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Urine Potassium Excretion, Kidney Failure, and Mortality in CKD

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Abstract

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 5 840) 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.

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SUPPLEMENTARY MATERIAL

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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.

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 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 m² were enrolled in study A, and individuals with mGFR of 13 to 24 mL/min/1.73 m² 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 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/m²]), 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.

Restricted cubic splines were used to graphically evaluate the association between continuous 24-hour urine potassium excretion at baseline and the hazard ratio (HR) for

kidney failure and all-cause mortality. The reference point chosen was mean baseline 24-hour urine potassium excretion.

The following sensitivity analyses were performed: (1) using a subset of individuals who had a measured creatinine excretion rate within 30% of estimated creatinine excretion rate,²⁰ and (2) incorporating time-dependent blood pressure with time-updated average urine potassium excretion.

In exploratory analysis, several prespecified interactions were evaluated between 24-hour urine potassium excretion using multivariable Cox regression models. Interaction terms included MDRD Study A or B, blood pressure randomization target, dietary protein randomization group, urine protein excretion (defined as <1 or ≥1 g/d), and urine sodium excretion (defined as <2 or ≥2 g/d). Urine protein excretion at a cutoff of 1 g/d was used because in the MDRD Study, lower target blood pressure reduced kidney disease progression in those with proteinuria with protein excretion > 1 g/d.²¹ A urine sodium excretion cutoff of 2 g/d was used because this is the recommended dietary intake of sodium based on NKF-KDOQI guidelines.² All analyses were performed using SAS software (version 9.3; SAS Institute Inc) and R language (version 3.2.2; R Foundation for Statistical Computing).

RESULTS

Baseline Characteristics

At baseline, mean age of the study sample (N 5 812) was 51.8 ± 12.4 (standard deviation [SD]) years, 60.1% were men, and 85.1% were white (Table 1). Causes of kidney disease included polycystic kidney disease (23.8%), glomerulonephritis (31.4%), and other forms of kidney disease (44.8%). Diabetes was present in 5.2% of study patients, and 13.3% had a history of CVD. Mean baseline GFR was 32.6 ± 12.0 mL/min/1.73 m² and median urine protein excretion was 0.3 (IQR, 0.1-1.4) g/d. Mean 24-hour baseline urine potassium excretion was 2.39 ± 0.89 g/d, whereas mean urine sodium excretion was 3.46 ± 1.49 g/d. In 36.1% and 40.2% of participants, respectively, ACE inhibitors and diuretics were used.

Participants with higher urine potassium excretion were more likely to be men, be white, and have diabetes. However, participants with lower urine potassium excretion were more likely to have lower mGFRs, lower urine sodium excretion, lower body mass index, and higher high-density lipoprotein cholesterol levels. Diuretic use was more common in the higher urine potassium excretion quartile. Use of ACE inhibitors was no different among urine potassium quartiles (Table 1).

24-Hour Urine Potassium Excretion and Long-term Outcomes

Kidney Failure—Median follow-up for kidney failure was 6.1 (IQR, 3.5-11.7) years. A total of 603 (74.3%) kidney failure events occurred with an event rate of 9.1 events/100 person-years. For each 1-SD increase in baseline and time-updated average urine potassium excretion, there was a nonsignificant change in the hazard of kidney failure in both unadjusted and adjusted models (Table 2). There was a trend toward increased kidney failure events in the lower quartiles using baseline urine potassium measurements; however, this

was not significant in adjusted analyses. The trend was not present using the time-updated average urine potassium measurements (Table 2). When continuous baseline 24-hour urine potassium excretion was modeled using restricted cubic splines, there was no statistical association between kidney failure and lower urine potassium excretion as compared to mean urine potassium excretion, but this association was not significant (Fig 1A).

