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Association Between Serum Magnesium Levels and Migraine Frequency and Severity in Adults: A Systematic Review

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Abstract **Objectives:** Migraine is a leading cause of disability worldwide and is associated with complex neurovascular and neuroinflammatory mechanisms. Magnesium (Mg) influences neuronal excitability, N-methyl-D-aspartate receptor activity, serotonin modulation, and vascular tone, suggesting a plausible role in migraine pathophysiology. Observational studies have reported reduced serum Mg in migraine; however, the relationship between serum Mg levels and migraine frequency and severity remains inconsistently reported. **Objective**: To synthesize evidence on the correlation between serum (total or ionized) Mg levels and the frequency and severity of migraine attacks in adults. **Methods**: This systematic review followed PRISMA 2020 guidance. PubMed, Google Scholar, Embase, Scopus, Web of Science, and Cochrane CENTRAL, ResearchGate were searched for English-language studies published from January 2010 to August 2025 assessing serum/ionized Mg levels in adults (≥18 years) diagnosed with migraine and reporting migraine frequency and/or severity outcomes. Study selection and data extraction were performed using a standardized approach, and risk of bias was assessed using RoB 2 for randomized trials and QUIPS for observational designs. Due to heterogeneity in designs, measurement methods, and outcome reporting, findings were synthesized narratively. **Results**: The search identified 211 records; after removal of 136 duplicates and full-text eligibility assessment, 13 studies were included. Included studies comprised predominantly observational designs (case–control and cross-sectional) and one clinical trial, with samples drawn from multiple countries. Most comparative studies reported lower mean serum Mg in migraine groups than controls, although not all findings were statistically significant. Several studies reported inverse associations between serum Mg levels and attack frequency and/or severity, while others found no significant correlations, indicating heterogeneity across settings and methodologies (e.g., total vs ionized Mg, interictal vs ictal sampling, and differing severity scales). **Conclusion**: Available evidence suggests an overall pattern of lower serum magnesium concentrations in adults with migraine compared with controls. Lower serum magnesium may be associated with greater migraine severity, while its association with attack frequency appears less consistent. However, the predominantly observational evidence and methodological heterogeneity limit causal interpretation. Standardized assessment of total and ionized serum magnesium, prospective migraine monitoring, and improved control of potential confounding factors are needed to clarify the consistency and clinical relevance of these associations.

Key Words Correlation, Serum Magnesium, Severity, Frequency, Migraine Attacks, Adults

INTRODUCTION

Background

Migraine is one of the most important neurological issues in the health of people of the world with significant effects on the quality of life of an individual, occupation, and economy [1]. According to the Global Burden of Disease Study 2021, the World Health Organization estimates that there are about million people worldwide with migraine.

In 1990, there were an estimated 733 million cases of measles, and in 2021, there were 1.16 billion cases, representing a 58% increase [1–3]. While the absolute prevalence and burden have been higher among females, recent epidemiological analyses have reported a higher rate of prevalence and incidence among males over the study period, this is a difference in trends over time and not a higher overall burden among males [4]. Migraine is also ranked as the second most common cause of disability in adults aged 20–59 years of age and continues to be among the top ten neuromuscular conditions that impair most of the world [1,5,6]. The age-standardized prevalence of migraine has been estimated to be around 14%, with higher prevalence among females (17.6%) than males (10.5%), and this gap remains consistent across all age groups and throughout the ages [4].

Migraine is defined as a primary headache disorder that calls in frequent attacks of 4-72 hours duration, generally one-sided and pulsating in character, of middle to severe pain intensity which can be accompanied by photophobia, phonophobia, nausea and vomiting [7,8]. The International Classification of Headache Disorders Third Edition (ICHD-3) recognizes migraine as having sub-phenotypes: migraine without aura (the most common, with occurrence in about 70% of migraine patients) and migraine with aura, which is associated with the occurrence of transient neurological symptoms in the lead up to or with the headache attack [7,9]. There is chronic migraine, which is defined as having 15 headache days per month, that develops in a smaller group of patients and is severe disease phenotype with significantly higher healthcare utilization and morbidity [7,10].

The pathophysiology of migraine is not fully understood but is now becoming recognized as a complicated neurovascular and neuroinflammatory disorder [11]. Recent mechanistic theories also focus on the contribution of the trigeminovascular system where the stimulation of the trigeminal nerve and axonal connections to intracranial blood vessels results in the development of a cascade of events such as vasodilation, release of neuropeptides, and neurogenic inflammation of the meninges [12,13]. A wave of neuronal and glial depolarization that propagates throughout the cerebral cortex, known as cortical spreading depression (CSD) is believed to be a major process connecting the aura phase to the development of headache by enabling the activation of trigeminovascular nociception [13,14].

Magnesium is a biologically necessary divalent cation and accounts for around 2 percent of body mass, 99 percent of which is located in the intracellular space, which is involved in more than 300 enzymatic reactions and is important in neuronal excitability, energy utilization, membrane stability, and neurotransmitter production and release [15,16]. Within migraine pathophysiology, magnesium operates in several ways that are related to the development and the progression of disease [17]. Magnesium is a natural antagonist of N-methyl-D-aspartate (NMDA) receptors, which inhibits flux of calcium ions and glutamate-induced excitotoxicity and neuronal hyperexcitability, which are involved in the pathogenesis of CSD as well as in central sensitization [18,19]. The ion also controls serotonin receptor sensitivity and availability and the vascular smooth muscle contractility and cerebrovascular tone and platelet aggregation and serotonin release [18]. Moreover, magnesium is involved in the production of nitric oxide and the control of the inflammatory and oxidative stress response in the form of mitochondrial stabilization and energy generation [18].

