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Impact of Renin-Angiotensin Aldosterone System Inhibition on Serum Potassium Levels among Peritoneal Dialysis Patients

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Keywords
Peritoneal dialysis · Potassium · Hyperkalemia · Hypokalemia · Renin-angiotensin aldosterone system · Angiotensin converting enzyme inhibitors · Angiotensin receptor blockers

Abstract
Background: The chronic use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blocker has been associated with hyperkalemia in patients with reduced renal function even after the initiation of hemodialysis. Whether such medications may cause a similar effect in peritoneal dialysis patients is not well established. So, the aim of our study was to analyze the impact of renin-angiotensin-aldosterone inhibitors on the serum levels of potassium in a national cohort of peritoneal dialysis patients. ***Method:*** A prospective, observational, nationwide cohort study was conducted. We identified all incident patients on peritoneal dialysis that had angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) prescribed for at least 3 months and a similar period of time without these medications. Patients were divided into 4 groups: Groups I and III correspond to patients using, respectively, an ACEi or ARB and then got the drug suspended; Groups II and IV started peritoneal dialysis without the use of any renin-angiotensin aldosterone system inhibitor and then got, respectively, an ACEi or ARB introduced. Changes in potassium serum levels were compared using 2 statistical approaches: (1) the non-parametric Wilcoxon test for repeated measures and (2) a crossover analysis. ***Results:*** Mean potassium serum levels at the first phase of the study for Groups I, II, III, and IV were, respectively, 4.46 ± 0.79, 4.33 ± 0.78, 4.41 ± 0.63, and 4.44 ± 0.56. Changes in mean potassium serum levels for Groups I, II, III, and IV were –0.10 ± 0.60, 0.02 ± 0.56, –0.06 ± 0.46, and 0.03 ± 0.50, respectively. ***Conclusion:*** The use of ACEi and ARB was not associated with a greater risk for hyperkalemia in stable peritoneal dialysis patients independently of residual renal function.

Introduction

Hyperkalemia is a life-threatening condition associated with a greater overall and cardiovascular mortality [1, 2]. Its incidence is greater in advanced chronic kidney disease and can be intensified with the use of renin-angiotensin-aldosterone system inhibitors [3–5]. Such ef-

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fect was reported even in anuric hemodialysis (HD) patients. This increase in potassium serum levels was attributed to a reduction in the colonic excretion of potassium and likely to be intensified during the interdialytic period. However, dialysis patients may benefit from renin-angiotensin aldosterone system (RAAS) inhibitors, including angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB). In particular, the use of ACEis and ARBs in peritoneal dialysis (PD) patients seems to have a positive impact on cardiovascular disease, residual renal function (RRF), and on the peritoneal membrane structure [6–12].

The effect of RAAS inhibition on PD patients is likely different from HD patients, given the absence of the large interdialytic period common to HD. This was suggested by a small single-center study that analyzed 29 patients using a crossover design [13]. Nevertheless, according to our knowledge, no other study has confirmed this finding. Therefore, our study aims to analyze the effect of ACEis and ARBs on potassium serum levels of a nationwide PD cohort.

Methods

BRAZPD II is a national representative cohort study that included patients from 122 Brazilian centers. Clinical and laboratorial data were prospectively collected monthly from December 2004 to January 2011 using specific software developed for this objective. Details about study design and general characteristics of the population have been previously published [14]. The cohort comprises around 65% of all PD patients of the country along the study period; all patients signed their informed consent and local Ethical Committees of all participating centers approved the study.

This analysis included incident patients on PD, who had an ACEi or ARB prescribed for at least 3 months and a similar period of time without the medication. All patients should have all 3 measures of potassium in both time periods (before and after switch); otherwise, they were excluded from the analysis. Therefore, 4 subgroups were included: (I) patients using ACEi only during the first period of the study; (II) using ACEi only in the second period; (III) using ARB only during the first period; and (IV) ARB prescribed only during the second study period. We compared potassium serum levels before and after the modality switch. Patients using ARB and ACEi concomitantly were not included in the study. The presence of RRF was defined as a daily urinary output >100 mL.

