Is there a relationship between dietary sodium and potassium intake and clinical findings of a migraine headache?

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Abstract

Few studies have assessed the association between sodium (Na) and potassium (K) and migraine headaches. In this study, we aimed to examine the relationship between 24-hour urine Na and K intakes and clinical findings of migraine in an Iranian sample. In this cross-sectional study, 262 participants, aged 20–50 years, were included with a body mass index (BMI) of 18·5–30 kg/m² and a diagnosis of migraine. One 24-hour urine sample was collected from each subject to estimate the Na and K intakes. The clinical features of migraine, including frequency, duration, severity, Migraine Headache Index Score (MHIS), and Headache Impact Test (HIT) score, were assessed. Besides, a multiple linear regression analysis was performed, and beta estimates and the corresponding 95% confidence intervals (CIs) were reported. Overall, 224 women and 38 men, with a mean age of 36·10 years and BMI of 25·55 kg/m² comprised our study population. After controlling for potential confounders, the 24-hour urine Na was positively associated with a longer headache duration ($\beta = 0.29$; 95% CI: 0·06, 0·53) in the group with the highest urine Na levels as compared to the group with the lowest levels. After adjustments for potential confounders, an increase of 13·05 in the MHIS was observed when the 24-hour urine Na level increased from the first to the third tertile ($\beta = 13.05$; 95% CI: 1·70, 24·41). Our findings suggested that a higher 24-hour urine Na level was positively associated with a longer duration of migraine headaches and a higher MHIS.

Key words: Na: K: 24-h Urine: Nutrition: Migraine

Migraine is a major public health concern due to its association with increased disability, affecting 18% of females and 6% of males[1]. It was ranked as the second cause of disability worldwide among 20- to 50-year-old males and females[2]. This medical condition is defined as recurrent episodes of headache and related symptoms (e.g. nausea, vomiting, photophobia and phonophobia) that last for 4–72 h[3]. It is a complicated neurovascular disorder, which involves multiple cortical, subcortical and brainstem areas of the brain[1]. Previous experimental studies have suggested an important role for NO in migraine pathogenesis[4]. The trigeminovascular system inflammation, which occurs during migraine attacks, and also the dilation of cerebral vessels, has been attributed to the role of NO in the central nervous system[5].

Despite major advances in our understanding of migraine, its exact pathophysiology is not fully understood. Among ionic constituents that directly contribute to neuronal excitability, evidence suggests that Na and to some extent K homoeostasis may play an important role in the pathophysiology of migraine headaches[6–9]. In the early 1950s, a preliminary report proposed that migraine patients excreted more Na and K in their urine as compared with non-migraineurs, suggesting a possible association between these electrolytes and migraine pathophysiology[10]. However, since then, studies have examined the possible association between Na and migraine, while the role of K has been overlooked. The Na levels in the cerebrospinal fluid (CSF) have been shown to increase during migraine attacks[7]. Moreover, the NO secretion was increased in response to elevated levels of Na intake[11]. A study by Pogoda *et al.* suggested an inverse association between dietary Na intake and migraine history[12], while other reports proposed the beneficial effects of Na intake reduction in terms of the occurrence of headaches[13,14]. On the other hand, another study by Evans *et al.* suggested no significant difference in the Na intake between women with and without migraine[15]. These findings, although contradictory, highlight the possible association of Na intake and partly K intake with migraine headaches.

Abbreviations: CSF, cerebrospinal fluid; HIT-6, The Headache Impact Test-6; MHIS, Migraine Headache Index Score.

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Almost all previous studies on the association between the dietary intake of Na and migraine headaches were conducted on Western populations, while this possible link has not been examined in non-Western countries. Moreover, previous studies have exclusively explored the role of Na in migraine headaches and ignored the possible role of K and also the Na:K ratio. So far, limited studies have used the 24-h urine sampling method as the gold standard for assessing the Na and K intake[16]. Therefore, the association between the dietary intake of Na and K and migraine headaches in a Middle-Eastern country, using an accepted methodology for estimating the dietary intake, may provide some novel insights into the diet–migraine relationship.

Based on the findings regarding the association of Na and K with migraine headaches, the current study was conducted in an Iranian population, using 24-h urine collections as the gold standard method. In this cross-sectional study that was conducted between 2019 and 2020, we hypothesised that 24-h urine Na, K and Na:K ratio are associated with the clinical findings of migraine headaches, quality of life and serum NO levels.

Materials and methods

Study design and population

In this cross-sectional study, 265 patients diagnosed with migraine were recruited consecutively based on the predefined inclusion and exclusion criteria. From August 2019 to June 2020, we consecutively evaluated 560 patients with a suspicion of migraine in Imam Musa Sadr Neurology Clinic and Khurshid Neurology Clinic, which are both affiliated to Isfahan University of Medical Sciences, Isfahan, Iran. After a confirmed diagnosis of migraine by a neurologist, patients were evaluated regarding the eligibility criteria, and subjects who met the inclusion and exclusion criteria were selected to participate in the current study. Patients were included if they met the following criteria: being in the age range of 20–50 years; being diagnosed with migraine by a neurologist (F.K.), based on the International Classification of Headache Disorders-3 criteria[17]; visiting a neurology clinic for the first time and having a BMI of 18·5–30 kg/m². On the other hand, the exclusion criteria were as follows: a history of CVD, hypertension, diabetes, cancer, hepatic, renal or thyroid disease and other neurological disorders (due to possible disease-related changes in diet); use of nutritional and herbal supplements, including riboflavin, Mg, coenzyme Q10 and feverfew and reported daily energy intakes < 800 kcal/d (3347 kJ/d) or > 4200 kcal/d (17 573 kJ/d), based on the FFQ[18]. All participants provided written informed consent forms. The study protocol was approved by the Research Ethics Committee of Isfahan University of Medical Sciences (IR.MUI.RESEARCH.REC.1398·352) on 26 August 2019.

24-h urine collection

The patients were given verbal and written instructions on how to complete the procedure during a 24-h headache-free period. It was highlighted that no changes in dietary habits on the day of collection were allowed. The 24-h sampling procedure was carried out over weekends from Friday to Saturday during a 24-h period.

