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Authors
Arif, Yousif
Wenziger, Cachet
Hsiung, Jui Ting
et al.

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Association of serum potassium with decline in residual kidney function in incident hemodialysis patients

Yousif Arif[1], Cachet Wenziger[1], Jui Ting Hsiung[1], Amanda Edward[1], Wei Ling Lau[1], Ramy M. Hanna[1], Yuji Lee[1], Yoshitsugu Obi[1], Csaba P. Kovesdy[2,3], Kamyar Kalantar-Zadeh[1,4], and Elani Streja[1,4]

[1]Harold Simmons Center for Kidney Disease Research and Epidemiology, Division of Nephrology & Hypertension, University of California Irvine Medical Center, Orange, CA, USA, [2]Division of Nephrology, Department of Medicine, University of Tennessee Health Science Center, Memphis, TN, USA, [3]Nephrology Section, Memphis Veterans Affairs Medical Center, Memphis, TN, USA and [4]Nephrology Section, VA Long Beach Healthcare System, Long Beach, CA, USA

Correspondence to: Elani Streja; E-mail: estreja@hs.uci.edu

ABSTRACT

Background. Hyperkalemia is associated with kidney function decline in patients with non-dialysis dependent chronic kidney disease, but this relationship is unclear for residual kidney function (RKF) among hemodialysis (HD) patients.

Methods. We conducted a retrospective cohort study of 6655 patients, who started HD January 2007 and December 2011 and who had data on renal urea clearance (KRU). Serum potassium levels were stratified into four groups (i.e. ≤4.0, >4.0 to ≤4.5, >4.5 to ≤5.0 and >5.0 mEq/L) and 1-year KRU slope for each group was estimated by a linear mixed-effects model.

Results. Higher serum potassium was associated with a greater decline in KRU, and the greatest decrease in KRU (−0.20, 95% confidence interval −0.50 to −0.06) was observed for baseline potassium >5.0 mEq/L in the fully adjusted model. Mediation analysis showed that KRU slope mediated 1.78% of the association between serum potassium and mortality.

Conclusions. Hyperkalemia is associated with a decline in RKF amongst incident HD patients. These findings may have important clinical implications in the management of hyperkalemia in advanced CKD if confirmed in additional clinical trials.

Keywords: hemodialysis, potassium, renal urea clearance, residual kidney function

INTRODUCTION

Residual kidney function (RKF) is the functional state of the kidney for chronic kidney disease (CKD) patients on dialysis [1]. The significance of RKF in dialysis patients has recently been highlighted, as greater RKF translates to better health outcomes [2, 3]. In particular, a decrease in RKF among hemodialysis (HD) patients during their first year of treatment is associated with higher all-cause mortality [3, 4]. On this basis, treatment strategies focused on preserving RKF in dialysis patients are of significant interest.

Serum potassium levels are associated with clinical outcomes in HD patients [5, 6]. Abnormal potassium levels, as in hypokalemia (<4.0 mEq/L) and hyperkalemia (>5.0 mEq/L), can lead to the development of cardiac arrhythmias and are associated with a higher all-cause mortality in HD patients [5, 6]. Additionally, both hypo- and hyperkalemia are also associated with an increased risk of progression to end-stage renal disease in patients who are not on dialysis [6], but no studies have examined the relationship between serum potassium levels and decline in RKF among HD patients [5, 7]. We hypothesized that abnormal serum potassium levels (<4.0 or >5.0 mEq/L) will result in a decline in RKF among incident HD patients.

MATERIALS AND METHODS

Subjects and data collection

A retrospective analysis was conducted on deidentified, incident HD patients who completed dialysis treatments from a large dialysis organization in the USA between January 2007 and December 2011. The HD patients were observed from the start date of dialysis until the occurrence of an organ transplant, the end date of dialysis, death, missing follow-up information or until 31 December 2011. The initial cohort of 208 820 patients was decreased by excluding patients treated with dialysis for <60 days and excluding patients who did not undergo in-center HD. Patient-quarters for the study were created in 91-day intervals from a patient's first dialysis treatment. Patients missing data for the first patient quarter were excluded from the cohort. There are several ways to measure RKF in HD patients. Residual kidney urea

KEY LEARNING POINTS

What is already known about this subject?

