Urinary Potassium Excretion and Progression From Advanced CKD to Kidney Failure

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Abstract
Background: Increased dietary potassium intake has well-proven beneficial effects on cardiovascular health and mortality. However, the association between dietary potassium intake and chronic kidney disease (CKD) progression remains unclear with prior studies reporting conflicting results.
Objective: To study the association between 24-hour urinary potassium excretion (a surrogate for dietary potassium intake) and progression to kidney failure.
Design: Retrospective cohort study.
Setting: Ottawa, Canada
Patients: Patients with advanced CKD referred to the Ottawa Hospital Multi-Care Kidney Clinic from 2010 to 2020.
Measurements: Twenty-four-hour urinary potassium excretion measured upon referral to the Ottawa Hospital Multi-Care Kidney Clinic as part of routine clinic protocol.
Methods: Multivariable Cox and Fine and Gray models provided hazard ratios (HRs) and 95% confidence intervals (CIs) to estimate the association between quartiles of 24-hour urinary potassium excretion and progression to kidney failure. A restricted cubic spline analysis examined the possible nonlinear relationship between 24-hour urinary potassium excretion (as a continuous variable) and progression to kidney failure.
Results: Overall, 432/695 (62%) patients progressed to kidney failure. Across all models, there was no significant difference in kidney failure risk by quartile of 24-hour urinary potassium excretion (all P values for trend ≥ .05). Hazard ratios (95% CIs) from the multivariable-adjusted Cox model were as follows: quartile 1, referent; quartile 2, 0.95 (0.71-1.27); quartile 3, 1.00 (0.76-1.33); and quartile 4 0.85 (0.63-1.14); P value for trend = .36. Restricted cubic spline analysis showed an overall linear and nonsignificant relationship between 24-hour urinary potassium excretion as a continuous variable and progression to kidney failure.
Limitations: Observational design, single center.
Conclusions: We found no association between 24-hour urinary potassium excretion and progression to kidney failure in patients with advanced CKD. Therefore, we identified no clear evidence that increasing or decreasing dietary potassium intake significantly associates with CKD progression in this population.
Trial Registration: Not registered.

Abrégé
Contexte: De nombreux facteurs influent sur le recrutement et la rétention des patients en dialyse péritonéale (DP); un des principaux défis étant une impression d’« inaccessibilité » aux cliniciens traitants. La télésurveillance des patients (TSP) a été suggérée comme possible moyen d’améliorer le suivi et, par conséquent, l’adhésion des patients à la DP.
Objectif: Décrire les points de vue des patients et des cliniciens à l’égard de la TSP et de l’utilisation d’applications adaptées aux téléphones intelligents, aux tablettes ou aux ordinateurs pour aider à la prise en charge de la DP.
Type d’étude: Étude qualitative menée par le biais d’entretiens semi-structurés.
Cadre: Tous les patients suivant des traitements de DP à domicile sous la supervision de l’unité de DP d’un centre urbain de Sydney (Australie). Les entretiens avec les patients et les cliniciens ont été menés au sein de l’unité de DP.
Participants à l’étude: 14 participants, soit 5 cliniciens (2 néphrologues, 3 infirmières et infirmiers en DP) et 9 patients sous DP.
Méthodologie: Des entretiens semi-structurés ont été menés à l’aide de guides d’entrevue adaptés aux cliniciens et aux patients participants. Les transcriptions ont été codées, puis une analyse thématique par un seul chercheur a été réalisée.

Résultats: Six thèmes ont été dégagés : 1) avantages perçus de la TSP (intervention pratique et efficace, patients rassurés par une surveillance accrue, données plus complètes et meilleur suivi de l’observance); 2) incertitude quant à la gouvernance des données (protection des données personnelles, fiabilité des données); 3) réduction de la participation des patients (transfert de responsabilité menant à la complaisance); 4) évolution de la relation patient-clinicien (réduction des échanges initiés par le patient, nécessité de maintenir l’indépendance du patient); 5) fardeau accru pour le patient et le clinicien (connaissances technologiques inadéquates, gestion excessive conduisant à de fréquents changements du traitement) et; 6) comportement du patient influencé par la préférence du clinicien.