All-Cause Mortality—Median follow-up for all-cause mortality was 19.2 (IQR, 10.8-20.6) years. A total of 430 (53.0%) participants died, giving an event rate of 3.4 events/100 person-years. In univariate analysis, the HR for mortality was 1.02 (95% confidence interval [CI], 0.93-1.12) for each 1-SD higher urine potassium excretion. After adjustment for age alone, the corresponding HR was 0.90 (95% CI, 0.82-0.99). In fully adjusted models, each 1-SD higher urine potassium excretion was significantly associated with a 17% (95% CI, 0.74-0.94) lower hazard of all-cause mortality (Table 2). Results were similar using time-updated average urine potassium excretion (Table 2). In quartile analyses, lower quartiles of urine potassium excretion were associated with higher risk for mortality after multivariable analysis. When continuous baseline 24-hour urine potassium excretion was modeled using restricted cubic splines, there was a statistically significant increased HR for all-cause mortality with lower urine potassium excretion as compared to mean urine potassium excretion (Fig 1B).

Sensitivity Analysis

There was no difference in the HR of kidney failure or all-cause mortality after exclusion of urine collections that had measured creatinine excretion rates > 30% of estimated creatinine excretion rates (Table S2). There was no significant change in results after incorporation of time-dependent blood pressure measurements in the time-dependent urine potassium excretion model (HRs for each 1-SD higher urine potassium excretion were 0.81 [95% CI, 0.70-0.95] and 0.98 [95% CI, 0.87-1.10] for all-cause mortality and kidney failure, respectively).

Interactions

There were no significant interactions between urine potassium excretion and blood pressure target randomization, dietary protein target randomization, and urine sodium excretion when evaluating kidney failure as the outcome (Fig 2). There was an interaction between MDRD Study A versus B when evaluating baseline urine potassium excretion and kidney failure, with a nonsignificant increased hazard of kidney failure in study A and a reduced hazard of kidney failure in study B (HRs per 1-SD higher urine potassium excretion of 1.02 [95% CI, 0.92-1.14] and 0.83 [95% CI, 0.72-0.96], respectively). Similarly, an interaction was noted between urine potassium and urine protein excretion with kidney failure, with increased urine potassium excretion associated with lower hazard of kidney failure for urine protein excretion < 1 g/d and no association for those with urine protein excretion > 1 g/d (HRs per 1-SD higher urine potassium excretion of 0.87 [95% CI, 0.76-0.99] and 1.06 [95% CI, 0.95-1.19], respectively).

When evaluating all-cause mortality as the outcome, there were no significant interactions of urine potassium excretion with MDRD Study (A vs B), blood pressure target randomization,

level of proteinuria, and urine sodium excretion (Fig 2). There was an interaction between dietary protein randomization group and urine potassium excretion with all-cause mortality, with a lower hazard of all-cause mortality in the usual-protein diet as compared to the low-protein diet and very low-protein diet (HRs per 1-SD higher urine potassium of 0.69 [95% CI, 0.56-0.83], 0.94 [95% CI, 0.80-1.09], and 0.85 [95% CI, 0.66-1.11], respectively).

DISCUSSION

In this prospective study of individuals with CKD stages 3 to 5, we demonstrated an inverse association between urine potassium excretion and all-cause mortality. Using fully adjusted linear models with both baseline urine potassium excretion and time-updated average urine potassium measurements, we observed a 17% lower all-cause death rate per 1-SD higher urine potassium excretion. The associations were consistent in quartile analyses. There was no significant association between urine potassium excretion and kidney failure. There were no significant interactions between urine potassium excretion and all-cause mortality with MDRD Study assignment, blood pressure randomization target, proteinuria, or sodium excretion. There was an interaction between urine potassium excretion and dietary protein randomization with all-cause mortality. There was also an interaction between urine potassium excretion and MDRD Study and degree of proteinuria when evaluating kidney failure outcomes. Given the multiple hypotheses testing, the significance of these interactions is unclear.

