The association between dietary acid load and the migraine odds

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Abstract

**Background:** According to previous evidence, it has been shown that high acidic load in human body could affect inflammatory factors and the nitric oxide pathway. On the other hand, these factors are thought to play a role in initiation of migraine attacks. Therefore, we aimed to explore the association between dietary acid load and the odds of migraine in a case-control study.

**Methods:** The migraine group (n=514, diagnosed according to the ICHDIII criteria) was recruited from a tertiary headache clinic. The controls consisted of 582 sex-matched healthy volunteers who were randomly selected from the general population. For dietary intake assessments, we used a validated 168-item semiquantitative food frequency questionnaire (FFQ). Using three different measures, such as potential renal acid load (PRAL), net endogenous acid production (NEAP), and protein/potassium ratio for estimation of the dietary acid load.

**Results:** According to multivariable logistic regression analysis, in comparison with the lowest tertile, highest tertile of dietary acid load measures including PRAL (OR=7.208, 95% CI 3.33– 15.55), NEAP (OR=4.108, 95% CI 1.924– 8.774), protein/potassium ratio (OR=4.127, 95% CI 1.933– 8.814) were shown to significantly increase odds of migraine (P for trend= <0.001).

**Conclusions:** In this study, it was found that high dietary acid load may be associated with higher odds of migraine. Consequently, restricting dietary acid load could be beneficial in reducing the odds of developing migraine in susceptible subjects.

Introduction

Migraine is one of the most disabling neurological problems in the world (1). According to report in 2019, the estimated prevalence of migraine is from 12–16% of the general population (2). This disease has been related to other health problems such as anxiety, depression, fibromyalgia, asthma, obesity, stroke, and coronary heart disease (3, 4). Although underlying mechanisms for the onset of migraine are not entirely realized, several abnormal conditions in the body are involved in the pathophysiology of this disorder. Some of these mechanisms include changes in cerebral blood flow, mitochondrial and hormonal dysfunction, genetic factors, obesity, neuroinflammation, in addition to increased levels of a number of neuropeptides especially nitric oxide (NO), and calcitonin gene-related peptide (CGRP) which are thought to be involved in the function of trigeminovascular system. On the other hand, activation of the trigeminovascular system could lead to excretion of substances such as CGRP, substance P and NO (5–8). These agents are associated with inflammation and vasodilation in cranial vessels, which lead to intense pain (5, 6, 8). NO is believed to play an important role in initiating of migraine attacks that perform its functions by NO/cyclic guanosine monophosphate (cGMP) pathway, and its levels are shown to be elevated in people with migraine during and between headache attacks (9, 10). Moreover, cytokines and inflammatory agents around nerves can activate trigeminovascular neurons and increase CGRP release (11). It has been shown that inflammatory factors such as tumor necrosis factor-alpha (TNF-α), C-
reactive protein (CRP), Interleukin 6 (IL6) increased in people with migraine headache compared to healthy subjects (10, 12–15).

The available evidence suggests that even a slight increase in acidic load may stimulate the expression of induced NO synthases, increase levels of inflammatory factors such as TNF, increase blood flow as well as adiposity measures such as body mass index (BMI) (16–20). High dietary acid load, that is known by high intake of acid precursors including phosphorus and protein containing sulfuric amino acid and low intake of base precursors such as potassium, magnesium and calcium, could shift the acid-base balance towards acidosis (21, 22). This type of diet is rich in meat, dairy, and grain and poor in fruits and vegetables (22). A previous case-control study (23) has addressed that the western diet, which is typically characterized by high consumption of meat and low content of vegetables and fruits, thus may have a high dietary acid load (24), could increase odds of migraine.

High acidic load in the human body could affect inflammation, NO pathways, blood flow and adiposity measures (16–20). On the other hand, these factors are thought to play a role in initiation of migraine attacks (5, 6, 8, 10, 12–15). Thus, it can be hypothesized that higher consumption of acidogenic foods including meat that yield higher dietary acid load might increase the odds of developing migraine in susceptible patients. Therefore, in current study, we aimed to explore the association between dietary acid load and the odds of migraine headache.

