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Hypokalemia and hyperkalemia in patients on peritoneal dialysis: incidence and associated factors

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Abstract

Background Hypokalemia is a well-described electrolyte disturbance in patients on peritoneal dialysis (PD). Hyperkalemia, however, is still overlooked, although it also represents a risk factor for mortality. Angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers (ACE/ARB), diuretics, and proton pump inhibitor (PPI) can interfere with potassium levels in these patients.

Methods This is a retrospective study that evaluated monthly serum potassium in a 5-year period. Serum potassium disturbances were evaluated as time-average and number of hypo- and hyperkalemia episodes per patient. Prescribed medication such as ACE/ARB, diuretics, and omeprazole were recorded.

Results We evaluated 2025 potassium measurements obtained from 146 patients on PD. Serum potassium ranged from 2.5 to 8.3 mEq/L with an average of 4.72 ± 0.74 mEq/L. Hypokalemia was found in 59 measurements (2.9%) obtained from 35 patients (23.9%) whereas hyperkalemia was demonstrated in 269 (13.3%) measurements obtained from 74 patients (50.7%). Hypokalemia was associated with low albumin ($p = 0.022$), and omeprazole use ($p = 0.024$). Black race was a protector factor ($p = 0.031$). Omeprazole-associated hypokalemia was seen only in non-anuric patients and remained an independent risk factor even after adjustments. Patients who had hyperkalemia were more likely to be anuric ($p = 0.001$) and in use of furosemide ($p = 0.0001$).

Conclusion Hyperkalemia and hypokalemia are very frequent in patients on PD and should be closely monitored. Interventional studies should address the impact of discontinuing omeprazole in the levels of potassium.

Keywords Hyperkalemia · Potassium · Proton-pump inhibitor · Black race · Anuria

Introduction

Hypokalemia has been described as a major concern in patients on peritoneal dialysis (PD) [1, 2] and has been found to vary from 9 to 58.6% [3–5]. Hypokalemia may affect gastrointestinal motility, favoring bacterial overgrowth, and peritonitis [3]. Oral potassium supplements and potassium-sparing diuretics such as spironolactone and amiloride are recommended in this clinical scenario [6]. The large variation in the prevalence of hypokalemia might be explained by several reasons: difference in demographics and clinical population, presence of residual diuresis, prescribed medication, and others. Another possible explanation on the variability of prevalence in potassium disturbance is the frequency and number of serum measurements that have been taken into account to define hypo- and hyperkalemia. Some authors have evaluated a 3-month average measurement [7–9], while others have assessed a unique potassium measurement [3–5].

Hypokalemia has been associated with peritonitis [1] and mortality in patients on PD [1, 2]. The mortality attributed to serum potassium is described as a U-shaped relationship [1], although little attention is paid to hyperkalemia in this population. Few studies have evaluated simultaneously hyperkalemia and hypokalemia in PD [7, 8]. This study

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attempted to address this evidence gap by: (1) analyzing the time-average serum potassium in patients and (2) examining the impact of the prescription of angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers (ACEI-ARB), diuretics, and proton pump inhibitor (PPI) on potassium disturbances.

Methods

In this retrospective study, all patients aged 18 years or older who were started on PD at the Hospital das Clinicas, Universidade de Sao Paulo, Brazil, from January 1, 2014, to December 31, 2018, were identified. Among 163 patients who were identified, 17 were excluded due to technical problems and transitioning to hemodialysis within the first 30 days of PD. After approval from the Institutional Ethical Review Board (Cappesq #45163715.4.0000.0068), 146 adult patients were included.

The following demographic and clinical data were extracted from charts at the initiation of PD: age, sex, race, the underlying cause of kidney disease, presence of diabetes, death, and peritonitis. Other clinical data collected included the duration of PD at the study entry and residual urine output. Anuria was defined as diuresis < 200 mL in 24 h. Monthly prescription information for ACEI/ARB, PPI, and the diuretics (furosemide, spironolactone, and hydrochlorothiazide) was recorded. Omeprazole was the only PPI in use during the study period. Only medications in use for at least 2 months were considered.