Statistical Analysis

Continuous variables were expressed as mean ± SD or median and interquartile range, while categorical variables (e.g., gender, race, primary renal disease, presence of comorbid conditions, initial therapy, current PD modality) were expressed as frequencies or percentages. The χ^2, *t* test, or Wilcoxon were used, as appropriate, to compare demographic and clinical characteristics at baseline. The main outcome, changes in potassium serum levels, was compared using 2 statistical approaches: one using the non-parametric Wilcoxon test for repeated measures; and given a similar characteristic to a crossover study in this analysis, we also used a new and specific Stata command that provide values for carryover, sequence, period, and intervention effects (pkcross). Statistical significance was set at the level of $p < 0.05$. All analyses were performed using STATA 14.0.

Results

We identified 636 patients that met the inclusion criteria, of whom 242 were in Group I, 243 in Group II, 66 in Group III, and 84 in Group IV. Patients' mean age was 58.6 ± 16.1 years, 44.0% were male, 43.5% were diabetics, and 45.7% had history of previous HD. Demographic characteristics by subgroups are presented in Table 1. Importantly, no patient analyzed included in this study changed PD modality, which could have affected potassium serum levels per se. In addition, Table 2 depicts the prevalence of patients with potassium serum levels above 5.5 mEq/L before and after changing the prescription of the study population and also according to the RRF status.

Model I – Nonparametric Paired Test (Wilcoxon) – Comparison of Means before and after Switch Prescription

Mean potassium serum levels at the first phase of the study for Groups I, II, III, and IV were, respectively, 4.46 ± 0.79, 4.33 ± 0.78, 4.41 ± 0.63, and 4.44 ± 0.56. Changes in mean potassium serum levels for Groups I, II, III, and IV were –0.10 ± 0.60, 0.02 ± 0.56, –0.06 ± 0.46, and 0.03 ± 0.50, respectively. The probability that the mean difference was different of zero was 0.01 (Group I), 0.59 (Group II), 0.26 (Group III), and 0.52 (Group IV). Figure 1 depicts a scatterplot showing the number of patients who had an increase (above the diagonal line) or decrease (below the line) in potassium serum levels after the transition, while Figure 2 depicts the mean values and SD of all 4 groups along the 6 months of follow-up.

Model II – Crossover Analysis (pkcross – Stata Command)

In this model, we compared the differences in the moment immediately before changing the prescription with the values obtained after 3 months of the change. Table 3

Table 1. Baseline characteristics of participants

Variable	BRAZPD II population	ARB patients		ACEi patients	
		starting with the drug	starting without the drug	starting with the drug	starting without the drug
Age, years	59.8±16.2	58.9±15.7	57.8±16.0	58.2±16.2	60.1±17.7
Body mass index, kg/m^2	24.6±4.7	24.9±4.9	24.2±4.1	25.2±4.4	25.2±5.3
Diabetes (yes), %	43	45.4	44.9	42.4	35.3
Gender, male, %	48	38.8	48.5	46.9	43.5
Hypertension (yes), %	71	83.5	69.9	83.3	0.80
Literacy (<4 years), %	66	73.6	67.1	57.6	55.3
Pre-dialysis care (yes), %	49	46.7	55.1	54.5	56.5
Previous hemodialysis (yes), %	37	45.0	43.2	48.4	52.9
Race, white, %	64	64.0	60.1	62.1	45.8
Residual renal function (yes), %	59.7	64.0	61.7	77.2	46.3

shows the change in potassium serum levels by groups. A small reduction of 0.17 mEq/L was observed in the subgroup of patients that had ACEi interrupted after at least 3 months of therapy (Group I). This fall was slightly more pronounced in patients with RRF at baseline compared with anuric patients (–0.22 vs. –0.09 mEq/L). When an ACEi was introduced after the 3 initial months without the medication (Group II), the effect on potassium was also practically none and there is no difference between those patients with and without RRF (0.05 vs. 0.05 mEq/L).

Regarding ARB, its discontinuation (Group III) had no effect on mean potassium levels (–0.01 mEq/L). Patients with RRF had a small reduction of –0.20 ± 0.83 mEq/L in potassium levels, while a small increase of 0.22 ± 9 was observed in the anuric patients.

