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Research Article

Evaluation of the Relationship Between Serum Level of Vitamin D3 and Endothelial Function Tests in Patients with Migraine Headache

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Abstract

Introduction: Migraine is a severe headache type and has a negative effect on quality of life**.** Studies have confirmed the presence of vitamin D receptors in different regions of the human brain and the relation between vitamin D deficiency and neurologic disorders. Here we evaluated the association between migraine features and serum vitamin D levels.

Method: In this case analytical study, we included patients who were referred to the General Neurology Clinic from march 2020 to march 2021 with these criteria: Over 18 years of age, having a diagnosis of migraine with at least 3 attacks per month. Exclusion criteria included risk of vascular diseases including a history of heart attack or stroke, diabetes, hypertension, smoking, peripheral vascular disease, patients using statins, and patients who were in the acute migraine attack phase. Flow mediated dilation (FMD) of the brachial artery depending on the blood flow and carotid intima-media thickness (IMT) score were measured for the participants.

Results: The correlation coefficient between FMD and IMT values was r = -0.428 (p = 0.003). This association was not notable in migraine patients with aura (p = 0.065) but in the group of patients without aura, the results were significant (r = 0.379, p = 0.025). FMD and IMT were not associated with serum vitamin D level in all patients (p = 0.802 and p = 0.785 respectively).

Conclusion: We did not found a correlation between serum vitamin D level and FMD or IMT in migraine. FMD and IMT were correlated with each other only in patients without aura. Further studies are needed to investigate the role of vitamin D level in migraine features.

Keywords: Vitamin D; Migraine; Flow Mediated Dilation; Carotid Intima-Media Thickness

Introduction

Migraine is a common, intense and disabling neurovascular disorder, which is the sixth cause of disability among neurological disorders in the world [1]. The prevalence of migraine is reported to be about 15% to 18% worldwide, and is increasing annually [2,3]. In the united states of America, one out of 4 individuals experience severe headaches including migraine [4]. The economic burden of migraine is estimated to be about 19.6 billion US dollars, considering chronic and episodic migraines [5]. Migraine is characterized by severe headaches on one side of the head, pain that throbs or pulses, photophobia (sensitivity to light), phonophobia (sensitivity to sound) and sensitivity to other triggers and has a negative effect on quality of life and functioning of individuals dealing with it [6,7]. Symptoms including tiredness, irritability, decreased focus and yawning can appear 48 hours prior to headache attacks [8]. The most common trigger to induce migraine is starvation and not having enough meals which is more prominent in young adolescent [9]. Migraine is associated with

cardiovascular incidents such as an increased risk of ischemic stroke, ischemic heart disease and claudication [10-13]. The reason for increased risk of such incidents in individuals with migraine is still unknown, though there are theories to explain the correlation. According to one of these theories, vascular endothelial disorders initiate the problem [14-16]. Vitamin D influences multiple organs in the body including the cardiovascular system. There are a few pathophysiologic pathways explaining the mentioned correlation such as the effect of vitamin D on endothelial functioning, cytokine release and endothelial growth factor release [17].

Low serum level of vitamin D is associated with a wide spectrum of disease and disorders. As an example of cardiovascular disorders, the low level of vitamin D is related to high blood pressure, diabetes, stroke, ischemic heart disease and heart failure [18]. Vitamin D deficiency is also connected to chronic pain, depression and various neurologic disorders [19-21]. Studies have confirmed the presence of vitamin D receptors in different regions of the human brain and confirmed the role of vitamin D as a neuroactive element in the body. Furthermore, vitamin D plays a major role in inflammation, immunity and neurotransmitter metabolism [22]. In addition, vitamin D is related with severe headaches and can be effective in management and control of migraine headaches [23,24]. Considering the cardiovascular disorder basis of migraine and the role of vitamin D in vascular endothelial functioning, we decided to evaluate the association between migraine and serum vitamin D levels.

