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Original Article

Associations between Dietary Acid Load and Migraine Headache Severity and Duration among Women: A Cross-Sectional Study

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Abstract

Background: Migraine is considered the most common cause of long-term disability in under-50s, which can lead to unbearable pain and neurological dysfunction. Many factors, especially dietary factors, are suggested to trigger migraine headaches. The present study aimed to examine the association between diet-dependent acid load and severity and duration of headaches among migraine patients.

Methods: In this cross-sectional study, a sample of 266 women (18-45 years) with history of migraine headaches was enrolled. Dietary data was collected by using a validated Food Frequency Questionnaire (FFQ). Then, diet-dependent acid load indices including Potential Renal Acid Load (PRAL) and Net Endogenous Acid Production (NEAP) were calculated for the participants. For all cases, anthropometric measurements and headache duration were assessed. Headache severity was determined by Visual Analog Scale (VAS) and Migraine Disability Assessment (MIDAS) questionnaires.

Results: In this study, individuals with higher PRAL (OR=1.87, 95% CI=1.19-2.96, p=0.007) and NEAP (OR=1.58, 95% CI=1.02-2.44, p=0.03) scores were 87 and 58%, respectively, more likely to have severe headaches. Moreover, our results showed a significant direct correlation between PRAL (β=0.14, 95% CI=0.56-2.94, p=0.04) and NEAP (β=0.18, 95% CI=0.45-3.34, p=0.01) scores and headache duration of participants.

Conclusion: The present study showed that higher diet-dependent acid load scores may be associated with higher headache severity and duration in migraine patients.

Keywords: Diet, Headache, Humans, Female Migraine disorders

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Introduction

Migraine is a common cerebral disease, characterized by a recurring type of headache, which could last up to 72 hours (1). It is often accompanied by nausea, vomiting, and sensitivity to light and sound. Though the exact underlying biological mechanism of migraine is still unknown, genetic and environmental factors have appeared to play a significant role. Migraine prevalence among adults is reported to be approximately 12%, which is the first common cause of disability in under-50s. It greatly affects the quality of life and is a huge economic burden (2-4). Therefore, finding the best approach to control and manage this disease is critical. Several medications have been introduced to alleviate the symptoms (5), and given that the major side effects may be created by these medications, proper dietary intervention could be a more reasonable approach towards migraine.

The right balance of acidic and basic compounds must be maintained to reach a proper body function (6). Diet and content of certain food components have a clear impact on acid-base balance. Sulfate and phosphorus as dietary factors contribute to acid load, whereas alkali load is associated with dietary intake of bicarbonate (7,8). In general, meat, cheese, and grain products are strongly acidic foods, while fruit, legumes, and vegetables are considered as alkalizing foods. It has been proposed that high dietary acid load may induce a low-grade metabolic acidosis which is related with the development of metabolic changes such as insulin resistance, diabetes, chronic kidney disease, bone disorders, and other complications (9-11); however, some studies have shown no deleterious effect (12-14). It has been suggested that no or average acid load may be the optimal state for humans (15). In recent studies, certain types of foods have been shown to trigger migraine. Processed foods, fast foods, fermented products, old cheese, coffee, chocolate, fish, beans, and citrus are some of the common dietary items, reported to be responsible for initiating migraine headaches (16). These foods are mostly acid-forming and high intake of them might shift the acid-base balance of the body towards more acidic conditions. Moreover, dietary acid load may lead to some conditions such as a rise in the blood pressure that are commonly regarded as precursors of migraine (11,17). Therefore, it could be assumed that the acidic load of the diet may have a role in initiating migraine headache. No study has been conducted till now to investigate the relationship between those two related factors. Therefore, this cross-sectional study was performed to examine the effect of dietary acid load on the intensity and duration of migraine headaches.

