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Review

Dietary acid load and risk of type 2 diabetes: A systematic review and dose–response meta-analysis of prospective observational studies

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SUMMARY

Background & aims: Existing evidence suggests a link between acid-forming potential of diet and type 2 diabetes. But the degree of the associations and shape of the dose–response relations across different indices of diet-dependent acid load and risk of type 2 diabetes and potential confounding by sex have not been established. We aimed to test the dose–response association of different measures of dietary acid load and risk of incident type 2 diabetes, with considering the sex as a potential confounder.

Methods: Systematic search was done using PubMed and Scopus, from inception up to September 2017. Prospective observational studies reporting the risk estimates of type 2 diabetes for three or more quantitative categories of potential renal acid load (PRAL), net endogenous acid production (NEAP) and animal protein-to-potassium ratio (A:P) scores were included. Pooled relative risks (RRs) were calculated using random effects models.

Results: Seven prospective cohort studies with 319,542 participants and 17,986 incident cases of type 2 diabetes were included. Pooled RRs for a 5 unit increment in dietary PRAL, NEAP and A:P was 1.04 (95% CI: 1.01, 1.06; $I^2 = 79\%$, $n = 7$), 1.03 (95% CI: 1.01, 1.04; $I^2 = 54\%$, $n = 7$), and 1.11 (95% CI: 1.07, 1.15; $I^2 = 41\%$, $n = 3$), respectively. Subgroup analysis resulted in significant positive relationship only among women, compared with men. There was a linear association between NEAP and A:P scores and risk of type 2 diabetes, whereas the association appeared to be U-shaped in analysis of PRAL.

Conclusions: Adherence to a diet with high acid-forming potential might increase the risk of type 2 diabetes. Shape of the dose–response relations across different indices of dietary acid load and potential sex differences in the associations need to be further explored. The interpretation of the results is limited by low number of studies.

1. Introduction

Prevalence of type 2 diabetes is increasing alarmingly around the world. It has been estimated that the worldwide prevalence of diabetes for all age-groups will increase from 2.8% in 2000 up to 4.4% by 2030 [1]. Despite the high prevalence and huge socioeconomic burden of diabetes, a high body of evidence has indicated that substantial proportion of new cases of diabetes can be prevented via life-style related changes [2,3]. It has been accepted that inflammation, oxidative stress and insulin resistance are underlying causes of type 2 diabetes [4,5]. Thus, dietary factors related to these conditions might have a role in development of type 2 diabetes.

Previous investigations have indicated that western-style dietary patterns are associated with higher risk of type 2 diabetes [6,7]. This association, at least in part, has been proposed to be mediated through diet-induced metabolic acidosis [8]. It has been suggested that greater adherence to western-style dietary patterns, characterized by high intake of acidogenic foods including animal products, as well as low intake of alkalizing foods including fruits and vegetables might result in excess endogenous acid production, which in turn might lead to acid–base imbalance and low-grade metabolic acidosis [9,10]. Existing evidence suggests that markers

Abbreviations: A:P, animal protein-to-potassium ratio; EPIC, European prospective investigation into cancer and nutrition study; HPFS, health professional follow-up study; JPHC, Japanese public health center-based prospective study; NEAP, net endogenous acid production; NHS, nurse's health study; PRAL, potential renal acid load.

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of metabolic acidosis including low serum bicarbonate, high serum anion gap, and hypocitraturia and low urine pH are associated with insulin resistance [11–16], which is the single most important underlying cause of type 2 diabetes [17]. A prospective evaluation within the Nurse's Health Study (NHS) indicated that higher serum bicarbonate, as a marker of low grade metabolic acidosis, was associated with lower odds of incident type 2 diabetes [18]. Additionally, metabolic acidosis has been shown to be associated with higher levels of blood pressure [19–21], which its elevated levels is associated with higher risk of type 2 diabetes [22].

Several studies investigated the association between diet-dependent acid load and risk of chronic disease, which suggested that adherence to diets with high acid-forming potential might increase the risk of hypertension [23,24], chronic kidney disease [25], and all-cause and cardiovascular mortality [26,27]. However, a prospective evaluation of 16,906 participants in NHANES III found inconsistent findings, in which higher acid-forming potential of diet was associated with lower risk of all-cause mortality after a mean follow-up of 8.7 years [28]. Additionally, a pooled analysis of three large prospective cohort studies in US suggested a potential sex difference in the association between indices of diet-dependent acid load and risk of type 2 diabetes, such that the association was statistically significant only among women, compared with men [29]. However, the potential sex difference in this regard has not been established. The European Prospective Investigation into Cancer and Nutrition (EPIC) study in France reported a positive association in French women [30], and a cohort of community-dwelling older men in Sweden showed no association [31]. Whereas, a large prospective cohort study in Japan showed positive association only among men, but not among women [32]. Furthermore, some investigations have suggested a modest U-shaped association between Potential renal acid load (PRAL), as indices of dietary acid load, and risk of all-cause and cardiovascular mortality [26,33], in which both excessively acid-forming and excessively base-forming diets might increase the risk. However, this hypothesis has not been examined in relation to type 2 diabetes. Generally, three measures were used as indices of dietary acid load:

