Association between hypokalemia, malnutrition and mortality in Peritoneal Dialysis patients

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ABSTRACT

Introduction: Hypokalemia is found in peritoneal dialysis (PD) patients. The problem may be severe and promote mortality. Several factors may trigger the hypokalemia in PD patients, such as preexisting malnutrition and the low protein and potassium food intake. **Objectives:** To verify the prevalence of hypokalemia and its association with mortality, nutrition status, clinical, laboratory and electrocardiographic variables in PD patients. **Methods:** Serum K+ levels were evaluated retrospectively in PD patients. Hypokalemia was defined when the average of serum K+ was < 3.5 mEq/L in six consecutive measurements. Other available biochemical tests were also evaluated. Subjective Global Assessment (SGA) and body mass index (BMI) were used to assess the nutrition status. A questionnaire was applied to identify the most common symptoms and signals associated to hypokalemia. An electrocardiogram was performed. Demographic data, dialysis characteristics and survival rate were collected. **Results:** Hypokalemia was present in 15 out of 110 patients (13.6%). The survival rate was lower in the hypokalemic group (p = 0.002). Hypokalemia was only associated with serum levels of albumin and urea, and with the SGA results. **Conclusion:** Low levels of serum potassium were associated to lower survival in PD patients and it seems to be related to malnutrition.

Keywords: hypokalemia, malnutrition, mortality, peritoneal dialysis, potassium.

INTRODUCTION

Compared to hemodialysis, peritoneal dialysis (PD) has the advantage of removing plasmatic fluid and metabolites daily, thereby reducing the risk of major hemodynamic changes. On the other hand, PD can cause a significant reduction in the serum levels of potassium.[1-6]

The daily removal of potassium by the dialysate in PD is approximately 30-40 mmoL.[7] The loss of this mineral significantly increases with the use of diuretics; presence of diarrhea; vomiting; or other conditions, such as fistula and drains. Moreover, patients may have low intake of protein and foods rich in potassium, preexisting malnutrition, and comorbid conditions. The intake of dietary potassium can vary significantly between individuals and on different days for the same person.[8] The combination of high loss and low reserve or intake may contribute to the severe hypokalemia in PD patients.

Increased blood levels of insulin accompany the constant absorption of glucose from PD. Consequently there is a constant flow of potassium into the cells.[9-12] However, possibly due to a temporary equilibrium in serum, it can be difficult to detect the blood electrolyte deficit. Thus, hypokalemia may not be easily detected in the routine laboratory assessment of PD patients.

Hypokalemia is defined as a serum potassium concentration below 3.5 mEq/L.[13] When the deficit is small, the patient may be asymptomatic or show mild symptoms. In this case, the main symptoms of hypokalemia are generalized weakness; muscle fatigue; apathy; malaise; nausea; vomiting; and, sometimes, abdominal distension. However, in cases of significant reduction of serum

potassium concentrations (below 3.0 mEq/L), symptoms such as muscle contractions and paralysis may occur. Individuals, especially those with a history of heart disease, may have cardiac arrhythmias. When serum potassium decreases below 2.5 mEq/L, the clinical manifestations may progress to severe muscle weakness, paralytic ileus, respiratory paralysis, and atrial and ventricular arrhythmias[13]. Therefore, patients with severe hypokalemia have a high risk of sudden death due to respiratory or cardiac arrest.

The aim of this study was to determine the frequency of hypokalemia in patients on PD and to study its associations with mortality, symptoms, nutritional markers, and other laboratory tests.

Methods

The study was approved by the Ethics Committee of the Pontifical Catholic University of Parana, Brazil. All patients included in the study signed a free and informed consent form.

The study was qualitative and quantitative. The recruited patients were involved in the chronic PD program of the Pro-Renal Foundation, located in Curitiba, Paraná, Brazil. The study was conducted between November 2004 and October 2007.

The total study population consisted of all active patients in a PD program, including those undergoing continuous ambulatory peritoneal dialysis (CAPD) and in automated peritoneal dialysis (APD). The inclusion criteria used were as follows: outpatients, aged above18 years, and receiving dialysis for over 3 months.

