

The potential role of serum vitamin D level in migraine headache: a case–control study

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Mona Hussein¹
Wael Fathy²
Rehab M Abd Elkareem³

¹Department of Neurology, Beni-Suef University, Beni-Suef, Egypt; ²Department of Anaesthesia and Pain Management, Beni-Suef University, Beni-Suef, Egypt; ³Department of Clinical and Chemical Pathology, Beni-Suef University, Beni-Suef, Egypt

Purpose: Much concern was directed toward exploring the relationship between vitamin D and migraine. There is strong evidence that vitamin D supplementation can decrease frequency, severity, and duration of migraine headache attacks. The aim of this work was to investigate the difference in serum levels of 25 (OH)-vitamin D between patients with migraine and healthy controls, to determine the differences in headache characteristics according to vitamin D status, and to correlate serum 25 (OH)-vitamin D level with duration, frequency, and severity of migraine headache attacks.

Patients and methods: This is a case–control study conducted on 40 patients diagnosed with migraine and 40 healthy controls. History was taken from patients with migraine regarding headache characteristics. Migraine severity scale (MIGSEV) and Headache Impact Test-6 (HIT-6) were used for migraine assessment. Serum 25(OH)-vitamin D was measured for all patients and controls using enzyme-linked immunosorbent assay (ELISA).

Results: Patients with migraine had significantly lower 25(OH)-vitamin D serum level in comparison to controls (P -value=0.019). The incidence of aura, phonophobia/photophobia, autonomic manifestations, allodynia, and resistance to medications were significantly higher in migraineurs with vitamin D deficiency than those with normal vitamin D. There was a statistically significant negative correlation between 25(OH)-vitamin D serum level and attack duration in hours (P -value<0.001), frequency of the attacks/month (P -value<0.001), MIGSEV scale (P -value=0.001), and HIT-6 scale (P -value=0.001).

Conclusion: Patients with migraine had significant vitamin D deficiency compared to healthy controls. Such deficiency significantly affects headache characteristics, duration, frequency, and severity of headache attacks.

Keywords: MIGSEV, HIT-6, 25(OH)-vitamin D, ELISA

Introduction

Migraine and tension headache are the most common primary headache disorders that affect 80% of the people all over the world.¹ Global estimation of migraine headache prevalence showed that migraine affects 1 in 10 people worldwide.² It affects 6% of the men and 18% of the women and has a peak incidence in ages between 25 and 55 years.³ A systematic analysis for the Global Burden of Disease (GBD) Study in 2015 considered migraine headache as the second largest contributor of disability-adjusted life years (DALYs) among all neurological disorders.⁴

Migraine attacks are characterized by being moderate-to-severe, pulsating, unilateral, associated with nausea, vomiting, phonophobia, and photophobia. The attack usually lasts from several hours to 2–3 days.⁵ About 25% of the patients with migraine perceive an aura, which is a transient disturbance in visual, sensory,

Correspondence: Mona Hussein
Department of Neurology, Beni-Suef University, Salah Salem Street, Beni-Suef 62511, Egypt
Tel +20 100 513 1318
Email mona.neuro@yahoo.com

language, or motor function preceding the migraine attack. Migraine headache is caused by the release of pain-producing inflammatory mediators around the cranial nerves and blood vessels. Such mediators induce vascular smooth muscle dysfunction.^{6,7}

Options for migraine treatment remain unsatisfactory because of the reported lack of effectiveness and the significant side effects. Thus, efforts to identify more effective well-tolerated therapy for preventing migraine remain urgent.⁸

In recent years, vitamin D deficiency has been reported as a global public health problem. Prevalence of vitamin D deficiency ranged between 30% and 50% in normal populations.^{9,10} Despite high sun exposure in middle eastern countries, these countries are considered among the highly prevalent areas for vitamin D deficiency in the world.¹¹