**Materials And Methods**

**Study population and design**

In current case-control study migraineurs were recruited from the tertiary headache clinic of Sina University Hospital and a private headache clinic. The data was collected from 2015 to 2018. Detailed information on the study methods has been reported previously (25). Our expert headache-specialist neurologist diagnosed migraine headache (episodic and chronic migraine) according to the international headache classification (ICHDIII criteria, beta version) (26). Due to the fact that episodic migraine patients are less likely to be referred to our tertiary headache clinic, a higher proportion of referred patients were diagnosed with chronic migraine. Based on ICHDIII-beta criteria, chronic migraine is defined as 15 or more headache days per month with at least 8 migraine headache types in the last 3 months and episodic migraine characterised by up to 14 days per month. Controls were consisted of 582 sex-matched healthy volunteers who were randomly selected from the general population. Inclusion criteria for both the patients and control group included: age between 18–60 years, body mass index (BMI) between 18.5 and 35 kg/m² and daily energy intake between 800 and 5000 kcal. Exclusion criteria for both groups were: the preganany or breastfeeding, having a history of chronic diseases such as gastrointestinal, liver or kidney disorders, diabetes mellitus, cardiovascular diseases, malignancy, tuberculosis, sarcoidosis, rheumatoid arthritis, psychiatric disorders and any type of neurological diseases except for migraine including parkinson, alzheimer disease, multiple sclerosis, etc., substance/alcohol- overusing or consistent smoking and following a specific diet over last year. The patients who referred to our tertiary headache clinic
prescribed medications by our expert headache-specialist neurologist. These drugs consisted of: Abortive
drugs for acute treatment of headache attack (i.e., nonsteroidal antinflammatory drugs (NSAIDs), other
analgesics (codeine), and triptans), prophylactic medications (i.e., propranolol (βblockers), topiramate
and sodium valproate/Depakene (antiepileptic drugs), selective serotonin reuptake inhibitor (SSRIs), and
tricyclic antidepressants (TCAs). The research methods and study design was reviewed and approved by
ethics committee of vice-chancellor in research affairs (ethics code: IR.TUMS.NI.REC.1398.010). Also, a
written informed consent was obtained from all studied subjects.

**Assessment of anthropometric measures**

For anthropometric variables, body weight was measured using a seca755 medical scale (weighing
accuracy of 0.5 kg), and height was measured by a standard stadiometer (accuracy of 0.1 cm). BMI was
calculated as weight (kg) divided by the square of the height (m2).

**Dietary assessment and calculation of dietary acid load**

Food intake was assessed by a validated 168-item semi-quantitative food frequency questionnaire (FFQ)
(27). Trained dietitians completed FFQ for all our participants. The food items were according to the US
department of agriculture (USDA) standard serving sizes. Household measures (e.g., beans, 1 tablespoon;
chicken meat, 1 leg or wing; rice, 1 large or small plate) were used, when standard serving sizes did not fit
(28). By FFQ questionnaire, participants reported their intake of each food item base on daily, weekly,
monthly or yearly. Then, data was converted to gram assuming each month equals 30.5 days. Daily
macronutrient intake for each individual was measured by use of the Iranian national food composition
table. Total macronutrient consumption was measured by summing up macronutrient intake from all
consumed foods(29).

In this study, we used three different measures, including potential renal acid load (PRAL), net
endogenous acid production (NEAP), and protein/potassium ratio for calculating dietary acid load, which
been validated in previous studies (30-32). The algorithms of these measures were as follows: first, PRAL
(mEq/day) = 0.49×protein (g/day) +0.037×phosphorus (mg/day) −0.021×potassium (mg/day)
−0.026×magnesium (mg/day) −0.013×calcium (mg/day) (30). Second, NEAP (mEq/d) = [54.5×protein
intake (g/d) ÷ potassium intake (mEq/d)]-10.2 (31). Third, protein/potassium ratio= total protein (g/d)/
potassium intake (g/d) (32).

**Statistical method**

Analyses were performed applying the Statistical Package for the Social Sciences (SPSS) software
(version 24 (Chicago: SPSS Inc. IBM Corp.). All dietary variables that aimed to be investigated concerning
migraine odds were classified in tertiles. Accordingly, baseline characteristics, anthropometric data, and
nutritional intakes were compared through tertiles of PRAL and NEAP. One-way analysis of variance and
the chi-squared test were used to compare continuous and categorical variables between PRAL and NEAP
tertiles, respectively, and mean (standard deviation, SD) or number (%) were reported as appropriate. To
explore the association between dietary acid load measures and migraine odds, adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were obtained using multivariable logistic regression models following adjustment for age (year, continuous), sex, BMI (kg/m2, continuous), total daily energy intake (Kcal/d, continuous) as well as daily intake of carbohydrates (g/d), total fat (g/d), Na (mg/d), and dietary food groups (i.e., total refined grains, whole grains, total sugar, vegetables, fruits, red meat, poultry and egg, processed meat, fish, dairy, and nuts). To test for linear trends across tertiles, the median value of each tertile of dietary acid load measures was considered a continuous variable. All reported P values were two-sided, and p-value less than 0.05 was considered statistical significance level.

Results

In total, 1096 participants (approximately 94% women) were assessed in this study of which 514 were migraine patients with a mean age of 36.20 (9.78) and 582 were healthy with a mean age of 44.58 (13.84). The mean BMI in migraine patients and healthy subjects was 25.9 (4.75) and 28.1(4.80) kg/m², respectively. Two-hundred seventy-nine patients had chronic migraine, and 235 had episodic migraine.

