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Original Investigation

Urine Potassium Excretion, Kidney Failure, and Mortality in CKD

Amanda K. Leonberg-Yoo, MD,[1] Hocine Tighiouart, MS,[2] Andrew S. Levey, MD,[1] Gerald J. Beck, PhD,[3] and Mark J. Sarnak, MD, MS[1]

Background: Low urine potassium excretion, as a surrogate for dietary potassium intake, is associated with higher risk for hypertension and cardiovascular disease in a general population. Few studies have investigated the relationship of urine potassium with clinical outcomes in chronic kidney disease (CKD).

Study Design: Longitudinal cohort study.

Setting & Participants: The MDRD (Modification of Diet in Renal Disease) Study was a randomized controlled trial (N = 840) conducted in 1989 to 1993 to examine the effects of blood pressure control and dietary protein restriction on kidney disease progression in adults aged 18 to 70 years with CKD stages 2 to 4. This post hoc analysis included 812 participants.

Predictor: The primary predictor variable was 24-hour urine potassium excretion, measured at baseline and at multiple time points (presented as time-updated average urine potassium excretion).

Outcomes: Kidney failure, defined as initiation of dialysis therapy or transplantation, was determined from US Renal Data System data. All-cause mortality was assessed using the National Death Index.

Results: Median follow-up for kidney failure was 6.1 (IQR, 3.5-11.7) years, with 9 events/100 patient-years. Median all-cause mortality follow-up was 19.2 (IQR, 10.8-20.6) years, with 3 deaths/100 patient-years. Baseline mean urine potassium excretion was 2.39 ± 0.89 (SD) g/d. Each 1-SD higher baseline urine potassium level was associated with an adjusted HR of 0.95 (95% CI, 0.87-1.04) for kidney failure and 0.83 (95% CI, 0.74-0.94) for all-cause mortality. Results were consistent using time-updated average urine potassium measurements.

Limitations: Analyses were performed using urine potassium excretion as a surrogate for dietary potassium intake. Results are obtained from a primarily young, nondiabetic, and advanced CKD population and may not be generalizable to the general CKD population.

Conclusions: Higher urine potassium excretion was associated with lower risk for all-cause mortality, but not kidney failure.

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INDEX WORDS: Urine potassium; potassium excretion; kidney failure; chronic kidney disease (CKD); kidney failure; all-cause mortality; dietary potassium intake; modifiable risk factor; end-stage renal disease (ESRD).

Recommendations for target dietary potassium intake have been developed as non-pharmacologic approaches to reducing the prevalence of hypertension and cardiovascular disease (CVD) in both the general population and those with chronic kidney disease (CKD).[1,2] Current guidelines recommend potassium intake of at least 3.51 g/d in the general population, which is in contrast to current potassium intake in the United States of 2.6 g/d.[3] In 2004, the NKF-KDOQI (National Kidney Foundation−Kidney Disease Outcomes Quality Initiative) published CKD-specific guidelines with a daily potassium intake recommendation of >4 g/d in a population with CKD stages 1 and 2, and 2 to 4 g/d for those with CKD stages 3 and 4.[4] However, dietary intervention guidelines in the CKD population have a low level of evidence and are primarily opinion based. Subsequent guidelines from KDIGO (Kidney Disease: Improving Global Outcomes) do not recommend modification of dietary potassium intake due to insufficient evidence.[2,5]

In the general population, clinical studies have shown that low dietary potassium intake is associated with increased risk for hypertension, and potassium-supplemented diets are associated with lower blood pressure and reduction in cerebrovascular mortality, cardiovascular events, and all-cause mortality.[6-14] There are few data that evaluate potassium intake and kidney disease outcomes and only one study that focused on a CKD cohort.[15-18] In the general population, higher potassium intake was associated with

From the [1]Division of Nephrology, Department of Medicine, Tufts Medical Center; [2]Research Design Center/Biostatistics Research Center, Tufts CTSI and Institute for Clinical Research and Health Policy Studies, Tufts Medical Center, Boston, MA; and [3]Department of Quantitative Health Sciences, Cleveland Clinic, Cleveland, OH.

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Address correspondence to Mark J. Sarnak, MD, MS, Box 391, Division of Nephrology, Tufts Medical Center, 800 Washington St, Boston, MA 02111. E-mail: msarnak@tuftsmedicalcenter.org

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lower odds of CKD.[15] Individuals with preserved glomerular filtration rate (GFR) but at high risk for kidney disease progression either due to diabetes or at high CVD risk also had lower risk for kidney function decline with higher urine potassium excretion.[16,18] In contrast, in a recent analysis using a cohort of individuals with moderate CKD, higher urine potassium excretion was associated with higher risk for progression of CKD.[17] The discrepancy between these observational studies highlights a knowledge gap in the interpretation of the relationship between urine potassium excretion and clinical outcomes, particularly in the CKD population.

