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The effects of concurrent alpha-linolenic acid, L-carnitine supplementation on clinical symptoms, mental health, and quality of life in women with migraine: a randomized, triple-blind, placebo-controlled trial

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Abstract

Background Migraine, as a widespread neurological condition, substantially impacts quality of life, particularly among women. Therefore, this study aimed to explore the potential effects of alpha-linolenic acid (ALA) and L-carnitine co-supplementation on migraine symptoms, mental health, and life quality in women with migraine.

Methods In this randomized, triple-blind, placebo-controlled trial, 80 women with migraine were randomly assigned to receive either ALA (1000 mg) plus L-carnitine (500 mg) or matching placebos daily for 12 weeks. Migraine characteristics, mental health parameters, and quality of life measures were assessed at baseline and study end.

Results The intervention group demonstrated a significant reduction in migraine frequency (-2.96; 95% CI (-3.48, -2.45) vs -0.07; 95% CI (-0.68, 0.53), $P < 0.001$), severity (-1.6; 95% CI (-2.05, -1.15) vs − 0.44; 95% CI (-0.91, 0.02), $P = 0.001$), and duration (-4.9; 95% CI (-6.34, -3.45) vs -0.5; 95% CI (-1.06, 0.66) hours, $P < 0.001$) compared to the placebo group. Mental health improvements were observed in depression (-7.4; 95% CI (-9.24, -5.55) vs 0.05; 95% CI (-1.16, 1.26), $P < 0.001$), and anxiety scores (-5.7; 95% CI (-7.26, -4.14) vs − 0.65; 95% CI (-2.33, 1.03), $P < 0.001$). Quality of life measures showed significant enhancement, with increased migraine-specific quality of life (9.75; 95% CI (8.01, 11.49) vs 1.22; 95% CI (-0.66, 3.11), $P < 0.001$) and decreased headache impact test-6 scores (-8.57; 95% CI (-11.79, -5.36) vs -1.35; 95% CI (-3.41, 0.71), $P = 0.005$) in the intervention group compared to the controls.

Conclusion Co-supplementation with ALA and L-carnitine may offer a promising adjuvant therapy for managing migraine in women, addressing both physical symptoms and psychological burdens.

Trial registration IRCT20121216011763N57.

Keywords Alpha-linolenic acid, L-carnitine, Migraine, Mental health

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Background

Migraine, as a prevalent neurological disorder, affects an estimated 14–15% of the world's population globally, ranking among the top 20 most disabling conditions [1]. In the Middle East, the burden of migraine is particularly pronounced, with some estimates suggesting that up to 25% of women may be affected [2]. Within this regional context, studies performed in Iran indicate a migraine prevalence rate of 7% to 18% among adults, with a notably higher incidence in women [3], highlighting the urgent need for effective and alternative management strategies and further research in this area.

Despite advances in pharmacological interventions, the search for effective, well-tolerated treatments remains ongoing. The complex pathophysiology of migraine, involving neurovascular mechanisms, cortical spreading depression, and trigeminovascular activation, necessitates a multifaceted approach to treatment [4]. Recent research has increasingly focused on the potential of nutraceutical approaches in migraine management, with particular interest in compounds that may modulate inflammatory processes and neuronal excitability [5]. Among these, ALA and L-carnitine have emerged as promising alternative nutraceutical modalities.

ALA, an essential omega-3 fatty acid found in plant sources like flaxseed, has shown anti-inflammatory properties that may help mitigate migraine attacks [6]. Its potential role in both modulating pain perception and reducing neurogenic inflammation makes ALA a subject of interest in migraine research [7]. L-carnitine, as a compound vital for cellular energy metabolism, can reduce oxidative stress and improve mitochondrial function [8], both of which are implicated in migraine pathophysiology [9]. The neuroprotective effects of L-carnitine and its role in fatty acid oxidation suggest that it may contribute to maintaining neuronal health and energy homeostasis [10].

While numerous studies have explored the effects of animal-derived omega-3 fatty acids on migraine, research specifically examining the impact of ALA on migraine is notably scarce. This gap is particularly significant given the growing interest in plant-based dietary interventions and the potential differences in bioavailability and metabolism between plant and animal-derived omega-3s [11]. Regarding L-carnitine, the limited studies conducted on its effects on migraine have yielded conflicting results. Some investigations have reported promising outcomes, suggesting improvements in migraine [12], while others have found no significant effects [13].

The paucity of research on the effects of ALA on migraine, combined with the inconclusive evidence surrounding L-carnitine, highlights a critical area for the investigation. Co-supplementation of these compounds may uncover synergistic effects that have been previously overlooked, potentially offering a novel approach to migraine management that addresses multiple facets of the disorder. The potential for ALA to modulate inflammation [14] and L-carnitine to support mitochondrial function [8] suggests a complementary mechanism of action that warrants exploration.

Furthermore, the impact of migraine extends beyond physical symptoms, significantly affecting mental health and overall quality of life [15]. The bidirectional relationship between migraine and mental health disorders, such as depression and anxiety, underscores the importance of considering psychological outcomes in migraine treatment strategies [16]. By examining the effects of ALA and L-carnitine co-supplementation on mental health parameters alongside clinical symptoms, this study aimed to provide a more comprehensive understanding of the potential benefits of this nutraceutical approach.

