Dietary Potassium Intake and Mortality in a Prospective Hemodialysis Cohort

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Objectives: Among hemodialysis patients, clinical practice guidelines recommend dietary potassium restriction given concerns about potential hyperkalemia leading to malignant arrhythmias and mortality. However, there are sparse data informing recommendations for dietary potassium intake in this population. We thus sought to examine the relationship between dietary potassium intake and death risk in a prospective cohort of hemodialysis patients.

Design and Methods: Among 415 hemodialysis patients from the prospective "Malnutrition, Diet, and Racial Disparities in Chronic Kidney Disease" cohort recruited across 16 outpatient dialysis clinics, information regarding dietary potassium intake was obtained using Food Frequency Questionnaires administered over October 2011 to March 2015. We first examined associations of baseline dietary potassium intake categorized as tertiles with mortality risk using Cox regression. We then examined clinical characteristics associated with low dietary potassium intake (defined as the lowest tertile) using logistic regression.

Results: In expanded case-mix Cox analyses, patients whose dietary potassium intake was in the lowest tertile had higher mortality (ref: highest tertile) (adjusted hazard ratio 1.74, 95% confidence interval 1.14-2.66). These associations had even greater magnitude of risk following adjustment for laboratory and nutritional covariates (adjusted hazard ratio 2.65, 95% confidence interval 1.40-5.04). In expanded case-mix restricted cubic spline analyses, there was a monotonic increase in mortality risk with incrementally lower dietary potassium intake. In expanded case-mix logistic regression models, female sex; higher serum bicarbonate; and lower dietary energy, protein, and fiber intake were associated with low dietary potassium intake.

Conclusions: In a prospective cohort of hemodialysis patients, lower dietary potassium intake was associated with higher mortality risk. These findings suggest that excessive dietary potassium restriction may be deleterious in hemodialysis patients, and further studies are needed to determine the optimal dietary potassium intake in this population.

Introduction

AMONG MAINTENANCE DIALYSIS patients, nutritional status is a major determinant of health and survival, given their predisposition to dialytic protein and amino acid losses, heightened catabolism, and protein-energy wasting.[1,2] As such, nutritional therapy is considered a cornerstone in the management of this population.[3] For example, under the Centers for Medicare and Medicaid Services Conditions for Coverage, multidisciplinary teams of outpatient dialysis clinics are required to provide ongoing dietary counseling and monitoring of hemodialysis patients' nutritional status.[4,5]

In healthy adults, a relatively high potassium intake of 4.7 g/day (120 mmol/day) is recommended given the critical

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importance of this electrolyte in cellular functions such as muscle contraction and nerve conduction.[6] In addition, potassium-rich foods such as fresh fruits and vegetables are a major source of micronutrients such as antioxidant vitamins, as well as dietary fiber needed to process and absorb nutrients.[7] Furthermore, prescribed diets such as the Dietary Approaches to Stop Hypertension diet that are high in potassium (4.5 g/day) have been associated with better control of cardiovascular risk factors, including hypertension and diabetes.[8,9]

However, among patients with advanced kidney dysfunction, consumption of a high potassium diet may lead to hyperkalemia, which may be further exacerbated by frequent use of medications that impair potassium excretion (e.g., angiotensin-converting enzyme inhibitors and angiotensin receptor blockers), or the presence of hyporeninemic hypoaldosteronism in those with diabetic kidney disease.[10] Given the potential life-threatening sequelae of hyperkalemia (e.g., malignant arrhythmia, sudden cardiac death), as well as growing evidence demonstrating the risks of dialytic management strategies that abruptly lower potassium (i.e., dialysate concentrations of 1 mEq/L, high dialysate-to-serum potassium gradients[11-14]), restriction of dietary potassium intake has emerged as an important target in the nutritional management of hemodialysis patients. Although current recommendations favor dietary potassium consumption of less than 3 g/day (77 mmol/day) in patients with advanced chronic kidney disease (CKD), including those receiving hemodialysis,[3] there are sparse data informing these guidelines. To date, 1 study has reported that higher dietary potassium intake (i.e., highest quartile of observed values) was associated with worse survival in hemodialysis patients; however, inference from these findings are limited by the lack of key covariates (e.g., dialysate potassium concentration) in analyses estimating dietary potassium—mortality risk, as well the modest sample size precluding ability to examine differences across subgroups.[15] Thus, to better inform the field, we sought to examine the association of dietary potassium intake with all-cause mortality risk in a multi-center prospective cohort of hemodialysis patients with detailed patient-level data on sociodemographics, comorbidities, dialysis treatment characteristics, and nutritional status. We also examined clinical characteristics associated with dietary potassium intake in this cohort.

Materials and Methods

Source Population

The study population was recruited from the Malnutrition, Diet, and Racial Disparities in Chronic Kidney Disease (MADRAD) study (ClinicalTrials.gov study number NCT01415570), an ongoing multi-center prospective study that was developed to evaluate racial and ethnic differences in dietary factors and nutrition status among hemodialysis patients.[16-19] Every 6 months (semesters), study participants underwent protocolized collection of information on sociodemographics, comorbidities, medications, and dialysis treatment characteristics; administration of questionnaires; blood collection; and laboratory testing during their routine outpatient hemodialysis treatments.

In this MADRAD substudy, patients were recruited from 16 outpatient dialysis facilities in Southern California over the period of October 2011 to March 2015. Patients were included provided that they were 18-85 years of age, received thrice-weekly in-center hemodialysis treatment for at least 4 consecutive weeks, signed a local Institutional Review Board-approved consent form, and completed at least one or more Food Frequency Questionnaires (FFQs). Patients were excluded if they were actively receiving peritoneal dialysis, had a life expectancy of less than 6 months (e.g., stage IV cancer), were unable to provide consent without a proxy (e.g., dementia), or had missing FFQ dietary potassium intake data. The study was approved by the Institutional Review Committee at the University of California, Irvine.

