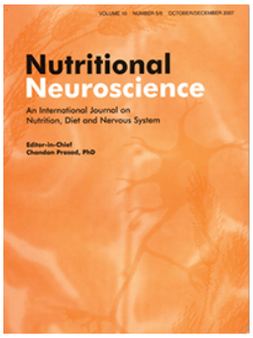

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The synergistic effects of nano-curcumin and coenzyme Q10 supplementation in migraine prophylaxis: a randomized, placebo-controlled, double-blind trial

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ABSTRACT

Introduction: Migraine is a disabling neurovascular disorder characterized by increasing levels of pro-inflammatory cytokines and oxidative stress biomarkers. Curcumin and coenzyme Q10 (CoQ10) can exert neuroprotective effects through modulation of inflammation and oxidative stress. The aim of the present study was to evaluate the combined effects of nano-curcumin and CoQ10 supplementation on migraine symptoms and quality of life in migraine patients.

Methods: One-hundred men and women (mean age 32 years) with episodic migraine based on the International Headache Society (IHS) criteria participated in this study. The subjects were randomly divided into four groups as (1) combination of nano-curcumin (80 mg) plus CoQ10 (300 mg), (2) nano-curcumin (80 mg), (3) CoQ10 (300 mg) and (4) the control (nano-curcumin and CoQ10 placebo included oral paraffin oil) beside usual prophylactic drugs for 8 weeks. Frequency, severity, duration of headache attacks, the headache diary results (HDR) and headache disability based on migraine-specific questionnaires were assessed at the baseline and end of the study.

Results: Ninety-one of 100 patients completed the study. The results showed a significant effect of nano-curcumin and CoQ10 supplementation on frequency, severity, duration of migraine attacks and HDR compared to other groups (All $P < 0.001$). Nano-curcumin and CoQ10 group also had better scores in migraine-specific questionnaires at the end of the study compared to other groups (All $P < 0.001$). There were no side effects reported by the participants.

Conclusions: These findings suggest a possible synergistic effect of nano-curcumin and CoQ10 on clinical features of migraine.

Trial registration number: IRCT2017080135444N1.

KEYWORDS

Curcumin; coenzyme Q10; CoQ10; headache impact test; international headache society; migraine; migraine-specific quality of life; migraine disability assessment; randomized controlled trial

Introduction

Migraine is a chronic neurovascular disease characterized by moderate to severe throbbing, recurrent unilateral headache attacks accompanied by nausea, vomiting, phono-, and photophobia [1]. According to the Global Burden of Disease report from WHO, migraine is the third most prevalent and the sixth most disabling disease in the world [2]. Migraine is three times more common in females with a worldwide prevalence of 14.7% [2]. Proper treatment of migraine improves the quality of life of patients and decreases the economic burden of the disease.

Migraine pathophysiology is not completely understood. The vascular and neuronal dysfunction observed in migraine can be explained by inflammation resulting from mitochondrial dysfunction, impaired oxygen metabolism and oxidative stress [3].

Patients with frequent migraine attacks need both preventive and acute therapies. Although a small number of migraineurs use prophylactic treatments, it could improve response to acute therapies and reduce the frequency, duration, and severity of the attacks [4]. Among the preventive drugs, nutraceuticals (a term derived from 'nutrition' and 'pharmaceutics') such as magnesium, Coenzyme Q10 (CoQ10), vitamins B2 and B12 are preferred because of their lower drug dependence, minimal side effects and potential role in migraine management [5–7]. Nutraceuticals have been found to play an important role in reducing some clinical features of migraine by direct and indirect mechanisms [7–10].

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Curcumin is a polyphenolic bioactive compound and the principal curcuminoid of turmeric (*Curcuma longa*), which is a member of the ginger family (Zingiberaceae) [11]. Neuroprotective effects of curcumin have been evaluated in the preclinical and clinical studies. Curcumin acts as a nutritionally-derived ligand for vitamin D receptor (VDR) [12], COX-2 (anti-inflammatory effects) [13] and β secretase or β-site amyloid precursor protein (APP) cleaving enzyme 1 (BACE1) (inhibit Aβ fibril formation, destabilize preformed fibril and reduce plaque burden in Alzheimer's disease) [14]. A recent meta-analysis of six randomized controlled trials concluded that curcumin supplementation significantly reduce depressive symptoms compared to the placebo group [15]. Several mechanisms of action for curcumin's neuroprotective and antidepressant activity have been proposed, such as anti-inflammatory effects, modulation of neurotransmitter levels in the brain, increasing brain-derived neurotrophic factor (BDNF) levels and inhibition of monoamine oxidase A and B enzymes [15]. Curcumin is a lipophilic agent and its absorption from the gastrointestinal tract with normal dosage forms such as capsules, tablets, and powders is very low due to its water insolubility. Nano-micellar forms of curcumin with an average size of 10 nm, dissolve the active ingredient, curcumin, in their lipophilic part and significantly increase its water solubility and absorption.

