

Association Between Vitamin D Levels and Chronic Migraine Severity: A Cross-Sectional Study in Saudi Arabia.

Abstract

Objective

Chronic migraine imposes a considerable economic burden and is closely linked to other health conditions. The purpose of this study is to look at the connection between the intensity of chronic migraine headaches and vitamin D levels.

Methodology

The purpose of this study is to evaluate the connection between the intensity of chronic migraine headaches and vitamin D levels. The study included 82 chronic migraine patients receiving botulinum toxin injections. Data was analyzed using IBM SPSS 21.

Results

The patients were between 21 and 63 years old, primarily females (87.8%) with half having university education. Only less than 10% maintained adequate vitamin D levels. The Migraine Severity score (MIDAS) indicates that two-thirds of smokers, older people, and people with chronic illnesses were moderately to severely disabled by migraines. The severity scores of migraines and vitamin D levels were found to be negatively correlated ($P = 0.049$).

Conclusion

A substantial number of chronic migraine patients, particularly among the younger demographic and those with higher severity scales, exhibited low Vitamin D levels, showing a significant negative correlation with migraine severity scores. Early screening and vitamin D replacement could improve their quality of life.

Key Words:

Botulinum toxin, Migraine, MIDAS, Severity, Vitamin D

Introduction

Migraine, a persistent neurological condition characterized by recurring episodes with diverse symptoms including headaches, light sensitivity, dizziness, anxiety, nausea, and vomiting, poses a significant global health challenge. Over a billion people worldwide suffer from migraines, which are the second most debilitating and third most common ailment worldwide, according to statistics from the World Health Organization (1). Rooted in the trigeminovascular system and stemming from disturbances in brain sensory processing, migraine's etiology involves a complex interplay of genetic and environmental factors, profoundly affecting affected individuals' quality of life (2,3,4).

The two main types of migraines that manifest are episodic and chronic. The frequency of episodic migraines varies, with 0–14 headache days per month and over 15 episodes per month for at least three months in the case of chronic migraines (5,6). Despite sharing common risk factors, these types diverge significantly in epidemiology, symptoms, disabilities, and therapeutic strategies. Chronic migraine, in particular, imposes substantial economic burdens and exhibits stronger associations with comorbidities such as vascular and psychiatric disorders (5,6).

Vitamin D, known for its roles in chronic pain, depression, and neurological conditions, interacts with numerous receptors within the brain (7). Despite ample sun exposure in regions like the Middle East, vitamin D deficiency remains prevalent, potentially due to other factors influencing its synthesis or metabolism (8). Studies suggest that there may be a link between low levels of vitamin D and the intensity of headaches, suggesting that vitamin D supplements may be used as a prophylactic or supplemental treatment for migraines (9). In addition, Vitamin D involvement in migraine pathogenesis, pain sensitization, inflammation, and immune functions, further

underscores its relevance in migraine management(7,8,9). The latitude-dependent risks associated with both vitamin D deficiency and migraines warrant further exploration of their relationship with migraine frequency and severity (7,8,9). Individuals with higher levels of serum vitamin D (50-100 ng/mL) were less likely to experience migraines compared to those with levels below 20 ng/mL (9). Therefore, the purpose of this study is to assess the relationship between the severity of chronic migraine headaches and vitamin D levels. Additionally, it aims to identify various predictors of severity within the studied patient population.

Methods

From the July 2023 to December 2023, a cross-sectional study took place at the Neurology clinics at King Fahad Hospital in Jeddah, Saudi Arabia.

Inclusion and Exclusion Criteria

The research included 82 patients who met the inclusion criteria for the study. These criteria included a diagnosis of chronic migraine, and recent measurements of their vitamin D levels within the last 3 months. Additionally, all included patients were receiving botulinum toxin injections at King Fahad Hospital in Jeddah, Saudi Arabia.

