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Association between Dietary Acid Load and Blood Pressure: A Systematic Review and Meta-analysis

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ABSTRACT

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Keywords:
Dietary acid load; Systolic blood pressure; Diastolic blood pressure

Background: Existing data on the association between dietary acid load and blood pressure are not conclusive. This systematic review and meta-analysis aimed to combine findings of evidence regarding the association between dietary acid load and blood pressure.

Methods: MEDLINE and EMBASE databases were searched for studies published up to November 2016. Effect sizes of eligible studies were pooled using random-effects models. Heterogeneity was tested using Cochrane's Q test. Subgroup analyses were done according to the method used for estimating dietary acid load.

Results: Of 7033 records, 8 articles (7 cross-sectional, 1 longitudinal) were eligible for inclusion. Higher dietary acid load was associated with high systolic blood pressure (SBP) (mean difference [MD] = 0.84 mm Hg; 95% CI, 0.04 to 1.64; I2 = 98.4%; p= 039) and diastolic blood pressure (DBO) (MD = 0.75 mm Hg; 95% CI, 0.27 to 1.24; I2 = 75.1%; p=002). Subgroup analyses showed that the type of populations involved and participant sex were sources of heterogeneity for both SBP and DBP, while baseline blood pressure and age were heterogeneity sources exclusively for DBP.

Conclusion: High dietary acid load is associated with greater blood pressure. Further studies are needed to explore the precise impact of low dietary acid load on blood pressure in patients with hypertension.

Introduction

Hypertension is a risk factor for stroke, cardiovascular, and renal diseases [1-3]. Effective interventions to reduce the risk of hypertension might help reduce the incidence of these chronic diseases. Therefore, the identification of dietary and lifestyle modifications or interventions to prevent hypertension is needed [4-5].

Acid-base homeostasis has been associated with cardiometabolic risk factors in recent studies [6-7]. Acidic or alkaline precursors from food intakes can affect the body's acid-base balance [8-11]. Diet can induce mild metabolic acidosis, which may change the blood pressure [12-15]. Studies indicated that sulfate (a by-product of protein metabolism) and phosphorus are dietary factors that may contribute to acid load [9-10, 16]. Typically, these elements are found in meat, fish, cheese, grains, and rice, whereas fruit, legumes, and vegetables contribute to the daily alkali load because of high bicarbonate content [11, 17].

Many studies have shown a positive correlation between high dietary acid load and increased risk of multiple conditions such as cardiovascular disease, bone disease, diabetes, high blood pressure, and kidney diseases [18-22]. Given the general tendency of people toward a Western diet [23-24], finding a link between dietary acid load and blood pressure is important. Moreover, contradictory reports are seen in relation to dietary acid load and these diseases, especially hypertension [25-28]. Therefore this meta-analysis was conducted to elucidate the association between dietary acid load and blood pressure.

Subjects and methods

Data source and search strategy

The present systematic review and meta-analysis was done based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines [23]. We used the PICOS (participants, interventions, comparisons,

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outcomes, and study design) criteria to define the research question (Table 1). PubMed/MEDLINE and Scopus databases were searched for relevant published English-language studies up to November 2016. Other papers were obtained by handsearching the list of references of relevant articles. Keywords from Medical Subject Headings (MeSH) and other related terms were used in this search strategy as follows: ("dietary acid load "OR "Net Endogenous Acid" OR "potential renal acid load" OR "Acid-Base Equilibrium" OR "Acid-Base" OR (("acid*" OR "alkaline" OR "Acid-ash") AND "diet*")) AND ("Blood Pressure" OR "hypertens*").

Eligibility criteria

Studies were included if they (i) were observational in design and (ii) reported means and standard deviations (SD) or standard errors (SE) or 95% confidence intervals (CI) for systolic blood pressure (SBP) and diastolic blood pressure (DBP) in low and high categories of dietary acid load (potential renal acid load [PRAL], net endogenous acid production [NEAP], and protein to potassium ratio [Pr:K]). We excluded reviews, editorials, non-human studies, and letters without sufficient information. Studies with different methods of calculation of dietary acid load were all acceptable.