CoQ10 is a natural lipophilic antioxidant, acts as a coenzyme in different energy-producing metabolic pathways. It also regulates the mitochondrial electron transport chain and ATP production [16]. Thus, it plays an important role in normal cellular functioning of the body. CoQ10 deficiency impairs the functioning of mitochondria and produces oxidative stress. Dysfunctions in cellular energetics cause neurological degeneration that may lead to secondary disease [17]. Therefore, CoQ10 supplementation is often prescribed to counteract such imbalances and improve neurodegenerative diseases, cardiovascular health, diabetes conditions and aging [18]. In the meta-analysis of four randomized controlled trials, CoQ10 supplementation significantly reduced the frequency of migraine attacks per month without affecting the duration or severity of attacks [19]. In addition, findings from recent studies suggest that CoQ10 supplementation significantly reduces depressive symptoms [20,21].

The potential of CoQ10 as a preventive/therapeutic agent is of great interest and has resulted in several randomized controlled trials that investigated the effect of CoQ10 in patients with migraine with conflicting results [7,8,22–25]. In addition, there was no study to investigate the effects of curcumin supplementation on clinical features of migraine. A recent animal study demonstrated the synergistic effects of curcumin and CoQ10 [26]. In this context, we hypothesized that curcumin and CoQ10 may potentially reinforce each other's effects in the suppression of oxidative stress, neuroinflammation and migraine symptoms. Therefore, we designed this study to determine the combined effects of curcumin and CoQ10 on clinical features of migraine such as frequency, severity, and duration of attacks.

Methods

Study design

The study was designed as a randomized double-blind placebo-controlled parallel trial with follow-up at 4 and 8 weeks. The study was conducted according to the Declaration of Helsinki and was approved by the ethics committee of Tehran University of Medical Sciences, Tehran, Iran (IR.TUMS.VCR.REC.1396.3025). This clinical trial also was registered in the Iranian Registry of Clinical Trials (http://www.irct.ir) as IRCT2017080135444N1.

Patients

This study included one-hundred patients recruited from outpatients referred to the clinic of Tehran University of Medical Sciences at the Imam Khomeini Hospital (Tehran, Iran) between April and November 2018. Episodic migraine (<15 headache days/month) was diagnosed according to the International Headache Society (IHS) criteria by a neurologist at the first visit session [27]. The patients were of both sexes, aged between 18 and 45 years. All participants had a history of migraine symptoms for more than one year with at least two attacks per month, prior to the study period. The protocol of the study was completely explained and all participants signed a written informed consent form for supplementation before participation.

Exclusion criteria

Patients suffering from tension-type or other types of headache, having continuous headaches, experiencing the menopause, having a serious organic or inflammatory diseases, past myocardial infarction, or stroke, using non-steroidal anti-inflammatory drugs (NSAIDs), patients on blood thinners or statins, smoking, patients on opioids, pregnancy or intention of pregnancy, lactation, using CoQ10, curcumin or other antioxidants supplementation for at least three months prior to enrollment, were excluded from the study. In addition, the patients who changed the type or dosage of prescribed drugs throughout the study were excluded.

Sample size

The sample size was calculated based on the clinical trial on headache's response to CoQ10 supplementation [7]. The sample size of 20 per group was calculated which was increased to 25 to accommodate the expectation of a 20% dropout rate. The power of 80% and a confidence interval of 95% were considered.

Characteristics of nano-curcumin and CoQ10

Since curcumin has a lipophilic nature, its water solubility and absorption is very low. To improve the oral bioavailability of curcumin, soft gelatin capsules containing nano-micellar curcumin with the brand name of Sina-Curcumin® (Exir Nano, Tehran, Iran) were used. Sina-Curcumin® is a certified curcumin product (IRC: 1228225765) extracted from the dried rhizomes of *C. longa L.* and comprises curcumin, bisdemethoxycurcumin, and desmethoxycurcumin. These three components are known as the C3 complex. Each capsule of SinaCurcumin® possesses 80 mg curcumin as nano-micelles. The encapsulation efficiency of curcumin in nano-micelles is approximately 100%. The mean diameter of nano-micelles is 10 nm, as measured by dynamic light scattering. In animal studies, the oral bioavailability of SinaCurcumin® was at least 50 times greater than the conventional curcumin powder [28].

