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The Association Between Serum Vitamin D Levels and Migraine Severity in Women

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Abstract

Background: Migraine is characterized by recurrent and intense headaches. Vitamin D deficiency has emerged as a noteworthy global public health issue. This study aimed to assess the correlation between serum vitamin D levels and the parameters of headache attacks in females with migraine.

Methods: This cross-sectional study enrolled female migraine patients in Tehran, Iran. Pain intensity was assessed using the 6-point behavioral rating scale. Serum 25-hydroxyvitamin D levels were measured employing the ELISA technique. To explore potential associations between vitamin D status and migraine characteristics, statistical analyses were conducted to assess correlations with the intensity, frequency, and duration of headache attacks.

Results: The study evaluated 138 female migraine patients (average age: 35.08 ± 0.80 years). Around 49.3% of the participants had sufficient vitamin D levels, with a mean serum concentration of 35.54 ± 1.92 ng/mL. The mean number of monthly migraine episodes was 6.95 ± 2.63, with each attack lasting approximately 24.7 ± 1.39 hours. A negative correlation was identified between pain intensity and both vitamin D levels (CC = -0.91, $P < 0.001$) and age (CC = -0.16, $P = 0.05$). Furthermore, elevated vitamin D levels were linked to reduced headache frequency (CC = -0.73, $P = 0.01$), although no statistically significant correlation was observed with headache duration ($P = 0.48$).

Conclusion: Our findings demonstrated a negative correlation between serum vitamin D levels and the intensity and frequency of headaches in female migraine patients. However, further investigations are needed to explore the potential therapeutic benefits of vitamin D in mitigating the severity of migraine disease.

Keywords: Migraine disorders, Vitamin D, Headache, Pain measurement, Women

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Introduction

Migraine is a neurological disorder characterized by recurrent and severe headaches. These headaches are frequently accompanied by symptoms such as nausea, vomiting, photophobia, and phonophobia. Migraine constitutes a significant health burden, impacting both individuals and society at large (1, 2). Notably, the prevalence of migraine exhibits a distinct gender bias, with women being three times more susceptible than their male counterparts (3). Hormonal fluctuations are posited as pivotal contributors to this observed gender disparity. Furthermore, current evidence suggests a decrease in the frequency and intensity of migraine attacks among people over 50 (4).

The recognized gender discrepancy in migraine prevalence necessitates a more profound inquiry into the intricate mechanisms perpetuating this phenomenon. Understanding the mechanisms behind this discrepancy can lead to the development of more efficient and targeted preventive and therapeutic strategies (5). Additionally, exploring the potential relationship between migraine attacks and serum biomarkers could offer valuable insights into the pathophysiology of migraine disease and provide new avenues for treatment (6).

The increasing prevalence of vitamin D deficiency has emerged as a noteworthy worldwide public health issue in recent years, with rates ranging from 30% to 50% (7). Despite the ample sun exposure in Middle Eastern countries, they are acknowledged as one of the most affected regions in terms of vitamin D deficiency worldwide (5). Vitamin D has been increasingly recognized as a critical factor in the underlying mechanisms of migraine, particularly through its involvement in modulating pain perception, regulating immune responses, and attenuating neuroinflammatory

processes (8, 9). Understanding the link between vitamin D levels and migraine severity can provide valuable insights into potential mechanisms and therapeutic targets for managing migraine patients (10, 11).

This study aimed to investigate the correlation between age and serum levels of vitamin D and attack parameters in migraine patients, while also examining the potential association between age and serum levels of vitamin D. Through the analysis of these factors, we hope to identify age-specific interventions and improve treatment outcomes for migraine females.

Methods

This retrospective study utilized a cross-sectional design and focused on female patients diagnosed with migraine in Tehran City, Iran. The study sample included female migraine patients aged 15–60 years who presented to the neurology outpatient clinic of Mostafa Khomeini Hospital over one year.