There is strong evidence supporting an association between vitamin D deficiency and chronic pain.¹² Much concern was directed toward the presence of a possible relationship between vitamin D and migraine.^{13–15} Vitamin D was found to have a role in the pathways involved in the pathogenesis of migraine including pain sensitization, inflammation, and immune dysfunction.^{16,17} On the molecular level, Motaghi et al revealed that vitamin D receptor (VDR) gene polymorphisms may increase the risk for developing migraine without aura.¹⁸

Aim of this work

The aim of this work was to investigate the difference in the serum levels of 25-hydroxy vitamin D (25(OH) vit D) between patients with migraine headache and healthy controls. The secondary objectives were to determine the differences in headache characteristics according to vitamin D status and to correlate serum 25(OH)-vitamin D level with duration, frequency, and severity of migraine headache attacks.

Materials and methods

Study design

The present study is a case–control study. It was conducted on 40 patients diagnosed as having migraine headache with or without aura and 40 normal healthy controls. The patients were recruited in the period between October 2017 and October 2018 from the Neurology outpatient clinic and Pain clinic in Beni-Suef University Hospital, Egypt. A written informed consent was obtained from each

participant in this study or from parent or legal guardian for participants under the age of 18 years. The study was conducted in accordance with the Declaration of Helsinki. The study was approved by local ethical committee in Faculty of Medicine, Beni-Suef University, Egypt. The committee's reference number is FWA00015574.

Inclusion criteria

Selected patients fulfilled the criteria for diagnosis of migraine headache based on International Classification of Headache Disorders-II (ICHD-II) diagnostic criteria.⁷ The age of the selected patients ranged between 15 and 55 years.

Exclusion criteria

Patients in the migraine group were excluded from the study if they have secondary headache, bilateral papilledema, or magnetic resonance imaging (MRI) showing structural brain lesion. Patients with a history of concomitant medical or metabolic illness known to affect vitamin D level, such as infectious disorders, liver or kidney disease, gastrointestinal disease, cancer, sarcoidosis, or tuberculosis, were also excluded. Participants in both groups were excluded from the study if they consumed vitamin D supplements in the preceding 3 months (any dose); or if they were taking medications that could affect vitamin D serum level such as glucocorticoids, thiazide diuretics, or statins. Pregnant were also excluded from the study.

Participants of this study were subjected to the following

History taking regarding

The frequency of headache attacks/month, the duration headache attacks, the presence of aura, nausea/vomiting, phono/photophobia, autonomic manifestations, allodynia, and resistance to medications.

Migraine assessment

The Headache Impact Test-6 (HIT-6)

It consists of six items: pain, role functioning, social functioning, vitality, psychological distress, and cognitive functioning. The patient has to answer each of the six questions using one of the following five responses: “always”, “very often”, “sometimes”, “rarely”, or “never”. The total HIT-6 score ranges between 36 and 78, where a higher score of the test indicates a greater impact of migraine headache on daily activities.^{19,20}

Migraine severity scale (MIGSEV)

It is used for assessment of migraine severity. It includes the following items: nausea, tolerability, disability in daily activities, and intensity of pain. It categorizes patients according to intensity of headache into three groups; mild, moderate, and severe.²¹

Laboratory assessment

Fasting early morning (5 mL) venous blood samples were collected from all included subjects in 6 mL plain tubes then centrifuged within 30 mins of collection. The serum samples were frozen at -20°C . Serum 25-hydroxyvitamin D [25(OH)D] was considered to be the most reliable indicator for assessment of vitamin D status, so it was measured using enzyme-linked immunosorbent assay (ELISA) using Stat Fax 303Plus equipment. Measuring range was 5–120 ng/mL. Results of serum vitamin D were classified into deficiency or insufficiency (serum vitamin D < 30 ng/mL) and sufficiency (serum vitamin D \geq 30 ng/mL).