On the other hand, certain exclusion criteria were applied to ensure the study's focus on chronic migraine and the impact of vitamin D levels. Patients with other types of headaches or migraine variants were excluded from the study. Furthermore, individuals who did not receive botulinum toxin injections or had no recent measurements of their vitamin D levels within the last 3 months were also excluded.

Data Collection

Patient data was gathered from medical records and by administering a structured questionnaire. This questionnaire, devised by the authors following an extensive literature review and expert consultations, collected demographic and clinical details, encompassing age, gender, education

level, disease duration, medications utilized, and the frequency of migraine attacks both pre and post botulinum toxin injections.

Using a widely used procedure for predicting proportions with given margins of error and confidence levels, the sample size for this study was established. Statistical power was ensured by using a 95% confidence level and a 5% margin of error. Important factors included in the method were the Z-score for the target confidence level and an expected percentage of 0.5 for the highest possible variability.

The Migraine Disability Assessment (MIDAS) is a reliable and valid scoring system used to measure the severity of migraines (11). The overall MIDAS score is categorized into four—No disability, Mild disability, Moderate disability, and Severe disability. Based on predetermined standards, vitamin D levels were categorized as severely deficient, deficient, inadequate, and adequate.

Ethical Approval:

The King Fahad General Hospital's ethics and research council granted ethical approval for this study in compliance with the principles delineated in the Declaration of Helsinki. The protocol underwent a comprehensive examination to guarantee the study's ethical conduct and protect the welfare of the participants.

Statistical Analysis:

IBM SPSS 21, the Statistical Package for Social Sciences, was used to statistically evaluate the data. A descriptive analysis produced the frequency distributions and percentages of the research variables. To find statistically significant variations in mean values, non-parametric procedures such as the Kruskal-Wallis Test and Mann-Whitney U Test were employed. The association between vitamin D levels and migraine severity was examined using Spearman correlation

analysis. A binary logistic regression model was also employed to find adjusted predictors of migraine-related severe impairment. Assumptions of the model were thoroughly evaluated, including binary outcome, independence of observations, absence of multicollinearity, linearity of predictors, and absence of outliers or influential observations. All statistical procedures used in the study were adequately described, exact p-values and confidence intervals were reported, ensuring transparency and accuracy in the presentation of results. Multivariate analysis was prioritized over bivariate analyses when appropriate, following standard reporting guidelines for clinical trials and diagnostic studies.

Results

This research conducted at the King Fahad General Hospital, examined the clinical and demographic traits of individuals with migraine who were undergoing Botox treatment. As shown in **Table 1**, A mean age of 46.3 years was observed among the 82 patients with the majority being female (87.8%). Most were married (56.1%), while 48.8% had university education. Notably, 51.2% experienced severe disability due to migraines, with a mean MIDAS score of 26.0 ± 18.4 . Additionally, 56.1% had a family history of migraine. Regarding migraine duration, 48.8% reported suffering for more than 10 years. Multiple preventive medications were tried by 52.4% of patients, while common abortive medications included Paracetamol (39.0%) and Triptan (36.6%).

Table 1. Demographic and clinical features of migraine patients receiving Botox at King Fahad General Hospital

Socio-demographics		Frequency (N)	Percentages (%)
Age in Years	< 30	22	26.8%
	30-39	22	26.8%
	40+	38	46.3%
	Mean \pm SD	46.3 \pm 10.1	
Gender	Male	10	12.2%
	Female	72	87.8%
Marital Status	Single	18	22.0%
	Married	46	56.1%
	Divorced	18	22.0%
Educational Level	Below secondary	26	31.7%
	Secondary	10	12.2%
	University	40	48.8%

