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Assessing the Effect of Zinc Supplementation on the Frequency of Migraine Attack, Duration, Severity, Lipid Profile and hs-CRP in Adult Women

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ABSTRACT

Migraine is a widespread incapacitating neurologic disorder with debilitating headaches which are usually throbbing due to inefficacy and several side effects, complementary therapies recommended as possible alternatives. The current randomized controlled trial was carried out to evaluate the effect of zinc gluconate supplementation on migraine-related symptoms, serum level of high sensitivity C-reactive protein (hs-CRP) and lipid profile in migraineurs. Present study was designed as randomized double-blind, placebo-controlled trial. Sixty women with migraine (mean age of 35.44 ± 7.42 years) were randomly allocated to obtain 15 mg per day of zinc gluconate or placebo for 12 weeks. Frequency, periods of headaches and severity of migraine based on numerical rating scale questionnaire and migraine disability assessment (MIDAS) test were checked. Fasting serum level of lipid profile and hs-CRP were assessed at the beginning and the end of trial. Zinc gluconate supplementation significantly reduced the frequency ($p = 0.001$), periods of migraine attacks ($p < 0.001$) and severity of migraine and MIDAS ($p < 0.001$) compared with control group. The serum level of low-density lipoprotein ($p < 0.001$), total cholesterol ($p < 0.001$) and hs-CRP ($p < 0.001$) decreased following zinc supplementation, but no significant differences in serum level of triglycerides ($p = 0.1$) and high-density lipoprotein ($p = 0.3$) was observed. However, after adjustment for baseline values using analysis of covariance test, none of lipid profile components and hs-CRP showed a significant difference. Zinc supplementation has beneficial effect on the migraine related complications like its severity, frequency.

Trial Registration: Iranian Registry of Clinical Trials Identifier: IRCT20191014045100N1

Keywords: Zinc; Migraine; Headache; Randomized controlled trial

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Conflict of Interest

The authors declare that they have no competing interests.

INTRODUCTION

Migraine is a widespread weakening neurologic disorder which is mainly defined as unilateral headache [1]. The worldwide prevalence of migraine reported to be 14.7% with 3 times higher in women than in men [2]. The common symptoms of this disorder are recurrent attacks of debilitating headaches which are usually throbbing and annoying [3]. The headaches may last between 7–24 hours and may accompanied with nausea, vomiting, phonophobia and photophobia [1]. International Headache Society (IHS) criteria based on the clinical presence of aura, migraine attacks classified as 2 major subtypes: Migraine with aura and migraine without aura [4]. Moreover, migraine with aura is characterized by disturbance in visual, sensory, speech or motor function that accompany a headache [1].

Although the exact etiology of migraine development remained to be unrevealed, likely mechanisms could be several vascular, neuroinflammatory; and neurological mechanisms [5].

Recently, the effect of different vitamins and nutraceuticals on migraine symptoms and patients' quality of life has been studied, and the findings showed promising effects of dietary supplements including zinc, magnesium, melatonin, vitamin D, riboflavin, vitamin B_6, folic acid, omega-3 polyunsaturated fatty acids, coenzyme Q10, butterbur and feverfew leaves on migraine patients [6,7].

Zinc is an essential trace element with proven anti-inflammatory effects [8]. Moreover, hypolipidemic effect of zinc was shown in previous studies [9]. In few studies decreased serum zinc level reported in patients with migraine [10,11]. In addition to an increased cardiovascular disease (CVD) risk factors such as serum levels of high sensitivity C-reactive protein (hs-CRP), total cholesterol (TC), triglycerides (TG), and low-density lipoprotein (LDL) cholesterol have been observed in migraine patients [3,12,13]. However, in some studies, no significant relationship was observed between increased hs-CRP levels and migraine headache attacks [14,15]. In previous limited studies, the positive effect of zinc supplementation alone or along with other dietary supplements (magnesium, B complex, vitamin E, and coenzyme Q10) on the frequency, duration and severity of migraine attacks have been reported [7,16]. Ahmadi et al. [7] showed that there is no significant difference in C-reactive protein (CRP) level between the intervention group (IG) and control group (CG). Since patients with migraine attacks are at higher risk of CVD and lower zinc levels as reported in previous studies and also lack of sufficient evidence for the effect of zinc supplementation on serum hs-CRP and lipid profiles [7,17], present RCT was designed to evaluate the effect of zinc gluconate supplementation on some CVD risk factors and migraine-related symptoms in migraineurs.