The inclusion criteria required a confirmed diagnosis of migraine for at least six months and experiencing either chronic or episodic headaches, based on a neurologist's diagnosis using the criteria set by the International Classification of Headache Disorders (ICHD-IIIβ).

The exclusion criteria included the following: recent consumption of vitamin D supplements, glucocorticoids, thiazide diuretics, or hormonal combinations within the last three months; being pregnant or breastfeeding; and presence of chronic or acute conditions such as infectious, gastrointestinal, kidney, or liver diseases, cancer, rickets, osteoporosis, or any neurological or psychological disorder as diagnosed by a physician or indicated in the medical history.

Through face-to-face interviews, participants were asked about their age and headache symptoms. The retrospective approach was employed to evaluate pain parameters, including the frequency, duration of headache attacks, and pain intensity. A physician calculated the pain intensity score using the 6-point behavioral rating scale (BRS-6). The BRS-6 scale, ranging from 0 to 5, assesses pain intensity based on clinical symptoms. Greater scores indicate higher levels of pain intensity (12).

A 5 mL sample of fasting venous blood was obtained from each participant and promptly centrifuged within 30 minutes of collection to ensure sample integrity. Specimens were stored at a temperature of -20°C. The enzyme-linked immunosorbent assay (ELISA) was utilized to quantify serum 25-hydroxyvitamin D (25OHD), which is considered the most reliable method for assessing serum vitamin D levels. The results of serum 25OHD were categorized into three groups based on the guidelines provided by the World Health Organization: vitamin D deficiency (serum 25OHD below 20 ng/ml), insufficiency (serum 25OHD between 20 and 29 ng/ml), and sufficiency (serum 25OHD of at least 30 ng/ml) (13).

Descriptive statistics, including means and standard deviations, were calculated to summarize the continuous variables. Categorical variables were presented as frequencies and percentages. The normality of the distribution for all variables was assessed using the Kolmogorov-Smirnov test. The Pearson correlation analysis was conducted to assess the strength of the relationship between the variables. A logistic regression analysis was conducted to examine the association between serum vitamin D levels and headache intensity while controlling for age as a potential confounding factor (14). This approach allowed for a more precise assessment of the independent effect of vitamin D on headache severity after adjusting for age-related influences. The statistical analysis was performed using SPSS software version 18 (SPSS Inc., Chicago, Illinois, USA). P values less than 0.05 were considered significant.

Informed consent was obtained from all participants, confirming both their voluntary involvement and their comprehensive understanding of the study's aims and procedures. The ethics committee approval for the study was obtained from the Shahed University Clinical Research Ethics Committee, ensuring that the study protocol adhered to ethical guidelines (Decision No. 41/215592).

Results

In this study, out of the 165 subjects at baseline, a total of 138 female migraine patients, with an average age of 35.08 ± 0.80 years, were included in the analysis. Approximately half of the participants (n = 68, 49.3%) exhibited sufficient vitamin D levels. The mean serum vitamin D levels in migraine patients were 35.54 ng/mL, with a standard deviation of 1.92. Participants experienced an average of 6.95 ± 2.63 migraine attacks per month, with reported frequencies ranging from 3 to 15 episodes. The mean duration of each headache episode was 24.7 ± 1.39 hours. The severity of migraine pain, evaluated using BRS-6, yielded a mean intensity score of 2.98 ± 1.20. The demographic profile, serum vitamin D levels, and characteristics of migraine headaches in the patients are presented in Table 1. The Kolmogorov-Smirnov test indicated that the quantitative data followed a normal distribution.

