Serum Potassium and Cause-Specific Mortality in a Large Peritoneal Dialysis Cohort

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Summary

Background and objectives Unlike hemodialysis (HD), peritoneal dialysis (PD) is a continuous therapy and does not induce myocardial stunning. Yet, the death risk in HD and PD patients is similar. This study tested the hypothesis that serum potassium abnormalities contribute more to the death risk in PD patients than in HD patients.

Design, setting, participants, & measurements Data from patients treated in DaVita facilities between July 1, 2001 and June 30, 2006 (n=10,468 PD patients; n=111,651 HD patients) were used to determine association of serum potassium with mortality.

Results PD patients were significantly more likely to have serum potassium <4 mEq/L, with an adjusted odds ratio of 3.30 (95% confidence interval [95% CI], 3.05, 3.56). There was a U-shaped relationship between time-averaged serum potassium and all-cause and cardiovascular mortality of PD patients, with adjusted hazards ratios of 1.51 for all-cause mortality for potassium <3.5 mEq/L (95% CI, 1.29, 1.76) and 1.52 for potassium ≥5.5 mEq/L (95% CI, 1.32, 1.75). The population-attributable risks for all-cause mortality for serum potassium <4.0 and ≥5.5 mEq/L were 3.6% and 1.9%, respectively, in PD patients, and 0.8% and 1.5%, respectively, in HD patients.

Conclusions Abnormalities in serum potassium contribute disproportionately to the high death risk in PD patients. This may, in part, account for the equivalent cardiac risk seen with the two therapies.

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Introduction

The annual mortality of US dialysis patients exceeds 20%, and >40% of these deaths are secondary to cardiac causes. More than 60% of all cardiac deaths in dialysis patients are attributable to sudden cardiac death and/or arrhythmias (1). Many factors are likely operative in mediating the high cardiac risk seen in dialysis patients and include factors related to underlying diseases (hypertension, diabetes mellitus) and uremia (myocardial fibrosis) (2–5). In patients treated with hemodialysis (HD), the long interdialytic interval and the myocardial stunning induced by the HD procedure may possibly be additional contributing factors (6–8). Unlike HD, peritoneal dialysis (PD) is a continuous therapy and does not induce myocardial stunning (9). However, the incidence of cardiac deaths, including sudden cardiac death, is similar in PD patients to HD-treated patients (1).

Abnormalities in serum potassium are a risk factor that may, in part, account for the overall cardiac risk in PD patients to be of the same magnitude as that for HD. Thus, whereas hyperkalemia is commonly associated with advanced kidney disease and seen not infrequently in HD patients, clinical experience and small, single-center studies suggest that hypokalemia may be more common with PD. Furthermore, single-center studies from Taiwan (N=140) and Hong Kong (N=266) have shown an association between hypokalemia in PD patients and Enterobacteriaceae peritonitis and all-cause mortality, respectively (10,11). However, cultural differences influence dietary intakes of potassium (12). To our knowledge, distribution of serum potassium levels and its contribution to the high cardiac risk have not been investigated in a large and widely representative population of PD patients. Thus, we analyzed the data of all patients treated in facilities owned by DaVita Inc, a large provider of dialysis services in the United States, to test the hypothesis that hypokalemia is significantly more common in PD patients than in HD patients and contributes more to the high cardiac risk seen in PD patients than in HD patients.

Materials and Methods

Data Sources

This observational cohort study is based on data from maintenance dialysis patients treated in facilities owned by DaVita Inc between July 1, 2001 and June 30, 2006. During this period, 151,090 patients completed at least 90 days of treatment in facilities owned by DaVita Inc. The study cohort was stratified by

dialysis modality, defined as the therapy being used at the time of entry into the cohort. Of the 151,090 participants, 7588 were excluded because of extremes in age (≤16 or ≥99 years). Of the 143,502 eligible participants (12,058 PD patients; 131,444 HD patients), data on serum potassium were missing for 21,383 individuals for the first 3-month period (1590 PD patients [13%]; 19,793 HD patients [15%]). This analysis is thus based on data from 122,119 participants (10,468 PD patients; 111,651 HD patients). The differences in characteristics of included and excluded patients, stratified by dialysis modality, are summarized in Supplemental Table 1.

The DaVita dataset was linked to that from the US Renal Data System (USRDS). Data from DaVita were used to determine a participant's sex, age, presence of diabetes, body weight, and baseline height. The MEDEVID file from the USRDS contains data from the Centers for Medicare and Medicaid Services Form 2728, which is completed for all new ESRD patients in the United States and was used to determine the first day of dialysis, race/ethnicity, marital status, primary insurance, tobacco smoking, and seven comorbid conditions (atherosclerotic heart disease, including ischemic heart disease, myocardial infarction, and cardiac arrest; congestive heart failure; other cardiac diseases, including pericarditis and cardiac arrhythmia; cerebrovascular disease; peripheral vascular disease; chronic obstructive pulmonary disease; and cancer). Dialysis vintage was defined as the interval between the first day of dialysis and the first day of entering the cohort. Follow-up data were available through June 2007. The date and cause of death were obtained from USRDS.

Each patient had laboratory tests performed at least monthly, including serum potassium. All tests were performed in a single central laboratory located in Deland, Florida, within 24 hours of collection, and serum potassium was measured using an ion-sensitive electrode.

For each patient the average of all repeated measures done during the entry quarter was used in all statistical models (baseline data). The calendar quarter in which the patient completed 90 days of dialysis therapy was considered the baseline quarter. Averaged serum potassium was obtained for up to 20 calendar quarters to calculate the time-averaged serum potassium. Patients were divided into the following six groups to determine the relationship of serum potassium with outcome: <3.5, 3.5–<4.0, 4.0–<4.5, 4.5–<5.0, 5.0–<5.5, and ≥5.5 mEq/L. Additional analyses were done using serum potassium as a time-varying covariate.

