Journal of Health and Rehabilitation Research (2791-156X)
Volume 4, Issue 3
Double Blind Peer Reviewed.
https://jhrlmc.com/
DOI: https://doi.org/10.61919/jhrr.v4i3.1077
www.lmi.education/

Serum Vitamin D, Calcium, and Magnesium Levels in Patients with Migraine Presenting to PEMH, Pakistan: A Case-Control Study

Muhammad Jaleel Khan[1], Khurram Haq Nawaz[1], Salman Khan[1], Fawad Ahmed[1], Muhammad Ibrar Saleem[1], Farah Mahboob[2], Muhammad Farrukh Habib[3]

Correspondence
Muhammad Farrukh Habib
muhammadfarrukhhabib@gmail.com

Affiliations
1 Department of Neurology, Pak Emirates Military Hospital, Rawalpindi, Pakistan
2 Department of Physical Medicine and Rehabilitation, Combined Military Hospital, Kharian, Pakistan
3 Shifa Tameer-e-Millat University, Islamabad, Pakistan

Keywords
Migraine, Vitamin D, Calcium, Magnesium, Micronutrient Deficiency, Case-Control Study, Neurology Research, Migraine Prevention

Disclaimers

Authors' Contributions	All authors contributed equally to the study design, data collection, analysis, and manuscript preparation
Conflict of Interest	None declared
Data/supplements	Available on request.
Funding	None
Ethical Approval	Respective Ethical Review Board
Study Registration	N/A
Acknowledgments	N/A

ABSTRACT

Background: Migraine is a common neurological disorder characterized by recurrent headaches of varying intensity and duration. Micronutrient deficiencies, particularly in vitamin D, calcium, and magnesium, have been implicated in migraine pathogenesis.

Objective: This study aimed to assess serum levels of vitamin D, calcium, and magnesium in migraine patients compared to healthy controls.

Methods: A case-control study was conducted at Pak Emirates Military Hospital, Rawalpindi, involving 180 participants, divided equally into migraine cases and healthy controls. Serum vitamin D levels were measured using electrochemiluminescence, while calcium and magnesium levels were determined using photometry. Data were analyzed using SPSS version 25.0, with p-values <0.05 considered significant.

Results: Migraine patients had significantly lower serum levels of vitamin D (18.2 ± 5.6 ng/mL vs. 28.4 ± 6.2 ng/mL, p<0.001), calcium (8.7 ± 0.6 mg/dL vs. 9.2 ± 0.5 mg/dL, p=0.013), and magnesium (1.8 ± 0.2 mg/dL vs. 1.9 ± 0.3 mg/dL, p=0.025). Multivariate analysis showed significant associations between higher levels of these nutrients and reduced migraine risk.

Conclusion: Lower serum levels of vitamin D, calcium, and magnesium are associated with an increased risk and severity of migraines, suggesting potential targets for preventive and therapeutic strategies.

INTRODUCTION

Migraine is a prevalent and debilitating neurological disorder marked by recurrent headaches, often accompanied by symptoms such as nausea, vomiting, and heightened sensitivity to light and sound. Despite extensive research, the precise etiology of migraines remains elusive, but it is widely accepted that migraines are a multifactorial disorder influenced by genetic, environmental, and physiological factors (1). In recent years, growing attention has been directed toward the role of micronutrients, particularly vitamin D, calcium, and magnesium, in the pathophysiology of migraines. These nutrients are integral to various neurological and systemic processes, and their deficiencies have been increasingly implicated in the onset and exacerbation of migraine symptoms (2).

Vitamin D, a fat-soluble vitamin essential for calcium homeostasis and bone health, is also implicated in various neurological functions, including the modulation of inflammatory cytokines, regulation of neurotrophic factors, and influence on the serotoninergic system, all of which are crucial in migraine pathogenesis (3). Emerging evidence suggests a potential link between low vitamin D levels and increased frequency and severity of migraines, with several studies reporting a higher prevalence of vitamin D deficiency among migraine sufferers compared to the general population (4, 5). However, the findings remain inconsistent, warranting further investigation to clarify the relationship between vitamin D status and migraine risk (6, 7).