Data was collected from patients' records. Data were collected in factors including age, gender, underlying disease, dialysis program, volume and concentration of glucose in the dialysis bags, number of exchanges, urine volume, laboratory tests routinely performed at the treatment centers, and medications used by the patients. For laboratory results, the average of the previous 6 blood collections from the date of interview of the subject was considered. Serum concentrations of potassium less than 3.5 mEq/L; phosphorus, less than 3.5 mEq/L; calcium, less than 8.4 mg/dL; and urea, less than 100 mg/dL were defined as low levels. Likewise, the serum concentration results for albumin less than 3.5 g/dL and creatinine less than 7.0 mg/dL were considered low levels. Other data collected were regarding the presence of peritonitis and the results of Kt/V and PET, when available. The most recent values were recorded for each patient.

Patients were interviewed once by the researchers for assessment of whether they had any of the 6 common symptoms in PD: cramps, vomiting, muscle aches, breathing difficulties, confusion, and hypotension. For this part of the study, only subjective information was used.

Regarding food intake, patients were asked about the overall quality and quantity of the food eaten. They were asked about how many meals they had, with options of 1 to 6. They were also questioned about the practice of physical exercises. It was considered regular when physical exercise was done 3 or more times per week, considering even mild exercises, such as hiking, with duration equal to or more than 30 minutes. Data on the use and frequency of medication were also collected. A pre-established list was used for this data collection. The drugs included were as follows: antihypertensive calcium antagonists, angiotensin II receptor antagonists, antihypertensive angiotensin-converting enzyme (ACE) inhibitors, antihypertensive α-2 agonists, antihypertensive β-blockers, antihypertensive direct vasodilators, antiarrhythmic, loop diuretics, potassium-sparing diuretics, iron supplements, folic acid, erythropoietin, multivitamins, and potassium chloride. The weight (with the peritoneal cavity empty) and height of the patients were also recorded, and the body mass index (BMI = kg/m^2) calculated. Subjective Global Assessment (SGA) scale was also applied.

In addition, electrocardiography was performed on a sample of 85 patients. The electrocardiographs were evaluated for non-ST-segment elevation signals, ventricular repolarization change, and T-wave inversion. The electrocardiographic (ECG) assessment was not performed in all patients because 18 of them died and 7 changed their facility and/or dialysis modality. At the end of the study, data were collected from the date of initial treatment with PD and death, where relevant.

The results were expressed as frequencies and percentages or averages, minimum and maximum, and standard deviation values. For intergroup comparison defined for dichotomous variables on the probability of having hypokalemia, the Fisher exact test was used. For this assessment, the odds ratios

and 95% confidence intervals were estimated. For the joint assessment on the association of the variables with the presence of hypokalemia, a logistic regression model was adjusted. Explanatory variables were considered when showing $p < 0.05$ in the univariate analysis and having at least 1 case of a patient with hypokalemia in both classifications of the variable. To assess the association of hypokalemia with the survival curve, a Cox regression model was adjusted, which included variables presenting a p-value < 0.05 in the univariate assessment (Log-rank test). The results were expressed by the Kaplan-Meier method. P values of < 0.05 were considered statistically significant. Data were analyzed using the SPSS v.11 software program.

Results

The sample comprised 110 patients. Of these, 53.6% (n = 59) were female patients. Regarding PD treatment, 60% (n = 66) of individuals underwent CAPD, and all others underwent APD. The age group ranged from 22 to 91 years (median, 62 years). The average time for dialysis was 43.82 months (± 28.11).

Regarding the etiology of chronic kidney disease, diabetic nephropathy was the most prevalent cause (40.9%), followed by hypertensive nephrosclerosis (26.4%). About 28% of patients had other causes, 6.4% had no established etiology.

The serum potassium levels varied from 2.7 to 5.6 mEq/L (4.35 ± 0.75). Hypokalemia was observed in 13.6% (n = 15). A significant association was observed between hypokalemia and SGA score ($p < 0.05$, OR 4.1) and blood urea nitrogen level ($p < 0.01$) (Table 1).

Of the 110 subjects studied, 46.8% (n = 51) died. Deaths related to infectious causes and cardiovascular disease had the same distribution (43.1%, n = 22), followed by cancer (2.0%, n = 1). Other causes of death were unknown (11.8%, n = 6).

A significant association was observed between death and low levels of serum potassium ($p = 0.002$). It was observed that 80% (n = 12) of the patients died hypokalemic and half of them, due to cardiovascular disease. The other causes of deaths of hypokalemic patients were infection (25%, n = 3) and unknown reasons (25%, n = 3).

