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The Association Between Dietary Acidity and Clinical Symptoms in Patients With Rheumatoid Arthritis

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ABSTRACT

This study aimed to investigate the relationship between dietary acidity load and clinical symptoms in the patients with rheumatoid arthritis (RA). This case-control study examined 55 patients with RA and 215 healthy individuals in a Ravansar non-communicable diseases (RaNCDs) cohort study, Iran. Participants' food intakes were assessed using a validated food frequency questionnaire. The dietary acidity was calculated using potential renal acid load (PRAL), net endogenous acid production (NEAP), and dietary acid load (DAL) scores. The patients with RA were identified based on the self-reporting, medications history, and the approval of the cohort center physician following patients' examination. The odds ratio (OR) of joint stiffness in fully adjusted model was greater in the upper median of dietary acidity than in the lower median (PRAL: odds ratio [OR], 1.18; 95% confidence interval [CI], 0.59–2.36), but there was no statistically significant difference. The OR of joint pain in the upper median of dietary acidity was less than in the lower median in fully adjusted model (PRAL: OR, 0.70; 95% CI, 0.46–1.29), but the difference was not statistically significant. After adjusting potential confounders, people in the upper median of dietary acidity had a higher OR of developing RA than those in the lower median (PRAL: OR, 1.39; 95% CI, 0.70–2.76); however, it was not statistically significant. There was not any statistically significant relationship among dietary acidity and the odds of joint pain, joint stiffness, and developing RA.

Keywords: Potential renal acid load; Net endogenous acid production; Dietary acid load; Rheumatoid arthritis

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease associated with joint abnormalities and systemic complications [1,2]. Most of these patients seek alternative or complementary therapies in terms of the lack of definitive treatment for RA and various side effects of medication [2,3]. The patients with RA have repeatedly reported positive effects

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Conflict of Interest
The authors declare that they have no competing interests.

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of dietary changes on their disease activity [4]. Therefore, dietary manipulation may play an important role to control and reduce the symptoms of RA patients [5,6]. Diet modification is an easy and economical intervention to control RA. According to researches, Western dietary patterns characterized by a high intake of acid foods such as animal products, and a low intake of alkaline foods such as fruits and vegetables can result in an excess of endogenous acids, which can induce acid-base imbalances and metabolic acidosis [7,8]. It was found that acidity in the synovial fluids of the patients with RA is significantly lower than the patients with osteoarthritis or the control group [9]. This change in local acidity may exacerbate pain, especially in connective tissues [4]. Studies found that the western acidogenic diet is associated with an increase in hydrogen ion charge [10]. Acid-base imbalance due to an acidogenic diet can lead to the mild (latent) metabolic acidosis [11]. Mild metabolic acidosis caused by diets can lead to tissue damage and exacerbation of inflammation [12-14]. In the patients with RA, the body's ability to regulate acid-base balance decreases, probably in terms of the renal and pulmonary disorders that are common in these patients [15-19]. Therefore, adherence to a Western diet pattern and the occurrence of latent systemic metabolic acidosis caused by diet may give rise to the development and worsening of RA. Additionally, it seems that alkaline diets, such as the Mediterranean and vegetarian diet, may help people with RA to alleviate their clinical symptoms [20-22]; hence, adjusting the dietary acidity may reduce complications of the disease and improve the quality of life in these patients.

There was not any study on the association between dietary acidity and joint problems in the patients with RA; thus, the present study aimed to investigate the relationship between dietary acidity and joint pain and stiffness in the RA patients in a case-control study in Ravansar non-communicable diseases [RaNCDs] cohort.

MATERIALS AND METHODS

The present case-control study examined 55 patients with RA and 215 healthy individuals in a RaNCDs cohort study in 2020–2021. RaNCDs is a population-based prospective cohort study and part of Prospective Epidemiological Research Studies in Iran (PERSIAN). Ravansar with a population of around 50,000 people is one of the cities with Kurdish ethnicity in Kermanshah province in the west of Iran.

The individuals were selected using the convenience sampling method based on the inclusion criteria from the participants in the cohort study of RaNCDs. The case group included RA patients who were selected based on the self-reporting of RA, disease history including use of RA medications, and approval of RaNCDs cohort center physician after participants' examination. All of the cases were selected based on census method. The control group included healthy individuals who participated in the RaNCDs cohort study. Case and control groups were matched based on age, intake of protein, total cholesterol, fiber, red meat, potassium and phosphorus at the beginning of the study using propensity score matching. Four controls were selected for each case. Individuals with incomplete information and those with a history of renal diseases, cardiovascular diseases, and cancer were excluded from the study due to the impact of these diseases on inflammatory factors and the possibility of changing their diets. Informed written consent was obtained from all participants. The ethics committee in Kermanshah University of Medical Sciences approved the study with ethical code of IRKUMS.REC.1400.059.