There is epidemiological and biochemical data that magnesium deficiency or hypomagnesemia is a possible major risk factor that predisposes to and increases the severity of migraine. Hypomagnesemia is considered serum magnesium level that is low below 1.8 mg/dl (or 0.70 mmol/L), but clinical magnesium deficiency can occur with normal serum magnesium levels as serum magnesium is only about 1 percent of total body magnesium stores [20]. Thus, serum magnesium is a biochemical indicator of the blood level of magnesium and not a reflection of the total-body or intracellular stores of magnesium [21]. The serum level of magnesium is under strict control and contains only a small proportion of the total body magnesium, so a normal serum level does not rule out magnesium depletion in tissues or in the intracellular compartment [15]. This is especially important for the present review, as magnesium levels in serum do not necessarily reflect tissue and/or central nervous system magnesium status [15,22]. In addition to serum assay, there is early data using electrophysiological tetany testing and magnetic resonance spectroscopy that latent magnesium deficiency can be more common in migraineurs than laboratory traditional tests [10].

The mechanistic relationship that exists between magnesium deficiency and migraine has been established by a series of neurophysiological pathways. The loss of magnesium enhances the activation of NMDA receptors, thus leading to glutamate-induced excitotoxicity and predisposing cells to cortical spreading depression [10,23]. Hypomagnesemia boosts the cerebrovascular responsiveness to vasoconstrictive agents and neuronal membrane hyperexcitability by dysregulating ion channels and transporters [10]. The deficiency further enhances oxidative stress by disrupting mitochondrial functionality and energy generation, facilitates persistent neuroinflammation, and can disrupt endogenous pathways of regulating pain [10]. Also, magnesium deficiency is related to platelet aggregation and disturbed serotonin metabolism, which are also important in the pathogenesis of migraine [10].

The available literature is mostly on the strategies of magnesium supplementation used to prevent migraine or to migraine therapy and not on exploring the relationship between serum magnesium levels and intrinsic migraine characteristics. Importantly, magnesium supplementation trials are evidence-based studies of the therapeutic effect of magnesium and therefore should not be assumed to show any association between naturally occurring levels of serum magnesium and migraine frequency or severity. Systematic reviews and meta-analyses of previous studies have found

that high-dose magnesium supplementation (usually 600 mg/day) produce small yet significant decrease in the frequency of migraine attacks, some of which have found 41.6% decreases in attack frequency and might have clinical importance on the frequency and also on migraine severity and subsequent disability [24,25]. These intervention studies give supportive biological and therapeutic background to the possible role of magnesium in migraine but are different in the exposure pattern to those of the observational studies that have measured endogenous serum magnesium levels. Thus, supplementation trials should not be interpreted as direct evidence of the link between baseline serum magnesium levels and the characteristics of migraine [24,25]. Nevertheless, there still exists an essential gap concerning the relationship between measured serum magnesium levels and the frequency, as well as the severity, of migraine attacks under natural or untreated conditions, which would give background evidence on the role of magnesium in the pathogenesis of migraine in the absence of any effects of migraine suppression.

Knowledge of this association would be of great clinical importance, potentially establishing magnesium deficiency as a risk factor that can be modified, guiding magnesium supplementation, and improving our mechanistic concepts of migraine pathogenesis. Additionally, it may be helpful to conclude whether serum magnesium levels can be correlated with a specific migraine phenotype (with/without aura, episodic/chronic) in order to understand how magnesium is differently involved in migraine subtypes. Thus, the systematic review fills out a substantive gap in the body of evidence by synthesizing the extant body of literature exploring the relationship between serum magnesium levels and the incidence and severity of migraine attacks in adults, relationship between magnesium and the migraine phenotype, and implications of magnesium on pathophysiological processes of migraine.

Objectives

Primary Objective: To determine the association between serum magnesium levels and the frequency and severity of migraine attacks in adult populations (≥18 years).

Secondary Objectives

- To examine whether serum magnesium levels differ between migraine patients and healthy controls
- To investigate potential correlations between serum magnesium concentrations and specific migraine phenotypes (with aura, without aura, chronic migraine)

PECO Framework

- **Population:** Adults (≥18 years) diagnosed with migraine according to ICHD-3 criteria
- **Exposure:** Measured serum magnesium levels (total or ionized) among adults with migraine
- **Comparator:** Different serum magnesium levels within the migraine population; where applicable, migraine patients with lower serum magnesium levels compared with those with higher levels. Healthy controls may be included for secondary comparisons of serum magnesium concentrations but will not constitute the primary comparator for the association between magnesium levels and migraine characteristics
- **Outcome:** Frequency of migraine attacks and severity of migraine attacks measured using validated scales (MIDAS, VAS, MIGSEV, or other standardized instruments)

Literature Review

Prior systematic reviews and meta-analyses on magnesium and migraine have mainly focused on the assessment of the efficacy of magnesium supplementation for migraine prophylaxis or acute treatment and not mainly on determining endogenous serum magnesium concentrations and its relationship with intrinsic migraine characteristics. A landmark meta-analysis of 21 randomized controlled trials on intravenous and oral magnesium effects, conducted by Chiu and colleagues (2016) shows that intravenous magnesium leads to a reduction in acute migraine pain within 15-45 minutes and 120 minutes after infusion, whilst oral magnesium supplementation (600 mg for 12 weeks daily) improves migraine frequency and intensity [26]. Peikert's groundbreaking 1996 randomized trial found that 600 mg oral magnesium trimagnesium dicitrate given daily for 12 weeks reduced the attack frequency by 41.6 to 15.8% of placebo groups in weeks 9-12 [27].

However, all of these reviews focused on supplementation do not answer the question of whether there is a correlation between naturally occurring variations in serum concentrations of magnesium and characteristics of migraine in untreated populations, which is a separate research question. The present review addresses this particular deficit by conducting a synthesis of observational and descriptive research on serum magnesium concentrations and migraine frequency and severity outcomes in patient populations.

Recent evidence from several case-control and cross-sectional studies has led to increasing documentation of lower serum concentrations of magnesium in migraine patients compared with healthy controls with effect sizes that vary greatly from one study to another. A comprehensive 2023 review by Yasin and colleagues of 168 Turkish patients revealed significantly lower serum magnesium in the migraine patients (1.98±0.15 mg/dL) compared to controls (2.04±0.14 mg/dL; $p = 0.021$), which is consistent with previous studies by Talebi (2011) showing much lower levels (26.14±4.3 ppm vs 31.09±4.32 ppm in controls; $p = 0.000$) [28,29]. Of significance, Talebi's larger Iranian sample group (280 total participants) found a significant linear correlation between lower serum magnesium and increased frequency of attacks ($r = -0.21$, $p = 0.016$) [29].