Therefore, the present study employed a rigorous randomized, triple-blind, placebo-controlled trial design to evaluate the efficacy of co-supplementation with ALA and L-carnitine on clinical symptoms, mental health, and overall quality of life in women with migraine. This study addressed the gap in research regarding plant-based omega-3 supplementation in migraine and explored the potential effects of combining ALA with L-carnitine, offering insights into a novel, integrative approach to migraine management.

Materials and methods

Ethical considerations and trial design

This study was designed as a parallel randomized, triple-blind, placebo-controlled trial. Prior to commencement, the study protocol was approved by the Ethics Committee of Isfahan University of Medical Sciences (ethical code: IR.MUI.RESEARCH.REC.1401.406) and registered in the Iranian Registry of Clinical Trials (Identifier: IRCT20121216011763N57). The "Trials" journal published the complete research protocol in 2024 [17].

Written informed consent was obtained from all participants before enrollment. The consent process ensured participants understood the research procedures and confirmed their voluntary participation. All assessments were conducted at baseline and study completion. The study was reported following the CONSORT statement guidelines [18].

This investigation represents one component of a larger research protocol, with additional findings presented separately following university policies and specific research considerations.

Participants, inclusion, and exclusion criteria

This study consisted of female subjects, aged 20–50 years, who met the diagnostic criteria outlined in the International Classification of Headache Disorders-3 (ICHD-3) assessed by an expert neurologist (F.K) [19]. The study inclusion criteria were a history of migraine symptomatology for at least one year, coupled with adherence to a stable migraine management protocol for at least four weeks before study initiation, and willingness to participate in the study.

The study exclusion criteria were individuals with migraine with aura, or those with a history of chronic conditions, including cardiovascular disease, diabetes mellitus, hypertension, hepatic or renal dysfunction, malignancies, or other neurological disorders. The pregnant or lactating females were similarly ineligible. The study protocol precluded individuals who had consumed dietary supplements, such as riboflavin, feverfew, magnesium, or coenzyme Q10 over the preceding three months. Additional exclusion criteria included the use of anticoagulants, tobacco usage, and alcohol abuse. Adherence to specialized dietary regimens for a minimum of three months before the study or known hypersensitivity to the study supplements also resulted in the exclusion from the study. Furthermore, participants were withdrawn from the study if they altered their treatment approach during the intervention period, or voluntarily withdrew from the protocol.

Sample size

The sample size was determined by data derived from a prior investigation examining the severity of migraine episodes [20]. Utilizing a statistical power of 90% and a type I error rate of 0.05, the calculation aimed to detect a standardized effect size of 0.7. To compensate for the potential attrition, a 10% dropout rate was incorporated into the estimation. Consequently, the required sample size was 40 participants per experimental arm.

Randomization and blinding

In this study, a stratified randomization approach was employed for participant allocation. The participants were initially divided into two age-based strata: individuals aged 20–35 years and those aged 35–50 years. A stratified permuted block randomization technique, utilizing a block size of 4 and maintaining a 1:1 allocation ratio between experimental and control groups, was subsequently implemented.

To ensure allocation impartiality, a computer-generated algorithm produced a random number sequence. This methodology facilitated the unbiased distribution of subjects to either the intervention arm, receiving L-carnitine plus ALA supplementation, or the control arm, administered the placebos.

For blinding maintenance, an independent individual not affiliated with the study identically labeled packs of L-carnitine/ALA supplements and placebos. Participants, laboratory personnel, and investigators remained blinded to treatment assignments throughout the study duration.

Intervention

The intervention group was prescribed a regimen consisting of a soft gel capsule containing flaxseed oil (1000 mg, yielding 350 mg of alpha-linolenic acid; Barij, Iran) and a separate L-carnitine tablet (500 mg; Behta darou, Iran) for 12 weeks. The control group, in contrast, received a placebo regimen comprising a soft gel capsule with paraffin oil (1000 mg) and a maltodextrin tablet (500 mg) for an equivalent period. To maintain blinding integrity, the active treatment and placebo packages were rendered visually indistinguishable in both color and form.

Participants continued their established medical care and treatment protocols under specialist physician guidance throughout the study. Compliance was assessed through the return of empty or unused packages, and also weekly telephone follow-ups were conducted to monitor adherence and potential adverse effects. Participants were considered compliant if they consumed $\geq 80\%$ of prescribed supplements. Although an 80% adherence threshold was initially defined, we ultimately retained all participants in the analysis using an intention-to-treat approach to maintain the statistical integrity of randomization and provide a conservative estimate of the intervention's effectiveness.

Participants were instructed to maintain their regular dietary habits, exercise routines, and current migraine treatment protocols throughout the 12-week intervention. Any modifications to existing treatment methods would result in immediate exclusion from the trial, ensuring the intervention's methodological integrity.

Assessment of variables

While traditional clinical trials often distinguish between primary and secondary outcomes, this study considered all pre-specified outcomes as equally important. This comprehensive approach was chosen to provide a holistic assessment of ALA and L-carnitine supplementation's effects on migraine, recognizing the complex, multifaceted nature of the condition.

Assessment of migraine attacks characteristic

Migraine attack characteristics were evaluated based on headache severity, frequency, and duration. Severity

was quantified using a visual analog scale (VAS), where patients rated their pain intensity from 1 to 10 [21]. Frequency was defined as the number of attacks per month. Duration was measured as migraine attacks' mean length (in hours). These characteristics were retrospectively assessed using validated questionnaires at baseline and study conclusion, capturing participants' recollection of migraine features over the preceding month, rather than through daily pain diaries.

