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Effect of Magnesium, Riboflavin, and Coenzyme Q10 Supplementation on Serum Magnesium and Coenzyme Q10 Levels in Patients with Migraine: A Prospective Clinical Study

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ABSTRACT

Background: Migraine is a prevalent and disabling primary headache disorder in which mitochondrial dysfunction, oxidative stress, and altered neuronal excitability play important roles in disease pathophysiology. Magnesium and coenzyme Q10 (CoQ10) are essential metabolic factors involved in neuronal stability and mitochondrial bioenergetics, and deficiencies of these nutrients have been reported in migraine patients. Although supplementation with magnesium, riboflavin, and CoQ10 has shown clinical benefit in migraine prophylaxis, objective biochemical evidence demonstrating correction of serum magnesium and CoQ10 levels following combined supplementation remains limited.

Materials and Methods: This prospective, randomized, open-label, controlled clinical study was conducted in patients aged 18–55 years diagnosed with migraine according to ICHD-3 criteria. Participants received standard migraine therapy alone or in combination with oral magnesium (400 mg/day as magnesium glycinate), riboflavin (400 mg/day), and coenzyme Q10 (100 mg/day) for 12 weeks. Serum magnesium and serum CoQ10 levels were measured at baseline and at the end of the intervention period. Changes in biochemical parameters were analyzed using paired t-tests, and repeated-measures analysis of variance (RM-ANOVA) was applied to assess treatment effects and the influence of demographic and clinical variables.

Results: Following 12 weeks of supplementation, serum magnesium levels increased significantly from 1.97 ± 0.18 mg/dL to 2.15 ± 0.20 mg/dL ($p < 0.001$), confirming effective physiological correction. Serum CoQ10 levels also showed a significant rise from 1.06 ± 0.25 µg/mL to 1.29 ± 0.33 µg/mL ($p < 0.001$), indicating improved mitochondrial bioenergetic status. RM-ANOVA demonstrated that these biochemical improvements were predominantly treatment-driven, with no significant influence of age, duration of migraine, or duration of attacks, and no meaningful interaction effects.

Conclusion: Combined supplementation with magnesium, riboflavin, and coenzyme Q10 for 12 weeks results in significant and consistent increases in serum magnesium and serum CoQ10 levels in patients with migraine. These findings provide objective biochemical validation for the mechanistic rationale underlying nutraceutical-based migraine prophylaxis and support this combination as a

biologically rational and well-tolerated adjunctive therapeutic strategy.

Keywords: *Migraine; Magnesium; Coenzyme Q10; Riboflavin; Nutraceutical supplementation; Mitochondrial dysfunction; Oxidative stress.*

INTRODUCTION

Migraine is a common primary headache disorder characterized by recurrent attacks of moderate to severe headache, often accompanied by nausea, vomiting, and hypersensitivity to sensory stimuli [1]. It is a leading cause of neurological disability worldwide and disproportionately affects women, likely due to hormonal and metabolic influences [2]. Although the precise etiology of migraine remains incompletely understood, accumulating evidence suggests that genetic susceptibility, environmental triggers, and metabolic dysfunction collectively contribute to its pathophysiology [3].

A growing body of research implicates mitochondrial dysfunction, oxidative stress, and altered neuronal excitability as central mechanisms in migraine generation [4,5]. Migraineurs frequently exhibit abnormalities in energy metabolism, increased production of reactive oxygen species, and heightened neuroinflammatory signaling, which together facilitate activation of the trigeminovascular system and cortical spreading depression [6,7]. These processes are further amplified by vasoactive neuropeptides such as calcitonin gene-related peptide (CGRP), leading to neurogenic inflammation and pain transmission [8].