The Institutional Review Board of the Los Angeles Biomedical Research Institute at Harbor-UCLA approved the study as exempt from informed consent.

Statistical Analyses

Data are summarized as means ± SD, medians (interquartile ranges), or proportions as appropriate. For the primary analysis, missing continuous data were imputed as the median and categorical variables as the prevalence in individuals with complete data. Data were complete for age, sex, diabetes, and race/ethnicity. Data for dialysis vintage, serum albumin, phosphorus, alkaline phosphatase, and hemoglobin were missing for <1%; serum creatinine, ferritin, total iron binding capacity, white blood cell count, and percentage of lymphocyte count were missing for 1%–2%; and comorbid conditions were missing for 5% of the cohort. Data for body mass index were missing for 7% of the cohort (PD, 42%; HD, 3%), primary insurance for 9%, serum parathyroid hormone for 12%, and marital status for 21%.

Logistic regression analysis was performed to determine the odds for PD patients to have baseline serum potassium below or above specific thresholds (<3.5, <4.0, ≥5.0, and ≥5.5 mEq/L), relative to HD patients. Survival analyses using Cox proportional hazards were utilized to determine the relationship of baseline and time-averaged serum potassium with all-cause, cardiovascular, and infection-related mortality in PD patients. Analyses with serum potassium as a time-dependent covariate were also done. Additional analyses were performed in the entire study cohort of PD and HD patients to compare the association of serum potassium with death risk between the two dialysis modalities, using time-averaged values and a time-dependent model. All outcomes were assigned to the initial dialysis modality. Patients were censored at time of transplantation. Secondary analyses were performed in which participants were censored at the time of transfer to another dialysis modality (PD to HD, or HD to PD, as appropriate). Data were analyzed using the following levels of adjustment: (*1*) unadjusted; (*2*) case-mix that included age, sex, race/ethnicity (Asians, Hispanics, blacks, whites, and others), seven comorbid conditions, history of tobacco smoking, categories of dialysis vintage (<6 months, 6 months to 2 years, 2–5 years, >5 years), primary insurance, and marital status; and (*3*) case-mix plus laboratory data that included all of the above covariates as well as body mass index, serum albumin, creatinine, ferritin, total iron binding capacity, calcium, phosphorus, parathyroid hormone, alkaline phosphatase, hemoglobin, white blood cell count, and percentage of lymphocyte count.

The population-attributable risk of death due to low and high time-averaged serum potassium in PD and HD patients was calculated according to the following equation: population-attributable risk = $P_e \times (RR - 1)/RR$, where P_e is the prevalence of low or high serum potassium among all who died, and RR is the relative risk of death (13).

All analyses were carried out using STATA software (version 11.2; StataCorp LP, College Station, TX).

Results

Patient Characteristics

Compared with HD patients, PD patients were younger, were less likely to be black or widowed, were less likely to have diabetes mellitus or underlying cardiovascular comorbidities, and were more likely to be white and married (Table 1). Furthermore, PD patients had higher baseline serum creatinine, total iron binding capacity, and parathyroid hormone levels, and lower serum ferritin levels (Table 1).

Distribution of Serum Potassium by Dialysis Modality

Figure 1 shows the distribution of baseline serum potassium by dialysis modality, and Table 2 summarizes the

Table 1. Baseline data of study cohort, stratified by modality

Variable	All Patients (*N*=122,119)	
	PD	HD
No. of patients	10,468	111,651
Age (yr)	56±16	62±15
>65	32	46
Female sex	47	45
Diabetes mellitus	49	58
Race and/or ethnicity		
Asian	4	3
blacks	24	32
Hispanics	13	15
whites	52	42
others	7	6
Vintage (mo)	35 (15, 65)	28 (12, 54)
Primary insurance		
Medicare	59	61
Medicaid	3	6
private	13	11
others	14	12
Marital status		
single	19	22
married	45	37
widow	7	13
divorced	6	7
Comorbid conditions		
atherosclerotic heart disease	15	21
congestive heart failure	16	28
other cardiac diseases	4	6
cerebrovascular disease	5	8
peripheral vascular disease	8	12
chronic obstructive pulmonary disease	3	6
cancer	4	4
Current smokers	5	5
Weight (kg)	74±19	75±21
Body mass index (kg/m^2)	26±6	27±7
Serum albumin (g/dl)	3.6±0.5	3.7±0.5
Serum creatinine (mg/dl)	8.6±3.7	8.0±3.3
Serum ferritin (ng/ml)	277 (122, 585)	383 (181, 712)
Serum total iron binding capacity (mg/dl)	229±54	209±46
Serum calcium (mg/dl)	9.2±0.8	9.2±0.7
Serum phosphorus (mg/dl)	5.4±1.5	5.6±1.5
Serum parathyroid hormone (pg/ml)	286 (159, 525)	245 (143, 418)
Serum alkaline phosphatase (U/L)	97 (75, 131)	98 (77, 131)
Blood hemoglobin (g/dl)	12.0±1.5	12.0±1.4
White blood cell count ($\times 10^3/\mu$l)	7.2 (5.9, 8.8)	7.1 (5.8, 8.7)
Percentage lymphocyte count	20±8	20±8

Data are presented as mean ± SD, median (interquartile range), or percentages. PD, peritoneal dialysis; HD, hemodialysis.

odds ratio of PD patients having values below and above clinically relevant thresholds. Serum potassium was <3.5 mEq/L in 10% of PD patients compared with 2% of HD patients, a difference in prevalence that persisted despite covariate adjustment (adjusted odds ratio, 4.17; 95% confidence interval [95% CI], 3.63, 4.79) (Table 2). Conversely, 20% of PD patients had serum potassium ≥5.0 mEq/L compared with 33% of HD patients (Figure 1). Thus, the adjusted odds for PD patients to have serum potassium ≥5.0 mEq/L were 44% lower (Table 2). Similar trends were observed for distribution of time-averaged serum potassium levels by dialysis modality.