Routine monthly blood samples were assessed for serum potassium, which was analyzed by standard laboratory procedures using an automated analyzer. During the study period, there was no change in laboratory methods. The normal range of serum potassium was considered between 3.5 and 5.5 mEq/L. All measurements of potassium during the study period were assessed, for the evaluation of any episode of hypokalemia and hyperkalemia. Outcomes were: number of episodes of hypokalemia and hyperkalemia, time-average of serum potassium, percentage of measures with hypokalemia and hyperkalemia. Levels of serum albumin, magnesium, bicarbonate, and calcium at the study entry were also recorded.

All patients were receiving dextrose PD solution and performed either continuous ambulatory peritoneal dialysis (4 exchanges a day, with 1.5% during the day and 2.5 overnight, dwell volume 1.5–2 L) or automatic peritoneal dialysis (4–5 cycles, 8–9 h total therapy time, 8–14 L). Automatic PD was performed either by Homechoice™ automated cycler machine (Baxter Inc., Deerfield, USA) or PD-NIGHT Peritoneal Dialysis Machine™ (Fresenius Medical Care, Brazil). Composition of the dialysis solution was as following: pH: 5.2, glucose 1.5%, 2.5%, and 4.5%, calcium 3.5 mEq/L and 2.5 mEq/L, sodium 132 mEq/L, magnesium 0.5 mEq/L, chloride 96 mEq/L, lactate 40 mEq/L, without potassium.

Statistical analysis

We expressed continuous variables as the mean standard deviation or median (25,75) according to distribution, tested by D'Agostino-Pearson Test. Categorical data were expressed as number and percentage (shown in brackets). Comparison between groups was done by Student *t* test or Mann–Whitney and Fisher or Chi-squared for continuous and categorical variables, accordingly. Serum potassium was analyzed as a single measurement at baseline of each patient and also as time-average. Relationships between single variables were examined by Spearman. Kaplan–Meier survival estimates were built to show unadjusted survival (censored for transplantation, transfer to hemodialysis, and study termination). Cox regression analysis adjusted for age and diabetes was used to evaluate all-cause mortality (censored for all causes of program exit except death). Analyses were performed using SPSS 22.0 (SPSS Inc., Chicago, IL) and GraphPad® Prism 8.0 (GrapPad Software Inc., San Diego, CA, USA). We considered two-sided p values < 0.05 statistically significant.

Results

We evaluated 2025 measurements of serum potassium obtained from 146 patients, whose clinical and demographic characteristics are illustrated in Table 1. Patients were relatively young, mostly male and Caucasian. Diabetes and nephrosclerosis accounted for the majority of primary kidney diseases. At the study entry, only five patients were anuric. There was no withdrawal from any medication of interest during the study period.

Mean serum potassium was 4.72 ± 0.74 mEq/L, varying from 2.5 to 8.3 mEq/L. Histogram of potassium distribution is depicted in Fig. 1.

We identified 59 measurements of serum potassium lower than 3.5 mEq/L, which correspond to 2.9% of all measurements and occurred in 35 patients (23.9%). In addition, 269 measurements (13.3%) were higher than 5.5 mEq/L and were identified in 74 patients (50.7%). Twelve of these patients presented at least one episode of hypokalemia and one episode of hyperkalemia. Differences between patients according to the presence of hypokalemia and hyperkalemia are shown in Table 2. Patients who presented hypokalemia had lower levels of serum albumin ($p = 0.022$) and were less likely to be black ($p = 0.031$). There was not PPI withdrawal during the study period. Utilization of omeprazole ($p = 0.024$) was higher among patients who had hypokalemia. The omeprazole-associated

Table 1 Characteristics of patients

	$n = 146$
Male gender, *n* (%)	77 (52.7)
Diabetes, *n* (%)	33 (22.6)
Age, years	55 ± 18
Race, *n* (%)	
White	105 (71.9)
Black	35 (24.0)
Asian	6 (4.1)
Primary kidney disease, *n* (%)	
Diabetes	43 (29.5)
Nephroesclerosis	36 (24.7)
Chronic glomerulonephritis	23 (15.8)
Interstitial disease	14 (9.6)
Other/unknown	30 (20.5)
Albumin, g/dL	3.7 ± 0.5
Time on PD at the study entry, years	1.34 (0.59, 2.30)
Residual diuresis at the study entry, *n* (%)	141 (96.6)