- Declining residual kidney function (RKF) is associated with poor outcomes in dialysis patients.
- Abnormal potassium levels are associated with higher all-cause mortality in hemodialysis (HD) patients.
- Both hypo- and hyperkalemia are associated with an increased risk of progression to end-stage renal disease in patients who are not on dialysis.

What this study adds?

- The first study to examine the relationship between serum potassium levels and decline in RKF among HD patients.

What impact this may have on practice or policy?

- Our results highlight the benefit of serum potassium management for the preservation of RKF of patients when initiating HD.

clearance (KRU), although it partially underestimates the true glomerular filtration rate, is the preferred RKF measurement approach according to the Kidney Disease Outcomes Quality Initiative and the International Society of Peritoneal Dialysis [8, 9]. Patients with missing data for baseline serum potassium, baseline KRU or with KRU values ≤0 were also excluded. This resulted in a cohort of 34 908 patients. For the main analysis, patients missing KRU data for the fifth patient quarter were excluded to create the main analytical cohort of 6655 patients (Supplemental data, Fig. S1).

Data on demographics, access type for dialysis, comorbidities and serum laboratory values were obtained from datasets provided by a large US dialysis organization.

This study was approved by the Institutional Review Committee of the University of California, Irvine. Since the subjects were deidentified and the research methods utilized were nonintrusive, this study was exempt from informed consent.

Exposures and outcomes

Baseline serum potassium levels were the primary exposure. The baseline potassium levels were divided into four exposure groups (≤4.0, >4.0 to ≤4.5, >4.5 to ≤5.0 and >5.0 mEq/L) using >4.0 to ≤4.5 mEq/L as the reference group. KRU (as a proxy for RKF) change over 1 year from the initiation of HD was the primary outcome. A follow-up period of 1 year was selected, as a decrease in RKF in the first year of treatment for HD patients has been shown to be associated with increased mortality [7]. In order to estimate the contribution of KRU decline in the association between serum potassium and mortality, the secondary outcome examined was all-cause mortality risk in the second year of HD treatment. KRU values were provided in the dataset and were calculated by the dialysis organization using the following formula [4]:

$$\text{KRU (mL/min)} = \frac{\text{Urinary urea nitrogen}\left(\frac{\text{mg}}{\text{dL}}\right) \times \text{urinary volume (mL)}}{\text{collected time (min)} \times \left[0.9 \times \text{serum urea nitrogen}\left(\frac{\text{mg}}{\text{dL}}\right)\right]}.$$

Statistical methods

Demographic variables, comorbidities and serum laboratory variables were recorded as mean [± standard deviation (SD)] or median [interquartile range (IQR)] if they were continuous variables, and as proportions if they were nominal variables. Linear regression analysis or non-parametric testing was used to analyze trends across potassium groups.

In order to analyze the relationship between baseline serum potassium levels and KRU change over 1 year, two different methods were used. Method 1 calculated KRU change by subtracting patient quarter 1 values from patient quarter 5 values, and method 2 used a mixed-effects regression model to calculate the slope of KRU change. Linear regression was used to analyze the association of baseline serum potassium levels with KRU change in four hierarchical models of adjustment. The four models of adjustment are as follows: (model 1) unadjusted, (model 2) case mix model that adjusted for age, gender, race (White, Black, Asian or Hispanic), insurance type (medicare, medicaid or other), diabetes, hypertension, arteriosclerotic heart disease (ASHD), congestive heart failure (CHF) and other cardiovascular diseases, (model 3) case mix and baseline KRU, which adjusted for the variables listed in model 2 and baseline KRU and (model 4) case mix with baseline KRU and malnutrition-inflammation cachexia syndrome (MICS), which adjusted for the variables in model 3 in addition to serum albumin, creatinine, albumin-corrected calcium, phosphorus, carbon dioxide (CO_2), body mass index (BMI) and hemoglobin. In a sensitivity analysis, associations using method 1 and method 2 for total urine volume change were analyzed.