Study selection

Pooling the retrieved papers and removing duplicates were conducted using EndNote (version X7, for Windows, Thomson Reuters, Philadelphia, PA, USA). Cross-sectional studies that investigated the association between dietary acid load and blood pressure were included. Studies were checked independently by two reviewers in terms of inclusion and exclusion criteria by reading the titles, abstracts, and the full text of the articles. We contacted the research groups for three relevant studies [19, 26-27] and asked them to provide us the necessary information [27].

Data extraction and quality assessment

All relevant information was extracted from eligible articles, including general information (first author, year, study location, journal name), the study population characteristics (age, sex, sample size, adjusted confounders), and the study results (means and their corresponding SDs, or SEs, or 95% CI of SBP and DBP from the lowest and highest categories of dietary acid load (PRAL, NEAP and Pr:K) (Table 2). The methodological quality of the included studies was evaluated using the Newcastle-Ottawa scale [29].

Statistical analysis

Since most of the studies reported mean± SD/SE for SBP and DBP, with only one reporting the odds ratio, we decided to conduct this present meta-analysis on means of the SBP and DBP. We converted the reported SEs to SDs by multiplying the SE times the square root of the sample size. All of the analysis was performed with STATA version 12 (STATA Corp, College Station, TX, USA). A random-effects model (DerSimonian-Laird method) was used to pool the effect sizes. Heterogeneity was tested using the Cochran Q statistic and measured with the I2 statistics. To explore the potential sources of heterogeneity, we performed the subgroup analyses by individual methods used for estimating dietary acid load, population (healthy subjects vs patients), baseline blood pressure (nonhypertensive vs hypertensive), sex (male vs female), and age (≤ 60 vs ≥ 60).

Results

Study selection and data extraction

The flow diagram for the study selection process is shown in (Figure 1). Of 7033 articles retrieved up to November 2016, 5954 articles remained after removing duplicates. Screening the titles and abstracts resulted in the exclusion of additional 5944 records. Of the 14 potentially eligible articles [19, 21-22, 25-26, 30-38], 3 studies were reviews [31, 34, 37], 1 presented hypertension as odds ratio (OR) [30], and another study showed the percent of hypertension [32]. One study did not report the means of blood pressure in tertile of dietary acid load [22]. Two studies investigated renal dietary acid load instead of the dietary acid load [32-33] and one study reported relative risk [21]. The design of one study was interventional which investigated dietary acid load in the form of a diet [36]. Finally, 4 studies which fulfilled our inclusion criteria were remained [25-26, 35, 38]. On the other hand, we obtained 4 articles by hand searching of the reference lists of these studies [19, 27-28, 39]. Finally, 8 studies were included in the review. Of these, two studies did not report the means of DBP in the grouping of dietary acid load, and one article did not report SBP and DBP in tertile of Pr:K [19, 26-27]. The authors of these papers were contacted via email; however, only two authors provided us with the needed data.

Study characteristics

Three of the included studies were conducted in

Iran [19, 26, 28], 2 in Japan [38], 1 in Korea [27, 39], 1 in the Netherlands [35], and 1 in Sweden [25]. Two studies involved patients with diabetic nephropathy and type 2 diabetes [26-27]. The population of three articles was healthy subjects [19, 28, 38], and other studies included both patients and healthy subjects. The average age of the participants varied from 19.6 to 70.5. The sample size of the studies ranged from 260 to 11 601. One study was conducted on women[38], and the subjects of one study were exclusively men [25]. Other studies used both men and women [19, 26-28, 35, 39].

Two different dietary acid load methods were used in the included studies. All studies reported PRAL, according to the formula developed by Remer et al[11]. In 4 studies, in addition to PRAL, the ratio of protein to potassium (Pr:K) or NEAP was presented [19, 26-27, 38].

Assessment of study quality

All studies scored ≥ 7 on the Newcastle-Ottawa Scale. Four studies failed to control for confounding factors [25, 27, 35, 39]. One study did not use validated tools for the measurement of dietary intakes [39]. Also, one study conducted on special population [35]. The last column of Table 2 presents the detailed results of the quality assessment for included studies.