Calcium, a critical mineral involved in numerous physiological processes such as neurotransmitter release and muscle contraction, plays a fundamental role in the nervous system. Dysregulation of calcium homeostasis has been hypothesized to contribute to migraine pathophysiology, particularly through its effects on neuronal excitability and synaptic transmission (8). Notably, calcium channel mutations have been identified in specific migraine subtypes, such as familial hemiplegic migraine, underscoring the potential link between calcium metabolism and migraine susceptibility (9).

Magnesium, another essential mineral, is involved in over 300 enzymatic reactions and is crucial for maintaining proper nerve and muscle function. It acts as a natural calcium antagonist, modulating calcium influx into cells and playing a role in neurotransmitter release (10). Several studies have demonstrated that magnesium deficiency can lead to increased neuronal excitability and susceptibility to cortical spreading depression, a phenomenon closely associated with migraine aura. Clinical trials have explored the therapeutic potential of magnesium supplementation in migraine prevention, with promising results suggesting that correcting magnesium deficiency may reduce the frequency and severity of migraines (11-13).

Manuscript Submitted under JHRR ID 1077: June 04/2024 | Accepted: July 22/2024

Given the potential involvement of these micronutrients in migraine pathophysiology, this study aimed to investigate the serum levels of vitamin D, calcium, and magnesium in patients with migraines compared to healthy controls. By elucidating the associations between these micronutrient levels and migraine occurrence, this study seeks to contribute to the understanding of migraine mechanisms and explore the potential for targeted nutritional interventions in migraine management.

MATERIAL AND METHODS

This study was a case-control investigation conducted to evaluate the serum levels of vitamin D, calcium, and magnesium in patients diagnosed with migraines compared to healthy controls. The research was carried out at the Pak Emirates Military Hospital (PEMH) in Rawalpindi, Pakistan, over a period from January 2024 to May 2024. The study included a total of 180 participants, comprising 90 patients with clinically diagnosed migraines and 90 healthy controls. The migraine diagnosis was confirmed according to the International Classification of Headache Disorders (ICHD-3) criteria, ensuring that only eligible patients aged between 18 and 60 years were included. The control group was matched for age and sex with the cases and consisted of individuals without any history of migraine or other chronic headaches.

Participants were excluded if they had any chronic illnesses or were on medications that could influence serum levels of vitamin D, calcium, or magnesium. Additionally, pregnant or lactating women, individuals with chronic kidney disease, liver disease, endocrine disorders, or those on supplementation of vitamin D, calcium, or magnesium were also excluded from the study. Recruitment of participants was conducted in the outpatient department of PEMH, and informed consent was obtained from all participants before enrollment in the study. Demographic information, including age, sex, and body mass index (BMI), as well as medical history and migraine characteristics for the cases, were recorded through structured interviews and medical record reviews.

Blood samples were collected from all participants after an overnight fast to ensure accuracy in the measurement of serum vitamin D, calcium, and magnesium levels. The serum vitamin D levels were measured using electrochemiluminescence, while calcium and magnesium levels were assessed using photometry. All laboratory procedures were carried out in accordance with standardized protocols to maintain consistency and reliability of the results.

Data analysis was performed using SPSS version 25.0. Descriptive statistics were utilized to summarize the demographic and clinical characteristics of the participants. The mean serum levels of vitamin D, calcium, and magnesium were compared between cases and controls using independent t-tests, while chi-square tests were employed to assess categorical variables. A p-value of less than 0.05 was considered statistically significant. Additionally, multivariate logistic regression analysis was conducted to evaluate the association between serum nutrient levels and the likelihood of experiencing migraines, adjusting for potential confounding factors such as age, sex, and BMI.

The study adhered to the ethical standards outlined in the Declaration of Helsinki, and ethical approval was obtained from the Institutional Review Board of Pak Emirates Military Hospital. The confidentiality of all participants was strictly maintained throughout the study, and data was anonymized to protect participant identity. The findings from this study were intended to contribute to a better understanding of the role of micronutrients in migraine pathophysiology, with the potential to inform future therapeutic strategies aimed at addressing nutrient deficiencies in migraine patients.

RESULTS

The results of this study are presented in a refined format, with tables and descriptions of findings provided below each table for clarity.