Statistical methods

The sample size calculation was done using G*Power version 3.1.9.2 Software based on a pilot study done preceding the present study. The probability of type I error (α) was 5%, and the power ($1-\beta$) was 80%. A total of 80 participants were required for the statistical significance (40 patients and 40 age- and sex-matched healthy controls). The data were coded and entered using: the statistical package for social science version 18 (SPSS v 18). Independent sample Student *t*-test was used for comparison between means of quantitative variables in migraine and control groups. Chi-square test was used for comparison between categorical data in migraine and control groups and also in migraine patients with normal vitamin D level and those with vitamin D deficiency. The Pearson correlation coefficient (*r*) was used to describe the degree of relationship between 25(OH)-vitamin D serum level and duration of migraine attack in hours, frequency of the attacks/month, MIGSEV scale and HIT-6 scale. The probability/significance value (*P*-value) \geq 0.05 is not statistically significant and < 0.05 is statistically significant.

Results

The mean age of patients in migraine group (*n*=40) was 32.18 ± 7.47 years, whereas, the mean age of subjects in control group (*n*=40) was 28.8 ± 8.25 years. In migraine group, 30% (*n*=12) of the patients were males and 70% (*n*=28) were females, whereas, in control group, 35%

(*n*=14) of the subjects were males and 65% (*n*=26) were females. There was no statistically significant difference between both groups in either age (*P*-value=0.059) or sex (*P*-value=0.633) (Table 1).

The clinical characteristics of migraine regarding attack duration in hours, frequency of the attacks/month, side of migraine, aura, phonophobia/photophobia, autonomic manifestations, allodynia, resistance to medications, MIGSEV scale, and HIT-6 scale are demonstrated in Tables 2 and 3.

The mean value of 25(OH)-vitamin D serum level for patients in migraine group (*n*=40) was 32.11 ± 18.93 ng/mL, whereas, the mean value of 25(OH)-vitamin D serum level for subjects in control group (*n*=40) was 41.86 ± 17.52 ng/mL. There was a statistically significant difference between both groups (*P*-value=0.019) (Table 4).

Table 1 Demographics of patients and control groups

		Migraine group (<i>n</i> =40)	Control group (<i>n</i> =40)	<i>P</i> -value
Age in years [mean (SD)]		32.18 (7.47)	28.8 (8.25)	0.059
Sex	Male [n (%)]	12 (30%)	14 (35%)	0.633
	Female [n (%)]	28 (70%)	26 (65%)	

Note: *P*-value \geq 0.05 (non significant).

Table 2 Clinical characteristics of migraine in patients group

		Patients (<i>n</i> =40)
Attack duration in hours [mean (SD)]		14.23 (13.2)
Frequency of the attacks/month		7.58 (5.14)
Side	Unilateral [n (%)]	24 (60%)
	Bilateral [n (%)]	16 (40%)
Aura	Present [n (%)]	17 (42.5%)
	Absent [n (%)]	23 (57.5%)
Phonophobia/ Photophobia	Present [n (%)]	25 (62.5%)
	Absent [n (%)]	15 (37.5%)
Autonomic manifestations	Present [n (%)]	12 (30%)
	Absent [n (%)]	28 (70%)
Allodynia	Present [n (%)]	20 (50%)
	Absent [n (%)]	20 (50%)
Resistance to medications	Resistant [n (%)]	17 (42.5%)
	Responsive [n (%)]	23 (57.5%)

Table 3 Scales for migraine assessment in patients group

		Patients (n=40)
MIGSEV scale [mean (SD)]	Intensity	2.15 (0.83)
	Disability	1.65 (0.7)
	Tolerability	1.55 (0.64)
	Nausea	2.13 (0.85)
	Total score	7.45 (2.58)
HIT-6 scale [mean (SD)]		60.05 (4.99)

Abbreviations: MIGSEV, migraine severity; HIT-6, The Headache Impact Test-6.

Table 4 25(OH)-vitamin D in migraine patients and control group

	Migraine group (n=40)	Control group (n=40)	P-value
25 (OH)-vitamin D in ng/mL	32.11 (18.93)	41.86 (17.52)	0.019*

Note: *P-value<0.05 (significant).

In migraine group, 35% of the patients (n=14) had normal vitamin D level (≥ 30 ng/mL) and 65% (n=26) had vitamin D deficiency (<30 ng/mL), whereas, in control group, 70% (n=28) of the subjects had normal vitamin D level (≥ 30 ng/mL) and 30% (n=12) had vitamin D deficiency (<30 ng/mL). There was a statistically significant difference between both groups (P-value =0.002) (Table 5).