MATERIALS AND METHODS

Ethical consideration

All procedures of present study were in keeping with Declaration of Helsinki. The ethics committee of Urmia University of Medical Sciences (UMSU) has approved the study protocol (IR.UMSU.REC.1398.045), and all participants of study completed written informed consent. The trial was registered in the Iranian website (http://www.irct.ir) for registration of clinical trials (IRCT code IRCT20191014045100N1).

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Study population

Present study was designed as a randomized, placebo-controlled, double-blind parallel clinical trial and conducted among women with proved migraine headaches attacks. Patients were introduced by a neurologist who confirmed their affliction based on IHS questionnaire [18] in Imam Khomeini Educational Hospital, UMSU, Urmia, Iran. Sixty migraine patients from Aprils 2019 to August 2019 were enrolled to this randomized double-blind placebo-controlled trial (**Figure 1**). Screened subjects must meet following inclusion criteria before allocation: 1) age range of 18 to 59 years; 2) use of migraine prophylactic medicine based on a same treatment protocol such as (nortriptyline, propranolol and naproxen); 3) residence of Urmia city; 4) have episodic or chronic migraine; 5) willingness for entrance in present study with 3 months follow up. Subjects were not included in the present study if they were: pregnant; lactating, smokers [19], or had a history of trauma or brain injury in previous 2 years [20], having a medical history of allergic, stroke, inflammation or autoimmune diseases, or other chronic disease including CVD, diabetes mellitus, rheumatoid arthritis, gastrointestinal disorders, other neurological diseases [19,21], or consuming antioxidants supplements over the last 3 months, taking contraceptives, non-steroids anti-inflammatory drugs, corticosteroids [22], history of drinking alcohol, or changing the dose(s) and types of their regular medication, having compliance lower than 80% based on supplements returned; changing diet or physical activity level during the study period and male subjects; due to 3-fold higher prevalence of migraine among women.

Study design

Randomization for assigned subjects to the IG or CG was performed using simple random method. According to table of random numbers, 60 participants selecting a number were randomly allocated into 2 groups by the secretary of neurologist, IG (n = 30) and CG (n = 30). According to previous studies, IG received 15 mg/day of zinc gluconate [23,24] (Simorgh attar Neyshabour Co., Neyshabur, Iran) and CG received placebo tablets (edible starch, Simorgh Attar Neyshabour Co.) before main meal along with to using migraine preventive medicine for 12 weeks [25]. Both zinc gluconate and placebo tablets were same in shape, color, size,