Individuals in the third tertile of PRAL (median score = 13.06) and NEAP (median score = 71.99) scores were younger and tended to have higher consumption of refined grains, sugar, process meats, total protein, total fat and lower consumption of vegetables, fruits, nuts, dairy, total energy, total carbohydrate, plants protein and sodium in comparison with the first tertile of PRAL (median score=-27.05) and NEAP (median score = 31.11) scores (P value < 0.05). Mean intake of fish, poultry, and eggs were similar across the PRAL and NEAP tertiles (P value > 0.05) (Table 1). Besides, regarding to PRAL score, individuals in the second tertile (median score= -1.53) had greater BMI and higher intake of red meat and animal protein in comparison with the first tertile (median score= -27.05) (P value < 0.05). Regarding NEAP score, subjects in third tertile (median score = 71.99) and second tertile (median score = 49.80) had greater whole grain consumption in comparison with first tertile (median score = 31.11) (P value < 0.05) (Table 1).
Table 1
Baseline characteristics and dietary intakes of study participants according to the tertiles of dietary acid load.

|                      | Dietary PRAL (mEq/d) |             |           | P a |        | Dietary NEAP (mEq/d) |             |           | P a |
|----------------------|----------------------|-------------|-----------|-----|--------|----------------------|-------------|-----------|-----|
|                      | T1                   | T2          | T3        |     |        | T1                   | T2          | T3        |     |
| **Age b**            | 41.79 ± 12.99        | 41.60 ± 12.86 | 38.95 ± 12.53* | 0.004 |        | 42.6 ± 13.19         | 39.8 ± 12.43* | 39.8 ± 12.76* | 0.004 |
| **Body mass index (kg/m2)** | 26.82 ± 4.53        | 27.66 ± 5.21* | 26.80 ± 4.89 | 0.029 |        | 26.8 ± 4.60          | 27.4 ± 5.14* | 26.9 ± 4.92 | 0.217 |
| **Nutrient intake**  |                      |             |           |     |        |                      |             |           |     |
| **Total energy (kcal)** | 2402 ± 716          | 1970 ± 533* | 2189 ± 514* | < 0.001 |        | 2316 ± 744          | 2087 ± 546* | 2159 ± 526* | < 0.001 |
| **Total carbohydrate (gr)** | 285.6 ± 111.8      | 210.5 ± 72.7* | 219.2 ± 73.6* | < 0.001 |        | 274.1 ± 117.5      | 221.3 ± 72.9* | 220.1 ± 74.6* | < 0.001 |
| **Total protein (gr)** | 92.8 ± 27.5         | 83 ± 22.8* | 97.1 ± 23.1* | < 0.001 |        | 88.4 ± 27.4         | 89.6 ± 24.0 | 94.9 ± 23.8* | 0.001 |
| **Total animal protein (gr)** | 41.2 ± 16.4        | 36.5 ± 13.3* | 41.6 ± 15.8 | < 0.001 |        | 40.4 ± 15.8         | 39.7 ± 14.4 | 39.2 ± 16.0 | 0.610 |
| **Total plant protein (gr)** | 41.1 ± 14.6        | 33.5 ± 12.5* | 35.8 ± 12.3* | < 0.001 |        | 38.6 ± 15.0         | 36.0 ± 12.9* | 35.9 ± 12.5* | 0.013 |
| **Total fat (gr)**    | 94.0 ± 38.2         | 83.8 ± 48.2 | 118.7 ± 133.4* | < 0.001 |        | 91.6 ± 36.9         | 90.2 ± 57.0 | 114.7 ± 131.3* | < 0.001 |
| **Na (mg/d)**         | 1838.1 ± 895.7      | 1476.6 ± 741.5* | 1506.7 ± 705.8* | < 0.001 |        | 1739.8 ± 842.1      | 1635.3 ± 852.5 | 1446.8 ± 671.7* | < 0.001 |

**Food groups**

PRAL; potential renal acid load, NEAP; net endogenous acid production.

* P value by post hoc analyses when compared with lowest tertiles.

a ANODA test for variables.