CoQ10 supplement (100 mg oral capsules, Health Burst, Davie, FL, USA) was provided by Pourateb Pharmaceutical Co., Tehran, Iran. Since CoQ10 is a lipid-soluble substance and its bioavailability is improved in the presence of dietary fatty acids, the study participants were asked to consume the CoQ10 supplements after meals.

Experimental design

A total of 160 men and women with migraine symptoms were assessed at the first visit by a neurologist to confirm the episodic migraine. After the assessment of the patients' eligibility based on predefined inclusion criteria, 100 patients were enrolled in the present study. The study duration was three months: a one-month run-in period (pre-intervention) was considered before starting the treatment phase (two months). Prophylactic medications included an anticonvulsant (Topiramate, 50 mg/day) and a tricyclic antidepressant (Amitriptyline, 25 mg/day) was started at the first visit session (run-in period) for all participants by a neurologist in consideration of ethical issues. At the end of the first month (run-in period), patients were randomly assigned to four age- and sex-matched groups. Group 1 received 80 mg nano-curcumin per day (single dose), group 2 received 300 mg CoQ10 per day divided into 3 equal doses of 100 mg, group 3 received both nano-curcumin (80 mg/day) and CoQ10 (300 mg/day) and group 4 received placebo capsules (oral paraffin oil) in addition to the preventive drugs, for 8 weeks. The placebo capsules were similar to supplements in shape, color, and odor. The doses of nano-curcumin and CoQ10 were chosen based on the previous studies and in consideration of the observed safe level (OSL) [29,30]. Since CoQ10 is a fat-soluble quinone, participants were asked to take the capsules with their main meals. Patients were also advised to keep their usual physical activity and dietary pattern throughout the study. The patient's compliance with oral supplementation intake was assessed by counting the remaining capsules that were returned at the end of the study. Both patients and researchers were blinded to group assignment. The study participants were visited monthly for probable side effects of nano-curcumin and CoQ10 supplementation.

Side effects

All participants were asked about side effects, adverse events, and medication compliance at every visit.

Anthropometry, physical activity, and food intake assessment

The anthropometric measurements, including height, body weight, body fat percent, and waist to hip ratio were obtained according to WHO standard procedures with the least amount of clothing and body mass index (BMI) was calculated as weight (kg) divided by the square of height (m). The body fat percent was assessed using a Bodystat Quadscan 4000 (Bodystat Ltd, Douglas, UK).

Physical activity level was evaluated using the short form of the international physical activity questionnaire (IPAQ) and divided into three levels of high, moderate and low physical activity [31].

Participants completed three 24-h dietary recalls (two weekdays and one weekend day) at the beginning, end of the fourth and eighth week. Dietary intake was analyzed by modified Nutritionist IV software (version 3.5; First Databank Division, The Hearst Corporation, San Bruno, CA, USA), which has been corrected for Iranian foods.

Clinical status assessment

Participants were given a migraine diary at the run-in period to have the baseline condition of each patient

and were asked to continue completing it during the entire study as well to measure response to treatment by assessing (1) average severity of migraine attacks using the visual analogue scale (VAS) on a 0–10 numeric scale [32], (2) headache frequency per month, and (3) average duration of attacks in hours. Moreover, the headache diary result (HDR) was measured as the frequency of headache × duration of headache [32].

Migraine-specific questionnaires

Previous studies have shown that quality of life is impaired in migraine sufferers [33,34] and specific questionnaires are useful tools for determining treatment goals and evaluating treatment in patients [35]. In the present study, we used three valid and reliable questionnaires to assess the impact of treatment on the patient's function and quality of life. The questionnaires included: MSQ (Migraine-Specific Quality of Life), MIDAS (Migraine Disability Assessment) and HIT-6 (Headache Impact Test).

The MSQ Version 2.1 is a 14-item questionnaire, designed to evaluate the impact of migraine headaches on patients' daily functioning during the past 4 weeks across three domains. The Role Preventive domain measures the degree to which normal work and social activities are prevented by headaches, the Role Restrictive domain describes the reduction of daily activities and the Emotional Functioning domain assesses emotions related with migraine headaches. The total MSQ score is the sum of the domains raw scores (0–100), with higher scores, indicate better Quality of life [36,37]. The internal consistency reliability for the MSQ questionnaire was assessed and confirmed in our study (Cronbach's $\alpha = 0.63$).