A prospective observational study by Shyamsundar and colleagues in India looking at 120 participants found significantly lower interictal magnesium levels in migraineurs (1.849±0.135 mg/dL) compared to ictal

measurements (1.822±0.149 mg/dL) and controls (2.090±0.205 mg/dL) and an inverse correlation between the levels of magnesium and frequency of attacks ($p<0.001$) [30]. These findings of depletion of magnesium during acute attacks with partial recovery interictally are consistent with mechanistic hypotheses involving mobilization of magnesium during neuronal depolarization and CSD.

Regarding the severity of migraines, Egyptian researchers Abdelwahab and colleagues recently reported extremely robust correlations in 80 subjects (40 with migraine and 40 control subjects), finding a strong negative association between serum magnesium levels and frequency of attacks ($r = -0.618$, $p<0.001$) and severity ($r = -0.729$, $p<0.001$) with 77.5% of migraine patients showing magnesium deficiency compared to 0% in controls [31]. Similarly, a case-control study by Elsayed and co-workers performed in Egypt in 2020 (60 migraine, 30 control) showed negative correlations between magnesium and both attack frequencies, duration and severity scores measured by VAS, MIGSEV and MIDAS scales (all $p<0.001$) [32].

Cross-sectional studies have shown more diverse results about magnesium-frequency links. Karim's 2021 study in Bangladesh (70 migraine, 70 controls) showed that serum magnesium was inversely associated with migraine severity ($p = 0.01$) but there was no significant correlation with the frequency of attacks ($p = 0.430$) [33]. On the contrary, in the Indian case-control study conducted by Bindu Sunda in 2017 (70 migraine, 70 controls), a reduction in serum magnesium was documented in migraineurs (1.60 ± 0.30) between serum magnesium and attack frequency ($p<0.05$), but not severity, which was not measured by validated scales [34]. A 2021 Polish preliminary case-control study by Cegielska and colleagues (35 migraine, 24 controls) using electrophysiological tetany testing to detect latent magnesium deficiency found significantly higher tetany test positivity in migraine with aura compared to without aura and controls ($p<0.05$), as if to suggest that magnesium deficiency is especially pertinent to aura pathophysiology [10].

Regarding migraine phenotype stratification, most of the studies could not reveal significant differences in serum magnesium between migraine with aura and migraine without aura subgroups despite the overall reductions in migraine populations. Talebi's investigation showed no difference between aura (26.22±4.42) versus non-aura (26.1±4.27) group, although both groups showed significantly lower levels than controls [29]. Yasin's study in 2023 found similar no differences in serum magnesium levels by migraine subtype, leading Yeh and colleagues to conclude that magnesium depletion is a pathologies general rather than phenotypes specific migraine pathophysiological feature [28].

Studies of ictal vs. interictal dynamics of magnesium administration yield conflicting results. Samaie's 2012 Iranian investigation showed insignificant difference between ictal (1.86 ± 0.41 mg/dL) and interictal (1.95 ± 0.35 mg/dL) serum magnesium, but both were significantly different from controls (2.10 ± 0.23 mg/dL) [35]. On the other hand, Mahajan's 2022 prospective study from India reported lower magnesium in acute attacks (1.822±0.149 mg/dL interictal; 1.822±0.149 mg/dL ictal; 2.090±0.205 mg/dL controls) with an inverse linear correlation between magnesium and the frequency of attacks [36].

METHODS

Study Registration and Protocol

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [37,38]. The review protocol specified the review objectives, PECO (Population–Exposure–Comparator–Outcome) framework, eligibility criteria, information sources, search strategy, study selection process, data extraction procedures, risk of bias assessment methodology, and data synthesis approach before the review was conducted. The review protocol was not prospectively registered in PROSPERO, OSF, or another public protocol registry.

Eligibility Criteria

Inclusion Criteria

- **Population:** Study population: Adults aged ≥18 years diagnosed with migraine according to established diagnostic criteria (ICHD-2 or ICHD-3)
- **Exposure:** Measured and reported serum or ionized magnesium levels
- **Outcomes:** Reported frequency of migraine attacks as primary or secondary outcome AND/OR reported severity of migraine attacks using standardized measurement scales (Visual Analogue Scale (VAS), Migraine Disability Assessment Scale (MIDAS), Migraine Severity Scale (MIGSEV)
- **Study Design:** Observational studies (cross-sectional, cohort, case-control) and randomized controlled trials
- **Publication Date:** January 2010 through August 2025 Language: English language publications
- **Data Availability:** Studies reporting correlation, comparison, or association between serum magnesium levels and migraine frequency or severity

Exclusion Criteria

- Animal or in vitro laboratory studies
- Studies focusing on headache types other than migraine
- Non-English language publications
- Case reports, narrative reviews, opinion articles, editorials
- Studies measuring only magnesium supplementation effects without reporting baseline serum magnesium levels or associations with migraine characteristics
- Studies not reporting both serum magnesium levels and migraine frequency or severity outcomes
- Studies available only as conference abstracts, dissertations/theses, preprints, or other unpublished

reports were excluded from the primary analysis because sufficient peer-reviewed methodological and outcome information was not consistently available
- The English-language restriction was applied during study selection and is recognized as a potential source of language bias

Information Sources and Search Strategy

A systematic search was performed in PubMed/MEDLINE, Embase, Scopus, Web of Science Core Collection, CINAHL and Cochrane Central Register of Controlled Trials (CENTRAL) databases from January 2010 to August 2025. ResearchGate was not regarded as a main bibliographic database due to the lack of reproducibility of the search and indexing procedures and was not included in the formal database search. Google Scholar was used as an additional source of search to find potentially relevant publications and additional records.

The search strategy used both Medical Subject Heading (MeSH) term and free text keywords, with the use of Boolean operators (AND, OR) to achieve maximal sensitivity and specificity. The search concepts focused on migraine and serum magnesium and the subject headings and syntax used depended on the database. The search strategies used in each database are detailed in Supplementary Table S1 to guarantee the repeatability of the searches, including the search fields, controlled vocabulary, free-text terms, Boolean operators, date limits, and language restrictions. PRISMA 2020 recommends that all search strategies used in all databases be reported and that the date of last search of each source be specified.