Main analysis

In total, 8 studies with 23 003 participants were included in the meta-analysis. The results of our analysis showed that a higher level of dietary acid load was associated with greater SBP (mean difference [MD] = 0.84 mm Hg; 95% CI, 0.04 to 1.64; I2 = 98.4%; p = 039) (Figure 2) and DBP (MD = 0.75 mm Hg; 95% CI, 0.27 to 1.24; I2 = 75.1%; p = 002) (Figure 3).

Subgroup analysis

Subgroup analysis showed that population type (healthy, patient, or both) and sex were potential sources of heterogeneity for SBP, while baseline blood pressure (non-hypertensive vs hypertensive) and age, as well as sex and population type, were potential sources of heterogeneity for DBP. Moreover, dietary acid load, assessed using the PRAL method, showed a significant association with SBP (MD: 0.70 mmHg; 95% CI, 0.67 to 0.73) and DBP (MD: 0.10 mm Hg; 95% CI, 0.08 to 0.13), whereas Pr:K score was negatively associated with blood pressure (MD: -0.87 mmHg; 95% CI, -0.98 to -0.75).

In subgroup analysis by baseline blood pressure of the participants, studies including only nonhypertensive subjects indicated a significant negative association between dietary acid load and SBP (MD: -0.84 mm Hg; 95% CI, -0.95 to -0.72) and a significant positive association between acid load and DBP (MD: 1.08 mm Hg; 95% CI, 0.50 to 1.66). However, in studies that included both hypertensive and nonhypertensive individuals, dietary acid load was positively associated with both SBP (MD: 0.70 mm Hg; 95% CI, 0.67 to 0.72) and DBP (MD: 0.10 mm Hg; 95% CI, 0.08 to 0.12).

Also, in studies involving only healthy participants or both healthy subjects and patients, a higher dietary acid load was significantly associated with higher SBP and DBP. In subgroup analysis by sex (men, women, or both sexes), significant associations between dietary acid load and SBP were observed in women compared with men (MD: 2.30; 95% CI, 1.13 to 3.48 vs MD: 2.00; 95% CI, -1.09 to 5.09), but the association between dietary acid load and DBP was significant for both sexes. Finally, dietary acid load was positively associated with SBP in individuals younger than 60 years but was negatively associated with SBP in individuals older than 60 years (Table 3).