PD peritoneal dialysis. Values expressed as mean ± SD or median (25, 75), unless otherwise specified

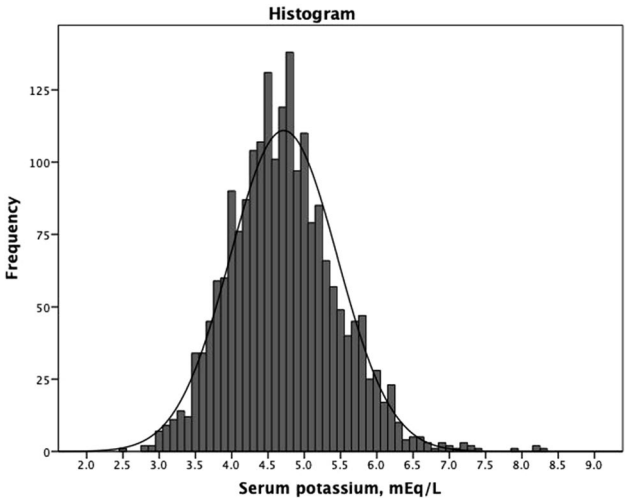

Fig. 1 Histogram of serum potassium distribution. Frequency distribution histogram for potassium levels in 146 patients (2055 measurements), expressed in mEq/L

hypokalemia was seen only in non-anuric patients (Fig. 2). Hypokalemia remained significantly associated to omeprazole prescription (RR 3.6, 95% CI 1.2–10.8, $p = 0.006$), race (Asian RR 8.2, 95% CI 3.5–68.7, $p = 0.024$, Black RR: 0.3, 95% CI 0.09–0.85, $p = 0.044$), and serum albumin (RR 0.3, 95% CI 0.1–0.7, $p = 0.006$) even after adjustment for serum magnesium, diabetes, and ACEI/ARB prescription ($p = 0.866$). Patients who had hyperkalemia were more likely to be anuric, had a lower volume of diuresis at the end of the study period, and were all in use of furosemide. Both factors remained significantly associated with hyperkalemia in a multivariate analysis, adjusted for diabetes and ACEI/ARB prescription. We identified at least one episode of peritonitis in 40 patients (27.4%). Presence of peritonitis was not associated with hypokalemia ($p = 0.295$) or hyperkalemia ($p = 0.701$). Kaplan–Meier curves did not show any association between survival and hypokalemia (log-rank test $p = 0.122$) or hyperkalemia (log-rank test $p = 0.101$). Cox regression analysis showed that age was the only independent variable associated with survival (RR 1.04 95% CI 1.01–1.07, $p = 0.009$), in a model adjusted for diabetes ($p = 0.814$). Neither hypokalemia nor hyperkalemia were significantly associated with survival when modeled in the Cox regression analysis.

Discussion

Our study adds to the body of literature on the incidence of abnormal serum potassium among patients on PD. We verified that both hypo- and hyperkalemia are not uncommon in this population and also that omeprazole was associated with hypokalemia in non-anuric patients.

The annual mortality of patients on dialysis due to a cardiovascular cause attributable to sudden cardiac death and/or arrhythmias is extremely high [10–12]. Besides the risk factors related to underlying kidney disease, arrhythmias can occur due to shifts in fluid status, and potassium disturbances [13].

Although hypokalemia is far more common in PD when compared to hemodialysis, the frequency of hyperkalemia in patients on PD is not negligible, albeit it is underappreciated. Plasma potassium concentration in CKD remains within normal range until the glomerular filtration rate falls below 15 mL/min. In this situation, the risk of hyperkalemia increases after an exogenous load, if compared with normal subjects. In fact, in the current study, hyperkalemia was more common than hypokalemia. The prevalence of hyperkalemia has been described between 2.9 and 9.7% in studies that considered either a unique measurement or the average of three measurements [4, 8]. In the current study, half of the patients had at least one episode of hyperkalemia. Potassium balance in PD, increased colonic secretion and residual renal excretion usually prevent patients from hyperkalemia [14]. In addition, transcellular shift driven by insulin in response to glucose absorption should also contribute to hyperkalemia prevention [14]. Intake of potassium rich food, anuria, and race might have accounted for this high prevalence of hyperkalemia in our and other studies. Since ACEI/ARB seems to not be associated with hyperkalemia among patients on PD, withholding these drugs does not resolve the potassium disturbance in this clinical scenario [15–17].

