24-h Urinary Sodium and Potassium and Their Association with Clinical Features of Migraine Headache

Arman Arab
Isfahan University of Medical Sciences
Fariborz Khorvash
Isfahan University of Medical Sciences
Zahra Heidari
Isfahan University of Medical Sciences
Gholamreza Askari (✉ askari@mui.ac.ir)
Isfahan university of sciences https://orcid.org/0000-0003-1194-9687

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Abstract

Aim: There is a paucity of evidence regarding the association between sodium and potassium with migraine. To explore the possible relationship between 24-h urinary sodium and potassium with clinical features of migraine patients, we conducted a cross-sectional study using a sample of the Iranian population.

Methods: In this cross-sectional study, 262 participants aged 20-50 years, with a diagnosis of migraine were included. One 24-h urine sample was collected by each subject to estimate sodium and potassium intake. Clinical features of migraine including frequency, duration, severity, migraine headache index score (MHIS), and headache impact test (HIT) were assessed. The serum nitric oxide values were assessed using the Griess method. Multiple linear regression analysis was used and beta (β) and 95% corresponding confidence interval (CI) were reported.

Results: The 24-h urinary sodium was significantly associated with frequency (Model 3: β=1.86, 95%CI (0.10, 3.62); P=0.038), duration (Model 2: β=0.38, 95%CI (0.11, 0.66); P=0.006) and MHIS (Model 3: β=0.19, 95%CI (0.01, 0.37); P=0.034). Also, there was a significant association between Na/K ratio and MHIS (Model 2: β=0.16, 95%CI (0.003, 0.33); P=0.045). There was no significant relationship between 24-h urinary potassium and any of the intended variables (all P values <0.05).

Conclusion: Our findings suggest that reducing sodium intake and increasing potassium intake could be used as a useful and novel approach to improve clinical findings of migraine and associated burden of disease. Additional studies are needed to replicate these findings and to discover mechanisms that mediate the association between sodium and potassium intake with migraine headache.

1. Introduction

Migraine is a pertinent public health concern due to its link with increasing disability, affecting 18% of females and 6% of males [1]. It was ranked as the second cause of disability worldwide among 20–50 years old males and females [2]. Migraine is defined as recurrent episodes of headache and related symptoms (e.g. nausea, vomiting, photophobia, and phonophobia) which last for 4–72 hours [3]. It is a complicated neurovascular disorder that involves multiple cortical, subcortical, and brainstem areas of the brain, but its exact pathophysiology is not fully understood [1].

Of the ionic constituents that directly contribute to neuronal excitability, the evidence is accumulating that sodium and to some extent, potassium homeostasis plays an important role in migraine pathophysiology [4–7]. Sodium levels in cerebrospinal fluid have also been shown to increase during migraine attacks [5]. Another interesting point is the increase in nitric oxide (NO) secretion in response to increased sodium intake [8]. Nitric oxide not only stimulates migraine attacks but also affects the duration of migraine headaches [9]. These findings collectively point to a sodium and potassium disturbance in migraine.

Only one study looked at the link between sodium intake and migraine [10]. An absence of a standard method for assessment of sodium intake, failure to use a precise diagnostic criterion for migraine, and the use of a 24-hour recall to examine food intake are some of the limitations of this study. Considering the lack of evidence regarding the association between sodium and potassium with migraine, the current study has conducted among the Iranian population using 24-hour urine collections as the gold standard method. Therefore, in the present cross-sectional study, the hypothesis was tested that 24-hour urinary sodium, potassium, and the Na/K ratio would be associated with clinical features of migraine, quality of life, and serum NO levels.

2. Methods And Materials

2.1. Study design and population

In this cross-sectional study, 265 patients diagnosed with migraine were recruited. From August 2019 to June 2020, we consecutively evaluated patients with a suspect of migraine in the Imam Moosa Sadr neurology clinic and Khurshid neurology clinic, both affiliated with Isfahan University of Medical Sciences, Isfahan, Iran. Using a simple random sampling method, participants were selected. Patients were included if they met the following criteria: individuals (20–50 years old) with a diagnosis of migraine by a neurologist (F.K) based on the International Classification of Headache Disorders 3 (ICHD3) criteria [11]; visiting the neurology clinic for the first time, and; body mass index (BMI) of 18.5–30. Participants with a history of cardiovascular disease, hypertension, diabetes, cancer, hepatic, renal or thyroid disease, and other neurological disorders were excluded due to possible disease-related changes in diet, along with those who were taking nutritional and herbal supplements including riboflavin, magnesium, coenzyme Q10, and feverfew. Patients with reported daily energy intakes lower than 800 kcal/d (3347 kJ/d) or higher than 4200 kcal/d (17573 kJ/d), were also excluded [12]. All participants provided written informed consent forms. From 298 invited participants, 262 of them completed the study (response rate 87%). The study protocol was approved by the research ethics committee of Isfahan University of Medical Sciences (IR.MUI.RESEARCH.REC.1398.352) on 3 November 2019.

