Dietary Acid-Base Load and Risk of Chronic Kidney Disease in Adults

Tehran Lipid and Glucose Study

Parvin Mirmiran,[1] Emad Yuzbashian,[1] Zahra Bahadoran,[1] Golaleh Asghari,[1] Fereidoun Azizi[2]

[1]Nutrition and Endocrine Research Center, Research Institute for Endocrine Science, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2]Endocrine Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Keywords. diet, acid-base load, chronic kidney disease

Introduction. The objective was to examine whether dietary acid load was associated with chronic kidney disease (CKD) in adults.
Materials and Methods. The cross-sectional analyses included 4564 participants, aged 20 years and older, who participated in the 4th phase of the Tehran Lipid and Glucose Study and had complete dietary and serum creatinine data. Dietary data were obtained from using a 147-item food-frequency questionnaire. Dietary acid load was calculated as the potential renal acid load (PRAL). Anthropometrics, blood pressure, and fasting plasma glucose, and lipids were measured. Chronic kidney disease was defined as an estimated glomerular filtration rate (GFR) less than 60 mL/min/1.73 m^2 calculated using the Modification of Diet in Renal Disease equation. Risk of CKD was obtained in quartiles of PRAL with logistic recreation.
Results. The mean dietary PRAL of the participants was -22.0 mEq/d. After adjustment for age, sex, and body mass index, the odds ratio for CKD in the highest compared to the lowest quartile of PRAL was 1.38 (95% confidence interval [CI], 1.02 to 1.83). After additional adjustment for energy intake and smoking, the odds ratio for CKD in the 4th quartile of PRAL compared to the 1st was 1.42 (95% CI, 1.06 to 1.91). In the final model, after additional adjustment for dietary intake of total fat, carbohydrate, dietary fiber, fructose, sodium, diabetes mellitus, and hypertension, the risk of CKD in the highest dietary PRAL category, compared to the lowest, increased by 42%.
Conclusions. After adjusting for possible confounding factors, we found that higher PRAL (more acidic diet) was associated with higher prevalent CKD in Iranian adults.

IJKD 2016;10:119-25
www.ijkd.org

Original Paper

INTRODUCTION

Chronic kidney disease (CKD), defined as the presence of microalbuminuria or reduction in glomerular filtration rate (GFR), is a growing public health problem worldwide, with a rising incidence and prevalence, only stages 3 and 4 estimates ranged from 6.3% to 18.6%.[1,2] Previously, many studies have demonstrated that age, sex, hypertension, diabetes mellitus, obesity, hyperlipidemia, and smoking are risk factors for development of CKD.[3] There has been a growing interest regarding the association of dietary factors and development of kidney disorders and CKD; however, limited and inconsistent data are available in this regard.[4,5]

Endogenous homeostasis of acid-base has been identified as an important determinant for cardiometabolic risk factors.[6] Current evidence indicates that acid-base status, which is affected by food intake, is a main factor for the development and progression of CKD.[7-9] Dietary acid load has been determined by food supply of acid precursors, ie, noncarbonic acids such as sulfuric acid, which are rich in animal proteins such as meats, eggs, and cheese, and base precursors (ie, alkali salts from organic acids, such as citrate and bicarbonate) are abundant in fruits and vegetables such as raisins, apple, peach, spinach, and cauliflower.[10] A common method used to estimate dietary acid load from dietary assessment in epidemiology studies is the potential renal acid load (PRAL) method. A negative PRAL value reflects a base-forming potential, whereas a positive one reflects an acid-forming potential.[11] It has been shown that dietary acid load is associated with the risk of hypertension and type 2 diabetes mellitus.[12-14][13]

To the best of our knowledge, there has been no report on the relationship between dietary PRAL and CKD. Hence, we investigated a community-based population of Iranian adults to investigate this association, independent of diabetes mellitus and hypertension.

MATERIAL AND METHODS

Participants

This study was conducted within the framework of the Tehran Lipid and Glucose Study (TLGS). Briefly, TLGS is a community-based ongoing prospective study, being conducted to investigate and prevent noncommunicable diseases, in a representative sample of residents, aged 3 years and older, from district 13 of Tehran, the capital city of Iran. The first phase of the TLGS began in March 1999 and data collection, at 3-year intervals, is ongoing.[15] During the 4th phase of TLGS (2009-2011), from a total of 12823 participants with complete data on their medical history and physical examinations, 7956 participants were randomly selected for dietary assessment, and for the current analysis, participants aged 20 to 70 years, with complete data for diagnosis of diabetes mellitus and hypertension and data on serum creatinine levels. Participants were excluded from the analysis if they were on specific diets or were diagnosed as under-reporters (≤ 800 kcal/d) or over-reporters (≥ 4200 kcal/d) of energy intake. Finally, data of 4564 individuals were considered for analysis.