Specific guidelines for dietary potassium intake are well established in the general population. These are based on data obtained from observational studies and randomized controlled trials that support a reduction in blood pressure and CVD outcomes with increased dietary potassium intake.^{6,11,16} A meta-analysis showed that supplemental oral potassium dosages of 1.9 to 4.7 g/d, in addition to regular dietary potassium intake, result in a 2- to 6-mm Hg reduction in systolic blood pressure.¹² Potassium supplementation has also been associated with a 24% reduction in cerebrovascular accident risk (95% CI, 0.66-0.89) in a meta-analysis of clinical trials and a trend toward reduction of CVD and coronary heart disease.¹⁰ Similarly, in a large international study of individuals free of known CVD, the Prospective Urban Rural Epidemiology (PURE) investigators demonstrated an association between lower dietary potassium intake and higher odds of death and major cardiovascular events after adjustment for cardiovascular risk factors and blood pressure variables.⁹

To our knowledge, 2 studies have specifically evaluated the relationship between urine potassium excretion and kidney outcomes. The first was a post hoc analysis of 2 clinical trials in 28,879 participants with mean estimated GFR of 68.4 mL/min/1.73 m² who were randomly assigned to treatment with renin-angiotensin system blockade (with either angiotensin receptor blocker, ACE inhibitors, both, or placebo). In this analysis, there was 30% lower risk for kidney function decline in individuals with high (median, 2.7 g/d) and moderate (median, 1.7 g/d) as compared with low urine potassium excretion.¹⁶ In this study, potassium excretion was estimated by a single spot urine potassium measurement, which could have introduced bias of the exposure variable. This post hoc analysis was done in a population that was largely receiving renin-angiotensin system inhibition, which could confound the association between potassium excretion and CKD outcomes. In a recent

prospective study using 3,939 participants of the CRIC (Chronic Renal Insufficiency Cohort) Study, the opposite relationship was observed: higher urine potassium excretion was associated with faster kidney disease progression, but was not associated with mortality. Mean age was 57 years, and at least 40% had diabetes. Estimated GFR was 42 mL/min/1.73 m² at baseline and the primary outcome included incident end-stage renal disease, as well as 50% reduction in estimated GFR. Urine potassium excretion was averaged from three 24-hour urine collections.¹⁷ Our study has evaluated a more advanced nondiabetic CKD population (stages 3-5, with baseline mean mGFR of 32.6 mL/min/1.73 m²) and includes multiple time-dependent urine collections, thus providing a more robust assessment of urine potassium excretion over time. Our results demonstrate that higher potassium excretion is associated with lower risk for all-cause mortality. We did not find a significant association between urine potassium intake and progression to kidney failure. We cannot be sure of the reason for discrepancies in results, but differences may be due to the distinct populations, as well as different outcome and exposure variable definitions.

There are several mechanisms through which potassium intake may influence clinical outcomes. First, higher potassium intake may lower blood pressure through mechanisms that may include natriuresis, decreased vascular resistance, or central-mediated mechanisms and, by decreasing blood pressure, lower mortality.²²⁻²⁵ However, we did not note attenuation in the relationship when adjusting for time-dependent blood pressure. We acknowledge that a blood pressure-dependent mechanism is still possible given the observational nature of our study and the fact that many of the outcomes occurred many years after assessment of urine potassium excretion and blood pressure. Second, lower potassium intake may result in endothelial dysfunction and left ventricular modeling through non-blood pressure-dependent mechanisms.^{14,22-25} Third, it is possible that lower potassium intake may reflect severity of illness or degree of kidney disease. Based on these outlined mechanisms, interactions among urine sodium excretion, blood pressure, proteinuria, and GFR were explored in both the mortality and kidney failure outcomes. Although there were significant interactions in the relationship with kidney failure and all-cause mortality, these were exploratory analyses and may not have true significance given the multiple comparisons. These will need to be assessed in future studies.

Study limitations should be noted in the interpretation of the present results. In the current study, an assumption is made that urine potassium excretion is a surrogate for potassium intake.²⁶ However, there is limited information for the relationship of urinary potassium with dietary intake in CKD, and it needs to be acknowledged that as GFR declines, there may be an increase in gastrointestinal potassium secretion.²⁷⁻²⁹ Second, due to the observational design, unmeasured and residual confounding remain possible; thus, we cannot make causal references from the associations between all-cause mortality and urine potassium excretion. Third, the MDRD Study includes primarily a nondiabetic advanced CKD population, which may not be generalizable to the CKD population as a whole. In particular, individuals with diabetes and advanced CKD may be at risk for hyperkalemia with a higher potassium diet due to increased use of renin-angiotensin system blockade, as well as a higher prevalence of type IV renal tubular acidosis. Strengths of the study include robust ascertainment of the exposure variable, with multiple 24-hour urine collections obtained, in addition to studying the association using a baseline urine collection. In sensitivity analysis, we were able to

show consistency in the associations with exclusion of inadequate urine collections. Additional strengths include long-term follow-up with multiple events of both kidney failure and all-cause mortality and detailed information about medication use (diuretics vs ACE inhibition).