Exposure Ascertainment

Our primary exposure of interest was self-reported daily dietary potassium intake (mg/day), which was ascertained by FFQ. The full-length, Block FFQ was originally developed by Dr. Gladys Block at the National Cancer Institute, and has since been updated.[15,20,21] Different versions of this questionnaire have been extensively studied and validated in various populations. Given the racial/ethnic diversity of the MADRAD cohort, we utilized the SWAN FFQ, distributed by NutritionQuest, which is a modification of the 1995 Block FFQ and is available in 4 versions, including a bilingual (i.e., Spanish and English) version used in our study.[22,23] The core food list, used for all racial/ethnic groups, contained 103 food items identified based on the responses of Black and White participants in the Second National Health and Nutrition Examination Survey (NHANES II); the Spanish-language version includes the 103-item core food list, plus 9 additional foods appropriate for several Hispanic subgroups and has been validated in the Hispanic population.

In our study, a team of trained research coordinators supervised the FFQ administration during participants' routine hemodialysis treatment sessions. The completed FFQ booklets were reviewed immediately after they were returned, and if any question remained unanswered, the FFQ was returned to the patient with the request to attempt to answer the blank questions. All completed FFQs were analyzed by NutritionQuest.

Given that FFQs have a tendency toward non-differential underestimation of nutrient intake in comparison to real-time dietary assessment, experts have recommended that FFQ nutrient intake should be reported and analyzed as either ranked values (e.g., tertiles, quartiles, percentiles, etc.) or as ratios of 2 different nutrients rather than absolute values per individuals.[15,21] Thus, in primary analyses, we examined dietary potassium intake collected from baseline

FFQs categorized as tertiles. To more granularly examine nutrient intake, we also conducted secondary analyses examining dietary potassium (1) categorized as quartiles and (2) as a continuous variable using restricted cubic splines with knots designated at the 10th, 50th, and 90th percentiles of observed values to assess differential cutoffs than used in the categorical (i.e., tertile, quartile) analyses.

Outcome Ascertainment

The primary outcome of interest was all-cause mortality. At-risk time began the day after baseline FFQ administration, and patients were censored for kidney transplantation, transfer to a non-affiliated outpatient dialysis unit or peritoneal dialysis, or at end of the study (February 10, 2018). Each semester, information regarding mortality, censoring events, and associated dates from the preceding 6 months was collected from event forms completed by the MADRAD research coordinators and reviewed by the MADRAD study nephrologist (C.M.R.).[11,17–19]

Sociodemographic, Comorbidity, Laboratory, and Dialysis Treatment Characteristics

Information on sociodemographics, comorbidities, medications, and dialysis treatment characteristics (i.e., vascular access type) were collected at study entry (i.e., date of FFQ administration) and every semester thereafter by the MADRAD research coordinators and study nephrologists. Routine dialysis laboratory measurements were performed by the outpatient dialysis laboratories on a monthly or quarterly basis using automated methods. In the present study, 3-month averaged laboratory values collected prior to study entry were examined as baseline covariates. With respect to baseline dialysis potassium concentrations, we utilized 3-month averaged data collected by research coordinators preceding study entry; in the event that dialysis potassium concentration data were missing, we imputed data collected up to 3 months following study entry as these dialysis prescription characteristics were likely to remain stable over follow-up.

Statistical Methods

Baseline characteristics between exposure groups were compared as mean ± standard deviation (SD) or median (interquartile range [IQR]) values as dictated by data type. We first estimated the association between dietary potassium intake and all-cause mortality using Cox proportional hazard models. We then examined clinical characteristics associated with low dietary potassium intake (defined as less than the first tertile) using logistic regression. The following 5 incremental levels of covariate adjustment were used in Cox and logistic regression models:

1. Unadjusted analyses (Model 1): No adjustment for covariates.
2. .Case-mix adjusted analyses (Model 2): Adjusted for age, sex, race, ethnicity, and diabetes status.
3. Expanded case-mix adjusted analyses (Model 3): Adjusted for case-mix covariates plus vintage, vascular access, insurance, congestive heart failure, coronary artery disease, cerebrovascular disease/transient ischemic attack, combined cardiovascular diseases, body mass index (BMI), and dialysate potassium concentration.

We a priori defined the expanded case-mix model as our primary model given its inclusion of key confounders and absence of missing data for the majority of its covariates. To account for the possibility that markers of malnutrition may be confounders versus pathway intermediates of low dietary potassium—mortality associations, we also conducted exploratory models that incrementally adjusted for various laboratory and FFQ indices of nutritional status:

4. Expanded case-mix + laboratory adjusted analyses (Model 4): Adjusted for expanded case-mix covariates plus serum potassium, serum bicarbonate, hemodialysis adequacy (i.e., single pool Kt/V), serum albumin, normalized protein catabolic rate (nPCR), serum creatinine, and serum phosphorus.
5. Expanded case-mix + laboratory + nutrition adjusted analyses (Model 5): Adjusted for expanded case-mix + laboratory covariates plus dietary energy intake, dietary protein intake, and dietary fiber intake.