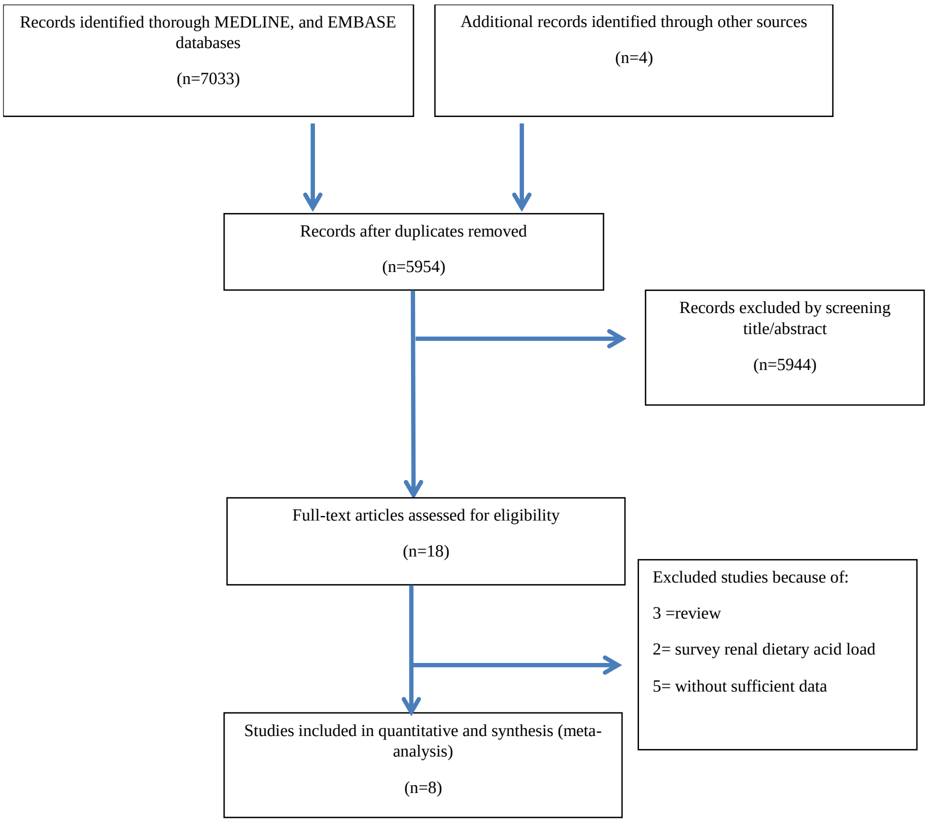

Figure 1. Flowchart of identification of included studies

Table 1. PICOS criteria used to define the research question

Parameter	Description
Participants	General population
Intervention/exposure	Dietary acid load indices (NEAP, PRAL, Pr:K, and DAL)
Comparison	Individuals in the highest category of dietary acid load compared with individuals in the lowest category of dietary acid load
Outcomes	Blood pressure changes
Setting	Cohort, cross-sectional studies

Table 2. Characteristics of included

Author	Year	Design	Country	Sample size (sex)	Age (year)	Acid load calculation method	SBP for lowest dietary acid load, mean±SD	SBP for highest dietary acid load, mean±SD	DBP for lowest dietary acid load, mean±SD	DBP for highest dietary acid load, mean±SD	Quality
Murakami et al	2008	Cross-sectional	Japan	1136 (F)	19.6	PRAL	105.2±9.03	107.3±9.03	68.1±7.53	69.7±7.53	8
Murakami et al	2008	Cross-sectional	Japan	1136 (F)	19.6	Pr:K	104.7±9.03	107.2±9.03	67.9±7.53	70.2±7.53	8
Engberink et al	2012	Cross-sectional	Netherland	2241 (M/F)	65	PRAL	121.1±12.2	122.4±11.7	68±8.7	68.6±8.4	8
Luis et al	2014	Cross-sectional	Sweden	637 (M)	70.5	PRAL	141±15.55	143±17.77	81±12.59	83±8.14	8
Bahadoran et al	2015	Cross-sectional	Iran	5620 (M/F)	39.8	PRAL	112.3±0.4	113±0.4	75.5±0.3	75.6±0.3	9
Bahadoran et al	2015	Cross-sectional	Iran	5,620 (M/F)	39.8	Pr:K	112.5±9.03	112.2±9.03	75±7.53	75.2±7.53	9
Haghighatdoost et al	2015	Cross-sectional	Iran	547 (M/F)	66.8	PRAL	103.6±11.56	106.1±11.58	72.65±10.6	73.58±10.49	9
Haghighatdoost et al	2015	Cross-sectional	Iran	547 (M/F)	66.8	Pr:K	105.3±0.7	104.4±0.7	-	-	9

Iwase et al	2015	Cross-sectional	Japan	260 (M/F)	65.7	PRAL	130.7±16	128.4±13	-	-	8
Iwase et al	2015	Cross-sectional	Japan	260 (M/F)	65.7	NEAP	129.9±15.7	129.2±13.4	-	-	8
Moghadam et al	2016	Longitudinal	Iran	925 (M/F)	40.3	PRAL	115±17.1	114±16.7	77.2±11.3	77.4±10.5	9
Han et al	2016	Cross-sectional	Korea	11601 (M/F)	59.5	PRAL	120.4±17.2	122.2±17.6	76.3±10.1	77.2±10.5	7

PRAL: potential renal acid load, NEAP: net endogenous acid production, Pr:K: protein to potassium ratio, SD: standard deviation, SBP: systolic blood pressure, DBP: diastolic blood pressure.