Each individual was provided with a polypropylene container (2·5 L) for the collection of 24-h urine samples. A single 24-h urine collection was obtained with the first voided urine on a Friday morning. The participants then collected all voided urine, including the first void on the next Saturday morning. All patients were asked to keep the containers in dry and cool places. The samples were then immediately transferred to a laboratory on Saturday for analysis to prevent microbial degradation. The Na and K levels were assessed using the ion-selective electrode method (ProLyte Electrolyte Analyzer), and urine creatinine (Cr) was measured by the Jaffe reaction method (BT 3000)[19]. Suspected urine collections were defined as urinary Cr < 6 mmol/d in men or < 4 mmol/d in women or a 24-h urine volume < 500 ml; these samples were excluded from the study[20]. For each individual, the 24-h Na and K excretion values (mmol/d) were calculated as the concentration of Na and K in the urine (mmol/L), multiplied by the urine volume (L/d); mmol was converted to mg through multiplication by 23 for Na and by 39 for K[20].

Dietary assessment

The dietary intake of the participants over the past year was assessed using a semi-quantitative FFQ. This questionnaire included a list of 168 food items, along with the standard serving size for each; its reliability and validity have been previously approved in an Iranian population[21–23]. 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 food portion sizes were converted into grams using household measures[24]. The FFQ was completed by a trained dietitian through a face-to-face interview, and data were analysed by Nutritionist IV software (First Databank, Hearst Corp.).

Anthropometric measurements

Body weight was measured to the nearest 100 g, using a digital scale (Omron BF511, Omron Corp.), while the subject was clothed minimally (i.e. no belts, sweaters or jackets), without any shoes. Height was also measured using an upstretched tape to the nearest 1 mm, while the subject was in a standing position without shoes, with the shoulders in a relaxed position. BMI was calculated based on height (m) and weight (kg) (BMI = weight/height²).

Assessments of migraine clinical features

Headache diaries about the clinical features of migraine in the past month were obtained from all of the participants prior to 24-h urine collection. A 30-d headache diary was given to the participants, along with verbal and written instructions on how to complete the procedure to provide information about the headache frequency, duration and severity. The time of migraine attack onset and end was recorded accurately after each migraine attack, regardless of the time of the day, to calculate the mean headache duration and frequency. Also, the frequency was defined as the number of attacks per month. The mean duration of headache attacks per month was considered as the headache duration.

The Visual Analogue Scale was used to assess the severity of headaches[25]. In this scale, the headache severity is ranked from zero to ten, with zero indicating 'no pain' and ten indicating 'the worst imaginable pain'. The participants selected an option that best represented their perception of pain intensity during migraine attacks. Besides, the Migraine Headache Index Score (MHIS) was calculated using the relevant formula (frequency × duration × severity)[26]. If the patients had any difficulties in completing 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 in the upcoming month[27] before the 24-h urine collection.

The Headache Impact Test-6 (HIT-6) was used to evaluate the impact of headaches on the patients' quality of life. The HIT-6 is a validated questionnaire[28], containing six questions with five options: never (score: 6), rarely (score: 8), sometimes (score: 10), very often (score: 11) and always (score: 13); the total possible score is 36–78. The scores of 36–49, 50–55, 56–59 and ≥60 indicate that the headaches have no effects, moderate effects, substantial effects and severe effects on the quality of life of the participants, respectively[29].

Assessment of other variables

Additional information was collected by the researchers, using a demographic questionnaire, which contained questions about age, sex, marital status, number of family members, family history of migraine, time since migraine diagnosis and medications. Besides, the physical activity status was assessed using the International Physical Activity Questionnaire, which is a self-administered, seven-day recall instrument. The validity and reliability of this questionnaire have been previously approved in the Iranian population[30]. The physical activity levels were expressed as the metabolic equivalents of hours per day (METs h/d).

For sampling, 10 ml of venous blood was collected after 8–12 h of fasting when the patients visited the laboratory to receive a 24-h urine collection container. The fasting blood samples were centrifuged (Avanti J-25) at 3500 rpm for 10 minutes to separate the serum immediately after collection and then maintained at –80°C for further analyses. The serum NO levels were also assessed using the Griess method via commercial kits (Kiazist Life Sciences).

Statistical analysis

A suggested formula for estimating the mean was used to compute the sample size. Based on the Na levels in patients with migraine headaches ($\alpha = 0.05$, $\sigma = 0.9$, $d = 0.1$), the sample size was estimated at 260 subjects[14]. Continuous and categorical variables are presented as mean ± standard error (SE) and number (percentage), respectively. The characteristics of the study population were compared across tertiles of 24-h urine Na, K and Na:K ratio, using the ANOVA or χ^2 test for continuous or categorical variables, respectively. The ANOVA test was used to compare the clinical features of migraine headaches across tertiles of 24-h urine Na, K and Na:K ratio, without any adjustments for confounders. To assess the relationships of 24-h urine Na, K and Na:K ratio with the clinical features of migraine headaches, a multiple linear regression analysis was performed in different models. The adjusted beta (β) estimates with the corresponding 95 % CIs are presented in two different models. First, we adjusted for age, sex, marital status, smoking status, migraine type (episodic/chronic), migraine characteristics (with aura/without aura), family history, mean arterial pressure (MAP) and physical activity. In the final model, further adjustments were made for BMI and energy intake. Data analyses were performed using SPSS version 21 (IBM Corp.). P-values less than 0·05 were considered statistically significant.

Results

Of 265 participants with 24-h urine collections, some samples were excluded (n 3) due to incomplete urine collections. Finally, 262 patients had complete and valid urinary samples and were included in the final analysis. Overall, 224 women and 38 men comprised our study population, with a mean urine Na level of 3189·38 mg/d, a mean urine K level of 1599·08 mg/d, Cr excretion of 9·15 mmol/l, urine output of 1·14 l/d, age of 36·10 years, BMI of 25·55 kg/m² and total energy intake of 2651·99 kcal/d.