In conclusion, we demonstrate an association between higher urine potassium excretion and lower all-cause mortality. The results suggest that higher potassium intake may provide some benefit even in a population with nondiabetic CKD. Further studies are needed to assess the consistency of these results in other cohorts of patients with kidney disease and understand the mechanisms explaining these relationships. Ultimately, we hope to provide more data on which to base CKD guidelines.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The data reported here have been supplied by the US Renal Data System. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as official policy or interpretation of the US government.

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References

1. American Heart Association Nutrition Committee. Lichtenstein AH, Appel LJ, Brands M, Carnethon M, Daniels S, et al. Diet and lifestyle recommendations revision 2006: a scientific statement from the American Heart Association Nutrition Committee. *Circulation*. 2006; 114(1):82–96. [PubMed: 16785338]
2. Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. *Kidney Int Suppl*. 2012; 2:337–414.
3. Drewnowski A, Rehm CD, Maillot M, Mendoza A, Monsivais P. The feasibility of meeting the WHO guidelines for sodium and potassium: a cross-national comparison study. *BMJ Open*. 2015; 5(3):e006625.
4. National Kidney Foundation. KDOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. *Am J Kidney Dis*. 2004; 43(5 suppl 1):65–230.
5. Chapter 2: lifestyle and pharmacological treatments for lowering blood pressure in CKD ND patients. *Kidney Int Suppl*. 2011; 2(5):347–356. No authors listed.
6. Kieneker LM, Gansevoort RT, Mukamal KJ, et al. Urinary potassium excretion and risk of developing hypertension: the Prevention of Renal and Vascular End-Stage Disease Study. *Hypertension*. 2014; 64(4):769–776. [PubMed: 25047575]
7. Stamler J. The INTERSALT Study: background, methods, findings, and implications. *Am J Clin Nutr*. 1997; 65(2 suppl):626S–642S. [PubMed: 9022559]
8. Mente A, O'Donnell MJ, Rangarajan S, et al. Association of urinary sodium and potassium excretion with blood pressure. *N Engl J Med*. 2014; 371(7):601–611. [PubMed: 25119606]
9. O'Donnell M, Mente A, Rangarajan S, et al. Urinary sodium and potassium excretion, mortality, and cardiovascular events. *N Engl J Med*. 2014; 371(7):612–623. [PubMed: 25119607]