Demographic evaluation

Demographic information including age, sex, education level, place of residence, physical activity, and smoking status was collected. Education status was divided into three categories based on their educational level and the amount of years spent in school, i.e. illiterate (a person who is unable to read or write), undergraduate education (including individuals with elementary, middle and high school degrees), postgraduate education (including individuals with bachelor's, master's and PhD degrees). Each participant completed the usual Persian Cohort physical activity questionnaire. The profile of the RaNCD study was published elsewhere [23].

Evaluation of diet and calculation of its acid load score

Food intake was assessed using a 118-item semi-quantitative food frequency questionnaire (FFQ) [24]. All questionnaires were completed in person by a trained interviewer. The amount of each food was eventually converted to the gram on a household scale [25]. Each food was then analyzed using Nutritionist IV software to assess energy and macronutrients intake. The dietary acid load score was calculated based on the dietary parameters for each individual extracted from FFQ. To facilitate research on the effect of the dietary acidity on RA, dietary acidity was calculated based on the grams of protein, potassium, calcium, magnesium, and phosphorus obtained from a 118-item FFQ by three scores of potential renal acid load (PRAL), net endogenous acid production (NEAP), and dietary acid load (DAL). The validity of PRAL and NEAP has already been compared with 24-hour renal net acid excretion (RNAE) in the healthy adults [7,26]. PRAL score was calculated based on the protein, potassium, calcium, magnesium, and phosphorus daily intake via the equation by Remer and Manz [26,27]. Negative PRAL values reflect an alkaline-forming potential, whereas positive values reflect an acid-forming potential [28]. NEAP score was determined using the algorithm published by Frassetto et al. [7] considering total protein and potassium intake as the primary components involved in acid production. The median of NEAP value for a western dietary pattern is estimated to be 34 to 76 mEq/day [29], whereas the score for a vegan pattern is 7.26 mEq/day [26]. DAL score was calculated by dividing PRAL by body surface area (BSA) [30,31]. The method of calculating PRAL [7], NEAP [26], and DAL [31] indices through the nutrient intakes is as follows:

$$\begin{aligned}\text{PRAL (mEq/day)} = {} & (0.49 \times \text{Protein [g/day]}) + (0.037 \times \text{Phosphorus [mg/day]}) - \\ & (0.021 \times \text{Potassium [mg/day]}) - (0.026 \times \text{Magnesium [mg/day]}) \\ & - (0.013 \times \text{Calcium [mg/day]})\end{aligned}$$

$$\text{NEAP (mEq/day)} = 54.5\ (\text{Protein [g/day]}/\text{Potassium [mEq/day]}) - 10.2$$

$$\text{DAL (mEq/day)} = \text{PRAL} + (\text{Body Surface Area [m}^2\text{]} \times 41\ \text{[mEq/day]}/1.73\ \text{m}^2)$$

BSA is calculated using the Du Bois equation as follows [31]:

$$\text{BSA} = 0.007184 \times \text{Height}^{0.725} \times \text{Weight}^{0.425}$$

PRAL and NEAP indices were used to assess the dietary acidity because they were calculated based on different nutrient intake and biological mechanisms [11]. In three equations, higher scores show higher acidity status.

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Anthropometric measurements and joints pain and stiffness evaluation

The participants' body weight and height were measured using Inbody 770 body analyzer (Inbody Co., Seoul, Korea), and an automatic height measuring instrument (BSM370; Biospace Co., Seoul, Korea), respectively; then body mass index (BMI) were calculated by dividing weight to height squared. The status of joints pain and stiffness was evaluated by examination of patients via the physician of RaNCDs cohort center.

