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Original article

Is low serum 25-hydroxyvitamin D associated with attack frequency and duration in migraine and tension-type headache?

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Summary. *Introduction:* Vitamin D insufficiency is related to a wide range of pathologies of many diseases such as migraine, and vitamin D supplementation may be sufficient for headache relief. The aim of this study was to evaluate the relationship between migraine attack parameters and dietary calcium and magnesium intake by examining the levels of vitamin D in individuals with migraine and tension-type headache, which are the most common headache types. We aimed to evaluate whether headache attack parameters were correlated with vitamin D levels in such patients. *Methods:* The study included 90 participants who were diagnosed with migraine without aura and tension type headache (TTH), aged 20-55 years, and a healthy control group. Individuals' serum vitamin D levels were analyzed. The correlation between migraine attack parameters (severity, frequency, duration) and serum vitamin D levels, dietary calcium and magnesium intake was assessed. The physician calculated the pain intensity score by applying a visual analog scale (VAS). *Results: S*erum vitamin D levels of the three groups were found to be similar ($P > 0.005$). Although the level of vitamin D was lower in TTH, VAS score values were significantly higher in migraine patients than in TTH patients ($P < 0.001$). In migraine patients, attack frequency was higher when vitamin D level was below 20 ng/dL ($P = 0.015$). Vitamin D level below 20 ng/dL was correlated with a higher attack frequency of migraines in the participants with migraine without aura ($r = -0.381$, $P = 0.046$). There was no significant relationship between dietary intake of calcium and magnesium and attack frequency, severity (VAS score) and duration of attack ($P > 0.05$). *Discussion:* Our results show that migraine patients in whom serum vitamin D deficiency is detected should be monitored.

Key words: vitamin D, migraine, tension type headache, attack frequency

Introduction

Migraine and tension-type headache are the most common primary headache types in the world, affecting 80% of people worldwide (1). Genetic, environmental, metabolic, and cultural factors are influential in headache (2). Although tension type headache (TTH) is not as thoroughly examined as migraine, it is the most common type of primary headache (3). Analgesics, antiemetics, anti-migraine medications and prophylactic medicines as well as lifestyle changes can be used to treat headache affecting quality of life (4). Recently, the use of vitamin D supplementation to treat headache has been discussed (5-8).

Insufficiency of vitamin D associated with the formation of many diseases is a common public health problem (9). Although the beneficial effects of vitamin D on the musculoskeletal system are well known, in recent years vitamin D insufficiency has been associated with cardiovascular diseases, hypertension, diabe-

tes mellitus (DM), obesity, metabolic syndrome, some cancer types (pancreas, breast, colon and prostate), autoimmune diseases, respiratory systemic diseases and neuropsychiatric diseases (9-11).

Different mechanisms are involved in the evaluation of vitamin D in relation to neuropsychiatric diseases. The α-1-hydroxylase enzyme, which catalyzes the 1, 25dihydroxy D_3 receptor and vitamin D in its active form, is found in both neurons and glial cells (12). In vitro studies have shown that vitamin D has a neuroprotective effect on brain cells. Dysregulation in the synthesis of various proteins has been found to be associated with cellular functions in rats deficient in vitamin D during the perinatal period (12, 13). The effect of vitamin D on the nervous system was examined and correlated with headache, extremity and joint pain (14). It has been reported that headache attack frequency increases in the autumn and winter months, while attack frequency is lowest in the summer months. This suggests an association with the lack of vitamin D (2).

Straube et al have shown that there is a relationship between a decrease in vitamin D level and incidence of chronic pain (e.g., extremity, joint, neck) (14). Some studies report that vitamin D deficiency may affect headache (4, 5). However, Zandifar et al. (6) found no difference in vitamin D level between patients with migraine and the control group. In addition, there was no relationship between severity of attack and vitamin D. There are also studies that show vitamin D supplementation reducing the frequency of migraine attacks (7, 8). In a few case reports, the effect of vitamin D supplementation on headache was investigated, but these studies have small sample sizes and are difficult to interpret because they are not placebo-controlled studies (5, 7). In the literature, it is reported that the number of studies that inspect the role of vitamin D deficiency in headache is inadequate (4-8, 14). The results of the studies examined were found to be contradictory. The studies comparing 25(OH)D level in migraine, TTH and control are also limited.

The aims of this study are 1) to compare levels of serum vitamin D of the migraine, TTH and control groups; 2) to evaluate the attack parameters of migraine patients according to serum vitamin D status; and 3) to examine the relationship between the attack parameters of migraine patients and vitamin D, dietary calcium and magnesium intake that affect serum vitamin D.