In sensitivity analyses, to account for protein-energy wasting as a potential confounder or pathway intermediate, we incrementally adjusted for patients' measurements of body anthropometry, namely mid-arm circumference (i.e., proxy of skeletal muscle) and near-infrared interactance body fat percentage (i.e., proxy of total body fat) in (6) expanded case-mix + laboratory + nutrition + body anthropometry adjusted analyses. As dietary potassium intake may vary among patients with presence versus absence of residual kidney function, we also incrementally adjusted for patients' self-reported presence versus absence of urine output (UOP) as a proxy of residual kidney function in (7) expanded case-mix + laboratory + nutrition + UOP adjusted analyses.

Effect modification of dietary potassium intake and mortality associations on the basis of sociodemographics (e.g., age, sex, race, ethnicity), specific comorbidities and health status (e.g., diabetes, combined cardiovascular diseases, dialysis vintage, BMI), dialysate potassium concentration, and laboratory tests (e.g., serum potassium, serum bicarbonate, serum albumin, nPCR) were explored through the addition of 2-way interaction terms with dietary potassium intake (separately) using likelihood ratio testing.

There were no missing values for age, sex, race, ethnicity, and comorbidities. The remaining covariates ascertained at baseline had <1% missing data, except for BMI (4%), dialysate potassium concentration (14%), serum potassium (4%), serum bicarbonate (5%), single pool Kt/V (4%), serum albumin (5%), nPCR (4%), serum creatinine (6%),

and serum phosphorus (4%). For the aforementioned covariates, missing data were addressed using multiple imputation with 15 imputed datasets. Baseline vascular access type had a greater proportion of missing data; hence for this specific covariate a dummy indicator for missing data was used in lieu of multiple imputation. The proportional hazard assumption was confirmed by Schoenfeld residual tests. Statistical analyses were performed using STATA version 13.1 (Stata Corp., College Station, TX) and SigmaPlot version 13 (Systat Software, San Jose, CA).

Results

Study Population

Among 415 patients who met eligibility criteria, the mean ± SD age of the cohort was 56 ± 15 years, among whom 45% were female, 36% were Black, and 48% were Hispanic. In the overall cohort, the mean ± SD, median (IQR), and minimum-maximum of baseline daily dietary potassium intake levels were 1,463 ± 1,105, 1,207 (728-1907), and 0-7,411 mg/day, respectively.

Baseline characteristics of the cohort stratified by dietary potassium tertiles are shown in Table 1. Compared with patients whose dietary potassium intake was in the highest tertile, patients in the lowest tertile were more likely to be female, less likely to be Black, and more likely to be Hispanic; were less likely to have an arteriovenous fistula/graft; were more likely to have diabetes and less likely to have coronary artery disease and combined cardiovascular diseases; and had lower levels of daily dietary energy, protein, and fiber intake. Notably, dialysate potassium concentrations, serum potassium levels, and certain nutritional markers (e.g., BMI, serum albumin, nPCR, serum creatinine) were similar across tertiles of dietary potassium intake. We observed similar trends when baseline characteristics were examined across quartiles of dietary potassium intake (Table S1).

Dietary Potassium Intake and Mortality Risk

Patients contributed a total of 1,425 person-years of follow-up, during which 151 death events were observed. The median (IQR) at-risk time was 3.7 (1.9-5.1) years. Upon examination of dietary potassium intake across tertiles, unadjusted analyses showed that the lowest tertile of dietary potassium intake was associated with higher death risk (ref: highest tertile): hazard ratio (HR) 1.54, 95% confidence interval (CI) (1.03-2.30) (Fig. 1 and Table S2). Following adjustment for case-mix, expanded case-mix, expanded case-mix + laboratory, and expanded case-mix + laboratory + nutrition covariates, we found that associations between the lowest tertile of dietary potassium intake and higher mortality were robust and that magnitudes of risk were amplified: adjusted HRs (95% CIs) 1.68 (1.11-2.55), 1.74 (1.14-2.66), 1.94 (1.25-3.01), and 2.65 (1.40-5.04), respectively. In sensitivity analyses that incrementally adjusted for expanded case-mix + laboratory + nutrition + body anthropometry and expanded case-mix + laboratory + nutrition + UOP covariates, significant associations between the lowest tertile of dietary potassium intake and higher mortality risk persisted: adjusted HRs (95% CIs) 2.91 (1.52-5.56) and 2.69 (1.41-5.13), respectively (Table S2).

In secondary analyses that examined dietary potassium intake across quartiles, we similarly observed that the lowest quartile was associated with higher mortality risk (ref: highest quartile): HR (95% CI) 1.51 (0.95-2.41) (Fig. S1 and Table S3). Following adjustment for case-mix and expanded case-mix covariates, we observed that point estimates for the lowest quartile of dietary potassium intake and higher mortality were magnified but associations narrowly missed statistical significance: adjusted HRs (95% CIs) 1.52 (0.95-2.44) and 1.58 (0.97-2.57), respectively. However, in expanded case-mix + laboratory and expanded case-mix + laboratory + nutrition analyses, we again observed a statistically significant relationship between the lowest quartile of dietary potassium intake and higher mortality with amplified magnitudes of risk: adjusted HRs (95% CIs) 1.89 (1.14-3.14) and 2.80 (1.25-6.28), respectively. In sensitivity analyses that incrementally adjusted for expanded case-mix + laboratory + nutrition + body anthropometry and expanded case-mix + laboratory + nutrition + UOP covariates, significant associations between the lowest quartile of dietary potassium intake and higher mortality risk persisted: adjusted HRs (95% CIs) 2.94 (1.30-6.63) and 3.01 (1.33-6.80), respectively (Table S3). In analyses examining the association of continuous dietary potassium intake and all-cause mortality using a restricted cubic spline function adjusted for expanded case-mix covariates, we observed that there was a monotonic increase in death risk with incrementally lower levels of dietary potassium intake (Fig. 2).