Table 3. Subgroup analyses of dietary acid load and blood pressure

	No.	MD (95% CI)	P within group	P heterogeneity	I2 (%)	P between subgroups
Systolic blood pressure						
Dietary method						< 0.001
PRAL	8	0.70 (95% CI, 0.67 to 0.73)	< 0.001	0.01	62.0	
NEAP	1	-0.70 (95% CI, -5.39 to 3.99)	0.77	-	-	
Pr:K	3	-0.87 (95% CI, -0.98 to -0.75)	< 0.001	< 0.001	89.4	
Type of participant						< 0.001
Healthy subjects	5	0.67 (95% CI, 0.67 to 0.73)	< 0.001	0.002	76.5	
Patients	4	-0.89 (95% CI, -1.01 to -0.77)	< 0.001	0.007	75.3	
Both	3	1.67 (95% CI, 1.04 to 2.30)	< 0.001	0.77	0.0	
Basline blood pressure						< 0.001
Nonhypertensive	6	-0.84 (95% CI, -0.95 to -0.72)	< 0.001	< 0.001	90.4	
Hypertensive	-	-	-	-	-	
Both	6	0.70 (95% CI, 0.67 to 0.73)	< 0.001	0.002	74.0	
Age						< 0.001
<60 years	6	0.70 (95% CI, 0.67 to 0.73)	< 0.001	< 0.001	80.0	
>60 years	6	-0.86 (95% CI, -0.98 to -0.75)	< 0.001	< 0.001	82.0	
Sex						< 0.001
Male	1	2.00 (95% CI, -1.09 to 5.09)	0.20	-	-	
Female	2	2.30 (95% CI, 1.13 to 3.48)	< 0.001	0.74	0.0	
Both	9	0.61 (95% CI, 0.58 to 0.63)	< 0.001	< 0.001	98.9	
Diastolic blood pressure						
Dietary method						0.14
PRAL	7	0.10 (95% CI, 0.08 to 0.13)	< 0.001	0.001	73.1	
NEAP	-	-	-	-	-	
Pr:K	2	0.49 (95% CI, -0.024 to 1.01)	0.06	0.006	86.8	
Type of participant						< 0.001
Healthy subjects	5	0.10 (95% CI, 0.08 to 0.12)	< 0.001	0.006	72.1	
Patients	1	0.93 (95% CI, -0.83 to 2.70)	0.30	-	-	
Both	3	0.88 (95% CI, 0.491 to 1.27)	< 0.001	0.44	0.0	
Baseline blood pressure						0.001
Nonhypertensive	5	1.08 (95% CI, 0.50 to 1.66)	< 0.001	0.24	27.0	
Hypertensive	-	-	-	-	-	
Both	4	0.10 (95% CI, 0.08 to 0.12)	< 0.001	0.001	81.0	
Age						0.04
<60 years	6	0.10 (95% CI, 0.08 to 0.13)	< 0.001	< 0.001	81.1	
>60 years	3	0.85 (95% CI, 0.12 to 1.57)	0.02	0.44	0.0	
Sex						< 0.001
Male	1	2.00 (95% CI, 0.04 to 3.96)	0.046	-	-	
Female	2	1.95 (95% CI, 0.97 to 2.93)	< 0.001	0.48	0.0	
Both	6	0.10 (95% CI, 0.08 to 0.13)	< 0.001	0.01	65.2	

PRAL: potential renal acid load, NEAP: net endogenous acid production, Pr:K: protein to potassium ratio, MD: mean difference.