Among metabolic factors, magnesium and coenzyme Q10 (CoQ10) have received particular attention due to their critical roles in neuronal stability and mitochondrial bioenergetics. Magnesium is an essential intracellular cation that modulates ion channels, neurotransmitter release, and enzymatic reactions involved in ATP synthesis. Magnesium deficiency enhances neuronal hyperexcitability by increasing N-methyl-D-aspartate (NMDA) receptor activity, promoting calcium influx, nitric oxide production, and cortical spreading depression—key events implicated in migraine pathogenesis [9,10]. Several studies have demonstrated reduced serum and brain magnesium levels in migraine patients compared to healthy controls [11,12].

Coenzyme Q10 is a lipid-soluble component of the mitochondrial electron transport chain that facilitates ATP production and functions as a potent endogenous antioxidant. Deficiency of CoQ10 impairs oxidative phosphorylation and increases oxidative stress, both of which are commonly observed in migraineurs [13,14]. Elevated oxidative stress has been linked to increased expression of matrix metalloproteinase-9 (MMP-9) and disruption of the blood–brain barrier, contributing to neuroinflammation and trigeminal activation [15-17]. Clinical studies have reported lower baseline CoQ10 levels in migraine patients, particularly in those with frequent or chronic attacks [18].

Although supplementation with magnesium, riboflavin, and CoQ10 has been shown to reduce migraine frequency in clinical trials, objective biochemical evidence demonstrating correction of serum magnesium and CoQ10 levels following combined supplementation remains limited. Establishing such biochemical changes is essential to validate the mechanistic rationale underlying nutraceutical-based migraine prophylaxis.

Therefore, the present study was designed to evaluate the effect of combined magnesium, riboflavin, and CoQ10 supplementation on serum magnesium and serum CoQ10 levels in patients with migraine, and to determine whether these changes occur independently of demographic and clinical variables.

MATERIALS AND METHODS

Study Design

This investigation was conducted as a prospective, randomized, open-label, controlled clinical study designed to evaluate the effect of combined supplementation with magnesium, riboflavin, and coenzyme Q10 on both clinical outcomes and objective biochemical parameters in patients with migraine. Particular emphasis was placed on assessing changes in serum magnesium and serum coenzyme Q10 levels following a 12-week supplementation period, along with determining whether these biochemical changes were influenced by demographic or clinical variables.

Place of Study

The study was carried out in the Department of Pharmacology, in collaboration with the Department of Neurology, Career Institute of Medical Sciences and Hospital, IIM Road, Ghaila, Lucknow–226013, Uttar Pradesh, India. Patient recruitment, clinical assessment, treatment administration, and follow-up were conducted through the Neurology outpatient department, while biochemical investigations and data analysis were supervised by the Department of Pharmacology.

Methodology

Patients aged 18–55 years diagnosed with migraine with or without aura according to the International Classification of Headache Disorders, 3rd edition (ICHD-3) criteria were enrolled after obtaining written informed consent. Eligible participants had a migraine history of at least one year with a frequency of 2–8 migraine attacks per month and were not receiving any preventive migraine medication for at least one month prior to enrollment.

Patients with secondary headache disorders, chronic daily headache, medication-overuse headache, major systemic illness, pregnancy or lactation, or known hypersensitivity to magnesium, riboflavin, or coenzyme Q10 were excluded.

Participants were randomized into two groups. The control group received standard migraine therapy as prescribed by the treating neurologist, while the intervention group received standard therapy along with oral supplementation of magnesium (400 mg/day as magnesium glycinate), riboflavin (400 mg/day), and coenzyme Q10 (100 mg/day). Supplements were administered once daily after meals for a total duration of 12 weeks. All supplements were pharmaceutical grade and obtained from certified manufacturers. Participants were instructed to maintain their usual dietary habits and to avoid any additional vitamin or mineral supplementation during the study period.

Baseline evaluation included demographic details, migraine history, attack frequency and duration, and pain intensity assessment using the Visual Analogue Scale (VAS). Venous blood samples were collected at baseline and at the end of the 12-week intervention period for estimation of serum magnesium and serum coenzyme Q10 levels using standard laboratory methods. Participants maintained headache diaries throughout the study period. Follow-up assessments were conducted at 4, 8, and 12 weeks to evaluate treatment compliance, clinical response, and adverse events.