Missing categorical data on patient demographics such as race ($n = 13$) was accounted for by creating a missing race variable. In addition, missing values for lab measurements: albumin ($n = 2$, 0.03%), CO_2 ($n = 10$, 0.15%), creatinine ($n = 285$, 4.3%), hemoglobin A1c ($n = 2979$, 45%) and BMI ($n = 36$, 0.54%) were calculated using multiple imputations using five datasets. The comorbidity variables did not have missing values.

Subgroup analyses were also conducted for race, age (≥65 or <65 years old), gender, diabetes, hypertension, serum albumin (≥3.7 or <3.7 g/dL) and BMI (<28 or ≥28 kg/m^2). Effect modification by race, age, gender, diabetes, hypertension,

Table 1. Baseline characteristics of 6655 incident HD patients stratified by baseline potassium

Variables	Total cohort	Serum potassium levels, mEq/L				
		≤4.0	>4.0 to ≤4.5	>4.5 to ≤5.0	>5.0	*P*-value
N (%)	6655	1267 (19)	2541 (38)	2036 (31)	811 (12)	
Age (year) (mean ± SD)	62 ± 14	63 ± 13	63 ± 14	61 ± 14	59 ± 14	<.0001
Female (%)	34	40	35	33	28	<.0001
Race (%)						
White	55	53	55	55	55	.4066
Black	25	33	28	23	16	<.0001
Asian	5	4	5	6	5	.0887
Hispanic	12	6	9	12	21	<.0001
Other	4	4	4	4	3	.4863
Insurance (%)						
Medicare	50	53	52	50	46	.002
Medicaid	7	5	6	7	10	<.0001
Other	43	42	42	43	44	.3016
Comorbidities (%)						
Hypertension	52	55	51	51	52	.0668
ASHD	16	17	17	14	15	.0103
CHF	46	43	46	47	48	.0157
Other cardiovascular	18	18	18	17	17	.2115
Diabetes	68	70	68	69	66	.3159
Serum laboratory values						
Potassium (mEq/L)	4.5 ± 0.5	3.8 ± 0.2	4.3 ± 0.1	4.7 ± 0.1	5.3 ± 0.3	<.0001
Albumin (g/dL)	3.6 ± 0.4	3.6 ± 0.48	3.6 ± 0.41	3.7 ± 0.40	3.7 ± 0.41	<.0001
Calcium corrected (mg/dL)	9.1 ± 0.5	9.2 ± 0.5	9.1 ± 0.5	9.1 ± 0.5	9.0 ± 0.6	<.0001
CO_2 (mEq/L)	23.2 ± 2.5	24.2 ± 2.5	23.4 ± 2.4	22.7 ± 2.4	22 ± 2.5	<.0001
Creatinine (mg/dL)	5.7 (4–7)	5.1 (4–6)	5.4 (4–7)	5.9 (5–7)	6.8 (5–9)	<.0001
Hemoglobin (g/dL)	11.5 ± 1	11.5 ± 1	11.6 ± 1	11.6 ± 1	11.6 ± 1	.0214
Hemoglobin A1c (%)	6.5 ± 1	6.4 ± 1	6.5 ± 1	6.6 ± 1	6.5 ± 1	.0637
KRU (mL/min/1.73 m^2)	3.8 (2.3–5.9)	4.1 (2.4–6.1)	4.0 (2.3–6.3)	3.7 (2.2–5.7)	3.3 (1.9–5.0)	<.0001
Phosphorus (mg/dL)	5.1 ± 1	4.7 ± 0.92	4.9 ± 0.96	5.3 ± 1	5.7 ± 1	<.0001
BMI (kg/m^2)	29.2 ± 7.3	29.8 ± 7.4	29.3 ± 7.2	29.2 ± 7.4	28.1 ± 7.0	<.0001