10. Aburto NJ, Hanson S, Gutierrez H, Hooper L, Elliott P, Cappuccio FP. Effect of increased potassium intake on cardiovascular risk factors and disease: systematic review and meta-analyses. *BMJ*. 2013; 346:f1378. [PubMed: 23558164]
11. Cook NR, Obarzanek E, Cutler JA, et al. Joint effects of sodium and potassium intake on subsequent cardiovascular disease: the Trials of Hypertension Prevention follow-up study. *Arch Intern Med*. 2009; 169(1):32–40. [PubMed: 19139321]
12. Houston MC. The importance of potassium in managing hypertension. *Curr Hypertens Rep*. 2011; 13(4):309–317. [PubMed: 21403995]
13. Whelton PK, He J, Cutler JA, et al. Effects of oral potassium on blood pressure. Meta-analysis of randomized controlled clinical trials. *JAMA*. 1997; 277(20):1624–1632. [PubMed: 9168293]
14. He FJ, Marciniak M, Carney C, et al. Effects of potassium chloride and potassium bicarbonate on endothelial function, cardiovascular risk factors, and bone turnover in mild hypertensives. *Hypertension*. 2010; 55(3):681–688. [PubMed: 20083724]
15. Sharma S, McFann K, Chonchol M, de Boer IH, Kendrick J. Association between dietary sodium and potassium intake with chronic kidney disease in US adults: a cross-sectional study. *Am J Nephrol*. 2013; 37(6):526–533. [PubMed: 23689685]
16. Smyth A, Dunkler D, Gao P, et al. The relationship between estimated sodium and potassium excretion and subsequent renal outcomes. *Kidney Int*. 2014; 86(6):1205–1212. [PubMed: 24918156]
17. He J, Mills KT, Appel LJ, et al. Urinary sodium and potassium excretion and CKD progression. *J Am Soc Nephrol*. 2016; 27(4):1202–1212. [PubMed: 26382905]
18. Araki S, Haneda M, Koya D, et al. Urinary potassium excretion and renal and cardiovascular complications in patients with type 2 diabetes and normal renal function. *Clin J Am Soc Nephrol*. 2015; 10(12):2152–2158. [PubMed: 26563378]
19. Klahr S, Levey AS, Beck GJ, et al. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. *N Engl J Med*. 1994; 330(13):877–884. [PubMed: 8114857]
20. Ix JH, Wassel CL, Stevens LA, et al. Equations to estimate creatinine excretion rate: the CKD Epidemiology Collaboration. *Clin J Am Soc Nephrol*. 2011; 6(1):184–191. [PubMed: 20966119]
21. Peterson JC, Adler S, Burkart JM, et al. Blood pressure control, proteinuria, and the progression of renal disease. The Modification of Diet in Renal Disease Study. *Ann Intern Med*. 1995; 123(10):754–762. [PubMed: 7574193]
22. Adroge HJ, Madias NE. Sodium surfeit and potassium deficit: keys to the pathogenesis of hypertension. *J Am Soc Hypertens*. 2014; 8(3):203–213. [PubMed: 24200471]
23. Lin HB, Young DB, Smith MJ Jr. Stimulation of renin release by hyperkalemia in the nonfiltering kidney. *Am J Physiol*. 1991; 260(2, pt 2):F170–F176. [PubMed: 1996669]
24. Katori M, Majima M. The renal kallikrein-kinin system: its role as a safety valve for excess sodium intake, and its attenuation as a possible etiologic factor in salt-sensitive hypertension. *Crit Rev Clin Lab Sci*. 2003; 40(1):43–115. [PubMed: 12627748]
25. Meneton P, Jeunemaitre X, de Wardener HE, MacGregor GA. Links between dietary salt intake, renal salt handling, blood pressure, and cardiovascular diseases. *Physiol Rev*. 2005; 85(2):679–715. [PubMed: 15788708]
26. Holbrook JT, Patterson KY, Bodner JE, et al. Sodium and potassium intake and balance in adults consuming self-selected diets. *Am J Clin Nutr*. 1984; 40(4):786–793. [PubMed: 6486085]
27. van Ypersele de Strihou C. Potassium homeostasis in renal failure. *Kidney Int*. 1977; 11(6):491–504. [PubMed: 875265]
28. Kopple JD, Coburn JW. Metabolic studies of low protein diets in uremia. I. Nitrogen and potassium. *Medicine (Baltimore)*. 1973; 52(6):583–595. [PubMed: 4748592]
29. Kahn T, Kaji DM, Nicolis G, Krakoff LR, Stein RM. Factors related to potassium transport in chronic stable renal disease in man. *Clin Sci Mol Med*. 1978; 54(6):661–666. [PubMed: 657736]

Figure 1.

Adjusted restricted cubic splines for baseline 24-hour urine potassium excretion and (A) kidney failure and (B) all-cause mortality. Splines were plotted using 4 default knots. *P* value for nonlinearity of urine potassium excretion is reported as analysis of variance (ANOVA) linearity in each graph. Dashed lines indicate 95% confidence intervals. Splines were adjusted for age, sex, race, cause of kidney disease, measured glomerular filtration rate, log urine protein, body mass index, systolic blood pressure, high-density lipoprotein cholesterol level, transferrin level, MDRD (Modification of Diet in Renal Disease) Study A or B, randomization to blood pressure and dietary protein target, diuretic use, angiotensin-converting enzyme inhibitor use, urine urea nitrogen excretion, daily caloric intake, and urine sodium excretion. Reference point where hazard ratio 5 1 is at baseline urine potassium excretion (2.39 g/d).