Material and Methods

Subjects

The study included patients aged 20-55 who were diagnosed according to the ICD3-beta version at Gazi University Faculty of Medicine Neurology Clinic and Headache Research and Application Center. The patients were diagnosed with migraine without aura (n:30) and TTH (n:30) between October 2015 and March 2016. Patients with migraine and TTH were diagnosed by a physician. Patients were compared with the control group (n:30), consisting of healthy individuals who were selected by the specialist physician's examination. Pain parameters of patients were assessed by recall method by physician. Women who were menstruating, using oral contraceptives, receiving hormone replacement treatment, pregnant or lactating, or postmenopausal were not included in the study.

At the beginning of the study, the researchers collected general information about the individuals (age, education level, smoking status, etc.) using the questionnaire form and face-to-face interview method. They questioned the individuals about headaches during the previous 1 year. The physician calculated a pain intensity score by applying a visual analog scale (VAS) to evaluate the pain intensity of the individuals. In addition, the migraine patients were questioned about frequency and duration of attacks.

The ethics committee approval for the study was obtained from the Gazi University Clinical Research Ethics Committee (30.06.2014, Decision no. 299, No: 25901600/2448).

Evaluation of Vitamin D Levels

The individuals were asked about duration of time spent in sunlight. Serum 25(OH) D_3 levels were analyzed. The World Health Organization defines "vitamin D deficiency" as serum 25(OH)D below 20 ng/dL and "insufficiency" as below 30 ng/dL (15). In the study, the insufficiency value for vitamin D (25(OH) D) was considered 20 ng/dL.

Dietary Calcium and Magnesium Intake

Researchers assessed dietary calcium and magnesium intake of migraine patients using a 24-hour dietary recall during the study. Dietary calcium and magnesium intakes were analyzed with BEBIS software. The relationship between dietary calcium/magnesium intake and frequency, duration, and severity of migraine attack was evaluated.

Statistical Analysis

Continuous quantitative data were analysed using visual (histogram and probability plots) and analytical methods (Kolmogorov-Smirnov and Shapiro-Wilk tests) to determine whether they were normally distributed. Numeric data were given as median values and interquartile range (IQR) and the differences between groups were evaluated using the Kruskal-Wallis test. Qualitative (categorical) data were given in numeric (N) and percentage (%) values; statistical significance was evaluated using a chi-square test. All analysis of the differences between two groups were performed using the Mann-Whitney U test. The relationships between serum vitamin D levels and attack frequency and between attack parameters and dietary calcium and magnesium intake were analysed using Spearman's correlation test. The statistical significance level was given within a confidence interval of 95%. All the analyses were performed using the Statistical Package for Social Sciences (SPSS) for Windows version 16 software (16).

Results

General characteristics, vitamin D levels, dietary intakes and attack markers of the participants are shown in Table 1. There was no difference in education levels, smoking status, duration of sunlight and vitamin D levels among the groups ($P = 0.942$, $P = 0.914$, $P = 0.056$ and $P = 0.418$ respectively). VAS score values were significantly higher in migraine patients than in TTH patients ($P < 0.001$). Dietary intake of calcium and magnesium also showed similarity between the groups ($P = 0.728$ and P = 0.853 respectively).

The evaluation of some disease parameters according to the vitamin D level of migraine patients is shown in Table 2. There was no statistically significant difference between the two groups related to the duration of sunlight, severity of attack, duration of attack, and dietary magnesium and calcium intakes. However, attack frequency was higher when patients' vitamin D level was below 20 ng/dL ($P = 0.015$).

In addition, there was an inverse correlation between vitamin D level and attack frequency in migraine patients ($R = -0.381$, $P = 0.046$) (Figure 1).

The relationship between dietary daily intakes and migraine attack parameters in migraine patients

Table 1. General characteristics of participants, vitamin D status and attack markers

Characteristics	Migraine (n:30)	Tension-type headache (n:30)	Control (n:30)	p*
Age (years)	35.0±22.00	33.0±20.00	39.0±20.5	0.747
Level of education				
< University level	8 (26.7%)	7 (23.3%)	7 (23.3%)	0.942
> University level	22 (73.3%)	23 (76.7%)	23 (76.7%)	
Smoking				
Yes	4 (13.3%)	5 (16.7%)	4 (13.3%)	0.914
No	26 (86.7%)	25 (83.3%)	26 (86.7%)	
Duration of sun light (min/day)	30.0±15.00	60.0±60.00	30.0±30.00	0.056
Vitamin D levels (ng/dL)				
< 20 ng/dL	15 (50.0%)	20 (66.7%)	18 (60.0%)	0.418
≥ 20 ng/dL	15 (50.0%)	10 (33.3%)	12 (40.0%)	
Attack severity (VAS score)	8.0±1.00	5.0±2.00	-	<0.001**
Dietary calcium intake (mg)	606.8±299.18	613.4±294.50	653.3±309.43	0.728
Dietary magnesium intake (mg)	264.4±111.57	252.7±105.11	263.8±127.62	0.853

