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Higher dietary acid load is associated with higher likelihood of peripheral arterial disease among American adults

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ABSTRACT

Objective: To explore the association between dietary acid load, potential renal acid load (PRAL) and net endogenous acid production (NEAP), and peripheral arterial disease (PAD) in a national representative sample of American adults.
Methods: The National Health and Nutrition Examination Survey (NHANES) database (for 1999–2002) was used. PAD was diagnosed by ankle brachial index assessment. Analysis of covariance was used to examine adjusted mean of different dietary acid load by PAD status; multivariable logistic regression was used to relate dietary acid load with prevalent PAD. Sample weighting was accounted for in all analyses.
Results: Of the 4864 eligible participants aged 40–85, 2482 (51.0%) were men, and 269 (5.5%) had PAD. After adjustment for age-, sex-, race-, estimated glomerular filtration rate (eGFR), smoking, dietary fat, carbohydrates, protein, saturated fat, and dietary fiber, and energy intake, body mass index, hypertension, cholesterol, triglyceride and diabetes, estimated glomerular filtration rate, participants with PAD had higher mean of (PRAL: 16.2 *vs* 9.1 mEq/d, NEAP: 56.2 *vs* 50.1 mEq/d, both $p < 0.001$) than PAD-free participants. In logistic regression with same cofounders, the top quarter of PRAL (more acidic) was associated with 31% higher odds of the PAD compared with the bottom quarter (more alkaline) [odds ratio: 1.31, 95% confidence interval: 1.11–1.57].
Conclusion: Our findings, for the first time, suggest that dietary acids load, an index of acid-base balance, is associated with the likelihood of PAD after adjustment for main clinical and anthropometrical confounding factors. These results support the hypothesis that diet plays an important role in chronic disease occurrence.

1. Introduction

Peripheral arterial disease (PAD) increases with age, and by the age of 65 years, up to one-fifth of adults have PAD. Diagnosis is critical, as people with PAD have a 4–5 times higher risk of myocardial infarction or stroke.[1] Well-known modifiable risk factors for PAD include smoking, obesity, diabetes mellitus, high blood pressure or physical inactivity.[2] Of note, in a 10-year follow-up study, PAD significantly increased the mortality from cardiovascular disease (relative risk = 5.9) and mortality from coronary artery disease (CAD) (relative risk = 6.6).[3]

The role of dietary acid-base balance on non-communicable disease has been the focus of growing attention.[4] Dietary acid-base load is a dietary factor that was recently considered as a possible risk factor for metabolic disorders, cardiovascular disease, increased risk of type 2 diabetes and high blood pressure.[5–9] Mild metabolic acidosis, caused by poor diets and impaired balance of calcium and citrate, and cortisol-induced acidosis have been identified as risk factors for the development of obesity, lipid disorders and subsequent cardiovascular disease.[10] A diet rich in acidogenic foods, such as meat, fish, and cheese, but low in alkaline foods, such as fruit and vegetables, can induce endogenous acid production.[4] Therefore, dietary intake can markedly influence the body's acid-base balance.[11]

In the epidemiologic studies, some scores have been used to assess acid load from diet. Fassetto et al. calculated the estimated net endogenous acid production (NEAP) from the diet's protein to potassium ratio. Others, like Remer et al.[12] estimated diet-induced potential renal acid load (PRAL) from average intestinal absorption rates of ingested protein and other minerals including, phosphorous, potassium, calcium, and

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magnesium intake as well as an anthropometry-based estimate for organic acid excretion.[13,14]

Recently, it has been reported that diet-induced acid load was associated with increased risk of CVD, independent of obesity and insulin resistance.[15] In addition, elevated PRAL scores were associated with high atherosclerotic cardiovascular disease (ASCVD) risk independent of obesity, exercise, and insulin resistance, similar trends were observed with dietary acid load (DAL) scores. The mechanism linking diet-induced acid load and metabolic disease incidence is mainly reported as insulin resistance,[6] therefore insulin binding affinity to its receptor was markedly decreased in individuals with metabolic acidosis.[15,16] Regarding the effect of diet-induced acid load on blood pressure, a diet depleted of potassium could affect vasodilatation and be toxic to the blood vessels.[17] Furthermore, it has been demonstrated that PRAL and DAL scores were positively associated with both systolic and diastolic blood pressure. Diet-induced insulin resistance could autonomously promote cardiovascular disease in various pathways; impair coronary microcirculatory, stimulate conduction dysfunction and increase arrhythmogenesis.[18,19] In addition, systemic metabolic acidosis, caused by the Western diet, is related with excessive cortisol levels and leads to ammoniagenesis, which cause loss of renal function.[15,20] However, some investigations reported that high-protein diets exerted neither specific beneficial nor detrimental effects on outcome markers of cardiovascular disease or glycemic control.[21]

As far as we are aware, no study examined the association between dietary acid-base load and PAD. We accomplished this by using data from the U.S. National Health and Nutrition Examination Survey (NHANES). We hypothesized that subjects with higher acid-base load score had greater odds of PAD.