The most recent search conducted in each database was on June 2026 for PubMed/MEDLINE, Embase, Scopus, Web of Science, CINAHL and Cochrane CENTRAL. Google Scholar was also searched on July 2026.

The reference lists of the studies included and relevant systematic reviews were also hand searched for potentially eligible studies not identified in the electronic database searches. Forward citations were conducted where possible in Web of Science and/or Scopus. No unpublished data was reached out to by authors or investigators.

Study Selection Process

Three independent reviewers screened titles and abstracts of all identified records using Rayyan (Qatar Computing Research Institute) systematic review software. Records appearing to meet inclusion criteria based on title and abstract were retrieved in full text. Full-text articles were independently assessed for eligibility by two reviewers against predetermined inclusion/exclusion criteria. Disagreements were resolved through consensus discussion or consultation with a fourth senior reviewer. The selection process was documented in a PRISMA 2020 flow diagram tracking identification, screening, and inclusion/exclusion decision-making.

Inter-reviewer agreement was assessed using Cohen's kappa statistic during the screening process. The kappa statistic was calculated separately for title/abstract screening and, where applicable, full-text assessment. Nine reports were excluded following full-text assessment.

Data Extraction

A standardized, pilot-tested data extraction form was developed and utilized for all included studies. Two independent reviewers extracted data from each included study using shared Google Sheets templates with discrepancies resolved through discussion.

The following domains were extracted from the extraction form: first author, year of publication, country, study setting, study design, sample size, age and sex of participants, migraine diagnostic criteria, migraine subtype, method of measuring serum magnesium, units, timing of measurement of serum magnesium in relation to migraine attack, total versus ionized magnesium, definition or threshold of hypomagnesemia if reported, number of migraine attacks, severity of migraine, outcome measures (e.g., VAS, MIDAS, MIGSEV), associations or between-group comparisons, effect estimates, measures of variability, potential confounding factors, and other relevant clinical characteristics. If more than one measure of either frequency or severity was reported, all outcome measures were retrieved and the one that most clearly matched the a priori outcomes was used in the narrative synthesis.

Risk of Bias Assessment

The Joanna Briggs Institute (JBI) critical appraisal tools appropriate to study design were used for observational studies: cross-sectional studies, JBI checklist for cross sectional studies; case-control studies, JBI checklist for case-control studies; cohort studies, JBI checklist for cohort studies [39]. These instruments were chosen because the observation studies included in them mainly examined associations between an exposure (serum magnesium) and migraine outcomes, not prediction. JBI offers design-specific appraisal tools for each of the domains relevant to analytical observational research such as exposure measurement, outcome measurement, confounding, participant selection, and statistical analysis.

The application of design specific JBI tools was also avoided from using the tool outside of its intended use. As the question in the present review focused on an etiological/associational biomarker question, design-specific JBI tools were deemed to be more suitable for the included observational designs.

Disagreements regarding the risk of bias were settled by discussion between the two reviewers, and in the absence of agreement, a third reviewer was consulted. The outcomes of the risk-of-bias evaluation were taken into account in the synthesis of the evidence.

Data Synthesis

The primary synthesis was performed narratively, as there was substantial heterogeneity in study design, population,

magnesium measurement methods and reporting of outcomes. The data extracted were first evaluated to determine whether quantitative analyses of the data could be done separately for each type of magnesium measurement (total versus ionized magnesium), outcome domain (migraine frequency versus migraine severity), study design, and comparison type (e.g., lower versus higher serum magnesium levels, or migraine patients versus healthy controls).

Studies were judged inappropriate for quantitative pooling when the definition of serum magnesium, timing of blood sampling in relation to migraine attacks, migraine diagnostic and/or phenotypic characteristics, outcome definitions and measurement instruments, statistical effect measures, and direction and/or form of reporting associations were significantly different. In particular, frequency and severity outcomes were presented in a variety of scales and statistical formats, and a common effect estimate could not be derived without potentially inappropriate transformations or assumptions.

Subgroup-specific quantitative synthesis was considered when there were enough studies reporting similar definitions of exposure and outcomes and similar effect estimates. The available evidence did not yield a sufficiently consistent set of studies within these pre-defined subgroups to allow for a clinically and statistically meaningful pooled estimate, however. Hence, a meta-analysis was not conducted.

Rather, descriptive/narrative synthesis integrating evidence across studies based on predetermined themes was used in the review. The narrative synthesis was organized around the following four questions: (1) Does there exist an association between serum magnesium concentration and migraine frequency? (2) Does there exist an association between serum magnesium concentration and migraine severity? (3) Are there differences in serum magnesium concentration between migraine patients and healthy controls, if they exist? (4) Are there differences in serum magnesium concentration according to migraine phenotype and magnesium measurement type? Consistency and direction of findings were considered with regard to study design, sample characteristics, measurement methods and risk of bias.

RESULTS

Study Selection and Characteristics

The systematic search identified 211 total records from databases. Following duplicate removal (136 records), 75 unique records underwent title and abstract screening. Twenty-three records were excluded at screening stage based on preliminary assessment and twenty eight studies were excluded based on abstract assessment. Twenty-four full-text articles were retrieved and assessed for detailed eligibility evaluation. Nine reports were excluded during full-text assessment: Eight for reporting wrong outcomes (magnesium supplementation effects without baseline level correlations), two for inappropriate study design (narrative reviews), and one for wrong population (non-migraine headache populations). Thirteen studies met full eligibility criteria and were included in the qualitative synthesis. No studies were excluded post-inclusion. The PRISMA 2020 flow diagram in Figure 1 shows the selection process.