Statistical Analysis

Data were entered into Microsoft Excel and analyzed using SPSS version 26.0 (I. Continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as frequencies and percentages. Changes in serum magnesium and serum coenzyme Q10 levels before and after treatment were analyzed using paired t-tests. To further evaluate the effect of treatment over time and to assess the influence of demographic and clinical variables—including age, duration of migraine, and duration of attacks repeated-measures analysis of variance (RM-ANOVA) was applied. Effect sizes (η^2) were calculated to determine the magnitude of treatment effects. A p-value < 0.05 was considered statistically significant.

Ethical Considerations

The study protocol was reviewed and approved by the Institutional Ethics Committee of Career Institute of Medical Sciences and Hospital, Lucknow (IEC Approval No.: _____). The study was conducted in accordance with the Declaration of Helsinki (2013) and Good Clinical Practice (GCP) guidelines. All participants were informed about the study objectives, procedures, potential benefits, and risks, and written informed consent was obtained prior to enrollment. Confidentiality of patient data was strictly maintained, and participants were free to withdraw from the study at any stage without affecting their standard medical care.

RESULTS

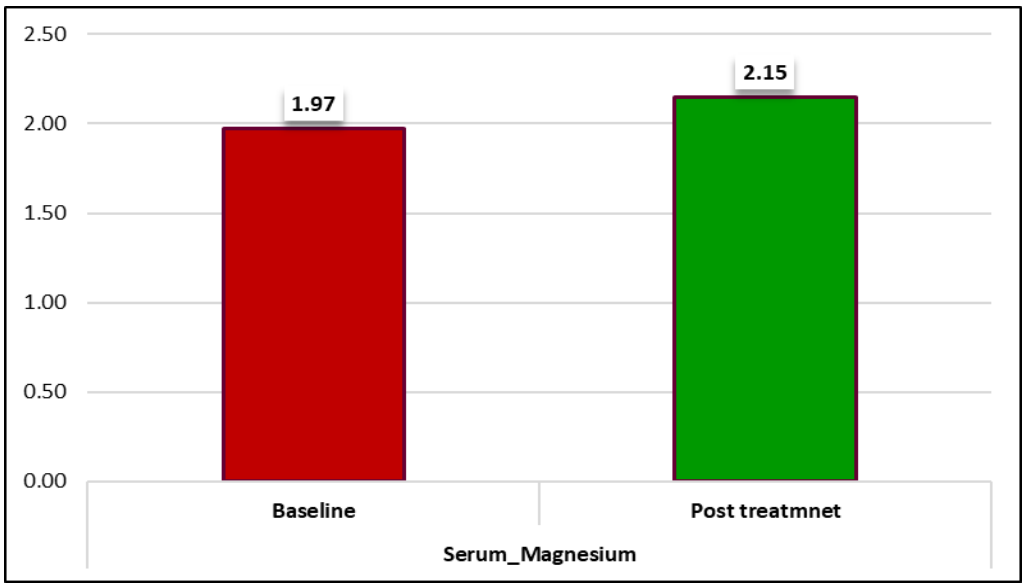

Figure 1 Effect of Treatment on Serum Magnesium Levels

The assessment of serum magnesium levels before and after combined supplementation with magnesium, riboflavin, and coenzyme Q10. At baseline, the mean serum magnesium level was **1.97 ± 0.18 mg/dL**. Following the 12-week intervention, serum magnesium levels increased significantly to **2.15 ± 0.20 mg/dL**. The mean increase of **0.18 mg/dL** was found to be statistically highly significant (**t = −8.59, p < 0.001**). This finding confirms effective absorption and physiological correction of magnesium levels following supplementation and supports the biochemical basis for the observed clinical improvements in migraine outcomes.