Statistical analysis

The normality of data was assessed using Kolmogorov-Smirnov test. First, the participants were divided based on the median of PRAL, NEAP, and DAL scores. The participants' general characteristics were evaluated based on the classification of PRAL, NEAP, and DAL scores separately in the case and control groups. Food intake was assessed based on the classification of PRAL, NEAP, and DAL scores. Descriptive quantitative and qualitative variables were reported as mean ± standard deviation and frequency (percentage), respectively. The t-test was used for quantitative variables and the Pearson test for qualitative variables to compare the means and frequencies between the 2 groups. The relationships between dietary acidity (PRAL, NEAP, and DAL) and RA and its symptoms were evaluated using the conditional logistic regression model in the crude model and adjusted models. In Model 1, age and sex were adjusted. In Model 2, age, sex, socio-economic status, and smoking were adjusted; finally, in Model 3, energy intake in addition to the items included in Model 2 were adjusted. Data analysis was performed in STATA 14.2. A p value of less than 0.05 was considered a statistically significant level for all tests.

RESULTS

As shown in **Figure 1**, the participants of this study were 55 RA patients as the case group and 215 healthy individuals as a control group. **Table 1** presents the participants' general characteristics. There was not any statistically significant difference between case and control groups in terms of age, education level, place of residence, smoking, and BMI. Among RA patients, 50 (90.91%) individuals were female and the rest were male, and the effect of gender in the models was adjusted. The level of physical activity was significantly higher in the control group than in the case group ($p = 0.03$).

As shown in **Table 2**, 53% of rheumatoid arthritis patients were taking methotrexate and the rest were using other disease modifying anti-rheumatic drugs. According to **Table 3**, daily intake of energy, macronutrients (carbohydrates, proteins, and fats), and the minerals such as potassium, magnesium, calcium, and phosphorus were not statistically significant between the case and control groups. Also, there was no significant difference regarding the intake of red meat, dairy products, fruits, and vegetables between 2 groups.

As presented in **Tables 4-6**, the mean scores of PRAL, NEAP, and DAL were higher in the case group than in the control group. Individuals in the upper median of PRAL had a lower intake of potassium ($p = 0.003$), fiber ($p = 0.04$), fruits ($p = 0.02$), and vegetables ($p = 0.007$). Individuals in the high median of NEAP had a higher intake of energy, protein ($p < 0.001$), red meat, and a lower intake of potassium ($p = 0.001$), and fiber ($p = 0.01$). Individuals in the upper median of DAL had a lower intake of potassium ($p = 0.03$), fiber ($p = 0.03$), and magnesium ($p = 0.01$).

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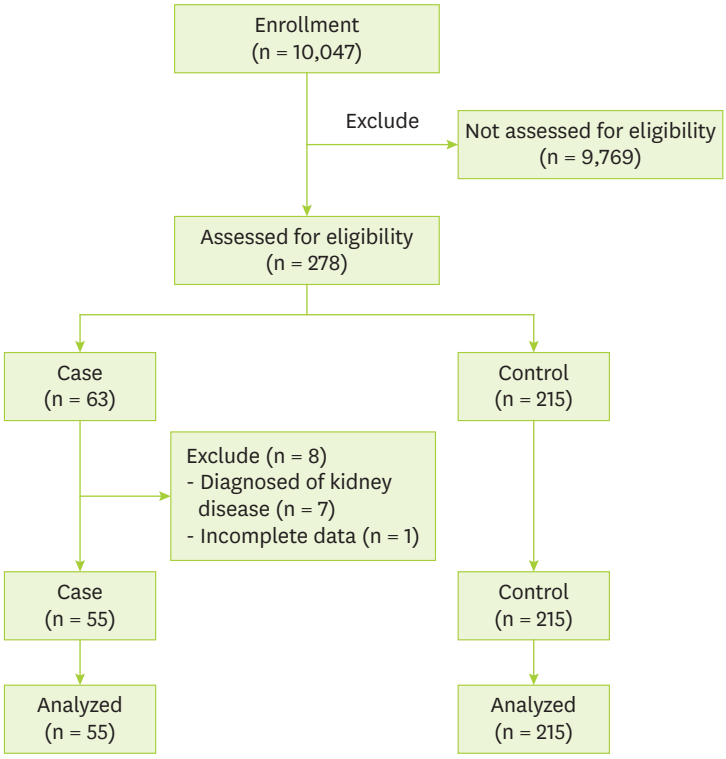

Figure 1. Flowchart of study.