	<i>Post-graduate</i>	6	7.3%
Smoking	<i>Non-smoker</i>	42	51.2%
	<i>Passive smoker</i>	20	24.4%
	<i>Ex-smoker</i>	6	7.3%
	<i>Current smoker</i>	14	17.1%
Chronic Diseases	<i>None</i>	42	51.2%
	<i>Thyroid disease</i>	12	14.6%
	<i>Bronchial Asthma</i>	10	12.2%
	<i>HTN</i>	9	11.0%
	<i>DM</i>	6	7.3%
	<i>Multiple Sclerosis</i>	2	2.4%
	<i>Others</i>	9	11.0%
Family history of migraine	<i>Yes</i>	46	56.1%
	<i>No</i>	36	43.9%
Vit-D Level	<i>Deficient</i>	14	17.1
	<i>Insufficient</i>	20	24.4
	<i>Sufficient</i>	48	58.5
Migraine Related Clinical Features			
Migraine Severity	<i>No disability</i>	8	9.8%
	<i>Mild disability</i>	8	9.8%
	<i>Moderate disability</i>	24	29.3%
	<i>Severe disability</i>	42	51.2%
	MIDAS score (mean \pm SD)	26.0 \pm 18.4	
Duration of Migraine	<i>Less than 5 years</i>	24	29.3%
	<i>5-10 years</i>	18	22.0%
	<i>More than 10 years</i>	40	48.8%
Preventive medications	<i>Topiramate</i>	15	18.3%
	<i>Amitriptyline</i>	13	15.9%
	<i>Beta-blockers</i>	6	7.3%
	<i>Valproic Acid</i>	5	6.1%
	<i>Tried more than one</i>	43	52.4%
Abortive Medications	<i>Paracetamol</i>	32	39.0%
	<i>Triptan</i>	30	36.6%
	<i>Paracetamol + NSAID</i>	12	14.7%
	<i>Others</i>	8	9.7%

(N) Frequency, (%) Percentages

Table 2 presents the variations in vitamin D levels among migraine patients who underwent Botox treatment. Gender ($p = 0.012$), educational level ($p = 0.282$), chronic illness ($p = 0.030$), and smoking status ($p = 0.015$) were shown to be significantly correlated with vitamin D levels among these variables. Men were found to have higher average levels of vitamin D than women, and patients who were better educated and free of chronic illnesses were more likely to have greater levels. Current smokers displayed notably higher mean vitamin D levels compared to other smoking categories. Conversely, age, marital status, family history of migraine, and previous surgery did not reveal significant associations with vitamin D levels ($p > 0.05$).

Table 2. Difference of Vitamin D Level among migraine patients who received Botox

Factors	Vit-D Level (ng/mL)			p-value
	No	Mean (SD)	Mean Rank	
Age in years				0.794 ^a
< 30	6	28.67 (11.9)	35.17	
30-39	16	32.00 (10.1)	42.25	
40+	60	35.40 (15.4)	41.93	
Gender				0.012^a
Male	72	35.61 (14.3)	43.97	
Female	10	24.40 (10.5)	23.70	
Marital Status				0.355 ^b
Single	18	32.44 (16.8)	39.50	
Married	46	36.57 (14.9)	44.63	
Divorced	18	30.11 (8.1)	35.50	
Educational level				0.282 ^b
Below secondary	26	34.08 (13.2)	41.35	
Secondary	10	29.60 (8.8)	34.10	
University	40	34.85 (16.8)	41.00	
Post-graduate	6	38.67 (5.1)	57.83	
Chronic diseases				0.030^a
No	32	29.87 (14.1)	34.38	
Yes	50	37.04 (13.8)	46.06	
Family history of migraine				0.597 ^a
No	36	34.89 (15.0)	43.11	
Yes	46	33.74 (13.8)	40.24	
Smoking				0.015^b
Non-smoker	42	34.43 (34.4)	41.98	
Passive smoker	20	36.80 (36.8)	41.00	
Ex-smoker	6	20.67 (6.3)	14.83	
Current smoker	14	35.86 (11.9)	52.21	
Previous Surgery				0.488 ^a
No	24	36.00 (17.9)	44.33	
Yes	58	33.52 (12.6)	40.33	