Values shown as percentages are for categorical variables. Values shown as mean ± SD or median (IQR) are for continuous variables.

serum albumin and BMI on the association of potassium with KRU change calculated by method 1 was analyzed using likelihood-ratio testing and was completed by including interaction terms between potassium and race, age, gender, diabetes, serum albumin and BMI, respectively, to linear regression models.

A mediation analysis was also conducted to analyze whether the relationship between potassium levels and mortality was mediated by KRU slope. Natural direct effect (NDE), natural indirect effect (NIE), total effect (TE) and controlled direct effect (CDE) were also calculated in this process. NDE, NIE, TE and CDE show changes in the outcome variable in relation to varying levels ($a^\star = 0$, $a = 1$) of the exposure or mediator variable. The levels $a^\star$ and a were derived from the models in the Vanderweele and Valeri paper on mediation analysis [10].

The statistical analyses of this study were completed using SAS Version 9.4, STATA Version 13.1 and SigmaPlot Version 14.0.

RESULTS

Patient characteristics

The cohort of 6655 patients had the following characteristics: mean ± SD age of 62 ± 14 years, 34% female, 55% White, 25% Black, 5% Asian, 12% Hispanic, 68% diabetic and 52% had hypertension, mean ± SD serum albumin 3.6 ± 0.4 g/dL, BMI of 29.2 ± 7.3 kg/m^2 and median (IQR) baseline KRU 3.8 (2.3–5.9) mL/min/1.73 m^2 (Table 1). At baseline, patients with higher potassium levels had lower KRU, calcium and CO_2 levels and higher albumin, creatinine, hemoglobin levels and phosphorus. Compared with the main analytical cohort, the cohort of 34 908 patients had similar characteristics with a lower average baseline KRU of 1.6 (1.4–1.8) mL/min/1.73 m^2 (Supplementary data, Table S1).

Association of potassium with estimated 1-year KRU change

The median (IQR) of 1-year KRU change using method 1 was −1.24 (−2.91 to 0.12), and that of the estimated 1-year KRU slope using method 2 was −1.64 (−2.53 to −0.95) mL/min/1.73 m^2. In model 1 (unadjusted analysis), KRU change was not associated with serum potassium. Associations were similarly non-significant after adjustment for case-mix covariates in model 2. However, upon further adjustment for baseline KRU in models 3 and 4, higher potassium levels were associated with larger declines in KRU, with potassium >5.0 mEq/L showing the largest change {[−0.28, 95% confidence interval (95% CI) −0.44 to −0.11] for model 3 and (−0.20, 95% CI −0.50 to −0.06) for model 4 (Fig. 1A)}. Associations between potassium and the estimated 1-year KRU slope showed similar results (Fig. 1B). In sensitivity analysis, associations between potassium and 1-year total urine volume change and 1-year