Serum Potassium and Death Risk in PD Patients

Table 3 shows the characteristics of the 10,468 PD patients stratified by time-averaged serum potassium. With increasing serum potassium, patients were younger, were less likely to be female or black, and were less likely to have diabetes or cardiovascular comorbidities; however, they were more likely to have Medicare as their primary insurance. In addition, patients with higher serum potassium levels had longer dialysis vintage and higher serum albumin, creatinine, ferritin, phosphorus, parathyroid hormone, and alkaline phosphatase levels (Table 3).

Follow-up data were available for 10,454 PD patients. The results showed that 4737 patients died over a median follow-up of 27 months. Patients with baseline serum potassium levels ≥5.0 mEq/L had a significantly higher adjusted risk for all-cause, cardiovascular, and infection-related mortality compared with those with levels between 4.0 and <4.5 mEq/L (Table 4). In contrast, there was no association between low baseline potassium and risk for either all-cause, cardiovascular, or infection-related mortality (Table 4).

In contrast, there was a U-shaped relationship between time-averaged serum potassium levels and all-cause and cardiovascular mortality (Table 4 and Figure 2). Thus, the magnitude of increase in the risk for all-cause mortality was similar in patients with time-averaged serum potassium levels <3.5 mEq/L (adjusted hazards ratio [HR], 1.51; 95% CI, 1.29, 1.76) to those with levels ≥5.5 mEq/L (adjusted HR, 1.52; 95% CI, 1.32, 1.75) (Table 4 and Figure 2). However, the increase in risk for infection-related mortality was seen only in individuals with time-averaged serum potassium <3.5 mEq/L (adjusted HR, 1.85;

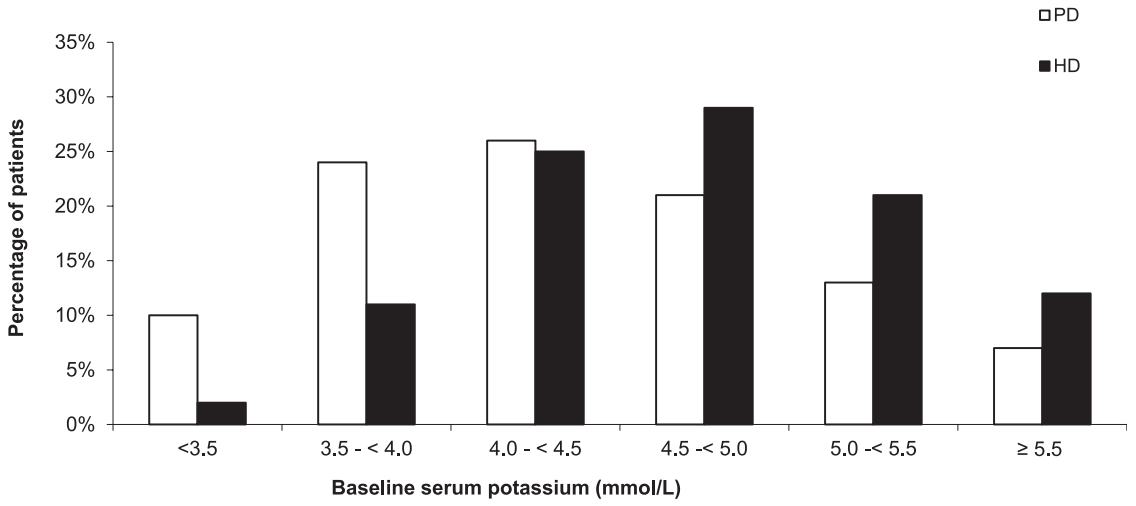

Figure 1. | Distribution of serum potassium levels in patients treated with PD (*n*=10,468) and HD (*n*=111,651). The data reflect the average of all measurements made during the first 3 months of entry into study cohort. PD, peritoneal dialysis; HD, hemodialysis.

Table 2. Odds ratios of PD patients having baseline serum potassium values below or above clinically relevant thresholds, using HD patients as the reference

Baseline Serum Potassium (mEq/L)	Odds Ratio (95% Confidence Interval)		
	Unadjusted (*n*=122,119)	Case-Mix Adjusted (*n*=122,119)[a]	Case-Mix and Laboratory Data Adjusted (*n*=122,119)[b]
<3.5	4.97 (4.6, 5.36)	5.84 (5.38, 6.35)	4.17 (3.63, 4.79)
<4.0	3.42 (3.27, 3.57)	4.23 (4.04, 4.44)	3.30 (3.05, 3.56)
≥5.0	0.51 (0.49, 0.54)	0.40 (0.38, 0.43)	0.56 (0.52, 0.61)
≥5.5	0.57 (0.53, 0.61)	0.45 (0.42, 0.49)	0.64 (0.58, 0.71)

PD, peritoneal dialysis; HD, hemodialysis.
[a]Variables include age, sex, diabetes, race/ethnicity, primary insurance, marital status, vintage category, atherosclerotic heart disease, congestive heart failure, other cardiac diseases, cerebrovascular disease, peripheral vascular disease, chronic obstructive pulmonary disease, cancer, and tobacco smoking.
[b]Variables include those above, as well as body mass index, serum albumin, creatinine, ferritin, total iron binding capacity, calcium, phosphorus, parathyroid hormone, alkaline phosphatase, hemoglobin, white blood cell count, and percentage lymphocyte count.

95% CI, 1.32, 2.55) (Table 4). Similar trends were seen in each of the three major racial groups (Supplemental Table 2).