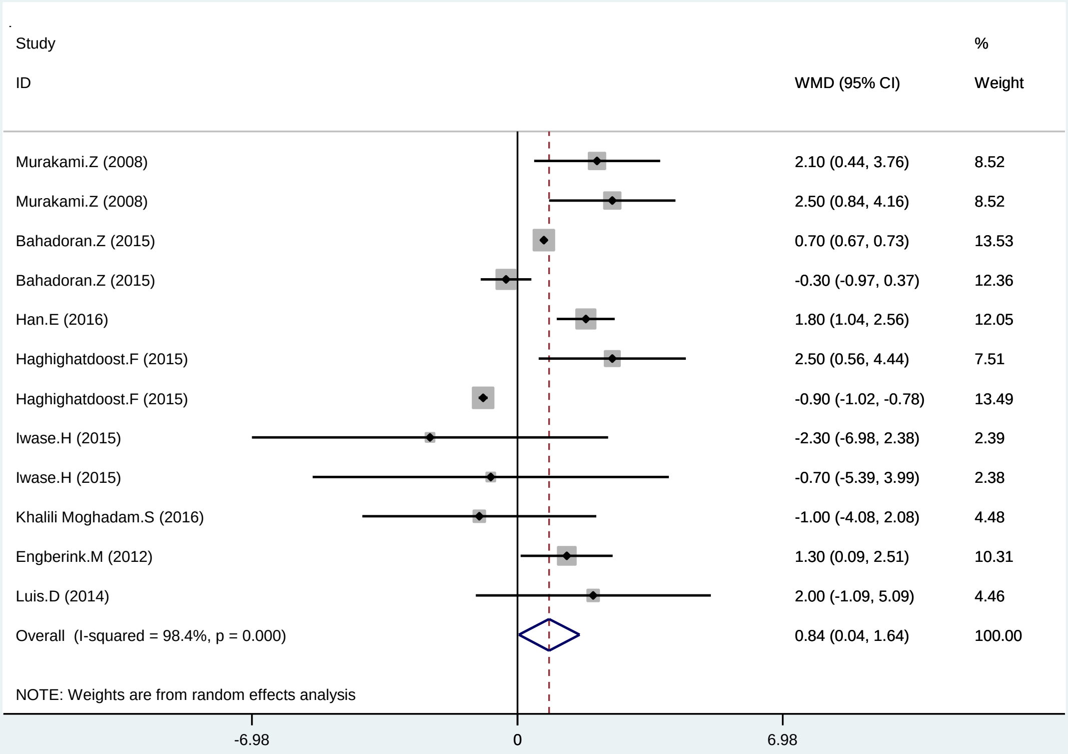

Figure 2. Forest plot for systolic blood pressure changes

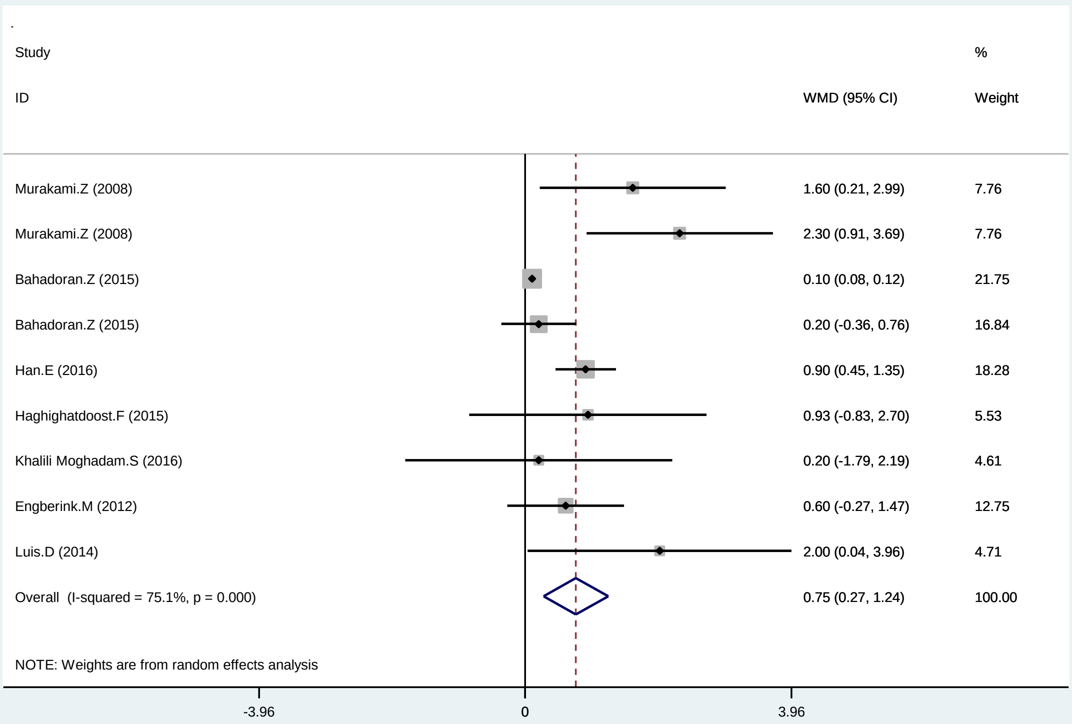

Figure 3. Forest plot for diastolic blood pressure changes

Discussion

The current meta-analysis was the first to investigate the most recent advances in our knowledge of the association between dietary acid load and blood pressure. Few cohort studies or trials have assessed the relationship between dietary acid load and hypertension [21, 36], but information from these studies could not be used for this meta-analysis because of the variability of reported outcomes. Overall, both cross-sectional and cohort studies reported associations between dietary acid load and high level of SBP and DBP.