Clinical parameters, including migraine index (MI), headache diary result (HDR), and migraine headache index score (MHIS), were subsequently calculated. The formulae used were as follows: MI = frequency multiplied by severity; HDR = frequency multiplied by duration; and MHIS = frequency multiplied by duration, further multiplied by severity [20, 22].

Assessment of mental status & quality of life

For the evaluation of mental well-being, the Iranian adaptation of the 21-item Depression, Anxiety, and Stress Scale (DASS-21) was utilized [23]. This assessment instrument comprises three subscales—depression, anxiety, and stress—each containing seven items, totaling 21 questions. Respondents are selected from four response options for each item, ranging from 0 (indicating no applicability) to 3 (denoting high applicability). The aggregate score for each subscale spans from 0 to 21, with elevated scores signifying increased levels of mental health. To maintain consistency with the DASS-42 scale, the total score for each subscale was doubled [24].

The present study employed two validated instruments to assess the impacts of ALA and L-carnitine supplementation on migraine patients' quality of life: the Headache Impact Test-6 (HIT-6) and the Migraine-Specific Quality of Life (MSQ) questionnaires.

The HIT-6 evaluates the headache-related effects on well-being and daily functioning among migraine sufferers [25]. It comprises six Likert-type items, with response options ranging from "never" (6 points) to "always" (13 points). The cumulative score ranges from 36 to 78, with higher scores denoting diminished quality of life. The validity and reliability of this questionnaire have been confirmed by previous studies [26].

The MSQ consists of 14 items, assessing the quality of life over the preceding month [27]. Responses are scored on a six-point scale, ranging from 1 ("never") to 6 ("always"). The sum of item scores yields a raw total between 14 and 84, which is then transformed to a standardized 0–100 scale using the formula: ((raw score—14) /70)* 100. On this scale, higher scores indicate a higher quality of life. A previous study has confirmed the validity of the MSQ in the Iranian population [28].

Demographic, anthropometry, and blood pressure assessment

The initiation of the research and the conclusion of the intervention phase were marked by comprehensive data collection from each study participant, employing validated instruments. The data encompassed demographic variables, including age, anthropometric parameters (height, weight, body mass index), educational attainment, medical anamnesis, pharmacological and supplementary regimens, marital status, migraine duration, and familial migraine history.

The participant's body mass was precisely measured in kilograms using a Seca scale, while their height was measured in centimeters utilizing a portable stadiometer. The body mass index (BMI) was subsequently computed for each participant by the standard formula: body mass (kg) divided by the square of height (m).

Systolic and diastolic blood pressure measurements were obtained from the right brachial artery using a standard mercury sphygmomanometer. The participants were seated and allowed a 10-min rest period before measurement. Two readings were taken, separated by a minimum interval of 30 s, and also the arithmetic mean of these measurements was employed for analytical purposes.

Assessment of diet and physical activity levels

To evaluate dietary intakes, participants were required to maintain detailed dietary records over three days, encompassing two representative weekdays and one weekend day. This data collection protocol was implemented at study initiation and again after the 12-week intervention. Reported food quantities were meticulously converted to gram measurements utilizing standardized Iranian Household Measures [29]. Subsequently, these quantified dietary inputs were analyzed using Nutritionist 4 (First Databank Inc., Hearst Corp., San Bruno, CA, 161 USA) to derive precise nutrient profiles and energy content.

The participants' physical activity levels were evaluated using the International Physical Activity Questionnaire (IPAQ), a validated instrument for use in Iranian populations [30]. This assessment tool quantifies physical activity over a one-week retrospective period, providing the results in metabolic equivalent hours per day (MET/h/day).

Statistical analyses

The statistical analyses were performed using SPSS version 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp). The data normality distribution was evaluated through

multiple approaches, including visual inspection of the quantile–quantile plot, assessment of the skewness coefficient, and the Kolmogorov–Smirnov test. The descriptive statistics for continuous variables were presented as mean ± standard deviation (SD), while the categorical data were expressed as frequencies and percentages. The estimated treatment differences from baseline to post-intervention were reported as mean differences with corresponding 95% confidence intervals (CI). Between-group comparisons of qualitative variables were evaluated using Pearson's chi-square test. Independent samples t-test was employed for intergroup comparisons, and paired samples t-test was used to assess intragroup changes over the three-month intervention. Analysis of covariance (ANCOVA) was performed to control for the potential confounding variables when comparing primary study outcomes between groups. All statistical tests were two-tailed, with a significance level set at $P<0.05$.

An intention-to-treat (ITT) approach was adopted for the analysis, including all randomized participants regardless of protocol adherence. Missing data were addressed using the last observation carried forward (LOCF) method, wherein the most recent available measurement for withdrawn subjects was applied in subsequent analyses [31].

Results

Seventy-five out of 80 participants completed the 12-week clinical trial (Fig. 1). Exclusions from the intervention and control groups (three and two, respectively) were due to pregnancy ($n=1$), treatment method alteration ($n=2$), and personal circumstances ($n=2$). An ITT approach was utilized to ensure that all participants were included in the final analysis.