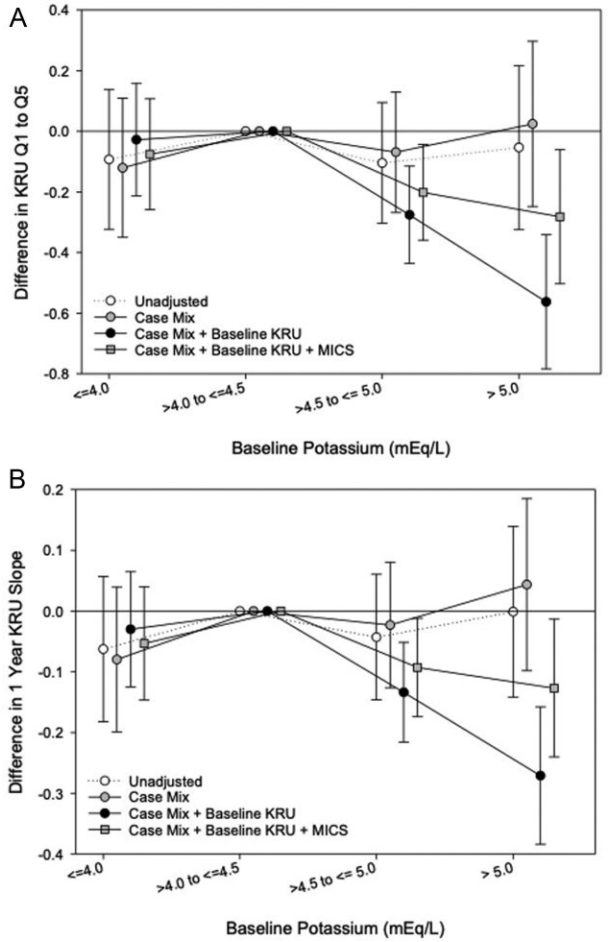

FIGURE 1: (**A**) The association of baseline serum potassium levels with 1-year change of renal urea clearance (KRU) (from patient quarter 1 to patient quarter 5) calculated with method 1 for 6655 incident HD patients. (**B**) The association of baseline serum potassium levels with 1-year change of renal urea clearance (KRU) calculated by method 2 for 6655 incident HD patients.

total urine volume similarly showed greater declines in total urine volume with higher potassium (Supplemental data, Fig. S2).

In subgroup analyses, hypertension ($P_{\text{interaction}} = .044$) modified the association between potassium and KRU change with a decrease in KRU for baseline potassium levels >4.5 mEq/L for hypertension patients, and a trend toward a decrease in KRU for potassium levels ≤4.0 mEq/L in non-hypertensive patients (Fig. 2). Age ($P_{\text{interaction}} = .63$), gender ($P_{\text{interaction}} = .80$), presence or absence of diabetes ($P_{\text{interaction}} = .21$), race ($P_{\text{interaction}} = .21$), serum albumin levels ($P_{\text{interaction}} = .41$) and BMI ($P_{\text{interaction}} = .74$) did not modify the association between baseline potassium and 1-year KRU change (Supplemental data, Fig. S3).

Association of baseline potassium with mortality

Serum potassium levels >5.0 mEq/L were associated with a higher risk of mortality in the second year of HD compared with the reference group (4.0–4.5 mEq/L) (Fig. 3, Table 2). Compared with the reference group, potassium levels

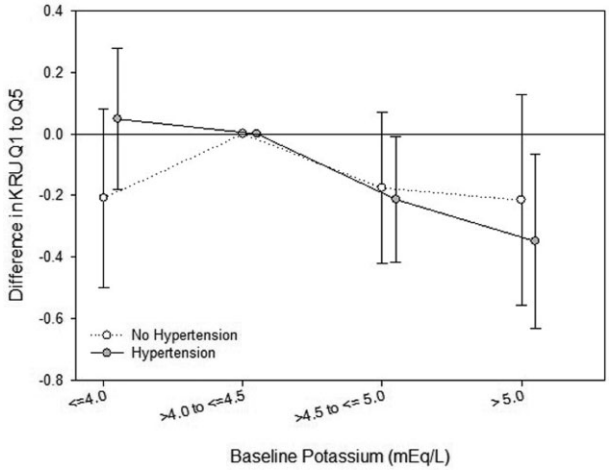

FIGURE 2: The association of baseline serum potassium levels with the difference in KRU was calculated by method 1 according to hypertension status for 6655 incident HD patients.