Methods

In this case analytical study, patients over 18 years of age with a diagnosis of migraine (according to IHS criteria with at least 3 attacks per month) who were referred to the General Neurology Clinic from march 2020 to march 2021 were enrolled. Patients were selected based on definite diagnosis of migraine according to International Classification of Headache Disorders (ICHD-3) criteria [23]. Exclusion criteria included risk of vascular diseases including a history of heart attack or stroke, diabetes, hypertension, smoking, peripheral vascular disease, patients using statins, and patients who were in the acute migraine attack phase. Before the inclusion in the study, a written consent was obtained from all the participants. Information was obtained from all the participants using research questionnaire that included age, gender, number of years of migraine, duration of headache attacks, number of monthly attacks and type of medication used. Also blood samples from both patients and control group were taken in order to determine the serum level of vitamin D3. The patients were sub-divided into two groups with and without aura based on ICHD-3 criteria [23]. Ultrasonic assessment was performed for the patients and carotid intima-media thickness (IMT) score were measured for them.

FMD measurement

According to the protocol, the endothelial function of the brachial artery was measured by FMD (flow mediated dilation of the brachial artery depending on the blood flow).We used high frequency Doppler ultrasound probe for the measurements of the brachial artery. Color mode adjustment was made prior to obtaining the images. For measuring the baseline value of the vessel diameter, we inflated the cuff to 50 mm Hg above the systolic pressure. After 5 minutes of blood flow interruption, the cuff was deflated. Due to sudden increase of blood in the artery, shear stress on the wall would cause NO release from the endothelial cells, leading to vasodilation. After 60 to 90 seconds, as the vessels became dilated, the vessel diameter was recorded and the FMD was obtained by dividing the vessel diameter change by basal diameter, multiplied by 100.

Statistical analysis

The statistical analysis was performed using SPSS v26. Descriptive statistics was described as mean ± SD. If the data distribution was not normal, it was presented as a median and a quarter. ANOVA was used to analyze the differences between the groups and Post hoc table was compiled to separate these differences by Bonferroni test. Pearson correlation was used to examine the relationship between different variables. The chi-square test was used to compare categorical variables. Independent sample t-test is used to compare non-normally distributed data and Mann-Whitney U test was used for normally distributed ones. P value <0.05 was considered significant.

Ethics

This research was conducted according to institutional and national policies. All stages of the project were approved by the Research Ethics Committee. The informed consent was obtained from all patients prior to using their clinical data.

Results

Demographics

47 patients were included in our study. 63.8% (30 patients) were female. The mean age of the participants was 35.77 ± 6.27 years. Twelve (25.5%) patients had migraine with aura and the remaining had no aura. The duration of migraine was 3.89 ± 3.42 years and the mean number of attacks per month was 9.28 ± 5.29. The mean duration of headache episodes was 13.81 ± 18.19 hours. The correlation coefficient between the duration of headache episodes and the duration of migraine was 0.389 (p = 0.007). In the group of patients without aura, the relationship between the duration of headache episodes and the duration of the migraine was 0.489 (p = 0.003). This was not significant for the aura migraine group (p = 0.436). Age and gender were not significantly different in aura and without aura patients. (p = 0.67 and p = 0.53 respectively). Gender was also not significantly correlated with the duration of migraine, number headaches per month, duration of headache episodes, and age (p = 0.421, p = 0.808, p = 0.385, p = 0.223, respectively). Detailed demographics and characteristics of patients are presented in table 1.

	Patients with aura	Patients without aura	Total patients
N	12	35	47
Age (Mean ± SD)	34.92 ± 6.09	36.06 ± 6.39	35.77 ± 6.27
Female (%,n)	66.7%,8	62.9%,22	63.8%,30
Male (%,n)	33.3%,4	37.1%,13	36.2%,17
mean number of attacks per month	10.33 ± 4.84	8.91 ± 5.45	9.28 ± 5.29
The mean duration of headache episodes	17.08 ± 22.10	12.69 ± 16.87	13.81 ± 18.19
Migraine Duration (years)	4.83 ± 4.92	3.57 ± 2.72	3.89 ± 3.42
IMT	0.45 ± 0.10	0.37 ± 0.12	0.39 ± 0.11
Number of the increased risk of cardiovascular accidents based on IMT (%,n)	33.3%,4	14.3%,5	47.6%,9
FMD	-7.07 ± 6.65	-8.28 ± 6.16	-7.88 ± 6.27
Serum Vitamin D level (ng/mL)	20.333 ± 9.828	19.500 ± 12.453	19.71 ± 11.74

Table 1: Demographic data of the patients with migraine.