The participants in the top tertile of 24-h urine Na excretion had higher weight, height, Cr excretion, urine output, Na, K, Na: K ratio and also dietary intake of Na, compared with those in the lowest tertile. The participants in the greatest tertile of 24-h urine K, as compared with those in the lowest tertile, were significantly less likely to be female. The weight, height, Cr excretion, urine output, Na, K, intake of energy, carbohydrate, fat, protein and K were also higher in this group. Besides, they had a lower 24-h urine Na:K ratio and a lower intake of sodium valproate. The subjects in the highest tertile of 24-h urine Na:K ratio showed higher urine Na, Na:K ratio and dietary intake of Na, despite lower urine K levels; also, they were less likely to be married. No significant differences were observed in terms of other variables across different tertiles of 24-h urine Na, K and Na:K ratio (Table 1).

The results of Pearson's correlation coefficient test for the correlation of FFQ-derived Na and K with 24-h urine Na and K are presented in Figs. 1 and 2. The urine Na was significantly correlated with the FFQ-derived Na ($r = 0.35$). Moreover, the 24-h urine K was found to be significantly correlated with the FFQ-derived K ($r = 0.29$). These findings imply that there is a moderate correlation between the FFQ-derived data and the urine levels of Na and K.

Overall, the subjects had a mean headache frequency of 7·80 attacks/month, a mean headache duration of 0·96 day/month, a mean headache severity of 7·77, a mean MHIS of 53·83, a mean HIT-6 score of 62·72 and a serum NO level of 34·13 nmol/mL. No significant differences were observed regarding the studied parameters across tertiles of 24-h urine Na, K and Na:K ratio (Table 2).

Table 2 presents descriptive statistics for Black, Latino, and white inmates. Black, Latino, and white inmates share similar profiles on most of the demographic, legal, and rehabilitation characteristics. One notable difference is that Latino inmates

Table 1. Characteristics of study population stratified by tetiles of 24-hour urinary Na, K, and Na/K ratio