(a) Mann-Whitney U Test, (b) Kruskal Wallis Test

Table 3 illustrates the variance in migraine severity, quantified by MIDAS scores, among patients who underwent Botox treatment. Within these parameters, there were significant correlations between the intensity of migraines and vitamin D level ($p < 0.001$) and educational level ($p = 0.026$) where patients with post-graduate training had the lowest mean MIDAS scores. Conversely, patients with low vitamin D levels (<30 ng/mL) scored substantially higher than those with sufficient (>50 ng/mL) or insufficient (30–50 ng/mL) levels. On the other hand, age,

gender, marital status, chronic diseases, family history of migraine, smoking status, and previous surgery did not show significant associations with migraine severity ($p > 0.05$).

Table 3. Difference of migraine severity (based on MIDAS) among migraine patients who received Botox

Factors	Migraine Severity Score			p-value
	No	Mean (SD)	Mean Rank	
Age in years				0.384 ^b
< 30	6	22.33 (8.5)	40.17	
30-39	16	34.75 (23.9)	48.88	
40+	60	24.07 (16.9)	39.67	
Gender				0.496 ^a
Male	72	25.39 (17.6)	40.83	
Female	10	30.60 (23.8)	36.30	
Marital Status				0.237 ^b
Single	18	33.00 (23.2)	46.50	
Married	46	25.57 (16.4)	42.63	
Divorced	18	20.22 (16.4)	33.61	
Educational level				0.026 ^b
Below secondary	26	22.38 (17.9)	36.04	
Secondary	10	23.40 (22.8)	36.50	
University	40	30.85 (17.7)	49.00	
Post-graduate	6	14.00 (6.1)	23.50	
Chronic diseases				0.094 ^a
No	32	30.75 (20.5)	47.00	
Yes	50	23.00 (16.4)	37.98	
Family history of migraine				0.290 ^a
No	36	29.72 (21.7)	45.67	
Yes	46	23.13 (14.9)	38.24	
Smoking				0.161 ^b
Non-smoker	42	28.24 (18.0)	45.45	
Passive smoker	20	22.50 (19.0)	35.30	
Ex-smoker	6	27.33 (12.7)	47.83	
Current smoker	14	23.86 (21.4)	35.79	
Previous Surgery				0.822 ^a
No	24	23.42 (16.2)	40.58	
Yes	58	27.10 (19.2)	41.88	
Vit-D Level				<0.001 ^b
Deficient (<30 ng/mL)	14	41.71 (16.9)	62.36	
Insufficient (30-50 ng/mL)	20	21.10 (21.5)	31.50	
Sufficient (>50 ng/mL)	48	23.50 (15.1)	39.58	

(a) Mann-Whitney U Test, (b) Kruskal Wallis Test

Based on different migraine-related characteristics, **Table 4** displays the variations in vitamin D levels among migraine sufferers. Among these factors, headache frequency before initiation of Botox injections ($p = 0.027$) and headache frequency after Botox injections ($p = 0.013$) showed significant associations with vitamin D levels. Patients experiencing headaches three times or more per week prior to Botox treatment exhibited lower mean vitamin D levels compared to those with less frequent headaches. Likewise, individuals experiencing daily headaches post-Botox treatment demonstrated lower mean vitamin D levels. However, there were no significant correlations seen between vitamin D levels and migraine severity, duration, preventive drug use, or abortive medication use ($p > 0.05$).