>5.0 mEq/L were associated with 39% and 56% higher risks of mortality for the case mix– and the case mix + MICS–adjusted models, respectively. Lower levels of potassium for all four models shared a lower risk for mortality, but the results observed for these models were not statistically significant.

Mediation effects of KRU slope on potassium and mortality

Mediation analysis in 34 908 patients with baseline potassium and KRU was carried out to further analyze whether KRU slope mediates the relationship between potassium and mortality. The analysis found that the proportion mediated was 0.0178. The NDE, NIE, TE and CDE obtained were as follows: NDE (1.04, 95% CI 1.00–1.08), NIE (1.00, 95% CI 0.99–1.00), TE (1.04, 95% CI 1.00–1.08) and CDE (1.04, 95% CI 1.00–1.08). Other major mediators indicated by further analysis include ferritin (26%), normalized protein catabolic rate (nPCR) (25%) and pre-systolic blood pressure (13%).

DISCUSSION

In this study, higher serum potassium levels were associated with a greater decline in RKF over the first year among incident HD patients. In addition, the presence of hypertension was found to modify the relationship between potassium levels and KRU change. KRU slope was found to mediate the association of potassium on mortality to a limited extent.

The mechanism underlying the association of hyperkalemia with a decline in RKF among incident HD patients is uncertain. One possible explanation is that the association can be potentially attributed to increased aldosterone production [11], since hyperkalemia can result in increased levels of aldosterone, which can have detrimental effects on renal function [12]. This relationship in turn can contribute to lower RKF among HD patients, as observed in our study. Furthermore, hyperkalemia may lead to discontinuation of

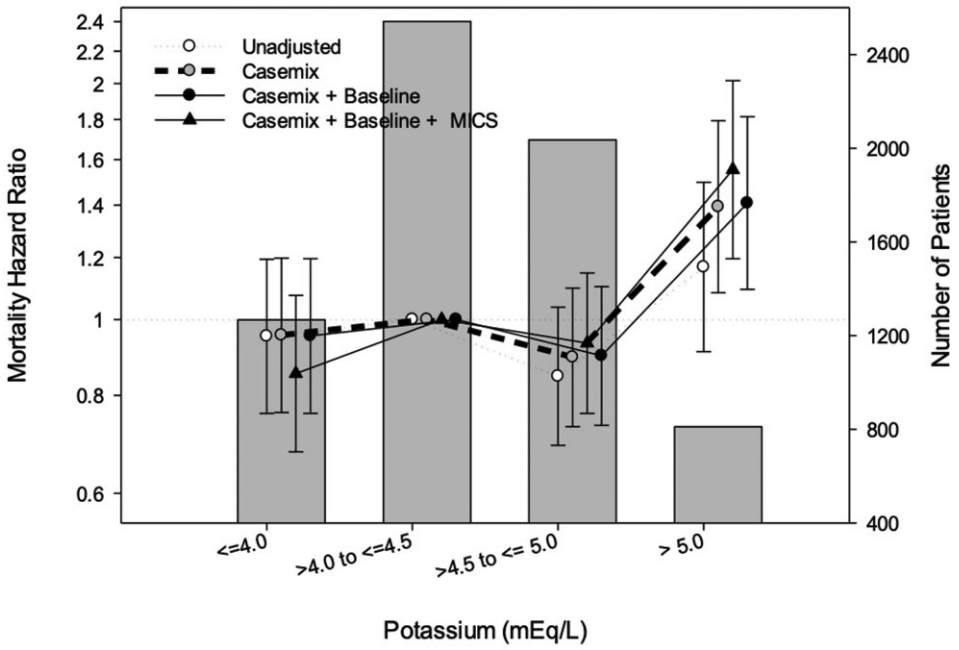

FIGURE 3: The association of baseline potassium groups with mortality in the second year of dialysis for 6655 incident HD patients.