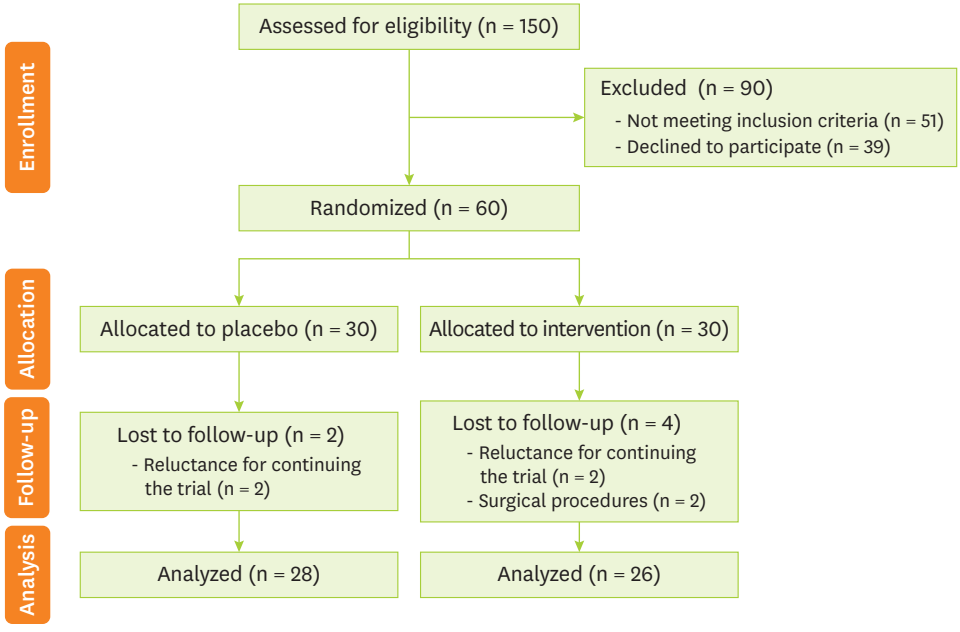

Figure 1. Flow diagram of patient enrollment in the study.

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and packaging and coding. All patients and researchers were uninformed about allocation till the last analysis. All subjects were monitored by phone calls weekly to ensure that they were taking the administrated supplements. All patients were advised not to change their nutritional habits and physical activity level during trial to limit their possible impacts on the study findings. At each visit, participants were evaluated about complaints such as side effects of zinc supplementation and usual prophylactic medicine migraine.

Sample size calculation

The sample size was calculated based on type 1 (α) and type 2 (β) errors as 0.05 and 0.20, respectively (power = 80%). Based on previous study, standard deviations (SDs) and mean difference of serum zinc level considered as 0.24 ± 0.01 (μg/dL) and 5.77 ± 0.71 (μg/dL) in the patient group and CG, respectively [10]. However, 26 patients were needed in each group, but due to possible dropouts, 30 subjects were enrolled in each arm.

Medical history and nutritional assessment

All participants filled up a general questionnaire including demographic variables (age), dietary habits (including supplementation), lifestyle habits (including history of smoking, alcohol consumption, and medicine history) and medical history (the onset of migraine disorder, family history of diseases and blood pressure including systolic and diastolic blood pressure were recorded according to available guidelines at the beginning and the end of trial) [26].

All participants were asked not to change their dietary intake, physical activity and lifestyle during the intervention. Dietary intakes of participants recorded 2 times using a 24-hour diet recall questionnaire each time for 3 different non-consecutive days, (including 2 working and 1 non-working day). All dietary recalls were analyzed using Nutritionist IV software (First Databank, San Bruno, CA, USA) adjusted for Iranian foods [27].

Anthropometry and physical activity assessment

Body weight and body mass index (BMI) were measured at baseline and at the end of intervention in week 12. Physical activity level was assessed based on International Physical Activity Questionnaire (short form) at the beginning and end of trial by all subjects [28]. The level of daily activity and physical activity reported as metabolic equivalent of task.

Migraine headache characteristics assessment

Frequency of attacks (expressed as the number of headaches in a month) and migraine attack period (the duration of each migraine attack in an hours) were checked at the beginning of trial and at the end of each month of trial [16]. Numerical rating scale (NRS) was applied for assessing the severity of pain. The perceived pain reported as a number between 0 to 10 [29]. It was assessed at baseline and end of each month of trial. The validity and reliability of the NRS were checked using 10% of the study population before allocation. The reliability of NRS was examined ($r = 0.7$) and the criterion validity of the measurement was tested between visual analogue scale and NRS among 6 subjects to check the possible differences; findings showed that differences were not statistically significant ($p > 0.05$). Moreover, migraine disability assessment (MIDAS) was used to assess lost days in the past 3 months. It was assessed at the beginning and the end of trial [30].