Table 4. Difference of Vitamin D Level among migraine patients based on Migraine Related Features

Factors	Vit-D Level (ng/mL)			p-value
	No	Mean (SD)	Mean Rank	
Migraine severity				0.598 ^b
<i>No disability</i>	8	33.75 (4.0)	43.25	
<i>Mild disability</i>	8	35.25 (7.6)	48.50	
<i>Moderate disability</i>	24	34.08 (9.2)	44.33	
<i>Severe disability</i>	42	34.24 (18.5)	38.21	
Duration of migraine				0.193 ^b
<i>Less than 5 years</i>	24	31.83 (9.2)	40.58	
<i>5-10 years</i>	18	28.22 (10.3)	33.50	
<i>More than 10 years</i>	40	38.40 (17.1)	45.65	
Headache frequency before Botox				0.027 ^b
<i>1 Time/ week</i>	4	45.00 (17.3)	54.50	
<i>2 Time/ week</i>	6	35.33 (2.5)	47.17	
<i>3 Time/ week</i>	6	39.33 (1.0)	62.17	
<i>>3 Time/ week</i>	26	29.08 (10.1)	31.35	
<i>Daily</i>	40	35.60 (17.3)	42.85	
Headache frequency after Botox				0.013 ^b
<i><1 Time/ week</i>	16	35.00 (12.1)	42.50	
<i>1 Time/ week</i>	22	33.27 (6.8)	43.05	
<i>2 Time/ week</i>	24	32.67 (11.8)	41.67	
<i>3 Time/ week</i>	8	55.50 (22.3)	62.00	
<i>>3 Time/ week</i>	6	28.00 (15.2)	31.17	
<i>Daily</i>	6	20.00 (8.9)	15.50	

Preventive medications				0.134 ^a
<i>No</i>	16	44.12 (23.1)	49.50	
<i>Yes</i>	66	31.85 (10.1)	39.56	
Abortive medication				0.112 ^a
<i>No</i>	10	29.60 (21.9)	30.30	
<i>Yes</i>	72	34.89 (13.0)	43.06	

(a) Mann-Whitney U Test, (b) Kruskal Wallis Test

Figure 1 displays the scatterplot and correlation statistics computed with Spearman's rho coefficient, showing a moderately negative correlation between MIDAS scores and vitamin D levels, among migraine patients ($\rho(r) = -0.195$, $p = 0.079$, $N = 82$). While the correlation did not show statistical significance at the conventional alpha level of 0.05, the negative correlation coefficient implies a tendency for higher vitamin D levels to be linked with lower MIDAS scores, indicating less severe disability due to migraine.

