamin D. There was no difference between the two groups in terms of vitamin D deficiency or insufficiency ($p=0.072$)[Table 2].

In the migraine group, VAS scores were mild in 2 (1%) patients, moderate in 31 (15.2%) patients, and severe in 171 (83.8%) patients. MIDAS score was found in 30 (14.7%) patients for 0-5 days, 72 (35.3%) patients for 6-10 days, 71 (34.8%) patients for 11-20 days, and 31 (15.2%) patients for 21 days and above. VAS and MIDAS scores and vitamin D levels are shown in the Table 3. There was no difference in terms of VAS criteria and vitamin D levels ($p=0.121$). There was a significant difference between MIDAS 1st degree and MIDAS 3rd degree in terms of vitamin D levels among MIDAS subgroups ($p=0.018$).

There was no significant correlation between VAS and MIDAS scores and vitamin D levels (respectively $p=0.819$, $p=0.747$)

DISCUSSION

According to the results of our study, no difference was found between the mean vitamin D levels of migraine patients and the normal population. Vitamin D levels were found to be similar among migraine subtypes. There was no correlation between migraine

severity, migraine attack frequency and vitamin D levels.

The prevalence of vitamin d deficiency and insufficiency in migraine patients varied between 40-68% and 13-80%, respectively (13-15). The results in our study were 74% for vitamin d deficiency and 19.1% for vitamin d insufficiencies, which were similar to the study of Song et al. (16). Different cut-off values were taken for vitamin d deficiency and insufficiency in different studies, and in our study, no difference was found between migraine patients and the control group in terms of vitamin d deficiency-insufficiency.

When we look at the literature, there are studies showing the relationship between various types of headache and vitamin D. In a study comparing patients with chronic tension-type headache and healthy controls, vitamin D was found to be significantly low in patients with chronic tension-type headache (17). In a study comparing cluster headache, migraine and healthy controls, no difference was found between the groups in terms of vitamin D levels (18). In a study in which migraine, tension-type headache and control groups were compared in the pediatric age group, no difference was found between the groups in terms of mean vitamin D levels (19).

In studies comparing migraine patients and the control group in terms of vitamin D levels, there are studies that found low vitamin D levels in migraine patients compared to the control group, as well as studies that did not find a difference (20-23). In the study of Kjaergaard et al.(13), vitamin D levels were found to be lower in migraine patients who did not smoke compared to the control group, and similar in smokers. In the cross-sectional study of Zandifar et al., in which 105 migraine patients and 110 healthy controls were compared, no difference was found between the case and control groups in terms of vitamin D levels, similar to our study, and vitamin D deficiency and vitamin D insufficiency were found to be similar between the case and control groups (14). Unlike our study, in the study of Rapisarda et al.(23), vitamin D levels in the migraine group were found to be significantly lower than in the control group. In the study conducted by Çelikkilek et al.(24) in which the vitamin D, vitamin D binding protein and vitamin D receptor levels of migraine patients and the control group were compared, significantly lower vitamin D levels were found in the migraine group.

Studies have found conflicting results between migraine type, frequency and severity, and vitamin D level. Similar to our study, in the study of Togha et

al.(25) in 2018 comparing 70 migraine patients and 70 healthy controls, no difference was found between chronic migraine patients and episodic migraine patients in terms of vitamin D levels. In another study comparing chronic migraine and episodic migraine patients, similar results were obtained between the groups in terms of vitamin D levels (26). In the study of Çelikbilek et al.(24), no correlation was found between the frequency of migraine severity and vitamin D levels, vitamin D binding protein, and the number of vitamin D receptors. Similarly, in the study of Zandifar et al.(14), no relationship was found between migraine severity and vitamin D levels. Unlike these studies, in the study of Rapisarda et al.(23), a negative linear correlation was found between vitamin D levels and headache days.

In the literature, high vitamin D levels were found in those living in low latitudes, and this was seen as the reason for the low prevalence of headaches. An increase in the frequency of headaches in the winter months and a decrease in the summer months suggested that low vitamin D levels play a role in the frequency of headaches (27).

The pathogenesis of migraine is not fully understood, and it is stated that vitamin D has an effect on inflammation, pain desensitization and the immune system. The increase in proinflammatory and neuroinflammatory factors in the nervous system causes vasodilation in the arteries and causes pain in the first place. It is stated that vitamin D has beneficial effects in the pathogenesis of migraine due to its anti-inflammatory and immune-regulatory effects (28). In addition, it has been stated that magnesium deficiency has a role in the pathogenesis of migraine, and a direct relationship has been found between magnesium deficiency and vitamin D deficiency (29). Another mechanism is the presence of vitamin D, vitamin D receptor, vitamin D binding protein and 1 alpha hydroxylase enzyme (converts vitamin D to active vitamin D) in the central nervous system, especially in the hypothalamus (30).

There are some limitations of our study. Firstly, our study was conducted in a relatively small group of patients. Absence of body mass index is another deficiency of our study. Dietary or supplementary products and alcohol use that may affect vitamin D levels were not evaluated. Vitamin D binding globulin and vitamin D receptor levels, which may help explain the migraine mechanism, have not been studied.

CONCLUSION

According to the results of our study, the high prevalence of vitamin D deficiency seems to be a common problem in both migraine patients and the healthy population. We did not find a relationship between vitamin D levels and migraine characteristics and severity. However, there is a need for randomized clinical studies with large sample numbers to be conducted on this subject.

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