2.2. 24-h urine collection

24-h urine collection containers were distributed among patients, along with verbal and written instructions on how to complete the procedure. It was highlighted that no alteration in dietary habits during the day of collection was allowed. 24-h sampling was done over the weekends from Friday to Saturday during a 24-h period. Each individual was provided with a polypropylene container (2.5 liters) used for the collection of the 24-h urine samples. A single 24-h urine collection was obtained with the first voided urine on waking on Friday morning being discarded and participants then collecting all voided urine up to and including the first void of the Saturday morning. All patients were asked to keep the containers in dry and cool places and samples were transferred immediately to the laboratory on Saturday for analysis to prevent microbial degradation. Sodium and potassium were assessed using the ion-selective electrode method (ProLyte Electrolyte Analyzer) and urine creatinine (Cr) was measured by

the Jaffe reaction method (BT 3000) [13]. Suspected inaccurate urine collections were defined as urinary creatinine < 6 mmol/day for men, or < 4 mmol/day for women, or a 24-h urine volume < 500 mL which were excluded [14]. For each individual, the 24-h sodium and potassium excretion value (mmol/day) was calculated as the concentration of sodium and potassium in the urine (mmol/L) multiplied by the urinary volume (L/day). The conversion from mmol to mg was made by multiplying by 23 for sodium and 39 for potassium, and the conversion from mg of sodium to salt by multiplying by 2.542 [14].

2.3. Dietary assessment

The dietary intake of participants over the past year was assessed using a semi-quantitative food frequency questionnaire (FFQ). This questionnaire included a list of 168 food items, along with a standard serving size for each, and its reliability and validity had been approved previously among the Iranian population [15–17]. The patients were asked to report the consumption frequency of a given serving of each food item on a daily, weekly, or monthly basis. All of the consumed foods portion sizes were transformed into grams using household measures [18]. FFQ was completed by a trained dietitian through face to face interview and data were analyzed by Nutritionist IV software (First Databank, Hearst Corp, San Bruno, CA, USA).

2.4. Anthropometric measurements

Bodyweight was measured to the nearest 100 g using a digital scale (Omron BF511 (Omron Corp, Kyoto, Japan)), while the subjects were clothed minimally (i.e. no belts, sweaters, or jackets) and not wearing shoes. Height was measured using an upstretched tape to the nearest 1 mm, while the subject was in a standing position without shoes, and the shoulders were relaxed. BMI was calculated from the height in m^2 and weight in kg, using the “weight (kg)/height^2 (m^2)” equation.

2.5. Assessments of migraine clinical features

Headache diaries regarding the clinical features of migraine during the previous month were obtained from all of the participants. A 30-day headache diary was given to all participants, along with verbal and written instructions on how to complete the procedure. Clinical features of migraine including the time of migraine attack onset, duration, and severity scores (ranged from 0–10 based on a visual analog scale (VAS)) had to be recorded accurately after each migraine attack no matter what time of day. If the patients had any difficulties in filling their diaries, there was a contact person (A.A) who would answer their questions via phone calls or text messages. The participants were asked to complete their headache diaries during the upcoming month [19]. The VAS questionnaire was used to assess the severity of headache [20]. Based on this scale, the headache severity is ranked from 0 to 10, with “0” indicating no pain and “10” the worst imaginable pain. The participants denote on the point that they feel represents their perception of their current pain. The frequency was defined as the number of attacks per month. The mean duration of headache attacks in hour was considered as the duration. Furthermore, migraine headache index score (MHIS) calculated using “frequency × duration × severity” equation [21].

The headache impact test (HIT-6) was used to evaluate the impact of headaches on the patients' quality of life. The HIT-6 is a validated questionnaire [22] containing 6 questions with 5 options for each including never (scored as 6), rarely (8), sometimes (10), very often (11), and always (13), with a total possible score of 36–78. The scores of 36–49, 50–55, 56–59, and ≥ 60 indicate that headache has no, moderate, substantial, and severe impact on the quality of life of the participants [23].

2.6. Assessment of other variables

Additional information was collected by researchers using a demographic questionnaire, which contains questions about age, gender, marital status, number of family members, family history of migraine, time since diagnosis of migraine, and drug consumption.

Physical activity (PA) status was assessed via International Physical Activity Questionnaire (IPAQ), a self-administered, 7-day recall instrument, which its validity and reliability had been approved previously among the Iranian population [24]. PA levels were stated as metabolic equivalent hours per day (METs h/day).