The correlation analysis revealed that pain intensity was not significantly associated with either the frequency of headaches or the duration of headache attacks ($P = 0.20$ and $P = 0.46$, respectively). There was a statistically significant negative correlation (correlation coefficient = -0.16, $P = 0.05$) between age and pain intensity. However, no significant associations were observed between age and the duration of headache attacks ($P = 0.12$) or between age and headache frequency per month ($P = 0.94$). The relationship between age and vitamin D level was examined using a correlation test, which revealed a

Table 1. Serum vitamin D levels and migraine headache attack characteristics

Variable	Mean	SD
Age (years)	35.08	0.8
Serum Vitamin D level (ng/mL)	35.54	1.92
Variable	**Frequency**	**Percentage %**
Serum Vitamin D status		
Vitamin D sufficiency	68	49.3
Vitamin D insufficiency	53	38.4
Vitamin D deficiency	17	12.3
Pain frequency (times/month)		
<4	21	15.2
4-6	40	29
7-9	50	36.2
>9	27	19.6
Pain duration (hours)		
6-12	33	23.9
13-24	51	36.9
25-48	35	25.4
>48	19	13.8
Pain intensity (BRS-6 score)		
1	21	15.2
2	23	16.7
3	46	33.3
4	34	24.6
5	14	10.2

SD: Standard deviation, BRS-6: 6-point behavioral rating scale.

significant negative correlation between these two variables (correlation coefficient = -0.65, $P = 0.05$).

An inverse correlation was observed between vitamin D levels and pain intensity (correlation coefficient = -0.91, $P < 0.001$). Considering the significant negative correlation between pain intensity and age, it was imperative to account for the potential confounding impact of age. To examine this, a logistic regression analysis was conducted to explore the combined effect of age and vitamin D level on pain intensity. The results unveiled a statistically significant inverse relationship between vitamin D level and pain intensity, even after adjusting for the confounding effect of age, with a *P*-value of less than 0.001.

A strong inverse relationship was identified between serum vitamin D levels and the frequency of migraine attacks, as evidenced by a correlation coefficient of –0.73 and a statistically significant p-value of 0.01. Further investigation was carried out to analyze the association between vitamin D levels and the duration of headache attacks. However, this investigation revealed no significant association, with the corresponding p-value calculated at 0.48.

Discussion

This retrospective cross-sectional study examined the associations between age, serum levels of vitamin D, and migraine attack parameters among 138 female patients with migraine in Tehran, Iran. The results revealed an inverse correlation between age and serum vitamin D levels, signifying a decline in vitamin D concentrations with increasing age. Additionally, our findings indicated that higher serum vitamin D levels were linked to reduced pain frequency and intensity, even after adjusting for age. Moreover, the study showed that older migraine patients experienced lower pain intensity.

Several uncontrolled published trials have indicated lower serum vitamin D levels in migraine patients (10, 15-17). In a recent cross-sectional study involving Egyptian migraine sufferers aged ≥ 18 years, vitamin D deficiency, with a prevalence of 41.8%, has been identified as the second most common comorbidity among migraine patients (18). Similarly, Hussein et al reported that individuals suffering from migraine exhibited notable vitamin D deficiencies compared to the healthy population (25% lower serum vitamin D levels than controls) (7).

In a study of 1009 participants, Kelman demonstrated that individuals aged 50 and above exhibited a decreased frequency of severe migraine attacks. These data indicate that the characteristics of migraine diminish over time, leading to a lower prevalence of migraine in older patients (4). Hormonal levels may serve as pain triggers, reaching their peak in women aged 30 to 49 years (19).

In a retrospective study conducted in Korea, Song et al examined 157 migraine patients aged 19 to 65 years. They found that patients with vitamin D deficiency had a significantly higher frequency of migraine attacks (20). Iannacchero et al conducted a prospective study on migraine and medication-overuse headache patients. The results of this study did not provide evidence to support the hypothesis that there is a direct relationship between blood levels of 25OHD and the frequency of headaches. Nevertheless, the levels of 25OHD were found to be below the established normal limit in all patients (21). Similar findings were obtained in a randomized, placebo-controlled study conducted by Gazerani et al who discovered that individuals with migraine who were administered vitamin D supplements exhibited a notable decrease in migraine attack frequencies compared to the placebo group. However, in contrast to our results, they reported a negative correlation between blood vitamin D levels and pain duration (22).