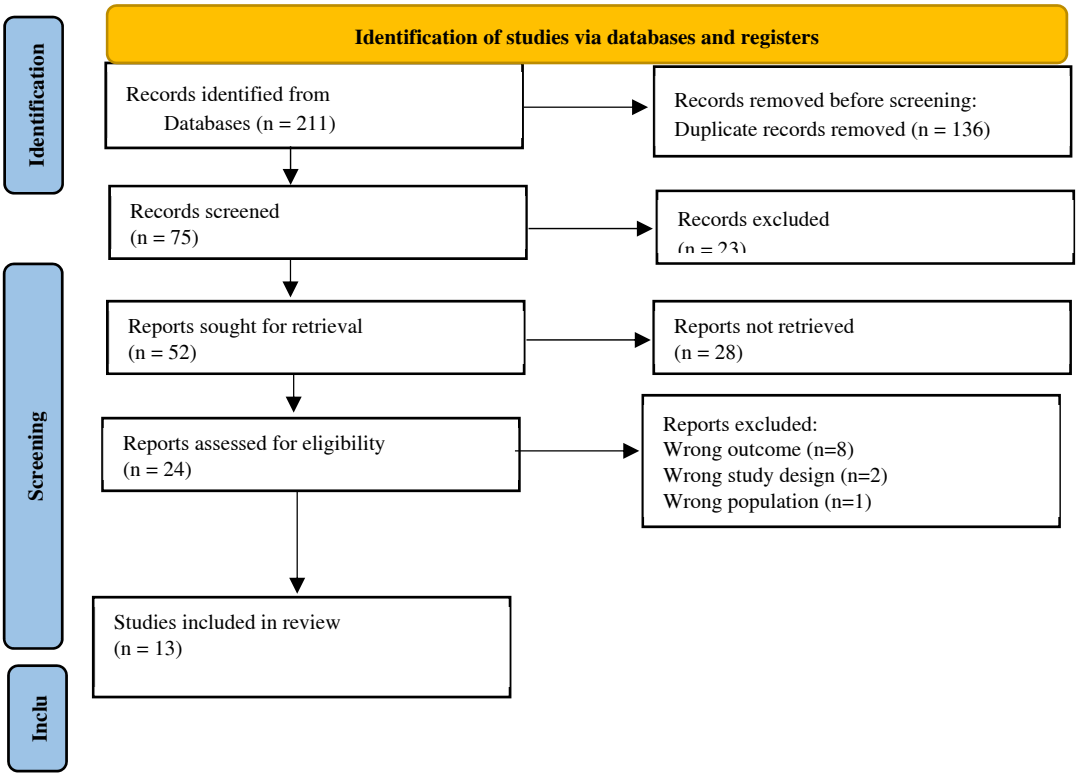


Figure 1: PRISMA 2020 Flow Diagram of the Present Study

Table 1: Evidence Table Summarizing the Main Results of the Included Studies

First Author, Year, Country	Study Design	Total sample, n	Migraine group, n	Control group, n	Serum magnesium measurement	Migraine frequency	Migraine severity/disability	Main association between serum magnesium and migraine
Yasin (2023, Turkey) [28]	Retrospective case-control, cross-sectional observational study	168	71	97	Serum Mg	No significant correlation reported	No significant correlation with severity	Serum Mg was significantly lower in migraine patients than controls (1.98 vs 2.04 mg/dl, p = 0.021); no significant difference among migraine subtypes
Samaie (2012, Iran) [35]	Case-control	100	50	50	Serum Mg	No significant difference between ictal and interictal measurements	NR	Serum Mg was significantly lower in migraineurs than controls (1.86 vs 2.10, P<0.001).
Talebi (2011, Iran) [29]	Case-control	280	140	140	Serum Mg	Lower Mg was associated with higher attack frequency	NR	Serum Mg was significantly lower in migraineurs than controls (26.14 vs 31.09, p = 0.000); no significant difference between migraine with and without aura
Karim (2021, Bangladesh) [33]	Analytical cross-sectional	140	70	70	Serum Mg	No significant association between low Mg and attack frequency	Lower Mg was associated with greater attack severity (p = 0.01)	Serum Mg was significantly lower in migraineurs than controls (1.70 vs 1.85, p = 0.001) and was associated with migraine severity
Assarzadegan (2015, Iran) [40]	Case-control	96	48	48	Ionized serum Mg	NR	NR	No significant difference in ionized serum Mg between groups (1.16 vs 1.13, p>0.05)
Ali Abdulridha Jabbar (2025, Iraq) [41]	Clinical cross-sectional	97	35	62	Serum Mg	Lower migraine frequency was reported with higher Mg serum level; this finding relates to magnesium intake rather than serum Mg concentration	Lower migraine intensity was reported with higher Mg intake; this finding relates to supplementation/intake rather than serum Mg concentration	Migraine patients had lower serum Mg than controls (1.62±0.39 vs 2.19±0.31)
Bindu Sunda (2017, India) [34]	Case-control	140	70	70	Serum Mg	Frequency was inversely correlated with serum Mg	NR	Serum Mg was significantly lower in migraine patients than controls; lower Mg was associated with greater attack frequency
Muhammad Jaleel Khan (2024, Rawalpindi, Pakistan) [42]	Case-control	180	90	90	Serum Mg	NR	Magnesium deficiency was associated with greater severity (r = -0.22, p = 0.030)	Migraine patients had lower serum Mg (1.8 vs 1.9,p = 0.025) together with lower vitamin D and calcium; magnesium deficiency was associated with greater migraine severity
Farhad Assarzadegan (2016, Tehran, Iran) [43]	Case-control	80	40	40	Serum Mg	Low Mg level was associated with increased 35.3 times in having acute migraine headaches	NR	Serum Mg was significantly lower in migraine patients during and between attacks compared with controls; very low Mg was associated with migraine attacks
Elsayed *et al.* (2020, Egypt) [32]	Case-control	90	60	30	Serum Mg	Lower Mg was associated with higher frequency	Lower Mg was associated with greater severity and disability	Serum Mg was lower in migraine patients (1.88 vs 2.21, p = 0.04) and magnesium deficiency was associated with frequency, severity, and disability
Abdelwahab *et al.* (2025, Egypt) [31]	Case-control	80	40	40	Serum Mg	Magnesium deficiency was associated with higher frequency	Magnesium deficiency was associated with greater severity	Serum Mg was significantly lower in migraine patients (1.52 vs 2.11, P=0.001); deficiency was reported in 77.5% of migraine patients versus 0% of controls
First Author, Year, Country	Study Design	Total sample, n	Migraine group, n	Control group, n	Serum magnesium measurement	Migraine frequency	Migraine severity/disability	Main association between serum magnesium and migraine