When the participants were censored at the time of transfer to the other dialysis modality, the risk with low serum potassium levels was attenuated to a nonsignificant level, whereas the risk with higher levels persisted (Supplemental Table 3). The trend, with increased death risk with both low and high levels, was observed in models that used serum potassium as time-varying covariates (Figure 3 and Supplemental Table 4).

Comparison of Association of Serum Potassium with Death Risk in PD and HD Patients

Follow-up data were available for 10,454 PD patients and 111,434 HD patients. Whereas a higher risk for all-cause and cardiovascular mortality was seen in HD patients with serum potassium <4.0 or ≥5.0 mEq/L, higher risk was seen in those PD patients with levels <3.5 or ≥5.5 mEq/L (reference group: HD patients with serum potassium between 4.0 and <4.5 mEq/L) (Table 5 and Figure 4). In contrast, a higher risk for infection-related mortality was seen in HD patients with serum potassium <3.5 or ≥5.5 mEq/L, but in PD patients with time-averaged levels <4.5 or ≥5.5 mEq/L (Table 5).

A similar trend, with increase in death risk with both low and high levels, was observed in analyses when patients were censored at the time of change in dialysis therapy (Supplemental Table 4) or in models that used serum potassium as time-varying covariates (Supplemental Table 5).

Population-Attributable Risk for Death to Low and High Serum Potassium Levels by Dialysis Modality

In patients treated with PD, the population-attributable risks of death associated with time-averaged serum potassium <4.0 and ≥5.5 mEq/L were 3.6% (95% CI, 1.7, 5.2)

Table 3. Baseline characteristics of patients treated with peritoneal dialysis at time of entry into cohort, stratified by time-averaged serum potassium

Serum Potassium (mEq/L)	All Peritoneal Dialysis Patients (n=10,468)					
	<3.5	3.5–<4.0	4.0–<4.5	4.5–<5.0	5.0–<5.5	≥5.5
No. of patients	371	2293	3261	2618	1457	468
Age (yr)	56±16	58±16	57±15	55±16	53±16	53±15
>65	34	36	34	29	26	24
Female sex	58	50	47	44	47	47
Diabetes mellitus	48	48	50	50	45	44
Race and/or ethnicity						
Asian	4	6	5	3	3	4
blacks	29	24	23	27	22	17
Hispanics	18	14	13	12	13	14
whites	40	50	53	51	55	56
others	8	6	5	7	7	8
Vintage (mo)	24 (9, 47)	24 (11, 44)	28 (14, 51)	43 (19, 81)	60 (29, 98)	60 (34, 102)
Primary insurance						
Medicare	53	57	56	60	67	66
Medicaid	3	3	3	3	3	5
private	13	11	14	13	11	10
others	17	17	17	12	8	6
Marital status						
single	22	17	16	20	23	26
married	43	47	46	44	43	44
widow	11	8	6	7	5	7
divorced	5	5	7	7	7	8
Comorbid conditions						
atherosclerotic heart disease	14	16	16	15	15	12
congestive heart failure	17	18	17	14	14	16
other cardiac diseases	4	5	5	3	3	3
cerebrovascular disease	4	5	6	4	5	3
peripheral vascular disease	9	8	8	8	7	7
chronic obstructive pulmonary disease	3	3	4	4	3	3
cancer	4	4	4	3	3	2
Current smokers	6	5	5	5	7	6
Weight (kg)	70±19	73±19	75±19	75±19	73±19	70±19
Body mass index (kg/m^2)	25±6	26±6	27±6	26±6	26±6	25±6
Serum albumin (g/dl)	3.4±0.6	3.5±0.5	3.6±0.5	3.6±0.5	3.7±0.4	3.8±0.5
Serum creatinine (mg/dl)	8.0±3.7	7.7±3.7	7.9±3.5	9.1±3.6	10.0±3.4	10.4±3.3
Serum ferritin (ng/ml)	268 (124, 535)	225 (99, 439)	237 (107, 500)	298 (136, 615)	439 (183, 766)	513 (249, 851)
Serum total iron binding capacity (mg/dl)	232±55	243±53	238±54	222±53	208±47	203±44
Serum calcium (mg/dl)	9.1±0.9	9.2±0.8	9.2±0.8	9.2±0.8	9.3±0.9	9.4±0.8
Serum phosphorus (mg/dl)	4.8±1.2	4.9±1.2	5.2±1.4	5.7±1.5	6.2±1.6	6.7±1.8

Table 3. (Continued)

Serum Potassium (mEq/L)	All Peritoneal Dialysis Patients (n=10,468)					
	<3.5	3.5–<4.0	4.0–<4.5	4.5–<5.0	5.0–<5.5	≥5.5
Serum parathyroid hormone (pg/ml)	318 (158, 587)	272 (152, 486)	273 (153, 503)	287 (162, 523)	319 (166, 584)	378 (190, 686)
Alkaline phosphatase (U/L)	100 (77, 142)	96 (75, 127)	94 (74, 125)	96 (74, 132)	102 (78, 140)	115 (81, 160)
Blood hemoglobin (g/dl)	11.9±1.6	12.2±1.5	12.1±1.5	11.9±1.5	11.7±1.4	11.6±1.4
White blood cell count ($\times 10^3/\mu l$)	7.9±4.5	7.5±2.5	7.6±2.6	7.4±2.4	7.6±2.5	7.5±2.3
Percentage lymphocyte count	20.3±7.7	19.0±7.4	19.5±7.7	19.9±8.0	20.3±8.3	19.0±8.2

Data are presented as mean ± SD, median (interquartile range), or percentages.

and 1.9% (95% CI, 1.3, 2.4), respectively. In patients treated with HD, the population-attributable risks of death associated with time-averaged serum potassium <4.0 and ≥5.5 mEq/L were 0.8% (95% CI, 0.6, 1.1) and 1.5% (95% CI, 1.3, 1.7), respectively.