Fasting Blood samples (10 ml) were centrifuged (Avanti J-25, Beckman, Brea, CA, USA) at 3500 rpm for 10 min to separate serum immediately after collection and were then maintained at − 80 °C for further analyses. The serum nitric oxide (NO) values were assessed using the Griess method via commercial kits (Kiazist Life Sciences, Iran).

2.7. Statistical Analyses

A suggested formula for estimating mean was used to compute the sample size. Based on α = 0.05, $\hat{\sigma}$ = 0.9, and d = 0.1 based on sodium level in patients with migraine, we reached to 260 subjects [25]. Continuous and categorical variables were presented as mean ± standard error (SE) and number (percentage), respectively. The characteristics distribution of the study population was compared by gender using independent t-test or Chi-square test as appropriate. Analysis of variance (ANOVA) was used for comparing clinical features of migraine headache across quartiles (Q) of 24-hour urinary sodium, potassium, and Na/K ratio. To assess relationships between the 24-hour urinary sodium, potassium, and Na/K ratio with clinical features of migraine headache, multiple linear regression analysis was performed in different models. Adjusted Beta (β)s with 95% confidence interval (CI) are presented in 2 different models. First, we adjusted for age, sex, marital status, smoking status, migraine type, migraine characteristic, family history, mean arterial pressure, and physical activity. In the last model, further adjustments were made for BMI and energy intake. Data analyses were performed using Statistical Package for Social Sciences (SPSS) version 21 (IBM Corp, Armonk, NY, USA). P-values < 0.05 were considered statistically significant.

3. Result

Of 265 participants who started the 24-h urine collection, some samples were excluded (n = 3) due to incompleteness of 24-h collection. Thus, 262 patients had complete valid urinary samples and were included in the final analysis.

Table 1 shows the demographic characteristics of participants and data on urinary excretion, migraine characteristics, and medication stratified by gender. Overall, 224 women and 38 men make up our study population. As can be seen, significant differences were found in terms of weight, height, physical activity, creatinine excretion, urinary salt, systolic blood pressure, smoking status, family history of migraine, and some medications (gabapentin) across men and women (all P values < 0.05).

Table 1
Characteristics of study population stratified by gender

Variables	Men (n = 38)	Women (n = 224)	P-values
Age (years)	35.18 ± 1.36	36.25 ± 0.57	0.479[1]
Weight (kg)	78 ± 2.03	66.09 ± 0.62	< 0.001[1]
Height (cm)	174.01 ± 1.06	160.96 ± 0.41	< 0.001[1]
BMI (kg/m^2)	25.73 ± 0.59	25.52 ± 0.22	0.731[1]
Physical activity (MET/h/day)	20.06 ± 6.98	6.98 ± 0.86	0.025[1]
Cr excretion (mmol/day)	12.40 ± 0.72	8.45 ± 0.18	< 0.001[1]
Urine output (l/day)	1.18 ± 0.10	1.14 ± 0.04	0.666[1]
Urinary salt (mg/day)	9083.72 ± 476.13	7941.78 ± 171.88	0.014[1]
SBP (mmHg)	117.39 ± 1.08	113.03 ± 0.87	0.032[1]
DBP (mmHg)	77.34 ± 1.43	75.53 ± 0.74	0.180[1]
Marital status	28 (10.7)	184 (70.2)	0.220[2]
Married	10 (3.8)	40 (15.3)	
Single			
Smoking	11 (4.2)	4 (1.5)	< 0.001[2]
Yes	27 (10.3)	220 (84)	
No			
Number of family members	3.47 ± 0.14	3.40 ± 0.06	0.699[1]
Migraine in first-degree relatives	17 (6.5)	150 (57.3)	0.008[2]
Yes	21 (8)	74 (28.2)	
No			

Data are presented as mean ± standard error or number (percent)

[1]Calculated by Independent-Samples T test

[2]Calculated by Chi-square test.

BMI: Body mass index, SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; TCA: Tricyclic Antidepressants; TeCA: Tetracyclic Antidepressant; SNRI: Serotonin-Norepinephrine Reuptake Inhibitor

Variables	Men (n = 38)	Women (n = 224)	P-values
Time since migraine diagnosis (years)	5.80 ± 1.13	7.59 ± 0.59	0.241[2]
Migraine type	31 (11.8)	70.6 (185)	0.880[2]
Episodic	7 (2.7)	39 (14.9)	
Chronic			
Migraine characteristic	5 (13 (5)	96 (36.6)	0.317[2]
with aura	25 (9.5)	128 (48.9)	
without aura			
Medication			
Beta-blockers	19 (7.3)	89 (34)	0.234[2]
Yes	19 (7.3)	135 (51.5)	
No			
Topiramate	4 (1.5)	9 (3.4)	0.102[2]
Yes	34 (13)	215 (82.1)	
No			
TCAs	17 (6.5)	105 (40.1)	0.807[2]
Yes	21 (8)	119 (45.4)	
No			
TeCAs	1 (0.4)	7 (2.7)	0.673[2]
Yes	37 (14.1)	217 (82.8)	
No			
SNRI	1 (0.4)	13 (5)	0.700[2]
Yes	37 (14.1)	211 (80.5)	
No			

Data are presented as mean ± standard error or number (percent)

[1]Calculated by Independent-Samples T test

[2]Calculated by Chi-square test.