FMD

The mean FMD calculated for all participants was -7.877 ± 6.277. The mean FMD in patients with aura and without aura was 07/7 ± 6.65 and 8.28 ± 6.16, respectively. There was no difference of FMD in gender and type of headache groups (p = 0.7 and p = 0.9 respectively). There was a significant association of the number of attacks per month and FMD in the aura group (0.613, p = 0.034). The association was not seen for patients without aura (p = 0.924).

IMT

The mean IMT score was 0.391 ± 0.119 in all patients. The mean IMT score among patients with aura and without aura was 0.45 ± 0.1 and 0.37 ± 0.12 respectively. The increased risk of cardiovascular accidents based on the IMT index was observed in 33.3% of the patients with aura (4 patients) and in 14.3% of patients without aura (5 patients) and the differences observed between them were not statistically significant (p = 0.148). There was no difference between the two genders in IMT (p = 0.372). The correlation between the duration of headache and IMT was statistically significant (0.303, p = 0.038).

Vitamin D

The mean serum vitamin D level was 19.713 ± 11.741 ng/mL in all patients. The mean serum vitamin D in patients with aura and without aura was 20.333 ± 9.828 and 19.500 ± 12.453 ng/mL respectively and there was no difference between them (p = 0.85). In females, serum vitamin D level was 19.250 ± 12.347 ng/mL and it was 20.259 ± 10.905 ng/mL in males. There was no significant difference between females and males (p = 0.724). FMD and IMT were not associated with serum vitamin D level in

all patients (p = 0.802 and p = 0.785 respectively). Also, FMD was not associated with serum vitamin D level in patients with aura (p = 0.306), without aura (p = 0.431), females (p = 0.431) and males (p = 0.472). Like FMD, IMT was not correlated with serum vitamin D level in patients with aura (p = 0.383), without aura (p = 0.571), females (p = 0.409) and males (p = 0.478).

Other

The correlation coefficient between FMD and IMT values was r = -0.428 (p = 0.003). This association was not notable in migraine patients with aura (p = 0.065) but in the group of patients without aura, the results were significant (r = 0.379, p = 0.025).

Data on the use of different medication were recorded in 18 patients (Table 2). There were no significant differences between the drug groups in terms of FMD and IMT values (p = 0.834 and p = 0.532). The intake of medications was also not significantly associated with duration of migraine, number of headaches per month, and duration of headache (p = 0.592, p = 0.394, and p = 0.971, respectively).

	Medication	Mean	Standard Deviation
FMD	NSAIDs	48/6	06/6
	Acetaminophen	26/5	59/2
	Ergotamine	92/7	20/7
	Total	45/6	44/5
IMT	NSAIDs	364/0	128/0
	Acetaminophen	400/0	182/0
	Ergotamine	467/0	115/0
	Total	389/0	136/0
Migraine Duration	NSAIDs	45/4	14/3
	Acetaminophen	00/6	05/6
	Ergotamine	00/3	00/2
	Total	56/4	69/3
The mean number of attacks per month	NSAIDs	73/10	72/6
	Acetaminophen	00/6	44/2
	Ergotamine	67/10	13/5
	Total	67/9	90/5
The mean duration of headache episodes	NSAIDs	27/14	18/20
	Acetaminophen	50/14	33/22
	Ergotamine	33/17	54/11
	Total	83/14	56/18

Table 2: Data on the use of different medication in patients with migraine.

Discussion

In this study, we reported that serum vitamin D level was not significantly correlated with FMD or IMT in patients having migraine with or without aura. FMD and IMT values were only significantly correlated in patients without aura. Also, number of attacks per month and FMD was significantly associated in those migraine patients with aura whereas this wasn't notable in patients without aura. The correlation between the duration of headache and IMT was statistically significant. There was no significant association between the intake of medication and migraine features surveyed in this study.

