Prev. Nutr. Food Sci. 2018;23(2):87-93
https://doi.org/10.3746/pnf.2018.23.2.87
pISSN 2287-1098 · eISSN 2287-8602

Dietary Sodium to Potassium Ratio and the Incidence of Chronic Kidney Disease in Adults: A Longitudinal Follow-Up Study

Parvin Mirmiran[1], Pantea Nazeri[2], Zahra Bahadoran[2], Sajjad Khalili-Moghadam[3], and Fereidoun Azizi[4]

[1]Department of Clinical Nutrition and Dietetics, Faculty of Nutrition Sciences and Food Technology, National Nutrition and Food Technology Research Institute, [2]Nutrition and Endocrine Research Center, Research Institute for Endocrine Sciences, [3]Student Research Committee, Nutrition and Endocrine Research Center, Research Institute for Endocrine Sciences, and [4]Endocrine Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran 19395-4763, Iran

ABSTRACT: The aim of this study was to explore the association of dietary sodium to potassium (Na/K) ratio and the risk of chronic kidney disease (CKD) in general Iranian adults. In this prospective cohort study, 1,780 adults, free of baseline CKD with complete follow-up data, were selected from among participants of the Tehran Lipid and Glucose Study and followed for 6.3 years for development of CKD. Dietary sodium and potassium were assessed using a valid and reliable 168-item food frequency questionnaire. Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease Study equation, and CKD was defined as eGFR <60 mL/min/1.73 m^2. Mean dietary intakes of sodium and potassium were 4,547±3,703 and 3,753±1,485 mg/d, respectively, and their ratio was 1.35±1.29. No significant association was found between dietary intakes of sodium and potassium and the risk of CKD after 6.3 y of follow-up, whereas in the case of dietary Na/K ratio, participants in the highest compared to lowest tertile (2.43 vs 1.61) had a significantly increased risk of CKD (odds ratio=1.52, 95% confidence interval=1.01~2.30); an increasing trend in the risk of CKD across tertiles of dietary sodium to potassium ratio was also observed (*P* for trend=0.05). Present findings demonstrate that the dietary Na/K ratio is a stronger predictor of CKD than the dietary sodium or potassium per se. Decreased dietary Na/K ratio may be considered as an effective dietary approach to modify the risk of kidney dysfunction.

Keywords: dietary sodium, dietary potassium, sodium to potassium ratio, chronic kidney disease

INTRODUCTION

Chronic kidney disease (CKD), also known as chronic kidney failure, is a condition characterized by a gradual and permanent loss of kidney function over a period of several months or years. Glomerular filtration rate (GFR) is the best test to measure the level of kidney function and determine the stage of kidney disease. People with CKD may have renal failure markers, i.e. albuminurea, and increased urinary sodium or GFR lower than 60 mL/min/1.73 m^2 for ≥3 months (1,2). Diabetes and hypertension are the leading causes of CKD, which are responsible for up to two-thirds of all cases of the disease; therefore, control of blood pressure and strict glycemic control are some of the proven strategies in preventing and slowing the progression of CKD (3,4).

Moreover, there has been some evidence indicating that dietary factors are major contributing factors for the development of kidney disorders and CKD (5-7). Dietary sodium and potassium intakes have been shown to play a crucial role in the renin-angiotensin system, arterial stiffness, the augmentation index, endothelial dysfunction, and consequent development of hypertension, cardiovascular, and kidney disease (8). Data from observational and interventional studies propose that moderation of sodium intake and increase of potassium intake might reduce cardiovascular events and prevent the onset of hypertension (9,10). It has been also reported that the sodium to potassium (Na/K) ratio may have a stronger association with blood pressure than either sodium or potassium alone due to the interaction of these nutrients; meta-analysis of observational studies also provided additional support for the Na/K ratio as a superior metric in the assessment of hypertension and relative outcomes (11).