BMI: Body mass index, SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; TCA: Tricyclic Antidepressants; TeCA: Tetracyclic Antidepressant; SNRI: Serotonin-Norepinephrine Reuptake Inhibitor

Variables	Men (n = 38)	Women (n = 224)	P-values
Sodium valproate	7 (2.7)	26 (9.9)	0.287[2]
Yes	31 (11.8)	198 (75.6)	
No			
Triptans	6 (2.3)	37 (14.1)	0.911[2]
Yes	32 (12.2)	187 (71.4)	
No			
Gabapentin	2 (0.8)	41 (15.6)	0.045[2]
Yes	36 (13.7)	183 (69.8)	
No			
Benzodiazepine	2 (0.8)	11 (4.2)	0.588[2]
Yes	36 (13.7)	213 (81.3)	
No			
Data are presented as mean ± standard error or number (percent)			
[1]Calculated by Independent-Samples T test			
[2]Calculated by Chi-square test.			
BMI: Body mass index, SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; TCA: Tricyclic Antidepressants; TeCA: Tetracyclic Antidepressant; SNRI: Serotonin-Norepinephrine Reuptake Inhibitor			

Based on Table 2, no significant differences were observed regarding clinical features of migraine headache across quartiles of 24-h urinary sodium, potassium, and Na/K ratio (all P values > 0.05).

Table 2
Clinical features of migraine headache across quartiles (Q) of 24-hour urinary sodium, potassium and Na/K ratio

	Quartiles of 24-hour urinary sodium				P-value
	Q1 (n = 65)	Q2 (n = 66)	Q3 (n = 66)	Q4 (n = 65)	
Frequency	8.36 ± 0.90	6.12 ± 0.71	8.63 ± 0.89	8.10 ± 0.91	0.152
Duration	0.73 ± 0.08	1.03 ± 0.10	1.02 ± 0.09	1.06 ± 0.11	0.077
Severity	7.80 ± 0.23	7.54 ± 0.22	7.72 ± 0.21	8.04 ± 0.20	0.449
MHIS	52.77 ± 9.40	41.37 ± 6.28	66.19 ± 8.83	54.97 ± 7.37	0.188
HIT-6	62.27 ± 0.93	63.39 ± 0.86	62.33 ± 0.89	62.87 ± 0.86	0.790
Nitric oxide	35.50 ± 2.86	32.75 ± 2.69	33.90 ± 2.42	34.39 ± 2.56	0.906
	Quartiles of 24-hour urinary potassium				P-value
	Q1 (n = 67)	Q2 (n = 64)	Q3 (n = 66)	Q4 (n = 65)	
Frequency	8.52 ± 0.96	7.82 ± 0.89	7.09 ± 0.71	7.76 ± 0.88	0.710
Duration	0.93 ± 0.09	0.78 ± 0.08	1.01 ± 0.10	1.12 ± 0.12	0.127
Severity	7.64 ± 0.22	7.64 ± 0.20	7.84 ± 0.24	7.98 ± 0.20	0.629
MHIS	65.69 ± 10.47	38.67 ± 6.18	52.70 ± 7.30	57.67 ± 7.35	0.085
HIT-6	63.23 ± 0.97	61.82 ± 0.79	63.19 ± 0.92	62.58 ± 0.84	0.650
Nitric oxide	36.00 ± 2.89	31.96 ± 2.37	33.00 ± 2.37	35.47 ± 2.83	0.654
	Quartiles of 24-hour urinary Na/K ratio				P-value
	Q1 (n = 65)	Q2 (n = 67)	Q3 (n = 65)	Q4 (n = 65)	
Frequency	7.29 ± 0.80	7.34 ± 0.84	**7.67** ± 0.77	8.92 ± 1.01	0.511
Duration	0.93 ± 0.10	1.03 ± 0.11	1.00 ± 0.09	0.88 ± 0.09	0.716
Severity	7.90 ± 0.24	7.61 ± 0.22	7.93 ± 0.16	7.66 ± 0.23	0.596
MHIS	49.23 ± 7.03	48.75 ± 7.01	61.94 ± 9.70	55.55 ± 8.42	0.661
HIT-6	62.41 ± 0.87	62.01 ± 0.79	63.49 ± 0.85	62.98 ± 1.02	0.348
Nitric oxide	33.14 ± 2.51	36.97 ± 3.06	35.59 ± 2.47	30.71 ± 2.37	0.443
Data are presented as mean ± standard error					
†P < 0.05 was considered statistically significant.					
P-value obtained from analysis of variance (ANOVA)					