Dietary Potassium Intake and Mortality Risk Across Clinically Relevant Subgroups

Upon examining the dietary potassium intake—mortality relationship across clinically relevant subgroups, we found there was a differential association on the basis of age, such that the lowest tertile of dietary potassium intake was associated with a 2-fold higher risk of death in those of older (≥55 years) age (ref: middle and highest tertiles), whereas a non-significant association was observed in those of younger (<55 years) age: adjusted HRs (95% CIs) 2.02 (1.31-3.12) and 0.63 (0.31-1.28), respectively (P for interaction = 0.01) (Fig. 3 and Table S4). However, we did not detect effect modification on the basis of sex, race, ethnicity, dialysis vintage, dialysate potassium concentration, BMI, diabetes, combined cardiovascular diseases, serum potassium, serum bicarbonate, serum albumin, or nPCR (all P for interaction > 0.10).

Table 1. Baseline Characteristics According to Tertiles of Dietary Potassium Intake

Characteristic	Overall	Dietary K Intake*		
		Tertile 1	Tertile 2	Tertile 3
No. of patients	415	138	138	139
Dietary K intake (mg/d)				
Median (IQR)	1,207 (728-1,907)	559 (366-728)	1,205 (1,100-1,376)	2,207 (1,902-2,919)
Mean ± SD	1,463 ± 1,105	543 ± 221	1,234 ± 198	2,606 ± 1,166
Minimum-maximum	0-7,411	0-899	904-1,625	1,631-7,411
Age (y), mean ± SD	56 ± 15	56 ± 15	56 ± 14	55 ± 14
Male (%)	55	41	61	65
Black race (%)	36	33	32	44
Hispanic ethnicity (%)	48	52	51	42
Vintage (y), mean ± SD	5 ± 4	5 ± 4	5 ± 4	5 ± 5
Vascular access (%)				
AV fistula/graft	47	43	46	53
Catheter	11	10	12	12
Unknown	41	46	42	36
Primary insurance (%)				
Medicare/Medicaid	75	76	78	71
Private	11	13	9	11
Other	14	11	12	18
Dialysate K concentration (mEq/L), mean ± SD	2 ± 1	2 ± 1	2 ± 0	2 ± 0
Dialysate K concentration (%)				
1 mEq/L	10	17	5	7
2 mEq/L	70	60	74	75
3 mEq/L	20	23	21	16
4 mEq/L	1	0	0	2
BMI (kg/m^2), mean ± SD	27.7 ± 6.6	27.1 ± 6.0	28.2 ± 6.7	27.8 ± 7.0
Comorbidities (%)				
Diabetes	55	62	49	53
CHF	8	8	7	10
CAD	9	7	8	12
CVD/TIA	1	1	1	1
Combined CV disease	17	14	14	22
Laboratory, mean ± SD				
Serum K (mEq/L)	4.9 ± 0.5	4.9 ± 0.6	4.9 ± 0.5	5.0 ± 0.5
Serum bicarbonate (mEq/L)	23.4 ± 3.1	23.7 ± 3.4	23.2 ± 3.1	23.2 ± 2.8
spKt/V	1.7 ± 0.3	1.7 ± 0.3	1.7 ± 0.3	1.6 ± 0.3
Serum albumin (g/dL)	4.0 ± 0.3	4.0 ± 0.3	4.0 ± 0.3	4.0 ± 0.4
nPCR (g/kg/d)	1.0 ± 0.3	1.1 ± 0.3	1.0 ± 0.2	1.0 ± 0.3
Serum creatinine (mg/dL)	9.7 ± 2.9	9.5 ± 3.0	9.7 ± 2.8	9.9 ± 2.8
Serum phosphorus (mg/dL)	5.1 ± 1.3	5.1 ± 1.2	5.0 ± 1.1	5.2 ± 1.4
Dietary intake, median (IQR)				
Calories (Kcal/d)	998 (566-1,527)	453 (331-613)	1,004 (787-1,266)	1,731 (1,372-2,375)
Protein (g/d)	45 (25-73)	20 (14-27)	45 (36-55)	82 (66-125)
Dietary fiber (g/d)	7 (4-12)	3 (2-5)	7 (5-10)	13 (9-19)

AV, arteriovenous; BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; CV, cardiovascular; CVD, cerebrovascular disease; IQR, interquartile range; K, potassium; nPCR, normalized protein catabolic rate; SD, standard deviation; spKt/V, single pool Kt/V; TIA, transient ischemic attack.

*Dietary potassium intake tertiles 1, 2, and 3 correspond to dietary potassium intake of <903, 903-<1,631, and 1,631-7,411 mg/d, respectively.

Clinical Characteristics Associated With Low Dietary Potassium Intake

In unadjusted logistic regression analyses, we found that male sex, presence of diabetes, as well as increased dietary energy, protein, and fiber intake were associated with lower likelihood of low dietary potassium intake, defined as the lowest tertile of dietary potassium intake (reference: middle and highest tertiles of dietary potassium intake) (Table 2). Except for diabetes status, these associations were robust following adjustment for case-mix and expanded case-mix covariates. In case-mix and expanded case-mix adjusted logistic regression analyses, we also observed that higher serum bicarbonate levels were associated with higher likelihood of low dietary potassium intake.