Limites: Les entretiens ont été menés uniquement en anglais, auprès de participants provenant d’une seule unité de dialyse en centre urbain, ce qui pourrait limiter la généralisabilité des résultats.

Conclusion: Selon les patients et les cliniciens interrogés, la TSP en contexte de DP pourrait offrir plusieurs avantages: confiance et assurance accrues pour les patients, meilleure surveillance du traitement, saisie plus complète des données et suppression des entraves liées à la documentation des données. Une sélection rigoureuse des patients et une formation adéquate du patient et du clinicien pourraient contribuer à optimiser les avantages de la TSP, à maintenir l’indépendance du patient et à réduire les risques de désengagement. L’utilisation d’une application pourrait appuyer la TSP; des participants ont cependant exprimé des inquiétudes quant à une augmentation du fardeau pour certains patients moins familiers avec ce type de technologie.

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Keywords
chronic kidney disease, diet, excretion, kidney failure, potassium

Introduction

Potassium is an essential nutrient critical to maintaining physiological balance within the body.1 Potassium-rich foods include primarily fruits and vegetable. As up to 90% of all potassium consumed is excreted in the urine, 24-hour urinary potassium excretion serves as a surrogate for dietary potassium intake.2 Increased dietary potassium intake, as reflected by 24-hour urinary potassium excretion, is associated with a number of beneficial health effects, including reductions in blood pressure, cardiovascular events, and mortality.3-5 However, the effect of dietary potassium intake on chronic kidney disease (CKD) progression is far less certain. The issue of dietary potassium intake on the CKD population is complex given that the increased cardiovascular risk inherent to CKD (where high dietary potassium intake may be beneficial) must be balanced against an increased risk for hyperkalemia (where high dietary potassium intake may be detrimental). Prior cohort studies examining the impact of dietary potassium intake on CKD progression have yielded highly discordant results.5-9 The conclusions from these studies have ranged widely from high dietary potassium intake slowing CKD progression7,8 to high dietary potassium intake accelerating CKD progression6 to dietary potassium intake having no impact on CKD progression.8 Given the uncertainty regarding the impact of dietary potassium intake on CKD progression, we evaluated the association between 24-hour urinary potassium excretion and progression to kidney failure in a large population of patients with advanced CKD.

Method

Study Design

We performed a retrospective cohort study of adults (≥18 years of age) with advanced CKD referred to the Ottawa Hospital Multi-Care Kidney Clinic.

Data Source and Study Cohort

This study was conducted at the Ottawa Hospital Multi-Care Kidney Clinic (Ottawa, Ontario, Canada). The Ottawa Hospital is a 1150-bed academic tertiary care center with a catchment area of approximately 1.3 million people. The

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Ottawa Hospital Multi-Care Kidney Clinic is a specialty nephrology clinic designed to provide comprehensive, multidisciplinary care for patients with advanced CKD and is the sole such program within the catchment area. Timing of referral is at the discretion of the primary nephrologist, although referrals are suggested when the estimated glomerular filtration rate (eGFR) is <25 mL/min/1.73 m² or the 2-year 4-variable Kidney Failure Risk Equation¹⁰ score is >20%. Patients are seen in the clinic typically every 3 months although this interval can vary from as often as every 2 weeks to as long as every 6 months per the discretion of the nephrologist. At each visit, patients are seen by a nurse, dietician, and nephrologist, with pharmacist and social work support available as needed. Patients are educated about kidney failure treatment options, including hemodialysis, peritoneal dialysis, kidney transplantation, and conservative management.