Materials and Methods

Participants

In this study, 266 pre-menopausal women aged 18-45 with history of episodic migraine headaches were recruited. The participants in the present cross-sectional study were selected from neurology clinics of Khatam Alanbia and Sina hospitals in Tehran, Iran in 2016. The patients were selected based on pre-determined inclusion and exclusion criteria. To be included in the study, women with migraine and the following criteria were the final candidates: (1) a neurologist's diagnosis of migraine according to the criteria of International Classification of Headache Disorders, 3rd edition (ICHD-3); (2) visiting the headache clinics of hospitals for the first time; and (3) the consent to participate in the research. Patients were excluded from the study if they were on specific diets, pregnant or lactating, had a Body Mass Index (BMI) lower than 18.5, or were diagnosed as under-reporters (≤800 *kcal/day*) or over-reporters (≥4,200 *kcal/day*) of energy intake (No: 28). Moreover, subjects were excluded if they experienced migraine headaches along with other chronic diseases such as diabetes, cancer, hepatitis, CVD, *etc*. due to the side effect of their disease-specific medications on migraine headaches. The study protocol was approved by the local ethics committee of Tehran University of Medical Sciences, and informed written consent was obtained from all participants.

Assessment of dietary intake and dietary acid load

Usual dietary intake was evaluated by using a 147-item semi-quantitative Food Frequency Questionnaire (FFQ) with acceptable reliability and validity (18). Participants were asked by dietitians during a face-to-face interview to report their consumption frequency for each food item over the past year on a daily, weekly, or monthly basis. Household measures were used to change portion sizes to weight in grams. Due to limited data on the nutrient content of some foods and beverages of Iranian Food Composition Table (FCT),

the US Department of Agriculture (USDA) FCT was applied to compute nutrient and energy content of dietary intake. Nutrient intakes in micro and macro levels were calculated using Nutritionist IV software (Hearst Corporation, USA) modified for Iranian foods. Data collected from dietary intake was used to compute dietary acid load. The dietary acid load score was determined by 2 measures of PRAL and NEAP. The PRAL score was computed according to some nutrient intakes using the following formula proposed by Remer *et al* (19): PRAL (*mEq/d*) =0.4888× protein (*g/d*) +0.0366× P (*mg/d*) −0.0205× K (*mg/d*) −0.0125×Ca (*mg/d*) −0. (*mg/d*). The latter one, NEAP score was based on the following algorithm outlined by Frassetto *et al* (20): NEAP (*mEq/d*) = 54.5×[protein intake (*g/d*) /K intake (*mEq/d*)]−10.2.

MIDAS and Visual Analog Scale (VAS) questionnaires

In the present study, a professional neurologist diagnosed episodic migraine according to ICHD-3 criteria (21). To evaluate headache-related disability, the Migraine Disability Assessment (MIDAS) questionnaire was applied. Reliability and validity of the MIDAS questionnaire were assessed in Iranian population (22). Participants answered five questions, about the number of days over the past 3 months in which their performance was limited because of migraine. Then, headache sufferers, based on their overall scores, were divided into 4 levels of grade I (0-5, little or no disability), grade II (6-10, mild disability), grade III (11–20, moderate disability), and grade IV (More than 20, severe disability) (23).

Moreover, assessment of headache pain was done by Visual Analog Scale (VAS) questionnaire. The VAS is comprised of a 10 *cm* horizontal line characterized with the word descriptors at the left end (No pain) and at the right end (Severe pain). Migraine patients mark on the line to show their level of pain. Cut-off points of pain score have been proposed in previous studies; the scoring scale ranged from 1 to 10 and pain categories in three groups included mild pain (1-3), moderate pain (4-7), and severe pain (8-10) (24).

Assessment of other variables

Weight was measured to the nearest 0.1 *kg* by a digital scale (SECA, Germany), while wearing one layer of clothing and no shoes. Height was recorded to the nearest 0.5 *cm* by a wall-mounted stadiometer whereas the shoulders were relaxed and shoes were removed. Body Mass Index (BMI) was calculated based on the equation of "weight (*kg*)/height^2 (m^2)". To acquire demographic characteristics, a questionnaire was given to all participants which contained questions regarding age, family history of migraine, marital status, specific diets, education level, chronic disease background, occupation, and medicine consumption.

A 30-day headache record list was given to all subjects to obtain headache duration, headache attack onset, and headache severity score based on VAS (Scores range from 0 to 10) after each migraine attack. If subjects encountered any problems, there was an experienced neurologist who would give instructions to participants and answer their questions. International Physical Activity Questionnaire (IPAQ) was used to acquire data on Physical Activity (PA), which was shown as metabolic equivalent hours per week (METs h/week). Activity levels were classified into low, moderate, and high categories, as described by the IPAQ scoring protocol (25).