Table 1. General characteristics of study subjects

Variable	Case (RA) (n = 55)	Control (Healthy) (n = 215)	p value*
Age (year)	51.67 ± 8.86	52.14 ± 8.76	0.72
Sex			0.001
Male	5 (9.09)	92 (42.79)	
Female	50 (90.91)	123 (57.21)	
BMI (kg/m^2)	27.86 ± 5.94	27.17 ± 4.50	0.34
Educational status			0.83*
Illiterate	36 (65.45)	132 (61.40)	
Under diploma	14 (25.45)	59 (27.44)	
Upper diploma	5 (9.09)	24 (11.16)	
Physical activity			0.03
Low	20 (36.36)	68 (31.63)	
Moderate	32 (58.18)	104 (48.37)	
High	3 (5.45)	43 (20.00)	
Smoking status			0.27
Never	29 (52.73)	56 (40.19)	
Passive	19 (34.55)	81 (37.85)	
Former	4 (7.27)	21 (9.81)	
Current	3 (5.45)	26 (12.15)	
Residence type			0.32
Urban	35 (63.64)	121 (56.28)	
Rural	20 (36.36)	94 (43.72)	
Dietary acid load			
PRAL	−7.54 ± 14.83	−9.86 ± 17.42	0.36
NEAP	47.92 ± 17.06	46.26 ± 15.84	0.49
DAL	32.52 ± 13.61	31.21 ± 19.05	0.63

RA, rheumatoid arthritis; BMI, body mass index; PRAL, potential renal acid load; NEAP, net endogenous acid production; DAL, dietary acid load.
*Calculated using t-test except variables indicated by strike calculated using Pearson test.

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Table 2. The status of medications intake in rheumatoid arthritis patients

Drug	Percentage (%)
MTX	53
Other DMARDs	47
Corticosteroids	78

MTX, methotrexate; DMARDs, disease modifying anti-rheumatic drugs.

Table 3. Comparison of dietary intake in case and control group

Variables	Case (RA) (n = 55)	Control (Healthy) (n = 215)	p value*
	Mean ± SD	Mean ± SD	
Energy (kcal/day)	2,201.50 ± 771.59	2,382.00 ± 958.74	0.19
Protein (g/day)	75.68 ± 28.88	79.70 ± 37.71	0.46
Carbohydrate (g/day)	341.87 ± 125.79	378.88 ± 159.64	0.11
Fat (g/day)	64.69 ± 26.15	66.35 ± 28.68	0.69
Potassium (mg/day)	2,913.87 ± 1,192.33	3,123.94 ± 1,507.14	0.33
Calcium (mg/day)	1,116.33 ± 487.74	1,214.80 ± 612.99	0.27
Magnesium (mg/day)	289.61 ± 110.33	308.68 ± 140.82	0.35
Phosphorus (mg/day)	1,043.26 ± 398.85	1,094.50 ± 492.79	0.47
Cholesterol (mg/day)	225.05 ± 135.87	236.66 ± 145.78	0.59
Fiber (g/day)	21.64 ± 8.59	23.57 ± 12.70	0.28
Omega-3 (mg/day)	0.03 ± 0.02	0.03 ± 0.03	0.76
Red Meat (g/day)	11.22 ± 16.51	12.41 ± 16.59	0.63
Dairy (g/day)	333.18 ± 285.10	420.53 ± 456.64	0.17
Vegetable (g/day)	101.97 ± 35.27	111.93 ± 49.32	0.16
Fruit (g/day)	134.89 ± 47.68	148.59 ± 66.92	0.15

RA, rheumatoid arthritis.
*Calculated by t-test.

Table 7 presents the adjusted odds ratios (ORs) and 95% confidence interval (CI) for joint pain and stiffness and being RA based on the median of PRAL, NEAP, and DAL. People in the upper median of PRAL, NEAP, and DAL had lower ORs to develop RA in the crude model than those in the lower median (PRAL: OR, 1.16; 95% CI, 0.62–2.1; NEAP: OR, 1.07; 95% CI, 0.56–2.04; and DAL: OR, 1.01; 95% CI, 0.54–1.8). After adjusting potential confounders, people in the upper median of PRAL, NEAP, and DAL had a higher OR of developing RA than those in the lower median (PRAL: OR, 1.39; 95% CI, 0.7–2.76; NEAP: OR, 1.48; 95% CI, 0.69–3.10; and DAL: OR, 1.58; 95% CI, 0.79–3.10), but the difference was not

