

Original Research Article

Effect of nutritional supplementation with omega-3, acetyl-L-carnitine and vitamin E on biochemical parameters and migraine outcome

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Abstract

Purpose: To investigate the impact of supplementation with omega-3, acetyl-L-carnitine, and vitamin E on symptoms and general well-being of migraine patients.

Methods: This study involved 40 male patients aged 20 - 65 years, who experienced 2 - 8 migraine attacks per month. The participants were recruited from outpatient clinics in Mosul City, Iraq. A total of 20 age-matched healthy individuals served as control group. Over a period of 30 days, the patients received daily supplements containing Omega-3 (180 mg of EPA and 120 mg of DHA) plus vitamin E (3 mg) and acetyl-L-carnitine (500 mg). Blood tests were conducted before and after supplementation to measure serum levels of serotonin, uric acid, indirect bilirubin, electrolytes, and lipid profiles.

Results: Serum levels of total cholesterol and triglycerides were significantly elevated ($p < 0.001$) in migraine patients (216.15 ± 36.41 mg/dL), when compared to control group (179.37 ± 33.84 mg/dL). Moreover, migraine patients had significantly increased serum triglyceride levels (255.36 ± 100.8), relative to control group (116.70 ± 49.03 mg/dL; $p < 0.001$). The nutritional supplementation led to marked increase in serum serotonin level from 103.03 ± 19.03 to 116.97 ± 36.61 ng/mL ($p < 0.01$). In contrast, there were significant reductions ($p < 0.01$) in total cholesterol (from 218.38 ± 36.73 to 201.34 ± 26.30 mg/dL) and triglycerides (from 256.28 ± 104.41 to 156.66 ± 72.66 mg/dL). The number of migraine attacks was significantly decreased from 4 to 2 ($Z = -4.737$, $p < 0.001$), and the severity of migraine episodes was decreased from 3 (severe) to 2 (moderate; $Z = -2.768$, $p = 0.006$).

Conclusion: Supplementation of omega-3, vitamin E and acetyl-L-carnitine is effective in correcting biochemical status and decreasing the frequency and severity of migraine attacks in migraine patients.

Keywords: Migraine, Severity, Supplementation, Omega-3, Vitamin E, Headache, Frequency

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INTRODUCTION

Migraine is a widespread neurological disorder characterized by episodes of moderate-severe headache, mostly accompanied by nausea and photalgia [1]. The pathophysiology of migraine combines neurovascular, inflammatory, and metabolic

mechanisms. One of the key neurotransmitters implicated in the pathology of migraine is serotonin (5-hydroxytryptamine, 5-HT) [2]. In addition to neurotransmitter imbalance, oxidative stress, mitochondrial dysfunction, and metabolic disturbances are causative factors for migraine [3]. Individuals with migraine exhibit

high levels of oxidative stress markers and reduced antioxidant capacity, which may enhance neuronal excitability and trigger migraine attacks [4]. Uric acid and indirect bilirubin are endogenous antioxidants that reflect the body's defense against oxidative damage [5,6].

Furthermore, disturbances in lipid metabolism such as altered cholesterol and triglyceride levels, have been associated with endothelial dysfunction and neuroinflammation in migraineurs [7]. Electrolyte imbalance, particularly magnesium deficiency, is also implicated in the pathogenesis of migraine. Magnesium plays a critical role in neuronal stability, neurotransmitter regulation, and vascular tone. Indeed, magnesium deficiency has been linked to cortical spreading depression and increased migraine susceptibility [8].

Evidence-based studies have demonstrated the effective role of nutritional supplementation in modulating endogenous, neural, and oxidative stress status in various illnesses [9,10]. Omega-3 polyunsaturated fatty acids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) exhibit anti-inflammatory and neuroprotective effects, partly through modulation of serotonin and dopamine signaling [11]. Acetyl-L-carnitine supports mitochondrial function, enhances energy production, and modulates neurotransmitter levels, while vitamin E acts as a potent antioxidant that inhibits pro-inflammatory pathways and stabilizes neuronal membranes [12]. Despite promising evidence, there is limited research on the combined effect of these supplements on clinical and biochemical outcomes in migraine, particularly in populations from the Middle East. Moreover, not much is known about how such interventions influence peripheral serotonin levels, lipid metabolism, endogenous antioxidants, and electrolytes in migraine patients.