Table 1: Demographic and Clinical Characteristics of Study Participants

Characteristic	Cases (n=90)	Controls (n=90)	p-value
Age (years)	38.5 ± 10.2	39.1 ± 9.8	0.68
Gender			
Male	47	42	0.76
Female	43	48	
BMI (kg/m²)	25.3 ± 4.5	24.9 ± 4.2	0.58
Duration of Migraine (years)	7.2 ± 5.1	-	-

The demographic and clinical characteristics of the participants are summarized in Table 1. The mean age of the cases was 38.5 years, while the controls had a mean age of 39.1 years, with no significant difference between the two groups (p=0.68). The gender distribution was balanced, with a nearly equal proportion of males and females in both groups (p=0.76). Additionally, the BMI values were similar between cases and controls, with no statistically significant difference (p=0.58).

Table 2: Serum Levels of Vitamin D, Calcium, and Magnesium

Parameter	Cases	Controls	p-value
Vitamin D (ng/mL)	18.2 ± 5.6	28.4 ± 6.2	0.001*
Calcium (mg/dL)	8.7 ± 0.6	9.2 ± 0.5	0.013*
Magnesium (mg/dL)	1.8 ± 0.2	1.9 ± 0.3	0.025*

As shown in Table 2, the serum levels of vitamin D, calcium, and magnesium were significantly lower in patients with migraines compared to the controls. The mean vitamin D level in cases was 18.2 ng/mL, significantly lower than the 28.4 ng/mL observed in controls (p=0.001). Similarly, mean calcium levels were significantly lower in the migraine group (8.7 mg/dL) compared to controls (9.2 mg/dL; p=0.013). Magnesium levels were also lower in cases (1.8 mg/dL) than in controls (1.9 mg/dL; p=0.025).

Table 3: Correlation between Vitamin D, Calcium, Magnesium Levels, and Migraine Severity

Parameter	Correlation Coefficient (r)	p-value
Vitamin D (ng/mL)	-0.45	0.004*
Calcium (mg/dL)	-0.28	0.001*
Magnesium (mg/dL)	-0.22	0.030*

Table 3 presents the correlation between serum nutrient levels and migraine severity. There was a significant inverse correlation between vitamin D levels and migraine severity (r = -0.45, p=0.004), indicating that lower levels of vitamin D were associated with greater severity of migraines. Similarly, calcium (r = -0.28, p=0.001) and magnesium (r = -0.22, p=0.030) levels also showed significant negative correlations with migraine severity, suggesting that lower levels of these minerals were linked to more severe migraine symptoms.

Table 4: Multivariate Logistic Regression Analysis for Migraine Risk Factors

Variable	Odds Ratio (OR)	95% Confidence Interval (CI)	p-value
Vitamin D (ng/mL)	0.82	0.76 - 0.88	0.001*
Calcium (mg/dL)	0.58	0.39 - 0.85	0.005*
Magnesium (mg/dL)	0.73	0.53 - 0.98	0.038*
Age (years)	1.02	0.98 - 1.05	0.221
Gender (Male)	1.12	0.64 - 1.95	0.680
BMI (kg/m²)	1.05	0.98 - 1.12	0.156

The results of the multivariate logistic regression analysis are displayed in Table 4. The analysis demonstrated that increased levels of vitamin D, calcium, and magnesium were associated with a reduced likelihood of experiencing migraines. Specifically, each 1 ng/mL increase in vitamin D levels was associated with an 18% reduction in migraine risk (OR = 0.82, p=0.001). Similarly, each 1 mg/dL increase in calcium levels was linked to a 42% reduction in migraine risk (OR = 0.58, p=0.005), while a 1 mg/dL increase in magnesium levels was associated with a 27% reduction in migraine risk (OR = 0.73, p=0.038). No significant associations were found between migraine risk and age, gender, or BMI.

Table 5: Summary of Laboratory Results for Different Migraine Types

Migraine Type	Vitamin D (ng/mL)	Calcium (mg/dL)	Magnesium (mg/dL)	p-value (t-test)
Episodic (n=50)	20.1 ± 5.4	8.8 ± 0.5	1.9 ± 0.3	0.002*
Chronic (n=40)	16.3 ± 5.8	8.6 ± 0.5	1.8 ± 0.2	0.030*

Table 5 compares the serum nutrient levels between patients with episodic and chronic migraines. Chronic migraine sufferers exhibited significantly lower levels of vitamin D (16.3 ng/mL) compared to those with episodic migraines (20.1 ng/mL; p=0.002). Additionally, calcium levels were lower in the chronic migraine group (8.6 mg/dL) compared to the episodic group (8.8 mg/dL; p=0.030). Magnesium levels followed a similar trend, with lower levels observed in chronic migraine patients (1.8 mg/dL) compared to those with episodic migraines (1.9 mg/dL).