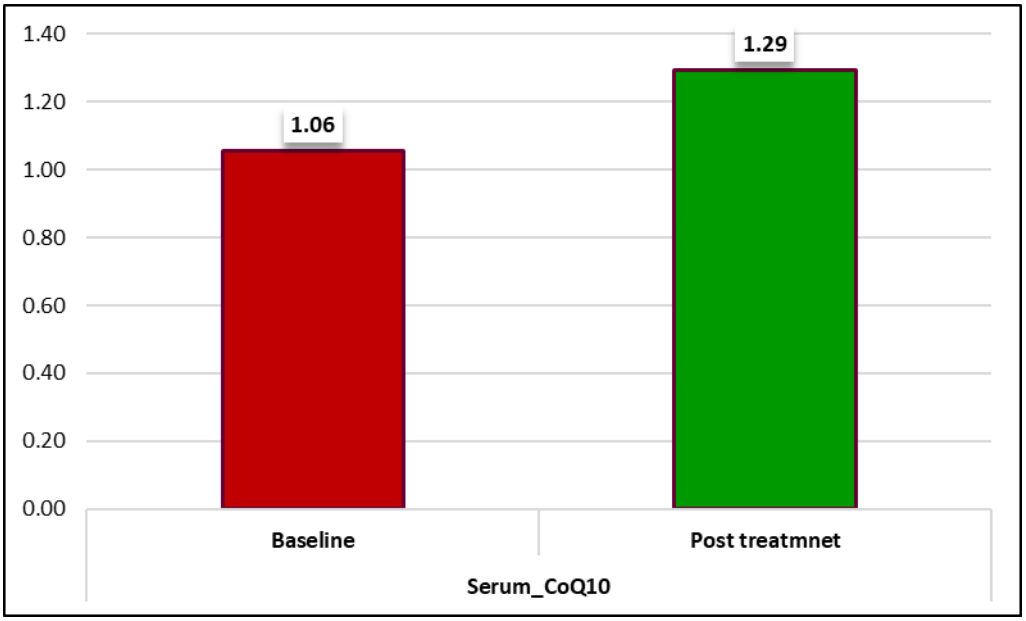

Figure 2: Effect of Treatment on Serum Coenzyme Q10 Levels

Figure 2 shows the effect of treatment on serum coenzyme Q10 concentrations. The baseline mean serum CoQ10 level was 1.06 ± 0.25 µg/mL, which increased significantly to 1.29 ± 0.33 µg/mL after completion of the treatment period. The mean rise of 0.24 µg/mL was statistically significant ($t = -6.46$, $p < 0.001$). This significant elevation in serum CoQ10 indicates improved mitochondrial bioenergetic status following supplementation and provides objective biochemical evidence supporting the therapeutic role of CoQ10 in migraine prophylaxis.

Table 1: Repeated Measures ANOVA Showing Effect of Treatment on Serum Magnesium with Other Influencing Factors

Source	F-value	p-value	effect size
Treatment	13.79	**<0.001**	0.115
Age	0.42	0.520	0.004
Duration of Migrain	0.01	0.935	0.000
Duration of Attack	0.39	0.534	0.004
Treatment × Age	1.77	0.186	0.016
Treatment × Duration of Migrain	0.61	0.438	0.006
Treatment × Duration of Attack	3.55	0.062	0.032

Table 1 presents the repeated measures ANOVA assessing the effect of treatment and other influencing factors on serum magnesium levels. The treatment effect was statistically significant ($F = 13.79$, $p < 0.001$) with a moderate effect size ($\eta^2 = 0.115$), indicating that supplementation was the primary determinant of increased serum magnesium levels.

Other factors, including age ($F = 0.42$, $p = 0.520$, effect size = 0.004), duration of migraine ($F = 0.01$, $p = 0.935$, effect size = 0.000), and duration of attack ($F = 0.39$, $p = 0.534$, effect size = 0.004), did not significantly influence serum magnesium levels. Similarly, interactions between treatment and these factors—treatment × age ($F = 1.77$, $p = 0.186$, effect size = 0.016), treatment × duration of migraine ($F = 0.61$, $p = 0.438$, effect size = 0.006), and treatment × duration of attack ($F = 3.55$, $p = 0.062$, effect size = 0.032)—were not statistically significant, although the treatment × duration of attack interaction showed a trend toward significance.