However, little is known regarding the association of dietary Na/K ratio and the risk of CKD in population-based studies. Therefore, the aim of the present study

Received 22 November 2017; Accepted 26 April 2018; Published online 30 June 2018
Correspondence to Zahra Bahadoran, Tel: +98-21-224-32-500, E-mail: z.bahadoran@endocrine.ac.ir

was to investigate whether the high dietary Na/K ratio was related to increased risk of CKD among an Asian adult population.

MATERIALS AND METHODS

Study population

This study was conducted within the framework of the Tehran Lipid and Glucose Study (TLGS), an ongoing community-based prospective study being conducted to investigate and prevent non-communicable diseases, in a representative sample in the district 13 of Tehran, the capital city of Iran (12). For the current analysis, 2,823 men and women (≥20 years) with complete data (demographics, anthropometrics, biochemical, and dietary data) who participated in the third (2006～2008) TLGS examination, were recruited. After exclusion of the participants with under- or over-reported energy intakes (< 800 or ≥4,200 kcal/d) or specific diets (including dietary recommendations for hypertension, hyperlipidemia, or diabetes) (n=261), and participants with prevalent CKD at baseline (n=487), the remaining non-CKD subjects were followed up to the fourth (2009～2011) and fifth (2012～2014) TLGS examinations. Participants who had left the study before follow-up examinations without diagnosed CKD (n=295) were also excluded, and final analyses were conducted on 1,780 adults (727 men and 1,053 women).

Written informed consent was obtained from all participants, and the study protocol with the ethics number of IR.SBMU.ENDOCRINE.REC.1395.369 was approved by the ethics research council of the Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences.

Demographic, anthropometric, and clinical measures

Trained interviewers collected the demographics data using pretested questionnaires. Weight was measured to the nearest 100 g using digital scales, while the subjects were minimally clothed, without shoes. Height was measured to the nearest 0.5 cm, in a standing position without shoes, using a tape meter. Body mass index (BMI) was calculated as weight (kg) divided by the square of the height (m^2). For blood pressure (BP) measurements, after a 15-min rest in the sitting position, two measurements of BP were taken, on the right arm, using a standardized mercury sphygmomanometer; the mean of the two measurements was considered as the participant's BP.

Smoking status was obtained using face-to-face interviews; subjects who smoked daily or occasionally were considered current smokers. Information on medication usage for the treatment of diabetes, hypertension, and lipid disorders was collected.

Biochemical measures

Fasting blood samples were taken after 12～14 h from all study participants at baseline and follow-up phases. Serum creatinine levels were assayed using the kinetic colorimetric Jaffe method. Fasting serum glucose (FSG) was measured by the enzymatic colorimetric method using glucose oxidase. The standard 2 h serum glucose (2-h SG) test was performed for all individuals who were not on anti-diabetic drugs. Triglyceride (TG) levels were measured by the enzymatic colorimetric analysis with glycerol phosphate oxidase. High-density lipoprotein cholesterol was measured after precipitation of the apolipoprotein B containing lipoproteins with phosphotungstic acid. Analyses were performed using Pars Azmoon kits (Pars Azmoon Inc., Tehran, Iran) and a Selectra 2 autoanalyzer (Vital Scientific, Spankeren, Netherlands). Both inter- and intra-assay coefficients of variation of all assays were <5%.

Dietary assessment

The principal dietary exposure of interest was Na/K ratio. A 168-item food frequency questionnaire (FFQ) was used to assess typical food intakes over the previous year. Trained dietitians, with at least 5 years of experience in the TLGS survey, asked participants to designate their intake frequency for each food item consumed during the past year on a daily, weekly, or monthly basis. The validity of the food frequency questionnaire was previously evaluated by comparing food groups and nutrient values determined from the questionnaire with values estimated from the average of twelve 24-h dietary recall surveys (13).

Portion sizes of consumed foods reported in household measures were then converted to grams (14). However, since the Iranian Food Composition Table is incomplete, and has limited data on nutrient content of raw foods and beverages to analyze foods and beverages for their energy and nutrient content, we used the US Department of Agriculture Food Composition Table. Usual dietary intakes of sodium and potassium as mg/d were also obtained from dietary data.