Table 2 Characteristics of patients according to the presence of hypokalemia and hyperkalemia

	Hyperkalemia		Hypokalemia	
	Without ($n=72$)	With ($n=74$)	Without ($n=111$)	With ($n=35$)
Age, years	52 ± 19	55 ± 17	54 ± 18	58 ± 18
Male gender, %	46.9	58.1	53.2	48.6
Race, %				
White	76	68	70	80
Black	20	29	28	11[#]
Asian	4	3	2	9
Diabetes, *n* (%)	42.9	35.5	38.7	28.6
PD duration, years	1.0 (0.4, 2.4)	1.3 (0.7, 2.2)	1.3 (0.6, 2.3)	1.4 (0.6, 2.3)
Initial diuresis, L	1.5 ± 0.6	1.3 ± 0.8	1.4 ± 0.7	1.3 ± 0.6
Final diuresis, L	1.2 ± 0.7	0.9 ± 0.6*	1.1 ± 0.7	0.9 ± 0.7
Anuria, %	8.8	31.5*	27.3	18.5
Average of K, mEq/L	3.9 ± 0.6	4.7 ± 0.4*	4.4 ± 0.7	3.9 ± 0.5[#]
Average of bicarbonate, mEq/L	21.6 ± 5.0	21.9 ± 2.1	21.4 ± 4.0	22.8 ± 3.0
Albumin, g/dL	3.7 ± 0.5	3.8 ± 0.5	3.8 ± 0.5	3.6 ± 0.6[#]
Mg, mg/dL	2.1 ± 0.4	2.2 ± 0.5	2.1 ± 0.4	2.1 ± 0.5
Total Calcium, mg/dL	8.8 ± 1.3	8.5 ± 1.3	8.6 ± 1.4	8.7 ± 0.9
Use of omeprazol, %	61.2	69.4	65.8	85.7[#]
Use of furosemide, %	75.5	100*	89.2	91.4
Use of hydrochlorothiazide, %	34.7	27.4	30.6	48.6
Use of spironolactone, %	12.2	6.5	9.0	20.0
Use of ACEI/ARB, %	38.8	35.5	36.9	34.3

PD peritoneal dialysis, *K* potassium, *Mg* magnesium, *ACEI/BRA* angiotensin converting enzyme/aldosterone receptor blocker. Values expressed as mean ± SD or median (25, 75), unless otherwise specified. *$p<0.05$ vs. without hyperkalemia; [#]$p<0.05$ vs. without hypokalemia