The MIDAS questionnaire can be used to measure migraine-related disability over the last 12 weeks by counting the numbers of lost days due to migraine headaches. The MIDAS contains five self-administered questions on three dimensions: social, housework and school/job dimension [38,39] where the higher scores represent a worse health condition of the patient. A score above 21 indicates severe disability, 11–20 indicates considerable disability, 6–10 indicates some disability and 0–5 indicates little or no disability. As MIDAS assesses the patient's migraine headaches in the past 12 weeks, our participants completed it at the baseline and end of the study. The internal consistency reliability for the MIDAS questionnaire was confirmed in our study (Cronbach's $\alpha = 0.89$).

The 6-item HIT-6 is a tool to measure the adverse impact of headache on daily performance and well-being of the patient. HIT-6 consists of six sections: social functioning, vitality, general activity, cognitive functioning, psychological suffering, and pain. The HIT-6 score ranges from 36 to 78 and the lower score indicates a less effect of migraine on the clinical status of the patient. A score above 60 indicates severe effect, 56–59 indicates considerable impact, 50–55 indicates some impact and 36–49 indicates little or no impact of migraine on the individual life [40]. The internal consistency reliability for the HIT-6 questionnaire was confirmed in our study (Cronbach's $\alpha = 0.81$).

In the present study, the Persian versions of the mentioned questionnaires were used. The validity and reliability of questionnaires were assessed and confirmed before in Iranian populations [39,41,42].

Statistical analyses

The Kolmogorov–Smirnov test was used to evaluate the normal distribution of variables. Quantitative variables were expressed as mean (SD) and categorical variables as frequency and percentage. A one-way ANOVA with a *post hoc* Scheffe test was used to analyze data within treatment groups. ANCOVA was also performed between treatment groups to explain the effects of nano-curcumin and CoQ10 on the headache's quality. Age, physical activity level, energy intake, changes in body mass index, body fat percent and years with migraine were considered as confounder variables. All statistical analysis was performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA) and $P < 0.05$ was considered significant.

Results

Patient's characteristics

Out of the 100 patients (female = 73, male = 27) recruited for the study, nine patients (five in the treatment groups and four in the placebo group) dropped out. Four subjects withdrew due to personal reasons and did not return to the clinic, two subjects failed to keep a diary, two subjects withdrew due to unrelated illnesses and one participant withdrew due to pregnancy. Therefore, 91 patients completed the study (the nano-curcumin group ($n = 23$), the CoQ10 group ($n = 24$), the nano-curcumin and CoQ10 group ($n = 23$) and the control group ($n = 21$); Figure 1).

There were no significant differences in baseline characteristics, including age, daily energy intake, body mass index, waist to hip ratio, body fat percent and years with migraine between the four groups, as presented in Table 1.

Based on the CONSORT BMJ 2010, non-adherence to the study protocol and missing outcomes are two main