Table 1: Evidence Table Summarizing the Main Results of the Included Studies (Continue)

Mahajan *et al.* (2022, India) [36]	Prospective observational	100	50	50	Serum Mg	Serum Mg was inversely related to attack frequency	NR	Serum Mg was lower during ictal and interictal periods than in controls and was significantly lower during attacks
Shyamsundar M (2023, India) [30]	Prospective observational	120	60	60	Serum Mg	Serum Mg was inversely correlated with attack frequency	NR	Migraine patients had significantly lower serum Mg than controls (1.84 vs 2.09, p = 0.001), with further reduction during attacks

NR: Not reported

Included studies (n = 13) spanned publication years 2011-2025, representing investigations from multiple geographic regions: Iran (4 studies), India (3 studies), Egypt (2 studies), Turkey (1 study), Bangladesh (1 study), Pakistan (1 study), Iraq (1 study). The majority of studies (12/13) enrolled adult participants exclusively, whilst one studies [30] included broader adult age ranges. Sample sizes ranged from 59 to 280 participants (median 100).

Serum Magnesium Levels: Migraine Patients versus Controls

Thirteen studies included comparisons of serum magnesium levels between migraine patients and control groups. In general, the serum magnesium levels were lower in the migraine patients than in controls significantly as reported by several studies [28–33,35,36,41–43]. However, Assarzadegan 2015, who specifically measured the ionized serum magnesium, did not find any significant difference between migraine patients and controls (1.16 vs 1.13, p>0.05) [40]. The overall evidence indicated that magnesium levels were lower in migraine patients, but the results were not always consistent across studies and may differ depending on the type of magnesium measurement.

Serum Magnesium and Attack Frequency Correlations

Nine studies reported on the association between magnesium and migraine attack frequency. The association between magnesium and migraine attack frequency was reported in nine studies. There was a correlation between lower serum magnesium and higher attack frequency as reported by Talebi [29]. Bindu Sunda, Elsayed *et al.* Abdelwahab *et al.* Mahajan *et al.* and Shyamsundar also found an inverse correlation between the serum magnesium and the frequency of migraine attacks, or a correlation between magnesium deficiency and the increased frequency of attacks [30–32,34,36]. A study by Farhad Assarzadegan found that low magnesium levels were significantly linked to a higher risk of having an acute migraine headache [43]. However, Yasin and Karim did not find any significant relationship between serum magnesium and attack frequency despite lower serum magnesium levels in migraine patients [28,33]. The reported frequency finding in the Ali Abdulridha Jabbar study was not directly related to serum magnesium level, but rather to magnesium intake, and was therefore not regarded as evidence of a serum magnesium–frequency association [41]. Overall, the results indicate that there is generally an inverse relationship between serum Mg status and migraine frequency, but this was not always the case.

Serum Magnesium and Migraine Severity

Five studies provided data on severity or disability of migraine. The study by Karim revealed that lower serum magnesium was linked to higher severity of migraine (p = 0.01) [33]. A similar correlation was observed between magnesium deficiency and severity (r =-0.22, p = 0.030), with Khan Muhammad Jaleel reporting this [42]. Elsayed *et al.* showed that lower serum magnesium was correlated with higher severity and disability [32], and Abdelwahab *et al.* reported that magnesium deficiency was correlated with higher frequency and higher severity [31]. The Ali Abdulridha Jabbar study found that higher magnesium exposure was associated with lower migraine intensity, but this was in regards to magnesium intake, not the serum magnesium level [41]. Overall, available evidence suggested that lower serum magnesium status was associated with increased severity of migraine in several studies, but the number of studies specifically examining this association was small and the measures used to assess the outcome were diverse.

Migraine Phenotype Stratification

In the studies included, the patients were mostly recruited with mixed migraine phenotypes and included migraine with and without aura. Few studies, however, gave explicit comparisons based on migraine phenotype. No difference in serum magnesium was found between the types of migraine, according to Yasin. Talebi also reported no difference in serum magnesium between migraine with aura and migraine without aura, but that the magnesium level in the total migraine group was lower than that of controls [28,29]. The results indicate that the serum magnesium decrease is not only limited to one type of aura; but due to the small number of studies to come to a conclusion about the differences between migraine subtypes.

Risk of Bias Assessment

The Joanna Briggs Institute (JBI) critical appraisal tools were used to evaluate risk of bias in the observational studies included. In general, the studies had acceptable methodological

Table 2: Shows The Risk of Bias Assessment Results for the Included Studies

Study	Design	Appraisal tool	Risk of bias	Main considerations
Samaie *et al.* [35]	Case-control	JBI critical appraisal tool	Moderate	Case-control design; potential selection and confounding limitations
Talebi *et al.* [29]	Case-control	JBI critical appraisal tool	Moderate	Potential selection/confounding bias; observational exposure assessment
Assarzadegan *et al.* [40]	Case-control	JBI critical appraisal tool	Moderate	Case-control design and limited sample size; ionized magnesium measurement
Assarzadegan *et al.* [43]	Case-control	JBI critical appraisal tool	Moderate	Case-control design; potential selection and confounding limitations
Bindu Sunda *et al.* [34]	Case-control	JBI critical appraisal tool	Moderate	Observational design and potential residual confounding
Karim *et al.* [33]	Analytical cross-sectional	JBI critical appraisal tool	Moderate	Cross-sectional design limits temporal interpretation; potential confounding
Yasin *et al.* [28]	Retrospective case-control/cross-sectional	JBI critical appraisal tool	Moderate	Retrospective data collection and potential selection/confounding bias
Shyamsundar *et al.* [30]	Prospective observational	JBI critical appraisal tool	Low–moderate	Prospective design strengthens temporal assessment, but observational confounding remains possible
Mahajan *et al.* [36]	Prospective observational	JBI critical appraisal tool	Low–moderate	Prospective design; possible residual confounding and limited sample size
Elsayed *et al.* [32]	Case-control	JBI critical appraisal tool	Moderate	Case-control design, relatively small sample, and possible confounding
Muhammad Jaleel Khan *et al.* [42]	Case-control	JBI critical appraisal tool	Moderate	Case-control design and potential confounding by related biochemical factors
Abdelwahab *et al.* [31]	Case-control	JBI critical appraisal tool	Moderate	Case-control design and limited sample size
Ali Abdulridha Jabbar *et al.* [41]	Cross-sectional	JBI critical appraisal tool	Moderate	Cross-sectional design; serum magnesium and magnesium intake were not consistently equivalent exposure measures