The findings of this study highlight significant differences in serum levels of vitamin D, calcium, and magnesium between migraine sufferers and healthy controls, with lower levels of these nutrients being associated with both the occurrence and severity of migraines. These results suggest that nutritional deficiencies may play a critical role in the pathogenesis of migraines, and addressing these deficiencies could potentially reduce the frequency and severity of migraine attacks.

DISCUSSION

The findings of this study revealed significant associations between lower serum levels of vitamin D, calcium, and magnesium with the prevalence and severity of migraines. These results align with a growing body of evidence suggesting that nutritional deficiencies may contribute to the pathogenesis of migraines. The significantly lower levels of these micronutrients in migraine patients compared to healthy controls underscore the potential role of vitamin D, calcium, and magnesium in modulating migraine susceptibility and intensity.

The inverse correlation between vitamin D levels and migraine severity observed in this study is consistent with previous research. Several studies have suggested that vitamin D deficiency might be linked to an increased risk of migraines, potentially through mechanisms involving the regulation of inflammatory cytokines, neurotrophic factors, and serotoninergic pathways (4, 13). The multivariate

analysis further supported these findings, showing that each 1 ng/mL increase in vitamin D levels was associated with an 18% reduction in the likelihood of experiencing migraines. These findings contribute to the understanding that vitamin D might have a protective effect against migraines, although the exact mechanisms remain to be fully elucidated.

Similarly, the study found that lower serum levels of calcium and magnesium were significantly associated with an increased risk of migraines. The role of calcium in neuronal excitability and neurotransmitter release has been well-documented, and disruptions in calcium homeostasis have been implicated in migraine pathogenesis, particularly in conditions such as familial hemiplegic migraine (8). The observed 42% reduction in migraine risk associated with each mg/dL increase in calcium levels highlights the importance of maintaining adequate calcium levels for neurological health. Furthermore, magnesium's role as a natural calcium antagonist and its involvement in over 300 enzymatic reactions make it a critical element in migraine prevention. Previous studies have demonstrated that magnesium supplementation can reduce the frequency and severity of migraines, particularly in individuals with low baseline magnesium levels (13, 18). The 27% reduction in migraine risk per mg/dL increase in magnesium levels observed in this study further corroborates these findings.

Despite the strengths of this study, including its well-matched case-control design and rigorous laboratory assessments, certain limitations must be acknowledged. The cross-sectional nature of the study limits the ability to establish causality between nutrient levels and migraine risk. Longitudinal studies are needed to determine whether correcting deficiencies in vitamin D, calcium, and magnesium can reduce the incidence of migraines. Additionally, the study did not account for dietary intake of these nutrients, which could have influenced the serum levels observed. Future research should include detailed dietary assessments to better understand the relationship between nutrient intake and migraine risk. Another limitation is the relatively small sample size, which, while sufficient to detect significant associations, may limit the generalizability of the findings to broader populations. Larger studies are needed to confirm these results and to explore potential differences in nutrient-migraine relationships across diverse demographic groups.

The study's findings have important clinical implications. The strong associations between lower levels of vitamin D, calcium, and magnesium and increased migraine risk suggest that nutritional assessment and supplementation could be beneficial components of migraine management. Clinicians should consider screening for and addressing deficiencies in these nutrients, particularly in patients with chronic migraines. However, randomized controlled trials are necessary to determine the effectiveness of supplementation as a preventive strategy.

CONCLUSION

In conclusion, this study provided compelling evidence that deficiencies in vitamin D, calcium, and magnesium are associated with a higher prevalence and severity of migraines. These findings highlight the potential role of nutritional factors in migraine pathogenesis and suggest that addressing micronutrient deficiencies could be a promising avenue for preventing and managing migraines. Further research is warranted to explore the causal mechanisms and to assess the therapeutic potential of nutrient supplementation in migraine prevention.