Migraine patients and controls were stratified according to 25(OH)-vitamin D serum level into subjects with severe vitamin D deficiency (<12 ng/mL), subjects with mild vitamin D deficiency (12–24 ng/mL) and subjects with optimal vitamin D (≥ 25 ng/mL). There was a statistically significant difference between migraine patients and controls (P-value =0.023) (Table 6, Figure 1).

Table 5 Frequency of vitamin D deficiency in migraine patients and control group

	Migraine group (n=40)	Control group (n=40)	P-value
Subjects with normal vitamin D (≥ 30 ng/mL) [n (%)]	14 (35%)	28 (70%)	0.002*
Subjects with vitamin D deficiency (<30 ng/mL) [n (%)]	26 (65%)	12 (30%)	

Note: *P-value<0.05 (significant).

Table 6 Stratification of migraine patients and controls according to 25(OH)-vitamin D serum level

	Migraine group (n=40)	Control group (n=40)	P-value
Subjects with 25 (OH) vitamin D <12 ng/mL [n (%)]	2 (5%)	0 (0%)	0.023*
Subjects with 25 (OH) vitamin D 12–25 ng/mL [n (%)]	17 (42.5%)	8 (20%)	
Subjects with 25 (OH) vitamin D ≥ 25 ng/mL [n (%)]	21 (52.5%)	32 (80%)	

Note: *P-value<0.05 (significant).

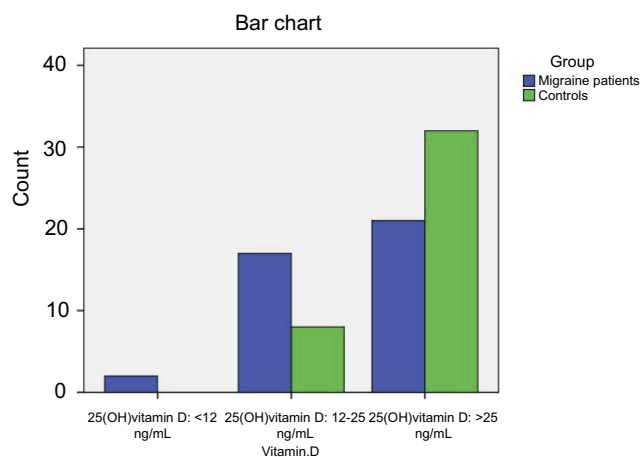


Figure 1 Stratification of migraine patients and controls according to 25(OH)-vitamin D serum level.

There was a statistically significant difference between migraine patients with normal vitamin D level and those with vitamin D deficiency regarding the presence of aura ($\chi^2=3.913$, P-value=0.048, Odds ratio=4.28, 95% CI=0.963–19.007), phonophobia/photophobia ($\chi^2=6.593$, P-value=0.01, Odds ratio=6, 95% CI=1.445–24.919), autonomic manifestations ($\chi^2=5.358$, P-value=0.021, Odds ratio=9.533, 95% CI=1.08–84.139), allodynia ($\chi^2=3.956$, P-value=0.047, Odds ratio=4, 95% CI=0.983–16.271), and resistance to medications ($\chi^2=3.913$, P-value=0.048, Odds ratio=4.28, 95% CI=0.963–19.007) (Table 7).

There was a statistically significant negative correlation between 25(OH)-vitamin D serum level and attack duration in hours (r coefficient=-0.552, P-value <0.001), frequency of the attacks/month (r coefficient=-0.629, P-value <0.001), MIGSEV scale (r coefficient=-0.492, P-value=0.001), and HIT-6 scale (r coefficient=-0.506, P-value=0.001) (Table 8).