Statistical analyses

Quantitative variables were expressed as mean± SD and qualitative variables were shown as numbers and percentages. The association between qualitative variables and PRAL and NEAP quartiles was evaluated with the chi-square test. The relationship between quantitative variables and PRAL and NEAP quartiles was determined by one-way analysis of variance (ANOVA). The dietary intakes of participants were compared using analysis of covariance (ANCOVA), and then were adjusted for the confounding factors, including age, PA, BMI, and energy intake among PRAL and NEAP quartiles. Confounding factors were determined from a best-fit model and those variables with higher Likelihood Ratio Test (LRT) scores were chosen. The Multinomial Logistic Regression (MLR) model was applied to assess the connection between PRAL and NEAP quartiles and headache severity and disability in crude and adjusted models. In this model, as dependent variables, VAS tertiles and MIDAS quartiles were used, and as covariates, quartiles of PRAL and NEAP were applied in MLR model. After that, to evaluate the adjusted odds ratio, confounding

factors were adjusted in MLR model. For determining the association between duration of each headache attack over the last month (Dependent variable) and the quartiles of PRAL and NEAP (Independent variables), linear regression analysis was applied, and then adjusted for confounding factors. To perform statistical analysis, SPSS statistics version 22.0 (IBM Inc., USA) was exploited and $p<0.05$ was considered as the level of statistical significance.

Results

Study population characteristics

The characteristics of 266 migraine patients were analyzed in this study. The mean (±SD) age, BMI, height, body weight, and physical activity of participants were 34.3 (7.8) years, 26.5 (4.8) *kg/m²*, 161.8 (5.1) *cm*, 69.4 (13.0) *kg*, 407.7 (519.1) MET/Min/week, respectively. The percentage of healthy weight (BMI of 18.5-24.9), overweight (BMI 25-29.9) and obesity (BMI ≥30) were 47.8, 29.3 and 22.9, respectively. Based on the self-report of our participants, 181 individuals (68.04%) of total participants had reported that some dietary items could increase their headache severity. Among them, 152 individuals (83.97%) eliminated these dietary items from their diet. Based on VAS questionnaire, the number (%) of severe, moderate, and mild pain were 114 (42.9), 115 (43.2), and 37 (13.9), respectively. Moreover, according to MIDAS questionnaire, the number (%) of cases with severe, moderate, mild, and without disability were 118 (44.4), 46 (17.3), 66 (24.8) and 36 (13.65), respectively. The mean (Range) duration of each headache attack over the previous month was 10.57 (0.5-72) hours.

Quantitative and qualitative variables and PRAL and NEAP quartiles

The general characteristics of the participants among quartiles of PRAL and NEAP are presented in table 1. Quantitative and qualitative variables across PRAL and NEAP quartiles did not indicate any significant differences among participants. However, mean duration of headache had a statistically significant difference across PRAL and NEAP quartiles ($p<0.05$), with the ascending trend from the lowest to highest quartiles.

Diet-dependent acid load and dietary intake

Food and nutrient intake of the study population among PRAL and NEAP quartiles is provided in table 2. Both diet-dependent acid loads (*i.e.*, PRAL and NEAP) were positively associated with total energy intake, carbohydrate, protein, fat, phosphorus, and sodium ($p<0.001$), and inversely were associated with potassium, calcium, and magnesium levels ($p<0.001$). With respect to some food groups, a diet with higher acid load significantly has more refined grain, red meat, and dairy ($p<0.001$), while a diet with lower acid load has more vegetables and fruits ($p<0.001$). However, legumes and nuts were not related with PRAL ($p=0.23$) and NEAP ($p=0.99$).

Diet-dependent acid load and migraine headache

The association between severity, disability, and duration of headaches in migraine patients and diet-dependent acid load quartiles in crude and adjusted model is shown in table 3. Multinomial logistic regression in the crude model showed that despite lower quartiles, individuals in the highest quartile of PRAL (OR=2.11, 95% CI=1.48-2.99, $p<0.001$) and NEAP (OR=1.72, 95% CI=1.23-2.40, $p=0.001$) were more likely to have severe headaches (Based on VAS). In adjusted model, subjects in the highest quartile of RPAL (OR=1.87, 95% CI=1.19-2.96, $p=0.007$) and NEAP (OR=1.58, 95% CI=1.02-2.44, $p=0.03$) compared with those in the lowest quartile were more likely to have severe headaches.