This study protocol was approved by the ethics committee of the Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, and informed written consent was obtained from all participants.

Dietary Assessment and Calculation of Dietary Acid-Base Load

Dietary data were collected by the trained dietitians using a valid and reliable semi-quantitative Food Frequency Questionnaire with 147-food items.[16] The interviewer asked participants to designate their consumption frequency for each food item during the past year on a daily, weekly, or monthly basis. Portion sizes of consumed foods that were reported in household measures were then converted to grams. The United States Department of Agriculture Food Composition Table (FCT) was used to calculate energy and nutrient intakes. The Iranian FCT was also used for some traditional foods that are not listed in the United States Department of Agriculture FCT.

Dietary acid-base load was evaluated by 2 indexes, PRAL and the protein-potassium ratio, using the following formulae[7,17]:

PRAL (mEq/d) = 0.4888 × dietary protein (g/d) + 0.0366 × dietary phosphorus (mg/d) - 0.0205 × dietary potassium (mg/d) - 0.0125 × calcium (mg/d) - 0.0263 × magnesium (mg/d)

protein-potassium ratio = dietary protein (g/d)/ dietary potassium (mg/d)

Both PRAL and protein-potassium ratio were calculated using residual energy-adjusted nutrient intake data estimated from the Food Frequency Questionnaire. Higher values of PRAL and protein-potassium ratio were considered as higher acidic dietary acid-base load.[9]

Clinical and Laboratory Covariates

The participants were interviewed by trained interviewers using pretested questionnaires, following which demographic data collection, anthropometric examinations, medical history of cardiovascular disease, and medication use were undertaken by trained general physicians. Weight was measured while the participants were minimally clothed without shoes using digital scales and recorded to the nearest 100 g. Height

was measured in a standing position, without shoes, using a tape measure while the shoulders were in a normal position. Body mass index (BMI) was calculated as weight in kilograms, divided by height in meters squared. Using a standard mercury sphygmomanometer, systolic blood pressure and diastolic blood pressure were measured twice in a seated position after a 15-minute rest period. Blood samples were taken after a 12- to 14-hour overnight fast. All blood analyses were done at the TLGS research laboratory on the day of blood collection.[18] Serum total cholesterol and triglyceride levels were measured using enzymatic colorimetric kits (Pars Azmon Inc, Tehran, Iran). Serum creatinine was measured according to the standard colorimetric Jaffe-Kinetic reaction method (Pars Azmon Inc, Tehran, Iran).

Definition of Terms

Hypertension was defined as systolic/diastolic blood pressure of 140/90 mm Hg and higher or current therapy for a definite diagnosis of hypertension.[19] We used the Modification of Diet in Renal Disease (MDRD) equation formula to express estimated GFR in mL/min/1.73 m^2 of body surface area.[20] The abbreviated MDRD study equation is as follows:

GFR = 186 × (serum creatinine)$^{-1.154}$ × (Age)$^{-0.203}$ × (0.742 if female)

Based on the estimated GFR levels, the patients were classified as not having CKD with a GFR of 60 mL/min/1.73 m^2 and higher (non-CKD) and as having CKD with a GFR less than 60 mL/min/1.73 m^2 (CKD) groups.[21]

Diabetes mellitus was defined as a fasting blood glucose of 126 mg/dL and higher, 2-hour blood glucose of 200 mg/dL and higher, or being on anti-diabetic medication.[22]

Statistical Analysis

The mean values and the proportions of baseline characteristics of the participants with and without CKD were compared using the independent sample *t* test or the chi-square test, respectively. Dietary PRAL was assigned as quartiles, based on their 25th, 50th, and 75th percentile values. The quartile ranges of dietary PRAL were less than -36.9 mEq/d, -36.9 mEq/d to -19.8 mEq/d, -19.8 mEq/d to -5.4 mEq/d, and ≥ -5.4 mEq/d. To determine the odds ratio (OR) and 95% confidence interval (95%CI) of CKD in each quartile category of dietary PRAL, multivariable logistic regression models were conducted with adjustment for potential confounding variables. A univariable analysis was performed for each potential confounder including age, sex, BMI, smoking, diabetes mellitus, hypertension, energy intake, and dietary intakes of fat, carbohydrate, fiber, fructose, and sodium. A *P* value less than .2 in the univariable analysis was considered the threshold for inclusion in the final multivariable models. To assess the overall trends of OR across quartiles of dietary PRAL, the median of each quartile was used as a continuous variable in the logistic regression models.