Table 2. Association of baseline potassium groups with mortality in the second year of dialysis for 6655 incident HD patients

				Unadjusted		Case mix		Case mix + baseline		Case mix + baseline + MICS	
Potassium (mEq/L)	*n*	Mortality *n* [row %]	Mortality rate per 1000 person (years)	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
≤4.0	1267	111 [8.8]	47 (39–56)	0.95 (0.76–1.19)	.6680	0.96 (0.76–1.20)	.6913	0.95 (0.76–1.20)	.6761	0.85 (0.68–1.07)	.1768
>4.0 to ≤4.5	2541	230 [9.1]	49 (43–55)	*1-referent*		*1-referent*		*1-referent*		*1-referent*	
>4.5 to ≤5.0	2036	157 [7.7]	41 (35–48)	0.85 (0.69–1.04)	.1071	0.90 (0.73–1.10)	.2860	0.90 (0.73–1.10)	.3060	0.93 (0.76–1.15)	.5107
>5.0	811	85 [10]	56 (46–70)	1.17 (0.91–1.50)	.2236	1.39 (1.08–1.79)	.0101	1.41 (1.09–1.82)	.0082	1.56 (1.20–2.02)	.0010

HR, hazard ratio.

renin–angiotensin system inhibitors therapy, which has a renoprotective effect and thereby may negatively affect the preservation of RKF. Another potential mechanism underlying the association of hyperkalemia with a decline in RKF in this patient population may be related to the pathophysiology of diabetes. In our analysis, 68% of the patient cohort had diabetes (Table 1). A lack of response or deficiency in insulin may lead to dysregulation of the sodium–potassium ATPase, potentially predisposing patients to hyperkalemia. This dysregulation of the sodium–potassium ATPase may lead to kidney cellular injury/burst via increased cellular sodium retention, potentially worsening kidney function.

The association of hyperkalemia with KRU decline was more pronounced among patients with hypertension when compared with those without hypertension. Hypertensive patients are more likely to be taking anti-hypertensive medications such as renin–angiotensin system inhibitors. Hyperkalemia may neutralize the reno-protective nature of renin–angiotensin system inhibitors, which may further exacerbate kidney injury due to hypertension [13]. Epidemiological studies have found that hypertension can result in adverse effects on organs, thus contributing to devastating effects in dialysis patients [14]. For example, hypertension can result in vascular constriction, which may affect kidney function [14]. However, there is debate about vascular constriction and its direct effects on renal function [15]. Studies have found that serum potassium levels affect hypertension, but evidence for the reverse is lacking [16–18]. Further data are needed to understand whether and how hypertension may modify the relationship between potassium and RKF decline in dialysis.

The results observed demonstrating a higher mortality risk associated with higher baseline potassium levels are consistent with previous findings [19–21]. Causal mediation analysis with survival data showed that the association of baseline potassium groups on mortality is mediated by change in KRU only by 1.78%. This suggests that very little of this effect materializes through a change in kidney function. Major mediators indicated by further analysis include ferritin (26%), nPCR (25%) and pre-systolic blood pressure (13%). Ferritin has been found to promote lipid peroxidation [22];

HD has been found to increase lipid peroxidation, and it has been hypothesized as a potential mechanism for the accelerated progression of atherosclerosis in patients with renal insufficiency [23]. The contribution of both elevated serum ferritin and nPCR may lead to intensifying the dyslipidemia, thereby negatively impacting survival in HD patients. Both hypo- and hyperkalemia have been found to be associated with a higher risk of mortality through electrophysiologic effects (arrhythmias) [24–26], which are short-term outcomes. If hypo- and hyperkalemia are associated with long-term outcomes, this could mean an association through a mechanism that is different from arrhythmias. This could be an effect on BP for hypokalemia (which has vaso-constricting and fibrosis-inducing effects), or an effect on aldosterone production for hyperkalemia (which could induce or worsen tissue fibrosis and contribute to cardiac and renal dysfunction). The fact that only 1.78% of the effect was mediated by KRU slope suggests that very little of this effect materializes through a change in kidney function, and therapeutic interventions should target other mechanisms (e.g. cardiac).