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Biochemical measurements

Fasting blood samples (10 mL) after 12 hours fasting over night were obtained from the antecubital vein at baseline and at the end of trial then immediately centrifuged 3,000 rpm for 10 minutes at 4°C. Serum stored at 80°C until the time of final analysis. Serum level of lipid profile including TG, HDL, LDL and TC measured commercial kits (Pars Azmoon, Tehran, Iran). Serum level of hs-CRP was also checked by immunotorbidimetric method according to manufacturer's instruction (Holzheim, Germany). Mean of serum zinc concentrations were measured using the atomic absorption spectrophotometry method in 2 groups at the beginning and the end of study (DIALAB, Wiener Neudorf, Austria). Intra and inter-assay for all above-mentioned kits were under coefficient of variation were < 3%.

Statistical methods

The quantitative variables were represented as mean and SD and the qualitative variables were expressed as frequency (percentage). The normal distribution of variables was tested by the Kolmogorov-Smirnov test. Moreover, to compare the categorical variables between the intervention and CGs, the Pearson chi-square test was conducted. Additionally, we used paired t-test and independent t-test to compare difference among the intra-groups and inter-groups. The repeated measure analysis of variance test was applied to identify the change of outcomes during the time checkpoints. To control the confounding effect the adjustments were performed using analysis of covariance (ANCOVA), which controls the baseline values for each outcome. The $p < 0.05$ was considered as statistically significant. All statistical analyses were performed by the Statistical Package for Social Science version 17 (SPSS Inc., Chicago, IL, USA).

RESULTS

Participant's characteristics

After screening 150 patients, 60 women with established migraine attacks (age range of 18–59) were randomized to the present trial (**Figure 1**). In the present study, no side effects were reported by IG or CG during 12 weeks of intervention. In the **Figure 1**, the withdrawal reasons of the participants were shown.

Baseline characteristics including demographic and general data (age, marriage status, literacy) anthropometric indices (weight, waist circumference, BMI), physical activity, blood pressure (systolic blood pressure and diastolic blood pressure) and serum zinc level were presented in **Table 1**; that none of above-mentioned variables were significantly different between 2 groups at the baseline of the study.

Furthermore, family history of migraine, type of migraine (with aura and without aura), affliction history, and medicine history were not significantly different between 2 groups of intervention at the baseline of the trial (**Table 1**).

Dietary intakes

Changes in total energy, dietary intake of protein, zinc and copper intake were not significant either within or between groups before and after the intervention. The intake of carbohydrates was significantly different within IG ($p = 0.04$), but no statistically significant differences in carbohydrates intake was observed within placebo group and between groups before and after the intervention. However, changes in fat intake within IG and between

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Table 1. Baseline characteristics of participants

Variable	Zinc group (n = 30)	Placebo group (n = 30)	p value
Age (yr)	37.51 ± 7.76	33.53 ± 6.65	0.466*
Height (cm)	162.23 ± 4.79	159.60 ± 5.47	0.320*
Weight (kg)	72.68 ± 4.34	71.20 ± 3.24	0.107*
Waist circumference (cm)	94.42 ± 5.94	92.51 ± 4.65	0.736*
Body mass index (kg/m^2)	27.33 ± 3.35	28.13 ± 6.28	0.862*
Physical activity (MET.h/day)	128.85 ± 4.07	144.73 ± 6.33	0.200*
SBP (mmHg)	109.04 ± 9.90	110.36 ± 9.51	0.620*
DBP (mmHg)	80.00 ± 6.92	80.00 ± 4.71	0.900*
Education level			0.288†
High school and lower	38.4 (10)	53.6 (15)	
Academic	61.5 (16)	46.4 (13)	
Serum zinc level (μg/dL)	68.84 ± 21.47	77.57 ± 16.84	0.103†
Family history			0.170†
Yes	80.80 (21)	64.30 (18)	
No	19.20 (5)	35.70 (10)	
Type of migraine			0.394†
Without aura	96.20 (25)	85.70 (24)	
With aura	3.80 (1)	14.30 (4)	
Affliction history (yr)			0.512†
1–4	34.60 (9)	46.40 (13)	
5–10	46.20 (12)	32.10 (9)	
11–15	11.50 (3)	17.90 (5)	
16–20	7.70 (2)	3.60 (1)	
Medicine used			
Nortriptyline			0.656†
Yes	65.40 (17)	71.40 (20)	
No	34.60 (9)	28.60 (8)	
Propranolol			0.103†
Yes	76.90 (20)	92.90 (26)	
No	23.10 (6)	7.10 (2)	
NSAIDs			0.240†
Yes	84.60 (22)	71.40 (20)	
No	15.40 (4)	28.60 (8)	
Light, smell and voice sensitivity			0.752†
Yes	38.50 (10)	46.40 (13)	
No	61.50 (16)	53.60 (15)	
Location of headache			0.763†
One-sided	88.50 (23)	85.70 (24)	
Two-sided	11.50 (3)	14.30 (4)	
Headache with nausea			0.545†
Yes	65.40 (17)	53.60 (15)	
No	34.60 (9)	46.40 (13)	