However, no statistically significant correlation was found between odds of severe disability (Based on MIDAS) and PRAL (OR=1.34, 95% CI=0.95-1.91, $p=0.09$) and NEAP score (OR=1.16, 95% CI=0.82-1.64, $p=0.39$) in crude model, or even after adjusting confounders.

Linear regression analysis in crude model showed a statistically significant direct correlation between duration of each headache attack and quartiles of PRAL ($\beta=0.21$, 95% CI=0.99-3.46, $p<0.001$) and NEAP ($\beta=0.22$, 95% CI=1.10-3.56, $p<0.001$). Even after adjusting for potential confounders, PRAL ($\beta=0.14$, 95% CI=0.56–2.94, $p=0.04$) and NEAP scores ($\beta=0.18$, 95% CI=0.45-3.34, $p=0.01$) indicated a significant positive correlation with headache duration.

Discussion

To the best of our knowledge, the present study is

Table 1. General characteristics of study population among quartiles (Q) of PRAL and NEAP

	PRAL				
	Q1 (n=66)	Q2 (n=66)	Q3 (n=68)	Q4 (n=66)	*p-value
PRAL, *mEq/day*					
Range	<-37.48	-37.48 to -13.2	-13.2 to 2.89	>2.89	
Mean± SD	-67.29±24.2	-25.61±8.04	-4.66±4.92	11.22±8.04	
Quantitative variables					
Age (years)	34.7±7.78	35.42 ±7.78	34.32 ±7.53	32.82 ±8.28	0.276
Height (*cm*)	161±5.24	161.88±5.72	161.96±4.73	162.64±4.8	0.337
Weight (*kg*)	70.97±12.27	69.1±11.19	71.09±15.07	66.42±12.91	0.132
BMI (kg/m^2)	27.35±4.46	26.43±4.45	27.11±5.76	25.07±4.47	0.059
PA (MET-*h/wk*)	454.21±438.6	485.9±472.79	365.27±686.06	326.82±425.09	0.251
Headache duration (hour)	7.75±4.41	9.79±13.47	11.07±11.76	13.23±13.87	0.190
Qualitative variables					
Current smoker					
Yes	3(23.1)	5(38.5)	4(30.8)	1(7.7)	0.423
No	63(24.9)	61(24.1)	64(25.3)	65(25.7)	
Education					
Undergraduate	26(25)	29(27.9)	31(29.8)	18(17.3)	0.143
Bachelor	30(29.4)	23(22.5)	22(21.6)	27(26.5)	
Master	10(16.7)	14(23.3)	15(25)	21(35)	
Marital					
Married	50(26.6)	48(25.5)	47(25)	43(22.9)	0.723
Single	15(20.3)	18(24.3)	20(27)	21(28.4)	
Divorced	1(25)	0(0)	1(25)	2(50)	
	NEAP				
	Q1 (n=66)	Q2 (n=67)	Q3 (n=67)	Q4 (n=66)	*p-value
NEAP, mEq/day					
Range	<22.87	22.87 to 35.41	35.41 to 44.27	>44.27	
Mean± SD	18.07±3.2	28.51±3.77	39.52±2.65	51.13±7.66	
Quantitative variables					
Age (years)	34.2±8.17	36.43±7.34	33.34±7.01	33.27±8.58	0.093
Height (*cm*)	161.42±5.56	161.39±5.26	161.99±4.86	162.68±4.84	0.462
Weight (*kg*)	70.48±12.53	70.22±11.68	69.58±14.54	67.34±13.22	0.508
BMI (kg/m^2)	27.03±4.54	27.02±4.63	26.53±5.59	25.4±4.6	0.220
PA (MET-*h/wk*)	464.97±420.69	437.92±447.82	316.26±393.91	412.70±740.01	0.351
Headache duration (hour)	7.12±4.44	9.26±12.23	11.2±12.02	14.28±14.32	0.010
Qualitative variables					
Current smoker					
Yes	4(30.8)	4(30.8)	4(30.8)	1(7.7)	0.541
No	62(24.5)	63(24.9)	63(24.9)	65(25.7)	
Education					
Undergraduate	28(26.9)	24(23.1)	32(30.8)	20(19.2)	0.116
Bachelor	28(27.5)	30(29.4)	18(28.3)	26(25.5)	
Master	10(16.7)	13(21.7)	17(28.3)	20(33.3)	
Marital					
Married	47(25)	51(27.1)	47(25)	43(22.9)	0.741
Single	18(24.3)	15(20.3)	20(27)	21(28.4)	
Divorced	1(25)	1(25)	0(0)	2(50)	