Table 1 presents the baseline characteristics of the study participants. Statistical analyses revealed no significant inter-group differences in terms of age, weight, BMI, systolic and diastolic blood pressure, marital status, physical activity levels, disease duration, family history, and medication use ($P>0.05$), except non-steroidal anti-inflammatory drugs (NSAIDs) ($P=0.041$). Additionally, as depicted in Table 2, dietary profiles showed no statistically significant differences between groups concerning energy intake, macronutrient consumption (carbohydrates, proteins, and fats), fiber intake, vitamin consumption (folate, C, and E), and mineral intake (zinc, sodium, potassium, calcium, and magnesium) ($P>0.05$). The consumption of omega-3 and omega-6 polyunsaturated fatty acids (PUFAs) was also comparable between groups ($P>0.05$).

The effects of ALA with L-carnitine supplementation on migraine characteristics, mental health, and quality of life are presented in Table 3. The intervention group showed significant reductions in the frequency of migraine attacks (−2.96; 95% CI (−3.48, −2.45) vs −0.07; 95% CI (−0.68, 0.53), $P<0.001$), severity (−1.6; 95% CI (−2.05, −1.15) vs −0.44; 95% CI (−0.91, 0.02), $P=0.001$), and duration (−4.9; 95% CI (−6.34, −3.45) vs −0.5; 95% CI (−1.06, 0.66) hours, $P=0.006$) compared to the placebo group. These differences remained significant after adjusting for baseline values and NSAIDs consumption ($P<0.001$ for frequency and duration, and $P=0.001$ for severity).

Regarding mental health, the intervention group demonstrated significant improvements in depression (−7.4; 95% CI (−9.24, −5.55) vs 0.05; 95% CI (−1.16, 1.26), $P<0.001$) and anxiety scores (−5.7; 95% CI (−7.26, −4.14) vs − 0.65; 95% CI (−2.33, 1.03), $P<0.001$) compared to the placebo group. These improvements in both psychological variables remained significant after adjustment for baseline values and NSAIDs consumption ($P<0.001$ for both). No significant difference was observed between the two groups in terms of stress levels ($P=0.295$), which were not significant after adjustment ($P=0.316$).

In terms of quality of life, the MSQ score increased significantly in the intervention group compared to placebo (9.75; 95% CI (8.01, 11.49) vs 1.22; 95% CI (−0.66, 3.11), $P=0.045$). HIT-6 score decreased significantly in the intervention group (−8.57; 95% CI (−11.79, −5.36) vs −1.35; 95% CI (−3.41, 0.71), $P=0.033$), indicating reduced headache impact. Both differences remained significant after adjustment ($P<0.001$ for MSQ and $P=0.005$ for HIT-6).

Table 4 presents the effects of supplementation with ALA and L-carnitine on clinical indices of migraine. The intervention group showed significant decreases in MI (−29.77; 95% CI (−34.76, −24.79) vs −3.78; 95% CI (−9.14, 1.59), $P<0.001$), HDR (−2.53; 95% CI (−3.06, −1.99) vs −0.25; 95% CI (−0.62, 0.11), $P<0.001$), and MHIS (−20.71; 95% CI (−24.28, −17.14) vs − 2.77; 95% CI (−5.72, 0.17), $P<0.001$) compared to the placebo group, which all remained significant after adjustment for baseline values and NSAIDs intake ($P<0.001$ for all).

Discussion

The results of the present study demonstrated that 12-week concurrent ALA and L-carnitine supplementation significantly impacted migraine symptoms, mental health, and quality of life in female migraine patients. To our knowledge, this is the first study evaluating the concurrent supplementation of ALA and L-carnitine on clinical features and subsequent outcomes of migraine attacks.

Recent research has suggested a potential link between mitochondrial dysfunction, inflammation, and oxidative stress in migraine pathogenesis [32, 33].