Figure 2.

Forest plot of baseline 24-hour urine potassium excretion and kidney failure and all-cause mortality in the entire cohort and predefined subgroups. Hazard ratios (HRs) (95% confidence intervals [CIs]) were per 1-standard deviation (0.89 g/d) higher urine potassium excretion. HRs were on log scale. HRs were adjusted for age, sex, race, cause of kidney disease, measured glomerular filtration rate, log urine protein, body mass index, systolic blood pressure, high-density lipoprotein cholesterol level, transferrin level, MDRD (Modification of Diet in Renal Disease) Study A or B, randomization to blood pressure and dietary protein target, diuretic use, angiotensin-converting enzyme inhibitor use, urine urea nitrogen excretion, daily caloric intake, and urine sodium excretion. Abbreviation: P-int, *P* for interaction.

Baseline Clinical Characteristics of Overall Study Population and Stratified According to Quartiles of Baseline 24-Hour Urine Potassium Excretion

Table 1

	Overall (N = 812)	Quartile 1 (n = 209)	Quartile 2 (n = 188)	Quartile 3 (n = 215)	Quartile 4 (n = 200)	P for Trend
Baseline urine potassium, g/d	2.39 ± .89	1.41 ± .27	2.01 ± .14	2.54 ± .20	3.60 ± .66	<0.001
Age, y	51.8 ± 2.4	48.1 ± 3.1	51.9 ± 1.6	53.7 ± 2.4	53.3 ± 1.7	<0.001
Male sex	488 (60.1)	80 (38.3)	105 (55.9)	138 (64.2)	165 (82.5)	<0.001
Race						<0.001
White	691 (85.1)	165 (79.0)	151 (80.3)	187 (87.0)	188 (94.0)	
Black	65 (8.0)	22 (10.5)	21 (11.2)	17 (7.9)	5 (2.5)	
Other	56 (6.9)	22 (10.5)	16 (8.5)	11 (5.1)	7 (3.5)	
Cause of CKD						0.7
PKD	193 (23.8)	58 (27.8)	41 (21.8)	46 (21.4)	48 (24.0)	
GN	255 (31.4)	63 (30.1)	64 (34.0)	63 (29.3)	65 (32.5)	
Other	364 (44.8)	88 (42.1)	83 (44.2)	106 (49.3)	87 (43.5)	
Diabetes	42 (5.2)	4 (1.9)	11 (5.9)	12 (5.6)	15 (7.5)	0.02
History of CVD	108 (13.3)	18 (8.6)	28 (14.9)	38 (17.7)	24 (12.0)	0.2
Current smoking status	79 (9.7)	22 (10.5)	21 (11.2)	18 (8.4)	18 (9.0)	0.4
Baseline mGFR, mL/min/1.73 m ²	32.6 ± 12.0	29.8 ± 11.7	32.3 ± 12.6	31.9 ± 11.6	36.5 ± 11.3	<0.001
Urine protein, g/d	0.3 [0.1-1.4]	0.3 [0.1-1.4]	0.3 [0.1-1.4]	0.3 [0.1-1.3]	0.3 [0.1-1.6]	0.5
Baseline urine creatinine, mg/d	1.41 ± 0.41	1.17 ± 0.34	1.36 ± 0.37	1.47 ± 0.40	1.63 ± 0.40	<0.001
Baseline urine sodium, g/d	3.46 ± 1.49	2.76 ± 1.14	3.32 ± 1.29	3.76 ± 1.49	4.00 ± 1.67	<0.001
BMI, kg/m ²	27.1 ± 4.5	26.0 ± 4.7	26.6 ± 4.2	27.8 ± 4.5	28.0 ± 4.2	<0.001
Systolic BP, mm Hg	131.9 ± 17.6	129.4 ± 16.6	133.3 ± 18.9	134.4 ± 18.1	130.7 ± 16.5	0.3
Diastolic BP, mm Hg	81.0 ± 10.1	81.6 ± 9.8	80.3 ± 10.8	81.0 ± 9.6	80.9 ± 10.3	0.6
HDL cholesterol, mg/dL	40.0 ± 14.3	43.0 ± 15.7	41.5 ± 14.7	39.9 ± 14.4	35.7 ± 10.8	<0.001
Transferrin, mg/dL	274.0 ± 45.7	272.0 ± 42.8	275.8 ± 50.0	275.1 ± 45.7	273.3 ± 44.5	0.9
Urine urea nitrogen, g/d	9.7 ± 2.8	8.4 ± 2.4	9.2 ± 2.7	10.2 ± 2.7	10.9 ± 2.9	<0.001
Caloric intake, kcal/kg/d	26.3 ± 7.6	25.3 ± 6.9	26.1 ± 8.3	25.6 ± 7.1	28.4 ± 7.8	<0.001
MDRD Study						<0.001
Study A	569 (70.1)	127 (60.8)	127 (67.6)	151 (70.2)	164 (82.0)	
Study B	243 (29.9)	82 (39.2)	61 (32.5)	64 (29.8)	36 (18.0)	