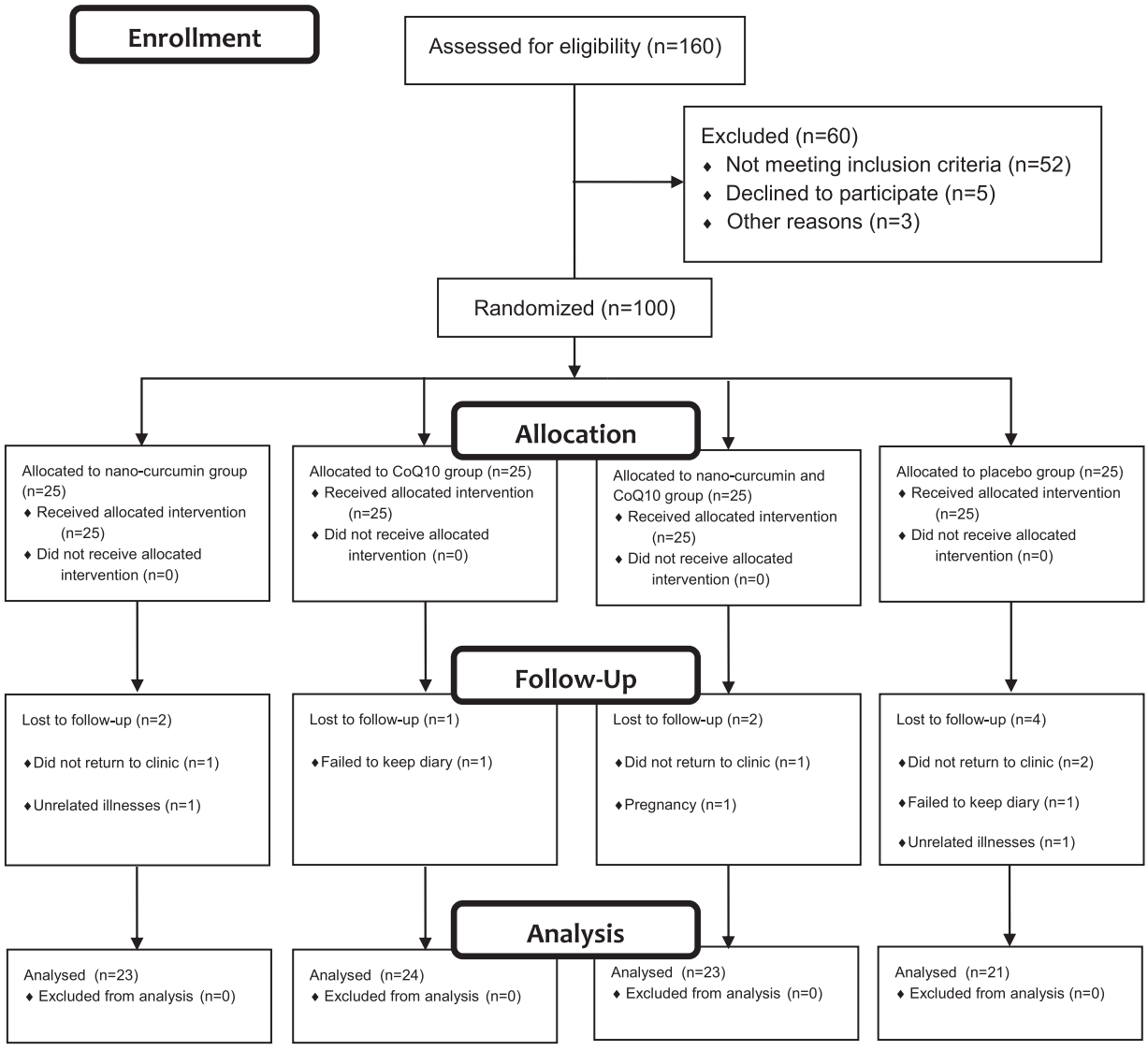

Figure 1. Study flow chart.

reasons for which, 'intention-to-treat' analysis is recommended; these two were not the case in our study.

Migraine frequency, severity, and duration

The within-group analysis showed a significant reduction from baseline to the end of the study, in frequency, duration of migraine attacks and HDR within four groups ($P < 0.001$ for all comparisons) (Table 2). However, the severity of migraine attacks showed a significant reduction only in treatment groups ($P < 0.001$ for all comparisons), with a significant increase in the control group from baseline to the end of the trial ($P < 0.05$).

Table 1. Baseline characteristics of participants[a] ($n = 100$).

Variable	Nano-curcumin[b] ($n = 25$)	CoQ10 ($n = 25$)	Nano-curcumin and CoQ10 ($n = 25$)	Placebo ($n = 25$)	*P*-value[c]
Age (years)	33.60 ± 8.65	32.05 ± 9.02	31.70 ± 8.87	31.75 ± 9.43	0.897
Energy intake in kcal	2493 ± 221	2615 ± 303	2571 ± 349	2696 ± 305	0.191
Height (cm)	172.70 ± 4.66	177.20 ± 6.25	175.15 ± 7.52	173.75 ± 4.58	0.097
Weight (kg)	73.65 ± 8.21	81.10 ± 11.83	76.01 ± 12.85	81.20 ± 11.65	0.090
Body mass index (kg m^{-2})	24.95 ± 2.23	25.90 ± 3.95	24.69 ± 3.40	26.80 ± 5.16	0.296
Waist to hip ratio (cm)	0.85 ± 0.06	0.86 ± 0.06	0.86 ± 0.07	0.87 ± 0.07	0.901
Body fat percent	23.95 ± 3.21	26.35 ± 4.19	24.75 ± 4.51	23.10 ± 5.81	0.143
Years with migraine	9.70 ± 3.62	8.65 ± 3.84	9.80 ± 3.86	9.95 ± 4.42	0.705

[a]Female ($n = 73$), male ($n = 27$).
[b]The results are presented as mean ± SD.
[c]*P*-value for comparing the baseline characteristics between groups based on one-way ANOVA test.

Table 2. The effects of nano-curcumin and CoQ10 supplementation on migraine symptoms[a].