Sensitivity Analyses

Two sets of sensitivity analyses were performed. In the first set, only individuals with complete data for all variables were included (PD, 4715; HD, 87,959). In the second set, analyses were repeated after excluding marital status and body mass index as covariates in the respective models. The same qualitative trends were observed for each analysis and are summarized in Supplemental Tables 6–8.

Discussion

To our knowledge, this is the first multicenter study to evaluate the distribution of serum potassium and its association with outcomes in PD patients. Our analyses of data from a large, contemporary cohort representative of the dialysis population in the United States indicates that over one-quarter of PD patients have time-averaged serum potassium <4.0 mEq/L, a level that is associated with a significant increase in risk for death in this population. Moreover, the population-attributable risk for all-cause mortality for serum potassium <4.0 mEq/L in PD patients was two-fold higher than with levels ≥5.5 mEq/L. Finally, the population-attributable risk for all-cause mortality for abnormalities in serum potassium levels in PD patients was two-fold higher than in those treated with HD, primarily due to substantially larger proportion of deaths associated with serum potassium <4.0 mEq/L.

Our study confirms the findings from previous small, single-center studies that low, rather than high, serum potassium levels are more common in PD patients. Thus, whereas 26% of patients had time-averaged serum potassium <4.0 mEq/L, 18% had levels ≥5.0 mEq/L. However, the prevalence of serum potassium <3.5 mEq/L (4% time-averaged values) in our cohort is lower than previously reported (7%–36%) from single-center studies (10,14–16). Our estimates likely have greater external validity because they were derived from a large multicenter cohort of PD patients. Nevertheless, other reasons for the varying estimates of prevalence may include differences in dietary intakes of potassium and PD prescription (volume and tonicity of dialysate). Furthermore, cohorts may differ in the use of oral potassium supplements; previous studies suggest that 10%–29% of PD patients require potassium supplements (15,17,18). The high prevalence of hypokalemia in ESRD patients treated with PD is likely directly attributable, at least in part, to the dialysis modality. None of the commercially available PD solutions have any added potassium. However, in a patient with ambient serum potassium concentration of 4 mEq/L and 13 L drain volume, the maximum potassium losses cannot exceed 52 mEq/d. The average daily intakes of potassium in the adult US population range from 54 to 86 mEq/d (12). Thus, dialysate potassium losses are unlikely to be sufficient to induce hypokalemia in most patients and likely require the presence of other factors such as inadequate dietary intakes and/or transcellular shifts induced by

Table 4. Association of baseline serum potassium and time-averaged serum potassium with all-cause, cardiovascular, and infection-related mortality in patients treated with PD at time of entry into the cohort (*n*=10,454)

Serum Potassium (mEq/L)	% of Population	Baseline Serum Potassium [Adjusted Hazards Ratio (95% Confidence Interval)][a]			% of Population	Time-Averaged Serum Potassium [Adjusted Hazards Ratio (95% Confidence Interval)][a]		
		All-Cause	CV	Infection-Related		All-Cause	CV	Infection-Related
<3.5	10	1.08 (0.97, 1.21)	1.05 (0.88, 1.25)	1.11 (0.86, 1.43)	4	1.51 (1.29, 1.76)	1.50 (1.18, 1.92)	1.85 (1.35, 2.55)
3.5–<4.0	24	1.03 (0.94, 1.11)	0.94 (0.83, 1.08)	1.13 (0.94, 1.37)	22	1.12 (1.03, 1.21)	1.04 (0.91, 1.18)	1.15 (0.96, 1.38)
4.0–<4.5	25	Reference	Reference	Reference	31	Reference	Reference	Reference
4.5–<5.0	21	1.04 (0.95, 1.13)	0.98 (0.86, 1.12)	1.15 (0.95, 1.40)	25	0.90 (0.83, 0.98)	0.92 (0.81, 1.04)	0.85 (0.71, 1.01)
5.0–<5.5	13	1.17 (1.06, 1.29)	1.18 (1.02, 1.38)	1.26 (1.01, 1.58)	14	1.00 (0.91, 1.10)	1.02 (0.88, 1.19)	0.85 (0.68, 1.07)
≥5.5	7	1.32 (1.17, 1.49)	1.27 (1.05, 1.52)	1.35 (1.02, 1.77)	4	1.52 (1.32, 1.75)	1.51 (1.23, 1.87)	1.31 (0.95, 1.80)

Follow-up information was missing for 14 of the 10,468 participants. Data adjusted for age, sex, race and/or ethnicity, diabetes, dialysis vintage, primary insurance, marital status, atherosclerotic heart disease, congestive heart failure, cerebrovascular disease, other cardiac diseases, peripheral vascular disease, chronic obstructive pulmonary disease, cancer, current smoking, body mass index, serum albumin, total iron binding capacity, ferritin, creatinine, calcium, phosphorus, parathyroid hormone, alkaline phosphatase, hemoglobin, white blood cell count, and percentage lymphocyte count. PD, peritoneal dialysis; Pop, population; CV, cardiovascular.

[a]Using PD patients with serum potassium between 4.0 and <4.5 mEq/L as the reference group.