Statistical analysis was performed using the SPSS software (Statistical Package for the Social Sciences, version 15.0, SPSS Inc, Chicago, IL, USA).

RESULTS

The mean age of the participants was 39.8 ± 12.8 years and 54% of the participants were women. The mean estimated GFR was 72.4 mL/min/1.73 m^2 and 11.7% of the participants were diagnosed with CKD (6.8% and 18.8% in men and women, respectively). The mean dietary PRAL of the participants was -22.0 mEq/d (-15.6 mEq/d and -26.8 mEq/d in men and women, respectively). General characteristics of the CKD and non-CKD participants are shown in Table 1. Participants with prevalent CKD, compared to non-CKD ones, had higher body weight, serum triglyceride levels, systolic blood pressure, and serum creatinine levels

Table 1. Characteristics of the Study Participants With and Without Chronic Kidney Disease (CKD)*

Characteristic	CKD Group (n = 534)	Non-CKD group (n = 4030)	*P*
Age, y	54.4 ± 0.5	42.6 ± 0.1	.001
Body weight, kg	75.8 ± 0.6	74.5 ± 0.2	.04
Body mass index, kg/m^2	27.9 ± 0.2	27.6 ± 0.1	.18
Serum triglyceride, mg/dL	157.0 ± 3.8	142.0 ± 1.3	.001
High-density lipoprotein, mg/dL	46.3 ± 0.5	46.9 ± 0.2	.25
Systolic blood pressure, mm Hg	116.0 ± 0.7	114.0 ± 0.2	.047
Diastolic blood pressure, mm Hg	76.8 ± 0.5	76.6 ± 0.1	.82
Serum creatinine, mg/dL	1.30 ± 0.01	1.02 ± 0.00	.001
Glomerular filtration rate, mL/min/1.73 m^2	58.5 ± 0.4	74.5 ± 0.1	.001

*Data are shown as mean ± standard deviation. Analysis of covariance was used with adjustment for age and sex.

as well as lower estimated GFR ($P < .05$).

Dietary intakes of the CKD participants and non-CKD ones are compared in Table 2. Participants with CKD had lower dietary PRAL (-22.71 ± 045 mEq/d versus -19.46 ± 1.52 mEq/d, $P < .05$) and lower protein-potassium ratio (0.019 ± 0.005 versus 0.02 ± 0.013, $P < .05$). There were no significant differences between dietary intakes of the participants with and without CKD.

The ORs (95% CI) of CKD across quartile categories of PRAL are presented in Table 3. In the 1st model, after adjustment for age, sex, and BMI, a significant increased risk of CKD was observed in the highest compared to the lowest quartile of dietary PRAL (OR, 1.38; 95% CI, 1.02 to 1.83). In the 2nd model, after additional adjustment for energy intake and smoking, the risk of CKD in the 4th quartile of PRAL was 1.42 (95% CI, 1.06 to 1.91). In the 3rd model, after additional adjustment for dietary intake of total fat, carbohydrate, dietary fiber, fructose, sodium, diabetes, and hypertension, the risk of CKD in the highest compared to the lowest dietary PRAL category increased by 43% (OR, 1.43, 95% CI, 1.03 to 1.95); moreover, there was a significant trend in CKD risk across increasing quartile of dietary PRAL (P for trend = .03).

DISCUSSION

This study, conducted in an Iranian adult population, showed an increased risk of CKD in individuals with higher dietary PRAL; this positive association remained significant after additional adjustment for all potential confounding variables including energy intake, smoking, diabetes mellitus, hypertension, and dietary intake of total fat, carbohydrate, dietary fiber, fructose, and sodium.