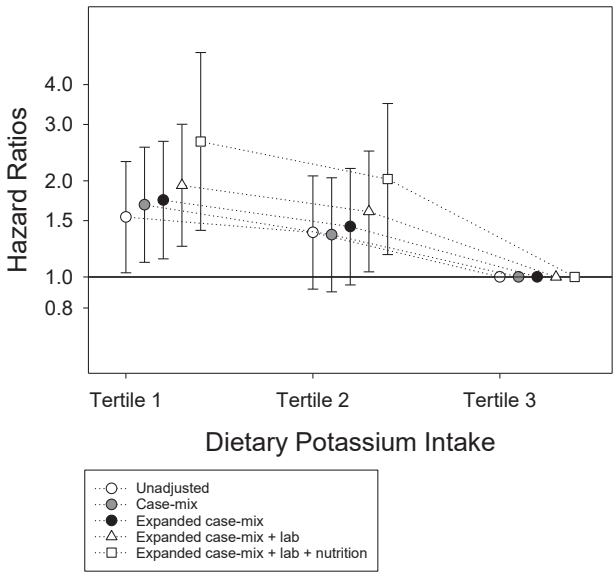

Figure 1. Association of baseline dietary potassium intake categorized as tertiles with all-cause mortality risk. Case-mix adjusted analyses adjusted for age, sex, race, ethnicity, and diabetes. Expanded case-mix adjusted analyses adjusted for case-mix covariates plus vintage, vascular access, insurance, congestive heart failure, coronary artery disease, cerebrovascular disease/transient ischemic attack, combined cardiovascular diseases, body mass index, and dialysis potassium concentration. Expanded case-mix + laboratory adjusted analyses adjusted for expanded case-mix covariates plus serum potassium, serum bicarbonate, single pool Kt/v, serum albumin, normalized protein catabolic rate, serum creatinine, and serum phosphorus. Expanded case-mix + laboratory + nutrition adjusted analysis adjusted for expanded case-mix + laboratory plus dietary energy intake, dietary protein intake, and dietary fiber intake. Dietary potassium intake tertiles 1, 2, and 3 correspond to dietary potassium intake of <903, 903-<1,631, and 1,631-7,411 mg/day, respectively.

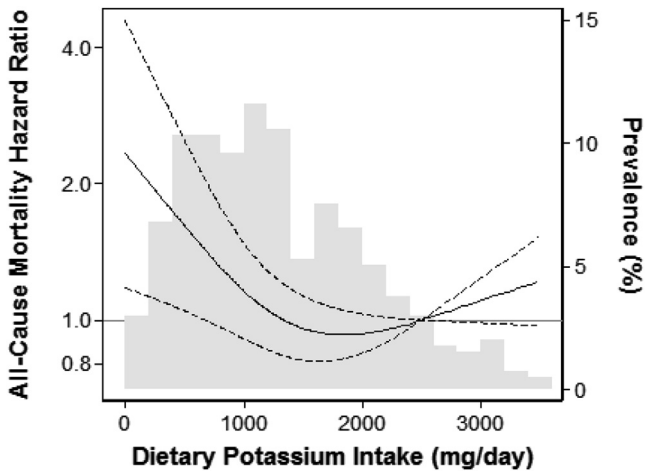

Figure 2. Association between dietary potassium intake examined as a continuous variable and all-cause mortality using expanded case-mix adjusted restricted cubic splines. The figures present hazard ratios (short dashed lines indicate 95% confidence intervals) for dietary potassium intake analyzed as a spline with 3 knots. Horizontal solid line indicates a hazard reference ratio of 1. A histogram of observed baseline dietary potassium intake values is overlaid.

Discussion

In this prospective multi-center cohort of hemodialysis patients, we found that those with lower self-reported dietary potassium intake ascertained by FFQs had higher mortality risk independent of their sociodemographics, comorbidities, and dialysate potassium concentrations. After accounting for differences in nutritional status ascertained by laboratory markers and FFQ data, we found that dietary potassium intake in the lowest tertile was associated with a 2.5-fold higher death risk. These patterns were robust across secondary and sensitivity analyses that examined exposure—outcome associations across multiple subgroups and also examined dietary potassium intake as a continuous variable using restricted cubic splines.

In the general population, several epidemiologic studies have observed that higher levels of dietary potassium intake are associated with greater survival,[24] presumably due to improvement in blood pressure, endothelial function, cardiac function and structure, and progression of CKD and cardiovascular disease.[25] However, in patients with moderate-to-advanced CKD, high dietary potassium consumption may lead to hyperkalemia, due to their limited capacity for renal potassium excretion and presence of co-existing factors that may further amplify serum potassium levels (i.e., use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and beta-blockers; hyporeninemic hypoaldosteronism in the context of diabetes). To our knowledge, there has been only one previous study that has examined the relationship between dietary potassium intake and survival in hemodialysis patients.[15] In this prospective analysis of 224 hemodialysis patients conducted by Noori et al., higher dietary potassium intake (defined as the highest quartile of intake) determined from FFQs was associated with higher mortality risk after accounting for case-mix and malnutrition-inflammation complex syndrome covariates.