b values are mean ± standard deviation.
|                          | Dietary PRAL (mEq/d) | Dietery NEAP (mEq/d) |
|-------------------------|----------------------|----------------------|
| Whole Grains (g/d)      | 37.4 ± 51.1          | 33.4 ± 46.2          |
|                         | 44.1 ± 61.6          | 46.4 ± 58.9*         |
|                         | 43.2 ± 63.2          | 44.9 ± 68.8*         |
|                         | 0.252                | <0.001               |
| Refined Grains (g/d)    | 293.4 ± 162.6        | 269.4 ± 151.4        |
|                         | 333.9 ± 144.7        | 352.0 ± 144.3*       |
|                         | 458.6 ± 168.0*       | 464.3 ± 166.1*       |
|                         | 0.000                | <0.001               |
| total sugar (g/d)       | 40.8 ± 53.8          | 39.3 ± 53.7          |
|                         | 53.0 ± 73.1          | 59.9 ± 79.0          |
|                         | 97.3 ± 115.9*        | 91.9 ± 113.5*        |
|                         | <.0001               | <0.001               |
| Vegetables (g/d)        | 463.4 ± 217.9        | 454.4 ± 216.1        |
|                         | 356.4 ± 155.9*       | 364.1 ± 166.3*       |
|                         | 236.5 ± 122.1*       | 238.0 ± 120.8*       |
|                         | <0.001               | <0.001               |
| Fruit (g/d)             | 1047.7 ± 859.4       | 1027.6 ± 868.6       |
|                         | 387.0 ± 178.7        | 410.1 ± 212.7*       |
|                         | 247.2 ± 128.6*       | 246.0 ± 125.3*       |
|                         | <0.001               | <0.001               |
| Nuts (g/d)              | 18.2 ± 21.8          | 18.3 ± 23.3          |
|                         | 8.9 ± 16.4*          | 9.8 ± 15.0*          |
|                         | 6.9 ± 10.4*          | 6.0 ± 9.0*           |
|                         | <0.001               | <0.001               |
| Dairy (g/d)             | 383.3 ± 233.0        | 385.1 ± 232.0        |
|                         | 301.6 ± 165.5        | 320.3 ± 166.9*       |
|                         | 281.3 ± 147.3*       | 261.0 ± 141.0*       |
|                         | <0.001               | 0.000                |
| Red meat (g/d)          | 30.5 ± 22.5          | 29.1 ± 22.3          |
|                         | 25.7 ± 21.5*         | 28.3 ± 22.8          |
|                         | 31.6 ± 25.7          | 30.3 ± 25.1          |
|                         | 0.002                | 0.490                |
| Processed meat (g/d)    | 4.2 ± 8.4            | 3.6 ± 6.8            |
|                         | 4.4 ± 8.3            | 5.7 ± 10.2*          |
|                         | 11.1 ± 15.2*         | 10.4 ± 15.0*         |
|                         | <0.001               | 0.000                |
| Fish (g/d)              | 9.5 ± 12.2           | 8.9 ± 11.7           |
|                         | 8.4 ± 10.1           | 9.5 ± 10.8           |
|                         | 9.9 ± 9.8            | 9.3 ± 9.7            |
|                         | 0.142                | 0.708                |
| Poultry and Eggs (g/d)  | 53.0 ± 32.5          | 51.8 ± 31.5          |
|                         | 48.5 ± 28.7          | 52.9 ± 30.5          |
|                         | 58.6 ± 37.2*         | 55.5 ± 37.2          |
|                         | <0.001               | 0.311                |

PRAL: potential renal acid load, NEAP: net endogenous acid production.

* P value by post hoc analyses when compared with lowest tertiles.

*a* ANODA test for variables.

*b* values are mean ± standard deviation.

The ORs and corresponding 95% CIs for migraine according to tertiles of dietary acid load measures intake are shown in Table 2 and Fig. 1. According to multivariable logistic regression analysis, in comparison with the lowest tertile, individuals in the third tertile of PRAL scores had increased odds of migraine by approximately seven times (OR = 7.208, 95% CI 3.33– 15.55; P for trend = <0.001). Also, the
subjects in the third tertile of each of NEAP score or protein/potassium ratio were shown to have approximately four-fold elevation in migraine odds when comparing to those in the first tertiles (OR = 4.10, 95% CI 1.92– 8.77; P for trend = < 0.001) (OR = 4.12, 95% CI 1.93– 8.81; P for trend = < 0.001), respectively (Table 2 and Fig. 1).

Table 2
Odds ratio and 95% confidence interval for migraine according to the tertiles of dietary acid load.

| Dietary indexes of acid load | T1  | T2                  | T3  | P for trend |
|-----------------------------|-----|---------------------|-----|-------------|
| PRAL (mEq/d)                |     |                     |     |             |
| Cases/non-cases             | 197/169 | 138/227              | 179/186 |             |
| Multivariable model         | 1.00 | 2.190 (1.242–3.861)  | 7.208 (3.339–15.558) | < 0.001 |
| NEAP (mEq/d)                |     |                     |     |             |
| Cases/non-cases             | 207/158 | 142/224              | 165/200 |             |
| Multivariable model         | 1.00 | 1.574 (0.910–2.722)  | 4.108 (1.924–8.774) | < 0.001 |
| protein/potassium ratio     |     |                     |     |             |
| Cases/non-cases             | 207/158 | 141/224              | 166/200 |             |
| Multivariable model         | 1.00 | 1.573 (0.910–2.720)  | 4.127 (1.933–8.814) | < 0.001 |

PRAL; potential renal acid load, NEAP; net endogenous acid production.

Discussion
The result of this large population-observational study showed that high dietary acid load intake had a direct association with odds of migraine. Participants with higher PRAL scores, that had high daily intake of protein as well as phosphorus as acid-producing components and less potassium, magnesium, and calcium consumption per day as base-producing components (30, 33, 34), had approximately seven times increased odds of migraine, compared to those who had the lowest scores. Also, increased scores of NEAP and protein/potassium ratio that shows higher daily consumption of protein divided by potassium (31, 32) were related to about four-fold elevation in migraine odds.