The findings of linear regression of migraine and 24-h urinary sodium are shown in Table 3. The 24-h urinary sodium was significantly associated with frequency (Model 3: β = 1.86, 95%CI (0.10, 3.62); P = 0.038), duration (Model 2: β = 0.38, 95% (0.11, 0.66); P = 0.006) and MHIS (Model 3: β = 0.19, 95%CI (0.01, 0.37); P = 0.034). Other variables did not show any significant relationship with 24-h urinary sodium (all P values > 0.05).

Table 3
Beta (β) and 95% confidence interval for clinical features of migraine headache according to quartiles of 24-hour urinary sodium

	Quartiles of 24-hour urinary sodium			
	Q1	**Q2**	**Q3**	**Q4**
Frequency	Ref	-2.24 (-4.61, 0.12)	0.26 (-2.10, 2.63)	-0.26 (-2.64, 2.11)
Model 1	Ref	-0.92 (-2.62, 0.77)	0.83 (-0.85, 2.53)	0.03 (-1.68, 1.74)
Model 2	Ref	-0.29 (-2.11, 1.52)	**1.86 (0.10, 3.62)** †	0.53 (-1.31, 2.38)
Model 3				
Duration	Ref	**0.29 (0.01, 0.57)** †	**0.29 (0.01, 0.57)** †	**0.33 (0.05, 0.61)** †
Model 1	Ref	0.27 (-0.004, 0.54)	**0.34 (0.07, 0.61)** †	**0.38 (0.11, 0.66)** †
Model 2	Ref	0.18 (-0.13, 0.50)	0.30 (-0.004, 0.60)	0.29 (-0.02, 0.61)
Model 3				
Severity	Ref	-0.25 (-0.86, 0.35)	-0.07 (-0.67, 0.53)	0.24 (-0.36, 0.85)
Model 1	Ref	-0.22 (-0.81, 0.36)	-0.008 (-0.59, 0.58)	0.43 (-0.16, 1.03)
Model 2	Ref	-0.39 (-1.03, 0.25)	-0.02 (-0.65, 0.59)	0.19 (-0.46, 0.85)
Model 3				
MHIS	Ref	0.02 (-0.15, -0.20)	**0.25 (0.07, 0.43)** †	0.16 (-0.01, 0.34)
Model 1	Ref	0.08 (-0.08, 0.23)	**0.31 (0.15, 0.47)** †	**0.21 (0.05, 0.37)** †
Model 2	Ref	0.02 (-0.15, 0.20)	**0.33 (0.16, 0.50)** †	**0.19 (0.01, 0.37)** †
Model 3				
HIT-6	Ref	1.11 (-1.33, 3.56)	0.05 (-2.39, 2.50)	0.60 (-1.85, 3.05)
Model 1	Ref	1.02 (-1.39, 3.43)	0.04 (-2.36, 2.44)	0.42 (-2.01, 2.85)
Model 2	Ref	0.84 (-1.84, 3.52)	0.50 (-2.09, 3.10)	0.26 (-2.46, 2.99)
Model 3				

Data are presented as β (95% confidence interval)

†P < 0.05 was considered statistically significant.

Model 1: Unadjusted.

Model 2: Adjusted for age, sex, marital status, smoking status, migraine type, migraine characteristic, family history, mean arterial pressure and physical activity.

Model 3: Model 2 + body mass index and energy intake per day

	Quartiles of 24-hour urinary sodium			
	Q1	Q2	Q3	Q4
Nitric oxide	Ref	-2.75 (-10.02, 4.51)	-1.59 (-8.86, 5.67)	-1.10 (-8.40, 6.19)
Model 1	Ref	-2.91 (-10.07, 4.25)	-1.75 (-8.87, 5.37)	-1.51 (-8.72, 5.70)
Model 2	Ref	-4.43 (-12.51, 3.63)	-4.74 (-12.56, 3.07)	-3.60 (-11.82, 4.61)
Model 3				
Data are presented as β (95% confidence interval)				
†P < 0.05 was considered statistically significant.				
Model 1: Unadjusted.				
Model 2: Adjusted for age, sex, marital status, smoking status, migraine type, migraine characteristic, family history, mean arterial pressure and physical activity.				
Model 3: Model 2 + body mass index and energy intake per day				

Table 4 shows the results of the association between migraine parameters and 24-h urinary potassium. There is no significant relationship between 24-h urinary potassium and any of the intended variables (all P values > 0.05).