The study cohort was derived from a database of all patients referred to the Multi-Care Kidney Clinic since January 1, 2010, with follow-up data available through July 1, 2020. The database undergoes random data audits every 6 to 12 months where the data are compared with the electronic medical record to ensure accuracy. As part of routine clinic protocol, 24-hour urinary potassium excretion (along with 24-hour creatinine excretion) is measured upon initial clinic referral. Patients were included in the study if they had a 24-hour urinary collection for potassium and creatinine (N = 1469). Patients were excluded if the 24-hour urinary sample collection was deemed inadequate due to undercollection (n = 692) or overcollection (n = 82) as defined by a 24-hour urinary creatinine excretion outside of the ranges of 10 to 20 mg/kg for females and 15 to 25 mg/kg for males.¹¹ Ultimately, 695 patients were included in the data analysis. Patients were subclassified by quartiles based on their 24-hour urinary potassium excretion measurements. All baseline data were captured at the time of the initial referral visit to the Multi-Care Kidney Clinic. All protocols were approved by the Ottawa Health Science Network Research Ethics Board (Protocol ID 20210228-01H). Informed consent requirements were waived due to the retrospective nature of the data.

### Outcome

The outcome of interest was progression of CKD to kidney failure, defined as dialysis or kidney transplantation.

### Predictor

The predictor used in this study was the first 24-hour urinary potassium excretion measured upon referral to the Ottawa Hospital Multi-Care Kidney Clinic.

### Statistical Analysis

For baseline data, continuous variables were expressed as mean (standard deviation [SD]) if normally distributed and as median (25th-75th percentile interquartile range [IQR]) if non-normally distributed, whereas categorical variables were expressed as numbers (%). To explore the association between quartiles of 24-hour urinary potassium excretion and progression to kidney failure, we used Cox proportional hazard models (with death prior to kidney failure treated as a censoring event) as well as Fine and Gray subdistribution hazard models (with death prior to kidney failure treated as a competing event). We used 4 models adjusting for different variables. Model 1 was unadjusted. Model 2 was adjusted for age, sex, race, systolic blood pressure, body mass index, diabetes mellitus, and a history of cardiovascular disease. Model 3 was adjusted for eGFR and 24-hour urinary protein excretion, in addition to the variables included in model 2. Model 4 was adjusted for medication use (angiotensin-converting enzyme [ACE] inhibitors/angiotensin II receptor blockers [ARBs] and diuretics), in addition to the variables included in model 3. The results were reported as hazard ratios (HRs) along with 95% confidence intervals (CIs). P values for trend were reported with each model and were calculated by treating quartiles of 24-hour urinary potassium excretion as a continuous variable. Patients who were lost to follow-up were censored at the date of the last clinic visit. Next, we examined the possible nonlinear relation between 24-hour urinary potassium excretion (now as a continuous variable) and progression to kidney failure nonparametrically with restricted cubic splines.¹² Tests for nonlinearity used the likelihood ratio test, comparing the model with only the linear term to the model with the linear and the cubic spline terms. The spline model used a Cox proportional hazards model adjusted for age, sex, race, systolic blood pressure, body mass index, diabetes mellitus, history of cardiovascular disease, eGFR, 24-hour urinary protein excretion, ACE inhibitor/ARB use, and diuretic use (ie, model 4 as described above). All statistical analyses were performed using SAS version 9.4. All P values are 2-sided with values <.05 considered significant. The data underlying this article will be shared upon reasonable request to the corresponding author.

### Results

The quartiles of 24-hour urinary potassium excretion for the study population (N = 695) were as follows: <37, 37–49, 50–63, and ≥64 mmol/day. The baseline characteristics of the study population both overall and by quartile of 24-hour urinary potassium excretion are displayed in Table 1. The mean (SD) age of the total population was 69 (16) years. The majority of the population was female (59%) and of white race (78%). The mean (SD) eGFR was 15 (6) mL/min/1.73 m². These characteristics were similar across quartiles of 24-hour urinary potassium excretion.