The SGA score was also significantly associated with death ($p < 0.01$). According to the SGA score, patients classified as malnourished had the worst survival rate ($p = 0.002$, HR: 3.5, with 95% CI: 1.6 to 7.6). There was also a significant association between death and low levels of serum albumin ($p < 0.05$).

As for the practice of physical exercise, there was a significant inverse association with mortality ($p = 0.003$). That is, regular exercise was protective for survival ($p = 0.029$, HR: 2.3 with 95% CI:1, 1-4, 9).

Regarding drugs, the following was the frequency of use: calcium antagonists, n = 23; angiotensin receptor antagonists, n = 12; ACE inhibitors, n = 59; centrally-acting α-2 agonist, n = 6; β-blocker, n = 20; direct-acting vasodilators, n = 1; antiarrhythmic drugs, n = 3; loop diuretics, n = 69; potassium-sparing diuretics, n = 2; ferrous sulfate, n = 43; folic acid, n = 2; erythropoietin, n = 79; vitamin supplements, n = 79; potassium chloride, n = 3; and insulin, n = 42. Regarding this subject, an interesting result was that the use of multivitamin supplements significantly increased patient survival ($p < 0.05$). Further, the reverse occurred with the use of a potassium-sparing diuretic ($p < 0.05$). It was observed that none of the study subjects took multivitamin supplements concomitantly with a potassium-sparing diuretic. However, there was no association between multivitamin use and hypokalemia. The patients who were taking antihypertensive drugs, such as calcium antagonists and/or potassium-sparing diuretics, were significantly less affected by hypokalemia ($p < 0.05$). Hypokalemia was not associated with the other drugs used by patients.

No significant association was found between serum potassium and age; gender; BMI; physical activity patterns; occurrence of symptoms; presence of diabetes or insulin therapy; type of dialysis; urine volume; test results of PET and Kt/V; peritonitis episodes; number of meals per day; and serum levels of creatinine, phosphorus, and calcium. There was no significant association between these variables and death.

ECG abnormalities occurred in 5.1% of hypokalemic patients when the non-ST-segment elevation variable ($p = 0.683$, OR 0.6) was evaluated.

Table 1 Association between hypokalemia and subjective global assessment (SGA) and biochemical variables

Variables	Classification	With hypokalemia n (%)	Without hypokalemia n (%)	*p*-value*	HR (CI 95%)
SGA	Mild/moderate malnutrition Nourished	9 (22%) 4 (6%)	32 (78%) 59 (93.7%)	0.031	4.1 (1.2-4.5)
Serum albumin (g/dL)	< 3.5	13 (20.3%)	51 (79.7%)	0.023	5.3 (1.1-5.1)
Serum urea (mg/dL)	< 100	15 (22.7%)	51 (77.3%)	< 0.001	-
Serum creatinine (mg/dL)	< 7.0	9 (19.1%)	38 (80.9%)	0.172	2.2 (0.7-6.7)
Serum phosphorus (mg/dL)	< 3.5	2 (16.7%)	10 (83.3%)	0.667	1.3 (0.3-6.6)
Serum calcium (mg/dL)	< 8.4	3 (20%)	12 (80%)	0.428	1.7 (0.4-7.0)

* *p* value based on Fisher's exact test.

When we assessed the change in ventricular repolarization, the percentages was 4.9% (p = 0.344, OR 0.4). With regard to T-wave inversion, there were 10.5% (p = 0.612, OR 1.8) of abnormalities on the electrocardiogram. However, no association was found between hypokalemia and the ECG findings. There was no significant association between mortality and the variables non-ST-segment elevation, ventricular repolarization, and T wave inversion.

Discussion

In this study, hypokalemia was found in 13.6% of the 110 individuals undergoing PD. Previous studies have shown similar results. In the study by Kim *et al.*,[6] 10.3% (n = 7) of the patients had low levels of serum potassium. Szeto *et al.*[3] showed that 20.3% (n = 54) of the patients were hypokalemic. The prevalence of the problem was 23.6% in the study by Chuang *et al.*[5] In the study by Oreopoulos *et al.*[10], out of the 152 patients studied, 25 had a history of hypokalemia. Hypokalemic patients were divided into 2 groups: Group 1 (n = 20), with serum potassium > 3 mmol/L, and Group 2 (n = 5), with serum potassium ≤ 3 mmol/L. Therefore, hypokalemia is a problem for people on PD in different locations and deserves special attention in the clinical routine.