Table 7 Effect of Vitamin D deficiency on clinical characteristics of migraine

	Migraine with normal vitamin D (n=14)		Migraine with vitamin D deficiency (n=26)		P-value	Odds ratio	95% confidence interval	
	Present [n (%)]	Absent [n (%)]	Present [n (%)]	Absent [n (%)]			lower	Upper
Aura					0.048*	4.28	0.963	19.007
	3 (21.4%)	11 (78.6%)	14 (53.8%)	12 (46.2%)				
Phonophobia/Photophobia					0.01*	6	1.445	24.919
	5 (35.7%)	9 (64.3%)	20 (76.9%)	6 (23.1%)				
Autonomic manifestations					0.021*	9.533	1.08	84.139
	1 (7.1%)	13 (92.9%)	11 (42.3%)	15 (57.7%)				
Allodynia					0.047*	4	0.983	16.271
	4 (28.6%)	10 (71.4%)	16 (61.5%)	10 (38.5%)				
Resistance to medications					0.048*	4.28	0.963	19.007
	3 (21.4%)	11 (78.6%)	14 (53.8%)	12 (46.2%)				

Note: *P-value<0.05 (significant).

Table 8 Correlation between 25(OH)-vitamin D serum level and clinical characteristics of migraine

		25 (OH)-vitamin D in ng/mL	
		(r) coefficient	P-value
Attack duration in hours		-0.552	<0.001*
Frequency of the attacks/month		-0.629	<0.001*
MIGSEV scale	Intensity	-0.497	0.001*
	Disability	-0.427	0.006*
	Tolerability	-0.441	0.004*
	Nausea	-0.272	0.089
Total score		-0.492	0.001*
HIT-6 scale		-0.506	0.001*

Notes: (r) using Pearson coefficient, P-value≥0.05 (non significant), *P-value<0.05 (significant).

Abbreviations: MIGSEV, migraine severity; HIT-6, The Headache Impact Test-6.

Discussion

The role of vitamin D is recently discussed as a key factor in neurovascular diseases.^{22,23} The causal relationship between vitamin D deficiency and migraine headache remains unknown mainly due to the small number of studies, contradictory results, and the lack of large randomized clinical trials that evaluate the beneficial effects of vitamin D supplementation in migraine headache.²⁴

The objective of this work was to investigate the difference in the serum levels of 25(OH)-vitamin D between patients with migraine headache and healthy controls. The secondary objectives were to determine the differences in headache characteristics according to vitamin D status and to correlate serum 25 (OH)-vitamin D level with duration, frequency, and severity of migraine headache attacks.

The present study revealed that patients with migraine headache had significantly lower 25(OH)-vitamin D serum level in comparison to controls. The incidence of aura, phonophobia/photophobia, autonomic manifestations, allodynia, and resistance to medications were found to be significantly higher in migraineurs with vitamin D deficiency than those with normal vitamin D. There was a statistically significant negative correlation between 25 (OH)-vitamin D serum level and attack duration in hours, frequency of the attacks/month, MIGSEV scale, and HIT-6 scale.

Such results were broadly consistent with a number of recent studies. Wheeler reported a significant decrease in vitamin D serum level in patients with chronic migraine in

comparison to controls. In his study, he revealed that 14.8% of the patients with chronic migraine had vitamin D serum level below 20 ng/mL and 25.9% of the patients had vitamin D serum level between 20 and 30 ng/mL.¹³ Additionally, Togha et al found that a serum vitamin D level between 50 and 100 ng/mL was associated with 80–83% lower odds of migraine headache than those with serum 25(OH)D levels below 20 ng/mL.²⁵

A case report was done on two female patients with menstrual migraine suffering from vitamin D deficiency. With the consumption of vitamin D (1600–1200 IU per day) over 2 months treatment, there was a significant decrease in the frequency of migraine headache attacks in both patients.¹⁵ Another study was done on postmenopausal patients with migraine and vitamin D deficiency. After supplementation of vitamin D, there was a significant reduction in the frequency and duration of migraine headache attacks.¹⁴