BMI, body mass index; NEAP, net endogenous acid production; PA, physical activity; PRAL, potential renal acid load.
Quantitative variables (age, height, weight, BMI, PA, Headache duration) reported as Mean± SD.
Qualitative variables (current smoker, education and marital) reported as number (%).
* Chi-square test and ANOVA were applied for qualitative and quantitative variables, respectively.

Table 2. Dietary intake of study population among quartiles (Q) of PRAL and NEAP

	PRAL				
	Q1 (n=66)	Q2 (n=66)	Q3 (n=68)	Q4 (n=66)	*p-value
Nutrient intake					
Energy[a] (*kcal/d*)	1875.84±403.78	2026.13±436.91	2504.86±516.53	2524.53±363.35	<0.001[a]
Carbohydrate (*g/d*)	268.83±67.02	265.84±56.5	313.78±71.09	322.78±58.43	<0.001
Protein (*g/d*)	77.09±19.63	73.49±14.68	80.42±13.58	86.4±12.48	<0.001
Fat (*g/d*)	64.79±13.76	80.6±29.6	108.29±31.1	103.33±23.93	<0.001
Phosphorus (*mg/d*)	1404.17±350.11	1306.74±270.61	1430.1±303.5	1435.22±299.24	<0.001
Potassium (*mg/d*)	5730.28±1505.7	3957.6±680.78	3466.4±627.94	3036.76±616.37	<0.001
Calcium (*mg/d*)	1820.3±495.14	1232.86±270.52	1082.84±273.47	928.57±235.98	<0.001
Magnesium (*mg/d*)	471.71±144.19	385.22±90.1	380.2±112.57	361.22±76.86	<0.001
Sodium (*mg/d*)	3478.52±588.39	3575.02±649.66	3964.42±841.33	3973.89±926.74	<0.001
Food intake					
Vegetables (*g/d*)	375.76±103.21	256.7±82.2	175.93±77.9	146.51±76.32	<0.001
Fruits (*g/d*)	289.73±199	198.04±159.49	131.76±87.99	120.14±71.2	<0.001
Dairy (*g/d*)	258.1±73.35	248.94±104.05	303.54±105.97	303.11±112.99	<0.001
Legumes and nut (*g/d*)	70.53±43.05	49.79±41.6	55.95±39.32	63.65±50.52	0.231
Refined grain (*g/d*)	187.91±73.99	288.43±123.45	380.72±173.34	410.09±145.82	<0.001
Red meat (*g/d*)	7.95±5.86	22.12±30.03	17.55±14.93	22.63±13.21	<0.001
	NEAP				
	Q1 (n=66)	Q2 (n=67)	Q3 (n=67)	Q4 (n=66)	*p-value
Nutrient intake					
Energy[a] (*kcal/d*)	1804.8±367.35	2156.32±440.39	2417.73±560.11	2543.49±354.21	<0.001[a]
Carbohydrate (*g/d*)	258.48±59.07	286.79±65.18	306.7±74.61	318.15±59.08	<0.001
Protein (*g/d*)	73.04±18.07	75.61±17.65	83.29±10.33	85.23±13.52	<0.001
Fat (*g/d*)	62.95±13.83	85.15±27.04	100.83±33.72	107.7±24.64	<0.001
Phosphorus (*mg/d*)	1333.59±305.3	1374.85±341.62	1463.51±262.33	1400.58±316.41	<0.001
Potassium (*mg/d*)	5526.39±1550.3	4111.62±1044.1	3594.27±511.71	2969.99±633.53	<0.001
Calcium (*mg/d*)	1750.77±533.72	1254.7±352.29	1139.2±266.3	926.53±248.21	<0.001
Magnesium (*mg/d*)	447.12±138.68	408.84±117.39	392.38±103.89	349.36±76.68	<0.001
Sodium (*mg/d*)	3340.07±556.32	3506.44±604.41	4085±739.17	4048.89±942.62	<0.001
Food intake					
Vegetables (*g/d*)	377.19±102.26	261.98±83.96	185.29±68.39	131.99±69.82	<0.001
Fruits (*g/d*)	290.64±192.99	206±164.65	128.19±76.53	114.28±74.6	<0.001
Dairy (*g/d*)	256.24±68.49	257.76±119.64	295.88±90.66	303.95±116.04	<0.001
Legumes and nut (*g/d*)	61.57±37.27	61.55±47.32	57.87±48.35	58.36±43.73	0.999
Refined grain (*g/d*)	181.11±70.18	303.47±139.47	361.26±163.96	419.46±141.44	<0.001
Red meat (*g/d*)	7.7±6.21	15.07±21.09	23.97±25.59	23.25±12.02	<0.001