Definition of terms

To calculate eGFR, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation was used. As a single equation, CKD-EPI has been expressed as follows:

$$\text{eGFR} = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{\text{age}} \times 1.018\ [\text{if female}] \times 1.159\ [\text{if black}]$$

In this equation, S_{cr} is serum Cr in mg/dL; κ is 0.7 and 0.9 for women and men, respectively, α is -0.329 and -0.411 for men and women, respectively; min indicates

the minimum of S_{cr}/κ or 1, and max indicates maximum of S_{cr}/κ or 1 (15). CKD was defined as estimated eGFR <60 mL/min per 1.73 m^2 (1).

Creatinine clearance rate (eC_{Cr}) was calculated using Cockcroft-Gault formula (16) as follows:

$$eC_{Cr} = \frac{(140 - age) \times body\ weight\ (kg) \times (0.85\ if\ female)}{72 \times creatinine\ (mg/dL)}$$

Diabetes was defined as FSG ≥126, 2-h SG ≥200 mg/dL or use of anti-diabetic medications (17). Cardiovascular events were considered as a composite measure of any CHD event, stroke, or cerebro-vascular death (18). Coronary heart disease (CHD) includes cases of definite myocardial infarction (MI) diagnosed by electrocardiogram (ECG) and biomarkers, probable MI (positive ECG findings plus cardiac symptoms or signs and biomarkers showing negative or equivocal results), unstable angina pectoris (new cardiac symptoms or changing symptom patterns and positive ECG findings with normal biomarkers), angiographic-proven CHD, and CHD death (18).

Hypertension was considered as systolic BP ≥140 or diastolic BP ≥90 or current use of antihypertensive medications (19).

Statistical analysis

Mean±standard deviation (SD) values, and the proportions of baseline characteristics of the participants with and without the CKD were compared using the independent sample *t*-test or chi-square test, respectively.

The univariate analysis was performed for common risk factors of CKD or potential confounding variables, including age (≥65 years), BMI categories (<25, 25~30, and ≥30 kg/m^2), smoking (yes/no), history of kidney disease (yes/no), using of medications (yes/no), prevalent diabetes (yes/no), history of cardiovascular disease (CVD) (yes/no), hypertension (HTN) (yes/no), daily energy intake (continuous), dietary intake of fat (continuous), and protein (continuous); variables with P_E (*P* value for entry) <0.2 in the univariate analysis were selected for the final multivariable models; P_E determines which variables should be included in the multivariable model.

We assessed dietary intakes of Na/K ratio as both continuous and categorical variables in the models. In the categorical model, the ratio was categorized into tertiles, given the 1st tertile as reference. In the continuous model, the risk of CKD was calculated for each 1 SD increases in the Na/K ratio.

A linear association of Na/K ratio at baseline with changes of eGFR and creatinine clearance rate during the follow-up period were estimated using linear regression models.

To assess the odds [95% confidence interval (CI)] of CKD across tertiles of Na/K ratio, logistic regression models with adjustment for potential confounding variables were used. The first model was adjusted for age and sex; the second model was additionally adjusted for BMI categories, smoking, history of kidney disease, diabetes (yes/no), HTN (yes/no), medications (yes/no), and history of CVD (yes/no). Finally, we added energy intake (kcal/d), dietary intake of protein (g/d), and total fat (g/d) to the logistic regression model.

To assess the overall trends of odds ratios across quartile categories, the median of each tertile was used as a continuous variable in the logistic regression models. The association of Na/K ratio with changes in creatinine clearance rate, eGFR, and blood pressure during the study follow-up was also assessed using linear regression analysis, with adjustment for all potential confounders. All statistical analyses were conducted using SPSS (version 20.0, SPSS Inc., Chicago, IL, USA), and *P*-values <0.05 were considered significant.