Variable	Nano-curcumin ($n = 23$)	CoQ10 ($n = 24$)	Nano-curcumin and CoQ10 ($n = 23$)	Placebo ($n = 21$)	P-value[b]
Migraine frequency (per month)					
Baseline	8.52 ± 4.68	8.54 ± 4.27	6.39 ± 3.51	7.10 ± 4.41	0.230
8th week	6.61 ± 4.34	5.46 ± 3.56	2.78 ± 1.62*	4.90 ± 3.93	0.002
MD, P-value[c]	−1.91, <0.001	−3.08, <0.001	−3.61, <0.001	−2.2, <0.001	
Migraine severity (VAS score)[d]					
Baseline	7.74 ± 1.88	8.25 ± 1.89	7.52 ± 1.80	7.10 ± 2.02	0.209
8th week	7.17 ± 2.01	7.67 ± 1.71	6.61 ± 1.75	7.57 ± 1.53	0.089
MD, P-value[c]	−0.57, <0.001	−0.58, <0.001	−0.91, <0.001	0.47, 0.021	
Migraine duration (hour)					
Baseline	12.65 ± 7.31	11.21 ± 6.95	11.22 ± 7.44	10.33 ± 6.26	0.841
8th week	10.30 ± 7.15	10.08 ± 6.74	7.48 ± 6.80	9.24 ± 6.07	0.488
MD, P-value[c]	−2.35, <0.001	−1.13, <0.001	−3.74, <0.001	−1.09, <0.001	
HDR[e]					
Baseline	101.04 ± 83.86	100.50 ± 87.49	77.17 ± 72.16	84.76 ± 80.95	0.700
8th week	61.73 ± 60.96	58.12 ± 60.38	22.43 ± 26.04	54.71 ± 61.67	0.060
MD, P-value[c]	−39.31, <0.001	−42.38, <0.001	−54.74, <0.001	−30.05, <0.001	

[a]All data are means ± SD.
[b]P-value for comparing the changes of migraine characteristics between groups based on ANCOVA adjusted for confounder variables (including Age, physical activity level, energy intake, changes in body mass index, body fat percent and years with migraine).
[c]MD: mean difference; P-value for comparing the changes of migraine characteristics within groups based on the analysis of paired sample t-test.
[d]Visual analogue scale.
[e]Headache dairy results: frequency of headache × duration of headache.
*$P < 0.01$ from the post hoc comparisons (Scheffe test) between nano-curcumin and CoQ10 group compared to nano-curcumin group.

In addition, between-groups analysis based on ANCOVA adjusted for baseline values and confounder variables, including age, physical activity level, energy intake, changes in body mass index, body fat percent and years with migraine showed significant reduction in frequency of migraine attacks ($P = 0.002$) in nano-curcumin and CoQ10 group compared to nano-curcumin group, at the end of the study (Table 2).

Patients treated with both supplements had a mean reduction of 3.61 in the frequency of migraine attacks per month in comparison with −1.91 and −3.08 for the nano-curcumin group and CoQ10 group, respectively.

Migraine-specific questionnaires scores including MSQ, MIDAS, and HIT-6

As Table 3 shows, baseline total scores for migraine-specific questionnaires were similar in four groups based on the one-way ANOVA test. Most of the participants (80.2% based on HIT-6 score and 93.4% based on MIDAS score) were considered as severely affected by migraine headaches. Within-group comparison showed a significant reduction in MIDAS ($P < 0.001$) and HIT-6 ($P < 0.001$) scores from baseline to the end of the study in all study groups and also a significant increase in MSQ ($P < 0.001$) scores during the treatment period, which lead to improvement in quality of life of patients.

Considering between-group analysis, using ANCOVA adjusted for baseline values and confounder variables, including age, physical activity level, energy intake, changes in body mass index, body fat percent and years with migraine, the changes in total scores from baseline to the end of the study showed a significant reduction in HIT-6 and MIDAS scores ($P < 0.05$) and a significant increase in MSQ score ($P < 0.001$).

Table 3. The effects of nano-curcumin and CoQ10 supplementation on migraine specific questionnaires scores[a].

Variable	Nano-curcumin ($n = 23$)	CoQ10 ($n = 24$)	Nano-curcumin and CoQ10 ($n = 23$)	Placebo ($n = 21$)	P-value[b]
MSQ score					
Baseline	29.02 ± 9.05	32.83 ± 10.17	31.39 ± 10.68	30.52 ± 9.85	0.629
8th week	61.08 ± 9.34	60.91 ± 9.86	68.17 ± 10.03**	54.19 ± 10.31	<0.001
MD, P-value[c]	32.06, <0.001	28.08, <0.001	36.78, <0.001	23.67, <0.001	
MIDAS score					
Baseline	28.04 ± 5.93	26.75 ± 4.94	29.65 ± 3.42	27.14 ± 5.61	0.109
8th week	18.34 ± 6.49	18.54 ± 5.56	16.17 ± 4.96*	21.71 ± 6.21	0.023
MD, P-value[c]	−9.7, <0.001	−8.21, <0.001	−13.48, <0.001	−5.43, <0.001	
HIT-6 score					
Baseline	65.01 ± 5.22	64.79 ± 6.08	66.02 ± 7.46	65.62 ± 7.59	0.907
8th week	52.43 ± 4.79	54.50 ± 5.97	51.86 ± 7.39*	58.04 ± 8.10	0.012
MD, P-value[c]	−12.58, <0.001	−10.29, <0.001	−14.16, <0.001	−7.58, <0.001	