REFERENCES

1. Kowalska M, Prendecki M, Kozubski W, Lianeri M, Dorszewska J. Molecular Factors In Migraine. Oncotarget. 2016;7(31):50708-18.
2. Pleș H, Florian IA, Timis TL, Covache-Busuioc RA, Glavan LA, Dumitrascu DI, et al. Migraine: Advances In The Pathogenesis And Treatment. Neurology International. 2023;15(3):1052-65.
3. Rosignoli C, Ornello R, Onofri A. Applying A Biopsychosocial Model To Migraine: Rationale And Clinical Implications. J Headache Pain. 2022;23(100):1-12.
4. Nowaczewska M, Wiciński M, Osiński S, Kaźmierczak H. The Role Of Vitamin D In Primary Headache-From Potential Mechanism To Treatment. Nutrients. 2020;12(1):243.
5. Dell'Isola GB, Tulli E, Sica R, Vinti V, Mencaroni E, Di Cara G, et al. The Vitamin D Role In Preventing Primary Headache In Adult And Pediatric Population. J Clin Med. 2021;10(24):5983.
6. Di Molfetta IV, Bordoni L, Gabbianelli R, Sagratini G, Alessandroni L. Vitamin D And Its Role On The Fatigue Mitigation: A Narrative Review. Nutrients. 2024;16(2):221.
7. Yu E, Sharma S. Physiology, Calcium. [Updated 2023 Aug 14]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482128/
8. Bron C, Sutherland HG, Griffiths LR. Exploring The Hereditary Nature Of Migraine. Neuropsychiatr Dis Treat. 2021;17:1183-94.
9. Souza AC, Vasconcelos AR, Dias DD, Komoni G, Name JJ. The Integral Role Of Magnesium In Muscle Integrity And Aging: A Comprehensive Review. Nutrients. 2023;15(24):5127.
10. Grech O, Mollan SP, Wakerley BR, Fulton D, Lavery GG, Sinclair AJ. The Role Of Metabolism In Migraine Pathophysiology And Susceptibility. Life (Basel). 2021;11(5):415.
11. Maier JA, Pickering G, Giacomoni E, Cazzaniga A, Pellegrino P. Headaches And Magnesium: Mechanisms, Bioavailability, Therapeutic Efficacy And Potential Advantage Of Magnesium Pidolate. Nutrients. 2020;12(9):2660.
12. O'Hare L, Asher JM, Hibbard PB. Migraine Visual Aura And Cortical Spreading Depression—Linking Mathematical Models To Empirical Evidence. Vision. 2021;5(2):30.
13. Buettner C, Nir RR, Bertisch SM, Bernstein C, Schain A, Mittleman MA, et al. Simvastatin And Vitamin D For

Migraine Prevention: A Randomized, Controlled Trial. Ann Neurol. 2015;78(6):970-81.
14. Domitrz I, Cegielska J. Magnesium As An Important Factor In The Pathogenesis And Treatment Of Migraine-From Theory To Practice. Nutrients. 2022;14(5):1089.
15. Martami F, Togha M, Qorbani M, Shahamati D, Salami Z, Shab-Bidar S. Association Of Dietary Patterns With Migraine: A Matched Case-Control Study. Curr J Neurol. 2023;22(2):87-95.
16. Stewart WF, Roy J, Lipton RB. Migraine Prevalence, Socioeconomic Status, And Social Causation. Neurology. 2013;81(11):948-55.
17. Dresler T, Caratozzolo S, Guldolf K, et al. Understanding The Nature Of Psychiatric Comorbidity In Migraine: A Systematic Review Focused On Interactions And Treatment Implications. J Headache Pain. 2019;20(1):51.
18. Togha M, Razeghi Jahromi S, Ghorbani Z, Martami F, Seifishahpar M. Serum Vitamin D Status In A Group Of Migraine Patients Compared With Healthy Controls: A Case-Control Study. Headache. 2018;58(10):1530-40.
19. Ghorbani Z, Rafiee P, Fotouhi A, et al. The Effects Of Vitamin D Supplementation On Interictal Serum Levels Of Calcitonin Gene-Related Peptide (CGRP) In Episodic Migraine Patients: Post Hoc Analysis Of A Randomized Double-Blind Placebo-Controlled Trial. J Headache Pain. 2020;21(1):22.
20. Kachhadia MP, Khalil ZM, Shah S, Fawad M, Sajjad H, Yadav KP, et al. Role Of Yoga As Adjunctive Therapy For Migraines: A Narrative Review Of The Literature. Cureus. 2023;15(11).