RESULTS

General characteristics of the participants

The mean age of participants was 33.8±15.3 y at baseline and 40.8% were male. Mean dietary intakes of sodium and potassium was 4,547±3,703 and 3,753±1,485 mg/d, respectively, and their ratio was 1.35±1.29. During the average of 6.3 y of follow-up, 318 participants (17.9%) experienced CKD. Participants with CKD were more likely to be women, had lower rate of smoking,

Table 1. Baseline characteristic of the participants (n = 1,780)

	Participants with CKD outcome (n = 318)	Participants without CKD outcome (n = 1,462)
Age (y)	33.8±15.3	34.3±15.7
Men (%)	35.2	42.1*
Smoking (%)	5.8	9.5*
History of kidney disease (%)	5.7	3.1*
BMI (kg/m^2)		
<25	20.3	33.1*
25~30	47.4	44.0*
≥30	32.4	22.9*
eGER (mL/min/1.73 m^2)	68.9±7.8	80.7±12.5*
Cardiovascular disease (%)	14.5	8.8*
Hypertension (%)	28.1	10.0*
Sodium (mg)	4,726±4,784	4,508±3,424
Potassium (mg)	3,695±1,441	3,765±1,495
Na/K ratio	1.42±1.64	1.33±1.21

Data are mean±SD unless stated otherwise (independent *t*-test and chi-square test was used for continuous and dichotomous variables, respectively).
*P<0.05.
BMI, body mass index; CKD, chronic kidney disease; eGER, estimated glomerular filtration rate.

Table 2. Baseline characteristics of the study population across tertile categories of Na/K ratio

	Tertile 1 (n = 592)	Tertile 2 (n = 593)	Tertile 3 (n = 592)
Age (y)	34.4±16.3	34.3±14.9	33.2±14.9
Men (%)	39.5	42.3	40.7
Smoking (%)	8.7	9.8	8.0
History of kidney disease (%)	3.5	3.9	3.4
BMI (kg/m^2)			
<25	31.8	31.1	29.4
25~30	40.7	47.3	46.0
≥30	27.4	21.5	24.6
eGER (mL/min/1.73 m^2)	78.7±13.0	78.5±11.9	78.6±13.0
Creatinine clearance rate (mL/min)	96.2±26.4	94.7±23.7	96.9±24.4
Diabetes (%)	10.9	11.9	11.8
Cardiovascular disease (%)	10.6	9.1	9.8
Hypertension (%)	14.2	13.1	12.1
Dietary sodium (mg)	3,345±1,389	3,863±2,063	6,448±5,433*
Dietary potassium (mg)	4,945±1,415	3,545±1,063	2,768±1,028*
Na/K ratio	0.61±0.13	1.02±0.14	2.43±1.79*

Data are mean±SD unless stated otherwise (analysis of variance or chi-square test were used for continuous variables and dichotomous variables, respectively).
*P<0.05.
BMI, body mass index; CKD, chronic kidney disease; eGER, estimated glomerular filtration rate.

and higher prevalence of kidney disease history at baseline (P for all <0.05); moreover, a higher rate of overweight (47.4% vs. 44.0%) and obesity (32.4% vs. 22.9%) was observed in CKD compared to non-CKD subjects. In addition, a lower rate of eGFR (68.9 mL/min/1.73 m^2 vs. 80.7 mL/min/1.73 m^2, P=0.001) as well as higher prevalence of CVD (14.5 vs. 8.8%, P=0.002) and hypertension (28.1% vs. 10.0%, P=0.001) was observed. A higher rate of Na/K intake was observed at baseline in the incident compared to non-incident cases of CKD (1.42 vs. 1.33, P=0.26) (Table 1).

The characteristics of the study population were compared across tertile categories of Na/K ratio (Table 2). There was no significant differences in demographic and anthropometric measurements, history of disease as well as eGFR, and creatinine clearance rate across tertile categories of dietary Na/K ratio.

A linear association of Na/K ratio at baseline, with changes of eGFR and creatinine clearance rate during the follow-up period, showed a borderline association between Na/K ratio and change of eGFR (β=−0.81, P=0.12) and creatinine clearance rate (β=0.49, P=0.18) (Table 3).