In contradistinction to these findings, our study has shown for the first time that lower self-reported dietary potassium intake ascertained by FFQs is associated with higher all-cause mortality risk in a large prospective cohort of 415 hemodialysis patients, independent of sociodemographic, comorbidity, laboratory, dialysis treatment, and nutritional characteristics. The discrepant findings across these 2 studies may be due to several factors. First, in contrast to the Noori et al. investigation, our study was able to account for dialysate potassium concentration as a key covariate of the dietary potassium—mortality association. In clinical practice, modulation of dialysate potassium concentrations is frequently used in conjunction with dietary potassium

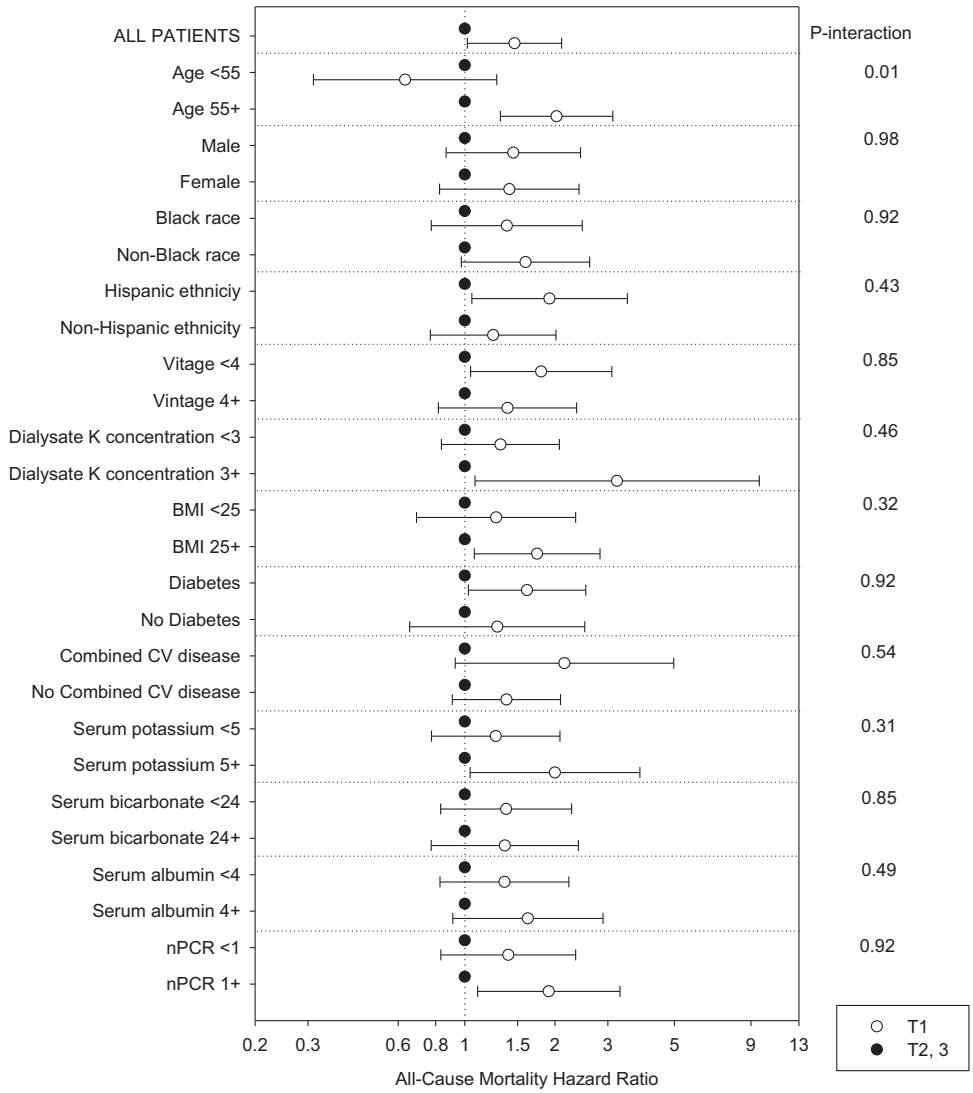

Figure 3. Subgroup analyses of the association between baseline dietary potassium intake (lowest tertile vs. middle and highest tertiles) and all-cause mortality adjusted for expanded case-mix covariates. Expanded case-mix analyses adjusted for age, sex, race, ethnicity, diabetes, vintage, vascular access, insurance, congestive heart failure, coronary artery disease, coronary artery disease, cerebrovascular disease/transient ischemic attack, combined cardiovascular diseases, body mass index, and dialysis potassium concentration. Dietary potassium intake tertiles 1, 2, and 3 correspond to dietary potassium intake of <903, 903-<1,631, and 1,631-7,411 mg/day, respectively. BMI, body mass index; CV, cardiovascular; nPCR, normalized protein catabolic rate; T, tertile.

restriction to maintain physiologically normal levels of serum potassium in hemodialysis patients. There is an increasing body of evidence showing that lower dialysate potassium concentrations (i.e., 1 mEq/L) as well as high serum-to-potassium dialysate gradients are independently associated with heightened death risk,[11–14] likely due to precipitation of malignant ventricular arrhythmias and sudden cardiac death. After accounting for both dialysate potassium and serum potassium concentrations in expanded case-mix + laboratory models, we observed robust associations between low dietary potassium intake and death risk. Second, while the Noori et al. study utilized the 1998 version of the Block FFQ, given the racial/ethnic diversity of our cohort, we elected to use the bilingual (English and Spanish) SWAN FFQ, which has been validated in the Hispanic population and may have resulted in more accurate ascertainment of dietary potassium intake among minority dialysis patients.[23] Third, in contrast to the Noori et al. study, our analyses also took into consideration vascular access type as a confounder of the dietary potassium—mortality association, given its implications as a potential proxy of (1) adequate solute (e.g., potassium) clearance, (2) patient compliance, and (3) attentiveness by physicians (i.e., "good vs. bad doctor" effect). Finally, while both our and the Noori et al. studies accounted for total dietary energy and protein intake as

Table 2. Clinical Characteristics Associated With the Lowest Tertile of Dietary Potassium Intake (Ref: Middle and Highest Tertiles)