Data are shown as mean ± standard deviation or percent (number).
MET, metabolic equivalent of task; SBP, systolic blood pressure; DBP, diastolic blood pressure; NSAID, non-steroids anti-inflammatory drug.
*The p values obtained from independent sample t-test for quantitative between the 2 groups; †The p values obtained from χ^2 test for qualitative variables between the 2 groups.

groups before of intervention was not significant, but statistically significant differences in fat intake were found within placebo group and between groups after the study ($p < 0.001$, $p = 0.018$) (**Table 2**).

Biochemical and anthropometric measurements

As shown in **Table 3**, at the baseline of the study, hs-CRP was non-significant across 2 groups but zinc gluconate supplementation (15 mg/day) after 12 weeks, lead to reduction of hs-CRP significantly in the IG compared to the placebo group ($p = 0.01$). After performing ANCOVA test baseline values, the differences of hs-CRP between groups were non-significant ($p =$

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Table 2. Dietary intakes of participants of intervention and placebo group at the baseline and end of trial

Variable	Zinc group (n = 30)			Placebo group (n = 30)			p value		
	Baseline	End of trial	p value*	Baseline	End of trial	p value*	Base line†	End of trial†	p value‡
Total energy intake (kcal)	1,598.77 ± 464.32	1,723.50 ± 317.25	0.212	1,748.50 ± 548.12	1,764.79 ± 319.40	0.869	0.286	0.636	0.210
Carbohydrates intake (g/day)	246.11 ± 73.35	285.17 ± 70.77	0.040	275.21 ± 122.23	286.26 ± 78.85	0.520	0.260	0.947	0.251
Proteins intake (g/day)	78.72 ± 38.55	67.74 ± 13.01	0.131	80.02 ± 45.80	66.27 ± 19.25	0.108	0.899	0.742	0.810
Fat intake (g/day)	46.76 ± 16.96	43.91 ± 14.93	0.301	40.85 ± 14.34	50.47 ± 12.84	< 0.001	0.170	0.010	0.110
Zinc intake (mg/day)	7.23 ± 1.04	7.45 ± 1.41	0.181	7.53 ± 1.08	7.76 ± 1.06	0.203	0.330	0.712	0.325
Copper intake (mg/day)	1.24 ± 0.44	1.28 ± 0.49	0.735	1.56 ± 1.43	1.40 ± 0.61	0.619	0.280	0.430	0.268

Data are shown as mean ± standard deviation.
*The p values obtained from paired sample t-test; †The p values obtained from independent sample t-test; ‡The p values obtained from analysis of covariance test adjusted for baseline values.