Table 2. Prevalence of hyperkalemia before and after change prescription in the whole population and according to the residual renal function status

	Before, *n* (%)	After, *n* (%)
Group		
ACEi-no	37 (15.3)	14 (5.8)
No-ACEi	18 (7.41)	22 (9.0)
ARB-no	9 (13.6)	5 (7.6)
No-ARB	7 (8.24)	3 (3.5)
Anuric		
ACEi-no	13 (14.9)	5 (5.7)
No-ACEi	7 (7.5)	11 (11.8)
ARB-no	0	1 (6.7)
No-ARB	1 (3.8)	0
With RRF		
ACEi-no	24 (15.5)	9 (5.8)
No-ACEi	11 (7.3)	11 (7.3)
ARB-no	9 (17.6)	4 (7.8)
No-ARB	6 (10.2)	3 (5.1)

Discussion

This is the largest cohort study to analyze the impact of the use of ACEi and ARB on potassium serum levels. Our findings suggest that the clinical effect of these drugs on potassium serum levels of PD patients is not significant and unlikely to cause any harm, independently of RRF.

Hyperkalemia is a well-known clinical complication of patients with kidney dysfunction. It may affect up to 40% of patients with CKD stage IV and can be accentuated with the use of inhibitors of the RAAS [15]. This effect occurs frequently with both ACEi and ARBs but seems to be more pronounced with ACEi than with ARB as shown in a recent nested-case control study [15].

The higher risk for hyperkalemia persists even after the initiation of HD and can be twice as great among those taking ACEi or ARB compared to other patients taking only anti-hypertensive drugs of other classes [4]. This effect that increases the prevalence of hyperkalemia was observed even in anuric patients and was attributed to a reduction in the gastrointestinal excretion or even in a disturbance of the cellular uptake of potassium acting during the interdialytic period [16]. In contrast to HD, PD is characterized as a continuous therapy, which in turn allows for a continuous removal of potassium and a more effective removal of this electrolyte in the long term as already observed in