Table 4
Beta (β) and 95% confidence interval for clinical features of migraine headache according to quartiles of 24-hour urinary potassium

	Quartiles of 24-hour urinary potassium			
	Q1	Q2	Q3	Q4
Frequency	Ref	-0.69 (-3.08, 1.69)	-1.43 (-3.80, 0.93)	-0.75 (-3.13, 1.62)
Model 1	Ref	-0.18 (-1.88, 1.51)	-0.15 (-1.88, 1.56)	-0.58 (-2.28, 1.10)
Model 2	Ref	0.23 (-1.56, 2.02)	0.37 (-1.46, 2.19)	-0.74 (-2.61, 1.12)
Model 3				
Duration	Ref	-0.14 (-0.42, 0.13)	0.07 (-0.20, 0.35)	0.19 (-0.09, 0.46)
Model 1	Ref	-0.17 (-0.44, 0.09)	0.12 (-0.14, 0.40)	0.24 (-0.02, 0.51)
Model 2	Ref	-0.26 (-0.56, 0.03)	0.01 (-0.29, 0.31)	0.30 (-0.01, 0.61)
Model 3				
Severity	Ref	-0.001 (-0.60, 0.60)	0.20 (-0.39, 0.80)	0.34 (-0.26, 0.94)
Model 1	Ref	-0.16 (-0.75, 0.42)	0.07 (-0.52, 0.67)	0.27 (-0.32, 0.86)
Model 2	Ref	-0.25 (-0.88, 0.37)	-0.05 (-0.69, 0.58)	0.41 (-0.24, 1.06)
Model 3				
MHIS	Ref	-0.12 (-0.30, 0.05)	-0.002 (-0.18, 0.17)	0.04 (-0.13, 0.22)
Model 1	Ref	-0.12 (-0.29, 0.03)	0.05 (-0.10, 0.22)	0.06 (-0.10, 0.22)
Model 2	Ref	-0.12 (-0.29, 0.06)	0.04 (-0.14, 0.22)	0.08 (-0.10, 0.26)
Model 3				
HIT-6	Ref	-1.41 (-3.85, 1.03)	-0.04 (-2.46, 2.38)	-0.65 (-3.09, 1.78)
Model 1	Ref	-1.24 (-3.63, 1.15)	0.23 (-2.19, 2.66)	-0.27 (-2.66, 2.11)
Model 2	Ref	-1.14 (-3.76, 1.46)	-0.03 (-2.69, 2.62)	0.45 (-2.26, 3.17)
Model 3				

Data are presented as β (95% confidence interval)

†P < 0.05 was considered statistically significant.

Model 1: Unadjusted.

Model 2: Adjusted for age, sex, marital status, smoking status, migraine type, migraine characteristic, family history, mean arterial pressure and physical activity.

Model 3: Model 2 + body mass index and energy intake per day

	Quartiles of 24-hour urinary potassium			
	Q1	Q2	Q3	Q4
Nitric oxide	Ref	-4.04 (-11.30, 3.21)	-3.00 (-10.20, 4.19)	-0.53 (-7.75, 6.69)
Model 1	Ref	-4.27 (-11.36, 2.80)	-4.06 (-11.25, 3.13)	-1.46 (-8.54, 5.61)
Model 2	Ref	-2.80 (-10.68, 5.08)	-2.54 (-10.57, 5.49)	1.69 (-6.51, 9.89)
Model 3				
Data are presented as β (95% confidence interval)				
†P < 0.05 was considered statistically significant.				
Model 1: Unadjusted.				
Model 2: Adjusted for age, sex, marital status, smoking status, migraine type, migraine characteristic, family history, mean arterial pressure and physical activity.				
Model 3: Model 2 + body mass index and energy intake per day				

Beta and 95% confidence interval for clinical features of migraine headache according to quartiles of 24-hour urinary Na/K ratio are presented in Table 5. There is a significant association between Na/K ratio and MHIS (Model 2: β = 0.16, 95%CI (0.003, 0.33); P = 0.045), although other variables did not associate with Na/K ratio (all P values > 0.05).