Table 4. Dietary intakes by median of PRAL in case and control groups

Variable	Case (RA)			Control (Healthy)		
	PRAL < −7.64	PRAL > −7.64	p value*	PRAL < −7.64	PRAL > −7.64	p value*
Energy (kcal/day)	2,181.04 ± 688.50	2,221.20 ± 856.35	0.84	2,450.60 ± 1,029.00	2,306.00 ± 873.00	0.27
Carbohydrate (g/day)	343.17 ± 99.00	340.62 ± 149.01	0.94	398.10 ± 177.25	357.58 ± 135.22	0.06
Protein (g/day)	73.04 ± 26.91	78.25 ± 30.93	0.50	78.74 ± 38.81	80.76 ± 36.60	0.69
Fat (g/day)	64.08 ± 27.29	65.28 ± 25.50	0.86	67.74 ± 28.23	64.80 ± 29.22	0.45
Calcium (mg/day)	1,075.12 ± 423.20	1,156.08 ± 547.71	0.54	1,226.41 ± 652.12	1,201.94 ± 569.44	0.70
Magnesium (mg/day)	315.00 ± 109.64	265.13 ± 107.27	0.09	340.77 ± 158.73	273.13 ± 107.94	0.001
Phosphorus (mg/day)	1,058.55 ± 383.80	1,028.51 ± 419.35	0.70	1,123.45 ± 515.27	1,062.44 ± 467.06	0.36
Potassium (mg/day)	2,374.40 ± 1,232.80	2,469.70 ± 981.40	0.003	3,692.90 ± 1,634.50	2,493.50 ± 1,042.30	0.001
Sodium (mg/day)	4,138.90 ± 1,570.20	3,847.30 ± 1,469.30	0.40	4,519.40 ± 2,242.90	4,277.60 ± 2,025.90	0.40
Cholesterol (mg/day)	218.60 ± 126.40	231.28 ± 146.40	0.73	231.00 ± 143.56	242.86 ± 148.67	0.50
Fiber (g/day)	23.98 ± 8.44	19.38 ± 8.25	0.04	27.29 ± 14.48	19.45 ± 8.77	0.001
Omega-3 (mg/day)	0.03 ± 0.02	0.03 ± 0.02	0.57	0.03 ± 0.03	0.04 ± 0.03	0.03
Red Meat (g/day)	8.37 ± 9.86	13.97 ± 20.88	0.21	12.75 ± 18.37	12.03 ± 14.44	0.75
Dairy (g/day)	330.12 ± 292.93	336.14 ± 282.69	0.93	475.42 ± 486.00	359.72 ± 415.67	0.06
Vegetable (g/day)	107.62 ± 34.79	96.52 ± 35.49	0.24	120.38 ± 51.97	102.58 ± 44.62	0.007
Fruit (g/day)	140.11 ± 46.75	129.87 ± 48.87	0.43	158.64 ± 70.38	137.45 ± 61.29	0.02

PRAL, potential renal acid load; RA, rheumatoid arthritis.
*Calculated by t-test.

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Table 5. Dietary intakes by median of NEAP in case and control groups

Variable	Case (RA)			Control (Healthy)		
	NEAP < 44.80	NEAP > 44.80	p value*	NEAP < 44.80	NEAP > 44.80	p value*
Energy (kcal/day)	2,120.70 ± 715.39	2,291.50 ± 834.73	0.41	2,281.59 ± 868.26	2,497.40 ± 1,045.70	0.09
Carbohydrate (g/day)	333.19 ± 106.79	351.56 ± 145.66	0.59	370.64 ± 154.01	388.35 ± 166.15	0.41
Protein (g/day)	69.81 ± 26.97	82.26 ± 30.03	0.10	71.92 ± 30.51	88.65 ± 43.01	0.001
Fat (g/day)	63.24 ± 27.91	66.31 ± 24.49	0.66	63.90 ± 25.51	69.15 ± 31.83	0.18
Calcium (mg/day)	1,021.42 ± 395.05	1,222.20 ± 562.98	0.12	1,094.69 ± 490.10	1,352.93 ± 706.80	0.001
Magnesium (mg/day)	304.00 ± 112.79	273.57 ± 107.43	0.31	318.80 ± 143.84	297.05 ± 137.05	0.25
Phosphorus (mg/day)	1,058.90 ± 419.33	1,025.81 ± 382.20	0.76	1,053.24 ± 450.16	1,141.95 ± 536.00	0.18
Potassium (mg/day)	3,264.60 ± 1,288.90	2,522.60 ± 952.92	0.01	3,468.40 ± 1,562.30	2,727.70 ± 1,342.60	0.001
Sodium (mg/day)	3,678.00 ± 1,368.40	4,339.00 ± 1,614.20	0.10	4,122.23 ± 1,710.00	4,729.50 ± 2,518.70	0.03
Cholesterol (mg/day)	214.40 ± 127.86	236.94 ± 145.89	0.54	208.05 ± 106.22	269.57 ± 175.79	0.001
Fiber (g/day)	23.27 ± 8.80	19.82 ± 8.13	0.13	25.51 ± 13.13	21.35 ± 11.88	0.01
Omega-3 (mg/day)	0.04 ± 0.02	0.04 ± 0.03	0.96	0.03 ± 0.03	0.04 ± 0.03	0.008
Red Meat (g/day)	8.28 ± 9.61	14.51 ± 21.55	0.16	11.86 ± 18.01	13.04 ± 14.85	0.60
Dairy (g/day)	267.56 ± 175.11	406.38 ± 361.47	0.07	386.70 ± 384.90	459.35 ± 526.59	0.24
Vegetable (g/day)	99.95 ± 33.22	104.22 ± 37.96	0.65	110.35 ± 41.42	113.76 ± 57.24	0.61
Fruit (g/day)	130.47 ± 43.67	139.84 ± 52.22	0.47	144.79 ± 55.45	152.95 ± 78.13	0.37