The current study was aimed at investigating changes in serum serotonin, lipid profile, endogenous antioxidants (uric acid and indirect bilirubin), and electrolytes (magnesium, sodium, potassium, and chloride) in migraine patients, relative to healthy controls. The study was also aimed at determining the effect of a 30-day supplementation with omega-3 fatty acids, vitamin E, and acetyl-L-carnitine on these parameters, as well as on migraine frequency and severity.

METHODS

Study participants

A total of 40 male patients diagnosed with migraine (with or without aura) were recruited from outpatient clinics in Mosul City, Iraq. Migraine diagnosis was confirmed by a neurologist, based on the International Headache Society (IHS) criteria. Individuals recruited in the current study were males within the age range of 20 - 65 years who had a history of 2 - 8 migraine attacks per month within the previous three months before enrolment in the study. Exclusion criteria comprised female sex, presence of other headache disorders, or the use of dietary supplements within the preceding three months. Additionally, 20 age-matched healthy individuals without a history of migraine or supplement use were recruited as control cohort for baseline biochemical comparisons.

Ethical approval and study protocol

The study was approved by the Collegiate Committee for Medical Research Ethics at the University of Mosul (approval no. CCMRE-phA-23-21). Written informed consent was obtained from each participant prior to enrollment.

Before initiating the nutritional supplementation, each participant was instructed to maintain a headache record diary for one month so as to document the incidence and severity of headaches. The severity of headache was scored on a scale of 0 - 3, where 0 = no headache; 1 = mild headache which did not interfere with daily activities; 2 = moderate headache which slowed down daily activities; and 3 = severe headache which interfered with normal function, thereby requiring rest or sleep. The use of symptomatic medications such as zolmitriptan or over-the-counter analgesics was allowed during migraine episodes.

After the baseline observation period, the study participants were given single daily doses of Omega-3 plus Vitamin E comprising 180 mg of EPA, 120 mg of DHA and 3 mg of vitamin E: *Mera Omega-3 plus Vitamin E®* (Starpharma Ltd, Poland for Mera Pharma GmbH/Switzerland), and 500 mg of acetyl-L-carnitine: *Adicarnit®* (Dipharma EAD, Bulgaria). The supplements were taken daily along with a meal for 30 days. During the supplementation period, the frequency and severity of headaches were recorded daily in the headache diary.

Measurement of biochemical parameters

Venous blood samples were collected at time zero from all participants in both migraine and control groups. In the migraine group, additional blood samples were obtained after 30 days of supplementation. To avoid acute-phase effects, all blood samples from migraine patients were collected during headache-free periods.

The blood samples were analyzed for serum levels of serotonin, lipid profile (total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C)), uric acid, indirect bilirubin, and electrolytes (magnesium, sodium, potassium, and chloride).

Serum serotonin levels were quantified using a Human Serotonin (ST) ELISA Kit (Catalog no. YLA0836HU; Shanghai YL Biotech Co. Ltd.). Lipid profile and uric acid were measured using ACCENT-200 Automatic Clinical Chemistry Analyzer reagent kits (PZ Cormay S.A., Poland). Bilirubin and serum electrolytes were measured using Fujifilm NX 500i Dry Chemistry Analyzer.

Statistical analysis

Data were analyzed using IBM SPSS Statistics, version 26. Shapiro–Wilk test was employed to assess the normality of data distribution. For comparisons between migraine patients and healthy controls at baseline, independent samples *t*-test was used for normally distributed variables. Within the migraine group, pre- and post-supplementation changes were evaluated using paired sample *t*-test for normally-distributed data, while Wilcoxon signed-rank test was used for variables that did not meet normality assumptions. Categorical variables were compared using the Chi-square test. A *p*-

value less than 0.05 ($p < 0.05$) was considered indicative of statistical significance.