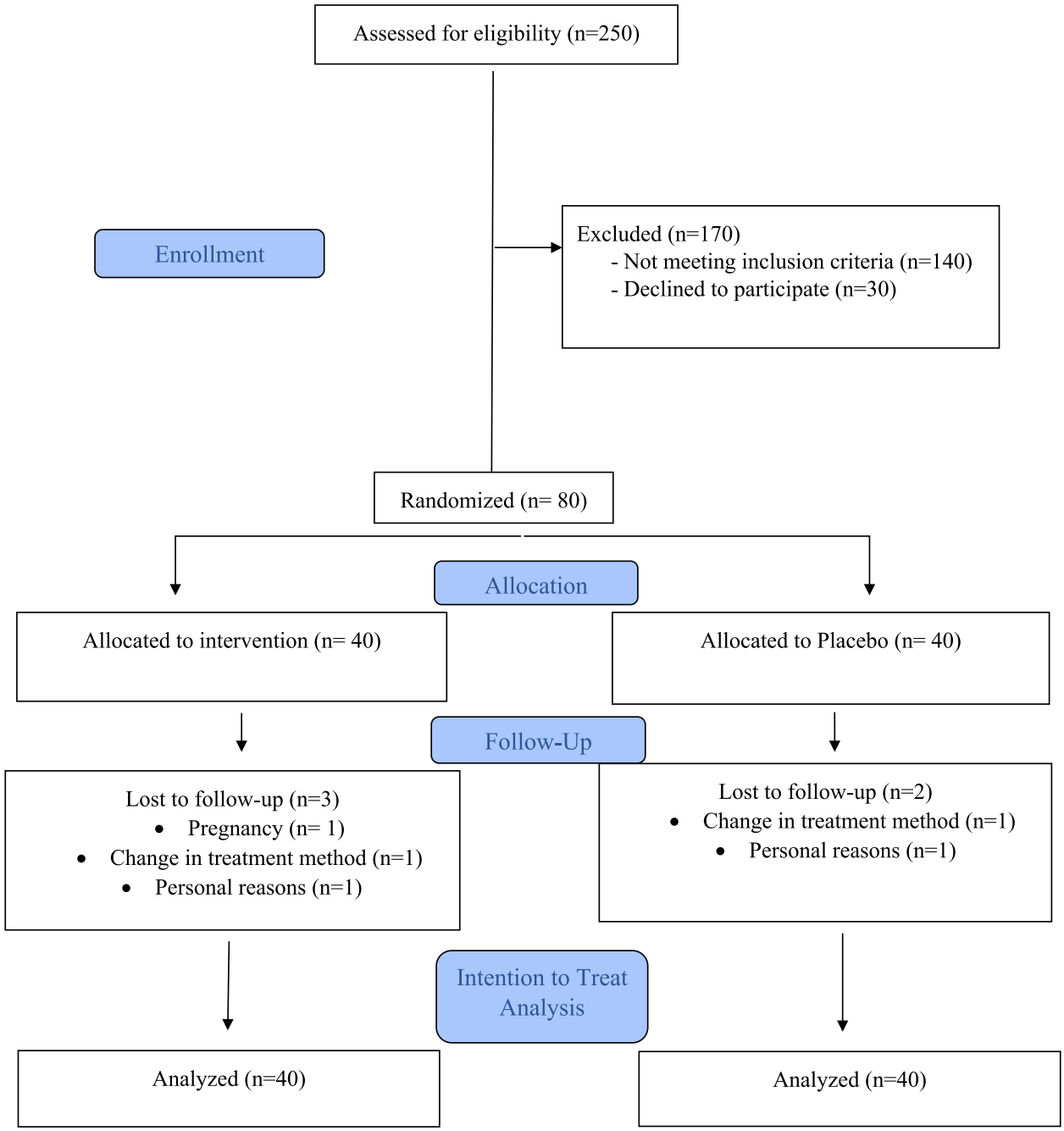

Fig. 1 Flowchart of study

ALA, a precursor to omega-3 fatty acids, possesses anti-inflammatory properties [34] and may modulate mitochondrial function [35]. Concurrently, L-carnitine plays a crucial role in mitochondrial energy production and exhibits antioxidant effects [36]. We hypothesized that a combination of ALA and L-carnitine might synergistically address multiple aspects of migraine pathophysiology by potentially enhancing mitochondrial function, reducing inflammation, and combating oxidative stress.

Our findings revealed that the ALA combined with L-carnitine significantly reduced the frequency, severity, and duration of migraine attacks, and also improved MI, HDR, MHIS, and HIT-6 scores. Moreover, the

Table 1 Baseline characteristics of study subjects

Variables		Alpha-linolenic plus L-carnitine group ($n=40$)		Placebo group ($n=40$)	P^*
Age (year)		38.47 ± 5.70		39.17 ± 6.22	0.601
Weight (kg)		73.63 ± 8.83		74.04 ± 7.44	0.824
Height (cm)		165.48 ± 4.20		164.93 ± 4.97	0.595
BMI (kg/m2)		26.89 ± 2.97		27.13 ± 1.40	0.651
SBP (mmHg)		125.17 ± 11.41		124.35 ± 5.71	0.684
DBP (mmHg)		80.23 ± 3.13		80.60 ± 3.94	0.645
Disease duration (year)		5.07 ± 1.91		4.12 ± 2.37	0.052
Physical activity (MET/h/day)		33.81 ± 4.26		32.08 ± 6.06	0.144
Migraine type	Episodic	26 (65)		24 (60)	0.649
	Chronic	14 (35)		16 (40)	
Job	Housewife	17 (42.5)		19 (47.5)	0.702
	Freelance	10 (25)		9 (22.5)	
	Employee	13 (32.5)		12 (30)	
Education status	University graduated	21 (52.5)		24 (60)	0.558
	Diploma	12 (30)		10 (25)	
	Under diploma	7 (17.5)		6 (15)	
Marital status	Married	28 (70)		30 (75)	0.622
	Single	12 (30)		10 (25)	
Familial history	Yes	25 (62.5)		29 (72.5)	0.346
	No	15 (37.5)		11 (27.5)	
Medication	Beta-blockers	Yes	28 (70)	25 (62.5)	0.484
		No	12 (30)	15 (37.5)	
	TCAs	Yes	21 (52.5)	17 (42.5)	0.377
		No	19 (47.5)	23 (57.5)	
	Benzodiazepine	Yes	18 (45)	16 (40)	0.656
		No	22 (55)	24 (60)	
	Sodium valproate	Yes	10 (25)	13 (32.5)	0.456
		No	30 (75)	27 (67.5)	
	NSAIDs	Yes	21 (52.5)	12 (30)	0.041
		No	19 (47.5)	28 (70)	
	Gabapentin	Yes	14 (35)	9 (22.5)	0.222
		No	26 (65)	31 (77.5)	
	Triptans	Yes	7(17.5)	4 (10)	0.336
		No	33 (82.5)	36 (90)	
	Topiramate	Yes	6 (14)	5 (12.5)	0.749
		No	34 (85)	35 (87.5)	

