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The Potential Role of Serum Magnesium and Vitamin D Levels in Patients with Migraine

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Abstract

Background: Migraine is one of the most prevalent primary headache disorders. The exact underlying mechanisms remains unclear, and effective treatment strategies are still limited. deficiencies in essential micronutrients, particularly magnesium and vitamin D, could be implicated in both the development and exacerbation of migraine attacks.

The aim of the work: This study aimed to examine the difference in serum magnesium and vitamin-D concentrations in patients with migraine and to assess their correlation with the disease.

Patients and Methods: Forty patients with migraine headache [with or without aura] were included. In addition, forty normal, apparently healthy subjects were included as the comparison group. The clinical characteristics of migraine were documented. In addition, serum levels of vitamin D and magnesium were measured for both groups and correlation between these elements and disease characteristics were calculated.

Results: Magnesium concentrations were significantly decreased in the cases [1.52 ± 0.28 mg/dL] than the control groups [2.11 ± 0.21 mg/dL, p = 0.001]. Magnesium deficiency was recorded for 77.5% of cases, while all controls had normal concentrations, highlighting a clear distinction. There was a significant reduction of vitamin D in cases than the control groups. However, there was a statistically insignificant association between Vitamin-D concentrations and clinical characteristics of migraine [e.g., side, aura, phonophobia/ photophobia, autonomic manifestations, and allodynia.

Conclusion: Serum magnesium and vitamin D concentrations were reduced in migraine and were negatively correlated with disease severity, and migraine-related disability. These results highlighted the potential role of these elements in migraine pathophysiology and management.

Keywords: Magnesium; Migraine; Vitamin D; Headache.

INTRODUCTION

Migraine is one of the primary headaches, which is considered to be a neurovascular disorder. It has been known to mankind since ancient times, as evidenced by Hippocrates' [c. 460-c 370 BC] descriptions of recurrent episodes of headache with migrainous features [1]. Migraine attacks are defined as moderate-to-severe, unilateral, pulsating attacks accompanied by vomiting, nausea, photophobia, and phonophobia. If left unmanaged or inadequately managed, the attack typically lasts several hours to three days. Around twenty-five percent of migraine cases experience an aura, characterized by a temporary disturbance in language, visual, motor, or sensory functions before the onset of the migraine attack [2].

Although the exact pathophysiology of migraine is not yet fully explained, the available evidence supports a neurovascular mechanism, with a key role played by the trigemino-vascular system. This is constituted by trigeminal afferents that innervate meningeal and cerebral vessels and project to the trigeminocervical complex [TCC]. Activation of this pathway leads to the release of neuropeptides like CGRP and PACAP, which contribute to the pain of migraine through vasodilation and central sensitization. Higher levels of CGRP have also been linked to impaired descending inhibition, thereby increasing susceptibility to migraines [3]. Another key mechanism is cortical spreading depression [CSD], a wave of neuronal hyperactivity followed by inhibition that travels across the cortex. CSD is associated with brief reductions in cerebral blood flow and may be responsible for the aura observed in certain patients with migraines [4]. In migraines, the frequency, severity or both of attacks may worsen. Prevention of migraine progression has been a therapeutic objective in headache subspecialty practice. Thus, there is a need to look further into preventive strategies for migraines, and this requires greater insight into the interaction between risk factors and migraine. These may include hypomagnesemia and vitamin D deficiency [5].

Magnesium and vitamin D play significant roles in the pathophysiology of migraine. Magnesium is an antagonist at the NMDA receptors, which inhibits the influx of calcium and cortical spreading depression, a process associated with migraine aura. Magnesium also inhibits substance P release and the modulation of NO production and is implicated in its analgesic properties [6]. Vitamin D exerts its primary effects through anti-inflammatory action, inhibiting the production of pro-inflammatory cytokines and T-cell activity, both of which are linked to chronic migraine headache. Vitamin D also regulates magnesium absorption, and its deficiency may augment migraine severity by lowering magnesium levels [7]. Vitamin D also regulates serotonin synthesis, further positioning it as a target within migraine mechanisms [8].

The current research aimed to examine the difference in blood magnesium and vitamin D concentrations between migraineurs and controls, and subsequently to compare serum levels with migraine attack severity.

PATIENTS And METHODS

This case–control investigation has been performed on forty cases diagnosed as having migraine headache with or without aura and forty normal healthy controls. Cases were recruited from the Neurology outpatient clinics, Al-Azhar University Hospital – New Damietta.

Inclusion criteria: Selected cases met the diagnostic criteria for migraine headache regarding the International Classification of Headache Disorders-III [ICHD-III]. Their ages varied from eighteen to fifty years, and all migraineurs were studied in the post-ictal phase.