Table 3. The effect of zinc supplementation on serum zinc level, anthropometric indices, lipid profile, and inflammatory markers

Variable	Zinc group (n = 30)			Placebo group (n = 30)			p value		
	Baseline	End of trial	p value*	Baseline	End of trial	p value*	Baseline†	End of trial†	p value‡
Weight (kg)	72.68 ± 4.34	65.20 ± 4.23	< 0.001	71.20 ± 3.24	76.72 ± 3.21	< 0.001	0.107	< 0.001	0.810
BMI (kg/m^2)	27.33 ± 3.35	24.20 ± 3.21	< 0.001	28.13 ± 6.28	29.35 ± 3.50	< 0.001	0.362	< 0.001	0.305
WC (cm)	94.42 ± 5.94	84.52 ± 4.97	< 0.001	92.51 ± 4.65	100.00 ± 8.19	< 0.001	0.176	< 0.001	0.001
SBP (mmHg)	109.04 ± 9.90	104.23 ± 11.37	0.082	110.36 ± 9.51	104.29 ± 9.97	0.025	0.620	0.985	0.632
DBP (mmHg)	80.00 ± 6.92	78.84 ± 3.25	0.523	80.00 ± 4.71	78.92 ± 3.14	0.415	0.190	0.925	0.107
PA (MET.h/day)	128.85 ± 4.07	137.76 ± 4.13	0.358	144.73 ± 6.33	125.73 ± 3.20	0.195	0.283	0.235	0.225
Serum zinc (μg/dL)	68.84 ± 21.47	114.15 ± 25.93	< 0.001	77.57 ± 16.84	67.89 ± 14.60	0.026	0.190	< 0.001	0.130
LDL (mg/dL)	153.83 ± 32.85	78.97 ± 11.21	< 0.001	150.35 ± 27.71	195.14 ± 29.49	< 0.001	0.605	< 0.001	0.663
HDL (mg/dL)	46.69 ± 10.12	48.23 ± 11.48	0.613	48.56 ± 9.69	45.78 ± 9.24	0.326	0.491	0.390	0.456
TG (mg/dL)	160.85 ± 118.66	139.81 ± 56.59	0.412	136.07 ± 84.59	117.00 ± 44.59	0.288	0.378	0.105	0.310
TC (mg/dL)	200.54 ± 48.14	139.92 ± 30.42	< 0.001	198.82 ± 46.87	243.04 ± 50.36	< 0.001	0.890	< 0.001	0.886
hs-CRP (mg/L)	2.56 ± 2.43	0.28 ± 0.61	< 0.001	2.48 ± 2.14	3.58 ± 2.24	0.031	0.535	0.010	0.920

Data are shown as mean ± standard deviation.
BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; PA, physical activity MET, metabolic equivalent of task; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglycerides; TC, total cholesterol; hs-CRP, high sensitivity C-reactive protein.
*The p values obtained from paired sample t-test; †The p values obtained from independent sample t-test; ‡The p values obtained from analysis of covariance test adjusted for baseline values.

0.9). Among evaluated lipid profile components, only LDL and TC decreased significantly in the IG at the end of trial ($p < 0.001$ for LDL and TC), however, after adjusting for baseline values using ANCOVA test, none of them showed as significant difference. In addition, zinc supplementation significantly increased serum zinc levels in the IG compared to placebo group ($p < 0.001$; **Table 3**).

There were no significant differences regarding weight, waist circumference and BMI between 2 groups at the baseline but all of them decreased significantly after zinc supplementation in the IG compared with the placebo group ($p < 0.001$ for weight, waist circumference and BMI). Moreover, adjusting for baseline values using ANCOVA test showed that waist circumference decreased significantly in the IG compared to CG at the end of the trial ($p = 0.001$; **Table 3**).

Migraine-related complications

Frequency of migraine attacks and their duration showed decreasing trend following zinc supplementation ($p = 0.001$ and $p < 0.001$, respectively; **Table 4**). Severity of migraine attacks and the effect of migraine attacks on habitual life (MIDAS) also confirmed decreasing effect of zinc supplementation compared with placebo group ($p < 0.001$ for severity of migraine attacks and MIDAS; **Table 5**).