Variables	Teriles of 24-hour urinary Na				Teriles of 24-hour urinary K				Teriles of 24-hour urinary Na/K ratio			
	T1 (<2620·37 mg)	T2 (2620·37-3600·56 mg)	T3 (>3600·56 mg)	P value	T1 (<1319·44 mg)	T2 (1319·44-1757·71 mg)	T3 (>1757·71 mg)	P value	T1 (<1·67)	T2 (1·67-2·41)	T3 (>2·41)	P value
N	86	87	89		86	88	88		86	87	89	
Age (y)	37·11 ± 0·93	35·77 ± 0·94	35·44 ± 0·89	0·403	36·04 ± 1·01	35·92 ± 0·87	36·34 ± 0·89	0·947	37·68 ± 0·91	35·79 ± 0·90	34·87 ± 0·93	0·090
Female	77 (89·5)	76 (87·4)	71 (79·8)	0·066	77 (89·5)	78 (88·6)	69 (78·4)	0·037	72 (83·7)	76 (87·4)	76 (85·4)	0·758
Married	73 (84·9)	69 (79·3)	70 (78·7)	0·297	67 (77·9)	70 (79·5)	75 (85·2)	0·219	74 (86·0)	72 (82·8)	66 (74·2)	0·045
Current smoker	3 (3·5)	6 (6·9)	6 (6·7)	0·358	4 (4·7)	5 (5·7)	6 (6·8)	0·539	5 (5·8)	5 (5·7)	5 (5·6)	0·956
Number of family members	3·43 ± 0·09	3·33 ± 0·10	3·48 ± 0·10	0·598	3·43 ± 0·10	3·45 ± 0·10	3·36 ± 0·10	0·821	3·33 ± 0·09	3·41 ± 0·10	3·49 ± 0·11	0·578
Weight (kg)	66·12 ± 1·06	66·87 ± 1·20	70·39 ± 1·12	0·019	65·03 ± 1·15	67·98 ± 1·09	70·38 ± 1·13	0·004	68·42 ± 1·09	68·57 ± 1·22	66·50 ± 1·12	0·363
Height (cm)	161·45 ± 0·83	162·13 ± 0·73	164·90 ± 0·89	0·008	161·81 ± 0·79	161·88 ± 0·88	164·83 ± 0·78	0·014	163·01 ± 0·83	162·07 ± 0·83	163·46 ± 0·83	0·487
BMI (kg/m²)	25·40 ± 0·38	25·37 ± 0·36	25·87 ± 0·35	0·557	24·85 ± 0·40	25·92 ± 0·33	25·86 ± 0·35	0·070	25·73 ± 0·35	26·03 ± 0·36	24·89 ± 0·37	0·074
Physical activity (MET/h/d)	10·34 ± 3·06	6·48 ± 1·18	9·81 ± 2·01	0·413	8·87 ± 2·76	6·56 ± 1·42	11·20 ± 2·27	0·333	8·43 ± 1·78	9·31 ± 2·05	8·88 ± 2·70	0·962
Cr excretion (mmol/l)	8·04 ± 0·30	8·88 ± 0·30	10·59 ± 0·52	<0·001	7·84 ± 0·28	8·84 ± 0·31	10·95 ± 0·50	<0·001	9·41 ± 0·44	9·07 ± 0·42	9·02 ± 0·35	0·789
Urine output (l/day)	0·90 ± 0·06	1·16 ± 0·06	1·37 ± 0·07	<0·001	1·02 ± 0·07	1·07 ± 0·06	1·37 ± 0·07	0·001	1·07 ± 0·07	1·13 ± 0·05	1·24 ± 0·09	0·295
Urine Na (mg/day)	2055·97 ± 41·42	3100·10 ± 27·69	4371·85 ± 62·26	0·001	2906·12 ± 112·70	3298·26 ± 103·07	3357·31 ± 114·08	0·008	2481·10 ± 81·92	3320·56 ± 101·44	3745·54 ± 104·80	<0·001
Urine K (mg/day)	1421·52 ± 50·93	1596·87 ± 68·48	1772·82 ± 59·35	0·001	987·73 ± 23·08	1564·19 ± 13·70	2231·43 ± 43·18	<0·001	1971·90 ± 57·43	1668·54 ± 53·84	1170·92 ± 40·03	<0·001
Urine Na/K ratio	1·61 ± 0·06	2·32 ± 0·12	2·74 ± 0·11	<0·001	3·08 ± 0·13	2·11 ± 0·06	1·52 ± 0·03	<0·001	1·27 ± 0·02	2·00 ± 0·02	3·38 ± 0·10	<0·001
SBP (mmHg)	111·51 ± 1·12	113·33 ± 1·03	113·11 ± 0·96	0·407	112·34 ± 1·05	112·42 ± 0·97	113·18 ± 1·09	0·826	112·44 ± 1·16	113·27 ± 0·87	112·26 ± 1·07	0·767
DBP (mmHg)	75·09 ± 0·77	75·93 ± 0·73	75·42 ± 0·82	0·748	74·65 ± 0·83	75·71 ± 0·73	76·06 ± 0·76	0·410	76·37 ± 0·66	75·58 ± 0·75	74·52 ± 0·87	0·241
MAP (mmHg)	87·23 ± 0·81	88·39 ± 0·77	87·98 ± 0·77	0·575	87·21 ± 0·83	87·95 ± 0·72	88·43 ± 0·80	0·547	88·39 ± 0·76	88·14 ± 0·73	87·10 ± 0·85	0·471
Migraine in first degree relatives	48 (55·8)	61 (70·1)	58 (65·2)	0·204	54 (62·8)	61 (69·3)	52 (59·1)	0·606	51 (59·3)	57 (65·5)	59 (66·3)	0·339
Time since migraine diagnosis (y)	7·31 ± 0·89	7·80 ± 0·93	6·89 ± 0·96	0·786	6·57 ± 0·90	8·28 ± 0·90	7·13 ± 0·98	0·419	7·59 ± 0·91	7·75 ± 0·96	6·67 ± 0·91	0·672
Episodic migraine	68 (79·1)	76 (87·4)	72 (80·9)	0·762	71 (82·6)	72 (81·8)	73 (83·0)	0·944	73 (84·9)	72 (82·8)	71 (79·8)	0·375
Migraine with aura	32 (37·2)	38 (43·7)	39 (43·8)	0·379	29 (33·7)	41 (46·6)	39 (44·3)	0·159	39 (45·3)	36 (41·4)	34 (38·2)	0·339
FFQ-derived dietary intake												
Energy (Kcal/day)	2541·03 ± 62·96	2657·85 ± 74·46	2755·57 ± 75·78	0·107	2521·48 ± 63·85	2484·24 ± 61·44	2949·48 ± 76·76	<0·001	2726·54 ± 72·97	2640·60 ± 73·68	2590·50 ± 68·82	0·400
Protein (g/d)	69·94 ± 3·48	71·65 ± 2·99	78·09 ± 3·01	0·162	69·81 ± 2·87	66·44 ± 2·85	83·51 ± 3·45	<0·001	73·62 ± 3·54	73·08 ± 3·31	73·02 ± 2·69	0·989
Fat (g/d)	105·91 ± 3·07	110·53 ± 3·20	116·57 ± 3·57	0·090	104·51 ± 3·33	106·53 ± 2·87	121·49 ± 3·40	<0·001	113·78 ± 3·34	109·37 ± 3·30	109·56 ± 3·30	0·572
Carbohydrate (g/d)	346·12 ± 10·70	365·10 ± 12·37	372·82 ± 12·18	0·260	344·61 ± 10·84	334·29 ± 10·48	405·40 ± 12·39	<0·001	373·96 ± 12·17	361·66 ± 11·80	348·96 ± 11·42	0·326
Sodium (mg/d)	6173·96 ± 230·93	7153·48 ± 130·81	7329·16 ± 114·40	<0·001	6637·80 ± 197·16	7025·27 ± 129·75	7006·07 ± 186·53	0·209	6499·22 ± 221·14	7071·12 ± 157·29	7095·37 ± 126·51	0·023
Potassium (mg/d)	3533·82 ± 139·11	3588·96 ± 126·99	3880·85 ± 133·05	0·140	3420·56 ± 129·02	3462·25 ± 114·58	4121·56 ± 143·47	<0·001	3833·65 ± 149·99	3692·97 ± 129·41	3489·45 ± 119·52	0·186
Medication												
Taking beta-blockers	39 (45·3)	38 (43·7)	31 (34·8)	0·157	37 (43·0)	34 (38·6)	37 (42·0)	0·899	34 (39·5)	39 (44·8)	35 (39·3)	0·971
Taking topitamate	5 (5·8)	2 (2·3)	6 (6·7)	0·767	3 (3·5)	8 (9·1)	2 (2·3)	0·702	3 (3·5)	3 (3·4)	7 (7·9)	0·181
Taking TCAs	39 (45·3)	37 (42·5)	46 (51·7)	0·397	38 (44·2)	41 (46·6)	43 (48·9)	0·537	39 (45·3)	40 (46·0)	43 (48·3)	0·694
Taking TeCAs	1 (1·2)	3 (3·4)	4 (4·5)	0·202	3 (3·5)	3 (3·4)	2 (2·3)	0·641	1 (1·2)	4 (4·6)	3 (3·4)	0·403
Taking SNRIs	4 (4·7)	6 (6·9)	4 (4·5)	0·957	6 (7·0)	3 (3·4)	5 (5·7)	0·710	4 (4·7)	4 (4·6)	6 (6·7)	0·537
Taking sodium valproate	13 (15·1)	8 (9·2)	12 (13·5)	0·754	17 (19·8)	9 (10·2)	7 (8·0)	0·019	9 (10·5)	8 (9·2)	16 (18·0)	0·132
Taking triptans	16 (18·6)	16 (18·4)	11 (12·4)	0·263	16 (18·6)	15 (17·0)	12 (13·6)	0·377	14 (16·3)	14 (16·1)	15 (16·9)	0·918
Taking gabapentin	17 (19·8)	15 (17·2)	11 (12·4)	0·186	18 (20·9)	15 (17·0)	10 (11·4)	0·089	17 (19·8)	13 (14·9)	13 (14·6)	0·360
Taking benzodiazepine	3 (3·5)	5 (5·7)	5 (5·6)	0·520	3 (3·5)	5 (5·7)	5 (5·7)	0·508	4 (4·7)	5 (5·7)	4 (4·5)	0·959