[a]All data are means ± SD.
[b]P-value for comparing the changes of migraine characteristics between groups based on ANCOVA adjusted for confounder variables (including Age, physical activity level, energy intake, changes in body mass index, body fat percent and years with migraine).
[c]MD: mean difference; P-value for comparing the changes of migraine characteristics within groups based on the analysis of paired sample t-test.
*$P < 0.05$ from the post hoc comparisons (Scheffe test) between nano-curcumin and CoQ10 group compared to placebo group.
**$P < 0.001$ from the post hoc comparisons (Scheffe test) between nano-curcumin and CoQ10 group compared to placebo group.

Although all study groups showed a significant reduction in MIDAS and HIT-6 scores, the greatest reduction was observed in nano-curcumin and CoQ10 group from baseline to the end of the study. Furthermore, subjects treated with both nano-curcumin and CoQ10 had the highest increase in MSQ score in comparison with the other study groups.

Safety

It was well-tolerated at the doses of 80 mg/day for nano-curcumin and 300 mg/day for CoQ10 and patients did not report any serious side effects throughout the trial (Table 4).

Discussion

The results of this randomized, double-blind, placebo-controlled trial among migraine patients showed that the combined supplementation of nano-curcumin with CoQ10 for 8 weeks could significantly affect migraine symptoms and improve the quality of life. Our findings are partially in line with previous studies conducted on nutraceuticals such as magnesium, riboflavin, and CoQ10 [5–7]. To the best of our knowledge, this is the first study to evaluate the synergistic effects of concurrent supplementation of nano-curcumin and CoQ10 on clinical features of migraine, including frequency, severity, and duration of migraine attacks.

We observed that the combination of nano-curcumin and CoQ10 synergistically reduces the frequency, severity, and duration of attacks, HDR, MIDAS and HIT-6 scores and also increases MSQ scores in patients with migraine. A previous animal study demonstrated the synergistic effects of curcumin and CoQ10 [26]. In this context, Valverde et al. reported that a combined supplementation therapy of curcumin-CoQ10 in a model of sickle cell anemia mice is able to modulate spinal glial activity and synergistically decrease reactive oxygen species generation. Our findings are also in agreement with the findings in earlier studies, that nano-curcumin or CoQ10 supplementation alone or in combination with other supplements might reduce migraine symptoms [22,43].

Table 4. Occurrence of side effects between entry and month 3 visit.

Side effect	Nano-curcumin ($n = 23$)	CoQ10 ($n = 24$)	Nano-curcumin and CoQ10 ($n = 23$)	Placebo ($n = 21$)
Stomach upset	1	3	2	1
Nausea	3	6	4	5
Vomiting	2	3	1	2
Diarrhea	1	1	3	0
Constipation	2	0	1	3
Loss of appetite	0	1	2	1
Dizziness	1	0	0	1
Dry mouth	0	1	0	2
Feeling sleepy	0	0	1	5
Feeling depressed	2	3	1	4

In contrast to our findings, some studies did not find a significant effect. Slater *et al.* [25] in a double-blinded crossover trial indicated that CoQ10 supplementation in 100 mg dosage for 16 weeks had no effects on headache outcomes. No significant differences in migraine symptoms between the CoQ10 and placebo groups were found in another parallel trial [7]. The difference between findings could be explained by the discrepancy in participants in terms of their age, gender and health conditions. Supplements type and dosage along with the duration of the trial might also explain some differences.

To assess the effect of prophylactic treatment (topiramate 50 mg/day and amitriptyline 25 mg/day) without the effects of nano-curcumin and/or CoQ10 supplements on clinical features of migraine, we compared migraine symptoms before and after the intervention in the control group. Prophylactic treatment significantly improved migraine symptoms and quality of life from baseline to the end of the study in the control group. However, the changes in the control group were lower than the third group (prophylactic treatment plus nano-curcumin and CoQ10 supplements), indicating the combined effects of nano-curcumin and CoQ10 supplements with prophylactic medications on migraine symptoms.

