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Association between Dietary Acid Load and Insulin Resistance: Tehran Lipid and Glucose Study

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ABSTRACT: In the current study, we investigated the longitudinal association between dietary acid load and the risk of insulin resistance (IR) in the Tehranian adult population. This longitudinal study was conducted on 925 participants, aged 22～80 years old, in the framework of the third (2006～2008) and fourth (2009～2011) phases of the Tehran Lipid and Glucose Study. At baseline, the dietary intake of subjects was assessed using a validated semi-quantitative food frequency questionnaire, and the potential renal acid load (PRAL) and net endogenous acid production (NEAP) scores were calculated at baseline. Fasting serum insulin and glucose were measured at baseline and again after a 3-year of follow-up; IR was defined according to optimal cut-off values. Multiple logistic regression models were used to estimate the risk of IR according to the PRAL and NEAP quartile categories. Mean age and body mass index of the participants were 40.3 years old of 26.4 kg/m^2, respectively. Mean PRAL and NEAP scores were −11.2 and 35.6 mEq/d, respectively. After adjustment for potential confounders, compared to the lowest quartile of PRAL and NEAP, the highest quartile was accompanied with increased risk of IR [odds ratio (OR)=2.81, 95% confidence interval (CI)=1.32～5.97 and OR=2.18, 95% CI=1.03～4.61, respectively]. Our findings suggest that higher acidic dietary acid-base load, defined by higher PRAL and NEAP scores, may be a risk factor for the development of IR and related metabolic disorders.

Keywords: dietary acid-base load, potential renal acid load, insulin resistance

INTRODUCTION

The prevalence of type 2 diabetes is increasing worldwide (1). Life style factors such as reduced physical activity, smoking, alcohol consumption, and diet played roles in the development of type 2 diabetes (2). Diet also has a very important role in the development of metabolic disorders, insulin resistance (IR), and type 2 diabetes (3). The crucial role of dietary acid load in predicting the risk of developing cardiovascular disorders has been investigated; increased dietary acid load could disturb insulin homeostasis and induce consequent metabolic disorders (4). It has been reported that even a small decrease in metabolic acidosis may decrease insulin sensitivity; thereby, reducing the dietary acid load plays a role in decreasing IR (5).

Dietary intake has an important influence in human metabolic acidosis (6) by supplying acid load indicators such as sulfate and phosphorus, and also base load indicators including potassium, calcium, and magnesium (7). In general, compared with plant protein, increased dietary intakes of animal protein increase metabolic acidosis (6). Dietary acid load has been measured by 2 scores commonly used in epidemiologic studies. The potential renal acid load (PRAL), which is based on intakes of 5 nutrients including protein, calcium, potassium, phosphorous, and magnesium (8), and the net endogenous acid production (NEAP) score, which is based on intakes of protein and potassium (9). In a recent Japanese study, a high dietary acid load, as assessed by both PRAL and NEAP, was associated with an increased IR risk (4). Increased cortisol secretion caused by metabolic acidosis (10) may also have an effect on IR risk (11). In a Swedish study of elderly men, no association was found between dietary acid load calculated with PRAL and NEAP, and insulin sensitivity or β-cell function (12).

Regarding the limited data available on the association between dietary acid load and IR risk, in the present study, we assessed the relationship between 2 scores of dietary acid load on IR risk in Tehranian adults.

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MATERIALS AND METHODS

Study population

This study was conducted within the frame work of the Tehran lipid and glucose study (TLGS). Briefly, the TLGS is a prospective community-based study being conducted to investigate and prevent non-communicable diseases by implementing and promoting healthy lifestyles. Baseline data were collected by trained interviewers from 15,005 participants, aged ≥3 years from district 13 of Tehran, Iran. The participants were followed every 3 years to assess any data changes on their demographic and lifestyle, clinical, dietary, and biochemical measurements (13).

In this longitudinal study, we recruited 1,141 subjects (men and women) aged 22～80 years, who participated in the third survey of TLGS (2006～2008). Participants were excluded if they were diagnosed as under-reporters (≤800 kcal/d) or over-reporters (>4,200 kcal/d) (n=35) of dietary intake or were on specific diets, or lacked follow up information on biochemical and anthropometrics measurements at the second examination (2009～2011) (n=24); we also excluded subjects who had IR at baseline (n=157): the final sample for analyses included 925 adults.