Quantitative variables are expressed as mean ± SD and qualitative variables are expressed as n (%)

Abbreviations: *BMI* Body mass index, *SBP* Systolic blood pressure, *DBP* Diastolic blood pressure, *TCAs* Tricyclic antidepressants, *NSAIDs* Non-steroidal anti-inflammatory drugs

* *P*-value resulted from independent samples t-test for continuous and chi-squared tests for categorical variables

intervention group experienced an increase in the MSQ score. These results align with those of previous studies conducted on nutraceutical combinations, such as nano-curcumin with CoQ10 [37] or L-carnitine with CoQ10 [20], demonstrating protective effects on migraine prophylaxis.

While no previous studies have examined the combined effects of ALA and L-carnitine in migraine, some have investigated the separate effects of animal-based omega-3s and L-carnitine, yielding conflicting results. Ramsden et al. reported that increasing omega-3 fatty acid intake was associated with reduced migraine attacks, and improved quality of life [38]. Conversely, Fayazi et al. found no connection between omega-3 supplementation and migraine symptoms [39]. Similarly, Tariqat et al. showed that 12-week supplementation with 500 mg

Table 2 Dietary intakes of participants, obtained from six dietary records, at baseline and end of the intervention

Variable	Alpha-linolenic plus L-carnitine (*N* = 40)	Placebo (*N* = 40)	*P* [a]
Energy (kcal/day)	1966.25 ± 299.08	2023.10 ± 471.68	0.522
Carbohydrate (g/day)	315.15 ± 21.19	308.90 ± 18.07	0.160
Protein (g/day)	75.85 ± 9.83	76.77 ± 15.16	0.747
Fat (g/day)	72.77 ± 7.61	70.87 ± 7.99	0.280
PUFAs (g/day)	17.85 ± 4.88	16.28 ± 2.14	0.067
MUFA (g/day)	13.73 ± 2.72	12.71 ± 1.84	0.052
Fiber (g/d)	12.46 ± 2.53	13.56 ± 2.73	0.066
Folate (µg/d)	419.90 ± 45.74	415.39 ± 32.95	0.614
Vitamin C (mg/day)	104.35 ± 19.42	101.50 ± 15.01	0.465
Vitamin E (mg/day)	5.05 ± 0.62	4.84 ± 0.62	0.135
Zinc (mg/day)	8.94 ± 1.35	8.72 ± 1.09	0.414
Sodium (mg/d)	2434.95 ± 418.89	2290.37 ± 362.27	0.103
Potassium (mg/d)	2093.25 ± 201.65	2042.50 ± 187.52	0.247
Calcium (mg/d)	812.40 ± 92.31	840.80 ± 92.70	0.174
Magnesium (mg/day)	226.72 ± 24.59	219.12 ± 14.07	0.095

Variables are expressed as mean ± SD

Abbreviations: *PUFAs* Polyunsaturated fatty acids, *MUFAs* Monounsaturated fatty acids

[a] Obtained from independent samples t-test

L-carnitine significantly reduced migraine symptoms [12], while Hagen et al. reported no protective effects of L-carnitine supplementation on migraine prophylaxis [13].

Experimental studies have shown that co-administration of omega-3 fatty acids and L-carnitine results in higher serum antioxidant enzyme levels compared to either alone, suggesting a synergistic effect [40]. Animal studies indicated that adding L-carnitine to an omega-3-rich diet could increase both omega-3 storage and antioxidant properties [41]. The rationale for combining ALA and L-carnitine is supported by previous research demonstrating enhanced effects when combining different supplements in migraine management. For instance, studies have shown synergistic effects between L-carnitine and CoQ10 [20], and between omega-3 fatty acids and other complementary compounds [42–44]. Most notably, Mohammadzadeh-Honarvar et al. demonstrated that combining omega-3 fatty acids and curcumin led to greater improvements in clinical migraine symptoms compared to monotherapy [45].

The improvements in mental health outcomes observed in our study align with growing evidence linking omega-3 fatty acids to improved mental well-being [46–48]. A recent meta-analysis found that omega-3 supplementation was associated with a significant reduction in depressive symptoms [49]. The relationship between migraine and mental health is well-established, with migraineurs often experiencing higher rates of depression and anxiety compared to the general population [50, 51]. In their study, Lampl et al. found that migraineurs had an approximately 2–threefold increased risk of depression and anxiety disorders compared to non-migraineurs [52].

The impact of these mental health improvements extends beyond symptom reduction, potentially leading to improved adherence to migraine management strategies, enhanced coping mechanisms, and overall better quality of life [53]. The bidirectional relationship between migraine and mental health suggested that improvements in one domain could positively influence the other, creating a beneficial cycle for patients [54]. These findings underscore the potential of ALA and L-carnitine supplementation as a holistic approach to migraine management, addressing both physical symptoms and psychological comorbidities.

Interestingly, despite improvements in depression and anxiety, no significant change was observed in stress levels in our study. This discrepancy might be attributed to the complex, multifaceted nature of stress, which can be influenced by a wide array of factors beyond the scope of our intervention [55]. Additionally, the relatively short duration of our study (12 weeks) may not have been sufficient to detect changes in this parameter.