In this study we used different methods for calculating dietary acid load, including PRAL, NEAP, and protein/potassium ratio. These methods are based on protein, potassium, phosphorus, calcium, and magnesium intake, which are acid-base precursors and probably related to PH homeostasis in the human
body (22, 30, 32). The higher value of PRAL, NEAP scores, and protein/potassium ratio are indications of more acidic food, while the lower amount of these measurements are pointing to more basic food consumption. Individuals with high dietary acid load had a lower intake of fruits and vegetables and more meat and protein consumption (22). In the present study, we found that high PRAL, NEAP, and protein/potassium ratio, which might be related to meats, grain, and sugar consumption, have a positive association with odds of migraine. Therefore, these findings demonstrated that a high acidic load in the human body, which could be induced by acidic food intake (21), may have an essential contribution to migraine pathogenesis and developing odds of this disorder.

To our knowledge, the association between the dietary acid load and odds of migraine has not been studied yet. Previous studies have only reported the consumption of single acidic and basic food items with odds of migraine (35, 36). In agreement to our finding, one case-control research showed that odds of migraine decreased by about 50 percent and 70 percent as consumption of vegetables and fruits increased in paediatrics (35). Furthermore, a study reported individual with migraine has a significantly higher frequency of using red meat than individuals without migraine (36). Also, according to the available evidences, individuals with western dietary patterns defied by high intakes of red and processed meat and lowe intake of fruits and vegetables had higher frequency of migraine attacks (23). Due to the high amount of acidic food items in the western dietary pattern, this type of diet may give an example of a high dietary acid load (24), which at least in part is in line with our findings.

Although protein intake can influence acid-base balance in the human body because of containing sulphuric amino acid (22), a recent study revealed that there were no differences in dietary protein intake among women with and without migraine (37). In the present study, we found that high PRAL, NEAP, and protein/potassium ratio, which significantly associated with high total protein intake, had positive associations with odds of migraine. The observed difference may be related to dietary patterns and dietary habits of the studied population as well as various controlled confounders. Moreover, another explanation for these difference probably due to the fact that dietary acid load measures such as PRAL, NEAP, protein/potassium ratio calculated by comparison between the acid and base precursors intake. Therefore, perhaps total protein intake as acid precursor, in comparison with base precursors have different effects on odds of migraine than consumption of total protein alone.

Chronic consumption of a diet with a high acid load could shift the acid-base balance toward acidosis (21). Besides, with the presence of abnormalities in acid-base balance, the dietary acid load is more likely to induce acidosis in the human body (18). It has been found that people with migraine could have abnormalities in the acid-base balance due to mitochondrial dysfunction (38, 39). Several possible mechanisms have been suggested that a high acidic load may play a role in the onset of migraine attacks or increasing headache attack frequency in migraineurs (16–20); these are explicated as follows. First, animal and human studies have reported that acidosis can cause high inflammation and NO due to its damaging effect on tissues or blood vessels (16–18, 40). The physiological ways to explain this issue is that TNF-α, myeloperoxidase, and NO synthases enzymes may be produced through acidosis condition in the human body (18). Inflammation and factors such as CGRP and NO are believed to play important
roles in migraine attacks initiation (41, 42). On the other hand, cytokines and inflammatory agents around nerves could activate trigeminovascular neurons and increase CGRP release by cellular mechanisms. Due to the existence of the majority of TNF-α receptors in trigeminal ganglion neurons, TNF-α, may increase CGRP gene expression in trigeminal ganglion neurons by increasing intra cellular MAP kinases signaling pathways, which might be attributed to the onset of headache (42–46). Additionally, NO can causes intense pain by increasing dilation and inflammation in cranial vessels through NO-cGMP pathway (9, 10). Therefore, acidosis condition by augmenting inflammation and NO synthesis may have a negative effect on the initiation of migraine attacks.

Second, a high acidic load might cause cortisol augmenting, which might have a negative impact on pain recovery in migraineurs (47). Also, elevated cortisol level, which may be augmented by acidosis, appeared to be associated with high blood flow and BMI in the human body (19, 20). It has been revealed that high blood flow and BMI may play negative roles in the onset of migraine pathogenesis. For example available evidence reported that the odds of migraine is increased in obese individuals (15, 48). Moreover, although there is controversial evidence regarding the association between hypertension and migraine, several findings delineated that long duration and uncontrolled hypertension, especially systolic blood pressure, may have a positive link with migraine with/without aura (49, 50).

Third, gut microbiota could be influenced by dietary acid load due to less intake of fruits and vegetables, which may lead to low microbial diversity in gastrointestinal systems then the adverse effects on human microbiomes (51). Recent shreds of evidence suggested the existence of a link between gut microbiota and migraine (7). Besides, studies have reported that there might be potential beneficial effects following probiotics supplementation in subjects with migraine headache (15, 52, 53).