NEAP, net endogenous acid production; RA, rheumatoid arthritis.
*Calculated by t-test.

Table 6. Dietary intakes by median of DAL in case and control groups

Variable	Case (RA)			Control (Healthy)		
	DAL < 3,319	DAL > 3,319	p value*	DAL < 3,319	DAL > 3,319	p value*
Energy (kcal/day)	2,205.40 ± 699.35	2,197.70 ± 848.35	0.97	2,370.70 ± 949.98	2,392.70 ± 971.25	0.86
Carbohydrate (g/day)	344.55 ± 104.94	339.30 ± 145.00	0.87	385.16 ± 167.93	372.88 ± 151.82	0.57
Protein (g/day)	71.79 ± 21.48	79.46 ± 34.55	0.32	75.05 ± 34.37	84.14 ± 40.29	0.07
Fat (g/day)	66.85 ± 28.38	62.61 ± 24.14	0.50	66.24 ± 26.19	66.45 ± 30.98	0.95
Calcium (mg/day)	1,089.60 ± 423.42	1,142.00 ± 549.31	0.69	1,175.10 ± 570.54	1,252.60 ± 651.29	0.35
Magnesium (mg/day)	305.53 ± 104.49	274.27 ± 115.48	0.29	331.50 ± 153.10	286.89 ± 124.84	0.01
Phosphorus (mg/day)	1,043.76 ± 356.40	1,042.70 ± 442.51	0.99	1,085.30 ± 487.08	1,103.20 ± 500.25	0.78
Potassium (mg/day)	3,251.80 ± 1,128.30	2,587.90 ± 1,180.10	0.03	3,611.30 ± 1,627.20	2,658.70 ± 1,218.90	0.001
Sodium (mg/day)	3,976.60 ± 1,632.60	4,003.80 ± 1,417.50	0.94	4,389.50 ± 1,897.30	4,419.10 ± 2,359.20	0.91
Cholesterol (mg/day)	214.95 ± 106.35	234.80 ± 160.71	0.59	212.90 ± 120.11	259.34 ± 164.00	0.01
Fiber (g/day)	24.11 ± 7.98	19.25 ± 8.62	0.03	26.89 ± 14.15	20.41 ± 10.25	0.001
Omega-3 (mg/day)	0.03 ± 0.01	0.04 ± 0.03	0.45	0.03 ± 0.02	0.04 ± 0.03	0.001
Red Meat (gr/day)	7.84 ± 9.67	14.48 ± 20.81	0.13	11.07 ± 15.19	13.68 ± 17.80	0.24
Dairy (g/day)	331.91 ± 293.89	334.42 ± 281.75	0.97	439.35 ± 424.61	402.56 ± 486.51	0.50
Vegetable (g/day)	104.93 ± 35.30	99.11 ± 35.64	0.54	116.47 ± 45.45	107.61 ± 52.59	0.18
Fruit (g/day)	137.57 ± 47.00	132.32 ± 49.05	0.68	152.93 ± 61.40	144.44 ± 71.84	0.35

DAL, dietary acid load; RA, rheumatoid arthritis.
*Calculated by t-test.