RESULTS

Baseline characteristics and biochemical comparisons

The study involved 20 healthy individuals with a mean age of 36.15 ± 7.3 years, and 40 patients diagnosed with migraine, whose mean age was 39.6 ± 8.8 years. Demographic analysis indicated non-significant differences between the two groups in terms of age and body mass index (BMI). Although serum serotonin level was lower in the migraine group (103.55 ± 18.92 ng/mL), the difference was not statistically significant when compared to control value ($p = 0.15$). These results are presented in Table 1.

The migraine group showed significant elevations in serum levels of total cholesterol (216.15 ± 36.41 vs. 179.37 ± 33.84 mg/dL and triglycerides (255.36 ± 100.8 vs. 116.70 ± 49.03 mg/dL), relative to control group ($p < 0.001$). However, serum levels of HDL-C and LDL-C were comparable in both groups ($p > 0.05$). In addition, there were no significant differences in serum concentrations of uric acid between the migraine group (5.80 ± 0.93 mg/dL) and healthy control group (5.78 ± 0.71 mg/dL). Similarly, no significant differences were noted for indirect bilirubin concentration between migraine patients (0.23 ± 0.14 mg/dL) and control group (0.22 ± 0.08 mg/dL). Serum magnesium levels were slightly lower in the migraine group (2.24 ± 0.18 mg/dL) than in control group (2.33 ± 0.19 mg/dL), but the difference was not statistically significant. Moreover, no significant differences were observed in serum concentrations of sodium, potassium, and chloride between the groups ($p > 0.05$).

Table 1: Demographic Characteristics and Baseline Levels of Biochemical Parameters in both Groups

Parameter (Unit)	Control Group (n=20)	Migraine Group (n=40)	P-value
Age (years)	36.15 ± 7.3	39.6 ± 8.8	> 0.05
BMI (kg/m ²)	27.3 ± 3.6	29.7 ± 5.0	> 0.05
Serotonin (ng/mL)	111.01 ± 19.26	103.55 ± 18.92	> 0.05
Cholesterol (mg/dL)	179.37 ± 33.84	216.15 ± 36.41	< 0.001
HDL (mg/dL)	52.41 ± 7.26	53.14 ± 5.94	> 0.05
LDL (mg/dL)	103.62 ± 26.13	111.94 ± 30.95	> 0.05
TG (mg/dL)	116.70 ± 49.03	255.36 ± 100.8	< 0.001
Uric acid (mg/dL)	5.78 ± 0.71	5.80 ± 0.93	> 0.05
Indirect bilirubin (mg/dL)	0.22 ± 0.08	0.23 ± 0.14	> 0.05
Magnesium (mg/dL)	2.33 ± 0.19	2.24 ± 0.18	> 0.05
Sodium (mmol/L)	134.15 ± 6.48	130.00 ± 10.16	> 0.05
Potassium (mmol/L)	3.98 ± 0.35	4.02 ± 0.44	> 0.05
Chloride (mmol/L)	100.30 ± 4.38	100.78 ± 6.49	> 0.05

Data are mean $\pm$ SD. *P*-values were obtained from independent sample *t*-test

Post-supplementation biochemical changes in the migraine group

A total of 37 patients completed the 30-day supplementation regimen, while three participants withdrew from the study. After the nutritional supplementation, there were marked improvements in several key parameters, as presented in Table 2. Serum serotonin levels were significantly increased following the supplementation period, rising from 103.03 ± 19.03 to 116.97 ± 36.61 ng/mL ($p < 0.01$). Serum total cholesterol level was significantly reduced from 218.38 ± 36.73 to 201.34 ± 26.30 mg/dL, and triglyceride concentration was markedly decreased from 256.28 ± 104.41 to 156.66 ± 72.66 mg/dL, reflecting improved lipid metabolism. However, no significant changes were observed in HDL-C and LDL-C levels ($p > 0.05$). Similarly, the supplementations did not result in significant alterations in serum levels of indirect bilirubin, uric acid, and electrolytes such as magnesium, sodium, potassium, and chloride ($p > 0.05$).

Impact of supplementation on migraine frequency and severity

In addition to biochemical assessments, the frequency and severity of migraine attacks were evaluated before and after the 30-day supplementation period. The median value of monthly migraine attacks was significantly decreased from 4, with interquartile range (IQR) of 3 – 6, to 2 (IQR of 1 – 3; $Z = -4.737$, $p <$

0.001). Similarly, the median severity score of migraine episodes was reduced from 3 (severe; IQR: 2 – 3) to 2 (moderate; IQR: 1 – 3; $Z = -2.768$, $p = 0.006$), indicating a clinically significant reduction in headache burden. These results are shown in Table 3.