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Table 4. Effect of zinc supplementation on frequency and periods of migraine attacks in patients with migraine attacks

Variable	Baseline	Treatment 2nd month	Treatment 3rd month	p value*		
				Time	Group	Time* group
Frequency of migraine attacks (days)				0.530	0.001	< 0.001
Zinc group	9.26 ± 6.09	7.69 ± 4.15	6.30 ± 2.67			
Placebo group	7.10 ± 3.99	7.50 ± 5.83	9.25 ± 5.18			
Period of migraine attacks (hr)				0.041	< 0.001	< 0.001
Zinc group	10.50 ± 5.20	9.34 ± 4.37	8.84 ± 3.25			
Placebo group	7.85 ± 4.30	8.25 ± 4.02	8.28 ± 3.62			

Data are shown as mean ± standard deviation.
*Repeated measure analysis of variance were performed.

Table 5. Effect of zinc supplementation on severity of migraine attacks and MIDAS among patients with migraine attacks

Variable	Time	Group	Negligible	Mild	Moderate	Severe	p value‡
Migraine attacks severity*	Baseline	Zinc group	-	3.80 (1)	42.30 (11)	53.80 (14)	0.651
		Placebo group	-	10.70 (3)	32.10 (9)	57.10 (16)	
	Treatment 2nd month	Zinc group	-	76.90 (20)	23.10 (6)	-	0.046
		Placebo group	-	50.00 (14)	50.00 (14)	-	
	Treatment 3rd month	Zinc group	-	100.00 (26)	-	-	< 0.001
		Placebo group	-	3.60 (1)	21.40 (6)	75.00 (21)	
MIDAS†	Baseline	Zinc group	23.10 (6)	30.80 (8)	23.10 (6)	23.10 (6)	
		Placebo group	14.30 (4)	25.00 (7)	42.90 (12)	17.90 (5)	
	Treatment 3rd month	Zinc group	76.90 (20)	23.10 (6)	0.00 (0)	0.00 (0)	< 0.001
		Placebo group	3.60 (1)	28.60 (8)	21.40 (6)	50.00 (14)	

Data are shown as percent (number).
MIDAS, migraine disability assessment.
*Mild:(1–4), moderate:(4–6), severe:(6–10); †Negligible:(0–5), mild:(6–10), moderate:(11–20), severe:(> 21); ‡The χ^2 test were performed.

DISCUSSION

The present study evaluates the effect of zinc supplementation on the frequency of migraine attack, duration, severity, lipid profile and hs-CRP among migraine patients. The results showed that zinc gluconate supplementation (15 mg/day) for 12 weeks significantly reduced the frequency and periods of migraine attacks, severity of migraine and MIDAS. However, findings of current study indicated that zinc supplementation cause improvements in the levels of LDL, TC and hs-CRP between intervention and CGs, but after adjusting for baseline values no significant differences were observed in the levels of lipid profile components and hs-CRP. Moreover, weight, BMI and waist circumference decreased significantly in IG compared with placebo group; however, after adjusting for baseline values only waist circumference showed significant reduction.

Deficiency of zinc in patients with migraine attacks was already reported in some studies [10,11]. The association between lower serum zinc level and higher frequency of migraine attacks was observed in 2 studies [31,32]. Moreover, in the current study, the normal range of baseline serum zinc levels in the intervention and CGs were observed. In agreement with our results, a previous study has shown that supplementation with zinc decreases the frequency and intensity of migraine headaches in patients with normal range of serum zinc levels [7]. However, the exact mechanism of zinc on migraine headache is not fully understood [7], but the possible mechanisms could be through the role of different aspect of insulin action in the body from inhibition of the lipolysis in adipose tissues, down to reducing free fatty acid release into the circulation and thus improved lipid profile, inhibition of nuclear factor-κB activity, decreased expression of inflammatory factors such as interleukin-6 and tumor necrosis factor α (TNF-α), and thus decreased serum levels of hs-CRP [8,33], so it seems that

zinc supplementation could be beneficial to management of migraine-related complications by improving CVD risk factors such as lipid profile and hs-CRP in migraineurs.