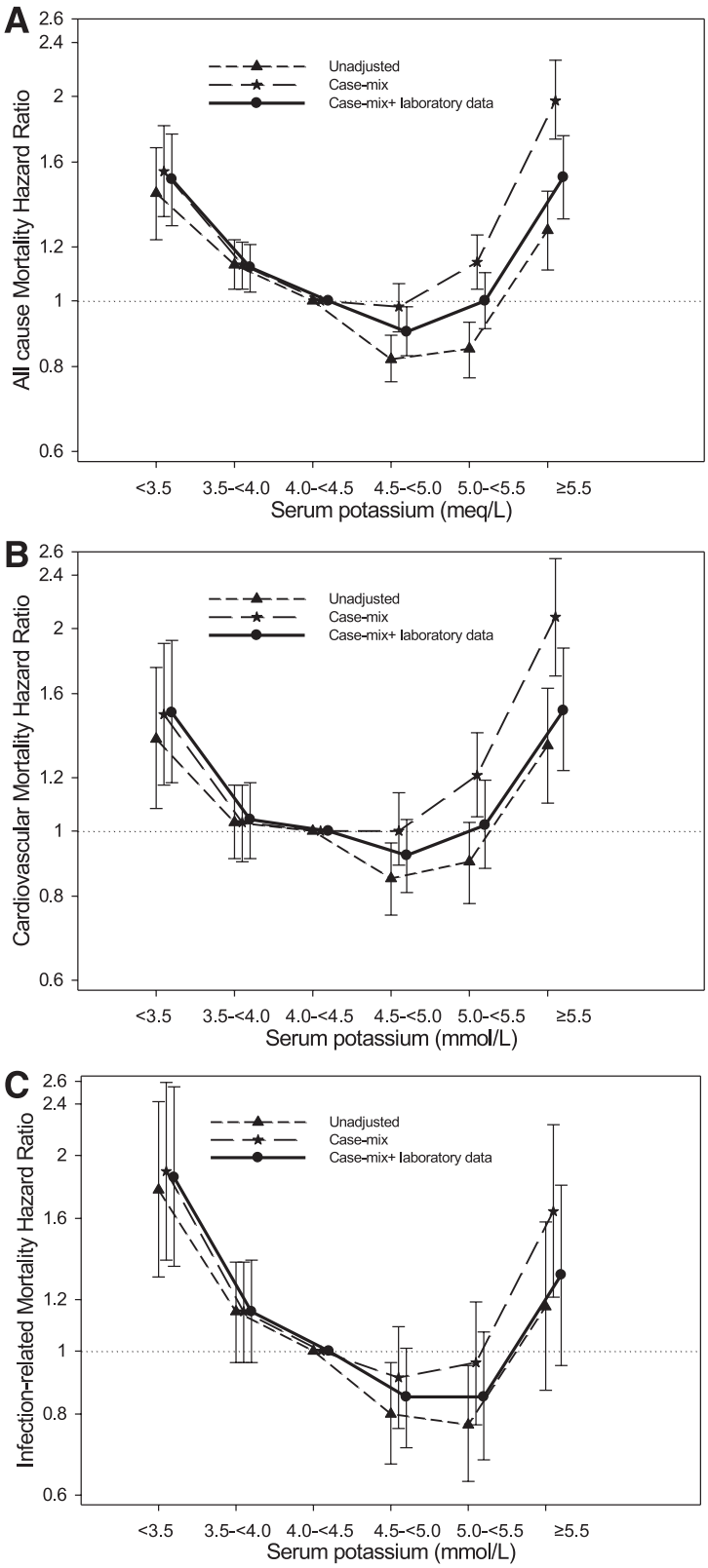

Figure 2. | **Association of time-averaged serum potassium concentration with mortality in patients undergoing PD (*n*=10,454).** (A) All-cause mortality, (B) cardiovascular mortality, and (C) and infection-related mortality. Reference group: PD patients with time-averaged serum potassium levels between 4.0 and <4.5 mEq/L. Error bars represent 95% confidence intervals. PD, peritoneal dialysis.

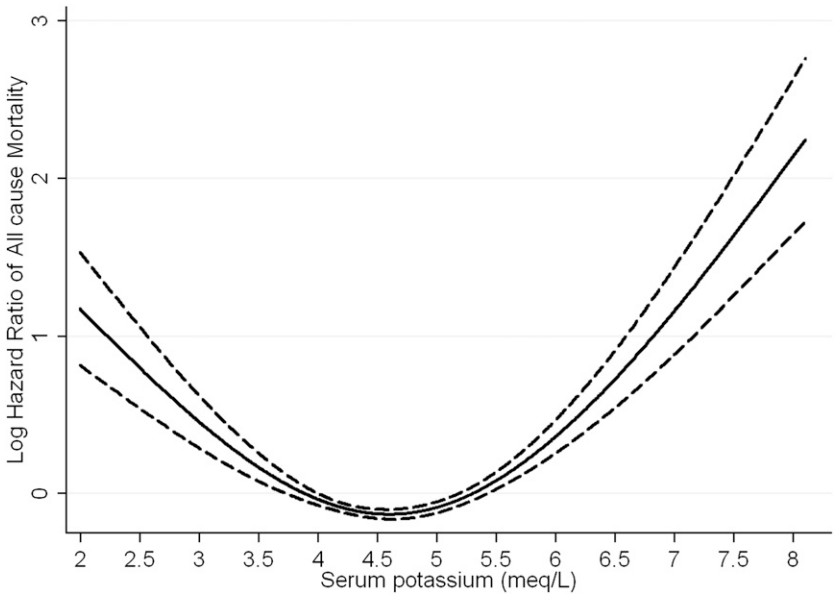

Figure 3. | Association of serum potassium, use as a time-varying covariate, with mortality in patients undergoing peritoneal dialysis (*n*=10,454). Error bars represent 95% confidence intervals.

insulin release from absorption of glucose from peritoneal dialysate (19,20).