DISCUSSION

Although it is known that migraine is more prevalent in females than in males, the present study was focused on males to avoid migraine attacks that are related to hormonal changes in females [2]. The results obtained present evidence of variations between migraine and healthy individuals in some health indicators, mostly lipid profile. Migraine patients showed significant increases in serum levels of total cholesterol and triglycerides, indicating impaired lipid metabolism in these patients. These results are in agreement with the findings from Pamela *et al*, who reported increased levels of total cholesterol in migraine patients with evidence of enhanced aura symptoms [13]. In another study on migraine patients with normal weight, Gruber *et al* demonstrated significant elevations in lipid profile [14]. This is consistent with the results obtained in the present study. The inflammation induced by dyslipidemia may contribute to endothelial dysfunction, which may affect cerebral blood flow usually encountered in migraine [7]. In the current study, serotonin levels were comparable in migraine patients and healthy controls.

Table 2: Comparison of levels of biochemical parameters before and after the supplementation period

Parameter	Pre-Supplementation	Post-Supplementation	P-value
Serotonin (ng/mL)	103.03±19.03	116.97±36.61	< 0.01
Cholesterol (mg/dL)	218.38±36.73	201.34±26.30	< 0.01
HDL-C (mg/dL)	53.43±5.94	51.57±4.96	> 0.05
LDL-C (mg/dL)	113.69±31.42	121.43±23.46	> 0.05
Triglycerides (mg/dL)	256.28±104.41	156.66±72.66	< 0.01
Uric Acid (mg/dL)	5.74±0.93	5.82±1.27	> 0.05
Indirect bilirubin (mg/dL)	0.24±0.14	0.22±0.10	> 0.05
Magnesium (mg/dL)	2.22±0.18	2.25±0.14	> 0.05
Sodium (mmol/L)	129.41±9.96	127.16±4.25	> 0.05
Potassium (mmol/L)	4.02±0.45	4.05±0.39	> 0.05
Chloride (mmol/L)	100.54±6.34	99.16±5.65	> 0.05

Data are mean $\pm$ SD. P-values obtained from paired sample t-test

Table 3: Comparison of migraine frequency and severity before and after supplementation period

Parameter	Pre-Supplementation	Post-Supplementation	Z	P-values
Frequency (attacks/month)	4 (3–6)	2 (1–3)	-4.737	< 0.001
Severity (scale 0–3)	3 (2–3)	2 (1–3)	-2.768	< 0.006

P-values were from Wilcoxon signed-rank test. Ranks for frequency: Negative = 31, Positive = 2, Ties = 4. A total of 31 patients showed reductions (negative ranks), while 2 patients had increases (positive ranks), and 4 patients showed no changes (ties). Ranks of severity: Negative = 15, Positive = 3, Ties = 19

Although not significant, the reduced serotonin level in the current study is in alignment with extant knowledge on lowered serotonin levels in migraine patients which may be correlated with headache episodes [15].

Inflammatory changes may be associated with disturbed oxidative stress which may damage sensory nerve endings at some point, thereby contributing to the pathogenesis of migraine [5]. In the current study, oxidative stress was assessed based on levels of some endogenous antioxidants such as uric acid and indirect bilirubin. In an earlier study, uric acid was identified as a major factor involved in the pathophysiology of migraine: uric acid elevation was linked to enhanced pulse and atrial tension [16]. Kang *et al* investigated the relationship between gout and migraine and found a strong link between elevated uric acid in gout and the incidence of migraine [17]. However, in the current study, uric acid level did not vary significantly between the migraine patients and healthy controls. Moreover, there were no significant differences in bilirubin levels between migraine patients and healthy controls. This is in agreement with the report of Yasin *et al*, which indicated no differences in total bilirubin levels between migraine patients and controls [18]. However, the present results are at variance with the findings in a previous study, which showed markedly decreased bilirubin levels in migraine patients [6].