There are limitations in our study that are important to address. This was an observational study with a retrospective design, regardless of multivariable adjustment for potential confounders, and thus a cause–effect relationship between serum potassium and the decline in RKF in incident HD patients over 1 year cannot be established. Residual confounding may serve as a potential limitation of our study despite having adjusted for potential confounders. Despite adjustment for baseline RKF, patients with higher baseline serum potassium levels may simply have more severe inflammatory and/or fibrotic tubulointerstitial involvement, which may explain a faster deterioration of RKF at follow-up. For example, the study cohort had 68% of subjects with diabetes, which has been found to be associated with a greater incidence of hyperkalemia [27]. The various deleterious pro-inflammatory changes associated with diabetes and diabetic nephropathy may predispose individuals to a faster decline in RKF [28, 29], potentially explaining the observed relationship between serum potassium and decline in RKF in some patients. Unmeasured confounders that we did not have the ability to adjust for include, but may not be limited to, dietary habits and medication use such as potassium-binding drugs and renin–angiotensin–aldosterone system (RAAS) inhibitors. RAAS blockade may obviously be associated with higher baseline serum potassium. It has been shown to provide a protective effect for RKF, mainly among PD patients [30], and hence may be a confounder in our study. Supposing those possible effects of RAAS blockade on hyperkalemia and RKF, the association between higher serum potassium levels and more rapid decline in RKF may be underestimated in our study. Additionally, another limitation of our study is that the KRU equation used has a small amount of bias since it slightly minimizes the value for glomerular filtration rates, but overall, this bias is minimal and does not have any significant effects on changing the trends observed [4]. Finally, although we investigated the association between baseline potassium and a 1-year change in RKF, serum potassium levels can change over time. Many HD patients experience wide variations in serum potassium levels. However, trajectories of potassium stratified by baseline potassium levels showed consistent separation during the first five patient quarters with a slight regression toward the mean (data not shown).

To conclude, hyperkalemia (>5.0 mEq/L) in incident HD patients was associated with a lower baseline KRU and a greater KRU decline over a 1-year period. These findings shed light on the relationship between serum potassium and renal health; however, further studies are needed to elucidate how serum potassium influences RKF in dialysis patients.

SUPPLEMENTARY DATA

Supplementary data are available at *ndt* online.

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AUTHORS' CONTRIBUTIONS

Research idea and study design: E.S., K.K.Z. and Y.O.; data acquisition: E.S. and K.K.Z.; data analysis/interpretation: Y.A., C.W., J.T.H., A.E., W.L.L., R.M.H., Y.L., Y.O., C.P.K., K.K.Z. and E.S.; drafting manuscript: Y.A., C.W., J.T.H., A.E., W.L.L., R.M.H., Y.L., Y.O., C.P.K., K.K.Z. and E.S.; and supervision: E.S. and K.K.Z. Each author contributed important intellectual content during manuscript drafting or revision.

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CONFLICT OF INTEREST STATEMENT

W.L.L. has received honoraria and/or support from the American Heart Association, Fresenius, Hub Therapeutics, National Institutes of Health, Roche, Sanofi and ZS Pharma. R.M.H. has received honoraria from Alexion Pharmaceuticals (Speaker's bureau) and Otsuka (for NephU—disease state programs for ADPKD). Y.O. has received honoraria and/or support from Vifor Pharma. E.S. has received honoraria or support from Edwards LifeSciences and AstraZeneca. C.P.K. has received honoraria from Abbott, Akebia, Bayer, AstraZeneca, CSL Behring, Cara Therapeutics, Rockwell and Vifor. K.K.Z. has received honoraria and/or support from Abbott, Abbvie, Alexion, Amgen, American Society of Nephrology, AstraZeneca, AVEO Oncology, Chugai, DaVita,

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