2. Methods

2.1. Population characteristics

The NHANES involves ongoing repeated cross sectional surveys conducted every two years in non-institutionalized adults by the US National Center for Health Statistics (NCHS).[22] The National Center for Health Statistics Research Ethics Review Board approved the NHANES protocol and consent was obtained from all participants.[23] Data collection for demographic information occurs through in-home administered questionnaires, while anthropometric and laboratory data are collected by trained personnel using mobile units.[24]

This current study was based on an analysis of data for two 2-year NHANES survey cycles that were conducted from 1999 to 2002. The ankle brachial index (ABI) assessment and lower extremity disease examination were limited to those who were aged ≥ 40 years.

Dietary intake was assessed *via* 24 h recall obtained by a trained interviewer during the mobile examination center visit, with the use of a computer-assisted dietary interview system with standardized probes, *i.e.* the United States Department of Agriculture Automated Multiple-Pass Method (AMPM).[25,26] Briefly, the type and quantity of all foods and beverages consumed in a single 24 h period before the dietary interview (from midnight to midnight) were collected with the use of AMPM. AMPM is designed to enhance complete and accurate data collection while reducing respondent burden.[26,27]

Data on demographic information are recorded using questionnaires administered during home visits, while anthropometric, inflammation and biochemistry data are collected by trained personnel using mobile exam units. A digital scale was used to measure weight to the nearest 100 g and a fixed stadiometer to measure height to the nearest mm. BMI was calculated as weight in kg divided by the square of height in m. Waist circumference (WC) was measured at the iliac crest to the nearest mm, using a steel tape.[24]

A blood specimen was drawn from the antecubital vein. Glycated haemoglobin (HbA_{1c}) was measured using a Tosoh A1C 2.2 Plus Glycohemoglobin Analyzer.[49] Fasting blood glucose (FBG) was measured by a hexokinase method using a Roche/Hitachi 911 Analyzer and Roche Modular P Chemistry Analyzer (NJ, USA). Insulin was measured using an ELISA immunoassay (Mercodia, Uppsala, Sweden).[28] Other laboratory-test details are available in the NHANES Laboratory/Medical Technologists Procedures Manual.[29] Details on high-sensitivity C-reactive protein (hsCRP) concentrations measurement are available elsewhere.[24] All methods were carried out in accordance with relevant guidelines and regulations.[24] All experimental protocols were approved by the NCHS.[24]

3. Dietary acid load calculation

The DAL score was characterized by 2 measures: PRAL and NEAP; the PRAL score was calculated based on several nutrient intakes using the following algorithm[12]: PRAL (mEq/d) = 0.4888 × dietary protein (g/d) +0.0366 × dietary P (mg/d) −0.0205 × dietary K (mg/d) − 0.0125 × Ca (mg/d) − 0.0263 × Mg (mg/d). The NEAP score was also calculated using the following algorithm[11]: NEAP (mEq/d) = /K intake (mEq/d) −10.2. Adjusted PRAL and NEAP for energy intake were applied in statistical analysis.

3.1. PAD diagnosis

The ABI was measured with the participants in the supine position, by trained health staff using an 8.1-MHz Doppler probe and following a standard operation protocol. The ABI was calculated by dividing the ankle mean systolic blood pressure by brachial mean systolic blood pressure on the same side. The presence of PAD was defined as an ABI < 0.9 in either side.[30] We excluded subjects (n = 40) with extremely high ABI (>1.4).

3.2. Statistical analysis

We conducted the analyses according to the guidelines set by the Centers for Disease Control and Prevention for analysis of complex NHANES datasets, accounting for the masked variance and using the proposed weighting methodology.[31,32,50] Continuous and categorical demographic variables were compared across quarters of PRAL and NEAP using analysis of variance (ANOVA) and Chi-square tests, respectively. Means and standard deviations for continuous measures and percentages for categorical variables were derived. We computed age-, sex-, race-, estimated glomerular filtration rate (eGFR), C-reactive protein (CRP) smoking, dietary fat, carbohydrates, protein, saturated fat, and dietary fiber, and energy intake, body mass index, hypertension, cholesterol, triglyceride, diabetes-adjusted values for dietary acids load using analysis of covariance (ANCOVA). Univariate and multivariate Logistic regression adjusted for age-, sex-, race-, eGFR, smoking, dietary fat, carbohydrates, protein, saturated fat, CRP, and dietary fiber, and energy intake, body mass index, hypertension, cholesterol, triglyceride, diabetes was used to determine the odds of PAD across dietary acids load quarters, with those in the lowest quarter serving as the reference category. All tests were two sided, and $p < 0.05$ was the level of significance. Data were analysed using SPSS® complex sample module version 22.0 (IBM Corp, Armonk, NY). Sample weights were applied to account for unequal probabilities of selection, nonresponse bias and oversampling.

4. Results

A total of 4864 participants were eligible for inclusion in the current analyses. Of these, 269 (5.5%) had PAD. The characteristics of the participants, overall and by status for prevalent PAD, are summarised in Table 1. Overall 2482 (51.0%) participants were men and 2382 (49.0%) were women, with no significant difference by PAD status ($p = 0.432$). Compared with those without PAD, participants with PAD comprised more non-Hispanic Whites (57.2 *vs* 52.4%), and non-Hispanic Black

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