** Kruskal-Wallis test was used, **p<0.05*

Table 2. Some variables according to vitamin D status of migraine patients

Variables	Vitamin D status		
	< 20 ng/dL	≥ 20 ng/dL	p*
Vitamin D levels (ng/dL)	12.3±4.82	33.6±43.75	<0.001**
Duration of sun light (min/day)	30.0±60.00	30.0±16.25	0.204
Attack severity	7.0±3.00	8.0±1.25	0.234
Attack frequency (mo)	3.0±5.00	1.0±1.00	0.015**
Attack duration (h)	6.0±56.00	19.5±24.25	0.274
Dietary calcium intake	616.0±336.47	597.5±268.36	1.000
Dietary magnesium intake	267.4±108.41	261.4±118.38	0.870

*mo: per month; h: hours *Mann-Whitney U test was used. **p<0.05*

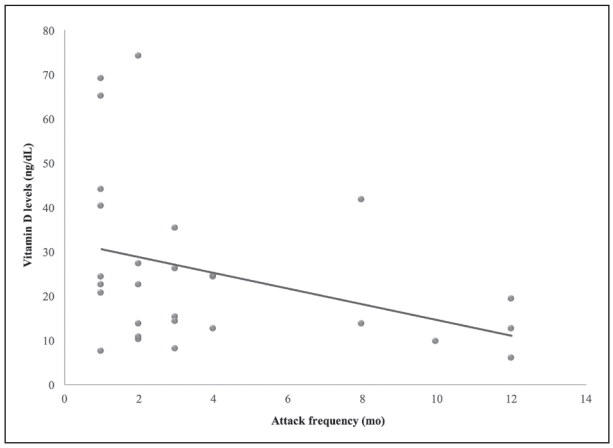

Figure 1. Relationship between vitamin D levels and attack frequency of migraine patients (r = -0.381, p:0.046) *Spearman's correlation test was used.

is shown in Table 3. There was no significant relationship between dietary calcium intake and attack severity, attack frequency (VAS score) or attack duration (P = 0.165, P = 0.422 and P = 0.927 respectively) or between dietary magnesium intake and these parameters (P = 0.093, P = 0.919 and P = 0.126 respectively).

Discussion

Headache is the most common disease of the nervous system. Migraine is the type of headache that involves recurrent attacks throughout the patient's life (17). Attacks of migraine without aura can be moderate or severe, characterized by vomiting and last 4-72 hours (18). TTH is often experienced pressure or tightness around the head, sometimes spreading into the neck during an attack (17). In TTH, muscle pain and weakness in the neck and other muscles can be seen (19). Epidemiological studies have reported a strong correlation between low vitamin D and chronic musculoskeletal pain (20). Studies investigating the effect of vitamin D on headache are also focused on some mechanisms. It is thought that the effect of vitamin D may be due to a decrease in the level of nitric oxide (NO) resulting from iNOS inhibition and an effect of down regulation of L-type calcium channels (21).

Other mechanisms include the regulation of intracellular signal activity and hypomagnesaemia (14), and the effect on the synthesis of serotonin (22), which is related to the development of endothelial dysfunction. However, the results of studies examining vitamin D and headache association are not clear (2,4,6-8,23-25). Lippi et al. (26) reported that the studies examining vitamin D and headache are inadequate. Virtanen et al. (27) found that low vitamin D level is significantly correlated with higher headache frequency in a large sample of men (n: 2601). On the contrary, some studies reported no association between vitamin D and migraine (6, 26). Kjaergaard et al. (23) found

Table 3. Correlations between migraine attack parameters with dietary calcium and magnesium intakes

Parameters	Calcium intake (mg)		Magnesium intake (mg)	
	r	p	r	p*
Attack severity	0.265	0.165	0.318	0.093
Attack frequency (mo)	0.158	0.422	-0.200	0.919
Attack duration (h)	-0.180	0.927	-0.296	0.126

*mo: per month; h: hours * Spearman's correlation test was used.*

no significant association between migraine and vitamin D levels, although they found lower vitamin D in non-migraine patients. Mottaghi et al. (28) showed that migraine had a mild positive correlation (r = 0.19, P = 0.042) with serum vitamin D and daily headache. However, they were not able to find a correlation between migraine severity and vitamin D levels. In this study, serum vitamin D level was found to be similar among the groups (P = 0.418), and it was thought that these results may be due to the similarity of time spent in the sun.