Increased risk of CVD markers in migraine patients has been reported previously; one likely reason could be abnormal metabolic profiles that trigger migraine in those predisposed patients. In several previous studies, the association between abnormal lipid profile and frequency and severity of migraine attacks among migraine patients were evaluated [34,35]. In a Meta-analysis, contradictory results about zinc supplementation on lipid profile were reported [17], but in several trials, zinc supplementation alone or with multi-nutrients in patients with type 2 diabetes lead to reduce TC, TG and LDL and increase HDL [9,36]. Current study showed that zinc supplementation has a decreasing effect but non-significant on the level of TC and LDL, and no significant differences in serum level of HDL cholesterol and TG was observed, that it may have been due to the short duration of the intervention, low dosages of zinc supplementation and different food culture of the participants. Furthermore, vitamin D deficiency in study populations due to inadequate exposure to sunlight [37] may lead to increase of serum level of HDL cholesterol and TG.

Consistent with our results, in several trials zinc supplementation in various diseases, have shown no significant difference of serum level of hs-CRP [7,38]. However, the decreasing effect of zinc supplementation on serum level of hs-CRP was reported in elderly subjects and adults with metabolic syndrome [8,39]. Possible reasons for this inconsistency between our founding and some of previous studies is maybe because of different dosages of zinc supplementation that was higher in previous studies [8,39]. Besides, supplementation with zinc, magnesium and chromium, could lead to a synergistically effect and cause different results compare with current study [39].

Anthropometric indices such as weight, BMI and waist circumference decreased significantly in IG compared with placebo group; whilst in the current study, after adjusting for baseline values, only waist circumference was reduced significantly. Although changes in energy intake and physical activity between and within the 2 groups of study were not significant, but significant decrease in anthropometric indices in the IG can be justified by the inflammatory mechanism. The inflammatory mechanism indicates a direct relationship between inflammatory status and obesity [40]. Thus, in the IG, independent of the decrease in total energy intake, the significant increase of serum zinc levels led to a reduction of inflammation and consequently weight loss [41]. A meta-analysis showed no significant changes in anthropometric measures after zinc supplementation (ranged from 4 to 48 week, in different disease) in the overall analysis [42]. According to previous study, insufficient data about the effect of zinc supplementation on anthropometric indices in migraine patients has been reported [42], that needs to be evaluated in the future studies. Among possible mechanisms involved in weight loss following zinc supplementation can be mentioned the role of zinc in regulating appetite by altering the metabolism of hypothalamic neurotransmitters and increasing leptin secretion, inhibiting gene mutations leading to obesity, improving insulin sensitivity and reduction of inflammation [41,43-45].

The present study benefits from several strong features. Firstly, the effects of zinc supplementation with zinc gluconate on serum lipid profile and hs-CRP of migraine patients was examined in an RCT setting. Secondly, physical activity level and dietary intakes of participants were investigated during the current study, which enabled the probing of any changes in these variables. Beside, in this study, in addition to serum CRP levels, serum lipid

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profile levels of migraine patients as one of the cardiovascular risk factor was also evaluated, that in the previous studies have not evaluated. However, one of the limitations of present study was small sample size and the lack of evaluation of serum level of hs-CRP in during a migraine headache attack.

CONCLUSION

Present study showed that zinc supplementation has promising effects on migraine related complications like its frequency, severity and its impact on life quality (MIDAS) after 12 weeks, but after adjustment for baseline values, no significant effect on serum levels of lipid profile and hs-CRP was shown. Future trials with larger sample sizes, long term interventions which takes into account the evaluation of the serum levels of migraine-specific inflammatory factors such as TNF-α are needed to confirm the positive effect of zinc supplementation on inflammation level and lipid profile in migraine patients.

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