Characteristic	Unadjusted	*P*-value	Case-Mix	*P*-value	Expanded Case-Mix	*P*-value
Age, per 10 y	1.05 (0.91, 1.21)	.51	0.99 (0.85, 1.16)	.95	1.00 (0.85, 1.17)	.96
Male (vs. female)	**0.40 (0.27, 0.61)**	**<.01**	**0.39 (0.26, 0.60)**	**<.01**	**0.38 (0.24, 0.58)**	**<.01**
Black race (vs. non-Black)	0.79 (0.52, 1.22)	.29	0.87 (0.48, 1.58)	.65	0.92 (0.50, 1.69)	.85
Hispanic ethnicity (vs. non-Hispanic)	1.25 (0.83, 1.88)	.28	1.15 (0.65, 2.05)	.62	1.14 (0.62, 2.09)	.65
Diabetes (vs. non-diabetes)	**1.52 (1.01, 2.31)**	**.05**	1.57 (0.98, 2.50)	.07	1.59 (0.97, 2.62)	.06
Vintage, per 1 y	0.99 (0.94, 1.04)	.67	0.99 (0.94, 1.05)	.63	0.99 (0.93, 1.05)	.61
Vascular access						
AV fistula/graft (vs. non-AV fistula/graft)	0.79 (0.52, 1.19)	.25	0.77 (0.50, 1.18)	.23	0.73 (0.46, 1.17)	.19
Catheter (vs. non-catheter)	0.86 (0.44, 1.68)	.67	0.83 (0.42, 1.66)	.61	0.68 (0.33, 1.45)	.33
Primary insurance						
Medicare/Medicare (vs. non-Medicare/Medicare)	1.08 (0.67, 1.73)	.76	0.89 (0.54, 1.46)	.63	0.89 (0.53, 1.51)	.64
BMI, per 5 kg/m^2	0.92 (0.78, 1.08)	.28	0.86 (0.72, 1.02)	.08	0.87 (0.73, 1.04)	.13
Dialysate K concentration, per 1 mEq/L	0.75 (0.50, 1.14)	.18	0.84 (0.55, 1.29)	.42	0.82 (0.52, 1.30)	.41
CHF (vs. non-CHF)	0.91 (0.43, 1.92)	.81	0.82 (0.38, 1.78)	.62	1.22 (0.16, 9.28)	.85
CAD (vs. non-CAD)	0.69 (0.33, 1.47)	.34	0.70 (0.32, 1.53)	.37	1.01 (0.14, 7.24)	.99
CVD/TIA (vs. non-CVD/TIA)	0.67 (0.07, 6.47)	.73	0.86 (0.09, 8.48)	.90	0.86 (0.06, 11.9)	.91
Combined CV diseases (vs. non-combined CV diseases)	0.77 (0.44, 1.35)	.36	0.74 (0.42, 1.33)	.32	0.68 (0.08, 5.79)	.72
Serum potassium, per 1 mEq/L	0.97 (0.65, 1.45)	.89	0.89 (0.59, 1.35)	.59	0.87 (0.56, 1.35)	.53
Serum bicarbonate, per 1 mg/dL	1.05 (0.98, 1.13)	.14	1.07 (1.00, 1.15)	.06	**1.08 (1.01, 1.17)**	**.04**
spKt/V, per 1 unit	1.81 (0.96, 3.41)	.07	1.16 (0.56, 2.38)	.69	0.90 (0.39, 2.07)	.81
Serum albumin, per 1 g/dL	0.78 (0.42, 1.48)	.45	0.98 (0.49, 1.96)	.95	0.93 (0.46, 1.90)	.85
nPCR, per 1 g/kg/d	1.85 (0.82, 4.16)	.14	1.69 (0.70, 4.06)	.25	1.54 (0.62, 3.82)	.35
Serum creatinine, per 1 mg/dL	0.96 (0.89, 1.03)	.24	1.03 (0.94, 1.14)	.50	1.05 (0.95, 1.16)	.36
Serum phosphorus, per 1 mg/dL	0.96 (0.81, 1.14)	.67	1.01 (0.84, 1.22)	.88	1.02 (0.84, 1.24)	.86
Dietary energy intake, per 200 Kcal/d	**0.21 (0.15, 0.29)**	**<.01**	**0.18 (0.13, 0.27)**	**<.01**	**0.14 (0.09, 0.23)**	**<.01**
Dietary protein intake, per 10 g/d	**0.17 (0.12, 0.25)**	**<.01**	**0.17 (0.11, 0.25)**	**<.01**	**0.14 (0.09, 0.22)**	**<.01**
Dietary fiber intake, per 5 g/d	**0.07 (0.04, 0.12)**	**<.01**	**0.05 (0.03, 0.10)**	**<.01**	**0.05 (0.02, 0.09)**	**<.01**

AV, arteriovenous; BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; CV, cardiovascular; CVD, cerebrovascular disease; K, potassium; nPCR, normalized protein catabolic rate; spKt/V, single pool Kt/V; TIA, transient ischemic attack.
Bold font indicates statistically significant estimates.

important confounders of proxies of nutritional status, ours has been the first to also incorporate dietary fiber intake in the multivariable models. Dietary fiber has putative benefits upon cardiovascular risk factors (e.g., diabetes) and disease, and a number of potassium-rich vegetables and fruits have high fiber content.[26–29] We observed that patients with lower dietary potassium intake tended to have lower dietary fiber consumption, and incremental adjustment for dietary fiber as well as caloric and protein intake further amplified the lower dietary potassium—higher mortality associations.