	Overall (N = 812)	Quartile 1 (n = 209)	Quartile 2 (n = 188)	Quartile 3 (n = 215)	Quartile 4 (n = 200)	P for Trend
BP target						0.9
Usual BP target	394 (48.5)	99 (47.4)	90 (47.9)	111 (51.6)	94 (47.0)	
Low BP target	418 (51.5)	110 (52.6)	98 (52.1)	104 (48.4)	106 (53.0)	
Diet group						<0.001
Very low-protein diet	121 (14.9)	50 (23.9)	29 (15.4)	29 (13.5)	13 (6.5)	
Low-protein diet	405 (49.9)	101 (48.3)	99 (52.7)	110 (51.2)	95 (47.5)	
Usual-protein diet	286 (35.2)	58 (27.8)	60 (31.9)	76 (35.4)	92 (46.0)	
ACE inhibitors	293 (36.1)	72 (34.5)	74 (39.4)	74 (34.4)	73 (36.5)	0.9
Diuretics	326 (40.2)	60 (28.7)	73 (38.8)	98 (45.6)	95 (47.5)	<0.001

Note: Values for categorical variables are given as frequency (percentage); values for continuous variables, as mean $\pm$ standard deviation or median [interquartile range]. Conversion factors for units: for cholesterol in mg/dL to mmol/L, $\times 0.02586$; urine potassium in g/d to mEq/d, $\times 0.039$.

Abbreviations and definitions: ACE, angiotensin-converting enzyme; BMI, body mass index; BP, blood pressure; CKD, chronic kidney disease; CVD, cardiovascular disease (includes coronary artery disease and peripheral vascular disease); GN, glomerulonephritis; HDL, high-density lipoprotein; MDRD, Modification of Diet in Renal Disease; mGFR, measured glomerular filtration rate; PKD, polycystic kidney disease; urine potassium, 24-hour urine potassium excretion.