Table 5
Beta (β) and 95% confidence interval for clinical features of migraine headache according to quartiles of 24-hour urinary Na/K ratio

	Quartiles of 24-hour urinary Na/K ratio			
	Q1	**Q2**	**Q3**	**Q4**
Frequency	Ref	0.05 (-2.32, 2.42)	0.38 (-2.00, 2.77)	1.63 (-0.76, 4.02)
Model 1	Ref	0.51 (-1.17, 2.19)	0.34 (-1.36, 2.05)	1.27 (-0.42, 2.98)
Model 2	Ref	0.70 (-1.07, 2.49)	0.51 (-1.28, 2.32)	1.34 (-0.49, 3.18)
Model 3				
Duration	Ref	0.10 (-0.17, 0.38)	0.07 (-0.21, 0.35)	-0.04 (-0.32, 0.23)
Model 1	Ref	0.06 (-0.21, 0.33)	0.08 (-0.19, 0.36)	-0.05 (-0.33, 0.22)
Model 2	Ref	0.02 (-0.28, 0.33)	-0.02 (-0.34, 0.28)	-0.09 (-0.41, 0.22)
Model 3				
Severity	Ref	-0.29 (-0.90, 0.30)	0.03 (-0.57, 0.64)	-0.24 (-0.85, 0.36)
Model 1	Ref	-0.27 (-0.85, 0.31)	0.20 (-0.39, 0.79)	-0.08 (-0.67, 0.51)
Model 2	Ref	-0.21 (-0.84, 0.41)	-0.01 (-0.65, 0.62)	-0.19 (-0.84, 0.45)
Model 3				
MHIS	Ref	0.05 (-0.12, 0.23)	0.15 (-0.03, 0.33)	0.07 (-0.10, 0.25)
Model 1	Ref	0.06 (-0.10, 0.22)	**0.16 (0.003, 0.33)** †	0.07 (-0.08, 0.24)
Model 2	Ref	0.06 (-0.11, 0.24)	0.12 (-0.05, 0.30)	0.08 (-0.10, 0.26)
Model 3				
HIT-6	Ref	-0.40 (-2.83, 2.03)	1.07 (-1.37, 3.53)	0.56 (-1.88, 3.02)
Model 1	Ref	-0.67 (-3.06, 1.70)	0.82 (-1.59, 3.23)	0.21 (-2.19, 2.62)
Model 2	Ref	-0.90 (-3.50, 1.70)	0.11 (-2.52, 2.75)	-0.08 (-2.77, 2.59)
Model 3				

Data are presented as β (95% confidence interval)

†P < 0.05 was considered statistically significant.

Model 1: Unadjusted.

Model 2: Adjusted for age, sex, marital status, smoking status, migraine type, migraine characteristic, family history, mean arterial pressure and physical activity.

Model 3: Model 2 + body mass index and energy intake per day

	Quartiles of 24-hour urinary Na/K ratio			
	Q1	Q2	Q3	Q4
Nitric oxide	Ref	3.82 (-3.37, 11.03)	2.45 (-4.80, 9.71)	-2.42 (-9.68, 4.83)
Model 1	Ref	4.38 (-2.65, 11.41)	2.91 (-4.21, 10.04)	-1.75 (-8.86, 5.36)
Model 2	Ref	5.44 (-2.32, 13.21)	1.29 (-6.58, 9.16)	-4.19 (-12.20, 3.81)
Model 3				
Data are presented as β (95% confidence interval)				
†P < 0.05 was considered statistically significant.				
Model 1: Unadjusted.				
Model 2: Adjusted for age, sex, marital status, smoking status, migraine type, migraine characteristic, family history, mean arterial pressure and physical activity.				
Model 3: Model 2 + body mass index and energy intake per day				

4. Discussion

The present study is the first to address the association between 24-h urinary sodium, potassium, and Na/K ratio in a sample of Iranian patients diagnosed with migraine headache. We found that 24-h urinary sodium is an independent predictor of greater levels of frequency, duration, and MHIS of migraine headache. Of note, the association between sodium and headache duration was not independent of BMI and energy intake, indicating that the potential effect of sodium is related to total body weight and other aspects of dietary intake and is not specific to dietary sodium alone. Furthermore, Na/K ratio was significantly associated with MHIS which was not independent of BMI and energy intake. Our findings show the importance of sodium intake reduction and the increase in potassium intake to improve clinical aspects of migraine headache. Accordingly, our results contribute to the existing literature and provide new and substantial information regarding the association between sodium, potassium, and Na/K ratio with migraine headache in a representative sample of the Iranian population diagnosed with migraine.

To date, only one cross-sectional study [10] and two trials [26, 25] have attempted to investigate the association between sodium and headache, while no study on potassium has done so far. Pogoda et al. [10] investigated the association between dietary sodium intake and history of migraine or severe headache which conclude that elevated levels of dietary sodium intake associated with decreased migraine history (odds ratio = 0.93, 95%CI = 0.87-1.00, P = 0.045). Another study has been conducted to determine the effect of sodium reduction on headache occurrence among the elderly population diagnosed with hypertension [26]. The occurrence of headache was significantly lower in the sodium-reduced group (10.5%) compared with control (14.3%) with a hazard ratio of 0.59 (95%CI = 0.40, 0.88, P = 0.009). Another document was the findings of post-hoc analyses of the DASH-Sodium trial among 390 subjects with hypertension. This study proposed a lower risk of headache on the low dietary sodium