Similar findings were obtained by Gazerani et al who found that migraine patients on vitamin D supplement demonstrated a significant decrease in frequency and duration of migraine headache attacks as compared with those on placebo. However, migraine severity, pressure pain thresholds, and migraine-related symptoms, ie, aura, nausea, photo/phonophobia, and allodynia, showed no significant pattern of change across time for either groups (vitamin D versus and placebo).²⁶

In contrast to our findings, Zandifar et al did not reveal any relationship between vitamin D plasma level and severity of the migraine headache attacks. Also, vitamin D plasma levels were not different among MIGSEV items.²⁷

Similarly, a cross-sectional study done on 11,614 participants revealed insignificant relationship between vitamin D deficiency and migraine. Surprisingly, there was a significant association between vitamin D deficiency and nonmigraine headache.²⁸

Different mechanisms for the causal relationship between vitamin D deficiency and migraine were suggested. One of them was the reported low serum level of magnesium in patients with vitamin D deficiency. Interestingly, it has been demonstrated that there was a positive correlation between serum concentrations of 25(OH)-vitamin D and magnesium. Magnesium deficiency is known to play a role in the pathogenesis of migraine (especially menstrual migraine). After correction of magnesium deficiency, migraine headache characteristics significantly improved.²⁹

Another explanation for the observed association between vitamin D deficiency and migraine may be the anti-inflammatory effects of vitamin D, which could affect

neuroinflammation associated with migraine.³⁰ Multiple studies showed that vitamin D, at physiologic levels, can suppress the production of proinflammatory cytokines such as tumor necrosis factor- α and interleukin-6.³¹ Vitamin D also causes an increase in the production of the anti-inflammatory cytokine, interleukin-10.³²

Additionally, vitamin D, in its active form 1,25(OH)2D, can inhibit the synthesis of inducible nitric oxide synthase, which generates nitric oxide (NO).³³ NO stimulates the synthesis and release of Calcitonin gene-related peptide (CGRP) from trigeminal ganglion neurons, which in turn stimulates the release of NO. Thus, this might lead to a positive feedback loop that can enhance and maintain inflammatory processes within the trigeminal ganglion. This contributes to the sensitization of meningeal nociceptors during migraine.³⁴

Taken together, these findings may explain the reported relationship between vitamin D deficiency and migraine, but the precise mechanism underlying the actual role of vitamin D in the pathogenesis of migraine remains to be elucidated.

Well-designed clinical trials should be conducted on a larger number of patients and for a longer duration to investigate effects of correcting vitamin D deficiency on the characteristics, frequency, severity, and duration of migraine headache attacks. Further researches should be also directed toward exploring the molecular and cellular mechanisms underlying the effect of vitamin D deficiency on increasing the odds of developing aura, phonophobia/photophobia, autonomic manifestations, allodynia, and resistance to medications in patients with migraine.

Conclusion

Patients with migraine have significantly lower 25(OH)-vitamin D serum level in comparison to controls and this raises awareness for the need for screening vitamin D status in patients with migraine. The incidence of aura, phonophobia/photophobia, autonomic manifestations, allodynia and resistance to medications were significantly higher in migraineurs with vitamin D deficiency than those with normal vitamin D. There was a statistically significant negative correlation between 25(OH)-vitamin D serum level and duration, frequency, and severity of migraine headache attacks.

Ethics approval and consent to participate

A written informed consent was obtained from each participant in this study or from parent or legal guardian for

participants under the age of 18 years. The study was conducted in accordance with the Declaration of Helsinki and it was approved by local ethical committee in Faculty of Medicine, Beni-Suef University. The committee's reference number is FWA00015574.

Data sharing statement

Authors report that the datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Abbreviations

25(OH) vit D, 25 hydroxyvitamin D; CGRP, Calcitonin gene-related peptide; DALYs, disability-adjusted life years; ELISA, enzyme-linked immunosorbent assay; GBD, Global Burden of Disease; HIT-6, Headache Impact Test-6; ICHD-II, International Classification of Headache Disorders-II; MIGSEV, migraine severity; MRI, magnetic resonance imaging; NO, nitric oxide; SPSS v 18, Statistical Package for Social Science version 18; VDR, vitamin D receptor.

Author contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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