* Based on ANCOVA, adjusted for confounders.
[a] Adjusted for confounders except total energy.
Mean ± SD (all such values).

Table 3. Association of headache severity, disability, and duration with PRAL and NEAP scores

PRAL						
	Crude models		p-value	Adjusted models		p-value
	OR	(0.95% CI)		OR	(0.95% CI)	
VAS						
Mild pain∞	-	-	-	-	-	-
Moderate pain	1.53	(1.08-2.16)	0.010	1.25	(0.81-1.93)	0.311
Sever pain	2.11	(1.48-2.99)	<0.001	1.87	(1.19-2.96)	0.007
MIDAS						
Without disability∞	-	-	-	-	-	-
Mild disability	1.17	(0.80-1.70)	0.407	1.15	(0.72-1.85)	0.542
Moderate disability	1.30	(0.86-1.95)	0.201	1.42	(0.84-2.42)	0.182
Severe disability	1.34	(0.95-1.91)	0.097	1.44	(0.89-2.33)	0.137
Each attack mean duration	*0.21	(0.99-3.46)	<0.001	*0.14	(0.56-2.94)	0.041
NEAP						
	Crude models		p-value	Adjusted models		p-value
	OR	(0.95% CI)		OR	(0.95% CI)	
VAS						
Mild pain∞	-	-	-	-	-	-
Moderate pain	1.36	(0.97-1.90)	0.061	1.09	(0.72-1.64)	0.671
Sever pain	1.72	(1.23 -2.40)	0.001	1.58	(1.02-2.44)	0.036
MIDAS						
Without disability∞	-	-	-	-	-	-
Mild disability	1.19	(0.82-1.73)	0.343	1.23	(0.77-1.95)	0.371
Moderate disability	1.19	(0.79-1.79)	0.384	1.41	(0.84-2.38)	0.184
Severe disability	1.16	(0.82-1.64)	0.391	1.34	(0.84-2.15)	0.212
Each attack mean duration	*0.22	(1.10-3.56)	<0.001	*0.18	(0.45-3.34)	0.010

MIDAS, Migraine Disability Assessment Questionnaire; NEAP, net endogenous acid production; PRAL, potential renal acid load; VAS, Visual analog scale.
* The β coefficient has been shown.
∞ Considered as reference group.

the first to examine the relationship between the acid load of the habitual diet of adult individuals with duration and intensity of migraine headaches. The main analyses showed that higher dietary acid load is associated with higher headache intensity and duration among migraine patients. To be more specific, dietary acid load, expressed as PRAL and NEAP, was related with higher VAS scores and headache duration. Nevertheless, there was no significant relation between MIDAS scores and any measurements of the diet-dependent acid load.