Data collection

Trained interviewers collected information using pretested questionnaires. In this longitudinal study, demographics and anthropometrics measures were assessed at baseline (2006～2008) and again after 3 years of follow up (2009～2011). Physical activity level was assessed, based on the frequency and time spent on light, moderate, high, and very high intensity activities, according to the list of common activities of daily life over the past year, using the Persian translated Modifiable Activity Questionnaire. The validity of the physical activity questionnaire was previously evaluated in a Tehranian sample (14). Physical activity levels were expressed as metabolic equivalent hours per week (MET-h/wk).

Body weight was determined to the nearest 100 g using digital scales, while participants were minimally clothed and without shoes. Body height was measured using a tape meter, while subjects were in the normal standing position without shoes, and height was recorded to the nearest 0.5 cm. Body mass index (BMI) was calculated as body weight (kg) divided by height in meters squared (m^2). Waist circumference (WC) was measured to the nearest 0.1 m, using a tape measure without pressure to the body surface, while participants were dressed in light indoor clothing. To measure blood pressure, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured twice, at least a 30-s interval using a standard mercury sphygmomanometer.

Biochemical measurement and insulin resistance indexes

Fasting plasma samples were obtained after participants had fasted overnight (12～14 h), at baseline and again after a 3-year follow up from all study participants. Fasting plasma glucose levels were measured by the enzymatic colorimetric method, using glucose oxidase. Plasma insulin concentrations were measured using an enzyme-linked immunosorbent assay kit (Mercodia AB, Uppsala, Sweden). Total cholesterol (TC) was measured with cholesterol esterase and cholesterol oxidase by using an enzymatic colorimetric method. Serum high density lipoprotein-cholesterol (HDL-c) was measured after precipitation of the apolipoprotein B-containing lipoprotein with phosphotungstic acid and serum triglyceride (TG) was assayed using an enzymatic colorimetric method with glycerol phosphate oxidase. Low density lipoprotein-cholesterol (LDL-c) was measured from the serum HDL-c, TC, and TG concentrations expressed in mg/dL, using the Friedewald formula (15). HOMA-IR (homeostatic model assessment-insulin resistance) was calculated using the formula: HOMA-IR=[fasting insulin (μU/mL)×fasting glucose (mmol/L)]/22.5 and HOMA-β-cell=20×[fasting insulin (μU/mL)/{fasting glucose (mmol/L)−3.5}] (16). In this study, we defined IR as a HOMA-IR ≥3.2 (17).

Dietary assessment

Dietary intake was collected at baseline (2006～2008), using a reliable, validated 168-item semi-quantitative food frequency questionnaire (FFQ) (18). Usual dietary intakes of subjects were assessed by trained dietitians, during face-to-face interviewers. Participants were asked to report to give their consumption frequency for each food item during the past year on a daily, weekly, or monthly basis. We used the US Department of Agriculture (USDA) food composition tables (FCT) to assess energy and nutrient content of foods and beverages because the Iranian FCT is incomplete, and has limited data on nutrient content of beverages and raw foods (19).

Dietary acid load calculation

The dietary acid load score was characterized by 2 measures: PRAL and NEAP; the PRAL score was calculated based on several nutrient intakes using the following algorithm (8): 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 (9): NEAP (mEq/d)=[{54.5×protein intake (g/d)}/K intake (mEq/d)−10.2. Adjusted PRAL and NEAP for energy intake were applied in statistical analysis.

Statistical methods

PRAL was adjusted for total energy intake, based on the

residuals method to control for total energy intake (20). The participants were categorized according to quartiles of PRAL (mEq/d). The general characteristics of the study population were reported as mean or percentage and compared across quartiles of PRAL, using the general linear model adjusted for sex and age, or the chi-square test for continuous and categorical variables, respectively. Mean dietary intakes of subjects were compared across quartiles of PRAL, using the general linear model adjusted for sex, age, and energy intake. Associations between confounding variables and PRAL scores were assessed using a univariate analysis; variables in the multivariable model are based on P_E (*P*-value for entry) with $P_E<0.2$ in the univariate analysis were selected for final multivariable models.