statistically significant. The OR of joint stiffness was higher in people with higher medians of PRAL, NEAP, and DAL than those in lower medians in the crude (PRAL: OR, 1.03; 95% CI, 0.52–2.00; NEAP: OR, 1.10; 95% CI, 0.56–2.14; and DAL: OR, 1.12; 95% CI, 0.57–2.19) and adjusted (PRAL: OR, 1.18; 95% CI, 0.59–2.36; NEAP: OR, 1.32; 95% CI, 0.66–2.64; and DAL: OR, 1.32; 95% CI, 0.65–2.68) models, but it was not statistically significant. The OR of joint pain in people in the upper median of PRAL, NEAP, and DAL was lower than in the lower median in the crude (PRAL: OR, 0.60; 95% CI, 0.40–1.06; NEAP: OR, 0.83; 95% CI, 0.52–1.35; and DAL: OR, 0.74; 95% CI, 0.45–1.19) and adjusted (PRAL: OR, 0.70; 95% CI, 0.46–1.29; NEAP: OR, 1.00; 95% CI, 0.60–1.67; and DAL: OR, 0.99; 95% CI, 0.58–1.69) models, but it was not statistically significant.

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Table 7. Odds ratio and 95% confidence intervals for the association between dietary acidity with RA and its clinical symptoms

Variable	PRAL Median		p value*	Median NEAP		p value*	Median DAL		p value*
	PRAL < −7.64	PRAL > −7.64		NEAP < 44.80	NEAP > 44.80		DAL < 33.19	DAL > 33.19	
Joint pain									
Crude Model	1	0.60 (0.40–1.06)	0.09	1	0.83 (0.52–1.35)	0.47	1	0.74 (0.45–1.19)	0.20
Model 1	1	0.72 (0.43–1.10)	0.20	1	1.00 (0.60–1.67)	0.97	1	0.99 (0.59–1.67)	1.00
Model 2	1	0.70 (0.46–1.28)	0.32	1	0.99 (0.59–1.65)	0.98	1	0.99 (0.58–1.68)	0.98
Model 3	1	0.70 (0.46–1.29)	0.30	1	1.00 (0.60–1.67)	0.99	1	0.99 (0.58–1.69)	0.90
Joint stiffness									
Crude Model	1	1.03 (0.52–2.00)	0.93	1	1.10 (0.56–2.14)	0.76	1	1.12 (0.57–2.19)	0.72
Model 1	1	1.13 (0.57–2.23)	0.72	1	1.28 (0.64–2.54)	0.47	1	1.44 (0.72–2.89)	0.29
Model 2	1	1.19 (0.59–2.37)	0.60	1	1.31 (0.66–2.62)	0.43	1	1.33 (0.72–2.89)	0.42
Model 3	1	1.18 (0.59–2.36)	0.60	1	1.32 (0.66–2.64)	0.42	1	1.32 (0.65–2.68)	0.43
RA									
Crude Model	1	1.16 (0.62–2.10)	0.62	1	1.07 (0.56–2.04)	0.83	1	1.01 (0.54–1.80)	0.97
Model 1	1	1.31 (0.67–2.50)	0.42	1	1.27 (0.62–2.50)	0.50	1	1.45 (0.74–2.80)	0.27
Model 2	1	1.38 (0.70–2.72)	0.35	1	1.47 (0.69–3.10)	0.31	1	1.56 (0.78–3.10)	0.20
Model 3	1	1.39 (0.70–2.76)	0.34	1	1.48 (0.69–3.10)	0.30	1	1.58 (0.79–3.10)	0.19

Model 1: adjusted for age, sex; Model 2: adjusted for age, sex, socioeconomic status and smoking status; and Model 3: adjusted for age, sex, socioeconomic status, smoking status and dietary energy intake.
RA, rheumatoid arthritis; PRAL, potential renal acid load; NEAP, net endogenous acid production; DAL, dietary acid load.
*Calculated by logistic regression.

DISCUSSION

The present study aimed to investigate the relationship between dietary acidity and RA and its clinical symptoms. In this case-control study after adjusting a wide variety of confounders, the dietary acidity estimated using PRAL, NEAP, and DAL scores had no significant relationship with the risk of RA, joint pain and joint stiffness in adults participating in the RaNCDs cohort study.

In the present study the medians of PRAL, NEAP, and DAL were −7.64, 44.80, and 33.19, respectively, indicating relatively the alkaline properties of diet of the participants in the study compared to other studies on Iranian adults (PRAL: 8.93, NEAP: 46.77) [32], Japanese adults (PRAL: 8.95, NEAP: 52.35) [33], and Chinese elderly people (NEAP: 47.3) [34]. A reason for the statistical insignificance of our results may be due to the less acidic diet of the participants in the study. Our study examined 55 Kurdish individuals with RA as a case group. Another reason for the lack of statistical significance may be the small sample size. It is possible that increasing the sample size and investigating different populations make the results statistically significant. Moreover, the individuals may change their diets after diagnosis of RA; hence, a reason why the results were not statistically significant is the unavailability of diets used by people before RA.