Patients with CKD represent an important population to study the effects of higher potassium intake not only due to the high risk for kidney failure, CVD events, and mortality, but also the potential for increased adverse outcomes related to high potassium intake. We therefore evaluated the association between dietary potassium intake (ascertained using urine potassium excretion as a surrogate for dietary intake) and clinical outcomes of kidney failure and all-cause mortality using data from the MDRD (Modification of Diet in Renal Disease) Study. In exploratory analysis, we also evaluated interactions between urine potassium excretion and GFR, blood pressure target, urine protein excretion, and urine sodium excretion.

METHODS

Participants and Measurements

The MDRD Study was a large, multicenter, randomized, controlled trial designed to evaluate the effects of strict blood pressure control and dietary protein restriction on CKD progression. Details of the study design and methods have been previously published.[19] From January 1989 to January 1993, patients with CKD (serum creatinine levels in men, 1.4-7 mg/dL; in women, 1.2-7 mg/dL) and aged 18 to 70 years were included in this trial. Exclusion criteria from the original study included pregnancy, insulin-dependent diabetes (type 1 or 2), urine protein excretion $>$ 10 g/d, and previous kidney transplantation. GFR was measured using urinary iothalamate clearance. After a 3-month baseline period, individuals with measured GFR (mGFR) of 25 to 55 mL/min/1.73 m^2 were enrolled in study A, and individuals with mGFR of 13 to 24 mL/min/1.73 m^2 were enrolled in study B. In studies A and B, individuals were randomly assigned to either a usual blood pressure target or low blood pressure target. Usual blood pressure target was defined as target mean arterial pressure $\leq$ 107 mm Hg (corresponding to blood pressure of 140/90 mm Hg). Low blood pressure target was defined as a target mean arterial pressure $<$ 92 mm Hg (corresponding to blood pressure of 125/75 mm Hg). Study A participants were randomly assigned to a usual-protein (1.3 g/kg/d) or low-protein (0.58 g/kg/d) diet. Study B participants were randomly assigned to a low-protein (0.58 g/kg/d) or very low-protein diet (0.28 g/kg/d), which was supplemented with a mixture of keto-acids and amino acids during the course of the trial. Baseline data were obtained prior to dietary counseling, and subsequent dietary counseling did not include dietary potassium restriction in either study arm. A total of 840 individuals were originally randomly assigned. Of these, 28 individuals were excluded due to missing baseline urine collections, leaving 812 participants in our post hoc analysis prior to randomization. There were no statistically significant differences between those excluded and included across covariates of interest (Table S1, available as online supplementary material). The Tufts Medical Center Institutional Review Board approved this study (IRB#4530) but waived the requirement for informed consent because the data for kidney failure and death were collected more than 17 years after completion of the MDRD Study.

Exposure Variable

Baseline 24-hour urine potassium excretion for each participant was measured prior to randomization and was used as the primary exposure variable. An additional primary exposure variable was time-updated average 24-hour urine potassium excretion, defined as average urine potassium excretion prior to time t for each participant. Twenty-four–hour urine collections were performed every month, and the median number of urine collections was 24 (interquartile range [IQR], 17-32).

Outcomes

Study outcomes were kidney failure (defined as initiation of dialysis therapy or transplantation) and all-cause mortality. Kidney failure outcomes were obtained from the US Renal Data System and survival status was obtained from the National Death Index. Survival time for each participant was defined as the time from randomization to kidney failure, death, or administrative censoring on December 31, 2010, whichever came first.

Covariates

Baseline covariates included demographic characteristics (age, sex, and race), cause of kidney disease (polycystic kidney disease, glomerulonephritis, or other), measures of kidney disease (mGFR using urinary iothalamate clearance and urine protein excretion), CVD risk factors (history of CVD, systolic blood pressure, history of tobacco use, and body mass index [in kg/m^2]), high-density lipoprotein cholesterol level, transferrin level, diabetes mellitus, medications (angiotensin-converting enzyme [ACE] inhibitors and diuretics), randomization assignment (blood pressure target and dietary protein intake), and additional surrogates for dietary intake including urine urea nitrogen excretion, total caloric intake per day (measured by 24-hour dietary recall and diet diaries), and urine sodium excretion (measured by 24-hour urine sodium excretion).

Statistical Analysis

The distribution of baseline covariate factors was compared across quartiles of baseline 24-hour urine potassium excretion using χ^2 test for categorical variables and analysis of variance or Kruskal-Wallis test for continuous variables.

Cox proportional hazards regression models were used to explore the association between 24-hour urine potassium excretion and kidney failure and mortality. This analysis was initially performed using urine potassium excretion as a continuous variable. To assess nonlinear relationships and because there are no standardized cutoffs for urine potassium excretion, analyses were repeated using quartiles of urine potassium excretion. Schoenfeld residuals were used to assess whether proportional hazards assumptions were satisfied.

Multivariable models were sequentially adjusted using the following model design: model 1: age, sex, and race; model 2: model 1 plus mGFR, log urine protein per doubling, and cause of kidney disease; model 3: model 2 plus history of CVD, diabetes, smoking, systolic blood pressure, body mass index, high-density lipoprotein cholesterol level, transferrin level, blood pressure randomization, and diet randomization; model 4: model 3 plus diuretics or ACE-inhibitor use (dichotomous), urine urea nitrogen excretion, daily caloric intake, and urine sodium excretion.