Exclusion criteria: Secondary headache, a history of concomitant metabolic or medical illnesses such as diabetes mellitus, hypertension, infectious disorders, liver, kidney, or thyroid illness, gastrointestinal illness, tumor, tuberculosis, malnutrition, sarcoidosis, and pregnancy. Cases using drugs that reduce magnesium concentrations by elevating renal excretion, like ethanol, cyclosporine, aminoglycosides, cisplatin, diuretics, amphotericin B, furosemide, ethacrynic a`, acetazolamide, thiazides, and chlorthalidone, have also been excluded. Additionally, participants in the two groups have been excluded if they had consumed Vitamin D supplements in the previous three months [any dose] or were administering drugs that can impact Vitamin D serum concentrations, like thiazides, glucocorticoids.

All patients have been subjected to full history and Complete general examination and neurological examination.

Outcome Measurements: Assessment of migraine severity by migraine severity scale [MIGSEV][9], migraine disability assessment test [MIDAS], and assessment of pain severity using visual analog scale [VAS].

MIGSEV Questionnaire scoring system

Scoring System

- High [Grade 3]: At least one item with the highest possible score, and no item with the lowest possible score, OR at least two items with the highest possible score.
- Intermediate [Grade 2]: All other cases
- Low [Grade 1]: At least one item with a baseline score, and no items with the highest score.

Migraine Disability Assessment Test [MIDAS] [10].

- Number of days missed work/school because of migraines [last 3 months]: 0. None, 1. 1–3 days, 2. 4–6 days, 3. 7–9 days, 4. 10+ days
- Days missed usual activities [past 3 months]: 0. None, 1. 1–3 days, 2. 4–6 days, 3. 7–9 days, 4. 10+ days
- Days with reduced usual activities [past 3 months]: 0. None, 1. 1–3 days, 2. 4–6 days, 3. 7–9 days, 4. 10+ days

The Scoring System:

- Grade I [Minimal Disability]: Total score 0–5
- Grade II [Mild Disability]: Total score 6–10
- Grade III [Moderate Disability]: Total score 11–20
- Grade IV [Severe Disability]: Total score >20

Visual Analog Scale [VAS] [11]**:** A 10-centimeter line is used to quantify pain severity, where: 0 centimeters = No pain 10 centimeters = Worst possible pain. The participant selects a point along the continuum to indicate the pain level.

Investigational Studies: Routine laboratory investigations involving erythrocyte sedimentation rate [ESR], complete blood count [CBC], renal and hepatic function tests, prothrombin time [PT], C-reactive protein [CRP], partial thromboplastin time [PTT], international normalized ratio [INR], and serum total calcium levels.

Assessment of Serum magnesium and vitamin D levels: Fasting venous blood samples [five milliliters] have been obtained from all participants in six milliliter plain tubes and subsequently centrifuged within thirty minutes of collection. The serum samples have been frozen at −20 degrees Celsius.

Serum magnesium level: The serum magnesium concentration was the predominant test utilized by medicine to evaluate magnesium status in cases. Normal magnesium levels range between 0.75 and 0.95 millimoles [mmol] per L. A serum magnesium level of below 1.7–1.8 mg/dL [0.75 millimoles per liter] was a condition defined as hypomagnesemia. Magnesium concentration superior to 2.07 milligrams per deciliters [0.85 millimoles per liter] was most likely related to systemic adequate magnesium concentrations **[12].**

Vitamin D level: Serum 25-hydroxyvitamin D [25[OH]D] is deemed the most accurate measure for evaluating Vitamin D status. Individuals faced the possibility of Vitamin D insufficiency when serum 25[OH]D concentration fell under 30 nanomoles per liter [12 nanograms per milliliter]. Certain individuals may have been at risk of deficiency at 30 to 50 nanomoles per liter [12–20 nanograms per milliliter]. Concentrations of 50 nanomoles per liter [20 nanograms per milliliter] or greater were sufficient for the majority of individuals **[13].**

Ethical consideration: The research, permitted by the Faculty of Medicine at Al-Azhar University, Egypt, involved confidential participant data and an informed consent process. Participants have been informed about the investigation's purpose, nature, and risk-benefit assessment before admission, ensuring anonymity in any reports or publications.

Statistical analysis: The recorded information will be evaluated utilizing the Statistical Package for the Social Sciences, version 23.0 [SPSS Inc., Chicago, Illinois, United States of America]. For parametric distributions [normal], quantitative data will be expressed as mean ± SD and ranges, whereas non-parametric data [non-normally distributed parameters] will be presented as median with interquartile range [IQR]. Qualitative parameters will be represented as percentages and numbers. The Kolmogorov-Smirnov and Shapiro-Wilk Tests will be utilized to evaluate the normality of the data.