(1) Potential renal acid load (PRAL) (mEq/day) = 0.4888 × protein [g/day] + 0.0366 × Phosphorus [mg/day] − 0.0205 × Potassium [mg/day] − 0.0125 × calcium [mg/day] − 0.0263 × magnesium [mg/day]
(2) Net endogenous acid production (NEAP) (mEq/day) = (54:5 × protein [g/day]/potassium [mEq/day]) − 10.2
(3) Animal protein-to-potassium ratio (A:P) = animal protein (g/day)/potassium (g/day)

Thus, we aimed to test the dose–response association between indices of diet-dependent acid load and risk type 2 diabetes, and possible confounding by sex.

2. Materials and methods

2.1. Data sources and searches

Systematic literature review was done using PubMed and Scopus, from inception up to September 2017, using following relevant keywords: [“acid–base equilibrium” OR “acid–base imbalance” OR “acid-ash” OR “alkaline-ash” OR “acid–base” OR “acid load”] AND [“diet-dependent” OR “dietary” OR “diet-related” OR “diet-induced” OR “diet”] AND [“diabetes” OR “type-2 diabetes” OR “type 2 diabetes” OR “diabetes mellitus”]. Reference list of all related articles and reviews also were manually searched. The search was restricted to the published English articles.

2.2. Study selection

Two independent authors (AJ, SS-b) reviewed titles and abstracts of all studies. Prospective observational studies obtained and included in this review if they (1) were conducted in general population aged more than 18 years, (2) reported type 2 diabetes incidence as the outcome of interest, (3) reported risk estimates (relative risk (RR) or hazard ratio (HR) or odds ratio (OR)) and their corresponding 95% confidence interval of incident type 2 diabetes in relation to three or more quantitative categories of at least one of the indices of dietary acid load including dietary PRAL, NEAP and A:P, and (4) reported number of cases and participants/person years in each category of abovementioned dietary acid load measures, or reported sufficient information to estimate those numbers.

2.3. Data extraction and quality assessment

Two independent authors (AJ, SS-b) reviewed full text of selected eligible studies and extracted following information: first author's name, publication year, study name, country, follow-up duration, mean age and/or age range, number of participants/cases, indices of dietary acid load reported in each study, method of dietary assessment, diagnosis criteria of type 2 diabetes, adjusted covariates and reported risk estimates and their 95% CI of type 2 diabetes incidence for each category of indices of dietary acid load. The models with most covariates adjustment were selected and included in meta-analysis. The Newcastle-Ottawa scale was used to assess the quality of included studies and studies with a score ≥ 7 were considered high quality [34]. Some of the information concerning the range of dietary PRAL, NEAP and A:P scores in each category in three large prospective cohort studies in US [29] were obtained by correspondence. Discrepancies were resolved through discussion to reach consensus between two authors.

2.4. Data synthesis and analysis

The relative risks (RRs) and 95% CIs were considered as the effect size of all studies. The reported ORs and HRs were considered as equal as RRs. For highest versus lowest category meta-analysis, the reported risk estimates for the highest versus lowest category of each dietary acid load measures were combined using the DerSimonian and Laird random-effects model [35]. Between-studies heterogeneity were explored using Cochrane's Q test of heterogeneity and I^2 statistic ($P < 0.05$) [36] and I^2 statistics. Publication bias was assessed using funnel plots asymmetry and tested by Egger's asymmetry test and Begg's test ($P < 0.10$) [37]. To assess the potential effect of each study on pooled effect sizes, influence analyses were done with one study removed at a time. Subgroup analysis was done on the basis of sex. Linear dose–response relation was estimated by using generalized least squares trend estimation, according to the methods developed by Greenland and Longnecker [38,39]. We used the two stage generalized least squares trend estimation method, which first estimated study specific slope lines and then combined with studies in which the slopes were directly reported to obtain an overall average slope [39]. Study specific results were combined using a random-effect model. The median point in each category of dietary PRAL, NEAP and A:P scores was assigned to the corresponding relative risk for each study. If medians were not reported, we estimated approximate medians by using the midpoint of the lower and upper bounds. If the highest or lowest categories were open-ended, we considered it to have the same widths as the closest category. Two-stage hierarchical regression model was used to test the potential nonlinear association [40], in which the difference between category-specific and reference-specific

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