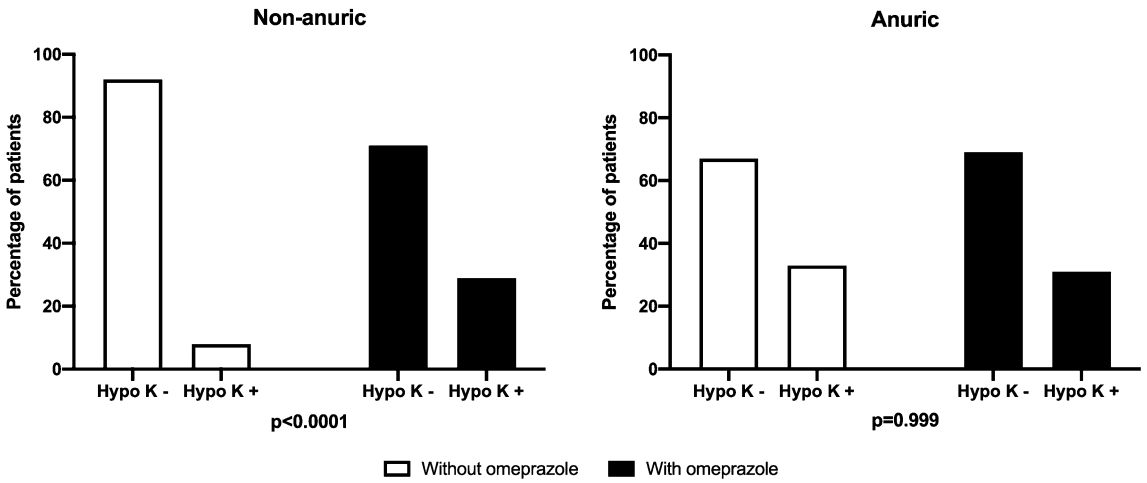

Fig. 2 Percentage of patients with hypokalemia according to use of omeprazole in non-anuric (left panel) and anuric patients (right panel). The omeprazole-associated hypokalemia was found among non-anuric patients ($p<0.0001$) but not in anuric patients ($p=0.999$). Hypo K^+, with hypokalemia; Hypo K^-, without hypokalemia

The association between furosemide and hyperkalemia seems to be an attempt to manage the high levels of potassium rather than a cause of this particular disturbance. However, since studies on PD are rare, further investigation is warranted to explore the real prevalence of hyperkalemia in patients on PD.

Due to loss through dialysis fluid, the auto-regulation capacity in potassium metabolism is impaired in patients on PD despite the residual renal function. Potassium levels in PD are affected by intracellular volume, dietary intake, and the number of exchanges a day [5]. The literature has suggested that hypokalemia is common in patients on PD [1–4, 6–9]. We have confirmed this finding extending the analysis to a time-average of thousands of values of serum potassium.

Interestingly and contrary to previous studies, hypokalemia was less likely to occur in Black individuals. Racial differences in potassium intake and excretion have been implicated as a potential mechanism to explain why Black individuals experience more severe hypertension and cardiovascular disease [18]. A large epidemiological study enrolling more than 2 million individuals showed that African Americans compared with non-African Americans are seen to have lower potassium levels, even after adjustment for demographics, comorbid conditions, and medication use with a potential to alter potassium levels [19]. Indeed, in the Atherosclerosis Risk in Communities (ARIC) Study, the African ancestry was associated to lower potassium levels [19]. The mortality risk associated with levels of potassium < 4.2 mmol/L was lower in African American than non-African Americans. In the scenario of chronic kidney disease, hypokalemia in black individuals was demonstrated to be a stronger death predictor than in Caucasian [20].

Another factor associated with hypokalemia were low serum albumin, which might be related to malnutrition, as previously described [21, 22], and the use of omeprazole. PPIs are among the most widely used prescription drugs [23]. Hypomagnesemia is a reported side effect of PPI described for the first time in 2006 [24], and confirmed by others [25–27]. Inhibitory effects of PPIs on H^+, K^+-ATPase are exerted only in acidic condition; therefore, hypokalemia is not a common side effect. However, in clinical situations marked by extreme alkalosis or impaired K^+-recycling system, which is the case of patients on PD, PPIs may cause hypokalemia unrelated to hypomagnesemia [28]. In the present study, omeprazole was associated with hypokalemia in non-anuric patients, a finding independent from the magnesium levels. The plausible explanation is that omeprazole might have induced higher urinary potassium excretion, although this is merely speculative.

We found no association between hypokalemia and mortality or peritonitis, which has been described in patients on PD [1, 3]. However, this result should be interpreted with caution since the current data collection was not prospective and several factors that might interfere with these outcomes could be not accurately identified.

Conclusions

In summary, we have reported novel data demonstrating that omeprazole is associated with hypokalemia in patients on PD, regardless the levels of serum magnesium. Due to the study design, we could not address a cause-effect relationship. Considering some limitations such as medication adherence, amount of potassium intake, adjusting of medication doses, and urinary measurements of magnesium and potassium, further studies are warranted to explore the causes of potassium disturbances in patients on PD. Nevertheless, our study highlights the importance of determining whether nutritional and medication intervention would reduce potassium disturbances in patients on PD.

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Author contributions Contributions to the conception and study design: FAG and RME; Data collection and analysis: RME. Data interpretation: RME, RMAM. Drafting of the manuscript: RME, RMAM. Revising manuscript content and approval of the final version of the manuscript: FAG, LCC, LC, MCTP, LKRPA, CSW, BCS, BJP, RMAM and RME. RME takes responsibility for the integrity of the data analysis.

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Compliance with ethical standards

Conflict of interest We have read and understood Peritoneal Dialysis International's policy on disclosing conflicts of interest and declare that we have none.

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