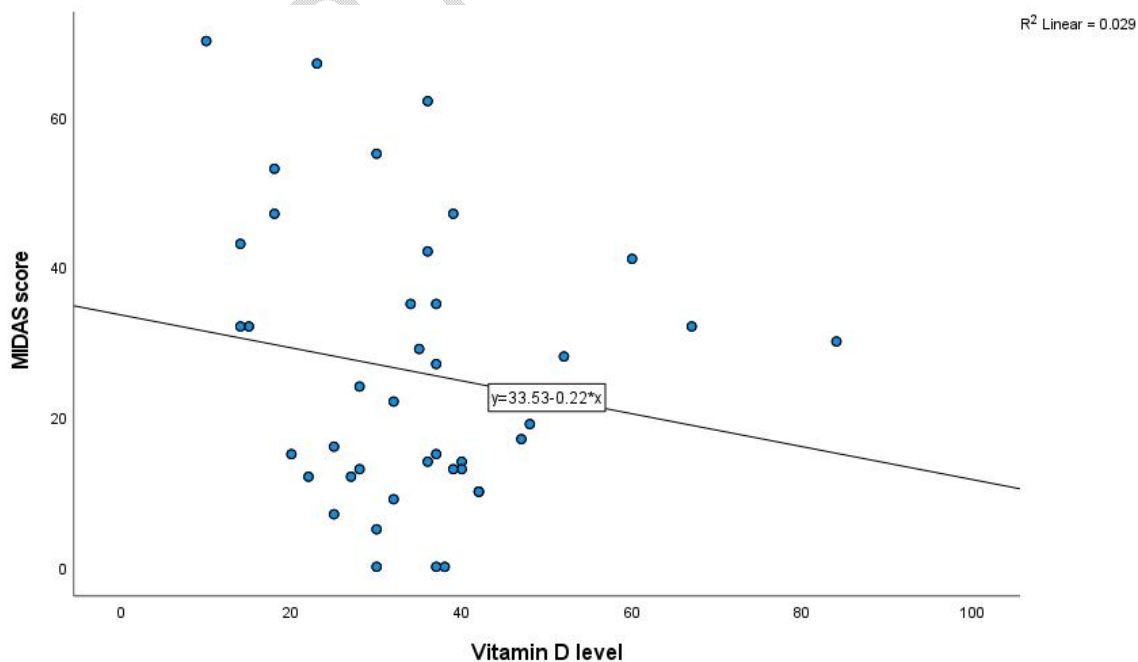


Figure1. Correlation plot between vitamin D level and migraine severity (MIDAS) among study patients ($r=-0.195$; $P=.079$ calculated with Spearman Correlation)

Table 5 shows the result of binary logistic regression model evaluated predictors of severe disability due to migraine, as indicated by MIDAS scores. Among the factors analyzed, gender showed some trend ($p = 0.166$), with males having 3.556 times higher odds of severe disability compared to females. Educational level also shows trend ($p = 0.068$), indicating that individuals with higher education had 1.983 times higher odds of severe disability. The odds ratio for vitamin D level ($\text{Exp(B)} = 0.969$, 95% CI: 0.920 - 1.020) did not achieve statistical significance ($p = 0.229$), indicating no substantial association between vitamin D levels and severe disability due to migraine. Other factors, including age, marital status, presence of chronic disease, family history of migraine, and smoking status, did not show statistically significant associations with severe disability.

Table 5. Binary Logistic Regression model to assess adjusted predictors of Severe Disability due to Migraine (MIDAS Score)

	B	Sig.	Exp(B)	95% CI	
				Lower	Upper
Age (Years)	.042	.272	1.043	.967	1.125
Gender (Male)	1.269	.166	3.556	.590	21.422
Marital Status (Divorced)	-.044	.914	.957	.426	2.146
Higher Education	.684	.068	1.983	.950	4.136
Presence of Chronic Disease	-.666	.312	.514	.141	1.869
Family Hx of Migraine	-.992	.088	.371	.119	1.159
Current Smokers (Yes)	-.312	.099	.732	.506	1.060
Vitamin D Level	-.032	.229	.969	.920	1.020
Constant	-1.240	.598	.289		

Exp(B)=Odd's Ratio

Discussion

Chronic migraine exerts a significant economic burden and is intricately connected to other health conditions. The goal of this research is to identify factors that predict the intensity of chronic migraine headaches in the patient population under investigation by examining the relationship between vitamin D levels and headache severity. While prior research suggests higher prevalence of migraine among young adult Saudis, our study unveils a greater occurrence of migraine in the younger age bracket, particularly among women, with over two-thirds being female, this aligns with numerous studies highlighting migraine onset at a young age and female predominance may be linked to estrogen's role in the increased prevalence among women. Additionally, over half of our patients have a higher level of education, showing a positive correlation between migraine and educational attainment. This association may be attributed to the stress and anxiety commonly experienced by individuals with higher education, known to trigger headache mechanisms. Notably, more than half of the patients have a first-degree relative with a positive family history of migraine. This aligns with the findings of a general population survey conducted in Jeddah city, Saudi Arabia, which reported a similar rate of family history (12-15).

Migraine profoundly affects the personal, social, emotional, and physical aspects of individuals experiencing it. Besides leading to noticeable functional limitations, it adversely impacts academic and occupational performance. Nearly two-thirds of our patients, especially among the younger population, those with chronic diseases, and smokers experienced moderate to severe disability due to migraine headaches, as revealed by the Migraine Severity score (MIDAS). This aligns with our study's emphasis on chronic migraines. Correspondingly, Edmeads et al. found a 47% association between reported migraine headaches and disability, and a similar score used in a

Turkish study demonstrated that 35% of their cohort faced moderate to severe disability. Bıçakçı et al. investigated university students with migraines and found that approximately one-quarter of them had a moderate to severe MIDAS severity level. (16,17,18). A local Saudi Arabian study further corroborated these patterns, emphasizing the substantial impact of headache severity on daily work, particularly in about one-third of those who get headaches similar to migraines. Moreover, another local study reported a positive correlation between symptom severity and a diminished quality of life (19,20).