In contrast to our study, a clinical trial study conducted by Gazerani., *et al*. reported that patients who took D3-Vitamin had less migraine attacks than those who took placebo by 24 weeks after follow-up, but the severity of migraine and pain threshold were not different [24]. A study by Mottaghi., *et al*. demonstrated a significant positive association between serum levels of vitamin D and headache diary results and no significant relationship between serum vitamin D and migraine severity [25]. Consistent with the present study, in the another study performed by Zandifar., *et al*. there was no significant relation between vitamin D concentration and frequency of headaches per month, presence of nausea, positive family history of migraine, duration of headache, and headache aggravation with menstruation [26]. It has been shown that vitamin D status has a much stronger relationship with headache rather than either musculoskeletal pain or fatigue [27]. In a review study, Straube., *et al*. claimed that high quality evidences had not found any convincing relationship between chronic pain and vitamin D status [28]. Kjaergaard., *et al*. in a cross-sectional study with a large sample concluded that low level vitamin D is related to non-migraine type headache [29]. They had some limitations since they used a questionnaire to identify patients rather than identifying them clinically and did not determine the relationship

between severity and frequency of headaches and vitamin D. According to these findings, more studies are needed to investigate this relationship in detail by eliminating confounding factors, in migraine and non-migraine type headaches.

Although some medications such as sodium valproate, propranolol, and topiramate are used in the prevention of migraine, the American Headache Society and the American Academy of Neurology listed riboflavin as a probably effective nutritional supplement in the guidelines [30]. Our study does not suggest vitamin D testing in patients with migraine as necessary, although due to the strong role of vitamin D in the nervous system function and cardiovascular system, its daily intake should be sufficient, but its exact role in the pathophysiology of migraine is still doubtful [31].

IMT as a marker of atherosclerosis and ischemic stroke is higher in patients with migraine and stroke since they share the similar physiopathology [32]. In the other hand, the intracranial dilation mediated by nitric oxide is another underline mechanism of migraine attacks and these patients have higher FMD index [33]. In a survey leaded by T Yan., *et al*. [34], which studied 1,578 middle-aged men without known cardiovascular disease, it has been shown that there is no significant correlation between carotid IMT and brachial artery FMD. In another cross-sectional study by Larsen., *et al*. no relationship between FMD and migraine or other headache disorders was found and therefore it is not a useful tool in the evaluation of migraine or other headaches in otherwise healthy people [34]. We found a negative correlation between FMD and IMT in patients with migraine. A study conducted by Gonza´lez-Quintanilla., *et al*. indicates that patients with chronic migraine had low FMD and high IMT compared to those with periodic migraine [35]. According to this study, IMT is increased in patients with chronic migraine independent of age, smoking habits, body mass index, and hypertension. Both intracerebral and systemic arteries in migraine patients had altered vasoreactivity. A strong positive correlation of endothelial dysfunction and increased IMT with erythrocyte sedimentation rate, C-reactive protein and fibrinogen, suggested that this findings are related to inflammation. From these results, it can be concluded that although these two indexes are increased in migraine patients, they have a negative correlation with each other. It has not revealed that which is a stronger predictor for severity and prognosis of migraine. Also, these IMT and FMD had no relationship with the level of vitamin D intake.

In contrary to our study, Yilmaz Avci., *et al*. reported that consumption of triptan and ergotamine were independently associated with right and left internal carotid artery IMT [36]. Our results showed no association between medication intake and FMD and IMT values which is due to lack of a large sample size.

There are some limitations to our study. First, the present study is cross-sectional, hence, we cannot show a causal link, and thus, more clinical trial studies are needed to be performed. Second, our sample size is relatively small and other studies with larger sample sizes should be performed to confirm our hypothesis. Third, migraine and migraine aura status were self-reported, leading to potential misclassification. Therefore, we recommend further studies regarding these issues.

Conclusion

So far, the relation between vitamin D and migraine features is not clear in previous studies. In this study, we found that serum vitamin D level was not correlated with FMD or IMT in migraine. More studies are needed to investigate this relationship.

Consent

We have obtained written informed consent to publish the details from the affected individuals.

Health and Safety

We confirm that all mandatory laboratory health and safety procedures have been complied within the course of conducting any experimental work reported in this paper.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author, FA. The data are not publicly available due to restrictions and their containing information that could compromise the privacy of research participants.

Disclosure if Interest

The authors report no conflict of interest.

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