intake, compared with high ($P < 0.05$) [25]. There are some points which should be taken into account when interpreting the previous findings and also in comparison to our results. First, the included population of previous studies were mostly hypertensive subjects. The close association between dietary sodium intake and hypertension is widely recognized and supported by several reports [27–29]. On the other hand, elevated blood pressure and headache have long been associated in the medical literature [30, 31]. So, it could be conjectured that lower headache occurrence in hypertensive subjects following a low sodium diet might be associated with reduced blood pressure [25]. In the present study, subjects with hypertension have excluded and also mean arterial pressure adjusted to resolve this issue. Second, none of the previous studies have used a valid evaluation and diagnostic criterion for participants' selection and was nonspecific to migraine. To address this important issue, we have used ICHD-3 to select patients with migraine to be included. Moreover, further adjustments have been done based upon migraine type (chronic/episodic) and migraine characteristic (with aura/without aura). Third, the only cross-sectional study which addresses the link between headache and sodium intake has used 24-h dietary recall, with inherent limitations [32], to evaluate the amount of sodium intake. To solve the above problem, we used 24-h urine collection as a gold standard method for assessment of dietary intake of sodium and potassium [14].

The mechanisms underlying the link between sodium, potassium, and migraine are uncertain. Cations are important in brain functions and are involved in the pathophysiology of several diseases, including migraine [5]. Previous documents have reported elevated levels of sodium in the blood [33] and cerebrospinal fluid (CSF) [5] during the migraine attacks. The absence of significant CSF changes of calcium, magnesium, and especially potassium, highlights the singular probable role of sodium in migraine [5]. Sodium levels of CSF equilibrate in less than 2 hours between blood and CSF, and much more rapidly with the brain extracellular fluid, especially in mobile subjects [34, 5]. Thus, we can assume that the observed change in CSF and brain extracellular fluid reflects a similar level in plasma. It has been reported previously that higher dietary sodium intake increases the sodium content of human CSF [35]. Increased extracellular sodium has been revealed to affect the inactivating peptide on voltage-gated sodium channels, directly displacing them from the extracellular orifice of the channel. While the resting potential of a cell membrane is mainly derived from the potassium gradient across the membrane (unchanged in the CSF based upon previous reports), elevated extracellular sodium in migraine patients will slightly lessen the resting membrane potential and consequently decreasing the threshold for action potentials [36]. Additionally, elevated extracellular sodium has been reported to diminish the threshold for repetitive neuronal firing via increasing sodium conductance and increasing pH-induced nociceptor discharge [37]. Brainard et al. also suggested salt loading as a trigger for migraine through elevated levels of angiotensin and aldosterone in plasma [38, 39]. In summary, more attempts are needed to elucidate the exact underlying mechanism of action of dietary sodium and potassium in migraine.

5. Strengths And Limitations

Our study has several strengths. We estimated dietary sodium and potassium intake using 24-h urine collection as the gold standard method. Besides, to the best of our knowledge, this is the first study to

show the association between sodium and potassium intake with clinical features of migraine patients through the representative sample of the Iranian population.

Potential limitations should be noted. The cross-sectional design of the present study precludes us from drawing a causal link between sodium and potassium with migraine. Furthermore, using a single 24-h urine collection might have underestimated or overestimated the actual sodium and potassium intake in the study population. Although we adjusted for several demographic, clinical, and nutritional factors, we cannot exclude the possible effect of residual confounding on our results.

6. Conclusion

In conclusion, reduced sodium intake was associated with significantly lower frequency, duration, and MHIS of migraine headache. Also, the Na/K ratio was significantly associated with MHIS. Our findings suggest that reducing sodium intake and increasing potassium intake could be used as a useful and novel approach to improve clinical findings of migraine and associated burden of disease. Additional studies are needed to replicate these findings and to discover mechanisms that mediate the association between sodium and potassium intake with migraine headache.

Declarations

Ethics approval and consent to participate

As part of the original study, all patients provided written informed consent and the trial was approved by all relevant review bodies. Because the subgroup analyses used existing data from the primary study, additional consent was not required.

Consent for publication

Not applicable.

Availability of data and materials

Anonymized data, as described in this manuscript, will be shared upon request from any qualified investigator by the author investigators

Competing interest

None.

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AUTHOR CONTRIBUTION

Conception and Design: Arman Arab, Gholamreza Askari

Acquisition of Data: Arman Arab, Fariborz Khorvash, Gholamreza Askari

Analysis and Interpretation of Data: Arman Arab, Zahra Heidari

Drafting the Manuscript: Arman Arab

Revising It for Intellectual Content: Arman Arab, Fariborz Khorvash, Zahra Heidari, Gholamreza Askari

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