A study by Talebi *et al* [8] demonstrated that migraine attacks are associated with significantly lowered levels of magnesium level [8]. In contrast, a case control study by Assarzaghan *et al* [19] revealed normal magnesium levels, with no significant variations during attacks, which is in agreement with the current findings [19]. The non-significant differences between patients and controls in the current study may be attributed to the low sample size which possibly was not enough to reflect all the observational changes in migraine.

After supplementation with Omega-3, acetyl-L-carnitine and vitamin E, serotonin level was significantly elevated, while serum levels of total cholesterol and triglycerides were significantly reduced. In migraine patients, supplementation with vitamin E and omega-3 has been shown to correct oxidative stress, inflammatory status and adjust the release of neurotransmitters, e.g., serotonin [28]. The current results are in agreement with a meta-analysis by Patrick *et al*, in demonstrating that supplementation with omega-3 significantly enhanced serotonin release and brain function [22]. Moreover, the

results are consistent with the findings of Bütün *et al*, who reported enhanced brain activity, reduced oxidative stress, and decreased headache incidents in rats following 10-day daily administration of vitamin E [23]. Musazadeh *et al* have reported the effectiveness of L-carnitine supplementation (given a dose of more than 2 g/day) in reducing serum levels of total cholesterol and triglycerides while enhancing HDL levels in adults [24]. Similar results were obtained in the present study, thereby confirming that L-carnitine reduces serum levels of total cholesterol and triglycerides. However, in the present study, L-carnitine supplementation did not significantly affect serum levels of LDL and HDL, while the study by Musazadeh *et al* [24] showed that LDL was significantly reduced and HDL was markedly enhanced after L-carnitine supplementation. This difference may be related to the duration of L-carnitine exposure, which was up to 16 weeks in the study by Musazadeh *et al* [24], while the duration of L-carnitine supplementation in the current study was just 4 weeks. Moreover, a lower dose of L-carnitine (500 mg/day) was used in the present study, relative to the dose of about 2 g/day or more used in the Musazadeh *et al* study. The lower L-carnitine dose might be just enough to support partial improvement in oxidative status and lipid profile during the short duration of our study.

In addition to the observed changes in the markers studied, the nutritional supplementations positively affected the clinical outcome of the patients through reduced frequency and severity of migraine attacks. These findings may contribute to the growing body of evidence in support of the potential role of nutrient supplementation in the management of migraine symptoms [25]. Moreover, in a study on the effect of daily supplementation of L-carnitine and alpha linoleic acid in 80 women with migraine, Golpour-Hamedani *et al* reported significant reductions in migraine severity, frequency, and duration, when compared to a placebo group [26]. In light of available evidence, the nutritional supplements used in the present study were effective in relieving migraine headaches. These effects may be attributed to the beneficial effects of these supplements in replenishing nutritional deficits in the body, thereby correcting the underlying metabolic and neural problems.

Study limitations

The present study has some limitations. The small sample size may limit the conclusions derivable from the current observations, especially with respect to disease intensity. In addition, the study focused on spotting the

differences between the two time points to highlight the changes induced by the supplementation. It might be useful to run a placebo-controlled trial, which could further validate the current findings.

CONCLUSION

The present findings indicated that supplementation with omega-3, acetyl-L-Carnitine, and vitamin E was effective in correcting metabolic status and biochemical markers in migraine patients, in addition to the clinical outcome of migraine. This was manifested by reductions in the frequency and severity of migraine attacks, which may eventually help in improving lifestyle and disease burden.

DECLARATIONS

Acknowledgement/Funding

None.

Ethical approval

The study was approved by the Collegiate Committee for Medical Research Ethics at the University of Mosul (Approval Number: CCMRE-phA-23-21).

Use of Artificial intelligence/Large language models

We also declare that we did not use Generative artificial intelligence (AI) and AI-assisted technologies in writing the manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the author(s) named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. All authors contributed to the conceptualisation and design of the study. Material preparation and data

collection were done by Manal Abdulmunem Ibrahim. All authors contributed equally to data interpretation, with statistical analysis designed and performed by Sameer M. Mahmood. Zaid M. Younus wrote a draft of the manuscript. All authors read and approved the manuscript for publication.

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