The following tests were done: Independent-samples t-test for comparing two means, Chi-square test for qualitative data [with Fisher's exact test used when the expected count in any cell is <5], and Pearson's correlation coefficient was calculated to assess correlations between parameters [positive if both increase, negative if one increases while the other decreases]. The confidence interval [CI] is 95%, with a 5% margin of error. Significance levels, [P-value below 0.05].

RESULTS

In the current work, patients were mainly in their fourth decade of life with increased females than males in both groups. Body mass index reflected that, the majority of patients were overweight. The difference between study and control groups was statistically non-significant [Table 1].

Regarding migraine characteristics, the mean age of onset was 29.38±7.45 years; duration of illness was 4.88±1.14 years. The attack duration was 7.88±1.71 hours, the frequency of attacks was 8.65±2.20 attacks per month. The migraine was mainly unilateral [65.0%] and aura present in 42.5%. The commonest clinical manifestation was Phonophobia/ Photophobia [77.5%], while autonomic manifestations were the lowest [35.0%] [Table 2]. Table [3] showed the value of MIGSEV and MIDAS Scores domains in study group; the pain was mainly moderate [47.5%], marked disability was marked in 42.5% and barely tolerable [42.5%]. The migraine severity was grade 2 in 37.5% and grade 3 in 30.0%. MIDAS showed that, the disability was moderate and severe in 40.0% and 27.5% respectively.

Serum levels of magnesium and vitamin D were significantly reduced study than the control group [1.52±0.28 and 14.81±3.62 vs 2.11±0.21 [mg/dl] and 25.09±3.10 [ng/ml], respectively]. The rate of magnesium and vitamin D deficiency was significantly higher in the study than the control groups [Table 4]. Both magnesium and vitamin-D levels were inversely correlated with different migraine parameters [duration, frequency and pain intensity] [Table 5].

Table [1]: Demographic Data Comparison Between Patients and Control Groups

Variable	Patients [n=40]	Control [n=40]	p
Age [years]	34.25±7.82	33.93±8.08	0.871
Female/Male	25 / 15	22 / 18	0.496
BMI [kg/m^2]	28.35±5.00	28.54±4.70	0.863

Table [2]: Clinical Characteristics of Migraine in study group

Characteristic	Mean ± SD / n [%]
Age of onset [years]	29.38 ± 7.45
Duration of illness [years]	4.88 ± 1.14
Attack duration [hours]	7.88 ± 1.71
Frequency of attacks/month	8.65 ± 2.20
Pain intensity [VAS]	5.98 ± 1.12
Side [Unilateral]	26 [65.0%]
Aura present	17 [42.5%]
Phonophobia/Photophobia	31 [77.5%]
Autonomic manifestations	14 [35.0%]
Allodynia	17 [42.5%]

Table [3]: MIGSEV and MIDAS Scores in Patients Group

Severity Domain	Distribution [%]
Pain Intensity [Moderate/Intense/Very Intense]	47.5 / 22.5 / 12.5
Nausea [Intense/Vomiting]	30.0 / 25.0
Disability [Marked]	42.5
Tolerability [Barely tolerable/Intolerable]	42.5 / 25.0
Migraine severity Grade 2 / 3	37.5 / 30.0
MIDAS [Moderate/Severe disability]	40.0 / 27.5

Table [4]: Serum Magnesium and Vitamin D Levels

Marker	Patients [Mean±SD]	Control [Mean±SD]	Deficiency Rate	p
Mg [mg/dL]	1.52 ± 0.28	2.11 ± 0.21	77.5% vs 0%	< .001
Vit-D [ng/mL]	14.81±3.62	25.09±3.10	85.0% vs 0%	< .001

Table [5]: Pearson Correlation Between Serum Levels and Migraine Parameters

Parameter	Mg [r, p]	Vitamin-D [r, p]
Attack duration	-0.524, <0.001	-0.591, <0.001
Frequency/month	-0.618, <0.001	-0.692, <0.001
Pain intensity [VAS]	-0.729, <0.001	-0.590, <0.001

DISCUSSION

This case-control study aimed to investigate the clinical and biochemical parameters associated with migraine in a population of 40 patients with migraine and 40 healthy controls from Al-Azhar University Hospital in New Damietta. The results provide important information regarding the demographic characteristics, clinical presentations, and biochemical parameters related to migraine and their potential clinical implications for the treatment of the condition.

The demographic characteristics of the participants revealed a statistically insignificant variance among the patient and control groups regarding sex, age, or BMI [p-value above 0.05]. The mean age of the patient group was 34.25 ± 7.82 years, which is in line with the typical age range for adult migraine sufferers. Similarly, the gender distribution and BMI were comparable between the two groups, ensuring the homogeneity of the study population and minimizing potential confounding factors that could influence the results. Several studies have corroborated the need for well-matched case-control groups in clinical research, as observed in the work of **Burch *et al.*** where comparable demographic characteristics between migraine patients and healthy controls provided more reliable results regarding migraine pathophysiology [14].