Moreover, the substantial improvements in quality-of-life measures, as evidenced by increased MSQ scores and decreased HIT-6 scores, underscore the comprehensive benefits of ALA plus L-carnitine supplementation. These improvements are particularly important from a patient-centered perspective and could have far-reaching implications beyond the individual patient, potentially translating to societal benefits through enhanced productivity and reduced healthcare utilization [54]. In their study, Vo et al. reported that migraines negatively affect productivity for both employees and employers, emphasizing the potential economic benefits of effective migraine management strategies [56].

The potential therapeutic effects of ALA and L-carnitine co-supplementation in migraine management can be attributed to their multifaceted cellular mechanisms addressing key pathophysiological processes of migraine, including mitochondrial dysfunction, inflammation, and oxidative stress.

At the cellular level, these compounds work synergistically to modulate neuronal function. ALA enhances membrane fluidity and ion channel function [57], while L-carnitine facilitates fatty acid transport into mitochondria, potentially improving energy metabolism and mitochondrial function [58]. This cooperative mechanism directly targets the mitochondrial dysfunction implicated in migraine pathogenesis [59].

Furthermore, their antioxidant properties provide comprehensive protection against oxidative damage. ALA acts as a lipophilic antioxidant protecting cellular

Table 3 The effects of 12 weeks' alpha-linolenic and L-carnitine supplementation on migraine headache characteristics, mental health, and quality of life in women with migraine

Outcome variables		Alpha-linolenic plus L-carnitine ($N=40$)				Placebo ($N=40$)				P [b]	P [c]
		Baseline	12th week	Mean difference (95% CI)	P [a]	Baseline	12th week	Mean difference (95% CI)	P [a]		
Migraine headache characteristic	Frequency	8.09 ± 1.44	5.13 ± 1.14	- 2.96 (−3.48, −2.45)	< 0.001	7.06 ± 1.52	6.99 ± 1.11	- 0.07 (−0.68, 0.53)	0.805	< 0.001	< 0.001
	Severity	7.4 ± 1.26	5.8 ± 1.22	- 1.6 (−2.05, −1.15)	< 0.001	7.22 ± 1.25	6.78 ± 1.35	- 0.44 (−0.91, 0.02)	0.063	0.001	0.001
	Duration	12.37 ± 5.38	7.47 ± 2.92	- 4.9 ± (−6.34, −3.45)	< 0.001	10.32 ± 5.44	9.82 ± 4.35	- 0.5 (−1.06, 0.66)	0.082	0.006	< 0.001
Mental status	Depression	25.35 ± 6.50	17.95 ± 2.73	- 7.4 (−9.24, −5.55)	< 0.001	22.1 ± 4.25	22.15 ± 4.06	0.05 (−1.16, 1.26)	0.934	< 0.001	< 0.001
	Anxiety	23.7 ± 5.01	18 ± 2.6	−5.7 (−7.26, −4.14)	< 0.001	22.05 ± 4.14	21.4 ± 4.64	- 0.65 (−2.33, 1.03)	0.440	< 0.001	< 0.001
	Stress	21.75 ± 6.73	20.77 ± 5.07	−0.97 (−2.0, 0.05)	0.062	20.65 ± 3.18	19.65 ± 4.46	−1 (−2.10, 0.10)	0.074	0.295	0.316
MSQ		57.52 ± 6.81	67.27 ± 6.93	9.75 (8.01, 11.49)	< 0.001	62.65 ± 7.36	63.87 ± 7.95	1.22 (−0.66, 3.11)	0.196	0.045	< 0.001
HIT-6		63.6 ± 7.66	55.02 ± 8.19	- 8.57 (−11.79, −5.36)	< 0.001	59.85 ± 7.47	58.5 ± 5.88	- 1.35 (−3.41, 0.71)	0.193	0.033	0.005

Variables are expressed as mean ± SD, and mean difference (95% CI) for changes from baseline to post-intervention

Abbreviations: *MSQ* Migraine-specific quality of life, *HIT-6* Headache impact test-6

[a] Paired t-test was used to compare outcomes in pre and post-intervention periods

[b] Independent samples t-test was used to compare the mean change between the two groups

[c] Obtained from ANCOVA in the adjusted models (adjusted for baseline value, and NSAIDs consumption)

Table 4 The effects of 12 weeks' alpha-linolenic and L-carnitine supplementation on clinical indices of migraine

Clinical indices of migraine	Alpha-linolenic plus L-carnitine ($N=40$)				Placebo ($N=40$)				P^b	P^c
	Baseline	12th week	Mean difference (95% CI)	P^a	Baseline	12th week	Mean difference (95% CI)	P^a		
MI (frequency * severity)	59.82 ± 14.94	30.05 ± 10.91	- 29.77 (−34.76, −24.79)	< 0.001	51.1 ± 14.49	47.32 ± 12.18	- 3.78 (−9.14, 1.59)	0.162	< 0.001	< 0.001
HDR ((frequency * duration)/24))	4.11 ± 1.84	1.58 ± 0.7	- 2.53 (−3.06, −1.99)	< 0.001	3.09 ± 1.82	2.84 ± 1.3	- 0.25 (−0.62, 0.11)	0.173	< 0.001	< 0.001
MHIS ((frequency * duration * severity)/24))	29.95 ± 12.46	9.24 ± 4.62	- 20.71 (−24.28, −17.14)	< 0.001	22.13 ± 13.85	19.36 ± 10.22	- 2.77 (−5.72, 0.17)	0.064	< 0.001	< 0.001