Kılıç et al performed a retrospective analysis on a group of 92 children (aged 6–18 years) diagnosed with migraine. In the research population, a statistically significant relationship was found between low levels of vitamin D and an increase in the frequency, duration, and severity of headache attacks (23). In Iran, Mottaghi et al conducted a cross-sectional study involving 76 migraine patients aged 10 to 61 years. The study findings are inconsistent with several published trials, as they demonstrated a

weak yet significant linear correlation between serum 25OHD levels and headache diary results (HDR), while no remarkable linear relationship was observed regarding migraine severity (24).

Contrary to our findings, Zandifar et al did not find a significant association between plasma 25OHD levels and the severity of migraine attacks. Furthermore, analysis of the Migraine Severity (MIGSEV) scale components revealed no significant variation in plasma 25OHD concentrations across different severity levels (25). Consistent with these findings, a study by Gazerani et al presented no meaningful differences in migraine intensity, associated symptoms, or pressure pain threshold between individuals receiving vitamin D supplementation and those given a placebo (22). Likewise, evidence from a large-scale cross-sectional investigation involving 11,614 participants failed to establish a significant association between vitamin D deficiency and the presence of migraine. However, it is worth noting that a significant correlation was found between a deficiency of vitamin D and non-migraine headaches (26).

The negative correlation between vitamin D and the severity of headaches can be attributed to multiple mechanisms of vitamin D's impact on the pathogenesis of migraine (27). One mechanism involves serum magnesium levels, which play a crucial role in maintaining energy homeostasis in the brain. Vitamin D deficiency may lead to migraine headaches due to the diminished absorption of magnesium (28, 29). Another potential explanation for the reported association between 25OHD deficiency and migraine is the inhibition of neuroinflammatory pathways in migraine disease (30). Vitamin D, at physiological levels, downregulates pro-inflammatory cytokines while upregulating the synthesis of anti-inflammatory cytokines (31, 32).

In addition, vitamin D can prevent the production of activated nitric oxide (NO) synthase, an enzyme that produces NO. This, in turn, leads to the production and release of calcitonin gene-related peptide (33). This approach ultimately results in a chain of positive feedback that amplifies and promotes inflammatory processes (34). These findings have the potential to elucidate the observed link between deficiency of vitamin D and migraine severity, although the precise mechanism by which vitamin D contributes to the development of migraine has yet to be fully understood (9).

An advantageous aspect of this study is its status as the first cross-sectional study examining the relationship between vitamin D serum concentrations and migraine severity in Tehran, Iran. Nevertheless, this study has some limitations. The present study is cross-sectional, which inhibits the establishment of a causal relationship. Therefore, further clinical trials are necessary to address this limitation. Additionally, adjusting for potential confounding factors such as physical activity levels, the use of migraine preventive medications, sun exposure habits, and alcohol consumption is essential, as these factors can influence serum vitamin D levels. Furthermore, dietary habits in individuals with migraines, which may be shaped by personal beliefs, individual experiences, societal influences, and medical recommendations, could also impact vitamin D status. Future research incorporating these variables, along with longitudinal studies in diverse age and gender groups, could provide more robust evidence on this relationship.

Conclusion

The results of the present study showed a significant inverse correlation between serum levels of vitamin D and the intensity and frequency of headache attacks in female migraine patients. This finding suggests that decreased serum vitamin D levels in migraine patients may contribute to the severity of headache episodes in females with migraine. However, further investigation is necessary through meticulously planned clinical trials to explore the potential therapeutic benefits of elevated serum vitamin D levels in reducing the severity of migraine headache attacks.

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Authors' Contribution

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Competing Interests

The authors declare that they have no conflict of interest.

Data Availability

Data generated and analyzed during the current study will be available by the corresponding author upon reasonable request.

Ethical Approval

This research study was approved by the Ethics Committee of Shahed University (Tehran, Iran) (Ethical code: SHAHED.REC.1393.22).

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