In our population, there was no significant difference among the causes of mortality. The major causes were infectious and cardiovascular diseases. In the study by Szeto *et al.*,[3] the major causes of death were cardiovascular disease and peritonitis, which resulted in 14.8% of deaths, each. In that study, it was observed that 80% (n = 12) of hypokalemic patients died, and half of them, due to cardiovascular disease. Similarly, in our study, hypokalemic patients had higher mortality rates than non-hypokalemic patients. Therefore, the assessment of serum potassium, which is a simple biochemical test, can be a good indicator for acute risk of cardiovascular death.

Hypokalemia appears to be directly associated with acute and chronic depletion of the nutritional status. As in our results, one study showed a significant association between malnutrition, as assessed by SGA score, and hypokalemia.[3] Furthermore, in ours as well as other studies,[3,5,6] hypoalbuminemia was observed in hypokalemic patients. The strong and significant relationship between hypoalbuminemia and mortality is already well known. Excluding etiology, hypoalbuminemia may reflect visceral protein depletion and global malnutrition.

Another variable that may reflect the nutritional status is serum urea. In our study, low serum urea was associated with hypokalemia. The low serum levels of urea in dialysis patients may reflect inadequate protein and, indirectly, potassium intake. Low serum creatinine, on the other hand, may reflect the depletion of body muscle mass of patients. In the study by Kim *et al.*[6] and in that by Chuang *et al.*,[5] serum levels of potassium were positively associated with serum creatinine. However, in our study, there was no association between

these 2 laboratory tests. Furthermore, patients who performed regular exercise had lower mortality. Muscle body mass is an important marker of nutritional status. Depletion of muscle body mass reflects chronic malnutrition, which may not have been a problem for our patients. Another aspect that supports this conclusion is that no difference was found between hypokalemia or mortality in relation to the BMI of our patients. The hypokalemic patients in our study, unlike in other published studies, apparently had acute nutritional depletion, which was evidenced by the SGA and the low serum urea levels.

In chronic malnutrition, BMI and serum creatinine levels are expected to be low. These results were not found in our study. Moreover, unlike other studies,[3,5] our results found no relationship between hypokalemia and serum levels of phosphorus and calcium. There was no association between hypokalemia and adequacy of dialysis, volume of urine, or episodes of peritonitis. Hypokalemia was also not associated with age or the presence of diabetes. One study[6] found that hypokalemic patients were significantly older and had higher prevalence of diabetes mellitus. It is well known that the elderly and patients with diabetes are major risk groups for malnutrition, particularly of the chronic type. From a practical point of view, our results indicate that a low serum level of potassium can be a good marker of acute nutritional depletion and, hence, death.

In hemodialysis, serum potassium levels tend to be high. In PD, they are normal or tend to be low. When hyperkalemia occurs during PD, the problem is usually associated with inadequate dialysis. However, for both dialysis modalities, changes in serum potassium levels do not seem to lead to significant ECG abnormalities. For patients on hemodialysis, Nakamura *et al.*[14] found no association between serum potassium levels and ECG results. However, to our knowledge, no other study had sought this association in PD patients, which was also nonexistent. That is, hypokalemia does not bring significant ECG changes in patients on dialysis, or the test is not effective for identifying cardiac changes promoted by changes in serum potassium levels in these patients.

In our opinion, the main limitation of this study was the short follow-up time. An assessment for a longer time period could generate a more complete data set.

Conclusion

Our study showed that hypokalemia occurred in approximately 14% of PD patients and that it was associated with a high mortality. Acute nutritional depletion, probably associated with low food intake, was the main factor causing hypokalemia. Therefore, serum potassium levels can be used in the diagnosis of acute malnutrition and for identifying risk of death.

This study also showed that patients might not show clear signs and symptoms of hypokalemia. Since monthly laboratory tests, unfortunately, do not capture all the instances of hypokalemia, frequent nutritional attention is essential in PD patients. The main nutritional focus should be food intake, in addition to identification of the sources of potassium loss. This would help the replacement of the mineral through food and medication may be indicated prematurely, and reduce the risk of death for these patients.

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