In terms of clinical characteristics, the majority of migraine patients reported moderate to severe pain intensity, with 47.5% falling into the moderate pain category. Additionally, 30% of patients experienced intense nausea, while 25% reported vomiting during their attacks. The impact of migraines on daily activities was significant, with 42.5% of patients experiencing marked disability. The variability in tolerability, with 32.5% of patients finding the pain tolerable, may reflect individual differences in pain perception and coping mechanisms, as discussed in the literature. These findings align with previous studies, such as those by **Simmonds *et al.,*** which found that a large proportion of migraine patients report moderate to severe disability, particularly due to the intensity of pain and associated symptoms like nausea and vomiting [15].

Our study also highlighted the association between magnesium deficiency and migraine severity. A significant proportion of patients [77.5%] had low serum magnesium levels, and those with magnesium deficiency were more likely to report increased migraine severity, including higher pain intensity, greater disability, and lower tolerability. These findings are consistent with studies by **Mauskop and Varughese,** who suggested that magnesium supplementation may decline both the severity and frequency of migraine attacks [16].

Additionally, **Peikert *et al.*** reported that magnesium-deficient patients experienced more severe migraine symptoms, further supporting the potential therapeutic role of magnesium in migraine management [17]. However, not all studies agree, with **Schürks *et al.*** [18] suggesting that magnesium levels may not correlate with migraine severity, indicating the complexity of this relationship.

Similarly, vitamin D deficiency has been observed to be significantly related to various aspects of migraine severity, including pain, nausea, intensity, disability, and overall severity. A large proportion of migraine patients [85.0%] had insufficient vitamin D levels, and these patients were more likely to report higher pain intensity and marked disability. These findings are consistent with research by **Thys-Jacobs,** who showed that vitamin D supplementation could decrease the frequency and intensity of migraines [19]. However, other studies, such as the one by **Tso *et al.*** [20] did not find a strong correlation between vitamin-D concentration and migraine characteristics, underscoring the need for further research to fully understand the role of vitamin D in migraine pathophysiology.

The correlation analysis revealed a significant inverse correlation between both magnesium and vitamin-D and migraine severity, including attack frequency, duration, and pain intensity [p < 0.001]. These findings suggest that lower levels of magnesium and vitamin D are associated with more severe migraine symptoms, reinforcing the potential importance of these nutrients in the modulation of migraine severity. These outcomes are by earlier investigations that emphasized the role of magnesium and vitamin D in migraine pathophysiology and suggested their potential utility as therapeutic targets [16,19].

Regarding laboratory parameters, insignificant variances have been observed among the patient and control groups in terms of WBC count, RBC count, platelet count, hemoglobin levels, or ESR [p-value above 0.05]. These results recommend that systemic inflammation is not a key contributor to migraine severity in this cohort, which is consistent with previous research that did not identify significant differences in laboratory values between migraine patients and healthy controls. This supports the hypothesis that migraine is primarily a neurological disorder rather than an inflammatory condition [15].

Whereas this investigation provides valuable insights into the association between magnesium and vitamin D deficiency and migraine severity, it does have certain limitations. The relatively small sample size [40 in each group] restricts the generalizability of the results. Future investigations with longitudinal designs and

larger sample sizes are required to better understand the temporal association between magnesium and vitamin D deficiencies and the development of migraine. Additionally, randomized controlled trials are required to evaluate the therapeutic effectiveness of magnesium and vitamin D supplementation in migraine management, to establish causality, and provide evidence-based treatment recommendations [16,19,20].

Conclusion: Migraine patients exhibited significantly reduced serum magnesium and vitamin D concentration, with a notably higher occurrence of vitamin D deficiency. Both magnesium and vitamin D concentrations were negatively related to migraine severity, influencing factors such as pain intensity, nausea, tolerability [as measured by the MIGSEV scale], and migraine-related disability [as evaluated by the MIDAS score]. These findings suggest that addressing magnesium and vitamin D deficiencies could have a critical role in managing migraine symptoms. Clinically, supplementation with magnesium and vitamin D may offer a promising adjunctive treatment strategy to reduce the severity of migraines and enhance patient quality of life. However, further research is required to confirm these results and refine therapeutic guidelines for the clinical management of migraine based on these deficiencies.

Recommendation: Larger, long-term, multicenter researches are necessary to confirm these results. Serum magnesium and vitamin D should be included in migraine screening, and their supplementation can help reduce attack severity and frequency.

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