Table 3: GRADE Assessment of the Certainty of Evidence

Outcome	No. of studies	Initial certainty	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty
Serum magnesium levels in migraine patients vs controls	13	Low	Not serious	Not serious	Not serious	Not serious	Not assessed	Moderate
Serum magnesium and migraine attack frequency	9	Low	Not serious	Serious	Not serious	Not serious	Not assessed	Moderate
Serum magnesium and migraine severity/disability	4	Low	Not serious	Not serious	Not serious	Serious	Not assessed	Moderate
Serum magnesium according to migraine phenotype	2	Low	Serious	Not serious	Serious	Serious	Not assessed	Low

quality, but there were some concerns due to observational study designs, limited sample size, selection bias, and potential for residual confounding. The methodological issues in the prospective observational studies were generally fewer compared to retrospective or case-control studies, as serum magnesium and migraine characteristics were measured prospectively. However, the observational evidence still had some inherent limitations with the lack of randomization. When interpreting the findings, differences in the timing of the serum magnesium measurement, the method used to measure magnesium, the classification of migraine and the frequency and severity of the attacks were taken into account. Overall, the evidence was found to be reasonably consistent and directly relevant to the main conclusions of the review, with recognition of the limitations of the underlying observational designs. Detailed study-level assessments are presented in Table 2.

Certainty of Evidence

The certainty of evidence for the principal outcomes was evaluated using the GRADE framework. Because the evidence was derived predominantly from observational studies, the initial certainty was rated as low. However, the certainty was upgraded for the principal outcomes where the available studies demonstrated relatively consistent associations, direct assessment of serum magnesium, and clinically coherent relationships between lower magnesium concentrations and migraine characteristics. The evidence for lower serum magnesium concentrations among migraine patients compared with controls was therefore judged to be moderate certainty. The evidence concerning the association between serum magnesium and migraine attack frequency was also judged to be moderate certainty, despite some inconsistency between individual studies. Similarly, the evidence relating serum magnesium to migraine severity or disability was considered moderate certainty, although the smaller number of studies and differences in outcome measures introduced some imprecision. Evidence concerning migraine phenotype was considered low certainty because only a limited number of studies provided phenotype-specific comparisons. Publication bias was not formally assessed because the number of included studies was limited and no quantitative meta-analysis was performed. Accordingly, no conclusion regarding the

presence or absence of publication bias could be made. The overall certainty assessments are summarized in Table 3.

DISCUSSION

This systematic review aimed to pool data from 13 studies investigating the relationship between serum magnesium and migraine frequency, severity and clinical characteristics in adults. In general, the studies included in this review revealed that serum magnesium levels in migraine patients were lower than in control subjects. Most comparative studies reported low levels of serum magnesium in migraine patients, with statistically significant differences reported in several studies, while Assarzadegan specifically investigated the ionized serum magnesium and found no difference between migraine patients and controls [40]. The results thus indicate a general trend towards lower Mg levels in adults with migraine, but this was influenced by the variation in measurements of serum Mg levels and the variation in study methodology. Importantly, the results are association and do not prove that low levels of magnesium in blood are a cause of migraine.

The relationship of serum magnesium to migraine attack frequency was less clear. This association was explored directly in nine studies, with some reporting a correlation between low magnesium levels and increased migraine attack frequency. The findings of Talebi, Bindu Sunda, Elsayed *et al.*, Abdelwahab *et al.*, Mahajan *et al.*, and Shyamsundar were in line with the inverse relationship between serum magnesium and attack frequency [29–32,34,36]. Farhad Assarzadegan also found that low levels of magnesium were linked to acute migraine headache [43]. But Yasin and Karim did not find any significant relationship between serum Mg and attack frequency, although they did find that migraine patients had lower serum Mg [28]. Thus, there is no evidence that there is a consistent association between serum magnesium level and migraine frequency. The observed variability could be due to differences in study populations, the nature of migraine, the magnesium measurement, timing of the blood sample, or the adjustment for potential confounding factors. Therefore, the association between serum magnesium and frequency of attacks should be regarded as indicative, but not conclusive.

There was slightly more consistency in the findings on the severity and disability of migraine attacks, with a smaller evidence base. The four studies directly addressed the relationship between serum magnesium and migraine severity or disability. Karim reported that those with lower levels of serum magnesium had more severe migraine [33], and Muhammad Jaleel Khan reported that there was a correlation between magnesium deficiency and severity [42]. Similarly, Elsayed *et al.* reported that lower serum magnesium levels were associated with higher severity and disability scores [32], and Abdelwahab *et al.* reported that there was an association between magnesium deficiency and severity [31]. The findings indicate that lower serum magnesium levels could be related to more severe migraine manifestations, although this interpretation is limited by the fact that the number of studies is relatively small and the differences in the measures of severity and disability. Therefore, the association of serum magnesium with clinical severity and not attack frequency should be considered a hypothesis that needs to be confirmed in prospective studies, rather than a biological relationship.

Limited migraine phenotype analyses were performed. While most of the included studies included patients with mixed migraine phenotypes, only a few studies made clear comparisons based on migraine subtype. Yasin and Talebi did not find any significant difference between serum magnesium level in migraine with and without aura [28,29]. These results indicate that the differences in serum magnesium are not limited to a specific aura phenotype but due to the small number of analyses performed for each phenotype, firm conclusions cannot be drawn. Future studies should thus be designed to specifically explore any differences between episodic and chronic migraine, migraine with aura and migraine without aura, and the relationship between serum magnesium and migraine characteristics.