Table 3. The association of Na/K ratio at baseline with changes of eGFR and creatinine clearance rate

	Na/K ratio	P
eGFR	−0.81	0.12
Creatinine clearance rate	0.49	0.18

Data are β regression.
eGER, estimated glomerular filtration rate.

Dietary sodium and potassium and the incidence of CKD

The risk of CKD across tertile categories of sodium, potassium, and their ratio are shown in Table 4. There is no significant association between dietary intakes of sodium and potassium and the risk of CKD after 6.3 y of follow-up, whereas when dietary Na/K ratio was considered as exposure in the fully-adjusted logistic regression model, participants in the highest compared to lowest tertile (2.43 vs. 0.61, Table 2) had a significantly increased risk of CKD (OR=1.52, 95% CI=1.01~2.30); an increasing trend in the risk of CKD across tertiles of dietary Na/K ratio was also observed (P for trend=0.05).

The odds (95% CI) of CKD per 1 SD increased dietary Na/K ratio was 1.12 (0.99~1.27) in the fully adjusted model.

DISCUSSION

In this prospective cohort study of well-characterized men and women with 6.3 years of follow-up, we observed that a higher Na/K ratio was associated with a considerable increased risk of CKD. This prospective association was independent of the known potential risk factors of CKD in our population. Each 1 SD increase in dietary Na/K ratio was related to a 12% increased risk of CKD during the study follow-up. In this study, dietary intakes of sodium or potassium alone were not related to risk of CKD.

Previous studies have reported the association between potassium and hypertension or cardiovascular disease (20). Although, the mechanisms underlying the association between potassium intakes and the development of CKD have not yet been clearly elucidated, there is evi-

Table 4. The risk of chronic kidney disease across tertile categories of dietary sodium and potassium

	Dietary sodium and potassium			
	Tertile 1	Tertile 2	Tertile 3	*P* for trend[1)]
Sodium (mg/1,000 kcal/d)	<1,320	1,320~1,912	≥1,912	
Crude	*Ref.*	1.08 (0.80~1.45)	0.98 (0.73~1.33)	0.89
Model 1	*Ref.*	1.07 (0.79~1.46)	1.02 (0.74~1.39)	0.91
Model 2	*Ref.*	0.97 (0.67~1.41)	1.08 (0.74~1.52)	0.93
Model 3	*Ref.*	1.06 (0.71~1.58)	1.18 (0.71~1.58)	0.88
Potassium (mg/1,000 kcal/d)	<1,432	1,432~1,775	≥1,775	
Crude	*Ref.*	0.92 (0.68~1.24)	0.98 (0.72~1.31)	0.85
Model 1	*Ref.*	0.88 (0.65~1.21)	0.91 (0.67~1.24)	0.88
Model 2	*Ref.*	0.90 (0.64~1.25)	0.88 (0.63~1.22)	0.90
Model 3	*Ref.*	0.92 (0.63~1.32)	0.83 (0.53~1.14)	0.91
Na/K ratio	<0.80	0.80~1.29	≥1.29	
Crude	*Ref.*	1.01 (0.74~1.36)	1.17 (0.87~1.57)	0.49
Model 1	*Ref.*	1.09 (0.80~1.50)	1.25 (0.92~1.71)	0.33
Model 2	*Ref.*	1.26 (0.86~1.83)	1.37 (0.95~1.98)	0.22
Model 3	*Ref.*	1.29 (0.88~1.90)	1.52 (1.01~2.30)	0.05

Data are odds ratio and 95% confidence interval.
Logistic regression models were used.
Model 1: Adjusted for sex and age (< and ≥ 65 years).
Model 2: Additional adjustment for body mass index categorized (<25, 25~30, and ≥30 kg/m), smoking (yes/no), serum creatinine (μmol/L), diabetes (yes/no), hypertension (yes/no), medications (yes/no), cardiovascular diseases (yes/no), and history of kidney disease (yes/no).
Model 3: Additional adjustment for daily energy intake (kcal/d), dietary intake of protein (g/d) and total fat (g/d).
[1)]A linear trend test was performed by considering each ordinal score variable as a continuous variable in the model.