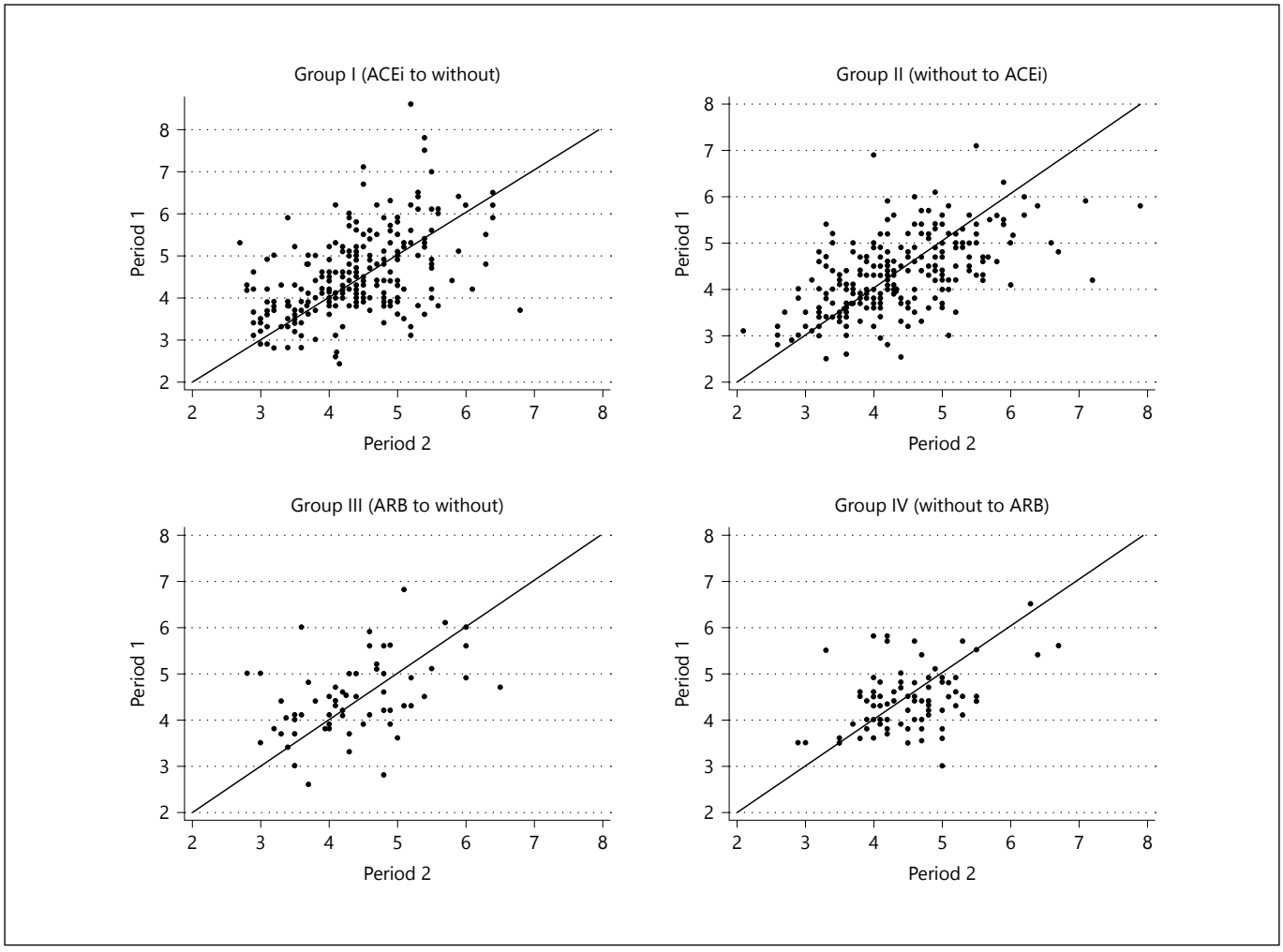

Fig. 1. Scatterplot showing the increase or decrease in potassium serum levels after the transition.

several large cohorts that compared the prevalence of potassium disturbances in both methods [1]. Our hypothesis was that the use of inhibitors of the RAAS in PD patients might be associated with a lower risk for hyperkalemia.

To the best of our knowledge, the only study to evaluate the effect of these drugs on serum potassium was a small single-center study with 29 patients and the authors found no increased risk for hyperkalemia [13]. However, this intervention was not tested in larger populations, particularly in cohorts with good external validity. Our study, more robust in terms of sample size, confirmed that these medications did not significantly increase potassium serum levels in daily clinical practice. In Figure 2, which depicts the changes in potassium serum levels for all patients, we can see a uniform distribution of patients that had an increase (above the diagonal line) or decrease (below diagonal line) in the serum potassium level with the use of each drug. Our findings were consistent even across the subgroup of patients divided according to the presence or absence of RRF.

Our study presents some important strengths, including a large sample size, the crossover design with a specific statistical analysis for this type of design, and the ability to capture the impact of daily clinical practice prescription of ACEi/ARB on potassium serum levels. Nevertheless, this study also presents some limitations, such as the lack of information about the reasons for the initiation or interruption of ACEi/ARB, the dose prescribed of these drugs or information about other drugs that could have had an influence on potassium serum levels including potassium supplements. In addition, we do not have nutritional information that could provide data on