There are some methodological considerations to be taken into account when interpreting these findings. First, there was a great deal of variation in the way serum magnesium was measured. Different analytical methods were employed in the studies, such as colorimetric, atomic absorption, and other lab-based methods, and the reference ranges were not always the same. Most importantly, the total serum magnesium and the ionized serum magnesium are not interchangeable. Total serum magnesium is the level of free (circulating) magnesium in the blood, and ionized magnesium is the active (biologically available) magnesium. The negative association in Assarzadegan, who measured ionized magnesium, from the mostly positive results reported in studies that measured total serum magnesium underscores the need to differentiate between the two when interpreting the literature [40]. The analytical method, units, reference range and time of sampling should be reported for future research.

Second, serum magnesium has a number of physiological restrictions as a measure of magnesium status. The extracellular compartment contains only a small fraction of the total body magnesium, with the remainder of the magnesium being bound to bone and intracellular. Thus, the serum magnesium level may not reflect the level of magnesium in tissues or cells. So a normal serum level of magnesium does not rule out a disturbed magnesium status at the cellular level. This restriction is important when examining the relationships between blood magnesium and neurological disorders like migraine. Other validated methods of measuring magnesium status, if applicable, would be added to serum magnesium measurements in future studies; however, the clinical significance and practicability of these methods should be explored.

Third, the associations observed need to be interpreted with caution, as there may be confounding factors. Factors that may be relevant include dietary magnesium intake, use of medication, stress, hormonal factors, renal or metabolic

disorders, and other factors related to magnesium status and migraine. Reporting of the assessment and adjustment for confounders, however, was inconsistent across the included studies. Several studies reported unadjusted comparisons or correlations, and the study summaries available did not always give enough information to assess whether other factors, including diet, stress, medication use, and characteristics of the menstrual cycle, were adequately controlled. Thus, variations in the measurement and adjustment of the confounders may have accounted for some of the differences in observed associations. Future studies should report on important confounders prespecified and, if applicable, perform multivariable analyses instead of limited comparisons.

Evidence on magnesium supplementation should also be separated from the findings. The efficacy of magnesium supplementation as a treatment for migraine has been investigated in previous clinical trials and systematic reviews for its ability to decrease the frequency and/or severity of migraine [44]. This evidence does not directly support an association between naturally occurring serum magnesium levels and characteristics of migraine but rather provides relevant context for the potential clinical role of magnesium. Therefore, the efficacy of magnesium supplementation should not be taken as direct evidence for the primary association in the present review, because this particular association was not measured. Supplementation studies can be considered as additional evidence regarding treatment effects but should be presented separately from the observational associations summarized in this review.

Differences between studies could also be due to the differences between populations and clinical settings. Variation in dietary patterns, background nutritional status, demographic factors, migraine phenotype, medication exposure and laboratory methods could account for the observed variation in serum magnesium levels and associations with migraine outcomes. These explanations, however, are still speculative since most of the studies included in this report did not fully examine all of these factors. Differences in the observed populations should therefore not be considered to be due to population-specific biological mechanisms without further investigation.

There are a number of strengths to the review. It specifically focused on the association of an objectively measured biochemical exposure with migraine characteristics, the distinction between serum magnesium and magnesium supplementation, and the synthesis of evidence on migraine frequency, severity and phenotype separately. The search and selection of studies for inclusion were conducted in a systematic-review fashion, and the study results were presented clearly and transparently. The review also took into account methodological differences in the measurement of magnesium, and the use of serum magnesium as an indicator of total magnesium status.

There are also some constraints to note. First, the evidence base was largely composed of observational studies and this precluded the ability to make causal interpretations, and also meant that the findings were vulnerable to residual confounding. Secondly, there was significant heterogeneity with regard to magnesium measurement, sampling time, migraine phenotype and outcome assessment measures, which made meaningful quantitative pooling impossible. Thirdly, the number of studies assessing some outcomes was small, especially for the association with migraine severity and migraine phenotype. Fourth, the review was limited to publications in the English language, which could have added language bias. Fifth, as only 13 studies were included and no quantitative meta-analysis was done, the publication bias was not formally tested with funnel plots or statistical tests. Finally, narrative synthesis is always an interpretive process, and while the review made an effort to minimize this by summarizing the findings of the individual studies, methodological heterogeneity was also taken into account.

The evidence available overall indicates some association of lower serum magnesium levels with migraine, especially when comparing migraine patients with controls. The association with attack frequency seems more variable, and the sparse data on the association with severity suggest a relationship with increased severity or disability of migraine attacks and lower serum magnesium. However, these results should be taken as associations and not as proof of causation. The nature of these relationships is not known and could be complex, involving several interacting biological and clinical factors.

CONCLUSIONS

This systematic review revealed a general trend of lower serum magnesium levels in adults with migraine than in controls, with results not being entirely congruent between studies. There was a heterogeneous relationship between serum magnesium and migraine attack frequency, with some studies showing an inverse relationship and others showing no relationship. Evidence indicating association between lower serum magnesium and increased clinical severity was more consistent but was based on fewer studies and smaller numbers of patients. There was limited evidence from the phenotype analysis that there were no significant differences in serum magnesium levels between the migraine subtypes.

The results should be interpreted with caution as the study was largely observational and there was heterogeneity in the methods of magnesium measurement, timing of blood sampling, migraine assessment, and confounder adjustment. Furthermore, total serum magnesium and ionized serum magnesium are two separate parameters, and serum magnesium may not adequately reflect intracellular or total body magnesium levels. The present results, therefore, provide evidence for an association between the serum magnesium status and migraine characteristics, but do not provide evidence for a causal relationship between magnesium deficiency and migraine or evidence that the severity of migraine is determined by the serum magnesium status.

Standardized migraine diagnostic criteria and migraine diaries, pre-defined and extensively quantified confounders,

and standardized timing of blood sampling in relation to migraine attacks should be applied in future prospective studies. The distinction between total and ionized serum magnesium should also be made clear and, if scientifically justified, complementary measurements of magnesium status should be taken. The observed associations should be confirmed by larger studies with prespecified analyses by migraine phenotype and standardized measures of frequency, severity and disability.

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