Nutraceuticals are commonly used by patients with migraine, despite little understanding of their biological and clinical activity. CoQ10 and curcumin are such candidates for migraine. They have pathophysiological modes of action in migraine headaches including both as an antioxidant that can manage the inflammatory nature of migraine and as a mitochondrial component involved in the electron transport chain, energy metabolism and also protects mitochondria from oxidative stress.

Oxidative stress and inflammation play an important role in the pathogenesis of migraine. Recent studies have demonstrated an impairment of the brain oxidative energy metabolism in patients with migraine [3]. Curcumin and CoQ10 are powerful antioxidants, play important roles in protection against reactive oxygen species injury and used to regenerate other antioxidants [44,45]. Furthermore, curcumin is a bifunctional antioxidant and exerts both direct and indirect antioxidant effects by scavenging reactive oxygen species and inducing the expression of antioxidant/detoxifying enzymes and scavengers such as superoxide dismutase, catalase, glutathione peroxidase and heme oxygenase 1 in a

nuclear factor E2-related factor 2 (Nrf2)-dependent pathway, respectively [45].

Migraine has also been associated with persistent vascular inflammation [46]. Recent studies have shown that calcitonin gene-related peptide (CGRP), pro-inflammatory mediators such as Monocyte Chemoattractant Protein-1 (MCP-1) and pro-inflammatory cytokines like TNF-α, IL-1β, and IL-6 may be involved in the pathogenesis of migraine headache [47–49]. Also, it has been demonstrated that curcumin and CoQ10 are negatively associated with inflammatory biomarkers, such as pro-inflammatory cytokines [50,51]. Curcumin and CoQ10 exert their anti-inflammatory effects by the upregulation of peroxisome proliferator-activated receptor-γ (PPAR-γ) activation and nuclear factor kappa B (NF-κB) signaling pathway inhibition, respectively [50–52]. These observations indicated the role of curcumin and CoQ10 in the suppression of neuroinflammation and improvement in neurogenic pain. However, most of these studies are conducted in cellular and animal models, and further human studies are needed to discover appropriate dosages. Our findings show an additive and synergistic association between nano-curcumin and CoQ10 on reducing pain in patients with migraine.

The mitochondrial hypothesis of migraine has been supported by genetic, morphologic, biochemical and therapeutic evidence [3]. Mitochondria play an important role in the functions of neurons by regulating energy metabolism, reactive oxygen species production, and control of calcium homeostasis [3]. Therefore, any abnormal mitochondrial function affecting ATP production, reactive oxygen species generation and calcium homeostasis in neurons could increase susceptibility to migraine [3]. Considering the important role of curcumin as an antioxidant and CoQ10 both as an antioxidant agent and mitochondrial electron transporter and taking into account the mitochondrial hypothesis in the pathogenesis of migraine, curcumin and CoQ10 can be considered as an effective agent in the prophylactic treatment of migraine.

The present study has several advantages. This is the first trial that examined the effects of concurrent supplementation of nano-curcumin and CoQ10 on migraine symptoms. Furthermore, since the bioavailability of curcumin is too poor to exhibit clinical efficacy in trials even in high doses, the nano-curcumin formula was used in this study. Nano-curcumin is nanoparticles of curcumin that safely increases the absorption of curcumin 27 times more than that of curcumin powder [53]. Moreover, the physical activity level and dietary intakes of participants were assessed throughout the trial, which enabled the exploration of any changes in these variables.

Despite the significant effects of nano-curcumin and CoQ10 supplements on migraine symptoms, one point deserves considerable attention. A significant point is that how much nano-curcumin and CoQ10 blood levels can exert the most effective clinical impacts in migraine symptoms. Due to budget limitations, serum levels of nano-curcumin and CoQ10 were not measured at the baseline and end of the study to ensure compliance with consumption of the supplements, which was one of the limitations of the present study. However, based on self-reports and pill counts, the compliance with consumption of nano-curcumin and CoQ10 supplements seems relatively appropriate. In addition, the serum level of amitriptyline was not measured at the baseline and end of the study to assess the interaction between nano-curcumin (80 mg/day) and (amitriptyline, 25 mg/day). It suggested these measurements to be considered in future trials to research the most effective dose of nano-curcumin and CoQ10.

Conclusions

Finally, considering the reported results from previous studies regarding the effect of curcumin and CoQ10 in neurogenic pain models and the results of the present study, it can be concluded that nano-curcumin and CoQ10 may have an additive effect on migraine symptoms and improvement in migraine-related disability. Therefore, these dietary factors, without adverse side effects, can be used as an adjuvant therapy to enhance the management of the migraine headache.

Disclosure statement

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