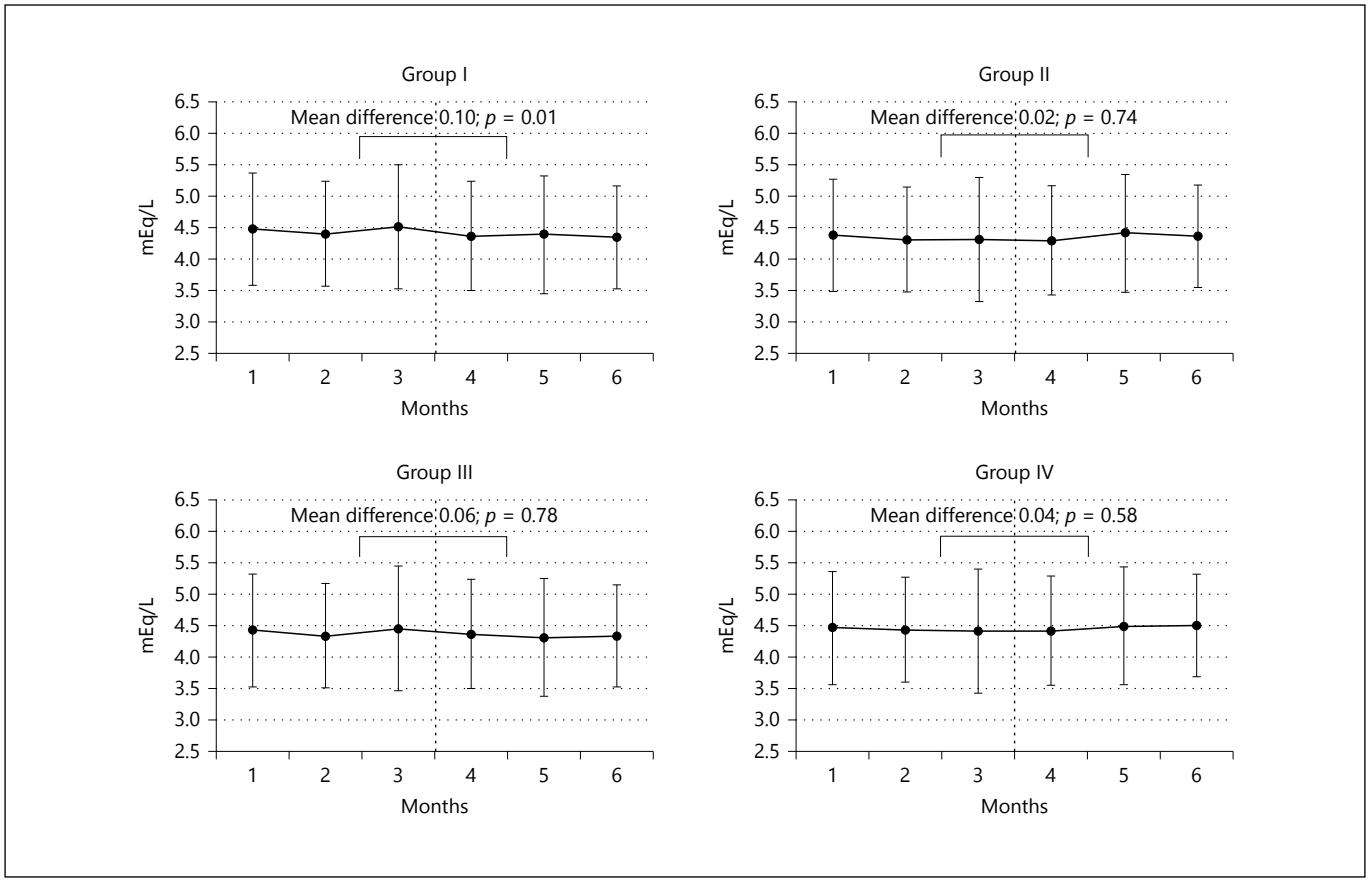

Fig. 2. Mean potassium levels during the 6 months of observation.

Table 3. Change in potassium serum levels by groups

	Baseline values		Mean change at 3 months		Mean change at 6 months		pkcross results			
	starting with medication	starting without medication	starting with medication	starting without medication	starting with medication	starting without medication	sequence	intervention	carryover	period
ACEi	4.47±0.90 (*n* = 242)	4.38±0.95 (*n* = 243)	0.04±0.86 (*n* = 242)	−0.07±0.79 (*n* = 243)	−0.17±0.91 (*n* = 242)	0.05±0.81 (*n* = 243)	0.33	<0.01	0.32	0.45
ARB	4.43±0.79 (*n* = 66)	4.47±0.74 (*n* = 85)	0.03±0.81 (*n* = 66)	−0.06±0.74 (*n* = 85)	−0.01±0.72 (*n* = 66)	0.10±0.72 (*n* = 85)	0.40	0.16	0.48	0.92
Patients without residual renal function										
ACEi	4.41±0.94 (*n* = 87)	4.43±0.96 (*n* = 93)	0.04±0.88 (*n* = 87)	−0.06±0.77 (*n* = 93)	−0.09±0.92 (*n* = 87)	0.05±0.76 (*n* = 93)	0.52	0.23	0.85	0.93
ARB	4.22±0.74 (*n* = 15)	4.35±0.61 (*n* = 26)	−0.02±0.63 (*n* = 15)	−0.06±0.66 (*n* = 26)	0.22±0.88 (*n* = 15)	0.16±0.81 (*n* = 26)	0.63	0.98	0.78	0.29
Patients with residual renal function										
ACEi	4.50±0.88 (*n* = 155)	4.35±0.94 (*n* = 150)	0.04±0.85 (*n* = 155)	−0.08±0.80 (*n* = 150)	−0.22±0.91 (*n* = 155)	0.05±0.84 (*n* = 150)	0.22	0.01	0.28	0.40
ARB	4.49±0.81 (*n* = 51)	4.52±0.79 (*n* = 59)	−0.04±0.86 (*n* = 51)	−0.05±0.77 (*n* = 59)	−0.20±0.83 (*n* = 51)	0.07±0.68 (*n* = 59)	0.29	0.13	0.38	0.62

daily potassium intake or information on Kt/V or weekly CCT. Finally, RRF was measured only at baseline.