dence that supports the protective effect of dietary potassium on the development of CKD. High intake of dietary potassium, shown to be accompanied with a reduced vascular smooth muscle cell proliferation, inhibited free radical formation from vascular endothelial cells and macrophages, and inhibited platelet aggregation and subsequently reduced renal vascular resistance as well as increased glomerular filtration rate; these mechanisms could lead to a better kidney function and prevention of CKD development (21,22). In contrast, low dietary potassium intake has been shown to be related to an undesirable increased activity of the renin-angiotensin-aldosterone system, a critical endogenous system for blood pressure regulation (23,24); however, in the current study we found no association between regular dietary intakes of potassium per se with the risk of CKD.

Since hypertension is a known risk factor for CKD, one hypothesis is that dietary sodium intakes would be associated with the risk of CKD and its progression. Available data suggests that higher sodium consumption may be an important risk factor for development of CKD; however, no association was observed between dietary intakes of sodium per se and the risk of CKD in our population. Increased dietary sodium has been shown to be involved in the initiation of oxidative stress in the renal cortex and vascular beds, which can lead to decreased renal blood flow and increased glomerular pressure, GFR and filtration fraction (25). Moreover, prior cross-sectional and cohort studies showed an association between sodium intake and albuminurea, a sign of early kidney damage (26).

Existing studies propose that a combined effect of dietary sodium and potassium, as the dietary Na/K ratio, is a stronger predictor of blood pressure and cardiovascular events than the dietary sodium or potassium alone (27,28). In our study, subjects who had a higher dietary Na/K ratio had a higher risk of CKD development, during the study follow-up. In contrast, no significant association was observed between urinary potassium excretion or urinary Na/K ratio with urinary albumin excretion, in a general Chinese adult population (29). In another study conducted in the adults in the US, it was shown that regardless of dietary sodium intake, higher intakes of potassium decreased the risk of CKD (25). The mechanisms responsible for the association between dietary Na/K ratio and CKD have not yet been clearly understood. However, it has been suggested that dietary potassium may exert a more protective effect in the presence of a high-sodium diet (24,30), which may be attributed to sympathetic nerve inhibition in salt-sensitive hypertension and also the generation of vasodilators such as nitric oxide and other endothelium derived factors (31-34).

The main strength of the current study was its prospective design and relatively large sample size with a long-term follow-up. The detailed data on the well-known risk factors and potential confounders of CKD, and comprehensive assessment of dietary intakes using a validated

comprehensive FFQ were other strengths of this study. The availability of multiple health examination data allowed us to simultaneously assess different aspects of CKD.

Lack of data on added salt intake, as main source of dietary sodium, may be considered as an important limitation of this study. As inherent into any prospective study, some degree of misclassification might have occurred due to potential changes in an individual's diet as well as changes in other CKD risk factors during the study follow-up. Furthermore, we tried to adjust the major confounding variables in our models; however, some residual or unmeasured confounders may remain unknown which could lead to a result in biased exposure effect estimates (35). It should be noted that due to different dietary patterns and food habits, and different genetic backgrounds among different populations, our findings may not be generalized to other populations.

In conclusion, this study supports the hypothesis that the combination of higher Na and lower K intakes may play an important role in the progression of the CKD; however, further investigations are still needed.

ACKNOWLEDGEMENTS

We thank the Tehran Lipid and Glucose Study participants and the field investigators of the Tehran Lipid and Glucose Study for their cooperation and assistance in physical examinations, biochemical evaluation, and database management. This study was supported by the Research Institute for Endocrine Sciences of Shahid Beheshti University of Medical Sciences.

AUTHOR DISCLOSURE STATEMENT

The authors declare no conflict of interest.

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