Vitamin D deficiency may represent a potential risk factor for various neurological diseases owing to its manifold effects on the nervous system. Despite Saudi Arabia's abundant sunshine year-round, approximately 30% of the general population, particularly younger individuals and females, experience vitamin D deficiency. Our observation of nearly half of our patients exhibiting vitamin D deficiency supports the hypothesis of a significant association between low vitamin D levels and headaches (21,7,8).

Many researches have shown a possible link between headaches and low vitamin D levels. In this study, we found a clear pattern indicating a negative relationship between blood vitamin D levels and migraine severity. According to one study, those with greater blood vitamin D levels (50-100 ng/mL) had a reduced odds ratio of having migraine headaches than people with lower serum vitamin D levels (<20 ng/mL) (10). Similarly, second research found that participants who had migraine had lower blood levels of vitamin D and vitamin D receptors than controls (22). On the other hand, some studies have not discovered any associations between serum vitamin D levels and particular headache characteristics, such as aura, severity, and duration (23,24). Notably, research has indicated that migraines and low levels of vitamin D are more prevalent at higher altitudes further from the equator (21,22,23,24).

Stewart et al. looked at the characteristics and intensity of headaches in connection to the grade on the Migraine Disability Assessment Scale (MIDAS). They discovered that patients under 25

years old had significantly higher MIDAS grades, indicating greater disability, and established the reliability of the MIDAS scale (10). A significant association was found in another investigation between higher headache severity and lower vitamin D levels (15).

Clinical Implications and Future Research

The study findings suggest a need for a multidimensional approach to migraine management among patients undergoing Botox treatment, particularly focusing on addressing the high prevalence of severe disability and the significant associations with vitamin D levels. Healthcare providers should consider individualized treatment plans that incorporate not only Botox therapy but also adjunctive interventions such as vitamin D supplementation and comprehensive migraine management strategies. Furthermore, attention to socioeconomic factors, gender disparities, and the potential impact of education on migraine severity is crucial for optimizing patient care and improving treatment outcomes.

Future investigations should look at the possible therapeutic benefits of vitamin D supplementation while conducting long-term trials to assess the long-term efficacy and safety of Botox treatment in migraine sufferers. To establish the effectiveness and ideal amount of vitamin D supplementation as a supplemental medication in the management of migraines, randomized controlled trials are crucial. Further investigation into the underlying mechanisms of gender disparities in migraine prevalence and treatment outcomes is necessary to tailor interventions accordingly and improve outcomes for all migraine patients.

Limitations

Several limitations of this study merit acknowledgment. The cross-sectional design impedes the establishment of causality and temporal relationships between variables. The results' applicability to broader groups may be constrained by the small sample size. Self-report measurements, such as migraine intensity and disability, may incorporate subjective interpretations and recall bias.

The results' applicability to different clinical contexts may be limited by their dependence on a single center.

Conclusion

This research studies factors that influence migraine headaches intensity and disability, and its association with vitamin D levels. The predominance of females, elevated prevalence of severe disability, and notable associations with vitamin D levels emphasize the significance of tailored treatment approaches. While Botox treatment shows promise in alleviating migraine symptoms, comprehensive management strategies that consider socioeconomic factors, gender disparities, and vitamin D supplementation may be necessary to optimize outcomes. Further research exploring longitudinal effects, randomized controlled trials assessing vitamin D supplementation, and investigating gender disparities in migraine outcomes is essential for advancing our understanding and improving care for migraine patients.

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Disclaimer (Artificial intelligence)

Option 1:

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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