In conclusion, the use of ACEi and ARB seems to be safe in terms of the risks involved in the development of hyperkalemia for stable PD patients independently of RRF.

Disclosure Statement

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References

1 Torlen K, Kalantar-Zadeh K, Molnar MZ, et al: Serum potassium and cause-specific mortality in a large peritoneal dialysis cohort. Clin J Am Soc Nephrol 2012;7:1272–1284.
2 Ribeiro SC, Figueiredo AE, Barretti P, et al: Low serum potassium levels increase the infectious-caused mortality in peritoneal dialysis patients: a propensity-matched score study. PLoS One 2015;10:e0127453.
3 Raebel MA: Hyperkalemia associated with use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. Cardiovasc Ther 2012;30:e156–e166.
4 Knoll GA, Sahgal A, Nair RC, et al: Renin-angiotensin system blockade and the risk of hyperkalemia in chronic hemodialysis patients. Am J Med 2002;112:110–114.
5 Han SW, Won YW, Yi JH, Kim HJ: No impact of hyperkalaemia with renin-angiotensin system blockades in maintenance haemodialysis patients. Nephrol Dial Transplant 2007;22:1150–1155.
6 Kolesnyk I, Noordzij M, Dekker FW, et al: A positive effect of aII inhibitors on peritoneal membrane function in long-term PD patients. Nephrol Dial Transplant 2009;24:272–277.
7 Hovind P, Tarnow L, Rossing P, et al: Improved survival in patients obtaining remission of nephrotic range albuminuria in diabetic nephropathy. Kidney Int 2004;66:1180–1186.
8 Eijkelkamp WB, Zhang Z, Remuzzi G, et al: Albuminuria is a target for renoprotective therapy independent from blood pressure in patients with type 2 diabetic nephropathy: post hoc analysis from the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial. J Am Soc Nephrol 2007;18:1540–1546.
9 Li PK, Chow KM, Wong TY, et al: Effects of an angiotensin-converting enzyme inhibitor on residual renal function in patients receiving peritoneal dialysis. A randomized, controlled study. Ann Intern Med 2003;139:105–112.
10 Suzuki H, Kanno Y, Sugahara S, et al: Effects of an angiotensin II receptor blocker, valsartan, on residual renal function in patients on CAPD. Am J Kidney Dis 2004;43:1056–1064.
11 Basturk T, Unsal A, Koc Y, et al: The effects of angiotensin-converting enzyme inhibitors on peritoneal protein loss and solute transport in peritoneal dialysis patients. Clinics (Sao Paulo) 2012;67:877–883.
12 Kolesnyk I, Dekker FW, Noordzij M, et al: Impact of ACE inhibitors and aII receptor blockers on peritoneal membrane transport characteristics in long-term peritoneal dialysis patients. Perit Dial Int 2007;27:446–453.
13 Phakdeekitcharoen B, Leelasa-nguan P: Effects of an ACE inhibitor or angiotensin receptor blocker on potassium in CAPD patients. Am J Kidney Dis 2004;44:738–746.
14 de Moraes TP, Figueiredo AE, de Campos LG, et al: Characterization of the BRAZPD II cohort and description of trends in peritoneal dialysis outcome across time periods. Perit Dial Int 2014;34:714–723.
15 Loutradis C, Tolika P, Skodra A, et al: Prevalence of hyperkalemia in diabetic and non-diabetic patients with chronic kidney disease: a nested case-control study. Am J Nephrol 2015;42:351–360.
16 Sandle GI, Gaiger E, Tapster S, Goodship TH: Evidence for large intestinal control of potassium homoeostasis in uraemic patients undergoing long-term dialysis. Clin Sci (Lond) 1987;73:247–252.