Table 2

Associations of Urine Potassium With Kidney Failure and All-Cause Mortality

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Continuous ^a	P
Association Between Baseline Urine Potassium and Outcomes						
Kidney failure						
No. of events	169	143	151	140	603	
Total follow-up, y	1,582	1,493	1,745	1,827	6,647	
Event rate, per 100-py	10.68	9.58	8.65	7.66	9.07	
Unadjusted	1.39 (1.11-1.74)	1.23 (0.98-1.56)	1.12 (0.89-1.42)	1.00 (reference)	0.92 (0.85-1.00)	0.06
Model 1	1.43 (1.12-1.82)	1.29 (1.02-1.65)	1.19 (0.94-1.50)	1.00 (reference)	0.92 (0.84-1.01)	0.08
Model 2	1.19 (0.93-1.51)	1.30 (1.02-1.66)	1.17 (0.92-1.48)	1.00 (reference)	0.96 (0.88-1.04)	0.3
Model 3	1.22 (0.95-1.56)	1.29 (1.00-1.65)	1.17 (0.92-1.49)	1.00 (reference)	0.95 (0.87-1.04)	0.2
Model 4	1.22 (0.94-1.58)	1.27 (0.99-1.64)	1.16 (0.91-1.47)	1.00 (reference)	0.95 (0.87-1.04)	0.2
All-cause mortality						
No. of events	96	110	132	92	430	
Total follow-up, y	3,393	2,828	3,160	3,201	12,582	
Event rate, per 100-py	2.83	3.89	4.18	2.87	3.42	
Unadjusted	0.98 (0.74-1.31)	1.39 (1.05-1.83)	1.49 (1.14-1.95)	1.00 (reference)	1.02 (0.93-1.12)	0.6
Model 1	1.62 (1.20-2.18)	1.72 (1.29-2.28)	1.56 (1.19-2.04)	1.00 (reference)	0.85 (0.77-0.95)	0.003
Model 2	1.52 (1.12-2.07)	1.71 (1.28-2.28)	1.53 (1.17-2.01)	1.00 (reference)	0.86 (0.77-0.96)	0.006
Model 3	1.60 (1.16-2.20)	1.64 (1.22-2.20)	1.50 (1.13-1.98)	1.00 (reference)	0.86 (0.77-0.96)	0.008
Model 4	1.71 (1.23-2.38)	1.70 (1.25-2.31)	1.53 (1.15-2.02)	1.00 (reference)	0.83 (0.74-0.94)	0.002
Association Between Time-Updated Average Urine Potassium and Outcomes						
Kidney failure						
No. of events	154	137	141	126	558	
Total follow-up, y	1,428	1,421	1,635	1,719	6,203	
Event rate, per 100-py	10.78	9.64	8.62	7.33	9.00	
Unadjusted	1.51 (1.19-1.92)	1.40 (1.10-1.78)	0.96 (0.75-1.23)	1.00 (reference)	0.83 (0.75-0.91)	0.02
Model 1	1.59 (1.22-1.06)	1.48 (1.16-1.89)	0.96 (0.75-1.23)	1.00 (reference)	0.81 (0.72-0.90)	0.03
Model 2	0.94 (0.72-1.23)	1.30 (1.01-1.66)	0.82 (0.64-1.06)	1.00 (reference)	0.98 (0.89-1.08)	0.2
Model 3	0.98 (0.72-1.32)	1.37 (1.06-1.78)	0.85 (0.66-1.10)	1.00 (reference)	0.95 (0.85-1.07)	0.2

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Continuous ^a	P
Model 4	0.96 (0.70-1.31)	1.36 (1.04-1.78)	0.85 (0.66-1.11)	1.00 (reference)	0.96 (0.86-1.08)	0.5
All-cause mortality						
No. of events	83	103	120	84	390	
Total follow-up, y	3,105	2,690	2,945	2,938	11,678	
Event rate, per 100-py	2.67	3.83	4.07	2.86	3.34	
Unadjusted	0.92 (0.69-1.23)	1.21 (0.92-1.60)	1.00 (0.76-1.33)	1.00 (reference)	1.04 (0.93-1.16)	0.4
Model 1	1.68 (1.23-2.28)	1.52 (1.15-2.03)	1.10 (0.83-1.46)	1.00 (reference)	0.81 (0.71-0.92)	0.007
Model 2	1.42 (1.03-1.97)	1.49 (1.11-1.99)	1.05 (0.79-1.39)	1.00 (reference)	0.86 (0.75-0.98)	0.01
Model 3	1.54 (1.05-2.26)	1.49 (1.08-2.06)	1.07 (0.79-1.46)	1.00 (reference)	0.85 (0.73-0.99)	0.01
Model 4	1.67 (1.12-2.48)	1.55 (1.11-2.16)	1.10 (0.80-1.50)	1.00 (reference)	0.83 (0.71-0.97)	0.02

Note: Each model reports a hazard ratio (95% confidence interval). Model 1: age, sex, and race; model 2: model 1 plus measured glomerular filtration rate, log urine protein per doubling, and cause of kidney disease; model 3: model 2 plus history of cardiovascular disease, 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 angiotensin-converting enzyme inhibitor use (dichotomous), urine urea nitrogen excretion, total caloric intake, and urine sodium excretion.

Abbreviations: py, person-years; SD, standard deviation.

^aContinuous: per 1-SD increase in urine potassium excretion (1 SD = 0.89 g/d).