Data are presented as mean±standard error or number (% within tertiles of 24-hour urinary sodium, potassium, and Na/K ratio)
P-value obtained from chi-square analysis for categorical variables and analysis of variance (ANOVA) for continuous variables.
BMI: Body mass index, SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; MAP: Mean Arterial Pressure; TCA: Tricyclic Antidepressants; TeCA: Tetracyclic Antidepressant; SNRI: Serotonin-Norepinephrine Reuptake Inhibitor
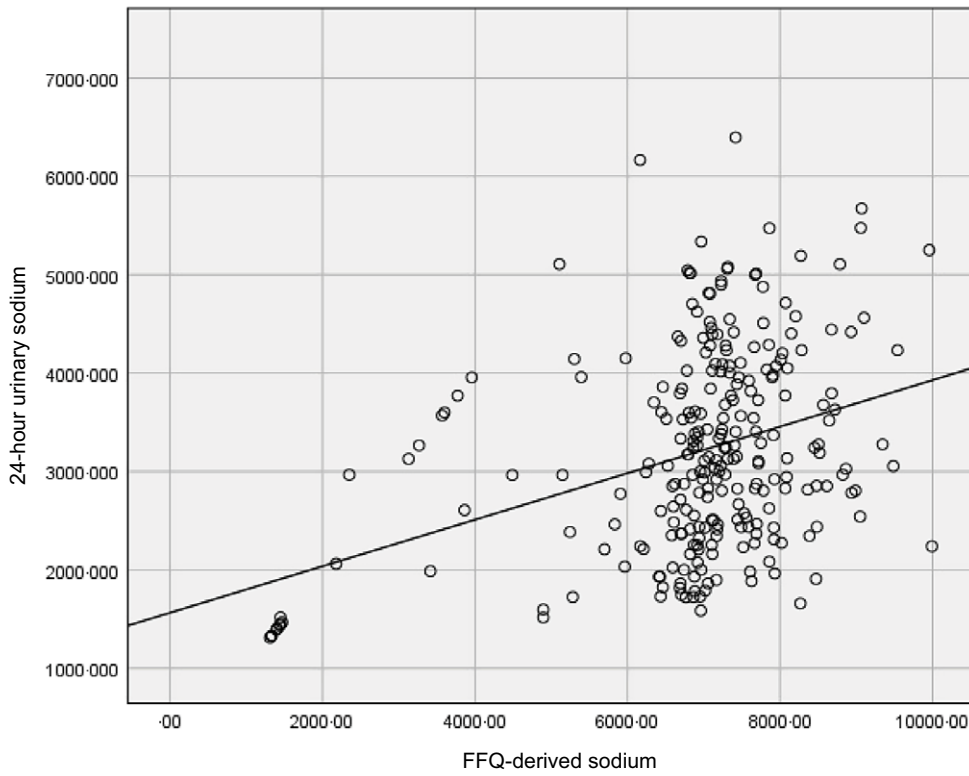
Fig. 1. The correlation between 24-h urinary sodium and dietary intake of sodium derived from FFQ. Urinary sodium was significantly correlated with FFQ-derived sodium ($r = 0.35$; $P < 0.001$).
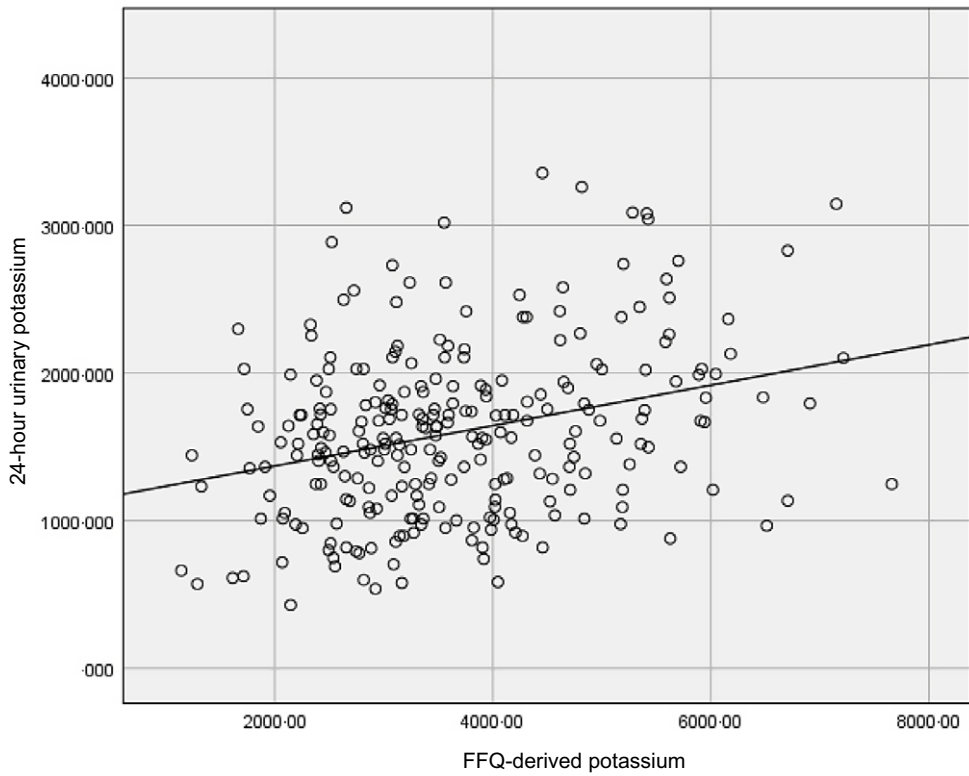
Fig. 2. The correlation between 24-h urinary K and dietary intake of potassium derived from FFQ. Urinary potassium was significantly correlated with FFQ-derived K ($r = 0.29$; $P < 0.001$).

are less likely (by 8–11 percentage points) to be serving life sentences for first-degree murder compared to Black or white inmates. However, Latino inmates are more likely to be serving life sentences for crimes that include multiple victims. Latino inmates are also the most likely to earn a degree in prison and to have a job or program secured upon release.