Therefore, a high acidic load may be contributed with high odds of migraine through increasing inflammatory state, elevating cortisol levels, modifying NO signaling pathway, blood flow, and gut-microbiota, in addition to affecting on body weight and hypertension risk (16–20, 40, 47, 51).

The present study consists of several strengths. Dietary acid load was assessed by various methods such as PRAL, NEAP, protein/potassium ratio that were estimated using a validated FFQ. Another strength was a relatively large population of migraineurs in the case group. Additionally, all migraine patients were diagnosed by our expert neurologist-headache specialist according to the ICHDIII beta criteria. To our knowledge, this was the first study that preformed to explore the association of dietary acid load measures with odds of migraine. However, the limitations of this study are needed to be considered. First, the exact dosage of medications used, and the frequency and intensity of migraine headache attacks were not considered in the calculations. Second, body acid-base balance assessment was based on dietary calculation, and even if urinary and serum pH were available then the result would be more accurate.

Conclusion
The result of this large population-observational study showed that high dietary acid load intake had a positive association with odds of migraine. Thus, as a strategy to reduce dietary acid load, restricting intake of acidogenic foods such as meat, grains, and sugar that are high in protein and phosphorous and low in basic precursors, may be considered a suggestion for reduction of migraine odds. However, our findings require further confirmation within large sample size cohort studies and well-designed clinical trials to identify the effects of dietary acid load on migraine clinical features and its related health outcomes.

Declarations

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Authors’ Contributions

MT and SRJ jointly conceived and designed the study and contributed to the draft. ZGh, PR, BT, PS, AK, MN, FK and MM involved in data gathering and performed the research. MM drafted the manuscript. All authors critically revised the manuscript for important intellectual contents. MT gave final approval of the version to be published.

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Availability of data and materials

All included references in the present review article are available on the Internet.

Ethics approval and consent to participate

The research methods and study design was reviewed and approved by ethics committee of vice-chancellor in research affairs (ethics code: IR.TUMS.NI.REC.1398.010). Also, a written informed consent was obtained from all studied subjects.

Consent for publication

Not applicable.

Competing interests
The authors declare that they have no conflict of interest.

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**Abbreviations**

FFQ: food frequency questionnaire; PRAL: potential renal acid load; NEAP: endogenous acid production; NO: nitric oxide; cGMP: cyclic guanosine monophosphate; TNF-α: tumor necrosis factor-alpha; CRP: C-reactive protein; IL6: Interleukin 6; BMI: body mass index; ICHDIII: international headache classification III; NSAIDs: nonsteroidal antiinflammatory drugs; SSRIs: selective serotonin reuptake inhibitor; TCAs: tricyclic antidepressants; USDA: US department of agriculture.