Table 2. Dietary Intakes of the Study Participants With and Without Chronic Kidney Disease (CKD)*

Dietary Intake	CKD Group (n = 534)	Non-CKD group (n = 4030)	*P*
PRAL, mEq/d	-19.46 ± 1.50	-22.71 ± 0.40	.04
Protein-potassium ratio	0.019 ± 0.005	0.02 ± 0.013	.05
Energy, Kcal	2336.0 ± 37.2	2388.0 ± 11.1	.18
Protein, % of energy	15.20 ± 0.20	14.90 ± 0.05	.15
Protein, g/d	88.6 ± 0.9	87.9 ± 0.3	.50
Carbohydrate, % of energy	59.3 ± 0.5	59.2 ± 0.1	.82
Fat, % of energy	29.4 ± 0.8	29.9 ± 0.2	.55
Sodium, mg/d	3491.0 ± 53.6	3574.0 ± 16.0	.14
Magnesium, mg/d	464.0 ± 5.1	471.0 ± 1.5	.23
Potassium, mg/d	4504.0 ± 66.1	4622.0 ± 20.0	.09
Calcium, mg/d	1438.0 ± 24.6	1459.0 ± 7.4	.41
Phosphorus, mg/d	1640.0 ± 15.1	1638.0 ± 4.5	.90
Meat, g/d	46.7 ± 2.1	44.9 ± 0.6	.40
Cereals, g/d	42.8 ± 2.2	46.0 ± 0.7	.17
Grains, g/d	469.0 ± 8.6	454.0 ± 2.6	.09
Dairy, g/d	426.0 ± 12.2	426.0 ± 3.6	.97
Vegetable, g/d	314.0 ± 10.2	329.0 ± 3.0	.17
Fruit, g/d	399.0 ± 18.0	400.0 ± 5.4	.96

*Data are shown as mean ± standard deviation. The independent *t* test was used for comparisons.

Table 3. Logistic Regression Models' Odds Ratios (95% Confidence Intervals) of Chronic Kidney Disease (CKD) Across Quartile Categories of Dietary Potential Renal Acid Load (PRAL)

	Dietary PRAL				
Model for CKD	Q1 (< -36.9) Median = -52.7	Q2 (-36.9 to -19.8) Median = -26.3	Q3 (-19.8 to -5.4) Median = -12.1	Q4 (≥ -5.4) Median = 6.0	*P* for Trend*
Model 1†	1.00	1.21 (0.93 to 1.57)	1.07 (0.80 to 1.39)	1.38 (1.02 to 1.83)	.13
Model 2‡	1.00	1.16 (0.89 to 1.52)	1.04 (0.79 to 1.37)	1.42 (1.06 to 1.91)	.09
Model 3§	1.00	1.24 (0.93 to 1.64)	1.17 (0.86 to 1.58)	1.42 (1.03 to 1.95)	.03

*Based on logistic regression model using median intake of dietary PRAL in each quartile as a continuous variable.
†Adjusted for age, sex, and body mass index.
‡Additionally adjustement for smoking and energy inatke.
§Additionally adjustement for dietary intake of fat, carbohydrate, fiber, fructose, and sodium; diabetes mellitus, and hypertention.

In this study, CKD patients had a more acidic diet, defined as lower dietary PRAL and protein-potassium ratio.

Similarly, in adult population of the National Health and Nutrition Examination Survey (1999-2004), a 2-fold higher risk of CKD in adults was associated with estimated net acid excretion as explained by PRAL plus organic anion production in an un adjusted model.[23] In this study, the association was attenuated to 75% risk of CKD after adjustment of age, sex, race or ethnicity, socio-economic status, smoking, diabetes mellitus, hypertension, self-reported cardiovascular disease, BMI, and total caloric intake.[24] In the current study, the final model was adjusted for diabetes mellitus and hypertension, which showed that PRAL could the increase risk of CKD up to 42%. These findings suggest that dietary acid load has considerable effect on kidney function and affects CKD risk. Kanda and coworkers, in a retrospective cohort study of 217 non-dialysis-dependent CKD patients with a normal serum bicarbonate level on low-protein diet, showed that high net endogenous acid production (NEAP) as net acid excretion was independently associated with CKD progression and the authors suggested that decreased NEAP might be an effective kidney-protective therapy.[25] It is important to note that dietary acid load is related to protein intake, a risk factor for CKD progression that has been widely studied.[26,27]

In the current study, we used PRAL for measuring dietary acid-base load balance. The NEAP and PRAL are estimates, which are affected by imprecision in the measurement of dietary intake as a result of inaccurate reporting and variation over time. Additionally, absorption of nutrients in the gastrointestinal tract and the actual nutrient composition of a specific food vary considerably across individuals and the methods of preparation, but these differences cannot be accounted for by the PRAL equation.