There are several potential interpretations of the robust and potent association between low dietary potassium intake and mortality in the hemodialysis population. For example, it has been suggested that the current paradigm of using dietary restrictions to control metabolic parameters may lead to depletion of vital nutrients and subsequent protein-energy wasting in hemodialysis patients.[5] As excessive potassium restriction may contradict current general population recommendations for a cardiovascular-healthy diet, further study of more tempered approaches such as (1) moderate restriction or even (2) liberalization of potassium intake with prescription of potassium binders in the hemodialysis population are needed.[30,31] Although our multivariable models accounted for a number of comorbidities and nutritional markers, we are not able to determine the underlying reasons for lower dietary potassium intake in the study cohort (i.e., intentional prescribed dietary restriction vs. unintentional sequelae of malnutrition), nor whether low dietary potassium consumption may have been an indicator of overall poor health and dietary status in our cohort. Notably, we conducted sensitivity analyses in which we adjusted for body anthropometry measures (i.e., mid-arm circumference and near-infrared body fat percentage as proxies of skeletal muscle and total body fat, respectively) to account for protein-energy wasting as a potential confounder and observed robust associations between lower dietary potassium intake and higher mortality risk. We also observed a differential relationship on the basis of age, such that low dietary potassium was

associated with higher death risk in patients of older (≥55 years) but not younger (<55 year) age, suggesting that certain subgroups may be more vulnerable to the ill effects of excess potassium restriction. It is also possible that there may have been differential reasons for lower dietary potassium intake in the older (i.e., unintentional restriction due to protein-energy wasting) versus younger (i.e., prescribed intentional dietary restriction).

Finally, it is important to highlight that our study was intended to examine relative as opposed to absolute dietary potassium intake, and we thus cannot draw inference regarding absolute thresholds of potassium consumption from these findings. Although the FFQ is the preferred dietary assessment method in nutritional epidemiologic research given its ability to provide comparative *long-term* estimates of dietary consumption across large populations, it may under- or overestimate intake at an individual level (i.e., the FFQ has high reliability in ranking patients across food items, and hence should be used for dietary comparisons of patients within a given population rather than individual assessment).[15,21] As this underestimation is typically non-differential, we utilized ranking methods (i.e., categorization as tertiles and quartiles) as the preferred approach in our analyses. Thus, future studies using alternative assessment methods that precisely measure dietary intake at the individual level are needed to define the optimal level of dietary potassium intake that confers the greatest health benefit in hemodialysis patients.

The strengths of our study include its examination of a diverse, prospective multi-center hemodialysis cohort; rigorous protocolized measurement of dietary intake using FFQs; and availability of detailed patient-level data on sociodemographics, comorbidities, laboratory results, dialysis treatment characteristics, and clinical events. However, several limitations bear mention. First, in this particular substudy, we did not have a sufficient number of patients who had repeated FFQ measurements over time to verify constancy of dietary potassium intake. As there may be variability in patients' dietary potassium intake over time, we had purposefully selected the FFQ as our dietary assessment tool given that it is representative of "habitual" food intake and is the preferred method for measuring nutrients with high day-to-day variability in epidemiologic studies.[21] Although the FFQ has been used in a growing number of studies of the end-stage renal disease population,[4,32-34] dialysis patients may be particularly prone to more dietary fluctuations (i.e., due to more frequent dietary counseling available in outpatient dialysis centers) compared to non-dialysis patients; hence, further studies examining the dietary potassium intake—mortality association using longitudinal assessments over time are needed. Second, while we were able to include serum albumin as a proxy of both nutritional status and inflammation (i.e., negative acute phase reactant), we were not able to examine other nutritional inflammatory markers and cannot exclude the possibility of residual confounding on this basis. Third, while all-cause death events were rigorously adjudicated, due to data limitations we did not have information regarding cause-specific deaths or intermediate outcomes (e.g., cardiovascular events) to examine mechanistic pathways. Finally, as with all observational studies, our findings do not establish a causal relationship between dietary potassium intake and mortality.

In conclusion, our study has shown that lower dietary potassium intake is independently associated with higher death risk in a prospective multicenter cohort of hemodialysis patients. Although dietary potassium restriction is currently a mainstay in the management of hemodialysis patients, our findings suggest that excessive restriction may be deleterious in this population. Hence, further studies are needed to precisely determine the ideal level of dietary potassium intake, as well as optimal dietary patterns and approaches in the hemodialysis population.

Practical Application

In a prospective cohort of hemodialysis patients, those whose dietary potassium intake was in the lowest tertile demonstrated the highest mortality risk. These observations raise awareness of the potential deleterious impact of excessive dietary potassium restriction among hemodialysis patients.

Credit Authorship Contribution Statement

Yoko Narasaki: Conceptualization, Methodology, Formal analysis, Writing - original draft, Writing - review & editing. **Yusuke Okuda:** Methodology, Formal analysis, Writing - review & editing. **Sara S. Kalantar:** Writing - review & editing. **Amy S. You:** Writing - review & editing. **Alejandra Novoa:** Writing - review & editing. **Theresa Nguyen:** Writing - review & editing. **Elani Streja:** Writing - review & editing. **Tracy Nakata:** Writing - review & editing. **Sara Colman:** Writing - review & editing. **Kamyar Kalantar-Zadeh:** Conceptualization, Methodology, Formal analysis, Writing - review & editing. **Danh V. Nguyen:** Writing - review & editing. **Connie M. Rhee:** Conceptualization, Methodology, Formal analysis, Writing - original draft, Supervision, Writing - review & editing.

Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1053/j.jrn.2020.05.008.

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