The risk of IR was estimated across quartiles of PRAL and also quartiles of NEAP, using multiple regression models, and presented in different models. In model 1, we adjusted for age (y) and sex, and in the second model we adjusted for the confounding effect of BMI (kg/m^2, continuous), smoking (yes or no), physical activity (MET-h/wk, continuous), energy intake (kcal/d), dietary fat (g/d), carbohydrates (g/d), saturated fat (g/d), and dietary fiber (g/d). Overall trends of odds ratios of IR across quartiles of PRAL and NEAP were assessed using the logistic regression model, considering median of each quartile in the model. To assess the overall trends of odds ratios across quartiles of PRAL and NEAP categories, the median of each quartile was used as a continuous variable in the logistic regression models.

Table 1. Characteristics of subjects across quartiles of potential renal acid load (PRAL): Tehran Lipid and Glucose Study

	Dietary PRAL (mEq/d)				
	Q1 (n=231)	Q2 (n=231)	Q3 (n=232)	Q4 (n=231)	*P*-value
Age (year)	43.2±12.5	41.1±11.9	39.5±11.3	38.7±12.4	0.001
Physical activity (MET-h/wk)	45.2±12.8	42.2±11.7	38.4±10.5	40.2±11.1	0.06
Current smoker (%)	9.9	11.7	12.5	13.9	0.60
Weight (kg)					
At baseline	71.5±13.2	72.1±12.3	71.7±13.6	71.1±12.4	0.86
After 3 years	73.4±12.9	73.5±12.2	73.6±13.7	73.1±12.4	0.95
Fasting serum sugar (mg/dL)					
At baseline	86.6±14.4	88.8±16.5	87.5±13.5	56.5±9.1	0.22
After 3 years	93.7±15.5	96.8±20.2	95.8±20.1	96.3±20.4	0.29
Serum insulin (mU/L)					
At baseline	7.6±3.1	7.7±3.1	7.6±2.9	7.2±2.9	0.41
After 3 years	8.4±4.1	8.1±3.8	8.9±4.6	8.8±4.2	0.19
HOMA-IR					
At baseline	1.6±0.6	1.7±0.7	1.6±0.6	1.5±0.6	0.21
After 3 years	1.9±1.02	1.9±1.03	2.1±1.3	2.1±1.3	0.13
HOMA-β-cell					
At baseline	135±76.6	129±70.9	130±68.3	125±67.3	0.52
After 3 years	110±74.1	100±55.6	109±60.7	105±49.1	0.22
Insulin resistance (%)	11.2	9.9	13.5	16.9	0.12
High density lipoprotein-cholesterol (mg/d)					
At baseline	42.7±9.9	42.9±9.4	42.1±10.1	41.5±8.7	0.38
After 3 years	48.1±11.6	48.1±10.8	48.4±11.8	46.6±11.1	0.33
Low density lipoprotein-cholesterol (mg/d)					
At baseline	120±37.7	114±31.9	113±31.4	112±33.4	0.70
After 3 years	115±35.9	114±33.5	116±34.9	113±34.7	0.75
Triglycerides (mg/d)					
At baseline	135±77.1	139±95.1	135±78.3	135±82.3	0.93
After 3 years	129±74.8	132±87.1	135±73.9	145±117.5	0.28
Systolic blood pressure (mmHg)					
At baseline	111±17.1	109±15.5	107±15.5	111±16.8	0.02
After 3 years	115±17.1	114±15.6	113±14.8	114±16.7	0.12
Diastolic blood pressure (mmHg)					
At baseline	72.8±10.9	72.1±9.9	70.4±11.1	73.5±10.5	0.01
After 3 years	77.2±11.3	76.7±10.9	75.5±10.3	77.4±10.5	0.23

Data are percent or mean±SD.
General linear model with adjustment for age was used for continuous variables and χ^2-test was used for dichotomous variables.
HOMA-IR: homeostatic model assessment-insulin resistance.
Quartile of PRAL (mEq/d) Q1, from −123 to −20.74; Q2, from −20.7 to −9.1; Q3, from −9.1 to −1.75; Q4, RRAL range from −1.74 to 11.6.

All analyses were performed using the statistical software SPSS (version 20.0; SPSS Inc., Chicago, IL, USA), and $P<0.05$ were considered statistically significant.