However, there are marked differences among the three racial/ethnic groups in terms of professional evaluations. Prosecutors opposed parole in 88 percent of hearings where the inmate was Black and 82 percent of hearings where the inmate was Latino, but only 73 percent of hearings where the inmate was white. Furthermore, only 35 percent of Black inmates but 44 percent of white inmates and 46 percent of Latino inmates were given a low-risk score based on their psychological evaluation. Finally, on average Black inmates received one more disciplinary citation than white or Latino inmates. Thus, in general, the professional assessments given to Latino inmates and white inmates appear to be fairly similar, while Black inmates fare differently in this regard.[15]

Regression Models

We first examine the impact of inmate demographic characteristics and characteristics of the commitment offense. We see from Model 1 in Table 2 that inmates who were older at the hearing and younger at the time of the crime have a higher likelihood of receiving a grant. However, neither the type or characteristics of the commitment offense nor the inmate's prior criminal history appear to influence the parole board's decisions. Additionally, hearings conducted after the implementation of Marsy's Law are more likely to result in a grant. In Model 1, there is not a significant difference between Latino inmates and white inmates in the likelihood of being granted parole.[16] However, Black inmates have a significantly lower likelihood of receiving a grant of parole than white inmates. As shown in Table 3 and Figure 1, using coefficients from Model 1, the predicted probability of a parole grant for white inmates is 15·8 percent. This is nearly twice the predicted probability for Black inmates (8·4 percent).

The beta estimates and the corresponding 95 % CI for the association of headache frequency, duration, severity, MHIS, HIT-6 score and serum NO levels with 24-h urine Na, K and Na:K ratio are presented in Table 3. In the crude model, the 24-h urine Na tended to be positively associated with a longer headache duration ($\beta = 0·23$; 95 % CI −0·01, 0·47) in those in the highest category of urine Na as compared with those in the lowest category. Adjustments for age, sex, marital status, smoking, migraine type, migraine characteristics, family history of migraine, MAP and physical activity made the association significant in a way that an increase in the urine Na from the first to the third tertile increased the duration of headaches by 0·29 days (95 % CI 0·06, 0·53). Further adjustments for the total energy intake and BMI attenuated this association ($\beta = 0·23$; 95 % CI −0·01, 0·47). The higher 24-h urine Na levels tended to be positively associated with higher MHIS among patients in the top tertile of urine Na ($\beta = 10·60$; 95 % CI −1·40, 22·61) as compared with those in the lowest tertile. After controlling for age, sex, marital status, smoking, migraine type, migraine characteristics,

Table 2. Clinical features of migraine headache across tertiles of 24-hour urinary Na, K, and Na/K ratio

Variables	Tertiles of 24-hour urinary Na				Tertiles of 24-hour urinary K				Tertiles of 24-hour urinary Na/K ratio			
	T1	T2	T3	P-value	T1	T2	T3	P-value	T1	T2	T3	P-value
Frequency (attacks per month)	8·01 ± 0·76	7·25 ± 0·69	8·14 ± 0·78	0·663	8·23 ± 0·82	7·68 ± 0·73	7·51 ± 0·69	0·779	7·22 ± 0·68	7·43 ± 0·74	8·73 ± 0·80	0·303
Duration (day/attack)	0·80 ± 0·07	1·04 ± 0·09	1·04 ± 0·09	0·099	0·89 ± 0·08	0·98 ± 0·08	1·02 ± 0·09	0·589	0·96 ± 0·09	1·03 ± 0·09	0·89 ± 0·07	0·554
Severity (visual analogue scale)	7·70 ± 0·20	7·62 ± 0·19	8·00 ± 0·17	0·336	7·66 ± 0·19	7·65 ± 0·19	8·01 ± 0·18	0·324	7·89 ± 0·20	7·78 ± 0·17	7·66 ± 0·18	0·691
MHIS	53·54 ± 7·97	52·62 ± 6·90	55·28 ± 6·15	0·963	57·02 ± 8·42	51·61 ± 6·55	52·93 ± 5·93	0·852	49·50 ± 6·32	55·43 ± 7·68	56·44 ± 6·98	0·754
HIT-6	62·41 ± 0·79	62·67 ± 0·71	63·05 ± 0·79	0·840	62·90 ± 0·84	62·39 ± 0·68	62·86 ± 0·78	0·874	63·01 ± 0·75	62·10 ± 0·72	63·04 ± 0·82	0·618
Nitric oxide (nmol/mL)	35·38 ± 2·35	31·70 ± 2·22	35·29 ± 2·25	0·429	35·61 ± 2·47	31·39 ± 1·94	35·41 ± 2·38	0·337	32·74 ± 2·17	37·00 ± 2·51	32·65 ± 2·12	0·306

Data are presented as mean ± standard error and obtained from analysis of variance (ANOVA)
P<0.05 was considered statistically significant.
MHIS: Migraine Headache Index Score; HIT: Headache Impact Test

Table 3. Beta (β) and 95% confidence interval for clinical features of migraine headache according to tertiles of 24-hour urinary Na, K, and Na/K ratio