Table 2 displays the number of kidney failure events (defined as dialysis or kidney transplantation) and event rates per 1000 person-years, whereas Table 3 displays the HRs and 95% CIs from Cox as well as Fine and Gray models. Overall,
432/695 (62%) patients progressed to kidney failure. Across all models, there was no significant difference in the risk of kidney failure by quartile of 24-hour urinary potassium excretion (all \( P \) values for trend \( \geq .05 \)). For instance, in the fully adjusted Cox model (model 4), the HRs (95% CIs) were as follows: quartile 1, referent; quartile 2, 0.95 (0.71-1.27); quartile 3, 1.00 (0.76-1.33); and quartile 4 0.85 (0.63-1.14); \( P \) value for trend = .36. Fine and Gray models, where death prior to kidney failure was treated as a competing rather than censoring event, yielded similar results (Table 3).

Restricted cubic spline analysis showed an overall linear and nonsignificant relationship between 24-hour urinary potassium excretion as a continuous variable and progression to kidney failure (Figure 1). Therefore, even when 24-hour urinary potassium excretion was treated as a continuous variable, there appeared to be no significant association with progression from advanced CKD to kidney failure.

**Discussion**

In this large retrospective cohort study of patients with advanced CKD, we found no significant association between 24-hour urinary potassium excretion (a surrogate for dietary potassium intake) and progression to kidney failure.

To date, the evidence behind the effect of dietary potassium intake on CKD progression has been conflicting. He et al studied the association between 24-hour urinary potassium excretion and CKD progression, defined as kidney failure or halving of eGFR, among 3939 CKD patients (mean eGFR = 40-50 mL/min/1.73 m\(^2\)) as part of the Chronic Renal Insufficiency Cohort (CRIC) Study.\(^6\) The authors found that high urinary potassium excretion was associated with a significantly heightened risk for CKD progression. In fact, the highest quartile of urinary potassium excretion associated with a 59% higher risk for CKD progression compared with the lowest quartile.\(^6\)

In contrast, other studies have reported completely contradictory results; that is, that low urinary potassium excretion was associated with a heightened risk for CKD progression. For instance, Kieneker et al studied the association between 24-hour urinary potassium excretion and development of incident CKD, defined as an eGFR <60 mL/min/1.73 m\(^2\) or albuminuria >30 mg/24 h, among 5315 non-CKD individuals as part of the Prevention of Renal and Vascular End-Stage Disease (PREVEND) Study.\(^7\) The
authors found that each decrease in 24-hour urinary potassium excretion by 21 mmol was associated with a 16% higher risk of developing CKD. Similarly, Kim et al found that 3 different measures of low urinary potassium excretion (↓ 24-hour urinary potassium excretion, ↓ spot urinary potassium concentration, and ↓ spot urinary potassium-to-creatinine ratio) were all associated with an increased risk for CKD progression (defined as kidney failure or halving of...
eGFR (eGFR) among a study population of 1821 CKD patients with a median eGFR of 47 mL/min/1.73 m² from the Korean Cohort Study for Outcome in Patients with CKD (KNOW-CKD) Study.⁸ Among the 855 patients who had a 24-hour urinary potassium excretion measurement, the lowest quartile of 24-hour urinary potassium excretion was associated with a greater than 3-fold higher risk of CKD progression compared with the highest quartile.⁸

Meanwhile, the results from our study land somewhere in the middle and suggest no significant association between 24-hour urinary potassium excretion and CKD progression. These results correspond with a post hoc analysis of the Modification of Diet in Renal Disease (MDRD) Study by Leonberg-Yoo et al which included 812 CKD patients (mean eGFR = 32.6 mL/min/1.73 m²) where the authors found no association between 24-hour urinary potassium excretion and progression to kidney failure.⁸