It is surprising that despite the well known association of both low and high serum potassium levels with all-cause and cardiovascular mortality in the general population, of hyperkalemia with kidney disease, and the high incidence of sudden cardiac death in dialysis patients, this is the first large-scale evaluation of the issue in patients treated with PD. Our study demonstrates a U-shaped relationship between time-averaged serum potassium and all-cause and cardiovascular mortality in PD-treated patients. Even though the association of low potassium levels with death risk was not seen with baseline values, time-averaged measures and time-dependent models provide more robust estimates of risk. A single-center study of Chinese patients from Hong Kong (n=266) previously demonstrated a higher risk for all-cause mortality in PD patients with serum potassium <3.5 mEq/L (10). However, unlike our study, Szeto *et al*. did not analyze association with cause-specific mortality or test the association of death risk with higher serum potassium levels. Thus, our findings build upon and extend those from the previous report. Given the large sample size used in our study and that the cohort was derived from centers distributed over most of the states in the United States, our findings also have considerable external validity (21,22).

To our knowledge, this is the first study to demonstrate an association between serum potassium and infection-related mortality in either PD- or HD-treated patients. Low time-averaged serum potassium was consistently associated with an increase in infection-related mortality in both PD and HD patients. In contrast, the higher risk for infection-related mortality with high serum potassium was evident in PD patients only when they were compared with HD patients with serum potassium between 4.0 and <4.5 mEq/L. Our findings are consistent with some previous observations about the association of low serum potassium levels with infectious risk in PD patients. In a recent study, Chuang *et al.* (11) found that the incidence of peritonitis was significantly higher among patients with hypokalemia; the risk was particularly high for infections with Enterobacteriaceae organisms. This is relevant because Gram-negative PD peritonitis is associated with significantly higher risk for either transfer to HD or mortality (23). Furthermore, a greater decline in serum potassium levels during the course of PD peritonitis has been reported to be associated with a higher likelihood of persistent infection (24). The biologic basis for the association of low serum potassium levels, however, either with risk for infection or infection-related mortality, is not known. It has been suggested that low serum potassium levels may alter intestinal motility, which, along with protein-energy wasting often associated with hypokalemia, may impair immunologic defenses. This, in turn, may lead to bacterial overgrowth and enhanced susceptibility to Enterobacteriaceae-associated peritonitis (10,11,25). However, these issues were not addressed in this study and remain speculative.

Even though the magnitude of death risk with low and high serum potassium levels is largely similar in both PD- and HD-treated patients, the importance of abnormal serum potassium levels differs by modality because of differences in prevalence. Thus, the population-attributable risk of deaths for levels of serum potassium <4.0 mEq/L was substantially larger in PD patients, because of a higher prevalence, compared with that in HD patients (26% versus 9%, respectively). Furthermore, in PD patients, the population-attributable risk for deaths with serum potassium <4.0 mEq/L was almost two-fold higher than seen with levels ≥5.5 mEq/L. These estimates indicate that abnormalities in serum potassium, particularly low levels, are a substantially more important contributor to death risk in PD patients than in HD patients.

Table 5. Association of time-averaged serum potassium and all-cause, cardiovascular, and infection-related mortality in patients treated with PD (*n*=10,454) and HD with dialysis modality defined at the time of entry into the cohort (*n*=111,434)

Time-Averaged Serum Potassium (mEq/L)	% of Population		Adjusted Hazards Ratio (95% Confidence Interval)[a]					
			All-Cause Mortality		Cardiovascular Mortality		Infection-Related Mortality	
	PD	HD	PD	HD	PD	HD	PD	HD
<3.5	4	<1	1.31 (1.13, 1.52)	1.40 (1.30, 1,52)	1.40 (1.11, 1.77)	1.20 (1.04, 1.38)	1.87 (1.39, 2.51)	1.40 (1.16, 1.68)
3.5–<4.0	22	8	1.06 (0.99, 1.13)	1.08 (1.04, 1.11)	1.07 (0.97, 1.19)	1.07 (1.02, 1.13)	1.30 (1.13, 1.50)	1.07 (0.99, 1.16)
4.0–<4.5	31	25	0.96 (0.91, 1.02)	Reference	1.05 (0.96, 1.14)	Reference	1.16 (1.02, 1.31)	Reference
4.5–<5.0	25	37	0.87 (0.82, 0.92)	0.98 (0.96, 1.00)	0.97 (0.88, 1.06)	1.00 (0.97, 1.03)	0.98 (0.85, 1.12)	0.99 (0.94, 1.04)
5.0–<5.5	14	23	0.99 (0.92, 1.07)	1.02 (1.00, 1.05)	1.10 (0.98, 1.24)	1.08 (1.04, 1.12)	1.02 (0.85, 1.22)	1.00 (0.94, 1.06)
≥5.5	4	7	1.47 (1.30, 1.66)	1.26 (1.21, 1.30)	1.63 (1.36, 1.96)	1.39 (1.32, 1.47)	1.51 (1.14, 2.00)	1.25 (1.15, 1.36)

Data adjusted for age, sex, race and/or ethnicity, diabetes, dialysis vintage, primary insurance, marital status, atherosclerotic heart disease, congestive heart failure, cerebrovascular disease, other cardiac diseases, peripheral vascular disease, chronic obstructive pulmonary disease, cancer, current smoking, body mass index, serum albumin, total iron binding capacity, ferritin, creatinine, calcium, phosphorus, parathyroid hormone, alkaline phosphatase, hemoglobin, white blood cell count, and percentage lymphocyte count. PD, peritoneal dialysis; HD, hemodialysis.
[a]Using HD patients with serum potassium between 4.0 and <4.5 mEq/L as the reference group.