	Teriles of 24-hour urinary Na				Teriles of 24-hour urinary K				Teriles of 24-hour urinary Na/K ratio			
	T1	T2	T3	P trend	T1	T2	T3	P trend	T1	T2	T3	P trend
Frequency												
Crude	Ref	−0·75 (−2·83, 1·32)	0·13 (−1·93, 2·20)	0·892	Ref	−0·55 (−2·62, 1·52)	−0·72 (−2·79, 1·35)	0·497	Ref	0·21 (−1·85, 2·28)	1·50 (−0·55, 3·57)	0·15
Model 1	Ref	0·08 (−1·41, 1·58)	0·09 (−1·38, 1·57)	0·903	Ref	−0·75 (−2·23, 0·71)	−0·74 (−2·23, 0·73)	0·324	Ref	−0·07 (−1·55, 1·39)	0·69 (−0·78, 2·16)	0·357
Model 2	Ref	0·71 (−0·85, 2·28)	0·49 (−1·08, 2·06)	0·55	Ref	−0·24 (−1·80, 1·30)	−0·63 (−2·26, 1·00)	0·452	Ref	−0·27 (−1·84, 1·30)	0·74 (−0·81, 2·31)	0·347
Duration												
Crude	Ref	0·23 (−0·008, 0·48)	0·23 (−0·01, 0·47)	0·064	Ref	0·08 (−0·15, 0·33)	0·12 (−0·11, 0·37)	0·311	Ref	0·07 (−0·17, 0·31)	−0·06 (−0·31, 0·17)	0·59
Model 1	Ref	0·26 (0·02, 0·50)	0·29 (0·06, 0·53)	0·016	Ref	0·11 (−0·12, 0·35)	0·18 (−0·05, 0·42)	0·129	Ref	0·05 (−0·18, 0·29)	−0·06 (−0·31, 0·17)	0·566
Model 2	Ref	0·20 (−0·06, 0·47)	0·24 (−0·02, 0·51)	0·074	Ref	0·03 (−0·22, 0·30)	0·25 (−0·02, 0·53)	0·124	Ref	−0·002 (−0·27, 0·26)	−0·10 (−0·37, 0·16)	0·454
Severity												
Crude	Ref	−0·08 (−0·61, 0·43)	0·29 (−0·23, 0·81)	0·274	Ref	−0·004 (−0·53, 0·52)	0·34 (−0·17, 0·87)	0·193	Ref	−0·11 (−0·64, 0·41)	−0·23 (−0·75, 0·29)	0·387
Model 1	Ref	−0·008 (−0·52, 0·51)	0·40 (−0·11, 0·91)	0·122	Ref	−0·04 (−0·56, 0·46)	0·29 (−0·22, 0·81)	0·263	Ref	−0·06 (−0·58, 0·44)	−0·08 (−0·60, 0·43)	0·745
Model 2	Ref	−0·07 (−0·63, 0·47)	0·27 (−0·28, 0·82)	0·33	Ref	−0·06 (−0·61, 0·48)	0·38 (−0·18, 0·96)	0·205	Ref	−0·17 (−0·73, 0·37)	−0·16 (−0·72, 0·38)	0·553
MHIS												
Crude	Ref	1·83 (−10·32, 13·98)	10·60 (−1·40, 22·61)	0·081	Ref	2·58 (−14·21, 19·38)	1·06 (−15·77, 17·91)	0·903	Ref	4·83 (−7·30, 16·97)	5·28 (−6·82, 17·39)	0·395
Model 1	Ref	6·11 (−4·71, 16·93)	11·87 (1·22, 22·53)	0·029	Ref	0·78 (−14·21, 15·77)	1·53 (−13·61, 16·67)	0·843	Ref	3·95 (−6·77, 14·69)	3·15 (−7·59, 13·91)	0·569
Model 2	Ref	3·07 (−8·31, 14·46)	13·05 (1·70, 24·41)	0·023	Ref	−1·53 (−18·31, 15·24)	8·00 (−9·61, 25·62)	0·39	Ref	1·01 (−10·46, 12·50)	3·30 (−8·09, 14·70)	0·569
HIT-6												
Crude	Ref	0·26 (−1·87, 2·39)	0·63 (−1·48, 2·75)	0·555	Ref	−0·50 (−2·63, 1·61)	−0·04 (−2·17, 2·08)	0·971	Ref	−0·90 (−3·03, 1·22)	0·03 (−2·08, 2·15)	0·968
Model 1	Ref	0·13 (−1·97, 2·24)	0·47 (−1·61, 2·56)	0·656	Ref	−0·78 (−2·85, 1·29)	0·07 (−2·02, 2·17)	0·944	Ref	−1·25 (−3·33, 0·82)	−0·43 (−2·51, 1·65)	0·695
Model 2	Ref	0·08 (−2·21, 2·37)	0·54 (−1·75, 2·84)	0·639	Ref	−0·63 (−2·88, 1·62)	0·69 (−1·67, 3·07)	0·599	Ref	−1·43 (−3·72, 0·84)	−0·59 (−2·86, 1·68)	0·617
Nitric oxide												
Crude	Ref	−3·68 (−9·99, 2·62)	−0·08 (−6·36, 6·18)	0·988	Ref	−4·21 (−10·50, 2·07)	−0·19 (−6·48, 6·09)	0·959	Ref	4·26 (−2·04, 10·56)	−0·08 (−6·35, 6·18)	0·967
Model 1	Ref	−3·95 (−10·18, 2·27)	−0·22 (−6·40, 5·94)	0·969	Ref	−3·75 (−9·90, 2·39)	−0·67 (−6·87, 5·53)	0·834	Ref	5·29 (−0·84, 11·42)	1·06 (−5·09, 7·22)	0·75
Model 2	Ref	−4·94 (−11·83, 1·94)	−1·54 (−8·44, 5·35)	0·68	Ref	−2·99 (−9·80, 3·81)	2·13 (−5·03, 9·29)	0·607	Ref	5·14 (−1·71, 12·01)	−1·09 (−7·94, 5·75)	0·749

Data are presented as β (95% confidence interval) and obtained from linear regression analysis.
Crude: Unadjusted.
Model 1: Adjusted for age, sex, marital status, smoking status, migraine type, migraine characteristic, family history, mean arterial pressure, and physical activity.
Model 2: Model 1 + body mass index and energy intake per day
MHIS: Migraine Headache Index Score; HIT: Headache Impact Test

family history of migraine, MAP, physical activity, total energy intake and BMI, an increase of 13·05 in the MHIS was observed when the 24-h urine Na level increased from the first to the third tertile (β = 13·05; 95 % CI 1·70, 24·41). No significant association was found between the 24-h urine Na and the serum NO levels, HIT-6 score, headache frequency or headache severity. Similarly, no significant association was detected between the 24-h urine K and Na:K ratio and the headache frequency, duration, severity, MHIS, HIT-6 score and serum NO levels.

Discussion

The present study is the first to address the association between 24-h urine Na, K and Na/K ratio in a sample of Iranian patients diagnosed with migraine headaches. We found that 24-h urine Na is an independent predictor of a longer duration and a higher MHIS of migraine headaches. Our findings suggest the importance of Na in the pathophysiology of migraine headaches and can contribute to the existing literature to provide new and substantial information regarding the association of Na with migraine headaches in a sample of Iranian patients seeking care in a specialty clinic.