What might we attribute the widely discrepant findings in the literature on the association between 24-hour urinary potassium excretion and CKD progression to?⁹ In general, the above studies⁶-⁹ and our present study used similar analytic techniques adjusting for similar variables among similarly aged populations. However, there are a number of factors within the individual study populations that may help to provide an explanation. First, the severity of CKD varied from the extremes of baseline CKD being an exclusion criterion⁷ to the present study where only patients with advanced CKD were included. The presence and severity of baseline CKD associate with more common use of medications such as ACE inhibitors, ARBs, and diuretics that may impact potassium homeostasis.¹³,¹⁴ Also, as the severity of CKD increases, so too does the proportion of potassium that is rectally excreted.¹⁵ Therefore, urinary potassium excretion may not fully reflect dietary potassium intake in these cases. Second, the makeup of the CKD populations between studies also varied widely. For instance, the MDRD study excluded patients with insulin-dependent diabetes (type 1 or type 2); therefore, a relatively small proportion of patients in the Leonberg-Yoo et al study likely had diabetic nephropathy as the etiology of their CKD.⁹ This is reflected in the lower rates of ACE inhibitor use that may have affected the association between 24-hour urinary potassium excretion and CKD progression in this study. Third, racial differences between the study populations cannot be ignored as this is known to affect urinary potassium handling. In particular, black individuals have been shown to have lower rates of urinary potassium excretion compared with white individuals, independent of dietary potassium intake.¹⁶-¹⁸ With the exception of the CRIC-based study by He et al where >40% of the study population was black, the racial diversity of the remaining studies was relatively low. Ultimately, there does not appear to be a “one size fits all” answer to the question of how does dietary potassium intake (and it surrogate of urinary potassium excretion) associate with CKD progression. The answer may very well depend on a variety of intrinsic factors related to the population you are asking this question of, including the presence and severity of CKD, the etiology of CKD, and the racial makeup.

Our study has several notable strengths. A unique feature to our study was that our population had more advanced CKD at baseline compared with prior studies examining the relationship between urinary potassium excretion and CKD progression.⁶-⁸ This allowed us to incorporate the hard clinical endpoint of kidney failure (which occurred in 62% of our cohort) rather than reliance on surrogate outcomes such as eGFR decline or incident albuminuria as prior studies have done.⁶-⁸ Moreover, we used a more strict definition of what entailed an adequate 24-hour urinary collection based on 24-hour urinary creatinine excretion (10-20 mg/kg for females; 15-25 mg/kg for males)¹¹ compared with prior studies.⁶-⁸ This helped to avoid the risk of bias that can result from inclusion of 24-hour urinary samples that were either undercollected or overcollected.

We acknowledge several limitations. First, this study was observational; therefore, we were able to examine association but not causation. Second, this was a single-center study, which may limit the generalizability of the findings to other clinical settings. Third, as our study population had advanced CKD at baseline, we must interpret the results within the advanced CKD context. For instance, medications such as ACE inhibitors, ARBs, and diuretics may affect potassium homeostasis and are commonly used in patients with CKD although this limitation is shared with most prior studies on
this topic and were adjusted for within our analyses. Fourth, urinary potassium excretion was based on a single index measurement rather than on repeated measures, which limited our ability to capture the dynamic nature of this variable.

Conclusion
In conclusion, we found no association between 24-hour urinary potassium excretion and progression to kidney failure in patients with advanced CKD. Therefore, we can find no clear evidence that increasing or decreasing dietary potassium intake significantly affects CKD progression in this population.

Ethics Approval and Consent to Participate
The study was approved by the Ottawa Health Science Network Research Ethics Board (Protocol ID 20210228-01H). Informed consent requirements were waived due to the retrospective nature of the data.

Consent for Publication
Consent for publication was provided by all authors.

Availability of Data and Materials
Not available.

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Declaration of Conflicting Interests
The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: M.M.S. has received speaker fees from AstraZeneca. All other authors declare that there is no conflict of interest.

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