There are possible mechanisms through which the hypothesis of the effect of metabolic acidosis on migraine is formed. Migraine is believed to be a neurovascular disorder induced through a set of actions starting within the brain and then spreading to the blood vessels (26). Thus, changes in brain excitability could be the main trigger of the disease. Acid-Sensing Ion Channels (ASICs) are a family of ion channels, expressed throughout the nervous system and are sensitive to different ranges of pH (27) and ASIC1 is the most prominent and the most highly expressed of all the ASICs which is activated in acidic condition (28). ASIC1 has been speculated to contribute to epilepsy (29). Several studies have also revealed that ASICs within CNS sites can come up with pain signaling. It has also been shown that blockade of these channels is related to attenuated pain behaviors in rats (30).

Several studies suggest a positive association between hypertension and migraine (17,31,32). In a study by Barton and Sibai, it was demonstrated that neurologic signs and symptoms such as persistent headaches are common in women with pre-eclampsia and eclampsia (33). Malignant hypertension, through imposing

pressure on cranium, could cause severe headaches. In addition, it was shown in a study by Mirzababaei *et al* that adherence to the DASH diet, which is the main approach to control blood pressure, is connected with lower headache severity and duration in migraine patients (34). Several studies have also found a link between dietary acid load and hypertension (35,36). It appears that a high dietary acid load may lead to an increased renal excretion which gradually induces negative effect on the renal function that could ultimately raise blood pressure (37,38). Increased calcium excretion is another outcome of high acid load that might culminate in high blood pressure (39,40). Nevertheless, it should be noted that the current data regarding the association of hypertension and migraine is inconclusive as several studies failed to support an association between the two (41). As it was stated by Secil *et al*, since both migraine and hypertension are prevalent in general population, the fact that a person is suffering from both diseases could be merely due to coincidence (42).

Studies have shown that migraineurs have low levels of brain magnesium during migraine attacks and may also have a magnesium deficiency (43,44). Furthermore, it was demonstrated that menstrual migraine could be due to magnesium deficiency (45). Two clinical trial studies have revealed that oral magnesium supplementation could have a major role in attenuating headaches (46,47). One study did not show any significant difference, but this result has been attributed to the use of a poorly absorbed magnesium salt (48). Under acidic conditions, the human buffer system tries to compensate for acidosis by excreting some elements such as magnesium and calcium. In an animal study, it was confirmed that systemic acid-base balance regulates the expression of proteins that have a role in reabsorbing magnesium (49). The similar results have been achieved by Rylander *et al* in a study conducted on adult population (50).

According to numerous studies, it appears that stress could be a prominent contributor to migraine. Since cortisol is consistently produced and secreted by the adrenal gland in response to stress, it is believed that this hormone may be involved in the pathogenesis of migraine. As it was shown in a clinical trial study by Peres *et al*, cortisol concentration was significantly high in migraine patients in comparison with the control group (51). There is much evidence that confirms chronic metabolic acidosis is associated with increased glucocorticoid production. Maurer *et al* have shown that the urinary level of cortisol was higher in the people having a sodium- and potassium chloride- rich regimen compared to the one with potassium bicarbonate (52). Also, in a study conducted on healthy children, it was revealed that even moderate elevations in diet-dependent acid loads will influence cortisol secretion (53). However, the role of stress as a trigger of migraine has been questioned recently as several studies have found no relation between the two (54,55), and some others contrarily reported that migraine headaches give rise to stress hormones as the level of cortisol was significantly higher in the control groups only after the onset of attacks (56).

There are certain limitations in our study which are worth considering. The main one might be the number of enlisted subjects that was relatively low. The cross-sectional design of the study is another important limitation as it prevented us from drawing causal inferences. In some epidemiological studies of migraine, significant sex and age differences have been shown (57,58) while in this study, only premenopausal women were recruited. It seems that better insight could be obtained by investigating the variable of sex if men were recruited as the subjects. One of the inevitable limitations of this type of study is that questionnaire responses are subjectively based on participants' memory and their perception of pain.

Conclusion

While it was found that a diet with higher acid load was statistically associated with a higher risk of migraine headaches, the diet acid load seems not to be a major trigger for migraines due to multiple comparisons, the small effect size, and many environmental and genetics confounders. Therefore, further prospective studies are necessary to confirm these initial findings in order to support the relationship between diet-dependent acid load and migraine.

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Conflict of Interest

The authors report no conflict of interest.

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