The mean PRAL in our population (-22.0 mEq/d) was less acidic compared to other populations including the British middle-aged women (27.6 mEq/d and 1.0 g/mEq, respectively) and young Japanese women (10.4 mEq/d and 1.2 g/mEq, respectively). In agreement with previous studies, we observed that higher intakes of meat, grains, egg, fish, and dairy were associated with higher PRAL, while higher intakes of vegetables and fruit were related to lower PRAL. In general, high dietary acid load foods include cheese, meat, and eggs, all of which are important sources of animal protein and grains, whereas alkali-providing foods include fruits and vegetables.[11] Western dietary patterns with high contents of animal and grain products represent a high acid supply for body. The average percent of energy from protein is raised in populations who follow Western diets to approximately 15% to 17%, predominantly from animal foods.[28,29] Also, in several general population cohorts in the United States, an average 50 mEq/d to 75 mEq/d of dietary acid load was reported,[30] because of low potassium-rich fruit and vegetables in the diet.[23] In countries on nutrition transition such as Iran, the animal-to-plant protein ratio was found to be approximately 1.3 to 2.1.[4] Many vegetable foods are sources of potassium, which binds to organic anions and metabolized to bicarbonate, which in turn, reduces the net rate of endogenous acid production in comparison to the rate of acid production from animal foods.[31]

Evidence available shows that if servings of sweets and grains were replaced by fruits and vegetables, or a diet enriched in fruits, vegetables, and low-fat dairy with reductions in fats, oils, and meats such as those observed in the Dietary Approach to Stop Hypertension (DASH) yields a substantially reduced dietary acid load compared to common diet (NEAP of 31 mEq/d versus 78 mEq/d), despite comparable protein intake.[32] Overall, these findings suggest that replacing low nutrient- and energy-dense foods, very common in recent decade diets, by greater intakes of fruits and vegetables, could lower NEAP without requiring excessive protein restriction.[33,34]

Some mechanisms may explain the effect of dietary acid load on developing kidney dysfunction; renal medullary ammonia level increases by acidosis without decrease in serum bicarbonate levels and the increase in resulting ammonia level by dietary acid load in the long term leads to high local intratubular and tissue ammonia concentrations accompanied by increased ammonia genesis; this pathway can exert toxic effects on progression of tubulointerstitial injury.[35,36] In diabetic nephropathy, these mechanisms are highlighted and can force the elimination of nephrons and progression of diabetic nephropathy to end-stage kidney failure.[37] In addition, metabolic acidosis has been associated with raised endothelin production in

CKD, which mediates tubulointerstitial injury and GFR decrease.[31] Another possibility is the rising production of oxygen-free radicals and oxidative stress induced by acidosis. Evidence has shown that with alkalinization of urine and the renal medulla, production of oxygen-free radicals declines and kidney is protected against oxidant injury.[38,39] Oxygen-free radicals and oxidant injury have been shown to play an important role in the pathogenesis of radiocontrast nephrotoxicity.[39]

The strength of the current study was using of a validated Food Frequency Questionnaire to assess regular dietary intake. Furthermore, we had detailed information on participants' medications, and therefore, adjusted for use of drugs which affect hypertension or diabetes mellitus. Our study had also some limitations; first, it was a cross-sectional study, and hence, the association between dietary acid load and kidney function could not provide a causal relationship. Second, as no complete Iranian FCT exists, we used the United States Department of Agriculture FCT. Third, our definition of CKD, as in most epidemiologic studies, was based on a limited number of isolated creatinine measurements that were not repeated within 3 months to confirm a chronic reduction in GFR.

CONCLUSIONS

After adjusting for possible confounding factors, we found that higher PRAL (more acidic dietary acid-base loads) was associated with increased risk of prevalent CKD in community-based Iranian adults.

FINANCIAL SUPPORT

This work was funded by a grant from the Research Institute for Endocrine Sciences, Shadid Beheshti University of Medical Sciences, Tehran, Iran.

ACKNOWLEDGMENTS

We would like to acknowledge Ms Niloofar Shiva for critical copy editing of the English manuscript.

CONFLICT OF INTEREST

None declared.

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Correspondence to:
Parvin Mirmiran, PhD
Nutrition and Endocrine Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran 19395-4763, Iran
Tel: +98 21 223 57 484
Fax: +98 21 224 16 264
E-mail: mirmiran@endocrine.ac.ir

Received September 2015
Accepted December 2015