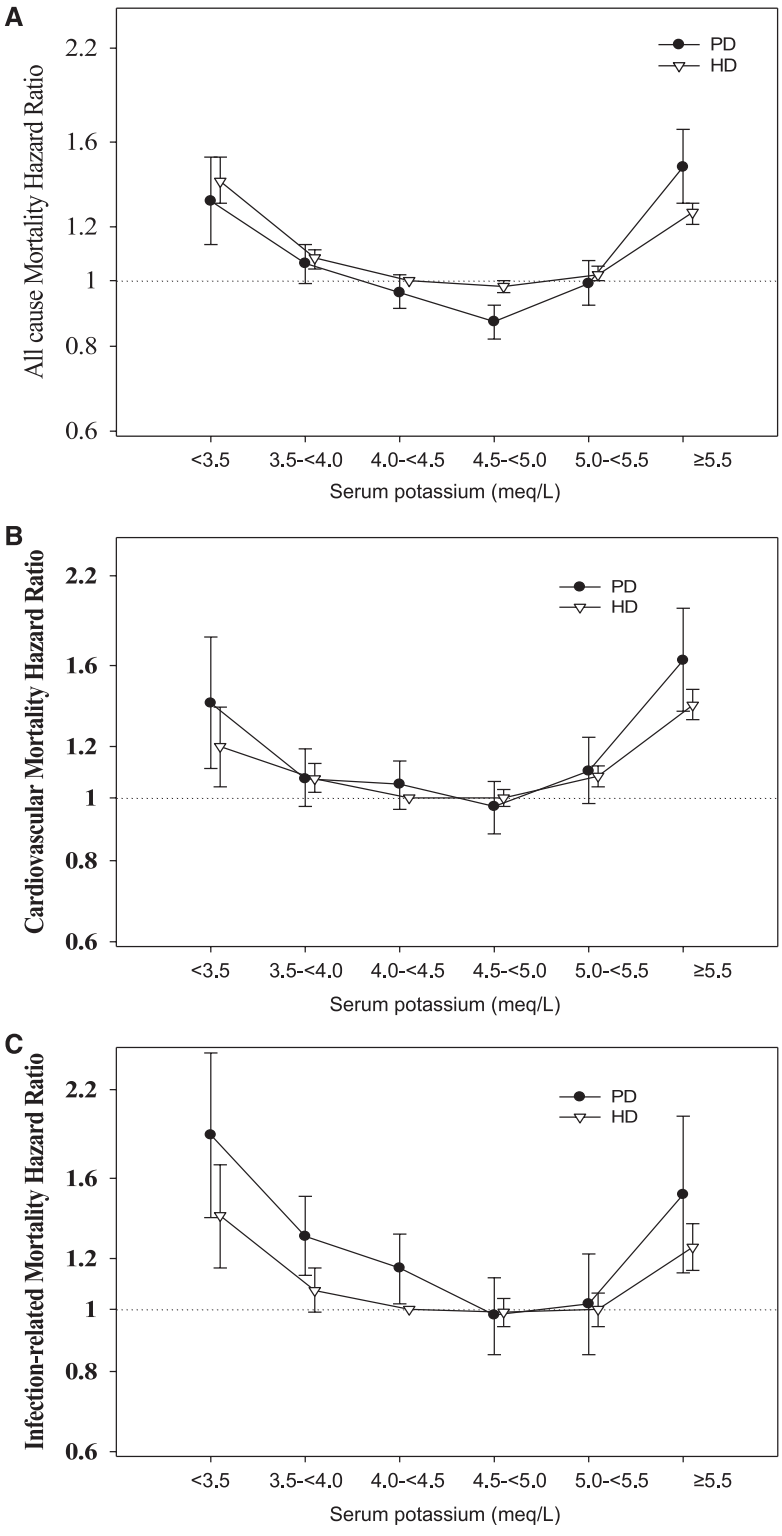

Figure 4. | Association of time-averaged serum potassium concentration with outcomes in patients undergoing PD (*n*=10,454) and HD (*n*=111,434). (A) All-cause mortality, (B) cardiovascular mortality, and (C) infection-related mortality. Reference group: hemodialysis patients with serum potassium levels between 4.0 and <4.5 mEq/L. PD, peritoneal dialysis; HD, hemodialysis.

Despite its strengths, our study has several important limitations. Observational cohort studies generate associations; it remains uncertain if these are causal. Despite adjustment for a large number of covariates, the risk for residual confounding remains. Furthermore, information about comorbidities was available only at the time of start of dialysis. Moreover, data on comorbidities were obtained from Centers for Medicare and Medicaid Services Form 2728

and there is concern that these data may underestimate the burden of coexisting diseases (26). Some patients had missing data on baseline serum potassium and they were excluded from analysis. Moreover, bias may have been introduced from missing data on some of the covariates used for adjustment. However, the proportion of patients with missing data on baseline serum potassium was small (15%). Moreover, we observed the same trends in death risk in our sensitivity analyses—both when the analyses were limited to those with complete data and those in which the statistical models did not include body mass index and marital status, the variables with the largest amount of missing data. Data on residual renal function, peritoneal transport type, PD modality, or prescription were unavailable; hence, we were unable to determine the association of these important variables with the distribution of serum potassium levels. Residual renal function facilitates the maintenance of potassium homeostasis and is an important determinant of death risk in dialysis patients (27). Our study cannot exclude the confounding influence of residual renal function on the association of higher serum potassium levels with death risk. Alternatively, hyperkalemia may be one of the mechanisms whereby loss of residual renal function increases death risk. Finally, data on medications, including potassium supplements and inhibitors of the renin-angiotensin-aldosterone system, were not available. This may have led us to underestimate the prevalence of low serum potassium in PD-treated patients; however, this is not important when testing the association with all-cause and cause-specific mortality.

In conclusion, our study demonstrates for the first time that abnormalities in serum potassium, particularly low levels, contribute substantially more to the death risk in PD-treated patients than in those treated with HD. Whether aggressive potassium supplementation would improve survival for these patients has yet not been tested. Until such studies are done, it may be prudent for physicians to carefully monitor and normalize potassium levels in PD-treated patients.

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