RESULTS

General characteristics of the participants

Mean (standard deviation; SD) PRAL and NEAP were −11.2 (20.5) and 35.6 (11.2) mEq/d, respectively. Mean (SD) age and BMI of participants were 40.3 (12.1) years and 26.4 (4.4) kg/m^2, respectively. Characteristics of participants, anthropometrics, biochemical values (blood glucose and lipid profiles), and blood pressure at baseline and after a 3-year follow-up across quartiles of PRAL are shown in Table 1. Participants in the upper, compared to lower quartile, were more likely to be younger (38.7 vs. 43.2, $P<0.01$).

Dietary information of the participants

Mean dietary intakes of the participants across quartiles of PRAL are reported in Table 2. Dietary intakes of protein, grains, meat, and sodium were significantly higher in subjects in the highest quartile compared to the lowest quartile of PRAL ($P<0.001$). Participants in the lowest quartile of PRAL had a significant increase in dietary intakes of carbohydrate, fruits, vegetable, energy, fiber, potassium, calcium, and magnesium ($P<0.001$), whereas dietary intakes of fat, phosphorus, fish, and egg did not significantly differ between the lowest and the highest quartiles of PRAL.

Association between PRAL and insulin resistance

Associations of dietary PRAL and NEAP with IR are shown in Table 3. The PRAL score was significantly and positively associated with IR in the adjusted model for age and sex ($P=0.027$), in the multivariable model also, after adjusting for age, sex, smoking, physical activity, energy intake, dietary fat, dietary carbohydrates dietary saturated, dietary fiber, and type 2 diabetes, this association remained significant [odds ratio (OR)=2.81, 95% confidence interval (CI)=1.32∼5.97, and $P=0.005$]. A similar relationship between the NEAP score and IR risk was found. After controlling for various confounders, NEAP was significantly related to IR risk (OR=2.18, 95% CI=1.03∼4.61, and $P=0.021$).

Table 2. Dietary Intake of adults, aged ≥22 years across tertiles of potential renal acid load (PRAL): Tehran Lipid and Glucose Study

	Dietary PRAL (mEq/d)				
	Q1 (n=231)	Q2 (n=231)	Q3 (n=232)	Q4 (n=231)	*P*-value
PRAL (mEq/d)	−37.71±16.9	−14.41±3.4	−4.18±3.1	11.37±9.5	0.001
NEAP (mEq/d)	23.91±4.6	31.14±2.9	37.48±3.4	50.12±9.1	0.000
Nutrient intake					
Energy (kcal/d)	2,516±692	2,233±609	2,067±663	2,312±805	0.000
Carbohydrates (% of energy)	60.2±6.6	57.5±7.1	57.06±7.1	56.1±7.4	0.000
Fat (% of energy)	30.4±6.3	31.9±7.5	31.5±7.2	30.9±6.9	0.113
Protein (% of energy)	13.2±2.2	13.2±2.1	13.6±2.4	14.5±2.7	0.000
Fiber (g/d)	42.5±19.1	36.5±15.5	37.3±19.2	36.8±29.4	0.001
Ca (mg/d)	1,386±524	1,239±444	1,201±469	1,110±501	0.000
P (mg/d)	1,426±484	1,434±462	1,450±503	1,480±576	0.240
K (mg/d)	4,794±1,416	3,824±1,020	3,429±114	2,908±1,122	0.000
Mg (mg/d)	416±128	369±112	361±122	353±154	0.000
Na (mg/d)	4,627±3,400	4,169±2,449	4,112±2,271	4,944±4,648	0.021
Food groups					
Grains (g/d)	339±140	418±164	464±183	550±322	0.000
Vegetables (g/d)	424±261	315±159	268±124	203±114	0.000
Fruit (g/d)	594±379	405±206	293±164	187±133	0.000
Dairy (g/d)	568±343	529±287	498±338	504±339	0.12
Meat (g/d)	44.6±31.9	51.3±30.9	53.9±36.5	68.5±5.35	0.000
Fish (g/d)	9.5±10.1	9.7±9.1	9.9±9.5	12.1±24.8	0.217
Egg (g/d)	15.3±13.1	14.3±12.6	15.8±12.8	14.8±13.2	0.771

Data are mean±SD.
General linear model with adjustment for age and energy intakes was used.
PRAL, potential renal acid load; NEAP, net endogenous acid production.
Quartile of PRAL (mEq/d) Q1, from −123 to −20.74; Q2, from −20.7 to −9.1; Q3, from −9.1 to −1.75; Q4, RRAL range from −1.74 to 11.6.