Our meta-analysis of cross-sectional studies indicated a significant association between dietary acid load and blood pressure. Similar to our results, several studies have shown such correlations between dietary acid load and blood pressure. Zhang et al indicated that women in the top categories of NEAP scores had an increased risk of hypertension [21]. Akter et al, too, showed that high dietary acid load (PRAL and NEAP) was significantly associated with increased prevalence of hypertension [30]. Furthermore, one trial investigated the effect of vitality diet (a low-sodium DASH-type diet with a low dietary acid load containing lean red meat) on blood pressure and reported a significant decrease in SBP and DBP after 14 weeks compared with a higher–acid load reference healthy diet [36]. On the other hand, a number of studies have demonstrated no significant relationship between dietary acid load and hypertension [26, 35, 39]. Some of the studies included in the present study documented a negative association between dietary acid load scores (NEAP and Pr:k) and SBP [19, 26-27], and this association was significant for Pr: K in one study [26]. After analysis for the type of population (healthy subjects vs patients), they found that higher Pr:K scores were associated with lower blood pressure in patients [26]. This finding may be related to the fact that the patients in that study had diabetic nephropathy.

The impact of dietary acid load on blood pressure may be mediated by urinary calcium excretion, cortisol production, or decreased citrate excretion [12, 13, 40-42]. The diet-dependent net acid load can be expressed as "potential renal acid load" (PRAL) [10] or "estimated net endogenous acid production" (NEAP) [8]. These indices are calculated by taking into account the intestinal absorption rates of nutrients such as protein, potassium, calcium, magnesium, and phosphorus, which account of acid-base balance in the body [8, 16]. A positive PRAL rate reflects an acid-forming potential, whereas a negative rate reflects a base (or alkaline)-forming potential [35]. Also, the NEAP score has a large variation in the general population (ranging from 10 to 150 mEq/day). For example, the NEAP score of the Western diet is ∼50 mEq/day [8, 43]. Moreover, several other mechanisms may explain the direct link between dietary acid load and hypertension: (i) increased cortisol production [44]; (ii) decreased citrate excretion [45]; (iii) decreased levels of growth hormone/insulin-like growth factor I [46].

The heterogeneity in the results of studies included in this meta-analysis is probably related to sex, age, type of population (healthy subjects/patients), or baseline blood pressure (nonhypertensive vs hypertensive). We were not able to exactly determine the source of heterogeneity because the number of studies in each subgroup was limited. In the assessment of study quality, most included studies were graded 8 points or above. Regarding study selection, most studies used valid methods and provided acceptable outcome criteria.

The strength of this meta-analysis was conducting subgroup analyses to identify the sources of heterogeneity. A potential limitation of our meta-analysis was the lack of access to unpublished results. Moreover, although we identified some sources of heterogeneity in the results of studies (methodology, sex, and populations involved), we were not able to evaluate all possible sources of heterogeneity because of the limited information about participants (such as medication or BMI). Finally, we could not determine the dose-response association between dietary acid load and hypertension.

Conclusion

In conclusion, the results of this meta-analysis suggest that high dietary acid load is associated with high blood pressure. However, further studies, specifically examining the association between dietary acid load and hypertension (especially in patients with hypertension) while controlling for possible confounders, are needed to fill the gaps that still remain.

Acknowledgment

SF designed the study. SF, ZA, and KD conducted the literature search, data extraction, and independent reviewing. SF and SS-b performed the statistical analyses and wrote a first

draft of the manuscript. SS-b and KD prepared the final draft.

Disclosure statement

There are no competing financial interests.

Conflict of interest

None of authors have conflict of interests.

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