In the present study, the association between Na and headache duration was not independent of BMI and energy intake, indicating that the potential effect of Na is related to the total body weight and other aspects of dietary intake and that it is not specific to Na alone. There are some explanations for this finding. Previous studies have suggested a direct link between adiposity measures and migraine headache symptoms, including headache frequency, duration and severity[31–33]. Besides, it was proposed that patients with a higher BMI had a higher 24-h urinary excretion of Na[34,35]. Moreover, the role of different aspects of diet in migraine headaches has been extensively investigated, showing that these dietary factors might attenuate the association between Na and migraine[36]. It seems that individuals with a higher energy intake consume higher amounts of Na, which subsequently increases the estimated 24-h urine Na.

A recent meta-analysis indicated that 93 % of the 24-h dietary intake of Na was excreted in the 24-h urine sample[37]. However, the Na and K intake usually varies among individuals from one season to another, from one day to another and from one meal to another. Therefore, using a single 24-h urine collection may not reflect a person's long-term dietary intake of Na and K, and multiple collections may improve the accuracy of this method. Previous reports have also revealed that migraine patients excrete more Na and K in their urine as compared with healthy individuals[10] and experience natriuresis and diuresis within 12 h of the migraine attack onset[38]. To resolve these issues, we also assessed the dietary intakes of Na and K using FFQ in the past year. Our findings suggested a moderate correlation between the 24-h urine and FFQ-derived data in terms of Na and K levels. However, further studies are needed to assess the validity of 24-h urine collection in migraine patients.

So far, several studies have attempted to investigate the association between Na and headaches[12–14]. In this regard, Pogoda et al.[12] investigated the association between dietary

Na intake and history of migraine or severe headache. They concluded that elevated levels of dietary Na intake were associated with a decreased migraine history (odds ratio = 0·93; 95 % CI 0·87, 1·00; P = 0·045). Another study aimed to determine the effect of a lower Na intake on headache occurrence in an elderly population diagnosed with hypertension[13]. The occurrence of headache was significantly lower in the low Na group (10·5 %) as compared with the controls (14·3 %), with a hazard ratio of 0·59 (95 % CI 0·40, 0·88; P = 0·009). Another finding was reported in the post hoc analyses of the Dietary Approaches to Stop Hypertension-Sodium (DASH-Na) trial among 390 subjects with hypertension. This study proposed a lower risk of headache in the low dietary Na group, as compared with the average Na level in Western diets ($P < 0.05$)[14]. However, some facts should be considered when interpreting and comparing previous findings with our results. First, the populations of previous studies were mostly hypertensive, and the close association between dietary Na intake and hypertension was widely recognised in several reports[39–41]. On the other hand, elevated blood pressure and headache have been long associated in the medical literature[42,43]. Therefore, it can be concluded that a lower incidence of headache in hypertensive individuals with a low-Na diet might be associated with reduced blood pressure[14]. In the present study, subjects with hypertension were excluded, and also, MAP was adjusted to resolve this issue. Second, none of the previous studies have used valid evaluation and diagnostic criteria for selecting the participants, and they are non-specific to migraine. To address this important issue, we used the International Classification of Headache Disorders-3 to select patients with migraine. Moreover, further adjustments were made, based on the migraine type (chronic/episodic) and migraine characteristic (with/without aura). Third, the only cross-sectional study addressing the link between headache and Na intake used the 24-h dietary recall with inherent limitations[44] to evaluate the amount of Na intake. To solve this problem, we used the 24-h urine collection as the gold standard method for assessing the dietary intake of Na and K[20].

The mechanisms underlying the link between the dietary intake of Na and K and migraine are uncertain. Generally, cations are important in brain functions and are involved in the pathophysiology of several diseases, including migraine[7]. Previous studies have reported elevated levels of Na in the blood[45] and CSF[7] during migraine attacks. The absence of significant CSF changes of Ca, Mg and especially K highlights the possible singular role of Na in migraine headaches[7]. The Na level in the CSF equilibrates between the blood and CSF in less than 2 hours and even more rapidly in the brain extracellular fluid, especially in mobile individuals[7,46]. Therefore, we can assume that the observed change in the CSF and brain extracellular fluid reflects a similar level in the plasma. It has been previously reported that a higher dietary Na intake increases the Na content of the human CSF[47]. Increased extracellular Na levels have been shown to inactivate peptides in voltage-gated Na channels, directly displacing them from the extracellular orifice of the channel. While the resting potential of a cell membrane is mainly derived from the K gradient across the membrane (unchanged in the CSF based on previous reports), an elevated extracellular Na level in

migraine patients can slightly reduce the resting membrane potential and consequently decrease the threshold for action potentials[48]. Additionally, elevated extracellular Na levels have been reported to diminish the threshold for repetitive neuronal firing by increasing the Na conductance and increasing the pH-induced nociceptor discharge[49]. Brainard et al. also suggested salt loading as a trigger for migraine headaches through elevated levels of angiotensin and aldosterone in the plasma [50; 51]. In conclusion, further research is needed to elucidate the exact underlying mechanism of action of Na and K in migraine headaches.

Strengths and limitations

The present study has several strengths. We estimated the dietary Na and K intakes using the 24-h urine collection as the gold standard. Besides, to the best of our knowledge, this is the first study to represent the association of Na and K with the clinical features of migraine in an Iranian sample.

The potential limitations of this study should be also addressed. The cross-sectional design of this study precluded us from drawing a causal link between Na and K and migraine. Migraine headaches may lead to salt craving and natriuresis; therefore, a higher 24-h urine Na may be a result of migraine headaches rather than a causative factor. Besides, using a single 24-h urine collection may not reflect a person's long-term dietary intake of Na and K, and multiple collections may improve the accuracy of this method. Although we adjusted for several demographic, clinical and nutritional factors, we could not exclude the possible effects of residual confounding factors on our results. Patients were asked to collect 24-h urine during a headache-free period; however, it is possible that some patients were done this procedure during a migraine attack. Multiple urine collection may improve this limitation.

Conclusion

The present findings suggest that a higher 24-h urine Na level is positively associated with a longer duration of migraine headaches and a higher MHIS. These findings, however, do not specify a cause-and-effect relationship, and there is a need for further research in this area to understand whether reduction of Na intake can improve these symptoms and also to discover the mechanisms that mediate this association.

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