**References**

1. Arnold M (2018) Headache classification committee of the international headache society (IHS) the international classification of headache disorders. Cephalalgia 38(1):1–211
2. Burch RC, Buse DC, Lipton RB. Migraine: Epidemiology, burden, and comorbidity. Neurologic clinics. 2019 Nov 1;37(4):631 – 49
3. Buse D, Manack A, Serrano D, Turkel C, Lipton RB (2010) Sociodemographic and comorbidity profiles of chronic migraine and episodic migraine sufferers. Journal of Neurology Neurosurgery Psychiatry 81(4):428–432
4. Martami F, Ghorbani Z, Abolhasani M, Togha M, Meysamie A, Sharifi A et al (2018) Comorbidity of gastrointestinal disorders, migraine, and tension-type headache: a cross-sectional study in Iran. Neurol Sci 39(1):63–70
5. Capuano A, De Corato A, Lisi L, Tringali G, Navarra P, Russo CD (2009) Proinflammatory-activated trigeminal satellite cells promote neuronal sensitization: relevance for migraine pathology. Molecular Pain 5:1744–8069
6. Dodick DW (2018) A phase-by-phase review of migraine pathophysiology. Headache: The Journal of Head Face Pain 58:4–16
7. Arzani M, Jahromi SR, Ghorbani Z, Vahabizad F, Martelletti P, Ghaemi A et al (2020) Gut-brain Axis and migraine headache: a comprehensive review. The Journal of Headache Pain 21(1):1–12
8. Ghorbani Z, Rafiee P, Fotouhi A, Haghighi S, Magham RR, Ahmadi ZS et al (2020) The effects of vitamin D supplementation on interictal serum levels of calcitonin gene-related peptide (CGRP) in episodic migraine patients: post hoc analysis of a randomized double-blind placebo-controlled trial. The Journal of Headache Pain 21(1):1–13
9. Fidan I, Yuksel S, Ymir T, Irkec C, Aksakal FN (2006) The importance of cytokines, chemokines and nitric oxide in pathophysiology of migraine. J Neuroimmunol 171(1–2):184–188
10. Ghorbani Z, Togha M, Rafiee P, Ahmadi ZS, Magham RR, Haghighi S et al. Vitamin D in migraine headache: a comprehensive review on literature. Neurological Sciences. 2019:1–19
11. Bowen EJ, Schmidt TW, Firm CS, Russo AF, Durham PL (2006) Tumor necrosis factor-alpha stimulation of calcitonin gene-related peptide expression and secretion from rat trigeminal ganglion neurons. J Neurochem 96(1):65–77
12. Yücel M, Kotan D, Gürol Çiftçi G, Çiftçi I, Cikriklar H (2016) Serum levels of endocan, claudin-5 and cytokines in migraine. Eur Rev Med Pharmacol Sci 20(5):930–936
13. Salehi H, Aminianfar M, RANJBAR NA, Saidi A, Rastgoo F. Comparison of serum CRP in migraine sufferers and normal population. 2014
14. Martami F, Jahromi SR, Togha M, Ghorbani Z, Seifshahpar M, Saidpour A (2018) The serum level of inflammatory markers in chronic and episodic migraine: a case-control study. Neurol Sci 39(10):1741–1749
15. Jahromi SR, Ghorbani Z, Martelletti P, Lampl C, Togha M (2019) Association of diet and headache. J Headache Pain 20(1):1–11
16. Pedoto A, Nandi J, Oler A, Camporesi EM, Hakim TS, Levine RA (2001) Role of nitric oxide in acidosis-induced intestinal injury in anesthetized rats. J Lab Clin Med 138(4):270–276
17. Kellum JA, Song M, Almasri E (2006) Hyperchloremic acidosis increases circulating inflammatory molecules in experimental sepsis. Chest 130(4):962–967
18. Wu T, Seaver P, Lemus H, Hollenbach K, Wang E, Pierce JP (2019) Associations between Dietary Acid Load and Biomarkers of Inflammation and Hyperglycemia in Breast Cancer Survivors. Nutrients 11(8):1913
19. Akter S, Eguchi M, Kurotani K, Kochi T, Pham NM, Ito R et al (2015) High dietary acid load is associated with increased prevalence of hypertension: the Furukawa Nutrition and Health Study. Nutrition 31(2):298–303
20. Farhangi MA, Nikniaz L, Nikniaz Z. Higher dietary acid load potentially increases serum triglyceride and obesity prevalence in adults: An updated systematic review and meta-analysis. PloS one. 2019;14(5)
21. Carnauba RA, Baptista AB, Paschoal V, Hübscher GH (2017) Diet-Induced low-grade metabolic acidosis and clinical outcomes: A review. Nutrients 9(6):538
22. Adeva MM, Souto G (2011) Diet-induced metabolic acidosis. Clinical nutrition 30(4):416–421
23. Hajjarzadeh S, Mahdavi R, Shalilahmadi D, Nikniaz Z. The association of dietary patterns with migraine attack frequency in migrainous women. Nutritional neuroscience. 2018:1–7
24. Frassetto LA, Todd KM, Morris RC Jr, Sebastian A (1998) Estimation of net endogenous noncarbonic acid production in humans from diet potassium and protein contents. Am J Clin Nutr 68(3):576–583
25. Jahromi SR, Togha M, Ghorbani Z, Hekmatdoost A, Khorsa F, Rafiee P et al (2019) The association between dietary tryptophan intake and migraine. Neurol Sci 40(11):2349–2355
26. Huang T-C, Wang S-J. The International Classification of Headache Disorders (ICHD-3 Beta Version). Modern Day Management of Headache: Questions and Answers. 2017:15
27. Esfahani FH, Asghari G, Mirmiran P, Azizi F (2010) Reproducibility and relative validity of food group intake in a food frequency questionnaire developed for the Tehran Lipid and Glucose Study. J Epidemiol 20(2):150–158
28. Ghafarpour MH-RA, Kianfar H (1999) The manual for household measures, cooking yields factors and edible portion of food. Nashre Olume Keshavarzy, tehran
29. Beltsville M. Food and Nutrition Information Center, US Department of Agriculture: Food composition table (FCT). 2009
30. Remer T, Dimitriou T, Manz F (2003) Dietary potential renal acid load and renal net acid excretion in healthy, free-living children and adolescents. Am J Clin Nutr 77(5):1255–1260
31. Frassetto LA, Todd KM, Morris RC Jr, Sebastian A (1998) Estimation of net endogenous noncarbonic acid production in humans from diet potassium and protein contents. Am J Clin Nutr 68(3):576–583
32. Zwart SR, Hargens AR, Smith SM (2004) The ratio of animal protein intake to potassium intake is a predictor of bone resorption in space flight analogues and in ambulatory subjects. Am J Clin Nutr 80(4):1058–1065
33. Moghadam SK, Bahadoran Z, Mirmiran P, Tohidi M, Azizi F (2016) Association between dietary acid load and insulin resistance: Tehran Lipid and Glucose Study. Preventive nutrition food science 21(2):104
34. Murakami K, Livingstone MBE, Okubo H, Sasaki S (2017) Higher dietary acid load is weakly associated with higher adiposity measures and blood pressure in Japanese adults: The National Health and Nutrition Survey. Nutrition research 44:67–75
35. Ariyanfar S, Jahromi SR, Rezaeimanesh N, Togha M, Ghorbani Z, Khadem E et al. Fruit and vegetable intake and odds of pediatric migraine. Nutrition & Food Science. 2019
36. Nazari F, Eghbali M (2012) Migraine and its relationship with dietary habits in women. Iranian journal of nursing midwifery research 17(2 Suppl1):S65
37. Evans EW, Lipton RB, Peterlin BL, Raynor HA, Thomas JG, O’Leary KC et al (2015) Dietary intake patterns and diet quality in a nationally representative sample of women with and without severe
headache or migraine. Headache: The Journal of Head Face Pain 55(4):550–561