Variables are expressed as mean ± SD, and mean difference (95% CI) for changes from baseline to post-intervention

Abbreviations: *MI* Migraine index, *HDR* Headache diary result, *MHIS* Migraine headache index score

[a] Paired t-test was used to compare outcomes in pre and post-test interventions

[b] Independent samples t-test was used to compare the mean change between the two groups

[c] Obtained from ANCOVA in the adjusted models (adjusted for baseline value, and NSAIDs consumption)

membranes from lipid peroxidation [60], while L-carnitine scavenges free radicals and chelates metal ions [61]. By reducing oxidative stress, these compounds may help prevent the neurological changes associated with migraine attacks [62].

The anti-inflammatory mechanisms of ALA and L-carnitine are also particularly noteworthy. ALA reduces pro-inflammatory agents while promoting anti-inflammatory mediators [63], and L-carnitine suppresses pro-inflammatory cytokine production [64]. This multi-targeted approach could attenuate neurogenic inflammation, a crucial process in migraine pathogenesis [65].

Neurotransmitter modulation offers another promising mechanism of action. L-carnitine impacts glutamatergic neurotransmission [66], while ALA, through its conversion to omega-3 fatty acids, modulates both serotonergic and dopaminergic pathways [67, 68], a key phenomenon in migraine pathogenesis [4].

Moreover, omega-3 fatty acids have been shown to influence pain perception through various mechanisms, including the modulation of ion channels involved in nociception [69]. This could contribute to the reduced pain severity observed in clinical studies.

These multifaceted mechanisms demonstrate why ALA and L-carnitine co-supplementation offers a comprehensive approach to migraine management, targeting multiple pathophysiological pathways simultaneously.

While our study provides compelling evidence for the efficacy of combined ALA and L-carnitine supplementation in migraine management, several limitations should be acknowledged. First, serum levels of ALA and L-carnitine were not measured at baseline and study end, which would have provided a definitive assessment of supplement adherence. However, compliance was monitored through weekly telephone interviews, and based on self-reports and pill counts, adherence to supplement consumption appeared to be relatively satisfactory.

Second, for ethical reasons, we were unable to evaluate the effects of ALA plus L-carnitine as a standalone therapy. Third, our study was limited to a specific dose and ratio of ALA and L-carnitine; further research is needed to determine the optimal dosing regimen and explore potential dose–response relationships.

Additionally, the relatively short duration of our study may not have captured long-term effects or potential changes in parameters such as stress levels. Longer-term studies would be valuable for assessing the sustainability of the observed benefits and identifying any potential long-term effects. Our study also lacked differentiation between episodic and chronic migraine; future research should investigate potential differential responses across migraine classifications.

Furthermore, our study did not fully align with International Headache Society (IHS) guidelines for controlled trials [70], particularly regarding the use of migraine attacks rather than migraine days as an outcome measure. This may affect comparability with other migraine prevention trials. All participants in this study were female, so caution should be exercised when generalizing the results to male populations.

Lastly, it is noteworthy to consider the placebo response in the context of our findings. Our study's nuanced placebo response aligns with Tepper et al.'s emerging research, which demonstrated significant variability in placebo effects across migraine prevention trials. Factors such as population characteristics, study design, and outcome measurement can substantially influence placebo responses [71]. While our study showed modest placebo effects, future research should explore population-specific variations and methodological factors that contribute to treatment perception and outcomes.

Conclusion

This study provides evidence that co-supplementation with ALA and L-carnitine may offer a promising adjunct therapeutic approach to migraine management, addressing both the physical symptoms and the psychological burden of the disorder. These findings warrant further investigation into the long-term efficacy and optimal dosing of this nutraceutical combination in larger and more diverse populations.

Abbreviations

ALA	Alpha-linolenic acid
ICHD-3	International Classification of Headache Disorders-3
VAS	Visual analog scale
MI	Migraine index
HDR	Headache diary result
MHIS	Migraine headache index score
DASS-21	21-Item Depression, Anxiety, and Stress Scale
HIT-6	Headache Impact Test-6
MSQ	Migraine-Specific Quality of Life
BMI	Body mass index
IPAQ	International Physical Activity Questionnaire
MET/h/day	Metabolic equivalent hours per day
ANCOVA	Analysis of covariance
ITT	Intention-to-treat
LOCF	Last observation carried forward
NSAIDs	Non-steroidal anti-inflammatory drugs
PUFAs	Polyunsaturated fatty acids
MUFA	Monounsaturated fatty acid
CoQ10	Coenzyme Q10
HIS	International Headache Society

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Authors' contributions

Authors' contribution: S. G.H, M. B, A.F, F.K, G. A. contributed to the design and developed the study. A.F. analyzed the data. S.G.H. prepared the first draft of

the manuscript. M.SH. revised the manuscript with critical feedback. G.A. supervised the study. All authors approved the final manuscript for submission.

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Data availability
Data described in the manuscript will be made available upon reasonable request by the corresponding author.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of Isfahan University of Medical Sciences (Approval No. IR.MUI.RESEARCH.REC.1401.406). Written informed consent was obtained from all individual participants included in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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