The VDR (vitamin D receptor) gene has broad expression in the central nervous system and VDR agonists have an anti-inflammatory effect (29). Mottaghi et al. (24) studied the relationship between VDR gene polymorphism (i.e., TaqIf/FandFokIt/T) and migraine without aura and found that the heterozygous gene was more frequent in subjects with migraine than in the control group (OR 1.81; 95% CI, 1.03-3.18; = 0.02 for TaqI and OR, 2.91; 95% CI, 1.47-5.77; = 0.001 for FokI, respectively). Although Çelikbilek et al. (30) found no correlation between the level of serum vitamin D and the characteristics of headache (aura, violence, migraine attack frequency and duration), VDR levels were found to be lower in subjects with migraine than in the control group (P = 0.012 and P = 0.038, respectively). In this study, although subjects with migraine and TTH diagnoses have similar serum vitamin D levels, there may be a potential VDR polymorphism in subjects. At this point, VDR agonists and VDR gene polymorphism have been suggested to be effective in preventing the development of migraine attacks (26).

People living in low-latitude regions were found to have a high level of vitamin D. The place of living can be an important factor for low headache prevalence. Migraine attack frequency is high in autumn and winter and lowest in summer. This condition has been reported to be due to the effect of vitamin D on the headache (2). In this study, another important aspect of the effect of serum vitamin D level is the frequency, duration, and severity of attacks in migraine patients. At the end of the study, there was found to be no correlation between serum vitamin D levels of the subjects with migraine and duration and severity of attack (P > 0.05), and the frequency of attack significantly increased as serum vitamin D level decreased (R = -0.381, P = 0.046) The frequency of attacks was also higher (P = 0.015) in subjects with migraine when vitamin D level was below 20 ng/dL. Similar to this study, Knutsen et al. (4) found an inverse relationship between headache frequency and vitamin D level. They showed that there is a correlation between a decrease in headache attack frequency and an increase in the level of vitamin D.

The pathogenesis of TTH involves an abnormality of magnesium metabolism. Brain, blood, monocyte, platelet and erythrocyte magnesium have been found in patients with TTH and other headaches (5). In addition, Altura (31) reported that magnesium supplementation is beneficial for muscle tension or scalp tension in any other type of headache. Vitamin D deficiency may cause TTH by reducing absorption of magnesium because absorption of magnesium from food is dependent on vitamin D (5, 32). However, in this study, dietary magnesium intake was not found to be associated with migraine attack frequency. It is noteworthy that dietary magnesium intake is below the recommended amount in all groups.

Overuse of headache drugs worldwide is remarkable (33). The effectiveness of vitamin D to treat headache is controversial. Theoretically, vitamin D supplementation has a beneficial effect on pain by affecting inflammation (4). In case-control studies, vitamin D and calcium supplementation have been shown to reduce migraine attack (7, 8). At the same time, vitamin D may be associated with migraine because of its neuroprotective and antioxidant effects in the central system (34). In other studies, inflammatory markers such as C-reactive protein have been shown to decrease with vitamin D supplementation (25).

In this study, a relationship between dietary calcium and attack frequency in migraine patients was not found. Tys-Jacobs (7) showed that vitamin D and calcium supplementation treatment significantly reduces the duration and frequency of migraine pain of postmenopausal women. Prakash and Shah (5) reported that patients with TTH (n:8) with osteomalacia and bone pain with a vitamin D level of ≤10 ng/mL showed improvement in headache in 4-6 weeks with high-dose D vitamin (1500 IU vitamin D_3) and 1000 mg of calcium. However, participants of these stud-

ies are postmenopausal women and individuals with bone disease. This effect may be related to vitamin D and calcium effect on bone metabolism. There was no vitamin D supplementation in our study. Although vitamin D supplementation is not routine therapy for migraine, further studies with larger sample groups may find a positive effect on headache patients.

Conclusion

When study data were evaluated, serum vitamin D levels were found to be similar between the migraine, TTH and control groups. The level of serum vitamin D may only influence migraine attack frequency. Especially in patients with migraine, vitamin D is associated with a decrease in the frequency of attacks, although not related to severity of pain, suggesting that the level of vitamin D in the patient group above 20 ng/dL may be even more important. Vitamin D deficiency plays a role in primary headaches. The mechanism in vitamin D and headache is still unclear. Dietary magnesium and calcium intake, which affect dietary vitamin D intake, were assessed but were not associated with migraine attack parameters. Therefore, it may be useful to perform randomized prospective vitamin D, magnesium and calcium supplement studies by expanding the sample group for migraine attack parameters.

Limitations

This study included a small sample size because of signed protocol time with the hospital. This study was not an intervention study. This was a case-sectional study based on retrospective patient reports and conclusions may be limited due to recall bias. Serum calcium and magnesium were not analyzed. This analysis may be useful for correlation with dietary calcium and magnesium intake.

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