There was not any significant relationship between dietary acidity and joint pain but Cseuz et al. [4] found that supplementation with alkyne (containing 400 mg of calcium, 250 mg of potassium, 250 mg of sodium, 100 mg of magnesium, 5 mg of iron, and 1 mg of copper as citrate, 5 mg of zinc gluconate, 0.1 mg of potassium iodide, 0.08 mg of sodium *molybdate*, 0.06 mg of chromium chloride, and 0.03 mg of sodium selenite) could reduce the daily requirement of non-steroidal anti-inflammatory drugs or steroids. The study indicated a significant decrease in level disease activity score 28 and an increase in plasma levels of plasma immunoreactive endorphin after several weeks of alkyne supplementation. The results may indicate that the reduction of mild metabolic acidosis in terms of alkaline can reduce pain. In another study, McDougall et al. [22] found that a low-fat vegetarian diet improved RA

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symptoms such as pain, stiffness, joint tenderness, and arthritis. In this regard, Paalani et al. [35] reported that a vegetarian diet was inversely related to C-reactive protein (CRP) levels. A vegetarian diet may mediate pathways that reduce inflammation and joint pain, and it is effective by lowering CRP levels and improving inflammatory scores [21]. The Mediterranean diet led to significant improvements in disease activity scores, health status (health assessment questionnaire), CRP, and the number of swollen joints in patients with RA [36-38]. There was no significant relationship between dietary acidity and the OR of developing RA. In this regard, Nguyen et al. [39] found an inverse relationship between the adherence to the Mediterranean diet and the risk of RA among female smokers. A case-control study found an inverse relationship between Mediterranean diet scores and RA [40]. Furthermore, the case-control study by Rezazadeh et al. [41] indicated that there was a positive relationship between Western diet model and RA. In confirmation of this study, Nezamoleslami et al. [42] found a positive association between Western dietary pattern and RA. It is worth noting that vegetarian and Mediterranean diets are low acid diets. Therefore, following a low-acid diet may effectively prevent RA, reducing pain, and arthritis in these patients.

Even though there was no precise mechanism to explain the possible association between dietary acidity and RA, the proposed mechanism for the effects of healthy diets (low-acid diet) and Western diet model (high-acid diet) on RA disease can be as follows:

The anti-inflammatory effects of fruits and vegetables which are sufficiently included in alkaline diets such as the vegetarian and Mediterranean diets, block the induction of inflammatory cytokines by inhibiting nuclear factor kappa B activation in terms of their high levels of antioxidants and polyphenols [43-45]. Cerhan et al. [46] conducted a ten-year prospective cohort study on women aged 55–69 years and found that eating diets rich in fruits and cabbage family vegetables and taking zinc supplements and antioxidants might prevent RA. On the contrary, Western diet pattern contains compounds that stimulate inflammatory processes. A positive association was observed among the consumption of red meat, meat products, and total protein with the risk of inflammatory polyarthritis [47]. Antioxidant levels in synovial fluid and serum of RA patients are lower than healthy individuals [44]. Moreover, the continuous production of free radicals from inflamed joints causes the antioxidant system (enzymatic and non-enzymatic) to fail and further tissue damage [44]. Some studies have indicated that using antioxidants has a protective role against tissue damage and leads to improved clinical symptoms in these patients [48]. Therefore, consumption of low-acid diets with high levels of antioxidants may help improve the symptoms of RA patients.

Our study was the first research on the association of dietary acid load with RA, joint pain, and joint stiffness. However, there were some limitations in the study. First, the study design was case-control and did not allow for causation. Second, FFQ was the tool used in the study to assess food intake; hence, there was a possibility of over-reporting and under-reporting for individuals. It is possible that people changed their diet after being diagnosed with RA. Third, we did not assess the disease activity score. As a consequence, the findings of current study may not imply an accurate link between dietary acidity and RA. Also, since this study focused on Kurdish adults, it cannot be applied to other age and ethnic groups.

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CONCLUSION

There was no statistically significant association between dietary acidity and the risk of RA, joint pain, and stiffness in the present study. Other studies including randomized clinical trials and observational studies with large population seem to be necessary to confirm the results of this study.

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