Table 3. The association of PRAL and NEAP with the risk of insulin resistance after a 3-year of follow-up

	Dietary indexes of acid load				
	Q1	Q2	Q3	Q4	*P*-value
PRAL (MEq/d)	<−20.7	−20.7 and −9.05	−9.06 and 1.75	≥1.75	
Model 1	1	0.91 (0.50~1.65)	1.32 (0.75~2.32)	1.77 (1.02~3.05)	0.027
Model 2	1	1.16 (0.59~2.31)	1.73 (0.86~3.49)	2.81 (1.32~5.97)	0.005
NEAP (MEq/d)	<28.04	28.04 and 33.8	33.9 and 41.3	≥41.3	
Model 1	1	0.83 (0.45~1.51)	1.26 (0.72~2.19)	1.55 (0.90~2.68)	0.046
Model 2	1	1.05 (0.54~2.05)	1.44 (0.73~2.82)	2.18 (1.03~4.61)	0.021

Data are odds ratio and 95% confidence interval.
Model 1, Adjusted for age (year) and sex (male/female), Model 2, Additional adjustment for smoking (yes/no), body mass index (kg/m^2), physical activity (Met-h/wk), energy intake (kcal/d), dietary fat (g/d), carbohydrates (g/d), saturated fat (g/d), and dietary fiber (g/d).
PRAL, potential renal acid load; NEAP, net endogenous acid production.

DISCUSSION

The results of this longitudinal study provide further evidence regarding the possible association of dietary acid base load with the risk of IR. In this study PRAL and NEAP were positively correlated to IR risk. In agreement with previous studies, we observed that participants in the high PRAL score had higher intakes of meat and grains but had lower intakes of fruits, vegetables (21-23). Mean NEAP and PRAL values in our study population (35.6 mEq/d and −11.2 mEq/d, respectively) reported lower acidity, as compared with previous data (24).

Although in a cross sectional study of an apparently healthy Japanese population, PRAL and NEAP were positively associated with IR (4). Another study did not confirm this association and observed a non-significant inverse association for PRAL and NEAP with insulin sensitivity (12). It has been reported that even a slight degree of metabolic acidosis results in decreased insulin sensitivity in healthy populations (25). In a prospective cohort study conducted on women, a positive association for PRAL and NEAP with diabetes incidence was reported (22).

In contrast to our results, in a cross-sectional study of 1,125 young women, a positive association was observed for IR with PRAL but not with NEAP (10).

In a cross-sectional study of healthy adults, markers of metabolic acidosis, including the anion gap was found to have an inverse association with fasting insulin levels, while bi-carbonate had a positive association with fasting insulin levels (26). Some studies reported a positive association between urine acidity and IR (27,28). For example, analysis of a cross-sectional study of healthy populations in the US reported an inverse association between 24-h urine pH and HOMA-IR (28). According to our findings, dietary acid load and acidosis markers play an important role in the development of IR risk.

Several possible mechanisms have been suggested for a relationship between dietary acid load and IR risk. First, a high dietary acid load leads to increased cortisol production (10), which can cause IR (11). Second, a high dietary acid load decreases urinary secretion of citrate (12); studies have also reported that low urinary excretion of citrate is related to IR (5,29). Third, diet induced metabolic acidosis may increase the secretion of magnesium, which in turn may lead to IR (30). Moreover, increasing dietary intakes of magnesium and potassium, present in the algorithm of PRAL have been associated with lower IR risk (5,31-33).

The main strengths of this study were the prospective nature and use of a validated questionnaire (FFQ) to evaluate regular dietary intakes. However, there are some limitations that should be considered. First, the use of the USDA FCT to assess energy and nutrient content of foods and beverages rather than a comprehensive Iranian FCT. Second, the lack of data on postprandial levels of insulin and glucose to calculate the disposition index.

CONCLUSION

We found that both PRAL and NEAP were positively associated with the risk of IR in this Tehranian population. We recommend that more studies should be conducted to clarify the effect of dietary acid load on IR.

AUTHOR DISCLOSURE STATEMENT

The authors declare no conflict of interest.

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