38. Altunkaynak Y, Ozturk M, Ertem DH, Guveli B, Okay FU, Yildirim Z et al (2013) Serum lactic acid and pyruvic acid levels in patients with migraine and tension type headache. Dusunen Adam 26(3):276

39. Okada H, Araga S, Takeshima T, Nakashima K (1998) Plasma lactic acid and pyruvic acid levels in migraine and tension-type headache. Headache: The Journal of Head Face Pain 38(1):39–42

40. PEDOTO A, Caruso JE, Nandi J, Oler A, Hoffmann SP, Tassiopoulos AK et al (1999) Acidosis stimulates nitric oxide production and lung damage in rats. Am J Respir Crit Care Med 159(2):397–402

41. Olesen J, Thomsen LL, Iversen H (1994) Nitric oxide is a key molecule in migraine and other vascular headaches. Trends Pharmacol Sci 15(5):149–153

42. Bowen EJ, Schmidt TW, Firm CS, Russo AF, Durham PL (2006) Tumor necrosis factor-α stimulation of calcitonin gene-related peptide expression and secretion from rat trigeminal ganglion neurons. Journal of neurochemistry 96(1):65–77

43. DeBustros A, Baylin SB, Levine M, Nelkin BD (1986) Cyclic AMP and phorbol esters separately induce growth inhibition, calcitonin secretion, and calcitonin gene transcription in cultured human medullary thyroid carcinoma. J Biol Chem 261(17):8036–8041

44. Tverberg L, Russo A (1993) Regulation of the calcitonin/calcitonin gene-related peptide gene by cell-specific synergy between helix-loop-helix and octamer-binding transcription factors. J Biol Chem 268(21):15965–15973

45. Covelli V, Munno I, Pellegrino N, Marinaro M, Gesario A, Massari F et al (1992) In vivo administration of propranolol decreases exaggerated amounts of serum TNF-alpha in patients with migraine without aura. Possible mechanism of action. Acta neurologica 14(4–6):313–319

46. Kopp S. Neuroendocrine, immune, and local responses related to temporomandibular disorders. Journal of orofacial pain. 2001;15(1)

47. Leistad RB, Stovner LJ, White LR, Nilsen KB, Westgaard RH, Sand T (2007) Noradrenaline and cortisol changes in response to low-grade cognitive stress differ in migraine and tension-type headache. J Headache Pain 8(3):157

48. Jahromi SR, Abolhasani M, Ghorbani Z, Sadre-Jahani S, Alizadeh Z, Talebpour M et al (2018) Bariatric surgery promising in migraine control: a controlled trial on weight loss and its effect on migraine headache. Obes Surg 28(1):87–96

49. Agostoni E, Aliprandi A (2008) Migraine and hypertension. Neurol Sci 29(1):37

50. Gardener H, Monteith T, Rundek T, Wright CB, Elkind MS, Sacco RL (2016) Hypertension and migraine in the Northern Manhattan Study. Ethn Dis 26(3):323

51. David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE et al (2014) Diet rapidly and reproducibly alters the human gut microbiome. Nature 505(7484):559–563

52. Yu-Jie Dai M, Hai-Yan Wang M, Xi-Jian Wang M (2017) Alan David Kaye M. Potential beneficial effects of probiotics on human migraine headache: a literature review. Pain Physician 20:E251–E255
Figures

a. PRAL (mEq/day)

Third Tertile

Second Tertile

Odds ratio (CI)

0 5 10 15 20

b. NEAP (mEq/d)

Third Tertile

Second Tertile

Odds ratio (CI)

0 2 4 6 8 10

c. Total protein/potassium ratio

Third Tertile

Second Tertile

Odds ratio (CI)

0 2 4 6 8 10

Figure 1
Multivariable adjusted odds ratios and 95% confidence intervals for migraine by tertiles of PRAL (mEq/day) (a), NEAP (mEq/d) (b), protein/potassium ratio (c) adjusted for age (year, continuous), sex, BMI (kg/m², continuous), total daily energy intake (Kcal/d, continuous) as well as daily intake of carbohydrates (g/d), total fat (g/d), Na (mg/d), and dietary food groups (i.e. total refined grains, whole grains, total sugar, vegetables, fruits, red meat, poultry and egg, processed meat, fish, dairy, and nuts).