Overall, the findings demonstrate that the improvement in serum magnesium levels was predominantly treatment-driven and consistent across demographic and clinical subgroups.

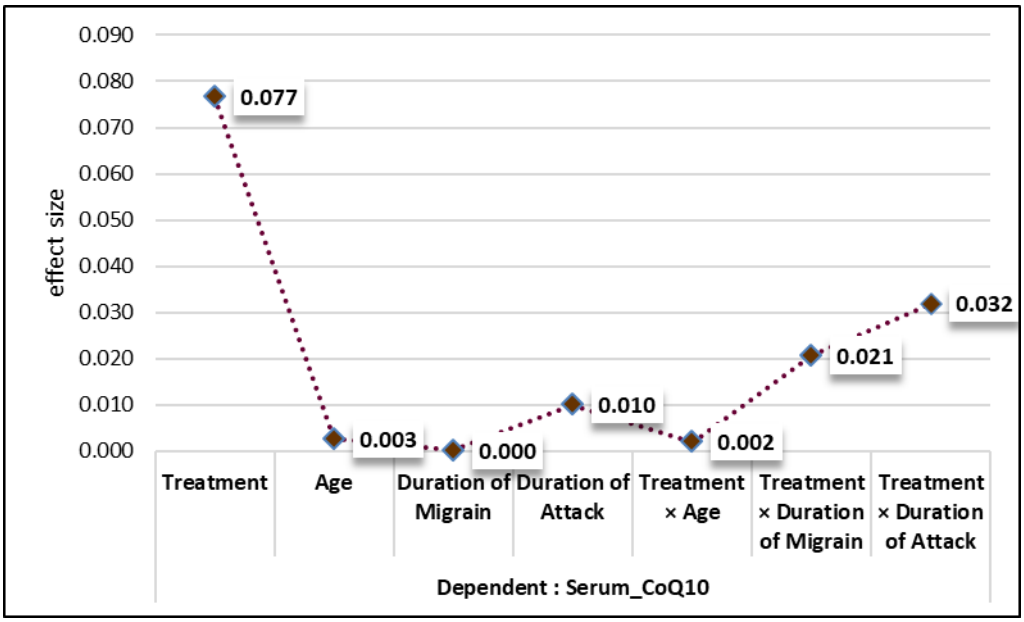

Figure 3: Repeated Measures ANOVA Showing Effect of Treatment on Serum Coenzyme Q10 with Other Influencing Factors

Figure 3 summarizes the repeated measures ANOVA evaluating the effect of treatment and other covariates on serum CoQ10 levels. The treatment factor showed a statistically significant effect ($F = 8.79$, $p = 0.004$) with a moderate effect size ($\eta^2 = 0.077$), confirming that supplementation significantly increased serum CoQ10 concentrations over time.

No significant main effects were observed for age, duration of migraine, or duration of attack. Interaction effects between treatment and these variables were also non-significant, although the interaction between treatment and duration of attack showed a borderline trend toward significance ($p = 0.064$). These results indicate that the rise in serum CoQ10 levels was primarily attributable to the intervention and was not substantially influenced by patient demographic or disease-related factors.

DISCUSSION

The present study demonstrates that combined supplementation with magnesium, riboflavin, and coenzyme Q10 for 12 weeks produces significant and treatment-driven improvements in key biochemical markers relevant to migraine pathophysiology. The observed increases in serum magnesium and serum coenzyme Q10 (CoQ10) levels provide objective biochemical evidence supporting the biological efficacy of this nutraceutical regimen and reinforce its mechanistic relevance in migraine prophylaxis.

A significant increase in serum magnesium levels was observed following treatment, with mean concentrations rising from 1.97 ± 0.18 mg/dL at baseline to 2.15 ± 0.20 mg/dL after the intervention ($p < 0.001$). This magnitude of improvement is consistent with earlier magnesium supplementation studies that reported modest but meaningful elevations in serum magnesium following oral therapy. Peikert et al. (1996) [19] and Trauninger et al. (2002) [20] similarly demonstrated significant increases in serum magnesium concentrations associated with clinical improvement in migraine. The present findings confirm effective absorption and physiological correction of magnesium levels, supporting its established role in stabilizing neuronal excitability and modulating vascular and neurochemical mechanisms involved in migraine.

The repeated measures ANOVA demonstrated that the increase in serum magnesium levels was predominantly treatment-driven, with a statistically significant main effect and a moderate effect size ($\eta^2 = 0.115$), while age, duration of migraine, and duration of attack showed no significant influence and no interaction effects reached statistical significance. This pattern indicates a consistent biochemical response to magnesium supplementation across demographic and clinical subgroups. Comparable findings have been reported by Peikert et al. (1996) [19] and Trauninger et al. (2002) [20], who observed significant elevations in serum magnesium following oral supplementation without subgroup-specific variability related to age or migraine characteristics. The absence of significant interaction effects in the present study aligns with these reports and supports the conclusion that magnesium supplementation produces a stable and uniform biochemical effect, primarily attributable to treatment rather than patient-related factors.

Serum CoQ10 levels also increased significantly following supplementation, rising from 1.06 ± 0.25 μg/mL at baseline to 1.29 ± 0.33 μg/mL after treatment ($p < 0.001$). This increase indicates improved systemic availability of CoQ10 and supports enhanced mitochondrial bioenergetic function. Mitochondrial dysfunction has been increasingly implicated in migraine pathogenesis, and CoQ10 plays a critical role in electron transport, ATP synthesis, and oxidative stress regulation. The magnitude of CoQ10 elevation observed in the present study is comparable to that reported by Nattagh-Eshtivani et al. (2018) [21], Dahri et al. (2018) [22], and Dahri et al. (2023) [23], all of whom demonstrated significant increases in serum CoQ10 concentrations following 12 weeks of supplementation.

Repeated measures ANOVA further confirmed that the increase in serum CoQ10 levels was primarily attributable to the intervention, with a statistically significant main effect and a moderate effect size ($\eta^2 = 0.077$). Age, duration of migraine, and duration of attack did not significantly influence CoQ10 levels, and interaction effects were non-significant. This uniform biochemical response is consistent with meta-analytic evidence reported by Sazali et al. (2021) [24], which demonstrated consistent CoQ10 elevation across diverse migraine populations following supplementation. The present findings therefore support the conclusion that CoQ10 supplementation produces a reliable and demographically independent biochemical effect.

In summary, the present study provides robust biochemical evidence that combined magnesium, riboflavin, and CoQ10 supplementation effectively corrects metabolic deficiencies commonly implicated in migraine. The improvements in serum magnesium and CoQ10 levels were treatment-driven, statistically significant, and consistent across demographic and clinical subgroups. These findings strengthen the mechanistic foundation for the use of this nutraceutical combination in migraine prophylaxis and support its role as a biologically rational and well-tolerated therapeutic strategy.

CONCLUSION

This prospective clinical study demonstrates that combined supplementation with magnesium, riboflavin, and coenzyme Q10 for 12 weeks results in a significant and treatment-driven increase in serum magnesium and serum coenzyme Q10 levels in patients with migraine. These findings confirm effective absorption and physiological correction of key metabolic factors implicated in migraine pathophysiology, particularly those related to neuronal excitability and mitochondrial bioenergetics. The observed biochemical improvements were independent of age, duration of migraine, and duration of attacks, indicating a consistent response across demographic and clinical subgroups. Overall, the study provides objective biochemical validation for the mechanistic rationale of nutraceutical-based migraine prophylaxis and supports the use of this supplementation strategy as a biologically rational and well-tolerated adjunct in migraine management.

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